The CLOTS Collaboration

CLOTS - 3

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

Protocol

Version 2
17Jan 2010

Modifications in Protocol since Version 1 (July 2008)

1. We have included the results of the CLOTS trials 1and 2 which are now available in the Lay Summary (Page 4) and background sections (Page 5).

2. We have removed the following from the exclusion criteria (Page 11).

   - Patients who are anticoagulated (taking Warfarin, unfractionated heparin, Low Molecular Weight Heparin or Direct thrombin inhibitors) at the time of enrolment in whom it is planned to continue the anticoagulation throughout the first week or two after the stroke. We have changed the randomisation form to reflect the changes in the eligibility criteria (Appendix 8, Page 34)

   This change was made because further analysis of the CLOTS trial 1 and 2 data showed that use of anticoagulants at baseline was not an independent predictor of risk of proximal DVT. This is not to say that anticoagulants would not be expected to lower the risk but they are probably used selectively in patients who are at particularly high risk – thus the residual risk even on anticoagulants is likely to be sufficiently high to justify attempts to further reduce the risk of DVT with external compression. Also by removing this exclusion criteria we will simplify the selection process, hopefully increase the proportion of patients eligibly for the trial and make our results more generalisable to situations where prophylactic anticoaglants are considered worthwhile. Whilst inclusion of patients on anticoagulants may reduce the event rate a little, our protocol allows for the total recruitment to be increased to allow for a lower event rate. Therefore the power of the trial will not be reduced.

3. We have included use of heparin, warfarin or thrombolysis (rt-PA) at the time of enrolment in our minimisation algorithm (Randomisation Procedure, Page 12).

   This was done to take account of the removal of anticoagulation from the exclusion criteria and to closely match the protocol of CLOTS trials 1 and 2.

4. We removed from the minimisation algorithm any account of which centre was randomising the patient (Randomisation Procedure, Page 12). This factor was never ultimately included in the algorithm

   This was done since analysis of the CLOTS trials 1 and 2 data did not suggest that centre was a significant factor in predicting the risk of proximal DVT. There was no evidence that centres varied in the sensitivity of their Doppler screening.

5. We have removed some references to the use of graduated compression stockings in the section on Allocated treatments (Page 12)

   This was done since their use is likely to become less common following the publication of the results of CLOTS 1 and 2

6. We have indicated that information regarding possible adverse effects of IPC – skins breaks and fall resulting in injury will only be collected for the period of 30 days after enrolment (Pages 14, 16 and 17). Changes have been made to the Discharge form to reflect this.(Appendix 10, Page 36)

   Skin breaks and falls resulting in injury which occur after IPC has been removed cannot be due to the IPC. Inclusion of later “adverse events” would add noise to the analysis and also place a greater burden on our collaborators. It is time consuming to review the medical and nursing notes in detail for an entire prolonged hospital admission.

7. We have included reference to the CLOTS trial 1 resulting in the reference list (Page 21).

8. We have removed reference to the use of below knee IPC in the discharge form because short sleeves are not provided by the trial (Appendix 10, Page 36).

9. We changed the follow up form to collect more structured information on adverse events (Appendix 10, Page 36).

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Lay Summary

A stroke occurs when the blood flow to part of the brain is interrupted by either a blocked or burst blood vessel. Stroke is the third biggest killer in developed countries, after heart attacks and cancer, and is the commonest cause of severe disability in adults. People who suffer a stroke are often drowsy and have weakness or numbness of the limbs on one side of their body. It may cause loss of speech or part of the vision. Patients are often bed-bound for several days or weeks after the stroke although if they survive, most will make some recovery. In stroke patients who are unable to walk, and who may be paralysed on one side, the blood flows only slowly through the veins of their legs. This encourages clots to form in the legs - so called deep venous thrombosis or DVT. Pieces of this clot may break off and are carried by the bloodstream to the lungs. These, so called pulmonary emboli, can stop the heart and can cause patients with stroke to die suddenly. This may occur without warning because often the clots in the legs do not cause any leg swelling or pain - DVTs are often clinically silent.

Blood thinning drugs can help reduce the risk of DVT and PE but in stroke patients they are not used routinely in the UK because they increase the risk of bleeding into the brain. Therefore, it is important to find alternative methods of reducing the risk of DVT. The CLOTS trials 1 & 2 tested whether graduated compression stockings - which are like long "flight socks" - reduce the risk of DVT after stroke. The results of these trials showed that routine use of graduated compression stockings in immobile stroke patients is not associated with a worthwhile reduction in risk of DVT. Another treatment which is used successfully to reduce the risk of DVT after surgery, but not currently in stroke units, is intermittent pneumatic compression (IPC). Sleeves which contain inflatable air sacs are wrapped around both legs and attached to a special air pump. The sleeves are then inflated around one leg at a time. The sleeves around the lower leg inflate before the ones around the thigh - this squeezes blood up the veins in the legs, increases the flow, reducing stagnation and the likelihood of clots forming - at least that is the theory! The sleeves inflate and deflate at regular intervals. Although this sounds uncomfortable, most people actually quite like the sensation!

The CLOTS - 3 trial will include patients who have had a stroke and who have been admitted to a stroke unit. Patients who cannot walk independently, and who are at greatest risk of DVT will be invited to join the study. If they agree they will be randomly allocated to having routine care plus IPC or just routine care. Patients in both groups will have routine ultrasound scans on their legs to detect DVTs about one and four weeks after the stroke. They will also be followed up at six months by telephone or postal questionnaire to find out how well they have recovered and to detect any clots which have occurred after leaving hospital. The trial aims to enrol at least 2000 patients which will provide a precise estimate of the effect of IPC on the risk of DVT.

The Importance of Post Stroke DVT

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, Tyrone & Skversky 1973, Warlow, Ogston & Douglas 1976). More recent studies with magnetic resonance imaging demonstrated DVT in 40% of stroke patients within the first three weeks, and above knee DVT in 18% (Kelly et al 2004). Studies using less sensitive screening techniques, such as Compression Doppler ultrasound, suggest a lower frequency of above knee DVT of perhaps 10% although the types of patients included and the duration and timing of follow up influences the estimates (Oczkowski et al 1992). Recent evidence from prospective studies in a Chinese population indicate that DVT is at least as common in that population as in white populations (de Silva et al 2006). Clinically apparent DVT confirmed on investigation is 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, Sandercock & Counsell 2000, McCarthy & 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, Ogston & Douglas 1976) but it is difficult to judge how often these PEs significantly contributed to the patients' death.

Anti-thrombotic 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, Sandercock & Counsell 2000). However, evidence from the International Stroke Trial (IST 1997) shows that even low dose heparin (5,000 units 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. The PREVAIL trial compared the effectiveness, and safety of standard prophylactic heparin with low molecular weight heparin (LMWH) (Sherman et al 2007). It demonstrated that LMWH was probably more effective than standard heparin in reducing the risk of mainly asymptomatic DVTs but it was not powered to identify clinically significant differences in risk. More importantly it does not, despite reports to the contrary, provide any evidence that routine heparin or LMWH use is associated with net benefit – it had no " avoid any heparin" control group (Ricci et al 2007).

Trials have demonstrated that aspirin is possibly effective in reducing the risk of 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 (Sandercock et al 2003). 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

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, Lensing & Hirsh 1994, Agu, Hamilton & Baker 1999, Roderick et al 2005). 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 odds of DVT after surgery. A more recent systematic review showed a 62% (95% CI 52 - 70%) reduction in the odds of DVT in 2582 patients randomised in 18 trials (Roderick et al 2005). The latter review also demonstrated a 53% (95% CI 3 – 83%) reduction in PE amongst 1466 patients entered into 12 trials. Only two of the trials included randomised high-risk medical (rather than surgical) patients (Kierkegaard & Norgren 1993, Muir et al 2000). Too few DVTs, occurred to provide any reliable estimate of their effectiveness in this context.

Prior to the CLOTS trials 1 and 2 there was 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 Compression 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 Compression 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.

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 & 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.

In response to the uncertainty about the effectiveness of GCS in stroke patients the CLOTS Trials 1 & 2 were established to address the four research questions. The questions and their answers are:

1. *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?*

   No - In CLOTS trial 1 the primary outcome (proximal DVT)) occurred in 126 (10.0%) patients allocated to thigh-length GCS and in 133 (10.5%) allocated to avoid GCS, resulting in a non-significant absolute reduction in risk of 0.5% (95% CI –1.9% to 2.9%). Skin breaks, ulcers, blisters, and skin necrosis were significantly more common in patients allocated to GCS than in those allocated to avoid their use (64 [5%] *vs.* 16 [1%]; odds ratio 4.18, 95% CI 2.40–7.27). (CLOTS Trials Collaboration 2009) These data do not lend support to the use of thigh-length GCS in patients admitted to hospital with acute stroke.

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

   Yes - In the CLOTS trial 2 the primary outcome occurred in 98 (6.3%) patients allocated to thigh-length GCS and in 138 (8.8%) allocated to below-knee GCS, a significant reduction in absolute risk of 2.5% (95% confidence interval 0.7% to 4.4%; p=0.008). This trial has provided robust evidence that thigh-length GCS are more effective than below-knee GCS (unpublished data). Whilst not influencing stroke care, where CLOTS trial 1 showed that thigh-length GCS are of very limited benefit, these results may impact on the choice of length of GCS in those undergoing surgery .

3. *What is the frequency of Compression Doppler ultrasound proven DVT in immobile stroke patients treated routinely with antiplatelet agents?*

   About 10% within 30 days - The overall rate of the primary outcome in Trial 1 was 10.3% compared with 7.6% in Trial 2. The difference might partly to be explained by the slightly greater use of anticoagulation in Trial 2 than Trial 1 (12.8% vs. 7.3% at baseline). Also in CLOTS trial 2, fewer patients had a second screening Doppler ultrasound. Prior to randomisation, clinicians elected to do both the 7-10 day and the 25-30 day CDU screens in 73% in Trial 1 and only 53% in Trial 2. If one compares the rate of the primary outcome just in those patients who had both screening CDUs then the rates of proximal DVT are less dissimilar (11.6% in Trial 1 and 9.6% in Trial 2). (unpublished data).

