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Citation for published version:

Digital Object Identifier (DOI):
10.1016/S1474-4422(14)70258-3

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Lancet Neurology

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Effect of intermittent pneumatic compression on disability, living circumstances, quality of life, and hospital costs after stroke: secondary analyses from CLOTS 3, a randomised trial

CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration*

Summary
Background The results of the CLOTS 3 trial showed that intermittent pneumatic compression (IPC) reduced the risk of deep vein thrombosis and improved survival in immobile patients with stroke. IPC is now being widely used in stroke units. Here we describe the disability, living circumstances, quality of life, and hospital costs of patients in CLOTS 3.

Methods In CLOTS 3, a parallel group trial in 94 UK hospitals, immobile patients with stroke from days 0 to 3 of admission were assigned with a computer-generated allocation sequence in a 1:1 ratio to IPC or no IPC through a central randomisation system. We followed up patients at about 6 months with postal or telephone questionnaire to assess the secondary endpoints: disability (Oxford Handicap Scale [OHS]), living circumstances, health-related quality of life (EQ5D-3L), and hospital costs (based on use of IPC and length of hospital stay). Patients and carers who completed the postal questionnaires were not masked to treatment allocation, but telephone follow-up in non-responders was masked. All analyses were by intention to treat. This trial is registered, number ISRCTN93529999.

Findings Between Dec 8, 2008, and Sept 6, 2012, we enrolled 2876 patients, with 1438 in each group. Despite the previously reported reduction in the risk of proximal deep vein thrombosis at 30 days (primary endpoint), there were no significant differences in disability (OHS 0–2 vs 3–6, adjusted odds ratio [OR] 0·98, 95% CI 0·86 to 1·11), living circumstances (institutional care vs not; adjusted OR 1·11, 95% CI 0·89 to 1·37; p=0·358), or health-related quality of life (median utility value 0·26, IQR –0·07 to 0·66 with IPC, and 0·27, –0·06 to 0·64, with no IPC; p=0·952). The estimated cost of IPC was £64·10 per patient (SD 28·3). The direct costs of preventing a deep vein thrombosis and death were £1282 (95% CI 785 to 3077) and £2756 (1346 to not estimable), respectively, with IPC. Hospital costs increased by £451 with IPC compared with no IPC because of a longer stay in hospital (mean 44·5 days [SD 37·6] vs 42·8 days [37·2]; mean difference 1·8 days, 95% CI –1·0 to 4·5). By 6 months, despite an increase in survival (IPC 152·5 days [SD 60·6] vs no IPC 148·1 days [64·3]; mean difference 4·5 days, 95% CI –0·2 to 9·1), there was a non-significant increase in quality-adjusted survival associated with IPC (IPC 27·6 days [SD 40·6] vs no IPC 26·7 days [39·6]; mean difference 0·9 days, 95% CI –2·1 to 3·9).

Interpretation IPC is inexpensive, prevents deep vein thrombosis, improves survival but not functional outcomes, and does not lead to a significant gain in quality-adjusted survival. When deciding whether to treat patients with IPC, clinicians need to take into account all these potential effects.

Funding National Institute of Health Research Health Technology Assessment Programme, Chief Scientist Office of Scottish Government, and Covidien.

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Introduction
About 110000 patients with acute stroke are admitted to hospitals in the UK each year. 30-day case fatality varies, but is about 20%. The direct medical cost of stroke in the UK is estimated as £2·8 billion per year.1 Venous thromboembolism is common after stroke, causes substantial morbidity, might delay hospital discharge, might increase costs, and has been estimated to account for a quarter of all deaths after stroke.1

The results of the CLOTS 3 trial showed that intermittent pneumatic compression (IPC) applied to the legs of immobile patients with stroke reduced the risk of the primary outcome proximal deep vein thrombosis (odds ratio [OR] 0·65, 95% CI 0·51–0·84; p=0·001) and secondary outcomes including any deep vein thrombosis (0·72, 0·60–0·87; p=0·001) and symptomatic deep vein thrombosis (0·72, 0·52–0·99; p=0·045) within 30 days after randomisation.1 IPC also reduced the hazard of death over the first 6 months (hazard ratio 0·85, 95% CI 0·73–0·99; p=0·042).1 To help guide the implementation of this intervention for patients with stroke, we aimed to describe additional secondary outcomes assessed at 6 months—disability, living circumstances, quality of life, and the hospital costs of patients recruited into CLOTS 3—to ascertain the cost-effectiveness of preventing deep vein thrombosis and deaths with IPC and quality-adjusted survival in quality-adjusted life-days (QALDs).
Methods

Study design and patients

The methods have been described in detail elsewhere.1,2 Briefly, CLOTS 3 was a multicentre trial with a parallel group design. Patients were enrolled at 94 centres in the UK from days 0 (admission) to 3 in hospital and allocated to the IPC group or the no IPC group; all patients received routine care.

