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# BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A

L Shaw,[1] H Rodgers,[1,2]* C Price,[2] F van Wijck,[3] P Shackley,[4] N Steen,[4] M Barnes,[5] G Ford,[1] L Graham,[5] on behalf of the BoTULS investigators

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 02/41/06. The contractual start date was in February 2005. The draft report began editorial review in May 2009 and was accepted for publication in January 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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# Abstract

## BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A

L Shaw,[1] H Rodgers,[1,2]* C Price,[2] F van Wijck,[3] P Shackley,[4] N Steen,[4] M Barnes,[5] G Ford,[1] L Graham,[5] on behalf of the BoTULS investigators

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**Objective:** To compare the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A plus an upper limb therapy programme with the upper limb therapy programme alone.
**Design:** A multicentre open-label parallel-group randomised controlled trial and economic evaluation.
**Setting:** Twelve stroke services in the north of England, UK.
**Participants:** Three hundred and thirty-three adults with upper limb spasticity at the shoulder, elbow, wrist or hand and reduced upper limb function due to stroke more than 1 month previously.
**Interventions:** The intervention group received botulinum toxin type A injection(s) plus a 4-week programme of upper limb therapy. The control group received the upper limb therapy programme alone. Participants were clinically reassessed at 3, 6 and 9 months to determine the need for repeat botulinum toxin type A injection(s) and/or therapy.
**Main outcome measures:** The primary outcome was upper limb function 1 month after study entry measured by the Action Research Arm Test (ARAT). A successful outcome was defined as: (1) a change of three or more points on the ARAT scale for a participant whose baseline ARAT score was between 0 and 3, (2) a change of six or more points on the ARAT scale for a participant whose baseline ARAT score was between 4 and 51, or (3) a final ARAT score of 57 for a participant whose baseline ARAT score was 52–56. Outcome assessments were undertaken at 1, 3 and 12 months by an assessor who was blinded to the study group allocation. Upper limb impairment and activity limitation were assessed by: Modified Ashworth Scale; Motricity Index; grip strength; ARAT; Nine-Hole Peg Test; upper limb basic functional activity questions and the Barthel Activities of Daily Living (ADL) Index. Stroke-related quality of life/participation restriction was measured using the Stroke Impact Scale, European Quality of Life-5 Dimensions (EQ-5D) and the Oxford Handicap Scale. Upper limb pain was assessed using numerical rating scales. Participant-selected upper limb goal achievement (1 month only) was measured using the Canadian Occupational Performance Measure. Adverse events were compared. Health-care and social services resource use was compared during the first 3 months postrandomisation. EQ-5D data were used to calculate the quality-adjusted life-years (QALYs) associated with intervention and control treatments, and the incremental cost per QALY gained of botulinum toxin type A plus therapy compared with therapy alone was estimated. The sensitivity of the base-case results to alternative assumptions was investigated, and cost-effectiveness acceptability curves, which summarise the evidence of botulinum toxin type A plus therapy being cost-effective for a range of societal willingness to pay for a QALY values, are presented.
**Results:** Randomisation groups were well matched at baseline. There was no significant difference between

the groups for the primary outcome of improved arm function at 1 month. This was achieved by 30/154 (19.5%) in the control group and 42/167 (25.1%) in the intervention group ($p = 0.232$). The relative risk of having a 'successful treatment' in the intervention group compared with the control group was 1.3 [95% confidence interval (CI) 0.9 to 2.0]. No significant differences in improved arm function were seen at 3 or 12 months. In terms of secondary outcomes, muscle tone/spasticity at the elbow was decreased in the intervention group compared with the control group at 1 month. The median change in the Modified Ashworth Scale was –1 in the intervention group compared with zero in the control group ($p < 0.001$). No difference in spasticity was seen at 3 or 12 months. Participants treated with botulinum toxin type A showed improvement in upper limb muscle strength at 3 months. The mean change in strength from baseline (upper limb component of the Motricity Index) was 3.5 (95% CI 0.1 to 6.8) points greater in the intervention group compared with the control group. No differences were seen at 1 or 12 months. Participants in the intervention group were more likely to be able to undertake specific basic functional activities, e.g. dress a sleeve, clean the palm and open the hand for cutting fingernails. At 1 month, 109/144 (75.7%) of the intervention group and 79/125 (63.2%) of the control group had improved by at least one point on a five-point Likert scale for at least one of these tasks ($p = 0.033$). At 3 months the corresponding proportions were 102/142 (71.8%) of the intervention group and 71/122 (58.2%) of the control group ($p = 0.027$). Improvement was sustained at 12 months for opening the hand for cleaning the palm and opening the hand for cutting the nails but not for other activities.

Pain rating improved by two points on a 10-point severity rating scale in the intervention group compared with zero points in the control group ($p = 0.004$) at 12 months, but no significant differences were seen at 1 or 3 months. There were a number of occasions when there were statistically significant differences in favour of the intervention group; however, these differences were small and of uncertain clinical relevance. These differences were: 3 months – upper limb function (change in ARAT score from baseline), pain (EQ-5D) and participation restriction (Oxford Handicap Scale); 12 months – anxiety/depression (EQ-5D) and participation restriction (Oxford Handicap Scale). No differences in grip strength, dexterity or the Barthel ADL Index were found at any time point. There were no differences between the groups for achievement of patient-selected goals. There was a higher incidence of general malaise/flu-like/cold symptoms in participants treated with botulinum toxin type A with a relative risk of 7.6 (95% CI 1.8 to 32.3). Only one serious adverse event (dysphagia) was potentially related to botulinum toxin type A. Time since stroke and severity of initial upper limb function were preplanned subgroup analyses. There was no significant difference in either subgroup for achievement of ARAT 'success' following treatment with botulinum toxin type A. The base-case incremental cost-effectiveness ratio was £93,500 per QALY gained and estimation of the cost-effectiveness acceptability curve for botulinum toxin type A plus the upper limb therapy programme indicated that there was only a 0.36 probability of it being cost-effective at a threshold ceiling ratio of £20,000 per QALY.

**Conclusions:** The addition of botulinum toxin type A to an upper limb therapy programme to treat spasticity due to stroke did not enhance improvement in upper limb function when assessed by the prespecified primary outcome measure at 1 month. However, improvements were seen in muscle tone at 1 month, upper limb strength at 3 months, upper limb functional activities related to undertaking specific basic functional tasks at 1, 3 and 12 months, and upper limb pain at 12 months. Botulinum toxin was well tolerated and side effects were minor. The addition of botulinum toxin type A to an upper limb therapy programme for the treatment of upper limb spasticity due to stroke was not estimated to be cost-effective at levels of willingness to pay for a QALY set by NHS decision-makers.

**Trial registration:** ISRCTN78533119; EudraCT 2004–002427–40; CTA 17136/0230/001.

# Contents

# List of abbreviations

| | |
|---|---|
| ADL | activities of daily living |
| AP | adductor pollicis |
| ARAT | Action Research Arm Test |
| AS | Ashworth Scale |
| AUC | area under curve |
| BNF | *British National Formulary* |
| BoTULS | Botulinum Toxin for the Upper Limb after Stroke |
| BTX | botulinum toxin |
| CEAC | cost-effectiveness acceptability curve |
| CI | confidence interval |
| COPM | Canadian Occupational Performance Measure |
| DAS | Disability Assessment Scale |
| DMEC | Data Monitoring and Ethics Committee |
| EQ-5D | European Quality of Life-5 Dimensions |
| FAT | Frenchay Arm Test |
| FCR | flexor carpi radialis |
| FCU | flexor carpi ulnaris |
| FDP | flexor digitorum profundus |
| FDS | flexor digitorum superficialis |
| FIM | Functional Independence Measure |
| FPL | flexor pollicis longus |
| ICER | incremental cost-effectiveness ratio |
| ICH-GCP | International Conference on Harmonisation – Good Clinical Practice |
| IQR | interquartile range |
| MAS | Modified Ashworth Scale |
| NE | north-east |
| NHS | National Health Service |
| NICE | National Institute for Health and Clinical Excellence |
| NIHR | National Institute for Health Research |
| NW | north-west |
| QALY | quality-adjusted life-year |
| RCT | randomised controlled trial |
| ROM | range of movement |
| SE | south-east |
| SF-36 | Short Form questionnaire-36 items |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SW | south-west |
| TENS | transcutaneous electrical nerve stimulation |
| TSC | Trial Steering Committee |
| VAS | visual analogue scale |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

# Executive summary

## Background

Between 50% and 70% of stroke patients have ongoing upper limb functional limitations. Upper limb spasticity may contribute to reduced function, pain and deformity. Botulinum toxin type A is used increasingly to treat focal spasticity in neurological rehabilitation, but its impact on upper limb function after stroke is unclear.

## Aim

The Botulinum Toxin for the Upper Limb after Stroke (BoTULS) trial evaluated the clinical effectiveness and cost-effectiveness of botulinum toxin type A plus an upper limb therapy programme in the treatment of post-stroke upper limb spasticity.

## Design

A multicentre open-label parallel-group randomised controlled trial and economic evaluation.

## Setting

Twelve stroke services in the north of England. Referrals were received from stroke units, outpatient clinics, day hospitals, community rehabilitation teams, stroke clubs and day centres.

## Participants

Three hundred and thirty-three patients with upper limb spasticity at the shoulder, elbow, wrist or hand and reduced upper limb function due to stroke more than 1 month previously were enrolled in the trial between July 2005 and March 2008.

## Intervention and control treatments

The intervention group received botulinum toxin type A injection(s) (Dysport®) plus a 4-week programme of upper limb therapy. The control group received the upper limb therapy programme alone. Participants were clinically reassessed at 3, 6 and 9 months to determine the need for repeat botulinum toxin type A injection(s) and/or therapy.

## Main outcome measures

The primary outcome was upper limb function 1 month after study entry measured by the Action Research Arm Test (ARAT). A successful outcome was defined as:

1. a change of three or more points on the ARAT scale for a participant whose baseline ARAT score was between 0 and 3
2. a change of six or more points on the ARAT scale for a participant whose baseline ARAT score was between 4 and 51
3. a final ARAT score of 57 for a participant whose baseline ARAT score was 52–56.

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assumptions was investigated, and cost-effectiveness acceptability curves, which summarise the evidence of botulinum toxin type A plus therapy being cost-effective for a range of societal willingness to pay for a QALY values, presented.

## Results

Randomisation groups were well matched at baseline. There was no significant difference between the groups for the primary outcome of improved arm function at 1 month. This was achieved by 30/154 (19.5%) in the control group and 42/167 (25.1%) in the intervention group ($p = 0.232$). The relative risk of having a 'successful treatment' in the intervention group compared with the control group was 1.3 [95% confidence interval (CI) 0.9 to 2.0]. No significant differences in improved arm function were seen at 3 or 12 months.

In terms of secondary outcomes, muscle tone/spasticity at the elbow was decreased in the intervention group compared with the control group at 1 month. The median change in the Modified Ashworth Scale was –1 in the intervention group compared with zero in the control group ($p < 0.001$). No difference in spasticity was seen at 3 or 12 months.

Participants treated with botulinum toxin type A showed improvement in upper limb muscle strength at 3 months. The mean change in strength from baseline (upper limb component of the Motricity Index) was 3.5 (95% CI 0.1 to 6.8) points greater in the intervention group compared with the control group. No differences were seen at 1 or 12 months.

Participants in the intervention group were more likely to be able to undertake specific basic functional activities, e.g. dress a sleeve, clean the palm and open the hand for cutting fingernails. At 1 month, 109/144 (75.7%) of the intervention group and 79/125 (63.2%) of the control group had improved by at least one point on a five-point Likert scale for at least one of these tasks ($p = 0.033$). At 3 months the corresponding proportions were 102/142 (71.8%) of the intervention group and 71/122 (58.2%) of the control group ($p = 0.027$). Improvement was sustained at 12 months for opening the hand for cleaning the palm and opening the hand for cutting the nails, but not for other activities.

Pain rating improved by two points on a 10-point severity rating scale in the intervention group compared with zero points in the control group ($p = 0.004$) at 12 months, but no significant differences were seen at 1 or 3 months.

There were a number of occasions when there were statistically significant differences in favour of the intervention group; however, these differences were small and of uncertain clinical relevance. These differences were: 3 months – upper limb function (change in ARAT score from baseline), pain (EQ-5D) and participation restriction (Oxford Handicap Scale); 12 months – anxiety/depression (EQ-5D) and participation restriction (Oxford Handicap Scale).

No differences in grip strength, dexterity, or the Barthel ADL Index were found at any time point. There were no differences between the groups for achievement of patient-selected goals. There was a higher incidence of general malaise/flu-like/cold symptoms in participants treated with botulinum toxin type A with a relative risk of 7.6 (95% CI 1.8 to 32.3). Only one serious adverse event (dysphagia) was potentially related to botulinum toxin type A.

Time since stroke and severity of initial upper limb function were preplanned subgroup analyses. There was no significant difference in either subgroup for achievement of ARAT 'success' following treatment with botulinum toxin type A.

The base-case incremental cost-effectiveness ratio was £93,500 per QALY gained and estimation of the cost-effectiveness acceptability curve for botulinum toxin type A plus the upper limb therapy programme indicated that there was only a 0.36 probability of its being cost-effective at a threshold ceiling ratio of £20,000 per QALY.

## Conclusions

The addition of botulinum toxin type A to an upper limb therapy programme to treat spasticity due to stroke did not enhance improvement in upper limb function when assessed by the prespecified primary outcome measure at 1 month. However, improvements were seen in muscle tone at 1 month, upper limb strength at 3 months, upper limb functional activities related to undertaking specific basic functional tasks at 1, 3 and 12 months, and upper limb pain at 12 months.

Botulinum toxin was well tolerated and side effects were minor.

The addition of botulinum toxin type A to an upper limb therapy programme for the treatment of upper limb spasticity due to stroke was not estimated to be cost-effective at levels of willingness to pay for a QALY set by NHS decision-makers.

## Implications for health care

Management of spasticity should focus upon realistic goals for treatment. These results will help to inform clinicians which outcomes may be improved by the addition of botulinum toxin type A to an upper limb therapy programme to treat upper limb spasticity due to stroke. Most patients will not achieve an enhanced improvement in active upper limb function by the addition of botulinum toxin to an upper limb therapy programme. However, botulinum toxin type A may have a role to play in improving the ability of some patients to undertake some basic upper limb functional tasks and may reduce pain at 12 months. Despite some clinical benefits, the addition of botulinum toxin type A to an upper limb therapy programme does not appear to be a cost-effective treatment for the patients included in this study.

## Implications for research

Further research is needed to increase our understanding of the natural history and impact of spasticity following stroke, and to explain the relationship between spasticity and functional limitation. Studies are needed to improve the measurement of spasticity and to develop valid measures for all upper limb joints for use in clinical practice and multicentre studies. The optimum dosage and pattern of injections of botulinum toxin type A to treat upper limb spasticity due to stroke and the efficacy of repeat injections need to be defined.

## Trial registration

This trial is registered as ISRCTN78533119; EudraCT 2004–002427–40; CTA 17136/0230/001.

# Chapter 1
# Introduction

The National Institute for Health Research (NIHR) Health Technology Assessment programme identified the need to evaluate the clinical effectiveness and cost-effectiveness of using botulinum toxin to treat chronic upper limb spasticity due to stroke in adults. This report describes the work commissioned to address this issue.

## Overview of stroke

Stroke is a major cause of death and disability in the UK. In England, over 900,000 people are living with the consequences of stroke, 300,000 of them are moderately or severely disabled.[1] The direct cost of stroke to the National Health Service (NHS) is £2.8B per annum, although the overall cost to the economy is much higher (£7B per annum) once informal care costs and lost productivity are taken into account.[1]

## Upper limb problems following stroke

Upper limb impairments such as muscle weakness, spasticity, poor co-ordination and sensory disturbance are common after stroke. These impairments alone, or in combination, can result in a range of functional limitations. Between 50% and 70% of stroke patients have long-term upper limb functional limitations[2–4] and many feel that insufficient attention is paid to upper limb rehabilitation.[5] In contrast, about 80% of stroke survivors are able to walk again.[6]

## Spasticity

Spasticity is traditionally defined as 'a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neurone syndrome.[7] A recent definition, which is broader and perhaps more clinically relevant, is 'disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles'.[8] However, put simply, spasticity is involuntary overactivity of muscles as a result of damage to the brain or spinal cord.

Spasticity may cause reduced function, pain and deformity, and in the longer term may lead to the development of contracture.[9] Patients with upper limb spasticity can develop abnormal limb posturing such as the classic adducted internally rotated shoulder, flexed elbow, flexed wrist and clenched fist[10] (*Figure 1*). These positions can make washing of the axilla, elbow crease and hand difficult, leading to hygiene problems, which in turn can lead to skin breakdown, infections and pressure sores.[10] Dressing can also be a challenge. Activities such as opening the hand for washing and putting an arm down a sleeve may need the assistance of a carer or the unaffected limb if the patient cannot carry out the task voluntarily with the affected limb. Tasks completed by another person or the unaffected limb are commonly described as 'passive' functional tasks.[11]

Although the relationship between spasticity and motor performance remains unclear,[12,13] upper limb spasticity is thought to lead to reduced 'active' function as overactive muscles around the shoulder and elbow limit reaching activities and spastic finger flexors impair potential finger extension.[10]

Upper limb spasticity after stroke is readily recognised clinically, but studies of the prevalence of the condition are lacking. The largest prospective cohort study to date ($n = 106$) found that 31% of patients had upper limb spasticity at 12 months.[15] A further study ($n = 95$) found that 20% of stroke patients had upper limb spasticity 5 days after stroke and 18% had upper limb spasticity at 3 months.[16] Despite the lack of prevalence or prospective cohort studies, upper limb spasticity after stroke is an important clinical issue and identification and treatment of spasticity is a key component of stroke rehabilitation.[17]


***FIGURE 1*** *Examples of severe upper limb spasticity. From Brashear and Mayer entitled* 'Spasticity and other forms of muscle overactivity in the upper motor neuron syndrome'.[14] *Reproduced with permission from WeMove; New York, NY: 2009.*

Because of the complex multifaceted definition, measurement of spasticity is a challenge and no tool covers all aspects of the definition.[18] Clinicians and researchers often measure resistance to passive movement (muscle tone) using a clinical assessment scale, e.g. the Modified Ashworth Scale.[19] Resistance to passive movement (muscle tone) in addition to measuring some components of spasticity such as hyperactive tonic stretch reflexes also measures muscle biomechanical/viscoelastic changes.[20] Biomechanical measures have been developed to measure resistance to passive movement[21] and the stretch reflex can be quantified using neurophysiological techniques,[22] but neither have been widely used in clinical practice or trials.