4. *What clinical factors might predict a greater risk of post stroke DVT?*

   Preliminary analyses of the combined datasets show that current smoking, diabetes and mild deficits (either ability to lift both arm or both legs) are associated with a lower risk of DVT. Also, prior DVT is associated with a greater risk. However, when these variables are included in a statistical model they

discriminate poorly between those at high and low risk of DVT (unpublished data). In addition, use of antithrombotic medication at baseline was not an independent predictor of a low risk of DVT.

A possible role for Intermittent Pneumatic Compression (IPC)

The intervention

This comprises a pair of inflatable sleeves which are wrapped around the legs and are secured by Velcro. They are attached via flexible tubing to a small bedside electric pump. The sleeves may be short (or below knee), wrapping around just the lower leg, or long (thigh length) to wrap around the thigh as well. They are inflated one side at a time to compress the legs at intervals. Some types inflate sequentially, first around the lower leg and then the upper, to “milk” the blood from the leg and increase venous flow. The frequency of inflation can be fixed, or in more sophisticated systems, varies depending upon the rate of venous refill. The sleeves may be applied over graduated compression stockings.

Rationale

IPC is thought to reduce the risk of venous thrombosis by:

- Increasing the flow of venous blood through the deep veins of the leg to reduce the likelihood of thrombosis (Lurie et al 2003).
- Stimulating release of intrinsic fibrinolytic substances (Knight & Dawson 1976, Comerata et al 1997, Kohro et al 2005, Killewich et al 2002).

The existing evidence for effectiveness

IPC has mainly been used in surgical patients during and immediately after operations. A systematic review, funded by the HTA identified 22 randomised trials of IPC, which included a total of 2779 patients. Use of IPC was associated with a 64% reduction in the odds of DVT ($p<0.00001$) (Roderick et al 2005) (Figure 1). This review concluded that a priority for future research was trials of "prevention of VTE with mechanical methods among high-risk medical patients (such as those with stroke)".

Figure 1. Figure taken from the HTA systematic review. (Roderick et al 2005)

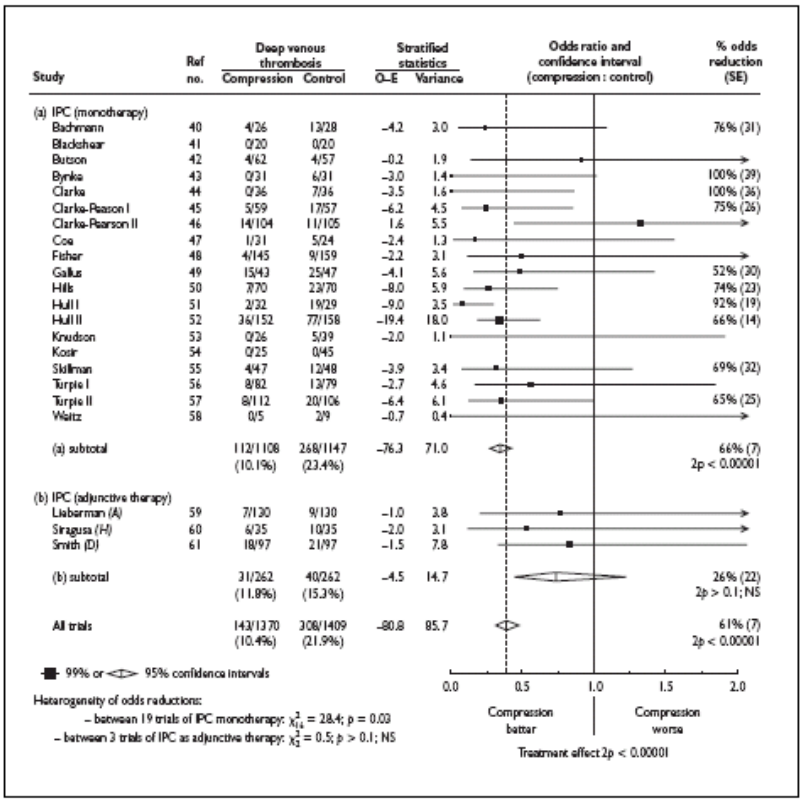
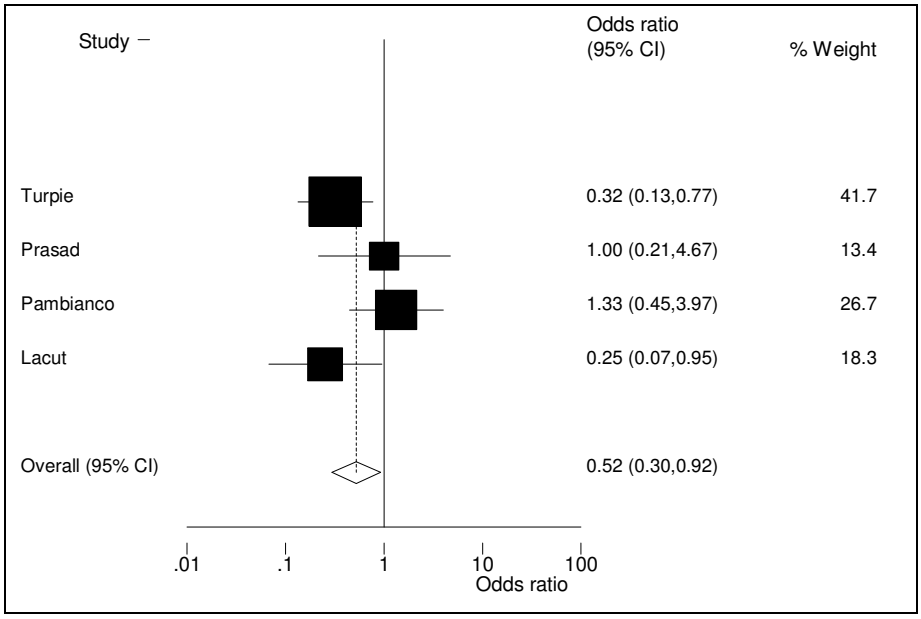


FIGURE 5 Effects of intermittent pneumatic compression (IPC) on deep venous thrombosis. Abbreviations: A, aspirin; D, dextran; H, unfractionated heparin; IPC, intermittent pneumatic compression.

A Cochrane review (Mazzone et al 2004) of the effectiveness of physical means of reducing the risk of venous thromboembolism after stroke identified only one small trial of IPC. This trial (Prasad, Banerjee & Howard 1982) included only 26 patients within 72 hours of onset of an acute stroke. Patients were randomised to receive below knee IPC or not for 10 days. 125-I-Fibrinogen was used for DVT diagnosis. Six (46%) patients developed DVT in each group, an odds reduction of 0% (95% CI -467% to 79%). We have recently updated this review and identified three additional trials of some relevance: Turpie et al (Turpie et al 1979) randomised 199 neurosurgical patients to calf IPC for up to 14 days or not. Seventy patients were non-operated and 40 had strokes. Unfortunately, they did not report the outcomes separately for these subgroups. Eight of 103 (7.8%) in the IPC group and 20 of 96 (20.8%) in the control group developed a DVT confirmed with a combination of methods (odds reduction 68%, 95% CI 23% to 87%). Pambianco et al (Pambianco, Orchard & Landau 1995) randomised patients several weeks after the stroke on admission to a rehabilitation unit. Eight of 117 (6.8%) allocated below knee IPC for eight hours overnight each day compared with six of 115 (5.2%) allocated control developed DVT confirmed by compression doppler ultrasound (CUS). Lacut et al (Lacut et al 2005) randomised 151 patients with an intracerebral haemorrhage (ICH) to elastic stockings (GCS) alone or combined with thigh length IPC. 133 (88%) patients were evaluated at Day 10 by CUS. Outcome assessment was blinded. Fourteen patients died before having a CUS but no death was definitely related to PE. Fourteen asymptomatic DVT were detected by CUS: three (4.7%) in the GCS + IPC group (all distal) and 11 (15.9%) in the GCS group (three proximal and eight distal) (odds reduction 75%, 95% CI 5% to 93%). In a meta-analysis of these four trials, IPC was associated with an odds reduction of 48% (8% to 70%) but there was moderate heterogeneity (I squared = 48.9% p=0.12), which may be because of the variation in types of patients and the timing of their enrolment (Figure 2).

Figure 2 . A forest plot showing the results of an updated systematic review of the effect of IPC in stroke.



A non-randomised study (Kamran, Downey & Ruff 1998) monitored the rate of DVT among non-haemorrhagic stroke patients admitted to their neurology service from October 1988 through June 1996. For some of this period patients (249 in total) received just 5,000 U subcutaneous heparin twice daily and "antiembolic hose". Another 432 non-ambulatory stroke patients had Sequential Compression Devices (SCD) applied to both legs in addition to subcutaneous heparin and antiembolic hose. They had IPC applied for at least 20 hours per day when lying or sitting, until they were independently mobile. Twenty-three of 249 patients (9.2%) treated with heparin alone developed DVT and six patients (2.4%) developed PE. Only one DVT (0.23%) and no PEs occurred among the 432 patients treated with SCD as well as heparin. Clearly this non-randomised trial is very prone to bias but it does suggest that the treatment is practical and acceptable to stroke patients.

Thus, the available evidence confirms that after stroke, even applying current prophylactic strategies, the risk of VTE is substantial. The available data suggest that IPC is a promising, practical but unproven and rarely used additional intervention. There are no other ongoing trials of IPC in stroke.