Patients were eligible for inclusion if they were admitted to hospital within 3 days of an acute stroke (ischaemic or haemorrhagic), could be enrolled between day 0 and day 3 in hospital, and were immobile (ie, unable to walk independently to the toilet). We excluded patients with subarachnoid haemorrhage and those with severe peripheral vascular disease, congestive heart failure, or skin lesions on the legs that were thought to be contraindications for IPC.

The study protocol was approved by the Scotland A Multicentre Research Ethics Committee (08/MREC00/73) and the Newcastle and North Tyneside 1 Research Ethics Committee for England (08/H0906/137). All patients provided written informed consent before they were randomly assigned to treatment.

Randomisation and masking

After obtaining consent, the clinician entered the patient’s baseline data into our computerised central randomisation service through a secure web interface. Once the computer program had checked these baseline data for completeness and consistency, it generated treatment allocation for the patient: routine care plus IPC or routine care without IPC. Patients were randomly assigned in a 1:1 ratio. Patients and their carers who completed follow-up questionnaires at 6 months were not masked to treatment allocation. However, the individual doing telephone follow-up of patients who did not respond to the postal follow-up was masked to treatment assignment.

Procedures

In patients allocated to the IPC group, nursing staff applied the Kendall Express Sequential Compression System (Covidien, Mansfield, MA, USA) with thigh-length sleeves to both legs, according to the manufacturer’s instructions. The sleeves were to be worn 24 h per day for 30 days or until one of the following criteria was met: a second screening compression duplex ultrasound had been done (after 30 days); the patient was independently mobile or discharged from the hospital in which he or she was randomly assigned; the patient refused to wear the sleeves; or the staff became concerned about the patient’s skin. We stipulated that both treatment groups should receive the same background general care, which included, depending on local protocols, early mobilisation, hydration, and antiplatelet or anticoagulant drugs.

We aimed to do a compression duplex ultrasound of the veins in both legs between days 7 and 10 after randomisation in all patients, and, whenever practical, a second scan between days 25 and 30. The local coordinator reviewed the medical record and extracted the information to complete our discharge form. We could not mask the local coordinator to group allocation because there was no sham version of IPC and because we were gathering data for adherence. At about 6 months, we sent a postal questionnaire to each patient’s family doctor to establish the patient’s vital status. We followed up surviving patients at 6 months after enrolment by postal questionnaire. The chief investigator did a telephone interview, masked to treatment allocation, with patients who did not respond to the postal questionnaire. Information about the timing and method of follow-up is provided in the appendix.

The numbers of IPC sleeves delivered to sites and the number remaining at the end of the trial were used to estimate the mean number of sleeves used per patient. We did not record the number of sleeves used by each participant.

Outcomes

The primary outcome in CLOTS 3 was the occurrence of a symptomatic or asymptomatic deep vein thrombosis in the popliteal or femoral veins (detected on the first or second compression duplex ultrasound as part of the trial protocol) or a symptomatic deep vein thrombosis in the popliteal or femoral veins, confirmed on imaging (compression duplex ultrasound or venography) within 30 days of randomisation. The secondary outcomes measured at 30 days were death, or any deep vein thrombosis or pulmonary embolism. These primary and secondary outcomes, and adverse effects of IPC, including skin breaks and falls, have been reported previously.1 The secondary outcomes reported here are disability (Oxford Handicap Scale [OHs]),4 living circumstances (institutional care or home), health-related quality of life (utilities based on EQ5D-3L)7 based on follow-up questionnaires returned after 6 months, and hospital costs. We attempted to detect post-phlebitic leg syndrome by asking patients about leg swelling and ulcers at the 6-month follow-up. However, these questions were not validated and unlikely to be specific because of the high frequency of swelling in stroke-affected limbs and leg ulcers of other types.