## Botulinum toxin

Botulinum toxins are proteins produced by the bacterial species *Clostridium botulinum*. Seven serotypes of toxin, labelled A–G, are produced from different strains of *C. botulinum*.[23,24] All serotypes of toxin can cause botulism, which is a life-threatening condition involving symmetrical flaccid paralysis, autonomic dysfunction and respiratory compromise.[25]

The clinical syndrome of botulism was first accurately described in 1820 when Justinus Kerner published his observations of 'sausage poisoning'.[26] Kerner correctly hypothesised that the syndrome was caused by a biological poison that interrupted nerve conduction. Although he was unable to isolate the toxin, he did suggest that it may be possible to use it therapeutically.[26]

Botulinum toxins act by blocking the release of acetylcholine from cholinergic nerves leading to blockage of transmission at the neuromuscular junction and paralysis, and blockage of cholinergic autonomic nerves with resulting autonomic disturbance.[27] When given by intramuscular injection, botulinum toxin causes local and temporary paresis. It has been suggested that botulinum toxin may also block transmission of sensory neurotransmitters providing an analgesic effect independent of muscle relaxation.[27–29] The effects of botulinum toxins are not permanent. Each serotype has a different length of activity with that of botulinum toxin type A being the longest – lasting for 3–4 months.[30]

Botulinum toxin was first used clinically in 1977 when it was given by local injection to treat a patient with squint due to overactive ocular

muscles.[31] Since then, botulinum toxin has been used to treat various conditions including dystonia, tremor, spasticity, achalasia, migraine, incontinence and sweating. Three preparations of botulinum toxin type A [Dysport® (Ipsen Ltd), Botox® (Allergan Inc.) and Xeomin® (MerzPharmaceuticals)] and one preparation of botulinum toxin type B [Neurobloc® (Eisai Ltd)] are currently available in the UK.[32] Only Dysport and Botox currently have a licence for treating spasticity. The potency of each product is different and doses are not interchangeable.[32,33]

Adverse effects following injection with botulinum toxin are generally mild and transient.[9,34] Local reactions such as erythema, rash and oedema have been reported at the injection site. Migration of toxin into adjacent tissues can lead to weakening of surrounding muscles and autonomic effects; for example, injections into the neck can result in dysphagia and dry mouth. Systemic effects such as fatigue, malaise and flu-like symptoms are reported and systemic transport of toxin to tissues distant to those injected can also occur. Systemic transport of toxin has given cases of botulism-like illness[35] or cases of muscle weakness distant from the injection site,[32] but these events are very rare.

## Review of the evidence for treating upper limb spasticity due to stroke with botulinum toxin

Sixteen randomised controlled trials (RCTs)[36–51] and five systematic reviews[52–56] evaluating the clinical effectiveness of botulinum toxin as a treatment for upper limb spasticity after stroke have been published. Eight trials[44–51] and four systematic reviews[53–56] were published following the start of this study in 2005. Details of our literature search strategy, methodological appraisal of the papers, overview of the studies, and a summary of the systematic reviews can be found in Appendix 1.

Trials have reported that treating upper limb spasticity due to stroke with botulinum toxin results in a measurable reduction in resistance to passive movement (muscle tone), which is evident by 1–2 weeks post-treatment. The treatment effect usually lasts for 3–4 months. Although trials varied in the dose and type of botulinum toxin used, the magnitude of initial change in muscle tone/spasticity was approximately a one-point decrease on the Modified Ashworth Scale, which reflects a clinically significant improvement.[36,38–42,44–46,48,49,51]

The main benefits of spasticity reduction appear to be in terms of improved global patient/physician ratings[36,38,41,42,44,51] and itemised passive functional tasks, notably hand hygiene.[37,40,42] Only one trial reported an improvement in active upper limb function.[45]

Botulinum toxin has also been shown to reduce shoulder pain associated with spasticity,[46,47] but its role in preventing or treating other types of upper limb pain associated with spasticity is unclear. Only one trial found that upper limb pain was reduced in those who received botulinum toxin compared with those in the control group.[45] Trials reported no unexpected adverse events, however, the event reporting system was often unclear. No trial considered the cost-effectiveness of treatment.

As the treatment effect of botulinum toxin lasts for 3–4 months, injections may need to be repeated to offer sustained benefit. There is limited evidence to support the continued use of repeated botulinum toxin injections for spasticity reduction. Two RCTs considered the impact of repeat injections demonstrating a decrease in resistance to passive movement following a second injection.[44,51] One of the trials also demonstrated sustained improvement in global ratings and patient-selected goals.[51] Six uncontrolled studies have examined the effects of repeated injections.[57–62] These studies are summarised in Appendix 1, *Table 36*. Repeat injections decreased muscle tone by a similar amount after each injection and improved passive functional scores by a similar amount to the initial injection.[58–60,62] Two studies measured active function[58,61] and one found improvement.[61]

## Botulinum toxin and upper limb rehabilitation

The use of botulinum toxin to treat spasticity forms only one part of upper limb rehabilitation following stroke. Guidelines for the use of botulinum toxin in the treatment of spasticity recommend that it should be used in combination with a rehabilitation programme to achieve optimal beneficial effect.[9,17,63] It is recommended that the rehabilitation programme should consist of 2–8 weeks of physical and/or occupational therapy.[17]

## Limitations of previous studies

Previous trials varied in methodological quality, size, type of patients included, muscles treated with

botulinum toxin, dose of botulinum toxin delivered and outcome measures used. It was often unclear how randomisation was undertaken, whether blinding was robust and follow-up complete. A number of trials developed outcome measures specifically for their studies which were not assessed for validity or reliability and which focused on passive benefits rather than active function. Participants were significantly younger (average age 52–66 years) than typical stroke patients (the average age of incident stroke is 74 years[64]). Studies were mostly undertaken in specialist rehabilitation centres and were small, lacking statistical power.

Studies published to date have not attempted to standardise upper limb therapy and the amount and content of the therapy received was usually poorly described. It was also often unclear what concurrent medication or additional antispasticity treatments patients received.

## Justification for the current study

Botulinum toxin is increasingly used to treat upper limb spasticity due to stroke. Although botulinum toxin does reduce muscle tone and facilitates activities such as hand hygiene and dressing, the impact of this treatment upon upper limb active function is unclear. In clinical practice, botulinum toxin injections may be repeated every 3–4 months, but the effectiveness of repeat injections has not been adequately studied. It is also important that botulinum toxin is evaluated as part of a rehabilitation programme which is clearly described. In addition, cost-effectiveness of treatment is not fully established.

Multidisciplinary care on a stroke unit is currently the gold standard for stroke care regardless of age or stroke severity.[65] Evaluations of botulinum toxin should recruit participants from stroke services rather than tertiary referral centres to avoid selection bias and ensure results are applicable to routine care.

The Botulinum Toxin for the Upper Limb after Stroke (BoTULS) trial was designed to evaluate the clinical effectiveness and cost-effectiveness of botulinum toxin type A plus an upper limb therapy programme for the treatment of post-stroke upper limb spasticity.

# Chapter 2
# Methods

## Study design

The BoTULS trial was a multicentre open-label parallel-group RCT comparing the clinical effectiveness and cost-effectiveness of botulinum toxin type A plus an upper limb therapy programme with the upper limb therapy programme alone for the treatment of upper limb spasticity due to stroke in adults.

## Primary objective

1. To compare the upper limb function of participants with spasticity due to stroke who receive botulinum toxin type A injection(s) to the upper arm and/or forearm flexors/hand/shoulder girdle plus a 4-week evidence-based upper limb therapy programme (intervention group) with participants who receive the upper limb therapy programme alone (control group) 1 month after study entry. Upper limb function was assessed using the Action Research Arm Test (ARAT).[66]

## Secondary objectives

1. To compare the upper limb function, impairment and activity limitation of participants with spasticity due to stroke who receive botulinum toxin type A injection(s) to the upper arm and/or forearm flexors/hand/shoulder girdle plus a 4-week evidence-based upper limb therapy programme (intervention group) with participants who receive the upper limb therapy programme (control group) 1, 3 and 12 months after study entry. Upper limb function, impairment and activity limitation was assessed by: ARAT,[66] Nine-Hole Peg Test,[67] basic upper limb functional activity questions used in previous upper limb spasticity studies,[37,39,41] Modified Ashworth Scale,[19] Motricity Index,[68] grip strength[69] and Barthel Activities of Daily Living (ADL) Index.[70]
2. To compare attainment of participant-selected upper limb goals, upper limb pain, and stroke-related quality of life/participation restriction between intervention and control groups at 1, 3 and 12 months. The following measures were used: attainment of participant-selected upper limb goals (1 month only) – Canadian Occupational Performance Measure (COPM);[71] upper limb pain – numerical rating scales;[72] stroke-related quality of life/participation restriction – Stroke Impact Scale,[73] European Quality of Life-5 Dimensions (EQ-5D) measure of health-related quality of life[74] and Oxford Handicap Scale.[75]
3. To seek the experience and views of participants about treatment.
4. To compare the health-care and social services resources used by control and intervention groups during 3 months following study entry.
5. To report adverse events and compare the use of other antispasticity treatments between intervention and control groups.
6. To investigate the influence of severity of initial upper limb function and time since stroke upon the efficacy of the intervention.

## Summary of design of randomised controlled trial

*Figure 2* summarises the study method.

A list of all case record forms used in the study is shown in Appendix 2.

## Setting

The study involved a collaborative network of 12 stroke services in the north of England. Expertise in the management of spasticity and use of botulinum toxin was provided by the regional spasticity clinic based at the International Centre for Neurorehabilitation, Newcastle upon Tyne, UK. This model, i.e. stroke units with close links to a specialist spasticity service, enabled stroke patients to access specialist care (both in terms of stroke and spasticity management) and could be replicated in other settings.

## Case ascertainment

Potential participants were identified from a number of sources in each study centre which were components of locally organised stroke

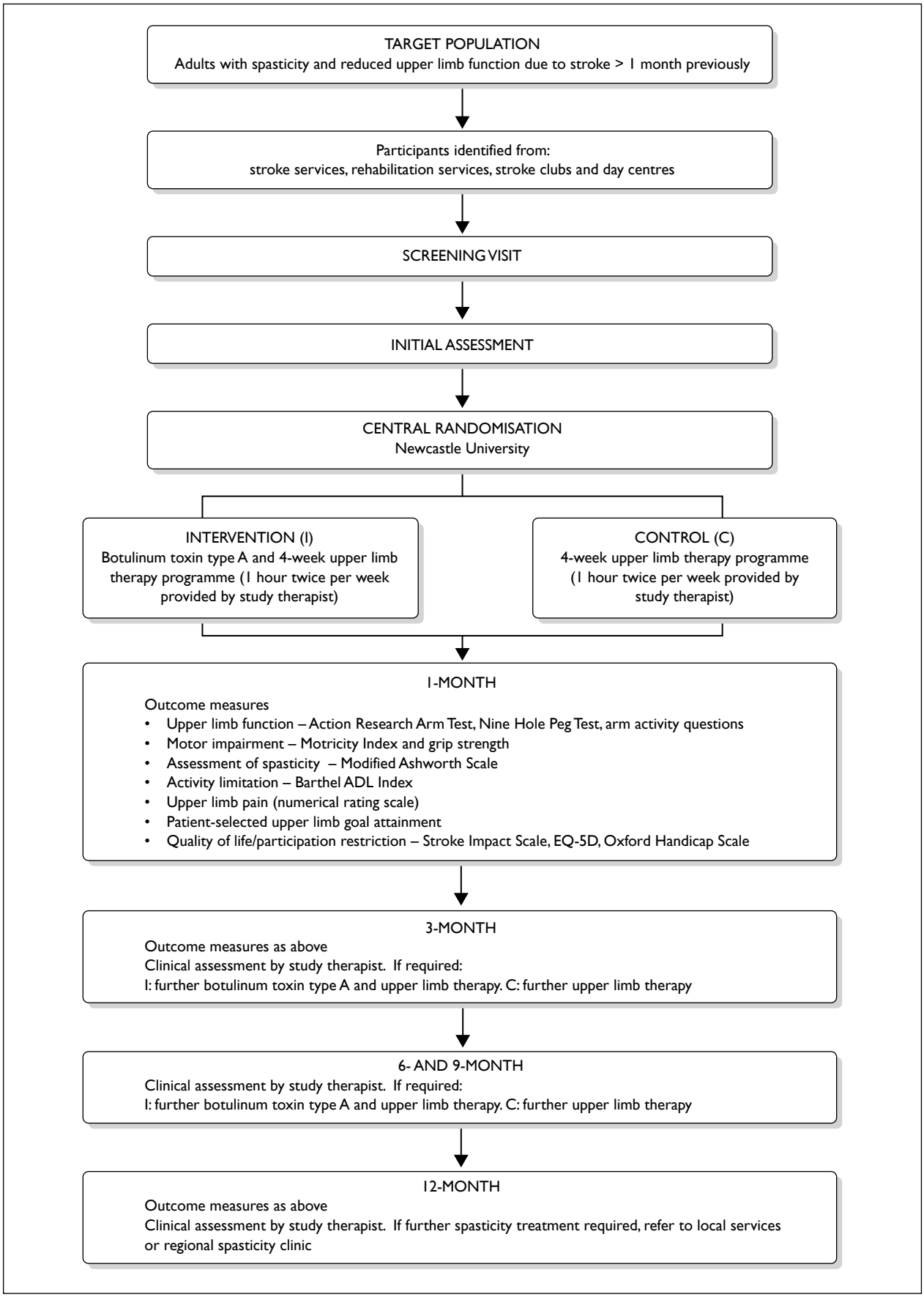


***FIGURE 2*** *Study method.*

services (stroke unit, outpatients, day hospital and community rehabilitation teams). They were given an information leaflet and had an opportunity to discuss the study with a member of the clinical team. Training was given to clinical teams about the project and research governance. A member of the research team then arranged to see the participant to discuss the study. Consent was sought at the screening visit.

Some potential participants were not in contact with rehabilitation or stroke services. Local community stroke clubs and day centres were given information about the study and individuals were able contact a member of the study team directly.

## Inclusion criteria

Adults with a stroke more than 1 month previously who had moderate/severe spasticity and reduced upper limb function who fulfilled all of following criteria were eligible:

- age over 18 years
- at least 1 month since stroke
- upper limb spasticity [Modified Ashworth Scale[19] > 2 at the elbow and/or spasticity at the hand, wrist or shoulder (there is no validated measure of spasticity at these sites)]
- reduced upper limb function (ARAT[66] score 0–56)
- able to comply with the requirements of the protocol and upper limb therapy programme
- informed consent given by participant or legal representative.

## Exclusion criteria

- Significant speech or cognitive impairment which impeded ability to perform the ARAT[66] assessment.
- Other significant upper limb impairment, e.g. fracture or frozen shoulder within 6 months, severe arthritis, amputation.
- Evidence of fixed contracture.
- Pregnancy or lactating.
- Female at risk of pregnancy and not willing to take adequate precautions against pregnancy for the duration of the study.
- Other diagnosis likely to interfere with rehabilitation or outcome assessments, e.g. registered blind, malignancy.
- Other diagnosis which may contribute to upper limb spasticity, e.g. multiple sclerosis, cerebral palsy.
- Contraindications to intramuscular injection.
- Religious objections to blood products [botulinum toxin type A (Dysport) contains human albumin].
- Contraindications to botulinum toxin type A, which include bleeding disorders, myasthenia gravis and concurrent use of aminoglycosides.
- Use of botulinum toxin to the upper limb in the previous 3 months.
- Known allergy or hypersensitivity to any of the test compounds.
- Previous enrolment in this study.

## Screening assessment

Having sought consent, the screening assessment was completed by a study therapist or clinical research associate. The assessment consisted of demographic details, review of medical history and medication, handedness, Abbreviated Mental Test Score,[76] Sheffield Aphasia Screening Test,[77] prestroke limitations (Oxford Handicap Scale),[75] time since stroke, stroke type and subtype,[78] self-reported current neurological impairment and activity limitation (Barthel ADL Index[70]), quality of life (EQ-5D[74]), assessment of spasticity (Modified Ashworth Scale[19]) and measurement of upper limb function (ARAT[66]). Details of antispasticity treatment and concomitant medications were recorded.

## Baseline assessment

The baseline visit was undertaken within 2 weeks of the screening visit by a study therapist or clinical research associate. The inclusion/exclusion criteria were reviewed to ensure that the participant was still eligible. Participants underwent a clinical assessment and were asked to complete the following assessments: Modified Ashworth Scale,[19] Motricity Index,[68] grip strength,[69] ARAT,[66] Nine-Hole Peg Test,[67] upper limb functional activity questions,[37,39,41] Stroke Impact Scale[73] and upper limb pain.[72] Female participants with child-bearing potential (i.e. those who were not either surgically sterile or at least 1 year post last menstrual period) had to have a negative urine pregnancy test to be included in the study. Such participants agreed to use adequate contraception throughout the study if they were randomised to receive botulinum toxin

type A. Participants were randomised once the baseline assessment was completed.

## Randomisation

Randomisation was by a central independent web-based randomisation service from the Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK. Participants were stratified according to research site and level of upper limb function (ARAT 0–3, ARAT 4–28, ARAT 29–56), and randomised to intervention or control in a 1 : 1 ratio using permuted block sequences.

## Botulinum toxin

Participants in the intervention group received botulinum toxin type A (Dysport). Dysport is available as a white lyophilised powder for reconstitution containing 500 units of *C. botulinum* type A toxin–haemagglutinin complex together with 125 $\mu$g of a 20% albumin solution and 2.5 mg lactose in a clear glass vial.

The range of muscles and dosages injected were as described in 'The management of adults with spasticity using botulinum toxin: a guide to clinical practice'.[9] The maximum dose of botulinum toxin type A (Dysport) that could be administered at any one time point was 1000 units. All injectors were clinicians trained in the assessment and injection of botulinum toxin in the context of upper limb spasticity.

The use of aminoglycosides was prohibited during the study because they enhance the effects of botulinum toxin, thereby increasing the risk of toxicity. Clinicians were advised to use muscle relaxants with caution because the effects of botulinum toxin are enhanced by non-depolarising muscle relaxants. The international normalised ratio of participants taking warfarin was checked before injection. Information about concomitant drug use was given in the patient information sheet and in letters to consultants and general practitioners.

If further treatment was necessary at 3, 6 or 9 months, further injections were provided to those in the intervention group. At each visit a letter was sent to the participant's stroke physician, general practitioner and physiotherapist. At the 12-month review, participants in both the intervention and control groups who required botulinum toxin were referred to the spasticity clinic.

If during the course of the trial the study therapist decided that a participant in the control group had an unacceptable degree of symptomatic spasticity, further management was discussed with the stroke physician, physiotherapist, occupational therapist and/or a member of the local or regional spasticity team and the participant could then be referred to a local spasticity service for botulinum toxin.

## The upper limb rehabilitation programme

Guidelines highlight that it is important that botulinum toxin is not used in isolation but as part of a comprehensive rehabilitation programme.[9,17,63,79,80] Focal reductions in upper limb spasticity from any pharmacological intervention are unlikely to translate into sustained improvements in function or patient-selected rehabilitation goals without a targeted therapy programme.

The upper limb therapy programme was based upon available research evidence from the stroke rehabilitation and skill acquisition literature as well as clinical practice[80–98] and consisted of two menus. Participants with ARAT 0–3 received menu 1, which was designed specifically for participants with no active upper limb function. Menu 1 aimed at improving and maintaining range of movement, encouraging active assisted upper limb movement in the context of functional activities, along with hand hygiene and positioning[88–93]. Menu 2 was for participants with some retained active upper limb movement (ARAT 4–56) and was piloted in a previous study.[99] Following stretching of soft tissues affected by spasticity, this menu specifically concentrated on task-orientated practise aimed at patient-centred goals. Upper limb goals were measured by the COPM.[71] Each menu standardised the category of tasks, the number and order of repetitions as well as the amount of feedback for each session, but within these parameters the therapist was able to tailor the specifics of each activity to the ability of the patient. Manuals and training programmes were developed for both upper limb therapy menus and all therapists were trained in the delivery of the programme.

The upper limb therapy programme was provided by study therapists and each participant received

1 hour per day, twice a week for 4 weeks, in addition to their other rehabilitation needs. The study therapist could transfer participants between menu 1 and menu 2 according to their clinical opinion. Participants were given a written exercise programme, which was based on the content of the face-to-face sessions with the therapist, to carry out by themselves or with a carer (following training) on the weekdays on which they were not attending therapy.

If the participant was already receiving rehabilitation, then the upper limb therapy programme was delivered in that setting, e.g. stroke unit, outpatients, day hospital or home. In each case, the study therapist liaised closely with the rehabilitation team to ensure the participant's needs were addressed and therapy was well co-ordinated. At the end of the 4-week intervention period participants were given advice by the study therapist regarding maintenance of upper limb function.