Potential problems of IPC in stroke units

Although the literature suggests that IPC has been used in stroke units and is a practical treatment, it is not used widely. Very few stroke units in the UK have any experience of IPC. Its introduction would require staff training.

In theory IPC might reduce patients' mobility and could lead to accidents if patients, especially those with cognitive problems, tried to walk with IPC attached. Also, the controller makes a noise and may disturb patients' sleep which might make the IPC unacceptable to some and impact adversely on their recovery. Some patients are incontinent which could lead to soiling of the sleeves which would then need to be replaced to maintain hygiene and avoid skin problems.

There is a concern that if one applied IPC to patients who may already have a DVT it may displace the thrombus and increase the risk of PE. However, this potential risk has not been documented and in practice few patients have investigations to exclude DVT prior to their application.

Detecting Deep Venous Thrombosis

Compression 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 adherence in a trial are likely to be more easily achieved than with alternatives. Indeed it was used in the CLOTS trials 1 & 2 and has been shown to be both sensitive, practical and acceptable to patients.

Research Questions in CLOTS 3

The primary research question is:

- Does early and routine application of IPC in addition to routine care reduce the risk of above knee DVT in the weeks following an acute stroke?

A secondary question is:

- Is IPC a practical and acceptable treatment for DVT prevention on stroke units?

Trial Design - overview

CLOTS 3 is a multicentre randomised controlled trial with blinded assessment of primary outcomes based on the methodology used in the original CLOTS trials. Indeed, it aims to exploit the existing CLOTS collaboration and trial systems to answer these new research questions efficiently.

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

Routine care plus Intermittent Pneumatic Compression

Or

Routine care and avoid the use of Intermittent Pneumatic Compression

Inclusion Criteria

- Any patient admitted to hospital within 3 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

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). Stroke should be the most likely clinical diagnosis but a visible infarction does not have to be seen on a brain scan.

Exclusion Criteria

- Patients with stroke due to subarachnoid haemorrhage. These are excluded because they are generally treated in neurology/neurosurgical centres, rather than stroke units, and their care often includes coiling or clipping of aneurysms under general anaesthetic. One could therefore argue that the existing evidence supporting the use of IPC in surgical patients is adequate to support its routine use in this group of patients.

- Patients who, in the opinion of the responsible clinician / nurse, are unlikely to benefit from Intermittent Pneumatic Compression – for instance those judged to have a very low risk of DVT. For instance, this would include patients who are expected to mobilise within the next day.

- Patients with contraindications for the use of IPC. These include:

    - patients with local leg conditions in which the IPC sleeves would interfere such as dermatitis, vein ligation (immediate postoperative), gangrene, venous stasis, or recent skin graft.

    - patients with severe arteriosclerosis or other ischaemic vascular disease as indicated by absence of pedal pulses or history of definite intermittent claudication.

    - patients who have massive leg oedema or pulmonary oedema from congestive heart failure.

- Patients who already have swelling or other signs of an existing DVT. Such patients may be recruited once a DVT has been excluded by normal D Dimers or Compression Doppler ultrasound.

- Patients under 16 year of age

Inclusion in another research study, including another randomised controlled trial, does not automatically exclude a patient from participating in CLOTS 3. As long as inclusion in the other study would not confound the results of CLOTS 3, co-enrolment is permissible. Also, local researchers must avoid overburdening patients. Patients should not be co-enrolled in another research study which aims to test an intervention which aims to reduce the risk of venous thromboembolism.

Consent

The patient, or their legal representative, should be approached by a member of the clinical team looking after that patient to ascertain their interest in participating in the CLOTS 3 trial or to obtain their permission to pass their details onto any research staff involved. Research nurses may approach patients directly if they are part of the clinical team and have a role in patient care e.g. a clinical responsibility for assessing patients' risk of venous thromboembolism to guide prophylaxis. This is important to maintain patient confidentiality. Laws governing consent procedures, and in particular those governing incapacitated adults and their involvement in research, must be followed. Relevant laws in the UK are Adults with Incapacity Act (2000) for Scotland and the Mental Capacity Act (2007) in England and Wales.

In all countries written informed consent should be sought where possible. If this is not possible the randomising clinician or nurse can gain witnessed verbal consent. Patient and consultee information brochures are available (Appendices 1 & 4). Enough time should be given to consider the trial fully and ask any questions they may have about the implications of the trial.

In England and Wales if potential patients are unable to provide written informed consent because of reduced conscious level, cognitive or communication problems a personal consultee can be identified and they can agree to participation on the patient's behalf. If a personal consultee is not available a nominated consultee can be approached. In either case, a Consultee Response Form needs to be completed (Appendix 5).

In Scotland if potential patients are unable to provide written informed consent or witnessed verbal consent the patients relative can agree to their participation. In this case a consent form needs to be completed (Appendix 2).

- If a patient with mental incapacity has been enrolled but then regains mental capacity the team should ensure that the patient is informed about the trial and should confirm that the patient is willing to continue to participate. Where practical the patient should be given the appropriate patient information brochure (Appendix 6) and sign a consent form (Appendix 7). If such a patient is unwilling to continue with follow up then only data collected up to that point will be stored and analysed. Patients allocated IPC who do not wish to continue with the treatment should be followed up as per protocol unless the patient (or consultee) explicitly withdraws consent to follow up.

Each collaborating centre will need to provide evidence of their local ethics committee approval.

Randomisation Procedure

The randomising clinician or nurse should try to identify potentially eligible patients as soon after their admission to hospital as possible. Prophylaxis for DVT will have greater effect if started early – ideally on the day of admission. The randomising clinician collects the baseline data necessary to complete a randomisation form (Appendix 8). He/she then either rings a telephone randomisation service, or enters data online, giving the baseline data (which are then stored securely) and receives the treatment allocation at the end of the session. 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 2-7)
- Stroke severity (using a validated prognostic model (Counsell et al 2002) 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

The randomisation form should be filed in the patients medical notes, along with one copy of the signed consent form and patient brochure. The patient should receive a patient brochure along with a signed copy of the consent form. Copies should also be kept in the site file. If the patient is agreeable their GP should be sent a letter to inform the GP of their enrollment in the CLOTS 3 trial (Appendix 11).

The Allocated Treatments

Routine Care

If allocated to ***Routine care and avoid the use of Intermittent Pneumatic Compression,*** Intermittent Pneumatic Compression should be avoided unless a clear indication for its use becomes obvious (e.g. patient requires surgery).

Routine care will usually include hydration and use of aspirin in patients with ischaemic stroke. However, exactly what comprises routine care will be monitored and may vary during the trial and will be guided by accumulating evidence from large RCTs and systematic reviews. For instance, the use of GCS is likely to become less frequent following the publication of the results of CLOTS trial 1 and the incorporation of this evidence into guidelines. All patients should receive aspirin as soon as a haemorrhagic stroke has been excluded by brain imaging 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.

Routine care plus Intermittent Pneumatic Compression

If allocated to ***Routine care plus Intermittent Pneumatic Compression*** this should be written up on the patients medication prescription chart to remind the nursing staff to apply the IPC and check the legs at least three times each day. This also facilitates monitoring of the treatment and completion of the discharge form (see Appendix 10). Where thigh-length GCS are part of routine care these should be applied and worn under the IPC sleeves on both legs. Thigh length IPC sleeves should be applied to both legs as soon as possible after the randomisation phone call and should be worn both day and night, whilst the patient is in

the bed or chair for 30 days from randomisation OR until a second screening Compression Doppler ultrasound has been performed (if after 30 days), OR it may be removed earlier if 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).

- patient is discharged from the participating hospital. If the patient is transferred to a rehabilitation unit where it is practical to continue the IPC and monitor its use appropriately then IPC should be continued until independently mobile or the patient declines to continue or an adverse effect of IPC occurs. If IPC cannot be continued after transfer to a rehabilitation unit a Discharge Form should be completed at the time of transfer to the rehabilitation unit.

- patient declines to continue to have IPC applied.

- healthcare staff identify any adverse effect of the IPC (such as pressure ulcers, falls due to the IPC) which they judge make continued application of the IPC unwise.

If the IPC is removed for any other reason e.g. checking the legs, bathing, screening Compression Doppler Ultrasound, then the IPC should be replaced as soon as possible. If the sleeves become soiled they should be replaced with new sleeves as soon as possible.

Follow up

Patients should have a Compression Doppler ultrasound examination of the veins in both legs between Day 7 and Day 10 and usually 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. The results of Compression Doppler ultrasounds performed later than stipulated will be included in the analyses as long as they occur prior to the final follow up at about six months.

Where the randomising person judges that it is likely to be impractical to perform a Compression Doppler ultrasound between Days 25 and 30, they may, prior to randomisation, stipulate that a Compression 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 Compression Doppler ultrasound facilities and is remote from the randomising centre.

If a definite above knee DVT is detected on the first screening Compression Doppler i.e. the patient has our primary outcome then the second screening Compression Doppler is no longer required.

IPC should be removed completely before the patient leaves the ward to have the Compression Doppler ultrasound to ensure optimal blinding of the primary outcome measure. The Compression 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. In those patients allocated IPC it should immediately be re-applied on return to the ward after the screening Compression Doppler ultrasound. Patients enrolled in CLOTS 3 will benefit from non invasive screening for DVT which is likely to lead to earlier and probably more effective treatment and prevention of PE.

The completed radiology report form (Appendix 9) should immediately be either faxed to the Co-ordinating centre or completed on line. A copy of the radiology report should be kept in medical notes and site file.

Discharge Form

A Discharge Form (Appendix 9) should be completed for all randomised patients on discharge from the randomising centre or in the event of earlier death. If a patient is transferred to a rehabilitation unit on a different site to the randomising centre, and it is impractical to continue the allocated treatment or its monitoring whilst the patient is in that unit a discharge form should be completed on transfer to that unit.