Statistical analysis

We estimated we would need 2800 patients to provide 90% power (α=0.05) to identify a 4% absolute reduction in our primary outcome (ie, from 12% to 8%). For the purposes of all analyses, we retained participants in the treatment group to which they were originally assigned (intention-to-treat analysis). We calculated the absolute difference between groups (and its 95% CI) in the proportion who had at least one outcome. We compared the proportions with primary or secondary outcomes using ORs and 95% CIs, adjusted with logistic regression for the four variables included in our minimisation algorithm (predicted stroke outcome, delay from stroke...
onset to randomisation, ability of the patient to lift both legs off the bed, and use of anticoagulants or alteplase). The OHS at final follow-up was analysed by dichotomisation (0–2 vs 3–6) with logistic regression and as an ordinal scale with ordinal regression. The health-related quality of life measured with the EQ5D-3L was converted into a utility value based on UK population preferences as a range of 1.0 (perfect health) to −0.5 (worst possible health).4 In this setting, the range of utility values account for health states worse than death (utility value 0). We used Stata (version 12) for the analysis.

**Economic analysis**

We did a within-trial cost-utility analysis to estimate the cost-effectiveness of IPC from a health-service provider’s perspective on the basis of intention to treat. Patient’s resource use was measured with the duration of hospital stay for the index episode after randomisation. Resource use was measured as length of stay in hospital and the direct costs of IPC capital and equipment. Length of stay distributions were converted into cost estimates based on a per-day hospital cost. Trial-centre-specific or region-specific per-day hospital costs were based on National Health Service (NHS) reference costs in England and cost information for NHS Scotland derived from the Scottish Health Service Costs resource.9,10 We did not cost information for NHS Scotland derived from the Health Service (NHS) reference costs in England and specific per-
day hospital costs were based on National Health Service (NHS) reference costs in England and cost information for NHS Scotland derived from the Scottish Health Service Costs resource.9,10 We did not assess the cost of nursing home or social care, or the cost of readmissions to hospital.

A standard multiplicative model was used to estimate quality-adjusted survival expressed as QALDs by the area under linear interpolation of the EQ5D-3L index trajectory for each individual with survival times, the EQ5D-3L utility index score at 6 months, and a modelled baseline EQ5D-3L utility index value (appendix).9 We did sensitivity analyses based on cases with complete data and follow-up and using multiple imputation of EQ5D-3L. Multiple imputation with chained equations was used to impute missing health-related quality-of-life data on the EQ5D-3L questionnaire using the mi suite of commands in Stata (version 12).

The primary treatment effect for the economic analysis was the mean incremental costs and incremental QALDs over 6 months after randomisation. We also estimated direct costs of preventing venous thromboembolism and deaths within 30 days of randomisation. Generalised linear models were used to analyse the distribution of costs and QALDs separately with a general specification that allowed for different parametric distributions.9 We also assessed differences in costs and effects using econometric methods that account for the dependency between each outcome. Simultaneous equation individual level regression models were used to estimate the joint distribution of costs and QALDs.11 Non-parametric bootstrapping was undertaken to assess the joint densities of incremental costs and incremental effects and explore uncertainty in the cost-effectiveness results based on 10 000 bootstrap replications using Stata (version 12). Probabilistic sensitivity analysis was done to assess the robustness of the reported results for both short-run QALD estimates and hospital cost distributions. We had planned to estimate the averted costs arising from the effects of IPC on the expected incidence of deep vein thrombosis or pulmonary embolism. However, the marginal effect of a change in the incidence of deep vein thrombosis or pulmonary embolism would be noted only for symptomatic and treated deep vein thromboses or pulmonary embolisms, and these were rare events. We did not note a substantial difference in hospital resource use between the treatment groups that could be attributed to a change in the incidence of deep vein thrombosis or pulmonary embolism so we did not enter this into our modelling.

This trial is registered, number ISRCTN93529999.

**Role of the funding source**

The funders of the study had no role in study design, data gathering, storage, analysis, or interpretation, drafting of the report, or the decision to publish. All the authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

**Results**

Between Dec 8, 2008, and Sept 6, 2012, we enrolled 2876 patients in 94 hospitals in the UK and completed...
follow-up in March, 2013. Figure 1 shows the trial profile. Patients were randomly assigned to routine care plus IPC (n=1438) or routine care without IPC (n=1438).