Participants were reviewed by the research team every 3 months. If further therapy was required, this was provided by a study therapist. Those in the intervention group could also receive further botulinum toxin type A injections. Participants in both the intervention and control groups who had symptomatic spasticity at the 12-month follow-up appointment were referred to the spasticity clinic.

Participants who made a good recovery before completing the 4-week upper limb therapy programme could be discharged from the programme provided that they had achieved a maximum score on the ARAT[66] and achieved their upper limb goals.

## Outcome assessments

Outcomes were measured 1 month (+/– 3 days), 3 months (+/– 5 days) and 12 months (+/– 5 days) after study randomisation.

Each outcome assessment consisted of two stages – stage 1 outcome assessment was a self completion postal questionnaire (Barthel ADL Index,[70] Oxford Handicap Scale,[75] Stroke Impact Scale,[73] EQ-5D,[74] upper limb functional activity questions[37,39,41] and resource utilisation) which was sent to participants 1 week before stage 2. Participants were asked to bring the completed proforma to their stage 2 appointment.

Stage 2 outcome assessments consisted of assessment of upper limb impairment and function (Modified Ashworth Scale,[19] Motricity Index,[68] grip strength,[69] ARAT,[66] Nine-Hole Peg Test[67] and upper limb pain[72]) and face-to-face interview seeking participant's experience and views of the study treatment. Information was sought about side effects, use of other antispasticity treatment and any change in the participant's concomitant medications. Any new adverse events or changes in existing adverse events that had occurred since the previous visit were sought. The stage 1 questionnaire was checked for completeness. The stage 2 assessment was completed by a study therapist or clinical research associate.

## Blinding

Outcome assessments were undertaken by an assessor who was blinded to the randomisation group. Participants and the study therapists who provided the upper limb therapy programme were not blind to the randomisation group. To enable blinding to be achieved, study therapists undertook screening and baseline assessments and provided the upper limb therapy programme in one research centre and undertook outcome assessments in adjacent centres. As it was possible for assessors to become unblinded, at each outcome assessment an evaluation of blinding was performed.

## Participant withdrawal criteria

No specific withdrawal criteria were defined for the study. If a participant discontinued the study prematurely (i.e. before completion of the protocol), the primary reason for discontinuation was recorded when given. In all cases the investigator ensured that the participant received medical follow-up as necessary. Withdrawn participants were not replaced.

## Study completion/early termination visit

Study completion was the last outcome visit. If a participant discontinued from the study prematurely, every effort was made to perform an early termination visit consisting of all outcome assessments. At the participant's last study visit details of their completion of the study/withdrawal

from the study were recorded. Female participants of child-bearing potential (i.e. those who were not either surgically sterile or at least 1 year post last menstrual period) in the intervention group were asked to undertake a urine pregnancy test.

## Safety evaluation

Side effects of botulinum toxin type A are generally mild and transient. Local muscle weakness may occur as a result of toxin spread to nearby muscles. Five per cent experience flu-like symptoms 1 week to 10 days after injection. Pain at the injection site and a dry mouth can occur. Transient dysphagia has been reported. Anaphylaxis rarely occurs. Excessive doses may produce distant and profound neuromuscular paralysis. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles.

The safety of botulinum toxin type A in the treatment of participants with upper limb spasticity post stroke was evaluated by examining the occurrence of all adverse and serious adverse events as defined by the *Medicines for Human Use (Clinical Trials) Regulations*, 2004.[100] Follow-up of each adverse event continued until the event or its sequelae resolved or stabilised at a level that was acceptable to the investigator.

## Study schedule

*Table 1* summarises the study schedule.

## Resource utilisation and economic evaluation

This is discussed in Chapter 4.

## Data completeness

Data quality checks were performed regularly throughout the study. Missing data and data queries were discussed with the local site teams and collected/resolved as possible.

## Statistical analysis

Analyses were undertaken on an 'intention-to-treat' basis; participants were analysed in the group to which they were randomised. Data were exported from the study MICROSOFT ACCESS database to SPSS for analysis. All available data were analysed, missing data were not imputed.

The primary end point was the ARAT score at 1 month. For each participant it was determined if there had been a significant improvement in function based on the change in ARAT score from baseline. It is suggested that the minimal clinically important difference for the ARAT is 10% of its range (six points);[101] however, we estimated that a smaller treatment effect would be clinically beneficial in those with poor initial upper limb function (ARAT 0–3) compared with those with some retained active function (ARAT 4–56).

***TABLE 1*** *Study schedule*

| Time point | Screening <2 weeks | Baseline | Visit 3 Month 1[a] | Visit 4 Month 3[b] | Visit 5 Month 6 | Visit 6 Month 9 | Visit 7 Month 12[b] |
|---|---|---|---|---|---|---|---|
| Informed consent | × | | | | | | |
| Record demographics and handedness | × | | | | | | |
| Review inclusion/ exclusion criteria | × | × | | | | | |
| Review medical history | × | × | | | | | |
| Details of stroke | × | | | | | | |
| Prestroke limitation (inc. Oxford Handicap Scale) | × | | | | | | |
| Abbreviated Mental Test Score | × | | | | | | |
| Sheffield Aphasia Screening Test | × | | | | | | |

***TABLE 1*** *Study schedule (continued)*

| Time point | Screening <2 weeks | Baseline | Visit 3 Month 1[a] | Visit 4 Month 3[b] | Visit 5 Month 6 | Visit 6 Month 9 | Visit 7 Month 12[b] |
|---|---|---|---|---|---|---|---|
| Action Research Arm Test | × | × | × | × | | | × |
| Motricity Index | | × | × | × | | | × |
| Grip strength | | × | × | × | | | × |
| Nine-Hole Peg Test | | × | × | × | | | × |
| Modified Ashworth Scale | × | × | × | × | | | × |
| Upper limb pain | | × | × | × | | | × |
| Patient selects upper limb goals | | × | | | | | |
| Review upper limb goal attainment | | | × | | | | |
| Oxford Handicap Scale[c] | × | | ×[c] | ×[c] | | | ×[c] |
| Barthel ADL Index[c] | × | | ×[c] | ×[c] | | | ×[c] |
| Upper limb functional activity questions[c] | × | | ×[c] | ×[c] | | | ×[c] |
| Quality of life – Stroke Impact Scale[c] | × | | ×[c] | ×[c] | | | ×[c] |
| Quality of life – EQ-5D[c] | × | | ×[c] | ×[c] | | | ×[c] |
| Resource utilisation questions[c] | × | | ×[c] | ×[c] | | | ×[c] |
| Pregnancy test[d] | | × | | ×[f] | ×[f] | ×[f] | |
| Randomisation | | × | | | | | |
| Treatment with Dysport[e] | | × | | ×[g] | ×[g] | ×[g] | |
| Commencement of 4-week upper limb therapy programme | | × | | ×[g] | ×[g] | ×[g] | |
| Clinical assessment by study therapist | | × | | × | × | × | × |
| Concomitant medications (inc. antispasticity treatment) | × | × | × | × | | | × |
| Adverse events | | × | × | × | | | × |
| Participants' views and experience | | | × | | | | × |

a Visit window is ± 3 days.
b Visit window is ± 5 days.
c Questionnaires will be sent to the participant for completion 1 week before the visit. Participants will bring completed forms to the visit.
d For female participants at risk of pregnancy.
e Participants in the intervention group only.
f Pregnancy test to be performed before any additional botulinum toxin injections.
g Additional botulinum toxin injections/upper limb therapy to be provided if clinically appropriate.

A successful outcome was defined as:

- a change of three or more points on the ARAT scale for a participant whose baseline ARAT score was between 0 and 3
- a change of six or more points on the ARAT scale for a participant whose baseline ARAT score was between 4 and 51
- a final ARAT score of 57 for a participant whose baseline ARAT score was 52–56.

The proportion of 'successes' in each group was compared using Fisher's exact test and an interval estimate of the effect of the intervention in the form of an approximate 95% confidence interval (95% CI) for the relative risk was calculated.

Secondary outcomes providing binary data were compared using Fisher's exact test (or chi-squared test if unable to compute exact form). Secondary outcomes providing ordinal or continuous data were compared using the Mann–Whitney *U*-test (exact form where possible). Two-tailed *p*-values are reported. All secondary outcomes were analysed using scale score at follow-up and change in scale score from baseline to follow-up. Change in score was believed to be the key analysis and is presented in the Results section. Scale score at follow-up is presented in Appendix 3.

Although the Mann–Whitney *U*-test gives an indication of statistical significance it does not provide any information about the magnitude of difference between the groups or whether the difference is clinically important. For some outcomes, the presentation of median values was not helpful in determining clinical importance because of the presence of skewness (changes in the tail of the distribution may not result in any change in the median score). To address this we used resampling methods (bootstrapping) to generate an interval estimate of the effect of the intervention on the group means for each outcome (changes in the tails of the distribution will affect the mean score). The 2.5 and 97.5 percentiles of the bootstrap distribution based on 10,000 replications are reported. This analysis was not prespecified in the study protocol because it was not anticipated to be necessary before viewing the results of planned non-parametric tests.

To enable comparison with previous studies, the basic upper limb functional activity questions were also analysed by comparing the proportion of participants in each randomisation group who had improved by one or more points on the scale from baseline.

As a secondary analysis, logistic regression modelling was used to estimate the effect of the intervention on the primary outcome (ARAT 'success') adjusting for randomisation strata (research site and baseline upper limb function).

There were two prespecified subgroup analyses. Response to treatment was compared for:

- participants who had a stroke ≤ 1 year ago and those who had a stroke > 1 year ago
- participants with no initial active upper limb function (with a baseline ARAT score of 0–3) and participants with some initial upper limb function (baseline ARAT 4–56).

Subgroup analysis of the primary outcome was undertaken using logistic regression procedures by adding a subgroup by treatment interaction term to a model that already included the main effects. For secondary outcomes, subgroup analysis was only undertaken where the difference between treatment groups in the main analysis had been statistically significant. For these secondary outcomes, resampling procedures were used to estimate the difference between the treatment effects in the two subgroups.

A power calculation was performed before the start of the study using prognosis based methodology.[102] A clinically important treatment effect was defined as a difference in good outcomes between intervention and control groups of 15% where a good outcome was defined as listed above for each ARAT group; it was expected to see 20% of the control group achieve good outcomes and 35% of the intervention group achieve good outcomes. Using Fleiss's method for a binary outcome[103] and inflating the sample size by 10% to allow for attrition, we needed to recruit a total sample of 332 participants to give 80% power to detect a 15% difference in good outcomes assuming a two-tailed test and a significance level of 5%. The study aimed to recruit 50% of the sample from the ARAT 0–3 group and 50% from the ARAT 4–56 group.

## Ethical arrangements and research governance

Multicentre Research Ethics Committee approval was granted. For each individual centre, a site-specific approval was obtained from the appropriate local research ethics committee. Research and development approval was obtained from each participating Trust. The trial was commenced subsequent to the UK *Medicines for Human Use (Clinical Trials) Regulations*, 2004[100] and was one of the first investigator-led trials of an investigational medical product to be undertaken in the UK following the introduction of this legislation. Regulatory approval was granted by the Medicines and Healthcare Products Regulatory Agency and the trial was conducted in accordance with the legislation, the International Conference

on Harmonisation–Good Clinical Practice (ICH-GCP),[104] and the *Research Governance Framework for Health and Social Care*.[105]

A Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) following Medical Research Council guidelines were established.[106] The TSC comprised an independent chairperson, two independent researchers (all of whom had expertise in rehabilitation research and clinical trials), a consumer representative and three members of the study team.

The DMEC was chaired by a clinical academic with expertise in RCTs of complex interventions in the field of stroke. A biostatistician with expertise in multicentre trials, a researcher experienced in running rehabilitation trials and the study statistician were also members.

An informal interim analysis was performed at the request of the DMEC following recruitment of 50% of the required sample size. Only the DMEC had access to these data. They were able to recommend discontinuation of the study if significant ethical or safety concerns arose, or if there was clear evidence of benefit (clinical or statistical).

The study was monitored for compliance with ICH-GCP by an independent monitor from the Newcastle Clinical Trials Unit.

## Amendments to the study following commencement

### Objectives

The initial study protocol included measurement of spasticity at the elbow by a biomechanical device that had been used in a previous pilot study.[107] This was to be used in addition to clinical measures. Unfortunately, the device was not at a stage of development where it could be used in a multicentre study.

### Setting

Initially the trial was planned in four geographical areas within the UK: North Tyneside, Wansbeck, Newcastle upon Tyne and Sunderland. As a result of low recruitment rates, eight further areas were added (Gateshead, South Tyneside, Durham, Hexham, Carlisle, Bishop Auckland, Hartlepool, North Tees).

### Case ascertainment

This was widened to include identification of participants from stroke clubs and day centres (in addition to clinical settings) because of initial low recruitment rates.

### Inclusion criteria

Prospective studies of upper limb recovery have shown that baseline impairment is a strong predictor of outcome. To demonstrate whether botulinum toxin plus upper limb therapy can improve upper limb function (primary outcome) it was initially thought important to exclude those participants with no retained upper limb function (ARAT 0–3). Because of the initial low recruitment and following reconsideration of the evidence of effectiveness of botulinum toxin in this group, this was later reviewed and a decision was taken in conjunction with the TSC and the Health Technology Assessment programme that it would be valuable to include stroke patients with all levels of reduced upper limb function (ARAT 0–56).

The study also initially excluded participants with cognitive impairment or significant speech problems measured by the Abbreviated Mental Test Score and Sheffield Aphasia Screening Test. This was felt to be too restrictive, excluding patients who were keen to participate. This inclusion criterion was relaxed to include all participants capable of performing the ARAT and complying with the upper limb therapy programme.

### Upper limb therapy programme

A second menu was developed for the upper limb therapy programme after the eligibility criteria were widened to include participants with no active upper limb function. This alternative menu was designed because the original menu contained activities that these participants would not have been able to undertake.

### Statistical analysis

Inclusion of participants with lower ARAT scores required revision of the primary analysis and power calculation. In the original protocol, the primary analysis was comparison of ARAT scores and 390 participants were required to provide 80% power to detect a difference of six points on the ARAT between intervention and control groups. However, participants with a baseline ARAT of 0–3 could not be expected to improve as much as those with a

baseline ARAT of 4–56. This led to the definition of successful treatment as improvement by three points on the ARAT for those with a starting ARAT of 0–3, six points by those with a starting ARAT of 4–51 and a final score of 57 for participants whose baseline ARAT was 52–56. Comparison of the proportions of successes between the groups (control/intervention) became the primary analysis. The power calculation was revised for the new binary outcome and 332 participants were required to provide 80% power to detect a 15% difference in treatment successes.

## Follow-up period

Participants recruited after 2 July 2007 were followed for 3 months only. This was a pragmatic decision taken because the trial was behind schedule as a result of initial low recruitment rates. Curtailing 12-month follow-up allowed the trial to be completed within the initial study timetable.

The initial study protocol specified comparison of health-care and social services resource usage between the randomisation groups for 12 months. Because of the curtailing of 12-month follow-up, it was felt more appropriate to compare health-care and social services resource usage over 3 months to include all study participants.

# Chapter 3
# Results

## Study recruitment

Between July 2005 and March 2008, 333 participants were recruited to the BoTULS trial. One hundred and seventy were randomised to the intervention group and 163 to the control group. Monthly and cumulative recruitment are shown in *Figure 3*.

Two hundred and eight (62%) participants were randomised before July 2007 and entered the trial for 12 month follow-up. The remaining 125 (38%) participants were followed for 3 months. Details of recruitment in each study site are given in Appendix 4.

## Study attrition

*Figure 4* shows participant flow through the trial. There were nine deaths during the study period and 12 participants withdrew. Reasons for attrition are described in *Table 2*.

One participant withdrew consent shortly after randomisation and asked for their data to be excluded from the analyses. Baseline data are therefore presented for 332 participants. The 1-month assessment was completed by 155/163 (95%) participants in the control group and 167/170 (98%) participants in the intervention group. The 3-month assessment was completed by 151/163 (93%) participants in the control group and 163/170 (96%) in the intervention group.

Of the 332 participants randomised into the study, 208 (63%) were enrolled for 12-month follow-up. The 12-month assessment was completed by 92/103 (89%) participants in the control group and 97/105 (92%) in the intervention group. Outcome data were missing at all time points for one study participant only.

## Study population

Randomisation groups were well matched at baseline with regard to demography, stroke characteristics and comorbidity (*Table 3*).

The median age of participants was 67 years [interquartile range (IQR) 59–74], 225 (67.8%) were male and the majority were living at home. One hundred and eighty-one participants (54.5%) were randomised within 1 year of stroke.

Randomisation groups were well matched for the distribution, severity and current treatment of upper limb spasticity (*Table 4*). The majority of participants had spasticity present throughout the upper limb and the median score on the Modified Ashworth Scale at the elbow was two. Previous treatment with botulinum toxin was not an exclusion criterion provided that it was given more than 3 months before study entry and potential participants were prepared to temporarily relinquish further upper limb injection(s) should they be randomised to the control group. Botulinum toxin treatment had been previously received by 27 (16.7%) of the control group compared with 21 (12.4%) of the intervention group. Randomisation groups were also well matched for other measures of upper limb impairment (*Table 4*).

One hundred and eighty-four participants (55.4%) had no active upper limb function (ARAT 0–3) and 148 (44.6%) had some retained active function (ARAT 4–56) at randomisation. The median initial ARAT in both intervention and control groups was three (*Table 5*). Most participants had no or poor dexterity and were unable to complete the Nine-Hole Peg Test. Participants experienced moderate difficulty with upper limb functional activities such as putting their arm through a sleeve or opening the hand to clean the palm and the majority were unable to use cutlery as a result of their stroke. The control group had a lower level of participation restriction when assessed using the Oxford Handicap Scale, but it is unlikely that this possible imbalance at baseline is clinically important or had an impact upon outcome assessments.

The median rating for pain was moderate in both groups. The median pain score was 5/10 in both the intervention and control groups (*Table 6*).