The data collected includes:

- Use of heparin, warfarin, and antiplatelet drugs during admission to monitor the components of routine care and to ensure equal use in the two treatment arms. However, an imbalance of heparin (or similar) and warfarin may occur if IPC is effective since more patients in the control arm will receive these drugs to treat the excess of VTE. The indication for their use will therefore be recorded.
- Use of full length or below knee graduated compression stockings to monitor the components of routine care and to ensure equal use in the two treatment arms.
- Timing of initiation of IPC and adherence to treatment allocation and use of IPC.
- Any clinical DVT or PE requiring treatment (diagnosis will be reviewed blind to the treatment allocation).
- Any complications of treatments in particular skin problems with legs, falls resulting in injuries occurring within the first 30 days after enrollment.

This form should be returned to the CLOTS Co-ordinating Centre in Edinburgh by post, FAX or completed online. A copy should be retained in the site file.

General Practitioner (GP) Questionnaire

A questionnaire (Appendix 13) will be sent by the national coordinating centre 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 from the randomising centre.

Six Month Follow up Form

For those patients who have been discharged, outcome is assessed via a postal or telephone questionnaire (Appendix 14). 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)
- whether the patient has suffered a DVT, or PE since discharge from the randomising centre, any late complication of DVT.

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 et al 1989), Simple Questions (Dennis, Wellwood & Warlow 1997) and Health Related Quality of Life (HRQoL) measured using EUROQol (EUROQol Group 1990)
- Their 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 (Appendix 9) should be completed for all Compression Doppler ultrasounds and venograms. This form, should be completed on line or sent by FAX to the CLOTS Co-ordinating Centre in Edinburgh. If there is evidence of DVT, the best image, still or video should also be sent to the coordinating centre for review. Patients names and other identifying information should be removed from these images before being sent to the coordinating centre. Images should be identified using the patient's CLOTS trial ID number. A radiologist will review the images, blind to treatment allocation, to confirm that the imaging has demonstrated a DVT.

If a popliteal or femoral vein DVT is detected during the routine Compression Doppler ultrasound examinations, the responsible clinician will need to decide whether to confirm the presence and extent of any thrombus using venography or MRI direct thrombus imaging. Although they may only perform confirmatory venography where the Compression Doppler ultrasound is equivocal in their normal practice, compared with treating patients with a swollen leg the positive predictive value of a screening Compression Doppler ultrasound study performed in an asymptomatic patient is likely to be lower. Put another way, the Compression Doppler result is more likely to produce a false positive result in an asymptomatic patient than in a patient with a clinical DVT. 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 Compression Doppler ultrasound and/or venography), the responsible clinician may anticoagulate the patient according to local protocols or alternatively arrange a follow up Compression Doppler ultrasound approximately seven days later to identify any propagation into the popliteal vein. If definite popliteal or femoral vein thrombus is detected the patient should be anticoagulated unless contraindicated.

If a patient develops symptoms or signs suggestive of DVT during their admission they should be investigated by either Compression Doppler ultrasound and / or venography or MRI direct thrombus imaging and treated according to local protocols if the diagnosis is confirmed. Use of heparin, low molecular weight heparin and Warfarin to treat DVT and /or PE during admission should be recorded on the discharge form. Continued use of IPC in such patients will be at the discretion of the responsible clinician.

Primary Outcome

Presence of definite or probable symptomatic or asymptomatic DVT in the popliteal or femoral veins detected on a screening Compression Doppler ultrasound scan or any symptomatic DVT in the popliteal or femoral veins confirmed on Compression Doppler ultrasound or contrast venography or MRI direct thrombus imaging within 30 days of randomisation.

This surrogate outcome can be justified because of the clinical significance attributed to even asymptomatic DVT in popliteal or femoral veins which most clinicians treat with anticoagulant therapy. To reliably confirm or refute an effect of IPC on survival and functional status a randomised trial would require a sample size of several tens of thousands of patients; this is not currently practicable. Also, IPC is very unlikely to have adverse effects beyond those which will be directly measured in the trial i.e. damage to skin on legs, or falls. IPC should not restrict mobilisation because it can be worn during bed to chair transfers and will be taken off when the patient is able to mobilise independently. Theoretically, IPC might influence blood pressure in the acute phase, which could in turn influence stroke outcome, by increasing venous return – however empirical studies have not demonstrated a significant effect of IPC on blood pressure. Anti shock and anti gravity suits raise blood pressure by compressing both legs and abdomen simultaneously (Jennings et al 1986).

Secondary Outcomes

In hospital:

- Death within 30 days
- Presence of definite or probable DVT in the popliteal or femoral veins detected on a screening Compression Doppler ultrasound scan which had not been suspected clinically before the scan (see below)
- Definite (i.e. excluding probable DVTs) symptomatic or asymptomatic DVT in the popliteal or femoral veins detected on either a Compression Doppler ultrasound scan or contrast venography or MRI direct thrombus imaging within 30 days of randomisation;,
- Any definite or probable symptomatic or asymptomatic DVT (i.e. including DVTs which only involve the calf veins),
- Confirmed fatal or non-fatal PE,
- Adherence to allocated treatment
- Adverse events related to IPC within 30 days of randomisation.

At six months:

- death from any cause
- any confirmed symptomatic or asymptomatic DVT or PE occurring between randomisation and final follow up
- any symptomatic DVT or PE occurring between randomisation and final follow up
- place of residence,
- post DVT syndrome,
- disability (modified Rankin),
- health related quality of life (EuroQol). The later effects of DVT/PE (e.g. breathlessness, leg pain or swelling, poor stroke recovery) or the adverse events related to IPC (falls with injury, fractures, 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 affecting the popliteal or femoral veins, which occurred within 30 days of randomisation, would be counted in the primary endpoint. A symptomatic DVT is defined for the purposes of this trial as a DVT confirmed on investigation with associated clinical features including leg swelling, pain, obvious erythema or a proven pulmonary embolus. Sometimes these features may not be recognised prior to a positive screening Compression Doppler ultrasound but if present the DVT should be reported as symptomatic. We will distinguish those DVTs which were identified primarily on a screening Compression Doppler from those which were diagnosed clinically and confirmed on subsequent investigation since the detection of the latter symptomatic DVTs is not blinded and hence prone to ascertainment bias. A secondary analysis excluding these symptomatic DVTs identified before any Compression Doppler will also be performed. Inevitably, some patients will not survive to have routine Compression 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 IPC is very effective in reducing the risk of fatal PE. Therefore, we will firstly present the numbers Alive with no DVT, Alive with DVT, Dead without prior DVT, and Missing. We will carry out our analyses in two ways: comparing DVT with no DVT with dead and missing patients excluded; and comparing DVT + dead with no DVT + missing.

Adverse Events

Stroke is a serious medical condition. About 20% of hospitalized patients would be expected to die. Serious medical complications are common. CLOTS 3 is evaluating IPC, a non-drug intervention which has a CE mark and has been approved for the purpose of reducing the risks of VTE. The risks associated with IPC and participation in the trial are very small and generally predictable e.g. skins problems on legs, falls resulting in injury. It should be relatively straightforward to attribute any serious adverse event to the IPC. In this trial we therefore do not require routine reporting of any adverse events since this is unlikely to be informative and places an unnecessary burden on the local researchers which would compromise the practicality of the trial. We do require prompt reporting of primary and secondary outcomes on the Radiology Report Form (within 2 working days), Discharge Form (within 10 working days), GP Questionnaire and Hospital follow up forms.

The following should be reported on the Radiology Report Form, Discharge Form or GP Questionnaire (if patient has been discharged) or Hospital 6 month Follow up Form (if the patient is still in hospital):

- Any confirmed DVT
- Any confirmed pulmonary embolus
- Any fall associated with significant injury occurring within 30 days of enrollment (when IPC might still be applied) – an injury requiring investigation, or specific treatment or which prolongs hospitalisation or leads to death, temporary or permanent disability.
- Any damage to the skin of the legs including necrosis, ulcers occurring within 30 days of enrollment
- Reasons for prematurely stopping the IPC

The following are expected complications of stroke and its co-morbidities and do not need to be reported as Adverse Events:

- Deaths – these should be reported as outcome events on the discharge or 6 month follow up forms
- Infections other than those affecting the skin of the legs
- Further vascular events (including recurrent strokes, myocardial infarction, bowel ischaemia)
- Cardiac, renal or liver problems
- Epileptic seizures
- Spasticity or contractures
- Painful shoulder and other joint problems
- Mood disturbances

Any other adverse events which the investigator feels may be due to either the treatment or participation in the trial should be reported within 10 working days to the coordinating centre. A serious adverse event (i.e. one resulting in death, is life threatening, results in significant disability or incapacity or prolongation of hospitalisation) should be reported immediately on a Serious Adverse Events Form (Appendix 12) on line or by FAX. Serious Adverse Events attributed to the trial treatment or participation in the trial will be reported to the DMC, Trial sponsors and ethics committees.

Analyses

All analyses will be based on intention to treat. We will analyse patients in the groups they were randomised to, regardless of treatment received. We will strive to obtain full follow-up data on every patient to allow a full intention-to-treat analysis, but inevitably some patients will be lost to follow up. We will exclude these patients from the analyses that they have no data for, and do sensitivity analyses to see the effect of these exclusions on our conclusions. For binary outcomes (e.g. occurrence of a primary or secondary outcome OR not), outcomes will be presented as odds ratios and 95% confidence intervals, adjusted using logistic regression for the factors used in the minimisation algorithm. We will calculate absolute reductions in risk from these values. The modified Rankin will be analysed in two ways – dichotomized in MRS 0-2 vs 3-6 (by logistic regression) and as an ordinal scale (by ordinal regression). The utility based on the EuroQol will be compared by t-tests if the data are Normally distributed, and using an appropriate nonparametric test otherwise.