Figure 2 shows the outcomes of patients with respect to OHS. The prespecified analyses for the comparison of OHS in the two groups showed no significant difference. The unadjusted and adjusted ORs based on the dichotomised OHS (OHS 0–2 vs 3–6) were 0.99 (95% CI 0.83–1.19; p=0.93) and 0.98 (0.80–1.19; p=0.83), respectively. The ordinal analysis of the OHS yielded common ORs of 0.98 (95% CI 0.86–1.12) and 0.97 (0.86–1.11), respectively. According to the results of post-hoc and exploratory analyses, done to investigate an apparent increase in the proportion of patients with OHS 5 in the IPC group, although non-significantly fewer deaths occurred in the IPC group (330 [23%] of 1421 vs 367 [26%] of 1420; p=0.12), more patients survived with very poor function in the IPC group (OHS 5; 309 [22%] vs 255 [18%]; p=0.013).

Of the patients allocated IPC, 266 (25%) of 1076 were living in a nursing home or were in hospital at the 6-month follow-up compared with 233 (22%) of 1039 allocated only routine care (unadjusted OR 1.14, 95% CI 0.93 to 1.39; p=0.214; adjusted OR 1.11 95% CI 0.89 to 1.37, p=0.358). The median health-related quality-of-life utility value for survivors (based on the EQ5D-3L) was 0.26 (IQR –0.07 to 0.66) and 0.27 (–0.06 to 0.64) in the IPC and no IPC groups, respectively (p=0.952).

Table 1 shows the estimated resource use and costs. Patients allocated IPC had a slightly longer hospital stay (mean difference 1.8 days, 95% CI –1.0 to 4.5; table 1), probably attributable to their improved survival. Individuals in the IPC group wore IPC for a mean of 11.7 days, using a mean of 2.5 pairs of sleeves (table 1). On the basis of the unit costs of sleeves (which included the cost of the controllers) and an estimate of the nursing time taken to fit and monitor them (based on our observations in one centre), we estimated the mean direct cost of IPC to be £64.10 per patient (SD 28.3) or £5.48 per day of treatment.

Table 2 shows the estimated direct costs of avoiding proximal deep vein thrombosis, any deep vein thrombosis, symptomatic deep vein thrombosis, pulmonary embolism, or death in the 30-day treatment. These costs do not include the increased costs (mean £387 [SD 306–3]) of the longer stay in hospital associated with the use of IPC.

Table 3 shows the difference between treatment groups with respect to survival and quality-adjusted survival (QALDs). Despite the improved mean survival in the IPC group of 4.5 days (95% CI –0.2 to 9.1), there was a mean gain of only 0.9 days (–2.1 to 3.9) in quality-adjusted survival over the 6-month follow-up because of poor quality of life in many survivors. Missing data were few, but sensitivity analyses based on multiple imputations of the EQ5D-3L did not alter our conclusions (table 3). Figure 3 summarises the cost-effectiveness results based on cases (n=2799) with complete data and follow-up. The incremental cost-effectiveness ratio indicates that IPC might be used if a decision maker is willing to pay more than £610.88 for an additional day of quality-adjusted survival (figure 3).

The data for the frequency of leg swelling and leg ulcers at 6-month follow-up are reported in the appendix.
Discussion

The previously reported results of CLOTS 3 showed that IPC use in hospitalised patients with stroke who are immobile reduces the risk of deep vein thrombosis and is associated with a significant improvement in survival over the first 6 months. However, here we show that IPC use is not associated with a significant improvement in disability, proportions of patients living at home, quality of life, or any gain in quality-adjusted survival. Nevertheless, IPC is an affordable and effective method of prophylaxis for venous thromboembolism, although it increases overall hospital costs due to increased length of stay associated with improved survival (panel). The direct treatment costs of preventing one deep vein thrombosis, or even one early death, are small.