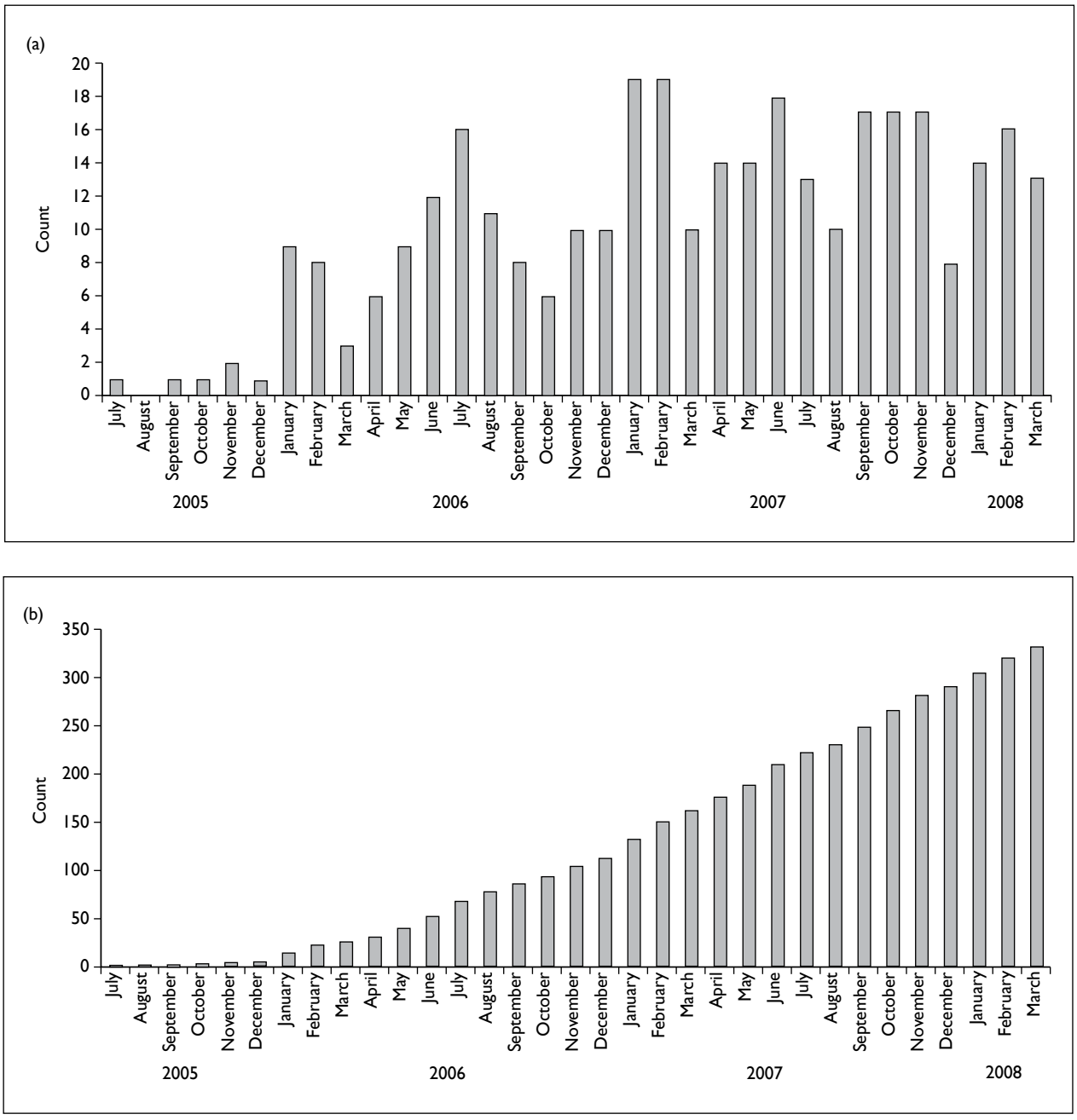


***FIGURE 3*** *BoTULS trial recruitment: (a) monthly recruitment, and (b) cumulative recruitment.*

# Primary outcome

Improved upper limb function (predefined treatment success on the ARAT) at 1 month was achieved by 30/154 (19.5%) participants in the control group and 42/167 (25.1%) in the intervention group. This difference was not significant ($p = 0.232$). The relative risk of having a 'successful treatment' in the intervention group compared with the control group was 1.3 (95% CI 0.9 to 2.0).

# Secondary outcomes

## Impairment

Changes in impairment from baseline to 1, 3 and 12 months are shown in *Tables 7a* and *7b*. At 1 month, muscle tone at the elbow (Modified Ashworth Scale) decreased in the intervention group compared with the control group; the median change from baseline to 1 month in the control group was zero; the median change in the intervention group was –1 ($p < 0.001$). The

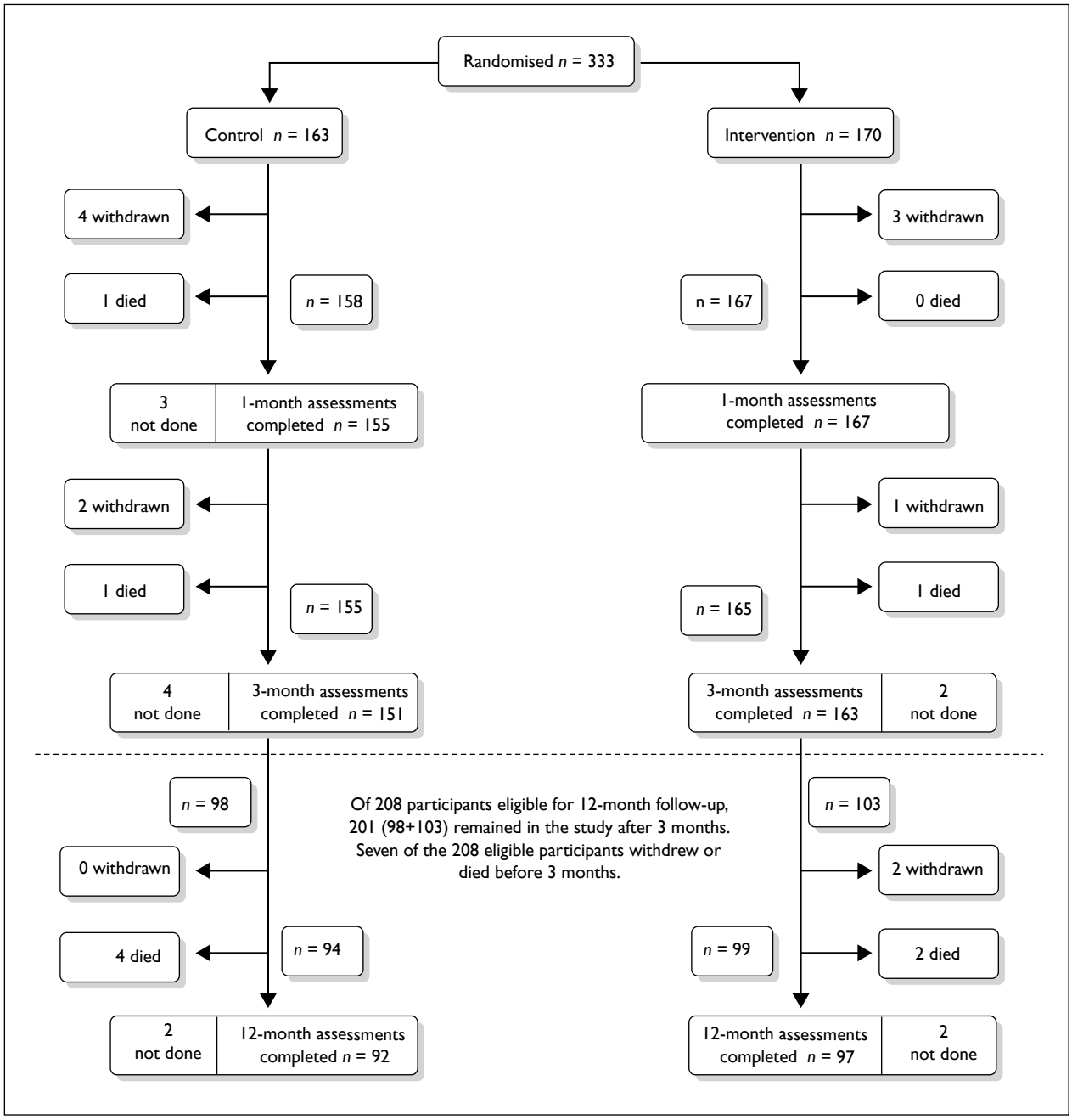


***FIGURE 4 BoTULS participant flow chart.***

corresponding differences in change in muscle tone between intervention and control groups seen at 3 and 12 months were not statistically significant.

The differences between the groups for change in upper limb motor impairment (Motricity Index) from baseline to 1 or 12 months were not significant. However, at 3 months the intervention group had improved by a median of four compared with a median of zero in the control group. This difference approached statistical significance when groups were compared using the Mann–Whitney $U$-test ($p = 0.055$). Examination of the difference between the mean change in the groups confirmed a similar magnitude of effect (3.5, 95% CI 0.1 to 6.8), which was statistically significant. Total motor impairment was also improved at 3 months in the intervention group compared with the control group ($p = 0.042$). There were no significant differences between intervention and control groups for change in grip strength at any assessment.

***TABLE 2*** *Reasons for study attrition*

| | Control (*n* and reasons) | Intervention (*n* and reasons) |
|---|---|---|
| ***Withdrawn*** | | |
| 0–1 month | 4; wanted injection; did not want to continue; wife unwell; no reason recorded | 3; did not want injection; unwell; in another trial |
| > 1–3 months | 2; wanted injection; thought no benefit | 1; unwell |
| > 3–12 months | 0 | 2; unwell; no reason recorded |
| ***Death*** | | |
| 0–1 month | 1; myocardial infarction | 0 |
| > 1–3 months | 1; pneumonia | 1; pneumonia |
| > 3–12 months | 4; pneumonia; further stroke; cancer; cause unknown | 2; pneumonia; further stroke |
| ***Assessment not done*** | | |
| 1 month | 3; unwell (*n* = 2);administrative error | 0 |
| 3 months | 4; unwell (*n* = 3); unable to contact | 2; unwell |
| 12 months | 2; assessment recorded as done but data missing | 2; unable to contact |

***TABLE 3*** *Demography, stroke characteristics and comorbidity*

| | Control (*n* = 162)[a] | Intervention (*n* = 170)[a] |
|---|---|---|
| ***Sex:* n *(%)*** | | |
| Male | 115 (71.0) | 110 (64.7) |
| Female | 47 (29.0) | 60 (35.3) |
| ***Age: median (IQR)*** | | |
| All | 66 (59.8 to 72.3) | 67 (58.8 to 74) |
| Male | 67 (61 to 73) | 68 (59 to 74) |
| Female | 64 (54 to 72) | 67 (56.3 to 74) |
| ***Current residence:* n *(%)*** | | |
| Own house | 133 (82.1) | 129 (75.9) |
| Living with family/friends | 0 (0.0) | 4 (2.4) |
| Sheltered | 3 (1.9) | 4 (2.4) |
| Residential care/nursing home | 7 (4.3) | 5 (2.9) |
| Hospital | 19 (11.7) | 28 (16.5) |
| ***Stroke type:* n *(%)*** | | |
| Infarct | 131 (81.9) | 140 (82.8) |
| Intracerebral haemorrhage | 21 (13.1) | 25 (14.8) |
| Subarachnoid haemorrhage | 3 (1.9) | 2 (1.2) |
| Unknown | 7 (4.3) | 3 (1.8) |
| ***Stroke subtype:* n *(%)*** | | |
| Total anterior circulation stroke | 68 (42.0) | 75 (44.1) |
| Partial anterior circulation stroke | 61 (37.7) | 57 (33.5) |

***TABLE 3*** *Demography, stroke characteristics and comorbidity (continued)*

| | **Control (*n* = 162)[a]** | **Intervention (*n* = 170)[a]** |
|---|---|---|
| Lacunar stroke | 26 (16.0) | 33 (19.4) |
| Posterior circulation stroke | 3 (1.9) | 2 (1.2) |
| Uncertain | 4 (2.5) | 3 (1.8) |
| ***Time from stroke to randomisation: median (IQR) days*** | 280 (148.8 to 1145.8) | 324 (128.5 to 1387.5) |
| ***Time from stroke to randomisation:* n *(%)*** | | |
| 1–6 months | 49 (30.2) | 60 (35.3) |
| > 6 months to 1 year | 43 (26.5) | 29 (17.1) |
| > 1–2 years | 19 (11.7) | 16 (9.4) |
| > 2–5 years | 29 (17.9) | 31 (18.2) |
| 5+ years | 22 (13.6) | 34 (20.0) |
| ***Comorbidity:* n *(%)*** | | |
| Previous stroke/transient ischaemic attack | 48 (29.6) (*n* = 162) | 49 (28.8) (*n* = 170) |
| Ischaemic heart disease | 36 (22.4) (*n* = 161) | 39 (23.1) (*n* = 169) |
| Peripheral arterial occlusive disease | 8 (5.0) (*n* = 160) | 6 (3.6) (*n* = 168) |
| Diabetes mellitus | 22 (13.6) (*n* = 162) | 22 (13.1) (*n* = 168) |
| Hypertension | 119 (73.5) (*n* = 162) | 124 (74.3) (*n* = 167) |
| Hyperlipidaemia | 103 (64.4) (*n* = 160) | 111 (65.7) (*n* = 169) |
| Atrial fibrillation | 21 (13.3) (*n* = 158) | 24 (14.5) (*n* = 166) |

a *n* values valid except where alternative *n* value is provided (under Comorbidity).

***TABLE 4*** *Baseline upper limb impairment, spasticity and antispasticity treatment*

| | **Control (*n* = 162)** | **Intervention (*n* = 170)** |
|---|---|---|
| ***Upper limb affected by spasticity:* n *(%)*** | | |
| Right | 65 (40.1) | 75 (44.1) |
| Left | 97 (59.9) | 95 (55.9) |
| ***Dominant hand affected:* n *(%)*** | | |
| Yes | 64 (39.5) | 80 (47.1) |
| No | 98 (60.5) | 90 (52.9) |
| ***Area affected by spasticity:* n *(%)*** | | |
| Shoulder | 95 (58.6) | 111 (65.3) |
| Elbow | 156 (96.3) | 161 (94.7) |
| Wrist | 141 (87.0) | 141 (82.9) |
| Hand | 140 (86.4) | 138 (81.2) |
| ***Distribution of spasticity:* n *(%)*** | | |
| Shoulder and elbow | 9 (5.6) | 15 (8.8) |
| Elbow and wrist | 8 (4.9) | 2 (1.2) |
| Wrist and hand | 5 (3.1) | 4 (2.4) |
| Shoulder and elbow and wrist | 1 (0.6) | 9 (5.3) |

*continued*

***TABLE 4*** *Baseline upper limb impairment, spasticity and antispasticity treatment (continued)*

| | **Control (*n* = 162)** | **Intervention (*n* = 170)** |
|---|---|---|
| Shoulder and elbow and hand | 4 (2.5) | 4 (2.4) |
| Elbow and wrist and hand | 47 (29.0) | 43 (25.3) |
| Shoulder and elbow and wrist and hand | 80 (49.4) | 81 (47.6) |
| Other | 8 (4.9) | 12 (7.1) |
| ***Antispasticity treatment:* n *(%)*** | | |
| Total | 67 (41.4) | 64 (37.6) |
| Dantrolene | 2 (1.2) | 3 (1.8) |
| Baclofen | 16 (9.9) | 20 (11.8) |
| Tizanidine | 0 (0.0) | 3 (1.8) |
| Gabapentin | 16 (9.9) | 14 (8.2) |
| Methocarbanol | 1 (0.6) | 0 (0.0) |
| Shoulder brace | 1 (0.6) | 0 (0.0) |
| Upper limb sling | 0 (0.0) | 2 (1.2) |
| Thumb strap | 1 (0.6) | 0 (0.0) |
| Elasticated glove | 1 (0.6) | 0 (0.0) |
| Functional electrical stimulation machine | 1 (0.6) | 1 (0.6) |
| Upper limb splint | 42 (25.9) | 36 (21.2) |
| ***Botulinum toxin treatment > 3 months before study entry:* n *(%)*** | | |
| Total | 27 (16.7) | 21[a] (12.4) |
| Arm | 12 (44.4) | 4 (19.0) |
| Leg | 7 (25.9) | 5 (23.8) |
| Both arm and leg | 8 (29.6) | 11 (52.4) |
| ***Modified Ashworth Scale at elbow:* n *(%)*** | | |
| 0 | 7 (4.3) | 8 (4.7) |
| 1 | 16 (9.9) | 20 (11.8) |
| 1 + | 53 (32.7) | 44 (25.9) |
| 2 | 57 (35.2) | 68 (40.0) |
| 3 | 28 (17.3) | 30 (17.6) |
| 4 | 1 (0.6) | 0 (0.0) |
| Median (IQR) | 2 (1 + to 2) | 2 (1 + to 2) |
| ***Motricity index: median (IQR)*** | | |
| Arm | 40 (29 to 62) | 40 (24 to 61) |
| Total | 47 (34.5 to 64.3) | 50 (33.5 to 64.5) |
| ***Grip strength (kg): median (IQR)*** | 1.8 (0.0 to 6.0) | 0.7 (0.0 to 5.0) |

a One participant had received previous botulinum toxin to the eyelid.

***TABLE 5*** *Baseline upper limb function, activity limitation and stroke-related quality of life/participation restriction*

| | **Control (*n* = 162)[a]** | **Intervention (*n* = 170)[a]** |
|---|---|---|
| ***ARAT: median (IQR)*** | | |
| Total | 3 (3 to 16) | 3 (3 to 16) |
| Grasp | 0 (0 to 5) | 0 (0 to 5) |
| Grip | 0 (0 to 4) | 0 (0 to 3) |
| Pinch | 0 (0 to 0) | 0 (0 to 0) |
| Gross | 3 (3 to 5) | 3 (2.8 to 4) |
| ***Nine-Hole Peg Test (pegs placed in 50 seconds): median (IQR)*** | 0 (0 to 0) | 0 (0 to 0) |
| ***Upper limb functional activities: median (IQR)*** | | |
| Put arm through sleeve | 3 (2 to 4) (*n* = 142) | 3 (2 to 4) (*n* = 159) |
| Open the hand for cleaning your palm | 3 (2 to 4) (*n* = 142) | 3 (2 to 4) (*n* = 159) |
| Open the hand for cutting fingernails | 2 (1 to 4) (*n* = 141) | 2 (1 to 3.3) (*n* = 158) |
| Use cutlery | 1 (1 to 1) (*n* = 140) | 1 (1 to 1) (*n* = 155) |
| ***Barthel ADL Index: median (IQR)*** | 15 (10 to 17) (*n* = 162) | 15 (10 to 17) (*n* = 170) |
| ***Stroke Impact Scale: median (IQR)*** | | |
| Strength | 31.3 (18.8 to 43.8) (*n* = 141) | 31.3 (18.8 to 43.8) (*n* = 157) |
| Memory | 82.1 (64.3 to 92.9) (*n* = 143) | 78.6 (57.1 to 92.9) (*n* = 159) |
| Emotion | 66.7 (52.8 to 80.6) (*n* = 141) | 66.7 (55.6 to 77.8) (*n* = 159) |
| Communication | 89.3 (67.9 to 100) (*n* = 142) | 85.7 (60.7 to 100.0) (*n* = 159) |
| ADL | 42.5 (32.5 to 57.5) (*n* = 142) | 40.0 (30.0 to 55.0) (*n* = 159) |
| Mobility | 50.0 (30.6 to 69.4) (*n* = 139) | 47.2 (25.0 to 64.3) (*n* = 158) |
| Hand function | 0.0 (0.0 to 10.0) (*n* = 139) | 0.0 (0.0 to 15.0) (*n* = 158) |
| Participation / handicap | 40.6 (21.9 to 65.6) (*n* = 141) | 34.4 (15.6 to 53.1) (*n* = 158) |
| Physical domain | 33.3 (22.7 to 42.5) (*n* = 143) | 30.5 (20.1 to 43.1) (*n* = 159) |
| Stroke recovery | 50.0 (30.0 to 60.0) (*n* = 136) | 40.0 (25.0 to 53.5) (*n* = 157) |
| ***EQ-5D: median (IQR)*** | | |
| Mobility | 2 (2 to 2) (*n* = 162) | 2 (2 to 2) (*n* = 170) |
| Self-care | 2 (2 to 2) (*n* = 162) | 2 (2 to 2) (*n* = 170) |
| Usual activities | 3 (2 to 3) (*n* = 162) | 3 (2 to 3) (*n* = 170) |
| Pain/discomfort | 2 (1 to 2) (*n* = 162) | 2 (1 to 2) (*n* = 170) |
| Anxiety/depression | 2 (1 to 2) (*n* = 162) | 2 (1 to 2) (*n* = 170) |
| Good/bad health scale | 60 (50 to 70) (*n* = 161) | 60 (50 to 70) (*n* = 169) |
| ***Oxford Handicap Scale: median (IQR)*** | 3 (3 to 4) | 4 (3 to 4) |

a *n* values valid except where alternative *n* value is provided in parentheses.

***TABLE 6*** *Baseline upper limb pain*

| | **Control (*n* = 162)** | **Intervention (*n* = 170)** |
|---|---|---|
| Pain description (excruciating, severe, moderate, mild, none)[a]: median (IQR) | 3 (moderate) (2 to 4) | 3 (moderate) (2 to 5) |
| Pain score (0–10)[b]: median (IQR) | 5 (1 to 7) | 5 (0 to 7) |

a A high score on this scale is less pain.
b A high score on this scale is more pain.