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 7 and Day 0 to 2 vs. 3-7). Since DVT may develop very soon after stroke onset and IPC may not influence propagation of thrombus which has already started it is plausible that IPC will be more effective if started earlier after stroke.

- Paralysis of leg (complete vs. incomplete)

Subgroup analyses will be performed by observing the change in log-likelihood when the interaction between the treatment and the subgroup is added into a logistic regression model.

A secondary, on treatment analysis will examine the extent to which non adherence to the trial intervention might explain the estimate of effect size.

Sample Size

We plan to enroll at least 2000 patients. This should give the Trial > 90% power (alpha 0.05) to identify an absolute reduction of risk of our primary outcome of 4% (about 10% to 6%). The frequency of our primary outcome is estimated from the CLOTS trials 1 and 2, which use the similar entry criteria and methods of follow up and has an attrition rate of 8% due to death and 6% missing Compression Dopplers in the first month. The estimated effect size (odds reduction = 43%) is based on the treatment effects in the systematic review of previous stroke trials (odds reduction = 48%) attenuated by the delays in applying the treatment due to trial recruitment and realistic estimates of adherence to the allocated treatment. If the event rate in both treatment groups combined is lower than expected the Trial Steering Committee may decide to increase the recruitment target. We aim to enrol at least 1500 patient on Days 0-2 after stroke onset. This will provide greater than 80% power to detect a reduction in proximal DVT from 10% to 6% in patients enrolled on Days 0-2. If the proportion enrolled after Day 2 exceeds 25% of the total then the Trial Steering Committee will consider raising the overall target beyond 2000 to ensure that at least 1500 are recruited on Days 0-2. This should help ensure that we do not miss a real treatment effect because of delays in recruitment. If the trial shows that IPC is effective in reducing the risk of DVT after stroke it is likely that IPC treatment will be started earlier than in the trial.

Proposed Timetable

Based on recruitment rates in the CLOTS trials we would expect to enroll 2000 patients in CLOTS 3 in less than 4 years – i.e. by May 31st 2013. If the recruitment rate approaches the maximum rate in CLOTS Trials 1 & 2 then recruitment could be completed in less than 2 years. The last patient enrolled would be followed up by the end of February 2014. The database would then be locked and analyses carried out. The trial would finish once the paper reporting the main results has been submitted for publication, hopefully before May 31st 2014. The Trial Steering Committee may modify this timetable as required in response to changing conditions and depending on the agreement of funding bodies and ethics committees.

Trial Organisation and Governance

The trial will be run under the auspices of “Edinburgh Clinical Trials Unit”. CLOTS 3 Trial Co-ordinating Centre Personnel include:

Chief Investigator:	Prof Martin Dennis
Co-investigator:	Prof Peter Sandercock
Co-investigator:	Dr John Reid
Senior Trial Manager:	Gina Cranswick
Assistant Trial Manager:	Janie Hunter
Recruitment Co-ordinator:	Carol Williams
Trial Statisticians:	Cat Graham/ Steff Lewis
Trial Programmer:	Vera Soosay
Trial Support Team:	Adam Young, Ann Deary and Anne Fraser

Trial Steering Committee: Prof Martin Dennis (Chief Investigator), Dr John Reid (Radiologist - Compression Doppler ultrasound & quality control), Professor Peter Sandercock (Neurologist and Trialist), and Pat Taylor (Stroke unit nurse), Ms Gill Bowler (Patient representative). The committee will also include a representatives of funding bodies including any organisation which has provided IPC equipment and an independent chair, statistician and members approved by the main funding organisation.

Independent DMC: Dr John Bamford (Stroke neurologist in Leeds), Jim Slattery (Statistician) and Colin Baigent (Trialist and author of HTA systematic review of IPC from CTSU in Oxford). They will define stopping rules for the study and monitor the data on at least an annual basis.

During the period of recruitment into the study, interim analyses of the primary outcome, 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 3 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 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 adverse effects, or about particular categories of patient requiring special consideration, or about any other matters that may be relevant.

Principal Investigator's (PI)' Responsibilities

Co-ordination within each participating hospital will be through a local collaborator or PI who will:

- Discuss the trial with medical and nursing staff who see stroke patients and ensure that they remain aware of the state of the current knowledge, the most recent trial protocol and its procedures.
- Only delegate roles to those with appropriate knowledge and skills.
- Ensure that patients admitted with stroke are considered promptly for the trial.
- Ensure that the randomisation forms, radiology report forms and discharge forms are completed and either entered on line or sent to the coordinating centre promptly and that copies are kept in a site file and patient notes.
- Ensure the trial is conducted in accordance with GCP and fulfils all national and local regulatory requirements.
- Ensure that the patients' confidentiality is not breached.
- Allow access to source data for audit and verification.

Co-ordinating Centre Responsibilities

- Provide study materials, a 24-hour randomisation service and Helpline.
- Give collaborators regular information about the progress of the study.
- Help ensure complete data collection at discharge.
- Respond to any questions (e.g. from collaborators) about the trial.
- Assure data security and quality in accordance with GCP and local guidelines.
- Ensure trial is conducted in accordance with GCP.

Monitoring

Intermittent Pneumatic Compression devices carry a CE mark and are licensed for use as a prophylaxis for venous thromboembolism. In surgical practice, their use appears to be associated with a low risk of adverse effects. The trial procedures are relatively simple and place only a small burden on the patients. No significant financial inducements are being offered to collaborating centres to encourage their active participation or to reward high recruitment rates. Central follow up of all patients at about six months after enrolment ensures that any fictitious patients enrolled would be detected. For all of these reasons we judge that the risks of patients being harmed by the trial interventions or participation are very small. Also, that the risk of major research misconduct are also very small. The intensity of monitoring which we will undertake is based on this risk assessment. The coordinating centre will monitor the completeness, internal consistency

and validity of the data. From the data collected it will monitor adherence to the trial protocol. It will not routinely carry out on-site monitoring or source data verification however, if concerns arise as a result of the routine central statistical monitoring, a more detailed investigation including on-site verification of data will be carried out.

The trial is jointly sponsored by NHS Lothian and the University of Edinburgh.

Publication of the Trial Results

All full publications in peer reviewed journals will be published in the name of the collaborative group which will include all those who have made a significant contribution to CLOTS 3. The trial steering committee, national coordinators and local principal investigators will decide who has made a significant contribution.

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.

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 3 Collaboration.

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CLOTS – 3 Patient Information Brochure (UK)

Introduction to the study

You have had a stroke, an interruption to the blood supply to part of your brain. A stroke may lead to leg weakness or reduced mobility which can cause blood clots in the veins of the legs. These occur in about a 10% of patients with stroke. These clots can be dangerous if they travel up the vein to the heart or lungs. You may receive aspirin or other blood thinning drugs, or stockings which reduce the risk of clots forming but we are trying to find out if a new treatment, Intermittent Pneumatic Compression (IPC) helps to reduce the risk further.

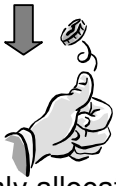
The CLOTS 3 study at a glance

Receive information about the CLOTS 3 study

↓

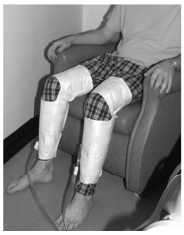
If willing to join sign consent form

↓



Randomly allocated to either

Normal care +



Intermittent Pneumatic Compression

↓

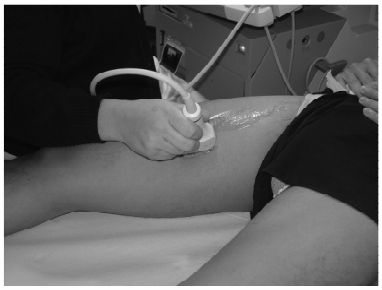
at 10 days 1st Ultrasound

↓

at 30 days 2nd Ultrasound

↓

At 6 months Postal questionnaire or Telephone follow up



Ultrasound of leg veins to look for clots

Normal care

including:
Aspirin
Hydration
& possibly stockings

↓

at 10 days 1st Ultrasound

↓

at 30 days 2nd Ultrasound

↓

At 6 months Postal questionnaire or Telephone follow up

We would like to invite you to join the CLOTS 3 study, which is testing whether intermittent pneumatic compression (IPC) reduces the risk of clots. In this treatment, inflatable sleeves (see picture) are wrapped around the legs and are inflated intermittently. This gently squeezes the legs and increases the blood flow in the veins. The sleeves are worn day and night and can be worn in bed, sitting or standing. This treatment

continues until you are either able to walk or you are discharged home. If you agree to join this study, you will be randomly allocated, by computer, to either wear thigh length sleeves or not. Whichever treatment you receive you will be carefully monitored throughout your hospital stay. An ultrasound scan (see picture), which takes about 30 minutes and causes little discomfort, will be carried out twice, once after 7 days and again after 25 days to check for clots in the veins in your legs. If this scan shows a clot your doctor can treat you with blood thinning drugs. You will leave hospital when your doctor thinks that you are well enough to go home and your discharge will not be delayed by taking part in the study. About six months after entering the study you will be sent a postal questionnaire to complete or telephoned by a doctor to find out how well you have recovered from the stroke. We need to include about 2000 patients like you in this study to find out whether this new treatment works or not.

What are the risks and benefits of the treatment?

IPC reduces the risk of blood clots in the legs in patients having surgery. We do not know if it reduces the risk of clots after stroke. IPC can be uncomfortable, although most people quite like the feeling. The risks of wearing the sleeves are very small. Very occasionally, the sleeves cause skin irritation and skin ulcers have rarely been reported. If you find the sleeves uncomfortable, please let your doctor know so you can discuss whether to continue using them. An alternative may be available. In addition, if you try to walk whilst the sleeves are attached to the air pump you might trip, fall and injure yourself.