The results of the post-hoc exploratory analysis of the OHS showed a significant increase in the proportion of patients surviving with an OHS of 5, indicating that they were bed or chair bound and required complete care. This finding suggests that most of the deaths that might result from pulmonary embolism and might be prevented with IPC occur in patients with severe strokes who would be expected to have a poor functional outcome. We have previously shown that dependency in activities of daily living before stroke, greater limb weakness, and a history of deep vein thrombosis or pulmonary embolism are independently associated with an increased risk of deep vein thrombosis after stroke. Previous dependency and increased limb weakness are also associated with worse functional outcomes. Therefore, if IPC effectively reduces the risk of deep vein thrombosis and improves survival by preventing fatal venous thromboembolism, many of the patients who survive because of IPC would be expected to have poor functional status. Patients with poor functional status have a utility as measured with EQ5D-3L that is little different from death. For this reason, there is little gain in quality-adjusted survival.

These secondary analyses of the CLOTS 3 trial have some limitations. The trial was powered to detect a 4% absolute reduction in the risk of proximal deep vein thrombosis within 30 days, but was not powered to detect the improvement in survival or the differences in the OHS, costs, or EQ5D-3L. Also, the statistical comparison of the proportion of patients with OHS 5 between treatment groups was not prespecified and was done after the analysis of the data. Patients and their families were not masked to their treatment allocation, but at 6 months provided the information on which the OHS and quality of life were based. This could theoretically have introduced some bias, but neither patients nor their carers were likely to have thought that IPC would affect outcomes other than venous thromboembolism. Although the EQ5D-3L has been used widely to estimate health-related quality of life and the utilities based on the preferences of UK and other populations are available, its validity for the measurement of quality of life early during hospitalisation with acute stroke might be questionable. Indeed, because of this potential caveat we modelled the baseline EQ5D-3L rather than attempting to measure it directly. This might have affected our estimates of quality-adjusted survival, which depend on a change in EQ5D-3L between baseline and follow-up. Also, the preferences on which utility values are based are those of a general sample of the UK population rather than stroke survivors. Stroke survivors might value survival with poor outcome differently. The lengths of stay and resulting costs of hospitalisation are based on UK practice where rehabilitation is often completed as part of the initial acute hospital admission episode. In countries where acute hospital stays for stroke are much shorter, IPC might lead to greater use of rehabilitation facilities or community care rather than acute hospital resources.

The results of previous studies have shown that poorer functional status 6 months after a stroke is strongly

### Table 3: Overall survival and 6-month QALDs

<table>
<thead>
<tr>
<th>Survival (multiple imputations, days)</th>
<th>IPC</th>
<th>No IPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1438</td>
<td>1396</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>152.5 (60.6)</td>
<td>148.1 (64.3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>183 (0 to 183)</td>
<td>183 (1 to 183)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QALDs of patients with complete data</th>
<th>IPC</th>
<th>No IPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1403</td>
<td>1396</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.6 (40.6)</td>
<td>26.7 (39.6)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>16.6 (-105.1 to 145.9)</td>
<td>15.4 (-84.3 to 145.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QALDs (multiple imputations)</th>
<th>IPC</th>
<th>No IPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1438</td>
<td>1438</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.2 (40.7)</td>
<td>27.5 (39.8)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>17.6 (-105.1 to 145.9)</td>
<td>15.9 (-84.3 to 145.9)</td>
</tr>
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</table>

The median survival was 183 days because the follow-up was curtailed at this timepoint. IPC=intermittent pneumatic compression. QALDs=quality-adjusted life-days.
Systematic review

In 2013, we reported the primary results of the CLOTS 3 trial that showed that intermittent pneumatic compression (IPC) reduced the risk of our primary outcome, symptomatic or asymptomatic proximal deep vein thrombosis in patients hospitalised after an acute stroke who were initially immobile. The results also showed a significant reduction in symptomatic deep vein thrombosis (proximal or distal) and an improved survival to 6 months. A systematic review\(^{14}\) updated in March, 2013,\(^{1}\) identified only two other trials of IPC, one including 151 patients with haemorrhagic stroke randomly assigned to IPC and graduated compression stockings or to graduated compression stockings alone,\(^{15}\) and the other including 26 patients with unspecified stroke randomly allocated to IPC or no IPC.\(^{16}\) When the results of CLOTS 3 were meta-analysed with the results of the other two trials, the estimates of treatment effects were an odds ratio (OR) of 0·66 (95% CI 0·52–0·84) for proximal deep vein thrombosis, 0·71 (0·59–0·85) for any deep vein thrombosis, and 0·81 (0·65–1·01) for deaths by the end of the treatment period.\(^{17}\) Neither small trial reported any symptomatic deep vein thrombosis or pulmonary embolisms, a survival analysis, or any data for long-term disability, living circumstances, quality of life, or hospital costs.