***TABLE 7a*** *Impairment change from baseline to each outcome assessment: median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Modified Ashworth Scale at elbow: median change (IQR)*** | | | |
| 1 month | 0 (–1 to 1) (*n* = 154) | –1 (–1 to 0) (*n* = 167) | **0.001** |
| 3 months | 0 (–1 to 0) (*n* = 151) | 0 (–1 to 0) (*n* = 163) | 0.145 |
| 12 months | 0 (–1 to 1) (*n* = 91) | 0 (–1 to 0) (*n* = 97) | 0.333 |
| ***Motricity index: median change (IQR)*** | | | |
| *Arm* | | | |
| 1 month | 0 (–9 to 11) (*n* = 153) | 3 (–5 to 11) (*n* = 167) | 0.138 |
| 3 months | 0 (–6 to 11) (*n* = 151) | 4 (–4 to 14) (*n* = 164) | 0.055 |
| 12 months | 5 (–3 to 11) (*n* = 92) | 5 (0 to 13) (*n* = 97) | 0.597 |
| *Total* | | | |
| 1 month | 1.5 (–5.5 to 8.8) (*n* = 153) | 2.5 (–4.5 to 11) (*n* = 167) | 0.277 |
| 3 months | 0 (–6.6 to 9) (*n* = 151) | 4 (–4.5 to 11.5) (*n* = 162) | **0.042** |
| 12 months | 2 (–5.9 to 9.4) (*n* = 92) | 3 (–2.5 to 9.5) (*n* = 97) | 0.588 |
| ***Grip strength (kg): median change (IQR)*** | | | |
| 1 month | 0.0 (–0.4 to 2.0) (*n* = 154) | 0.0 (–0.7 to 1.3) (*n* = 167) | 0.233 |
| 3 months | 0.0 (–0.7 to 2.0) (*n* = 151) | 0.0 (–0.0 to 2.7) (*n* = 163) | 0.139 |
| 12 months | 0.5 (–0.5 to 3.9) (*n* = 92) | 0.0 (–0.2 to 3.0) (*n* = 97) | 0.764 |

***TABLE 7b*** *Impairment change from baseline outcome assessment: mean and 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Modified Ashworth Scale at elbow: mean change (95% CI)*** | | | |
| 1 month | –0.1 (–0.2 to 0.1) | –0.6 (–0.8 to –0.4) | **–0.5 (–0.8 to –0.3)** |
| 3 months | –0.1 (–0.3 to 0.1) | –0.3 (–0.4 to –0.1) | –0.2 (–0.5 to 0.1) |
| 12 months | –0.2 (–0.5 to 0.1) | –0.3 (–0.5 to –0.1) | –0.1 (–0.4 to 0.2) |
| ***Motricity Index: mean change (95% CI)*** | | | |
| *Arm* | | | |
| 1 month | 1.4 (–0.9 to 3.7) | 3.6 (1.5 to 5.7) | 2.2 (–0.9 to 5.4) |
| 3 months | 1.7 (–0.6 to 4.1) | 5.2 (2.8 to 7.6) | **3.5 (0.1 to 6.8)** |
| 12 months | 3.6 (0.7 to 6.4) | 6.1 (3.5 to 8.8) | 2.5 (–1.4 to 6.3) |
| *Total* | | | |
| 1 month | 1.4 (–0.3 to 3.1) | 2.6 (0.9 to 4.3) | 1.2 (–1.2 to 3.7) |
| 3 months | 1.2 (–0.7 to 3.1) | 4.3 (2.5 to 6.2) | **3.2 (0.4 to 5.8)** |
| 12 months | 2.4 (0.1 to 4.8) | 3.6 (1.6 to 5.8) | 1.3 (–1.9 to 4.4) |
| ***Grip strength (kg): mean change (95% CI)*** | | | |
| 1 month | 0.6 (0.2 to 1.1) | 0.5 (0.0 to 1.0) | –0.2 (–0.8 to 0.5) |
| 3 months | 0.9 (0.4 to 1.5) | 1.9 (1.1 to 2.8) | 1.0 (0.0 to 2.0) |
| 12 months | 1.6 (0.7 to 2.6) | 1.5 (0.7 to 2.4) | –0.1 (–1.4 to 1.1) |

## Upper limb function and activity limitation

At 3 months, predefined treatment success (improvement in upper limb function) on the ARAT was achieved by 37/151 (24.5%) participants in the control group and 54/161 (33.5%) in the intervention group ($p = 0.083$). At 12 months treatment success was achieved by 27/92 (29.3%) participants in the control group and 36/97 (37.1%) in the intervention group ($p = 0.282$). The relative risk of having a 'successful treatment' in the intervention group compared with the control group was 1.4 (95% CI 0.9 to 1.9) at 3 months and 1.3 (95% CI 0.8 to 1.9) at 12 months.

The effect of botulinum toxin upon upper limb function was also examined by analysing change in ARAT score from baseline to each assessment (*Tables 8a* and *8b*). No significant differences were seen between intervention and control groups at 1 or 12 months. At 3 months, although the median change in upper limb function in both randomisation groups was zero, the Mann–Whitney *U*-test reached statistical significance ($p = 0.049$).

***TABLE 8a*** *Upper limb function and activity limitation change from baseline to each outcome assessment; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***ARAT: median change (IQR)*** | | | |
| 1 month | 0 (0 to 3) (*n* = 154) | 0 (0 to 4) (*n* = 167) | 0.427 |
| 3 months | 0 (0 to 3) (*n* = 151) | 0 (0 to 5) (*n* = 161) | **0.049** |
| 12 months | 0 (0 to 3) (*n* = 92) | 1 (0 to 5) (*n* = 97) | 0.227 |
| ***Nine-Hole Peg Test (pegs placed in 50s): median change (IQR)*** | | | |
| 1 month | 0 (0 to 0) (*n* = 155) | 0 (0 to 0) (*n* = 166) | 0.150 |
| 3 months | 0 (0 to 0) (*n* = 151) | 0 (0 to 0) (*n* = 162) | 0.062 |
| 12 months | 0 (0 to 0) (*n* = 92) | 0 (0 to 0) (*n* = 97) | 0.498 |
| ***Upper limb functional activities: median change (IQR)*** | | | |
| *Put arm through sleeve* | | | |
| 1 month | 0 ( to 0.5 to 1) (*n* = 125) | 0 (0 to 1) (*n* = 144) | **0.004** |
| 3 months | 0 (0 to 1) (*n* = 122) | 0 (0 to 1) (*n* = 142) | 0.127 |
| 12 months | 0 ( to 1 to 1) (*n* = 79) | 0 ( to 0.3 to 1) (*n* = 86) | 0.956 |
| *Open the hand for cleaning your palm* | | | |
| 1 month | 0 (0 to 1) (*n* = 124) | 0 (0 to 1) (*n* = 143) | 0.071 |
| 3 months | 0 (–1 to 1) (*n* = 122) | 0 (–1 to 1) (*n* = 142) | **0.047** |
| 12 months | 0 (–1 to 1) (*n* = 79) | 0 (0 to 1.3) (*n* = 86) | **0.029** |
| *Open the hand for cutting fingernails* | | | |
| 1 month | 0 (0 to 0.5) (*n* = 125) | 0 (–1 to 1) (*n* = 143) | 0.526 |
| 3 months | 0 (–1 to 1) (*n* = 122) | 0 (–1 to 1) (*n* = 141) | 0.342 |
| 12 months | 0 (–1 to 1) (*n* = 78) | 0 (–0.3 to 2) (*n* = 86) | 0.097 |
| *Use cutlery* | | | |
| 1 month | 0 (0 to 0) (*n* = 123) | 0 (0 to 0) (*n* = 141) | 0.376 |
| 3 months | 0 (0 to 0) (*n* = 120) | 0 (0 to 0) (*n* = 140) | 0.595 |
| 12 months | 0 (0 to 0) (*n* = 77) | 0 (0 to 0) (*n* = 83) | 0.066 |
| ***Barthel ADL Index: median change (IQR)*** | | | |
| 1 month | 0 (–2 to 1) (*n* = 134) | 0 (–2 to 1) (*n* = 142) | 0.335 |
| 3 months | 0 (–2 to 1) (*n* = 130) | 0 (–2 to 2) (*n* = 143) | 0.260 |
| 12 months | –1 (–2 to 1) (*n* = 75) | –1 (–3 to 1.3) (*n* = 82) | 0.833 |

***TABLE 8b*** *Upper limb function and activity limitation change from baseline to each outcome assessment: mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***ARAT: mean change (95% CI)*** | | | |
| 1 month | 1.5 (0.8 to 2.2) | 2.2 (1.3 to 3.0) | 0.7 (–0.4 to 1.8) |
| 3 months | 1.3 (0.4 to 2.1) | 3.0 (2.0 to 4.2) | **1.8 (0.4 to 3.2)** |
| 12 months | 2.0 (–0.5 to 0.1) | –3.1 (1.7 to 4.5) | 1.1 (–0.7 to 2.9) |
| ***Nine-Hole Peg Test (pegs placed in 50s): mean change (95% CI)*** | | | |
| 1 month | 0.1 (–0.1 to 0.3) | 0.3 (0.0 to 0.5) | 0.2 (–0.1 to 0.5) |
| 3 months | 0.1 (–0.1 to 0.3) | 0.5 (0.2 to 0.9) | 0.5 (0.1 to 0.8) |
| 12 months | 0.2 (0.0 to 0.3) | 0.3 (0.0 to 0.7) | 0.1 (–0.2 to 0.6) |
| ***Upper limb functional activities: mean change (95% CI)*** | | | |
| *Put arm through sleeve* | | | |
| 1 month | 0.0 (–0.2 to 0.2) | 0.4 (0.2 to 0.6) | **0.4 (0.1 to 0.6)** |
| 3 months | 0.1 (–0.1 to 0.3) | 0.3 (0.1 to 0.5) | 0.2 (–0.1 to 0.5) |
| 12 months | 0.1 (–0.2 to 0.3) | 0.1 (–0.2 to 0.3) | 0.0 (–0.4 to 0.4) |
| *Open the hand for cleaning your palm* | | | |
| 1 month | 0.1 (–0.1 to 0.3) | 0.4 (0.2 to 0.6) | 0.3 (0.0 to 0.6) |
| 3 months | 0.0 (–0.3 to 0.2) | 0.3 (0.0 to 0.5) | **0.3 (–0.1 to 0.7)** |
| 12 months | –0.1 (–0.4 to 0.2) | 0.4 (0.1 to 0.8) | **0.5 (0.0 to 1.0)** |
| *Open the hand for cutting fingernails* | | | |
| 1 month | 0.1 (–0.1 to 0.4) | 0.2 (–0.1 to 0.4) | 0.1 (–0.3 to 0.4) |
| 3 months | 0.0 (–0.3 to 0.2) | 0.1 (–0.2 to 0.3) | 0.1 (–0.3 to 0.5) |
| 12 months | 0.0 (–0.4 to 0.4) | 0.3 (–0.1 to 0.7) | 0.3 (–0.2 to 0.9) |
| *Use cutlery* | | | |
| 1 month | 0.1 (0.0 to 0.2) | 0.2 (0.1 to 0.3) | 0.1 (–0.1 to 0.3) |
| 3 months | 0.2 (0.0 to 0.3) | 0.2 (0.1 to 0.4) | 0.1 (–0.1 to 0.3) |
| 12 months | –0.1 (–0.3 to 0.1) | 0.2 (0.0 to 0.2) | 0.3 (0 to 0.5) |
| ***Barthel ADL Index: mean change (IQR)*** | | | |
| 1 month | –0.6 (– 1.0 to 0.2) | –0.4 (–0.8 to 0.1) | 0.2 (–0.4 to 0.8) |
| 3 months | –0.3 (–0.8 to 0.1) | 0.0 (–0.5 to 0.4) | 0.3 (–0.3 to 0.9) |
| 12 months | –0.5 (– 1.1 to 0.2) | –0.4 (– 1 to 0.2) | 0.1 (–0.8 to 1.0) |

Examination of the difference between the mean change in the groups showed that the intervention group had improved by a mean of 1.8 (95% CI 0.4 to 3.2) points on the ARAT compared with the control group. Although this demonstrates improved upper limb function in the intervention group compared with the control group, the size of the improvement is small and therefore of doubtful clinical significance.

Although the median change in score from baseline to 1 month for the ability put the affected arm through a sleeve was zero in both the control and intervention groups, comparison of scores reached statistical significance ($p = 0.004$). Examination of the difference between the mean change in the groups showed that the intervention group had improved by 0.4 (95% CI 0.1 to 0.6) compared with the control group (*Tables 8a* and *8b*). Similarly, at 3 and 12 months there were statistically significant differences between intervention and control groups in ability to open the hand for cleaning the palm despite the median change from baseline being zero in both groups. Further examination of the data showed that the intervention group had improved by 0.3 (95% CI –0.1 to 0.7) compared with the control group at 3 months and by 0.5 (95% CI 0.0 to 1.0) at 12 months. As self-reported arm function was assessed using an ordinal scale of 1 (unable to perform) to 5 (no difficulty), a mean

***TABLE 8c*** *Upper limb functional activity questions: improvement by at least one point*

| | Control | Intervention | *p*-value | Relative risk Intervention: Control (95% CI) |
|---|---|---|---|---|
| ***Dressing sleeve improvement by ≥ 1:* n *(%)*** | | | | |
| 1 month | 38 (30.4) (*n* = 125) | 65 (45.1) (*n* = 144) | **0.017** | **1.5 (1.1 to 2.0)** |
| 3 months | 39 (32.0) (*n* = 122) | 62 (43.7) (*n* = 142) | 0.057 | 1.4 (1.0 to 1.9) |
| 12 months | 32 (40.5) (*n* = 79) | 30 (34.9) (*n* = 86) | 0.521 | 0.9 (0.6 to 1.3) |
| ***Opening hand for cleaning palm improvement of ≥ 1:* n *(%)*** | | | | |
| 1 month | 41 (33.1) (*n* = 124) | 65 (45.5) (*n* = 143) | **0.045** | **1.4 (1.0 to 1.8)** |
| 3 months | 34 (27.9) (*n* = 122) | 64 (45.1) (*n* = 142) | **0.005** | **1.6 (1.2 to 2.3)** |
| 12 months | 25 (31.6) (*n* = 79) | 41 (47.7) (*n* = 86) | **0.040** | **1.5 (1.0 to 2.2)** |
| ***Opening the hand for cutting nails improvement of ≥ 1:* n *(%)*** | | | | |
| 1 month | 31 (24.8) (*n* = 125) | 52 (36.6) (*n* = 142) | **0.047** | **1.5 (1.0 to 2.2)** |
| 3 months | 31 (25.4) (*n* = 122) | 52 (36.9) (*n* = 141) | **0.048** | **1.5 (1.0 to 2.2)** |
| 12 months | 21 (26.9) (*n* = 78) | 39 (45.3) (*n* = 86) | **0.016** | **1.7 (1.1 to 2.6)** |
| ***Ability to use cutlery improvement of ≥ 1:* n *(%)*** | | | | |
| 1 month | 22 (17.9) (*n* = 123) | 31 (22.0) (*n* = 141) | 0.444 | 1.2 (0.8 to 2.0) |
| 3 months | 25 (20.8) (*n* = 120) | 31 (22.1) (*n* = 140) | 0.880 | 1.1 (0.7 to 1.7) |
| 12 months | 10 (13.0) (*n* = 77) | 17 (20.5) (*n* = 83) | 0.291 | 1.6 (0.8 to 3.2) |

improvement of 0.3–0.5 is of doubtful clinical importance.

To enable comparison with previous studies, responses to basic upper limb functional activity questions were also analysed by comparing the proportion of participants in each randomisation group who had improved by one or more points on the scale from baseline (*Table 8c*). For the ability to dress a sleeve, this improvement was seen for 65/144 (45.1%) of participants in the intervention group compared with 38/125 (30.4%) in the control group at 1 month ($p = 0.017$). No significant differences were seen at 3 and 12 months. For opening the hand to clean the palm and opening the hand to cut fingernails, significant differences in favour of the intervention group were seen at 1, 3 and 12 months. No significant differences were seen between the groups for improvement in ability to use cutlery.

Overall, at 1 month 109/144 (75.7%) of the intervention group and 79/125 (63.2%) of the control group had improved by at least one point on any of the four tasks ($p = 0.033$). At 3 months the corresponding proportions were 102/142 (71.8%) of the intervention group and 71/122 (58.2%) of the control group ($p = 0.027$). No significant difference was seen at 12 months [intervention group 59/86 (68.6%), control group 51/79 (64.6%), $p = 0.622$].

## Stroke-related quality of life/ participation restriction

*Tables 9a* and *9b* show stroke-related quality of life/ participation restriction at 1, 3 and 12 months. For the EQ-5D question about pain and discomfort, although the median change in score from baseline to 3 months was zero in both groups, comparison of scores between the groups reached statistical significance ($p = 0.025$). Examination of the difference between mean change in the groups showed that the intervention group had improved (decreased) their score by 0.2 points compared with the control group. Similarly, the median change in score from baseline to 3 months on the Oxford Handicap Scale was zero in both groups, but comparison of scores between the groups reached statistical significance ($p = 0.015$). The mean change in the groups showed that the intervention had improved (decreased) their score by 0.3 points compared with the control group.