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 take 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 Service complaints mechanisms are available to you.

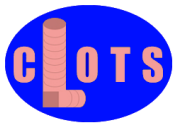
Who will be told about my illness?

We will inform your GP if you join the study unless you ask us not to. Any information we collect about you will be confidential. 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 individual patient will be identified. Some of the information collected may also be used for related research projects and possibly shared with other research groups, but none of your personal information (which would allow you to be identified) will be shared with another group.

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 IPC sleeves at any time, although we would like to continue monitoring your progress. You must be happy about any decision you make. Please ask the doctor or nurse about anything you are unsure about. Thank you for taking the time to read this brochure. You may keep a copy of this brochure along with the consent form. If you would like to know more, please contact _____ (or ask the nurse to contact).

This study is funded by The Chief Scientist Office, Scotland in the first instance.



CLOTS – 3 Consent Form (Scotland)

I confirm that I have received and understand the Patient Information Sheet for the CLOTS 3 study and have had the opportunity to ask questions.

I understand that my participation in the CLOTS 3 trial 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. ☐

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. ☐

I understand that data collected about me may be used for related research but that my personal details (i.e. identifiable data e.g. name, address, contact details) will not be shared with any other research group ☐

I agree to take part in the CLOTS 3 trial. ☐

Patients Name _____Signature* : _____Date: ____/____/____
day month year

Researchers Name _____ Signature* : _____Date: ____/____/____
day month year

Name of Witness_____ Signature* : _____Date: ____/____/____
to verbal consent (if applicable) day month year

Welfare Guardian / Nearest Relative Consent

Name: _____

Address:_____

I am the nearest relative of the patient ☐ (tick) if so state relationship:_____
OR
I am the Welfare Guardian for this patient ☐ (tick)

I confirm that, as far as I am aware, there is no closer relative in existence.

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

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

CLOTS – 3 Consent Form (England, Wales and Northern Ireland)

I confirm that I have received and understand the Patient Information Sheet for the CLOTS 3 study and have had the opportunity to ask questions.

I understand that my participation in the CLOTS 3 trial 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. ☐

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. ☐

I understand that data collected about me may be used for related research but that my personal details (i.e. identifiable data e.g. name, address, contact details) will not be shared with any other research group. ☐

I agree to take part in the CLOTS 3 trial. ☐

If during the course of the research I lose the capacity to consent for myself then:
(*Tick the box that applies*)

1. I should be withdrawn from the study and all data/tissue destroyed or anonymised (delete which does not apply) ☐

2. I should be withdrawn from the study but identifiable data/tissue obtained so far may be retained by the researcher ☐

3. I hereby express my wish to continue as a participant in the study and for this wish to be taken into account by my representative (Name of nominated consultee if appropriate: ……) ☐

Patients Name _____Signature: _____ Date: ___/____/____
day month year

Researchers Name _____ Signature : _____Date: __/____/____
day month year

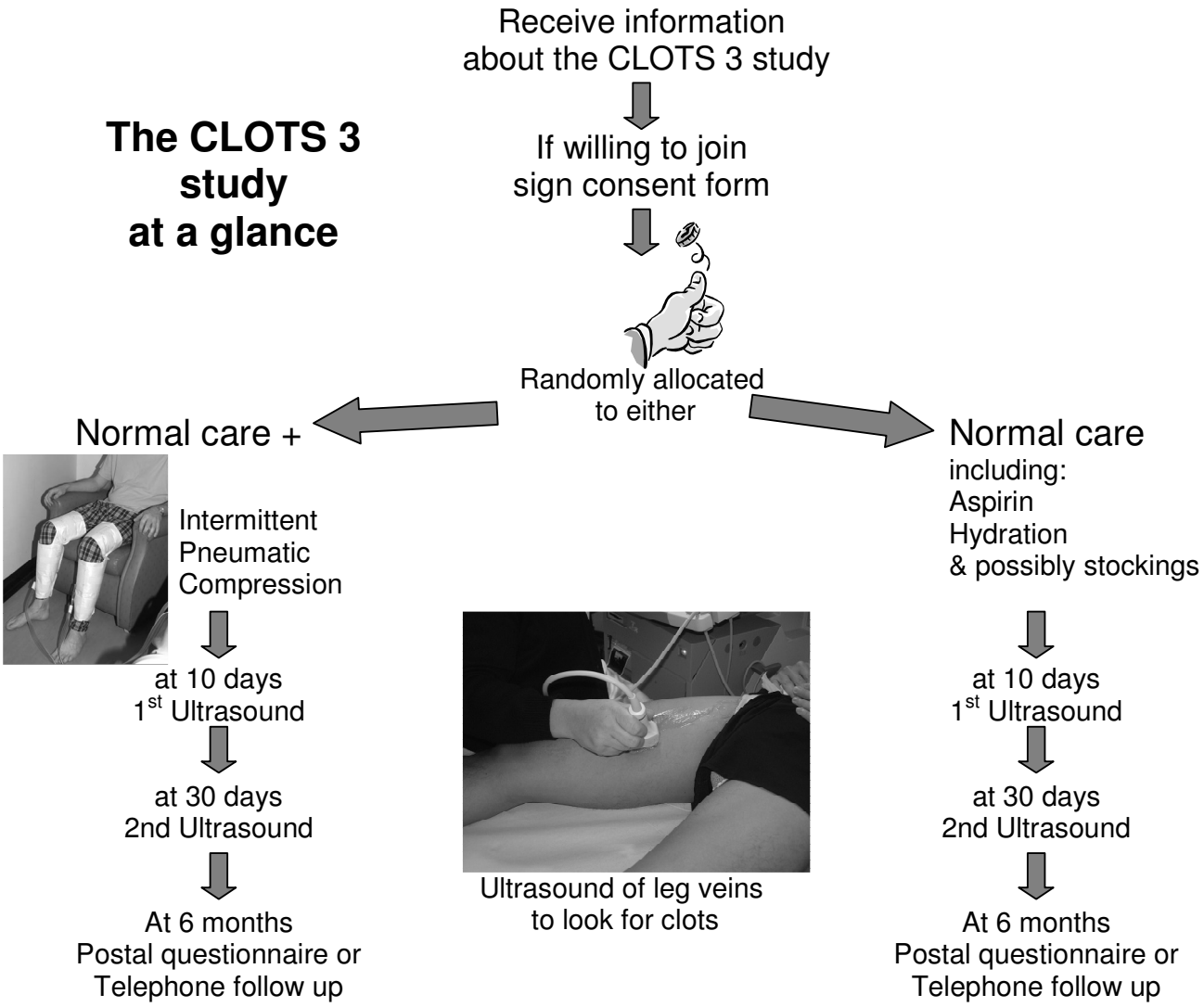
Name of Witness_____ Signature : _____Date:____/____/____
to verbal consent (if applicable) day month year

Please give a copy of this form once completed to the patient if requested.
Please file this form in the patient's notes and a copy in the site file.
Do NOT return it to the CLOTS Co-ordinating Centre.
(Note the Mental Capacity Act only applies to England and Wales)

CLOTS – 3 Consultee Information Brochure

Introduction to the study

…….. (*write in patients' name*) has had a stroke, an interruption to the blood supply to part of the brain. A stroke may lead to leg weakness or reduced mobility which can cause blood clots in the veins of the legs. These occur in about a 10% of patients with stroke. These clots can be dangerous if they travel up the veins to the heart or lungs. This person may receive aspirin or other blood thinning drugs, or stockings which reduce the risk of clots forming but we are trying to find out if new a treatment, Intermittent Pneumatic Compression (IPC) reduces the risk more.



We would like to invite you to consider whether this person would wish to participate in the CLOTS 3 study, which is testing whether intermittent pneumatic compression (IPC) reduces the risk of clots. In this treatment, inflatable sleeves (see picture) are wrapped around the legs and are inflated intermittently. This gently squeezes the legs and increases the blood flow in the veins. The sleeves are worn day and night and can be worn in bed, sitting or standing. This treatment continues until this person is either able to walk or

discharged home. If you decide that if they were capable of making a decision for themselves that they would agree to participate then they will be randomly allocated, by computer, to either wear thigh length sleeves or not. Whichever treatment they receive they will be carefully monitored throughout their hospital stay. An ultrasound scan (see picture), which takes about 30 minutes and causes little discomfort, will be carried out twice, once after 7 days and again after 25 days to check for clots in the veins of their legs. If this scan shows a clot the doctor might treat with blood thinning drugs. This person will leave hospital when their doctor thinks that they are well enough to go home and their discharge will not be delayed by taking part in the study. About six months after entering the study they will be sent a postal questionnaire to complete or telephoned by a doctor to find out how well they have recovered from the stroke. We need to include about 2000 patients in this study to find out whether this new treatment works or not.

What are the risks and benefits of the treatment?

IPC reduces the risk of blood clots in the legs in patients having surgery. We do not know if it reduces the risk of clots after stroke. IPC can be uncomfortable, although most people quite like the feeling. The risks of wearing the sleeves are very small. Very occasionally, the sleeves cause skin irritation and skin ulcers have rarely been reported. If this person finds the sleeves uncomfortable, please let the doctor know so you can discuss this as an alternative may be available. In addition, if this person tries to walk whilst the sleeves are attached to the air pump they might trip, fall and injure themselves.

If this person is harmed by taking part in this research project, there are no special compensation arrangements. If they are harmed due to someone's negligence, then they may take legal action but they may have to pay for it. Regardless of this, if you or this person wishes to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available.

Who will be told about <u>their</u> illness?