Interpretation

IPC is inexpensive, prevents deep vein thrombosis, improves survival but not disability, and does not achieve any significant gain in quality-adjusted survival. When deciding whether to treat individual patients with IPC, clinicians need to take account of these effects. All national guidelines recommending methods of prophylaxis of venous thromboembolism in stroke and other disorders have focused mainly on evidence of effects on deep vein thrombosis, primarily asymptomatic deep vein thrombosis. The CLOTS 3 results emphasise the importance of also taking account of outcomes such as survival, disability, and quality of life, which can be more important to patients and their families.

associated with worse long-term survival.\(^{18}\) Therefore, we might expect the improvement in survival associated with IPC over the first 6 months after randomisation to decrease with longer follow-up. We plan to use routinely gathered mortality data in the UK to investigate this possibility.

These data raise challenging clinical and ethical questions for clinicians who make decisions about whether to give prophylaxis for venous thromboembolism to patients after stroke. These decisions have to be made whether to give prophylaxis for venous thromboembolism with IPC is not easy to predict reliably within the first day or two after a severe stroke. In this respect, IPC might be likened to other treatments used in patients with stroke such as antibiotics for pneumonia and early nasogastric feeding in patients unable to swallow, which might increase the likelihood of survival but not improve functional outcomes.\(^{20,21}\) In view of the small direct costs of IPC, and the effect on deep vein thrombosis and survival, the rapid implementation of IPC in many stroke services is perhaps not surprising.\(^{22}\) However, clinicians need to take account of these data in relation to functional status and quality of life when making decisions for individual patients.

Contributors

MD participated in the steering committee, drafted this report, was involved in the design of the trial, and gathered, verified, and analysed the data. CG participated in the steering committee, commented on a draft of this report, was involved in the design of the trial, and gathered, verified, and analysed the data. JS did the health economic analyses in partnership with JF, and commented on drafts of this report. JF participated in the steering committee, was involved in the design of the trial, and analysed health economic data. PS participated in the steering committee, commented on a draft of this report, and was involved in the design of the trial. All authors here have seen and approved the final version of the report.

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Martin Dennis, Catriona Graham, Joel Smith, John Forbes, Peter Sandercock.

Declaration of interests

None of the writing committee had any personal financial competing interests. All authors reported grants from the Chief Scientist Office of the Scottish Government, grants from the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) board, non-financial support from NIHR Stroke research networks, and non-financial support from Covidien during the study. The support from Covidien comprised donation of free supplies of IPC sleeves to all participating hospitals, lending of IPC controllers, provision of staff training in IPC use, and logistics to keep centres supplied with IPC sleeves. MD also reports that since the primary CLOTS 3 results were published in 2013 he has worked with the Scottish Government, NHS Improving Quality, and Covidien to ensure that the results were rapidly implemented in the NHS. He has helped make a training video for Covidien and the company has provided video clips for an online training module that MD is producing. MD has spoken at meetings about the results of the trials, including meetings of Covidien’s sales staff. However, he has not received any speakers’ fees or travel expenses.

Acknowledgements

The study was jointly sponsored by the University of Edinburgh and NHS Lothian. The start-up phase of the trial (December, 2008, to March, 2010) was funded by the Chief Scientist Office of the Scottish Government (reference CZH/4/417). The main phase of the trial was funded by the NIHR HTA Programme (reference 08/14/03). Covidien lent its Kendall Express Sequential Compression System Controllers to our 105 centres and donated supplies of their sleeves. It also provided logistical help in keeping our centres supplied with sleeves and training materials relevant to the use of their devices. Recruitment and follow-up was supported by the NIHR funded UK Stroke research network and the Scottish Stroke Research network, which was supported by NHS Research Scotland. A full description of the trial will be published in the HTA journal series. The views and opinions expressed in this report are those of the authors and do not necessarily reflect those of the UK Department of Health or the Chief Scientist Office of the Scottish Government.
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