Statistically significant differences were also found between the groups for change in participation

***TABLE 9a*** *Stroke-related quality of life/participation restriction change from baseline to each outcome assessment: median and Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Stroke Impact Scale domains: median change (IQR)*** | | | |
| *Strength* | | | |
| 1 month | 0.0 (–6.3 to 12.5) (*n* = 124) | 0.0 (–6.3 to 12.5) (*n* = 142) | 0.544 |
| 3 months | 0.0 (–12.5 to 6.3) (*n* = 117) | 0.0 (–12.5 to 6.3) (*n* = 140) | 0.784 |
| 12 months | 0.0 (–12.5 to 12.5) (*n* = 76) | 0.0 (–12.5 to 10.9) (*n* = 84) | 0.408 |
| *Memory* | | | |
| 1 month | 0.0 (–7.1 to 7.1) (*n* = 125) | 0.0 (–6.3 to 7.1) (*n* = 144) | 0.204 |
| 3 months | 0.0 (–10.7 to 10.7) (*n* = 122) | 0.0 (–7.1 to 10.7) (*n* = 143) | 0.674 |
| 12 months | –3.6 (–14.3 to 0.0) (*n* = 79) | 0.0 (–10.7 to 7.1) (*n* = 86) | 0.060 |
| *Emotion* | | | |
| 1 month | 0.0 (–5.6 to 8.3) (*n* = 123) | 0.0 (–8.3 to 8.3) (*n* = 143) | 0.831 |
| 3 months | 0.0 (–8.3 to 8.3) (*n* = 120) | 0.0 (–12.6 to 8.3) (*n* = 140) | 0.771 |
| 12 months | –5.6 (–13.9 to 5.6) (*n* = 78) | 0.0 (–8.3 to 8.3) (*n* = 86) | 0.092 |
| *Communication* | | | |
| 1 month | 0.0 (–7.1 to 3.6) (*n* = 125) | 0.0 (–3.6 to 3.6) (*n* = 144) | 0.519 |
| 3 months | 0.0 (–7.1 to 3.6) (*n* = 122) | 0.0 (–3.6 to 7.1) (*n* = 141) | 0.115 |
| 12 months | –3.6 (–10.7 to 3.6) (*n* = 79) | 0.0 (–7.1 to 7.1) (*n* = 86) | **0.023** |
| *ADL* | | | |
| 1 month | 0.0 (–7.5 to 5.0) (*n* = 125) | 0.3 (–5.0 to 10.0) (*n* = 143) | 0.078 |
| 3 months | 0.0 (–7.5 to 7.5) (*n* = 122) | 0.0 (–6.3 to 7.5) (*n* = 142) | 0.642 |
| 12 months | –2.5 (–10.0 to 5.0) (*n* = 79) | 0.0 (–7.5 to 10.0) (*n* = 85) | 0.189 |
| *Mobility* | | | |
| 1 month | 0.0 (–8.3 to 5.6) (*n* = 124) | 0.0 (–5.6 to 8.3) (*n* = 142) | 0.217 |
| 3 months | 2.8 (–8.3 to 11.1) (*n* = 119) | 2.8 (–5.6 to 8.3) (*n* = 140) | 0.686 |
| 12 months | –1.4 (–11.1 to 8.3) (*n* = 78) | 0.0 (–8.8 to 8.3) (*n* = 86) | 0.686 |
| *Hand function* | | | |
| 1 month | 0.0 (0.0–10.0) (*n* = 124) | 0.0 (0.0 to 10.0) (*n* = 142) | 0.387 |
| 3 months | 0.0 (0.0–5.0) (*n* = 120) | 0.0 (0.0 to 10.0) (*n* = 141) | 0.908 |
| 12 months | 0.0 (–2.5 to 0.0) (*n* = 77) | 0.0 (0.0 to 11.3) (*n* = 86) | 0.096 |
| *Participation/Handicap* | | | |
| 1 month | –2.3 (–12.5 to 9.4) (*n* = 124) | 0.0 (–9.4 to 13.5) (*n* = 142) | 0.122 |
| 3 months | 0.0 (–18.7 to 14.5) (*n* = 122) | 3.1 (–9.4 to 21.9) (*n* = 140) | 0.091 |
| 12 months | 0.0 (–18.0 to 12.5) (*n* = 76) | 3.1 (–12.5 to 18.8) (*n* = 85) | 0.241 |
| *Physical domain* | | | |
| 1 month | 1.0 (–5.0 to 6.2) (*n* = 126) | 2.0 (–2.7 to 7.5) (*n* = 144) | 0.125 |
| 3 months | 1.1 (–5.6 to 7.1) (*n* = 123) | 2.0 (–4.6 to 7.0) (*n* = 143) | 0.790 |
| 12 months | –1.8 (–6.8 to 5.0) (*n* = 79) | –0.4 (–7.1 to 6.9) (*n* = 86) | 0.534 |
| *Stroke recovery* | | | |
| 1 month | 0.0 (–10.0 to 5.0) (*n* = 121) | 0.0 (–12.5 to 10.0) (*n* = 141) | 0.352 |
| 3 months | 0.0 (–10.0 to 10.0) (*n* = 117) | 0.0 (–10.0 to 15.0) (*n* = 141) | 0.464 |
| 12 months | 0.0 (–20.0 to 10.0) (*n* = 74) | 0.0 (–20.0 to 20.0) (*n* = 86) | 0.369 |

***TABLE 9a*** *Stroke-related quality of life/participation restriction change from baseline to each outcome assessment: median and Mann–Whitney U-test (continued)*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***EQ-5D: median change (IQR)*** | | | |
| *Mobility* | | | |
| 1 month | 0 (0 to 0) (*n* = 138) | 0 (0 to 0) (*n* = 151) | 0.914 |
| 3 months | 0 (0 to 0) (*n* = 134) | 0 (0 to 0) (*n* = 151) | 0.445 |
| 12 months | 0 (0 to 0) (*n* = 83) | 0 (0 to 0) (*n* = 87) | 0.542 |
| *Self-care* | | | |
| 1 month | 0 (0 to 0) (*n* = 138) | 0 (0 to 0) (*n* = 151) | 0.255 |
| 3 months | 0 (0 to 0) (*n* = 134) | 0 (0 to 0) (*n* = 152) | 0.256 |
| 12 months | 0 (0 to 0) (*n* = 82) | 0 (0 to 0) (*n* = 87) | 0.576 |
| *Usual activities* | | | |
| 1 month | 0 (0 to 0) (*n* = 138) | 0 (0 to 0) (*n* = 149) | 0.764 |
| 3 months | 0 (0 to 0) (*n* = 134) | 0 (0 to 0) (*n* = 151) | 0.311 |
| 12 months | 0 (0 to 0) (*n* = 83) | 0 (0 to 0) (*n* = 86) | 0.443 |
| *Pain/discomfort* | | | |
| 1 month | 0 (0 to 0) (*n* = 137) | 0 (0 to 0) (*n* = 150) | 0.247 |
| 3 months | 0 (0 to 0) (*n* = 133) | 0 (0 to 0) (*n* = 152) | **0.025** |
| 12 months | 0 (0 to 1) (*n* = 83) | 0 (0 to 0) (*n* = 87) | 0.270 |
| *Anxiety/depression* | | | |
| 1 month | 0 (0 to 0) (*n* = 133) | 0 (0 to 0) (*n* = 149) | 0.138 |
| 3 months | 0 (0 to 0) (*n* = 132) | 0 (0 to 0) (*n* = 151) | 0.818 |
| 12 months | 0 (0 to 1) (*n* = 81) | 0 (–1 to 0) (*n* = 86) | **0.002** |
| *Good/bad health scale* | | | |
| 1 month | –5 (–20 to 10) (*n* = 135) | –1 (–18 to 10) (*n* = 149) | 0.663 |
| 3 months | –1 (–22.5 to 15) (*n* = 133) | –5 (–20 to 10) (*n* = 148) | 0.755 |
| 12 months | 0 (–25.8 to 18.8) (*n* = 80) | –5 (–20 to 10) (*n* = 84) | 0.749 |
| ***Oxford Handicap Scale: median change (IQR)*** | | | |
| 1 month | 0 (–0.5 to 0) (*n* = 137) | 0 (–1 to 0) (*n* = 152) | 0.359 |
| 3 months | 0 (0 to 0) (*n* = 133) | 0 (–1 to 0) (*n* = 151) | **0.015** |
| 12 months | 0 (–1 to 0) (*n* = 83) | 0 (–1 to 0) (*n* = 87) | **0.045** |

restriction from baseline to 12 months as measured by the communication domain of the Stroke Impact Scale, the EQ-5D question about anxiety and depression, and the Oxford Handicap Scale. On all occasions where significant differences were found, however, the magnitude of the treatment effect was small and of doubtful clinical importance.

## Upper limb pain

No significant differences were found in change in pain rating on either pain scale from baseline to 1 month or 3 months (*Tables 10a* and *10b*). However, pain rating did decrease from baseline to 12 months in the intervention group compared with the control group on both of the pain scales. For the pain rating scale 0–10, the median change was a decrease of two points in the intervention group compared with zero points in the control group ($p = 0.004$).

## Additional antispasticity treatment

Antispasticity medication and physical treatments such as splints were used infrequently and use

***TABLE 9b*** *Stroke-related quality of life/participation restriction change from baseline to each outcome assessment: mean and 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Stroke Impact Scale domains: mean change (95% CI)*** | | | |
| *Strength* | | | |
| 1 month | 0.9 (–1.6 to 3.4) | 1.7 (–1.1 to 4.4) | 0.8 (–2.9 to 4.6) |
| 3 months | –1.6 (–5.1 to 1.8) | –0.2 (–3.4 to 3.0) | 1.4 (–3.3 to 6.2) |
| 12 months | 0.2 (–4.2 to 4.5) | –2.2 (–6.5 to 2.2) | –2.3 (–8.3 to 4.0) |
| *Memory* | | | |
| 1 month | –1.1 (–3.7 to 1.5) | 1.3 (–1.6 to 4.2) | 2.4 (–1.5 to 6.3) |
| 3 months | –2.0 (–5.0 to 1.0) | –0.8 (–2.3 to 4.0) | 2.8 (–1.5 to 7.2) |
| 12 months | –5.6 (–9.6 to –1.5) | –1.8 (–5.6 to 1.8) | 3.8 (–1.7 to 9.2) |
| *Emotion* | | | |
| 1 month | 0.6 (–2.0 to 3.1) | 0.3 (–1.8 to 2.4) | –0.3 (–3.6 to 3.0) |
| 3 months | –0.1 (–2.8 to 2.6) | –1.0 (–3.4 to 1.5) | –0.9 (–4.6 to 2.8) |
| 12 months | –3.5 (–6.9 to –0.1) | –1.0 (–4.0 to 1.9) | 2.5 (–2.0 to 7.0) |
| *Communication* | | | |
| 1 month | –1.6 (–3.6 to 0.4) | 0.6 (–1.7 to 2.8) | 2.1 (–0.9 to 5.1) |
| 3 months | –2.4 (–5.3 to 0.3) | 0.3 (–2.2 to 2.7) | 4.7 (1.1 to 8.5) |
| 12 months | –4.2 (–8.1 to –0.5) | 1.2 (–2.4 to 4.7) | **5.3 (0.2 to 10.6)** |
| *ADL* | | | |
| 1 month | –1.6 (–3.8 to 0.5) | 1.8 (–0.5 to 4.1) | 3.4 (0.4 to 6.6) |
| 3 months | –1.0 (–3.7 to 1.4) | 2.5 (0.0 to 5.0) | 1.4 (–2.2 to 4.9) |
| 12 months | –2.4 (–5.5 to 0.7) | 0.8 (–2.3 to 3.8) | 3.2 (–1.1 to 7.5) |
| *Mobility* | | | |
| 1 month | –1.0 (–3.6 to 1.7) | 1.1 (–1.4 to 3.5) | 2.1 (–1.5 to 5.7) |
| 3 months | 1.7 (–1.3 to 4.7) | 2.9 (–0.5 to 6.2) | 0.8 (–3.1 to 4.6) |
| 12 months | –2.0 (–5.4 to 1.4) | –0.8 (–3.9 to 2.2) | 1.2 (–3.5 to 5.8) |
| *Hand function* | | | |
| 1 month | 3.3 (0.2 to 6.1) | 4.7 (1.3 to 8.0) | 1.5 (–3.0 to 5.8) |
| 3 months | 3.2 (–0.5 to 6.8) | 5.0 (–0.5 to 10.4) | –0.3 (–5.2 to 4.7) |
| 12 months | –0.9 (–5.7 to 3.6) | 4.6 (1.0 to 8.5) | 5.6 (–0.2 to 11.6) |
| *Participation/Handicap* | | | |
| 1 month | –2.8 (–7.8 to 2.3) | 1.2 (–4.4 to 6.8) | 4.0 (–3.5 to 11.6) |
| 3 months | –2.0 (–6.5 to 2.6) | 1.4 (–0.6 to 3.4) | 7.0 (–0.1 to 14.2) |
| 12 months | –1.7 (–7.6 to 4.2) | 4.2 (–2.4 to 10.7) | 5.9 (–3.0 to 14.7 |
| *Physical domain* | | | |
| 1 month | 0.6 (–1.0 to 2.1) | 2.1 (0.2 to 3.8) | 1.5 (–1.0 to 3.9) |
| 3 months | 0.9 (–1.2 to 3.1) | 1.4 (–0.6 to 3.4) | 0.4 (–2.6 to 3.4) |
| 12 months | –1.2 (–3.8 to 1.2) | 0.5 (–1.9 to 2.9) | 1.7 (–1.8 to 5.2) |
| *Stroke recovery* | | | |
| 1 month | –2.1 (–4.6 to 0.3) | –0.6 (–3.8 to 2.5) | 1.6 (–2.5 to 5.5) |
| 3 months | –0.8 (–3.7 to 2.1) | 2.0 (–1.3 to 5.4) | 2.8 (–1.5 to 7.2) |
| 12 months | –2.1 (–6.8 to 2.7) | 0.5 (–4.5 to 5.7) | 2.6 (–4.2 to 9.4) |

***TABLE 9b*** *Stroke-related quality of life/participation restriction change from baseline to each outcome assessment: mean and 95% CI (continued)*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***EQ-5D: mean change (95% CI)*** | | | |
| *Mobility* | | | |
| 1 month | 0.0 (−0.1 to 0.1) | 0.0 (−0.1 to 0.1) | 0.0 (−0.1 to 0.1) |
| 3 months | 0.0 (−0.1 to 0.0) | 0.0 (−0.1 to 0.0) | 0.0 (−0.1 to 0.1) |
| 12 months | 0.0 (−0.1 to 0.1) | 0.0 (0.0 to 0.1) | 0.0 (−0.1 to 0.2) |
| *Self-care* | | | |
| 1 month | 0.1 (0.1 to 0.2) | 0.1 (0.0 to 0.2) | −0.1 (−0.2 to 0.0) |
| 3 months | 0.1 (0.1 to 0.2) | 0.1 (0.0 to 0.2) | −0.1 (−0.2 to 0.0) |
| 12 months | 0.1 (0.0 to 0.3) | 0.1 (0.0 to 0.2) | −0.1 (−0.2 to 0.1) |
| *Usual activities* | | | |
| 1 month | 0.0 (−0.1 to 0.1) | 0.0 (−0.1 to 0.1) | 0.0 (−0.1 to 0.2) |
| 3 months | 0.0 (−0.1 to 0.1) | 0.0 (−0.1 to 0.2) | 0.1 (−0.1 to 0.2) |
| 12 months | 0.0 (−0.1 to 0.2) | 0.1 (0.0 to 0.2) | 0.1 (−0.1 to 0.3) |
| *Pain/discomfort* | | | |
| 1 month | 0.1 (0.0 to 0.2) | 0.0 (−0.1 to 0.1) | −0.1 (−0.2 to 0.1) |
| 3 months | 0.1 (0.0 to 0.2) | −0.1 (−0.2 to 0.0) | **−0.2 (−0.3 to 0.0)** |
| 12 months | 0.1 (0.0 to 0.3) | 0.0 (−0.1 to 0.2) | −0.1 (−0.3 to 0.1) |
| *Anxiety/depression* | | | |
| 1 month | 0.0 (−0.1 to 0.1) | −0.1 (−0.2 to 0.0) | −0.1 (−0.3 to 0.0) |
| 3 months | −0.1 (−0.2 to 0.1) | 0.0 (−0.1 to 0.1) | 0.0 (−0.1 to 0.2) |
| 12 months | 0.1 (0.0 to 0.3) | −0.2 (−0.3 to −0.1) | **−0.3 (−0.5 to −0.1)** |
| *Good/bad health scale* | | | |
| 1 month | −5.2 (−9.4 to −0.9) | −4.9 (−8.6 to −1.4) | 0.2 (−5.4 to 5.7) |
| 3 months | −4.9 (−9.4 to −0.5) | −5.6 (−9.6 to −1.6) | −0.7 (−6.6 to 5.3) |
| 12 months | −2.7 (−9.3 to 4.0) | −4.8 (−10.6 to 0.9) | −2.1 (−10.9 to 6.5) |
| ***Oxford Handicap Scale: mean change (95% CI)*** | | | |
| 1 month | 0.0 (−0.2 to 0.1) | −0.1 (−0.3 to 0.0) | −0.1 (−0.3 to 0.1) |
| 3 months | 0.0 (−0.2 to 0.1) | −0.3 (−0.4 to −0.1) | **−0.3 (−0.5 to −0.1)** |
| 12 months | 0.0 (−0.2 to 0.2) | −0.3 (−0.5 to −0.1) | **−0.3 (−0.6 to 0.0)** |

was similar in both groups (*Table 11*). At 1 month, 3 months and 12 months, 41%, 39% and 36% were using some form of antispasticity treatment, respectively.

## Outcome assessment timing

One-month outcome assessments were scheduled for completion 28 +/– 3 days after randomisation. In the control group, 78.1% of assessments were performed within this time window and in the intervention group it was 81.4%. The median time from randomisation to the 1-month outcome was 30 days (IQR 28–31 days) for both intervention and control groups. Three-month assessments were scheduled for 84 +/– 5 days after study entry. In the control group, 81.6% were completed in the time window and in the intervention group it was 85.5%. The median time from randomisation to the 3-month assessment was 85 days (IQR 83.5–87 days) in the control group and 85 days (IQR 83–87 days) in the intervention group. Twelve-month assessments were scheduled for 336 +/– 5 days after study entry. In the control group, 68.5% of assessments were performed on time and in the intervention group it was 81.4%. The median time from randomisation to 12-month assessment was 337 days (IQR 334–341.5 days) in the control

***TABLE 10a*** *Upper limb pain change from baseline to each outcome assessment: median and Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Pain description: median change (IQR)*** | | | |
| 1 month | 0 (0 to 1) (*n* = 133) | 0 (0 to 1) (*n* = 133) | 0.119 |
| 3 months | 0 (0 to 1) (*n* = 133) | 0 (0 to 2) (*n* = 133) | 0.259 |
| 12 months | 0 (0 to 1) (*n* = 133) | 0 (0 to 2) (*n* = 133) | **0.036** |
| ***Pain score (0–10): median change (IQR)*** | | | |
| 1 month | 0 (–3 to 0) (*n* = 15) | 0 (–4 to 0) (*n* = 167) | 0.600 |
| 3 months | 0 (–4 to 1) (*n* = 149) | 0 (–4 to 0) (*n* = 163) | 0.269 |
| 12 months | 0 (–2.8 to 1) (*n* = 92) | –2 (–5 to 0) (*n* = 97) | **0.004** |

***TABLE 10b*** *Upper limb pain change from baseline to each outcome assessment: mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Pain description: mean change (95% CI)*** | | | |
| 1 month | 0.3 (0.1 to 0.6) | 0.6 (0.4 to 0.8) | 0.2 (–0.1 to 0.5) |
| 3 months | 0.4 (0.2 to 0.7) | 0.6 (0.4 to 0.8) | 0.2 (–0.1 to 0.5) |
| 12 months | 0.4 (0.1 to 0.6) | 0.8 (0.5 to 1.1) | **0.5 (0.1 to 0.8)** |
| ***Pain score (0–10): mean change (95% CI)*** | | | |
| 1 month | –1.1 (–1.6 to –0.6) | –1.3 (–1.9 to –0.8) | –0.3 (–1.0 to 0.5) |
| 3 months | –1.2 (–1.8 to –0.6) | –1.6 (–2.2 to 1.1) | –0.4 (–1.2 to 0.3) |
| 12 months | –0.8 (–1.5 to 0.1) | –2.2 (–2.9 to –1.4) | **–1.4 (–2.4 to –0.3)** |

group and 336 days (IQR 335.75–339 days) in the intervention group.

## Blinding of outcome assessments

The study aimed for outcome assessments to be performed by an assessor who was blinded to the randomisation group. This was achieved by having assessments carried out by a therapist who had not been involved in providing the upper limb therapy programme for that participant. As participants were not blinded it was possible for the therapist to become aware of the randomisation group. Correct identification of treatment group by the outcome assessor occurred for 36.1% (95% CI 30.8 to 41.6), 44.1% (95% CI 38.5 to 49.8) and 58.6% (95% CI 51.2 to 65.8), respectively, at 1, 3 and 12 months.

## Patient-selected goals

The COPM[71] was used to identify and measure patient-selected goals. Participants were asked at the first session of the upper limb therapy programme to identify and prioritise activities they would like to be able to undertake in three occupational areas – self-care, productivity and leisure. Each of these areas was subdivided into: (1) self-care: personal care, functional mobility, community management; (2) productivity: paid/unpaid work, household management, play/school; and (3) leisure: quiet recreation, active recreation and socialising. Participants were then asked to select up to five activities they would like to be able to undertake by the end of the therapy programme. These activities were then a focus for work during therapy sessions.

The COPM was completed by 145/163 (89.0%) participants in the control group and 155/170 (91.2%) in the intervention group. Participants in both groups tended to select self-care activities and the majority of these were related to personal care. The other common activity choices were household management and quiet recreation. The median number of final activities chosen in the control group was four (IQR 3–5) and in the intervention group was four (IQR 3–5).