We will inform their GP if they are entered into the study unless you ask us not to. Any information we collect about this person will be confidential. Information about them will only be available to research staff and the medical staff caring for them. The results of this study will eventually be published in a medical journal, however, no individual patient will be identified. Some of the information collected may also be used for related research projects and possibly shared with other research groups, but no personal information (which would allow them to be identified) will be shared with another group.

What happens now?

We would like you to think very carefully about whether or not this person would want to join the study. It is entirely voluntary and if you decide that they would not wish to join it will not influence this persons care in any way. You may also request that this person stops wearing the IPC sleeves at any time, although we would like to continue monitoring their progress. You must be happy about any decision you make. Please ask the doctor or nurse about anything you are unsure about. Thank you for taking the time to read this brochure. You may keep a copy of this brochure along with the consent form. If you would like to know more, please contact _____ (or ask the nurse to contact).

This study is funded by The Chief Scientist Office, Scotland in the first instance

(Note the Mental Capacity Act only applies to England and Wales)

CLOTS 3 - Consultee Response Form

I (Consultee name) _____

of (Address): _____

Relationship to patient if personal consultee _____

or Status if nominated consultee _____

agree to the participation of (Patient name) _____ in the CLOTS - 3 Trial

I understand that participation in the CLOTS 3 trial is voluntary and that the above named patient, or I on their behalf, am free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. ☐

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

I understand that data collected about them may be used for related research but that their personal details (i.e. identifiable data e.g. name, address, contact details) will not be shared with any other research group ☐

I agree to the above named person taking part in the CLOTS 3 trial. ☐

Consultee's Name _____ Signature* : _____Date: ____/____/____
day month year

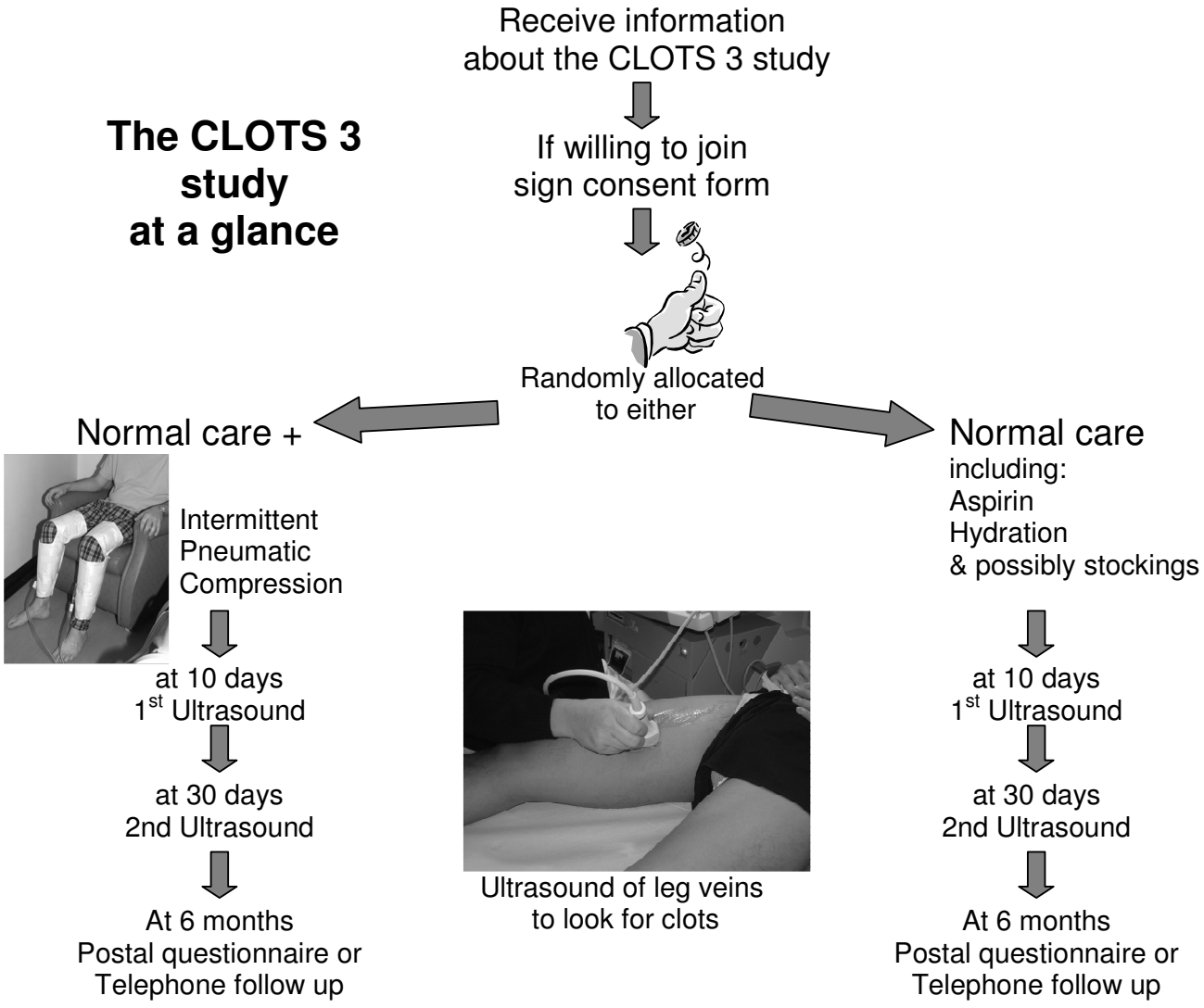
Researcher's Name _____ Signature* : _____Date: ____/____/____
day month year

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

CLOTS – 3 Patient Information Brochure – continuing in the trial (UK)

Introduction to the study

You have had a stroke, an interruption to the blood supply to part of your brain. A stroke may lead to leg weakness or reduced mobility which can cause blood clots in the veins of the legs. These occur in about a 10% of patients with stroke. These clots can be dangerous if they travel up the vein to the heart or lungs. You may receive aspirin or other blood thinning drugs, or stockings which reduce the risk of clots forming but we are trying to find out if a new treatment, Intermittent Pneumatic Compression (IPC) helps to reduce the risk further.



While you have been unwell your family agreed to you joining the CLOTS 3 study, which is testing whether intermittent pneumatic compression (IPC) reduces the risk of clots. You will have been treated in the normal way OR with inflatable sleeves (see picture) wrapped around your legs which are inflated intermittently

squeezing the legs and increasing the blood flow in the veins. If you agree to continue in this study, you will you will be carefully monitored throughout your hospital stay. An ultrasound scan (see picture), which takes about 30 minutes and causes little discomfort, will be carried out twice, once after 7 days and again after 25 days to check for clots in the veins in your legs. If this scan shows a clot your doctor can treat you with blood thinning drugs. You may already have had one or both of these scans. You will leave hospital when your doctor thinks that you are well enough to go home and your discharge will not be delayed by taking part in the study. About six months after entering the study you will be sent a postal questionnaire to complete or telephoned by a doctor to find out how well you have recovered from the stroke. We need to include about 2000 patients like you in this study to find out whether this new treatment works or not.

What are the risks and benefits of the treatment?

IPC reduces the risk of blood clots in the legs in patients having surgery. We do not know if it reduces the risk of clots after stroke. IPC can be uncomfortable, although most people quite like the feeling. The risks of wearing the sleeves are very small. Very occasionally, the sleeves cause skin irritation and skin ulcers have rarely been reported. If you find the sleeves uncomfortable, please let your doctor know so you can discuss whether to continue using them. An alternative may be available. In addition, if you try to walk whilst the sleeves are attached to the air pump you might trip, fall and injure yourself.

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 take 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 Service complaints mechanisms are available to you.

Who will be told about my illness?

We have informed your GP that you joined the study. Any information we collect about you will be confidential. 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 individual patient will be identified. Some of the information collected may also be used for related research projects and possibly shared with other research groups, but none of your personal information (which would allow you to be identified) will be shared with another group.

What happens now?

We would like you to think very carefully about whether or not to continue in the study. It is entirely voluntary and if you decide not to continue it will not influence your care in any way. You may also choose to stop wearing the IPC sleeves at any time, although we would like to continue monitoring your progress. You must be happy about any decision you make. Please ask the doctor or nurse about anything you are unsure about. Thank you for taking the time to read this brochure. You may keep a copy of this brochure along with the consent form. If you would like to know more, please contact _____ (or ask the nurse to contact).

This study is funded by The Chief Scientist Office, Scotland in the first instance.

(Note the Mental Capacity Act only applies to England and Wales)

CLOTS – 3 Consent Form – to continue in the trial (UK)

I confirm that I have received and understand the Patient Information Sheet for the CLOTS 3 study and have had the opportunity to ask questions.

I understand that my participation in the CLOTS 3 trial 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. ☐

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. ☐

I understand that data collected about me may be used for related research but that my personal details (i.e. identifiable data e.g. name, address, contact details) will not be shared with any other research group ☐

I agree to continue to take part in the CLOTS 3 trial. ☐

Patients Name _____Signature* : _____Date: ____/____/____
day month year

Researchers Name _____ Signature* : _____Date: ____/____/____
day month year

Name of Witness_____ Signature* : _____Date: ____/____/____
to verbal consent (if applicable) day month year

(Note the Mental Capacity Act only applies to England and Wales)
Please give a copy of this form once completed to the patient if requested. Please file this form in the patient's notes and a copy in the site file. Do NOT return it to the CLOTS Co-ordinating Centre.

CLOTS 3 - Randomisation Form

To randomise: WEB www.clotstrial.com OR PHONE ++ 44 (0)131 5372933
Please ensure you have supplies of appropriate sleeves too!