***TABLE 11*** *Additional antispasticity treatments*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Antispasticity treatments:* n *(%)*** | | | |
| 1 month | 67 (43.2) (*n* = 155) | 65 (38.9) (*n* = 167) | 0.496 |
| 3 months | 62 (41.1) (*n* = 151) | 62 (38.0) (*n* = 163) | 0.644 |
| 12 months | 33 (35.9) (*n* = 92) | 36 (37.1) (*n* = 97) | 0.881 |
| *Dantrolene* | | | |
| 1 month | 2 (1.3) | 3 (1.8) | 1.000 |
| 3 months | 3 (2.0) | 3 (1.8) | 0.500 |
| 12 months | 0 (0.0) | 1 (1.0) | 1.000 |
| *Baclofen* | | | |
| 1 month | 15 (9.7) | 22 (13.2) | 0.383 |
| 3 months | 17 (11.3) | 23 (14.1) | 0.500 |
| 12 months | 11 (12.0) | 14 (14.4) | 0.671 |
| *Tizanidine* | | | |
| 1 month | 0 (0.0) | 2 (1.2) | 0.499 |
| 3 months | 0 (0.0) | 2 (1.2) | 0.499 |
| 12 months | 0 (0.0) | 1 (1.0) | 1.000 |
| *Gabapentin* | | | |
| 1 month | 17 (11.0) | 16 (9.6) | 0.716 |
| 3 months | 17 (11.3) | 15 (9.2) | 0.580 |
| 12 months | 11 (12.0) | 10 (10.3) | 0.818 |
| *Methocarbanol* | | | |
| 1 month | 1 (0.6) | 0 (0.0) | 0.481 |
| 3 months | 1 (0.7) | 0 (0.0) | 0.481 |
| 12 months | 0 (0.0) | 0 (0.0) | – |
| *Thumb strap* | | | |
| 1 month | 1 (0.6) | 0 (0.0) | 0.481 |
| 3 months | 0 (0.0) | 0 (0.0) | – |
| 12 months | 0 (0.0) | 0 (0.0) | – |
| *Elasticated glove* | | | |
| 1 month | 1 (0.6) | 0 (0.0) | 0.481 |
| 3 months | 1 (0.7) | 0 (0.0) | 0.481 |
| 12 months | 0 (0.0) | 0 (0.0) | – |
| *Functional electrical stimulation machine* | | | |
| 1 month | 1 (0.6) | 1 (0.6) | 1.000 |
| 3 months | 2 (1.3) | 1 (0.6) | 0.610 |
| 12 months | 0 (0.0) | 1 (1.0) | 1.000 |
| *TENS machine* | | | |
| 1 month | 1 (0.6) | 3 (1.8) | 0.249 |
| 3 months | 0 (0.0) | 1 (0.6) | 1.000 |
| 12 months | 0 (0.0) | 0 (0.0) | – |
| *Upper limb splint* | | | |
| 1 month | 45 (29.0) | 39 (23.4) | 0.256 |
| 3 months | 35 (23.2) | 32 (19.6) | 0.492 |
| 12 months | 16 (17.4) | 18 (18.6) | 0.852 |

TENS, transcutaneous electrical nerve stimulation.

According to the standard COPM protocol, participants scored each final activity out of 10 for both performance and satisfaction. A total baseline performance and satisfaction score was calculated (scores were added and divided by the number of activities). At 1 month, the COPM assessment was completed by rescoring the final activities. Changes in performance and satisfaction were calculated (*Table 12*).

As the COPM was part of the upper limb therapy programme, the assessment was undertaken by the treating physiotherapist rather than a therapist who was blinded to the randomisation group. There were no statistically significant differences between the groups for baseline performance or satisfaction scores. Following treatment, performance and satisfaction increased in both groups but there were no statistically significant differences between the groups. Both performance and satisfaction increased by approximately two points in both groups.

## Views about the study upper limb therapy programme

Participant views about the study upper limb therapy programme were sought by including four questions in the 1-month assessment: how did you find the upper limb therapy programme; what was good; what was not so good; other comments.

To analyse responses a simple coding framework was developed for each question. Responses were coded blinded to the randomisation group. A relative risk calculation was performed to compare the coded responses between the groups.

*Table 13* shows comments about how participants found the upper limb therapy programme.

***TABLE 12*** *Canadian Occupation Performance Measure (COPM) scores*

| | Control (*n* = 145) | Intervention (*n* = 155) | *p*-value |
|---|---|---|---|
| Baseline performance: median (IQR) | 1.7 (1.0 to 2.8) | 2.0 (1.0 to 3.0) | 0.143 |
| Post-treatment performance: median (IQR) | 4.7 (3.1 to 6.7) | 4.8 (3.4 to 6.0) | 0.985 |
| Change in performance: median (IQR) | 2.3 (1.3 to 4.0) | 2.3 (1.2 to 3.8) | 0.535 |
| Baseline satisfaction: median (IQR) | 1.6 (1.0 to 2.8) | 2.0 (1.0 to 3.3) | 0.152 |
| Post-treatment satisfaction: median (IQR) | 4.8 (3.0 to 6.8) | 4.8 (3.5 to 6.2) | 0.792 |
| Change in satisfaction: median (IQR) | 2.4 (1.0 to 4.4) | 2.3 (1.0 to 4.0) | 0.342 |

***TABLE 13*** *Participant comments about how they found the study upper limb therapy programme*

| Code | Control (*n* = 148) | Intervention (*n* = 160) | Relative risk Intervention: Control (95% CI) | Examples |
|---|---|---|---|---|
| Excellent programme: *n* (%) | 29 (19.6) | 36 (22.5) | 1.1 (0.7 to 1.8) | *Control:* excellent great treatment<br>*Intervention:* the programme was terrific |
| Good programme: *n* (%) | 46 (31.1) | 55 (34.4) | 1.1 (0.8 to 1.5) | *Control:* it was good<br>*Intervention:* fine, enjoyed it |
| Benefit from programme: *n* (%) | 55 (37.2) | 57 (35.6) | 1.0 (0.7 to 1.3) | *Control*: very helpful and glad to have treatment focused on arm<br>*Intervention:* felt it was beneficial, has made progress |
| No benefit from programme: *n* (%) | 5 (3.4) | 3 (1.9) | 0.6 (0.1 to 2.3) | *Control:* no benefit from stretches or functional programme<br>*Intervention:* worth trying but not really any good |
| Difficult programme: *n* (%) | 8 (5.4) | 7 (4.4) | 0.8 (0.3 to 2.2) | *Control:* difficult at first but got better with practice<br>*Intervention:* difficult but managed |
| Programme not challenging: *n* (%) | 5 (3.4) | 2 (1.3) | 0.4 (0.1 to 1.9) | *Control:* didn't think it was good as just repeating things<br>*Intervention:* thought it was too easy |

Approximately half of the responders (50.7% control, 56.9% intervention) in both randomisation groups provided very general comments about how 'excellent' or 'good' they thought the programme had been. A further 37.2% of the control group responders and 35.6% of the intervention group felt that they had gained benefit from the therapy programme. Less favourable comments about therapy were provided by 18/148 (12.1%) in the control group and 12/160 (7.5%) in the intervention group; these were divided into responses about no benefit from the programme, the programme being too difficult or the programme being not challenging enough. There were no statistically significant differences between the groups for the type of comments made.

*Table 14* shows the comments of the participants about the positive aspects of the upper limb therapy programme. Nearly 50% of responders in both groups provided a comment about benefit they thought had been received from the programme, either upper limb benefit or more general benefit. Similarly, approximately 50% of responders in both groups provided a comment about an aspect of the therapy they thought had been good. These comments were about stretching, exercises and functional tasks. The relative risk calculations demonstrated that people in the intervention group were more likely to comment on contact with therapists than those in the control group (relative risk 2.3, 95% CI 1.2 to 4.2). This was the only statistically significant difference between the groups for the type of comment.

When asked to comment about what was not so good about the therapy programme (*Table 15*), approximately 60% of responders in both groups said that they had no negative comments. However, 15.2% in the control group and 18.0% in the intervention group described difficulties they had found with the programme. Pain was experienced as a result of the upper limb therapy programme by 25/192 (13%). There were no statistically significant differences between the groups for the type of comments made.

***TABLE 14*** *Participant comments about what was good about the upper limb therapy programme*

| Code | Control (*n* = 120) | Intervention (*n* = 132) | Relative risk Intervention: Control (95% CI) | Examples |
|---|---|---|---|---|
| Gained arm benefits: *n* (%) | 53 (44.2) | 60 (45.5) | 1.0 (0.8 to 1.4) | *Control:* being able to put things in left hand<br>*Intervention:* started to get arm moving |
| Gained general benefits: *n* (%) | 4 (3.3) | 3 (2.3) | 0.7 (0.2 to 3.0) | *Control:* given confidence<br>*Intervention:* felt better and more relaxed afterwards |
| Therapy – stretches: *n* (%) | 20 (16.7) | 21 (15.9) | 1.0 (0.5 to 1.7) | *Control*: enjoyed having the stretching done<br>*Intervention:* the stretches reduced the upper limb stiffness and pain |
| Therapy – exercises: *n* (%) | 21 (17.5) | 20 (15.2) | 0.9 (0.5 to 1.5) | *Control:* enjoyed the exercises<br>*Intervention:* exercises made arm feel more supple |
| Therapy – functional tasks: *n* (%) | 21 (17.5) | 17 (12.9) | 0.7 (0.4 to 1.3) | *Control:* being able to take jar lids and bottle lids off<br>*Intervention:* being able to choose everyday tasks to practice |
| Contact with therapist: *n* (%) | 12 (10.0) | 30 (22.7) | 2.3 (1.2 to 4.2) | *Control:* enjoyed one-to-one sessions with study therapist<br>*Intervention:* physio flexible to my needs |
| Organisation of programme, programme as whole: *n* (%) | 18 (15.0) | 11 (8.3) | 0.6 (0.3 to 1.1) | *Control:* the whole programme helped<br>*Intervention:* very impressed with it all |
| Negative comments: *n* (%) | 3 (2.5) | 2 (1.5) | 0.6 (0.1 to 3.6) | *Control:* nothing in particular<br>*Intervention:* painful shoulder limited movement |

One hundred and fourteen participants (35.4%) provided additional comments (*Table 16*). The majority of these responses, 66.0% in the control group and 77.0% in the intervention group, were further positive comments about the therapy programme or therapy staff. A few responders said they were pleased to be provided with the opportunity to take part in a research study and others gave altruistic comments about wanting to help future stroke patients. About 20% of responses in both groups were less favourable comments. These were mainly about feeling the programme

***TABLE 15*** *Participant comments about what was not so good about the upper limb therapy programme*

| Code | Control (*n* = 92) | Intervention (*n* = 100) | Relative risk Intervention: Control (95% CI) | Examples |
|---|---|---|---|---|
| Nothing bad: *n* (%) | 56 (60.9) | 58 (58.0) | 1.0 (0.8 to 1.2) | *Control:* felt everything therapist did was beneficial<br>*Intervention:* no negative points |
| Programme difficult: *n* (%) | 7 (7.6) | 8 (8.0) | 1.1 (0.4 to 2.8) | *Control:* found exercises difficult and frustrating<br>*Intervention:* sometimes very difficult |
| Specific things in programme difficult: *n* (%) | 7 (7.6) | 10 (10.0) | 1.3 (0.5 to 3.3) | *Control:* could not manage glove<br>*Intervention:* doing buttons was very difficult |
| Programme caused pain: *n* (%) | 10 (10.9) | 15 (15.0) | 1.4 (0.7 to 2.9) | *Control:* a little painful at times on stretching<br>*Intervention:* pain during exercises |
| Programme tiring: *n* (%) | 1 (1.1) | 6 (6.0) | 5.5 (0.7 to 45.5) | *Control:* a bit tiring<br>*Intervention:* sometimes got tired if he pushed himself too much |
| No benefit from programme: *n* (%) | 5 (5.4) | 0 (0.0) | | *Control:* lack of progress |
| Programme too short: *n* (%) | 6 (6.5) | 3 (3.0) | 0.5 (0.1 to 1.8) | *Control:* too short a programme<br>*Intervention:* would like more in that format" |

***TABLE 16*** *Participants' other comments about the upper limb therapy programme*

| Code | Control (*n* = 53) | Intervention (*n* = 61) | Relative risk Intervention: Control (95% CI) | Example |
|---|---|---|---|---|
| Benefit from programme: *n* (%) | 19 (35.8) | 26 (42.6) | 1.2 (0.7 to 1.9) | *Control:* like the feeling of achieving tasks that he thought he could no longer do<br>*Intervention:* very helpful, improved a lot |
| Enjoyment of programme: *n* (%) | 9 (17.0) | 8 (13.1) | 0.8 (0.3 to 1.9) | *Control:* really good, I liked it, it has given me something to work on<br>*Intervention:* enjoyed the therapy |
| Positive comments about staff: *n* (%) | 7 (13.2) | 13 (21.3) | 1.6 (0.7 to 3.7) | *Control:* enjoyed working with therapist<br>*Intervention:* therapist very encouraging with exercises |
| Opportunity to take part: *n* (%) | 5 (9.4) | 1 (1.6) | 0.2 (0.02 to 1.4) | *Control*: pleased to have participated<br>*Intervention:* appreciative of opportunity to take part |
| Altruism for future stroke survivors: *n* (%) | 1 (1.9) | 2 (3.3) | 1.7 (0.2 to 18.5) | *Control:* grateful, glad to have helped<br>*Intervention:* hoping the research will help people in future |
| Negative comments: *n* (%) | 12 (22.6) | 11 (18.0) | 0.8 (0.4 to 1.7) | *Control:* didn't feel it was long enough<br>*Intervention:* needs more exercises for fingers |

was too short or wanting additional treatment. There were no statistically significant differences between the groups for the types of comments made.

# Trial treatments

## Botulinum toxin

Participants in the intervention group received botulinum toxin type A injections to the upper limb immediately following study entry, plus repeat injections at 3 , 6 and 9 months if clinically indicated and they remained in the study for 12-month follow-up.

An initial set of injections was received by 164/170 (96.5%) intervention group participants. Six intervention group participants did not receive the planned initial treatment; three withdrew from the study before treatment, two became unwell following randomisation and a decision was taken not use botulinum toxin (although they did receive upper limb therapy) and one participant had insufficient hypertonicity when seen in the study injection clinic. The latter participant was believed to have variable tone, having been assessed as having increased tone at the screening visit. She remained in the intervention group for the purpose of analysis.

At 3, 6 and 9 months, further injections were received by 71/105 (67.7%), 64/105 (61.0%) and 54/105 (51.4%) intervention group participants, respectively. Muscles treated and botulinum toxin type A doses used are shown in *Table 17*. Muscles treated were also grouped as limb areas (*Table 18*).

The median (IQR) total botulinum toxin type A doses per participant at initial treatment, 3 months, 6 months and 9 months were 200 units (100–300), 300 units (150–400), 300 units (150–450) and 300 units (188–450), respectively.

The trial protocol allowed for participants in the control group to be considered for treatment with botulinum toxin injections if they had an 'unacceptable degree of symptomatic spasticity'. In addition, it was possible for trial participants to be referred to routine spasticity/botulinum toxin services by local health-care providers outside the study.

In the initial 3-month study period botulinum toxin was received by 4/163 (2.5%) control group participants. Only one participant in the control group received treatment before the study 1-month outcome assessment. Eight (7.8%) control group participants commenced botulinum toxin treatment after 3 months. *Figure 5* shows the use of botulinum toxin in both intervention and control groups during the study period. All participants treated with botulinum toxin in the control group remained in the control group for the purposes of analyses.

At the end of the study period (3 or 12 months) participants in both groups whom research therapists felt would benefit from botulinum toxin treatment were referred to local spasticity services. Following the last outcome assessment 87/170 (51.2%) in the intervention group and 67/163 (41.1%) in the control group were referred to a spasticity service for botulinum toxin.

***TABLE 17*** *Intervention group botulinum toxin type A treatment*

| Muscle | Participants injected *n* (%) | Dose (units) median (IQR) |
|---|---|---|
| ***Flexor digitorum superficialis*** | | |
| Initial | 90 (54.9) (*n* = 164) | 100 (50 to 100) |
| 3 months | 50 (70.4) (*n* = 71) | 100 (100 to 100) |
| 6 months | 46 (71.9) (*n* = 64) | 100 (100 to 100) |
| 9 months | 39 (72.2) (*n* = 54) | 100 (100 to 100) |
| ***Flexor digitorum profundus*** | | |
| Initial | 63 (38.4) (*n* = 164) | 100 (50 to 100) |
| 3 months | 37 (52.1) (*n* = 71) | 100 (100 to 100) |
| 6 months | 39 (60.9) (*n* = 64) | 100 (100 to 120) |
| 9 months | 35 (64.8) (*n* = 54) | 100 (100 to 100) |

*continued*

***TABLE 17*** *Intervention group botulinum toxin type A treatment (continued)*

| Muscle | Participants injected *n* (%) | Dose (units) median (IQR) |
|---|---|---|
| ***Flexor pollicis longus*** | | |
| Initial | 6 (3.7) (*n* = 164) | 100 (72.5 to 112.5) |
| 3 months | 5 (7.0) (*n* = 71) | 80 (50 to 100) |
| 6 months | 7 (10.9) (*n* = 64) | 50 (50 to 100) |
| 9 months | 7 (13.0) (*n* = 54) | 50 (50 to 80) |
| ***Forearm flexors*** | | |
| Initial | 17 (10.4) (*n* = 164) | 200 (200 to 300) |
| 3 months | 7 (9.9) (*n* = 71) | 300 (100 to 300) |
| 6 months | 4 (6.3) (*n* = 64) | 200 (100 to 300) |
| 9 months | 0 (0.0) (*n* = 54) | 0 (0 to 0) |
| ***Flexor carpis ulnaris*** | | |
| Initial | 57 (34.8) (*n* = 164) | 100 (50 to 100) |
| 3 months | 29 (40.8) (*n* = 71) | 100 (100 to 100) |
| 6 months | 31 (48.4) (*n* = 64) | 100 (100 to 100) |
| 9 months | 29 (53.7) (*n* = 54) | 100 (100 to 100) |
| ***Flexor carpis radialis*** | | |
| Initial | 10 (6.1) (*n* = 164) | 50 (28.8 to 100) |
| 3 months | 3 (4.2) (*n* = 71) | 100 (100 to 100) |
| 6 months | 1 (1.6) (*n* = 64) | 100 (100 to 100) |
| 9 months | 1 (1.9) (*n* = 54) | 100 (100 to 100) |
| ***Biceps brachii*** | | |
| Initial | 125 (76.2) (*n* = 164) | 100 (50 to 100) |
| 3 months | 55 (77.5) (*n* = 71) | 100 (100 to 100) |
| 6 months | 47 (73.4) (*n* = 64) | 100 (100 to 150) |
| 9 months | 41 (75.9) (*n* = 54) | 100 (100 to 175) |
| ***Brachioradialis*** | | |
| Initial | 25 (15.2) (*n* = 164) | 100 (50 to 100) |
| 3 months | 13 (18.3) (*n* = 71) | 100 (100 to 100) |
| 6 months | 8 (12.5) (*n* = 64) | 100 (100 to 100) |
| 9 months | 5 (9.3) (*n* = 54) | 100 (100 to 150) |
| ***Pronator teres*** | | |
| Initial | 2 (1.2) (*n* = 164) | 100 (100 to 100) |
| 3 months | 0 (0.0) (*n* = 71) | 0 (0 to 0) |
| 6 months | 0 (0.0) (*n* = 64) | 0 (0 to 0) |
| 9 months | 0 (0.0) (*n* = 54) | 0 (0 to 0) |
| ***Pectoralis major*** | | |
| Initial | 9 (5.5) (*n* = 164) | 100 (50 to 100) |
| 3 months | 5 (7.0) (*n* = 71) | 100 (50 to 100) |
| 6 months | 1 (1.6) (*n* = 64) | 200 (200 to 200) |
| 9 months | 2 (3.7) (*n* = 54) | 150 (100 to 200) |