CENTRE DETAILS

Country: _____ or code ☐☐

Centre name: _____ or code ☐☐☐

Responsible consultant: _____ or code ☐☐☐☐

Randomising person: _____

Has consent 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 since admission?	☐	☐
17.	Is on heparin or LMWH now?	☐	☐
18.	Is on oral anticoagulants e.g. 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) **CLOTS Patient ID** _____

Apply intermittent compression sleeves ☐ **Avoid sleeves until discharge** ☐

- Sleeves, if allocated, should be worn whilst in bed or chair and until independently mobile or discharged home.
- Record the allocation on this form, in the medical notes and 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 ultrasounds now so they will be done on Day 7-10 and Day 25-30.

Thank you for randomising this patient.

CLOTS 3 - Radiology Report Form

Enter online at www.clotstrial.com or return by fax +44 (0) 131 3325150

Hospital Number: ☐☐☐ or Hospital Name: _____

Patient ID: _____ Patient Initial: _____ Date of Birth: _____ / _____ / _____

Procedure performed today Doppler ☐ Venography ☐ Both ☐

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

Did this patient attend wearing compression sleeves? Yes ☐ No ☐

Results - Any D.V.T. present? 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/Examined	☐	☐

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

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

Procedure performed by: Name of person doing scan _____
Radiologist ☐
Sonographer ☐
Technician ☐
Doctor ☐
Other – please specify _____

Name of person completing form _____Signature_____Date: ____/____/____
day month year

Enter online at www.clotstrial.com or return by fax +44 (0) 131 3325150

CLOTS 3 - 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 Number OR Name: _____

Patient Identifiers: CLOTS ID: _____ Patient Initial: _____

ABOUT THE STROKE

Was stroke the final diagnosis in this patient? Yes ☐ No ☐
(a normal brain scan is compatible with a diagnosis of stroke)
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) ☐ Other antiplatelet ☐

Prophylactic dose heparin/LMWH ☐ Treatment dose heparin /LMWH ☐

Warfarin ☐ Other oral anticoagulant ☐ **None**☐

If patient was given heparin, LMWH or warfarin during admission please give reasons:

To prevent stroke ☐
Artificial heart valve ☐
Atrial fibrillation (AF) ☐

To **prevent** DVT or PE ☐
To **treat** DVT or PE ☐

Other ☐ Please specify _____ ☐☐
For office use

Has the patient worn Graduated Compression Stockings during this admission? Yes ☐ No ☐

If yes, which length were worn? Long only ☐ Short only ☐ Both ☐

USE OF COMPRESSION SLEEVES

Since randomisation, has this patient

Worn thigh- length Compression Sleeves at any time? Yes ☐ No ☐

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

If the allocated use of compression sleeves has not been followed, please give reasons below:

_____ ☐☐
For office use

If wore compression sleeves at any time since randomisation

Date sleeves first worn ___/____/____ Date sleeves last worn ____/____/____

Number of days (between these dates) sleeves **not** worn _____

If compression sleeves were taken off please tick <u>one</u> reason below:

Patient had 2nd Doppler after 30 days	☐	Patient refused to wear sleeves	☐
Patient completed 30 days of IPC	☐	Patient complained of discomfort	☐
Patient independently mobile	☐	Concerns about skin condition on legs	☐
Other difficulties encountered	☐	Please specify_____	☐☐

Please describe any skin problem on leg? _____ For office use ☐☐

Did the skin problem resolve after removal of the IPC? _____ ☐☐

For office use

MAJOR EVENTS SINCE RANDOMISATION

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?
(within 30 days of enrolment)
Yes ☐ No ☐
↳ If **yes** give date 1st diagnosed ____/____/__

Fall resulting in injury?
(within 30 days of enrolment)
Yes ☐ No ☐
↳ If **yes** give date 1st diagnosed ____/____/____

DETAILS ~ SYMPTOMATIC DVT

Were the symptoms of a DVT recognised before the Doppler ultrasound? Yes ☐ No ☐

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	Calf	☐	Popliteal	☐	Femoral	☐
Left leg	Calf	☐	Popliteal	☐	Femoral	☐

DETAILS ~ PULMONARY EMBOLISM

If Pulmonary embolism diagnosed how was this confirmed?

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

DETAILS ~ SKIN BREAKS ON LEGS

Was patient wearing compression sleeves when developed skin break? Yes ☐ No ☐ Unsure ☐

Do you think the skin break was caused by the IPC sleeves or tubing Yes ☐ No ☐ Unsure ☐

Did the skin break heal before discharge? Yes ☐ No ☐ Unsure ☐

Did the skin break require any operative treatment (e.g. amputation) Yes ☐ No ☐ Unsure ☐

DETAILS ~FALLS RESULTING IN INJURY

Was the patient wearing compression sleeves at the time of the fall(s)? Yes ☐ No ☐ Unsure ☐

Do you think the fall was caused by the IPC sleeves or tubing? Yes ☐ No ☐ Unsure ☐

Did the patient sustain a fracture? Yes ☐ No ☐

Please provide details of injury due to fall below

_____ ☐☐
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 compression sleeves*, 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: _____

AND

Family Doctor's Name:_____Full postal address:_____

_____

_____Postcode:_____Telephone:_____

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

Name: _____ Relationship:_____

Full postal address:_____

_____Postcode:_____Telephone:_____

AND ANOTHER

Name: _____ Relationship:_____

Full postal address:_____

_____Postcode:_____Telephone:_____

ADDITIONAL INFORMATION

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

_____

_____

_____

_____ ☐☐

For office use

Name of person completing form _____

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

Enter online at www.clotstrial.com or fax back on +44 (0) 131 3325150

CLOTS – 3 GP Letter

**** PLEASE PRINT ON HOSPITAL HEADED NOTEPAPER****

Date:

Dear _____,

The patient named below is under your care and has **given consent to participate** in the CLOTS – 3 Trial

Patients Name:

Date of Birth:

Address:

Ward:

CLOTS-3 is a randomised controlled trial which aims to establish if intermittent pneumatic compression (IPC) applied to both legs reduce the risk of above knee DVT in the weeks following acute stroke. Patients are randomly allocated to receive either:

Intermittent Pneumatic Compression + routine care OR Routine care only

Doppler ultrasound and/or venography will be used to detect clots. No action is required, on your part, at this time, however, the trial office will contact you in about six months time to

1. Confirm whether the patient is alive or not before we attempt to contact them.

2. Find out if this patient has had a DVT or PE since hospital discharge.

For further information about this trial please contact either myself or Prof. Martin Dennis (Chief Investigator Co-ordinator) at the CLOTS Trial Co-ordinating Centre, Neurosciences Trials Unit, Western General Hospital, Edinburgh, Scotland EH4 2XU Telephone: 44 (0) 131 537 1082, Fax: 44 (0) 131 332 5150.

In anticipation of your help, we thank you and will be in contact in the next few months.

Yours sincerely,

_____
Under my care

CLOTS -3 Serious Adverse Event Report Form

Please complete this form if any patient randomised into CLOTS experiences a **serious adverse event** (in particular one related to participating in the CLOTS trial). See definitions below.

Hospital Number / Name: _____

CLOTS ID: _____ Patient Initials: _____ Date of birth: ____/___/____(dd/mm/yyyy)

Date adverse event first experienced: _____/____/_____(dd/mm/yyyy)

Details of adverse event: _____

_____

_____

Signature of Principal Investigator (or delegated other): _____

DO report any serious adverse event (i.e. one resulting in death, is life threatening, results in significant disability or incapacity or prolongation of hospitalisation), especially one which relates to being in the CLOTS trial, but:

DO NOT use this form to report "outcome events" or Falls resulting in injury (use the Discharge Form) e.g.:

- DVTs,
- Pulmonary emboli
- Falls resulting in injury
- Skin problems on legs
- Deaths.

DO NOT use this form to report expected and/or common complications of stroke, (*unless you believe that they resulted from being in the CLOTS trial)*, e.g.:

- Infections
- Recurrent stroke or other vascular events,
- Epileptic seizures
- Pressure sores
- Mood problems

Enter online at www.clotstrial.com or fax back on +44 (0) 131 3325150

CLOTS – 3 GP Questionnaire

Patients Name: <<Patient name >>

Date of Birth: << Date of Birth >>

Is this patient alive? ☐Yes ☐ No

If patient is still alive, please confirm that the following contact details are correct and amend if necessary

<< address >> <<Tel No.>>

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

			If yes, what was the date first diagnosed?
Deep Vein Thrombosis?	Yes ☐	No ☐	__/__/____
Pulmonary Embolism?	Yes ☐	No ☐	__/__/____
Evidence of post-DVT leg syndrome? (i.e. swelling, pain, new ulcer)	Yes ☐	No ☐	__/__/____

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

Is this patient taking warfarin? Yes ☐ No ☐

Reason why (in particular have they had a DVT or PE)

If this patient has died, please confirm the date and cause

Date of death __/__/____

Cause of death. _____☐☐

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

Name of person completing form _____Signature_____Date: ____/____/____
day month year

Thank you very much for your assistance.

Now please fax 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

CLOTS - Follow-up Questionnaire

Dear <<patients name>> 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

Are you currently taking *(please tick appropriate boxes)?*

- Aspirin ☐
- Dipyridamole (Persantin) ☐
- Clopidogrel (Plavix) ☐
- Warfarin ☐

PROBLEM WITH YOUR LEGS?

YOUR RIGHT LEG

	Yes	No
Since discharge from hospital have you had a clot in this leg (deep vein thrombosis, DVT)?	☐	☐
Do you suffer from a swollen ankle or leg?	☐	☐
Have you had a leg ulcer since your stroke?	☐	☐

YOUR LEFT LEG

	Yes	No
Since discharge from hospital have you had a clot in this leg (deep vein thrombosis, DVT) ?	☐	☐
Do you suffer from a swollen ankle or leg?	☐	☐
Have you had a leg ulcer since your stroke?	☐	☐

YOUR LUNGS

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

Tick 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/ chair ☐

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 _____(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 return it using the pre-paid envelope provided