***TABLE 18*** *Intervention group botulinum toxin type A treatment grouped as limb area*

| Limb area | Participants injected *n* (%) | Dose (units) median (IQR) |
|---|---|---|
| ***Hand only (FDS and/or FDP and/or FPL)*** | | |
| Initial | 19 (11.6) (*n* = 164) | 100 (50 to 300) |
| 3 months | 9 (12.7) (*n* = 71) | 150 (100 to 250) |
| 6 months | 8 (12.5) (*n* = 64) | 100 (100 to 188) |
| 9 months | 5 (9.3) (*n* = 54) | 200 (100 to 200) |
| ***Wrist only (FCU and/or FCR)*** | | |
| Initial | 3 (1.8) (*n* = 164) | 50 (50 to 125)[a] |
| 3 months | 1 (1.4) (*n* = 71) | 10 (100 to 100) |
| 6 months | 3 (4.7) (*n* = 64) | 100 (100 to 100) |
| 9 months | 2 (3.7) (*n* = 54) | 100 (100 to 100) |
| ***Elbow only (Biceps and/or Brachioradialis)*** | | |
| Initial | 37 (22.6) (*n* = 164) | 100 (50 to 100) |
| 3 months | 10 (14.1) (*n* = 71) | 100 (50 to 163) |
| 6 months | 6 (9.4) (*n* = 64) | 100 (88 to 113) |
| 9 months | 6 (11.1) (*n* = 54) | 100 (88 to 225) |
| ***Shoulder only (Pectoralis major)*** | | |
| Initial | 2 (1.2) (*n* = 164) | 75 (50 to 100) |
| 3 months | 0 (0.0) (*n* = 71) | – |
| 6 months | 0 (0.0) (*n* = 64) | – |
| 9 months | 1 (1.9) (*n* = 54) | 100 (100 to 100) |
| ***Hand and wrist*** | | |
| Initial | 13 (7.9) (*n* = 164) | 300 (175 to 300) |
| 3 months | 6 (8.5) (*n* = 71) | 300 (275 to 325) |
| 6 months | 6 (9.4) (*n* = 64) | 300 (300 to 338) |
| 9 months | 5 (9.3) (*n* = 54) | 400 (300 to 425) |
| ***Hand and elbow*** | | |
| Initial | 45 (27.4) (*n* = 164) | 300 (150 to 400) |
| 3 months | 21 (29.6) (*n* = 71) | 300 (300 to 500) |
| 6 months | 19 (29.7) (*n* = 64) | 400 (200 to 500) |
| 9 months | 13 (24.1) (*n* = 54) | 300 (250 to 425) |
| ***Wrist and elbow*** | | |
| Initial; | 7 (4.3) (*n* = 164) | 100 (100 to 300) |
| 3 month | 2 (2.8) (*n* = 71) | 150 (100 to 200) |
| 6 month | 3 (4.7) (*n* = 64) | 150 (125 to 175)[a] |
| 9 month | 5 (9.3) (*n* = 54) | 150 (125 to 200) |
| ***Hand and wrist and elbow*** | | |
| Initial | 29 (17.7) (*n* = 164) | 400 (250 to 400) |
| 3 months | 17 (23.9) (*n* = 71) | 400 (400 to 500) |
| 6 months | 18 (28.1) (*n* = 64) | 450 (400 to 613) |
| 9 months | 16 (29.6) (*n* = 54) | 450 (400 to 575) |

*continued*

***TABLE 18*** *Intervention group botulinum toxin type A treatment grouped as limb area (continued)*

| Limb area | Participants injected *n* (%) | Dose (units) median (IQR) |
|---|---|---|
| ***Hand and wrist and elbow and shoulder*** | | |
| Initial | 4 (2.4) (*n* = 164) | 500 (363 to 600) |
| 3 months | 2 (2.8) (*n* = 71) | 700 (600 to 800) |
| 6 months | 0 (0.0) (*n* = 64) | – |
| 9 months | 0 (0.0) (*n* = 54) | – |
| ***Other*** | | |
| Initial | 5 (3.0) (*n* = 164) | 200 (150 to 300) |
| 3 months | 3 (4.2) (*n* = 71) | 150 (150 to 250)[a] |
| 6 months | 1 (1.6) (*n* = 64) | 700 (700 to 700) |
| 9 months | 1 (1.9) (*n* = 54) | 850 (850 to 850) |

FCR, flexor carpis radialis; FCU, flexor carpis ulnaris; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; FPL, flexor pollicis longis.

a Where there were three observations, the 25th percentile was calculated as the mean of the first and second value listed in order and 75th percentile as the mean of the second and third values listed in order.

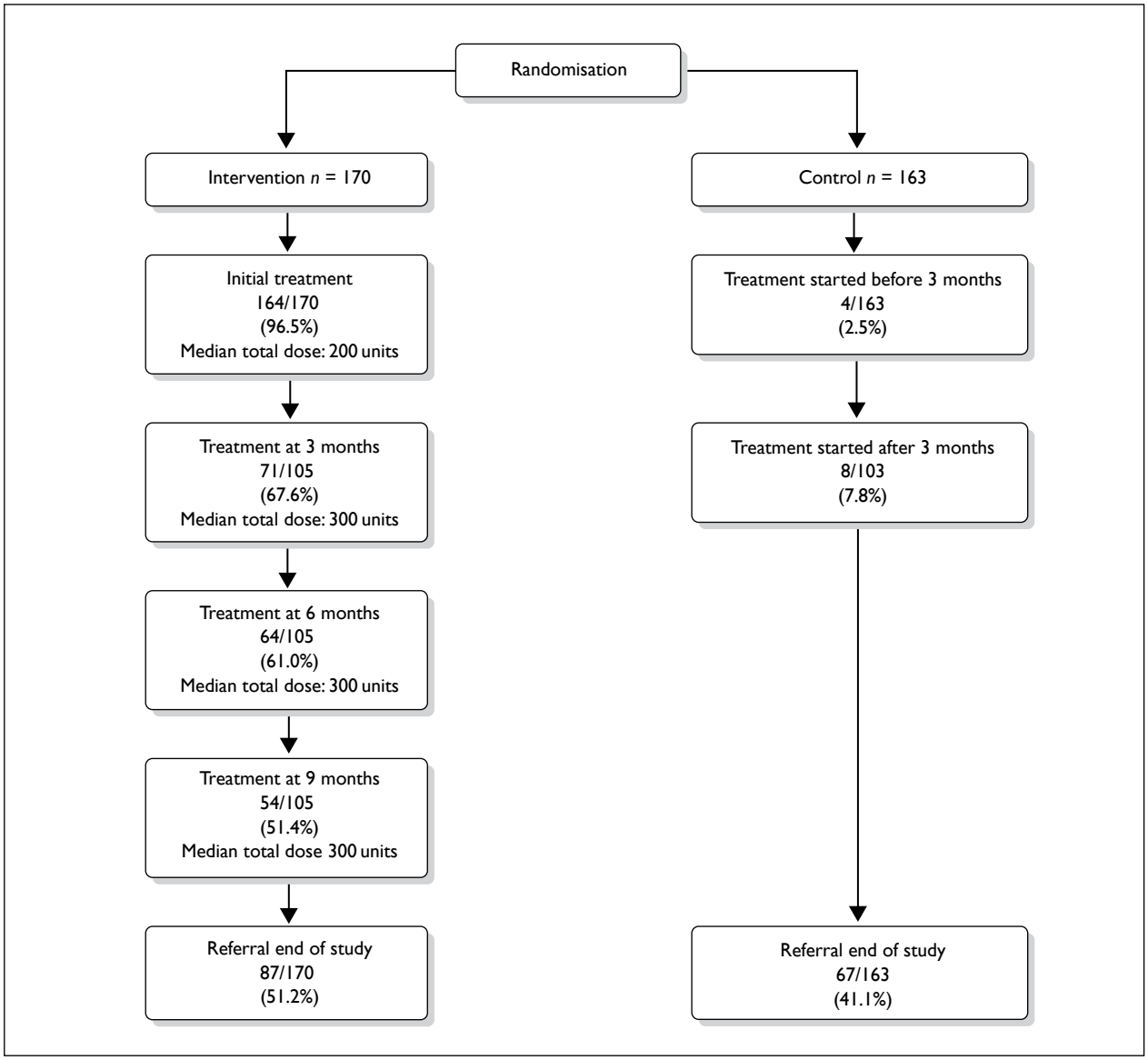


***FIGURE 5*** *Summary of botulinum toxin treatment in both randomisation groups.*

## Upper limb therapy

Participants in both groups received upper limb therapy immediately following study entry for 1 hour twice per week for 4 weeks. Participants were reassessed for further therapy at 3, 6 and 9 months. The therapy programme for the study consisted of two menus. Menu 1 was designed for participants with no active upper limb function at trial entry (ARAT 0–3) and menu 2 was designed for participants with some retained function (ARAT 4–56). At the end of the study participants were clinically reviewed and those requiring further therapy were referred to local services.

In the control group, 159/163 (97.5%) participants received initial study therapy and in the intervention group this was 168/170 (98.8%). The six participants who did not receive therapy withdrew from the study before treatment could commence. *Table 19* shows the therapy menu used and number of sessions delivered in each group. Therapy data were missing for one participant in the control group, although the study therapist confirmed that he was treated. Participants in both groups received a median of eight treatment sessions in the 4 weeks postrandomisation [110 (70%) participants in the control group and 129 (77%) participants in the intervention group received the full eight treatment sessions following randomisation]. There were no statistically significant differences between the groups for the therapy menu used or number of therapy sessions received.

One hundred and five participants randomised to the intervention group and 103 randomised to the control group entered the study for a 12-month follow-up and were therefore eligible for further therapy if necessary following reassessment at 3, 6 and 9 months. The number of participants completing clinical review at each time point is shown in *Table 20*.

The design of the therapy programme was such that once it had been taught it could be practised without the need for face-to-face contact with a therapist. Therefore, following review, the majority of participants were encouraged to continue with the programme previously demonstrated. Unfortunately, data regarding the amount and content of therapy received at 3, 6 and 9 months was of poor quality and was not suitable for analysis.

# Trial safety evaluation

For clinical trials using investigational medicinal products, trial safety is evaluated by examining the occurrence of all adverse events as defined by the *Medicines for Human Use (Clinical Trials) Regulations*.[100] All serious adverse events were

***TABLE 19*** *Initial study upper limb therapy*

| | Control ($n = 158$) | Intervention ($n = 168$) | $p$-value |
|---|---|---|---|
| ***Therapy programme:* n *(%)*** | | | |
| Menu 1 (ARAT 0–3) | 91 (57.6) | 97 (57.7) | 1.000 |
| Menu 2 (ARAT 4–56) | 67 (42.4) | 71 (42.3) | |
| ***Number of sessions (maximum 8): median (IQR)*** | 8 (7 to 8) | 8 (8 to 8) | 0.210 |

***TABLE 20*** *Completion of clinical review for upper limb therapy at 3, 6 and 9 months*

| | Control | Intervention |
|---|---|---|
| ***Completing clinical review:* n *(%)*** | | |
| 3 months | 92 (89.3) | 101 (96.1) |
| 6 months | 91 (88.3) | 102 (97.1) |
| 9 months | 90 (87.4) | 99 (94.3) |

assessed for causality and expectedness, and were immediately reported to the trial sponsor. Systems were in place for expedited reporting of suspected unexpected serious adverse reactions to the appropriate bodies. Annual safety reports were submitted to the Medicines and Healthcare Products Regulatory Agency and the Multicentre Research Ethics Committee as required.

Safety data were analysed according to treatment received. Serious adverse events occurred in 34/156 (21.7%) participants who had not received botulinum toxin type A during the study and in 36/176 (20.5%) participants who had received botulinum toxin type A treatment. However, for two participants who received botulinum toxin type A during the study, the serious adverse events occurred before receipt of injections so they were included in the 'no botulinum toxin' group for the purposes of the analyses.

Fifty serious adverse events were reported from the 'no botulinum toxin' group and 52 from the 'received botulinum toxin' group. These events were summarised and categorised blinded to treatment received (*Table 21*). The most commonly reported serious adverse events were neurological events, including further strokes and seizures. Several musculoskeletal and respiratory events were also reported from both groups. There were no statistically significant differences between the groups for any serious adverse event type.

All serious adverse events were assessed for their relationship to the study drug at the time of reporting. Only one event was reported as potentially related to botulinum toxin type A. This was an event recorded as dysphagia of unclear cause. As this is a known adverse reaction to botulinum toxin type A it was reported as a suspected serious adverse reaction. However, when further information became available about this event, it was assessed as unrelated to the study drug. No suspected unexpected serious adverse reactions were reported

Adverse events occurred in 70/156 (44.9%) participants who had not received botulinum toxin type A during the study and 90/176 (51.1%) participants who had received botulinum toxin type A treatment. However, for the participants who received botulinum toxin type A during the study, six had events that occurred before receipt of toxin and three had events that occurred both before and after botulinum toxin injection(s). For the purposes of the analyses those that had events before they received botulinum toxin type A were included in the 'no botulinum' group. Participants that had events both before and after botulinum toxin type A were included in the 'received botulinum toxin' group, which was a pragmatic decision as analyses were performed in exclusive categories.

One hundred and fourteen adverse events were reported from the 'no botulinum toxin' group and 147 from the 'received botulinum toxin' group. Adverse event descriptions were summarised and categorised blinded to treatment received (*Table 22*). It was not intended to calculate relative risk for any of the individual adverse events (only the categories), but on examining the data it appeared that there were several more 'chest infections' and 'general malaise/flu-like/cold symptoms' in the 'received botulinum toxin' group. A relative risk estimate was therefore calculated for these. For chest infection, the botulinum toxin relative risk was 1.4 (95% CI 0.5 to 3.5) and for general malaise/flu-like/cold it was 7.6 (95% CI 1.8 to 32.3). General malaise/flu-like/cold symptoms are recognised side effects of botulinum toxin type A.

As with serious adverse events, all adverse events were assessed for their relationship to botulinum toxin type A at the time of reporting. In addition, adverse events were also assessed for their relationship to study upper limb therapy. Twenty-eight events were reported as possibly or probably related to botulinum toxin type A and 16 events were reported as possibly or probably related to study upper limb therapy (*Table 23*). All other events were assessed as not related to study botulinum toxin or study therapy.

## Secondary analysis of primary outcome

A logistic regression model was used to adjust the primary outcome (predefined treatment success on the ARAT at 1 month) for randomisation strata factors (*Table 24*). Adjustment for research centre and baseline upper limb function (ARAT 0–3, 4–28, 29–56) had very little impact on the magnitude of the estimated effect of botulinum toxin; the relative odds of a 'treatment success' changed from 1.39 to 1.41.

## Preplanned subgroup analyses

The effect of time since stroke and severity of initial upper limb function upon the primary outcome

***TABLE 21*** *Summary of serious adverse events*

| | **No botulinum toxin (*n* = 158)** | | **Received botulinum toxin (*n* = 174)** | | |
|---|---|---|---|---|---|
| **Serious adverse event** | **No of participants (%)** | **Total number of events** | **No of participants (%)** | **Total number of events** | **Botulinum toxin relative risk (95% CI)** |
| ***Cardiac*** | 4 (2.5) | 4 | 3 (1.7) | 3 | 0.7 (0.2 to 3.0) |
| Arrhythmia | | 3 | | 1 | |
| Cardiac failure | | 0 | | 1 | |
| Chest pain unknown cause | | 0 | | 1 | |
| Myocardial infarction | | 1 | | 0 | |
| ***Endocrine*** | 0 (0.0) | 0 | 1 (0.6) | 2 | |
| Unstable diabetes mellitus | | 0 | | 2 | |
| ***Gastrointestinal*** | 2 (1.3) | 2 | 2 (1.1) | 2 | 0.9 (0.1 to 6.4) |
| *Clostridium difficile* diarrhoea | | 0 | | 1 | |
| Gastrointestinal bleed | | 1 | | 1 | |
| Irritable bowel syndrome | | 1 | | 0 | |
| ***Musculoskeletal*** | 5 (3.2) | 5 | 10 (5.7) | 11 | 1.8 (0.6 to 5.2) |
| Fracture following fall | | 3 | | 7 | |
| Soft tissue injury following fall | | 0 | | 2 | |
| Fracture following road traffic accident | | 1 | | 0 | |
| Chronic osteomyelitis | | 1 | | 0 | |
| Decreased mobility ? cause | | 0 | | 1 | |
| Elective musculoskeletal surgery | | 0 | | 1 | |
| ***Neurological*** | 19 (12.0) | 22 | 10 (5.7) | 11 | 0.5 (0.2 to 1.0) |
| Seizure | | 11 | | 6 | |
| New stroke | | 7 | | 5 | |
| Transient ischaemic attack | | 1 | | 0 | |
| Elective neurosurgery | | 1 | | 0 | |
| Headache | | 1 | | 0 | |
| Possible tardive dyskinesia | | 0 | | 1 | |
| ***Psychiatric*** | 0 (0.0) | 0 | 1 (0.6) | 1 | |
| Self-harm | | 0 | | 1 | |
| ***Respiratory*** | 6 (3.8) | 8 | 9 (5.2) | 11 | 1.4 (0.5 to 3.7) |
| Chest infection | | 8 | | 8 | |
| Elective respiratory surgery | | 0 | | 2 | |
| Non-infective exacerbation of chronic obstructive airway disease | | 0 | | 1 | |

*continued*

***TABLE 21*** *Summary of serious adverse events (continued)*

| Serious adverse event | No botulinum toxin (*n* = 158) | | Received botulinum toxin (*n* = 174) | | Botulinum toxin relative risk (95% CI) |
|---|---|---|---|---|---|
| | No of participants (%) | Total number of events | No of participants (%) | Total number of events | |
| ***Urinary tract*** | 4 (2.5) | 4 | 7 (4.0) | 7 | 1.6 (0.5 to 5.3) |
| Urinary tract infection (UTI) | | 2 | | 3 | |
| UTI and renal failure | | 0 | | 1 | |
| Urinary retention/catheter issue | | 2 | | 3 | |
| ***Miscellaneous*** | 5 (3.2) | 5 | 4 (2.3) | 4 | 0.7 (0.2 to 2.7) |
| Burn | | 1 | | 0 | |
| Cellulitis | | 1 | | 1 | |
| Deep vein thrombosis | | 1 | | 0 | |
| Death, cause unknown | | 1 | | 0 | |
| Dysphagia unknown cause | | 0 | | 1 | |
| Elective sinus surgery | | 0 | | 1 | |
| Metastatic cancer | | 1 | | 0 | |
| Vasovagal event | | 0 | | 1 | |

***TABLE 22*** *Summary of adverse events*

| Adverse event | No botulinum toxin (*n* = 162) | | Received botulinum toxin (*n* = 170) | | Botulinum toxin relative risk (95% CI) |
|---|---|---|---|---|---|
| | No of participants (%) | Total number of events | No of participants (%) | Total number of events | |
| Cardiac | 8 (4.9) | 9 | 8 (4.7) | 9 | 1.0 (0.4 to 2.5) |
| Ear | 1 (0.6) | 1 | 2 (1.2) | 2 | 1.9 (0.2 to 20.8) |
| Eye | 2 (1.2) | 2 | 3 (1.8) | 3 | 1.4 (0.2 to 8.5) |
| Endocrine | 1 (0.6) | 1 | 1 (0.6) | 1 | 1.0 (0.1 to 15.1) |
| Gastrointestinal | 4 (2.5) | 4 | 10 (5.9) | 12 | 2.4 (0.8 to 7.5) |
| Haematological | 1 (0.6) | 2 | 3 (1.8) | 3 | 2.9 (0.3 to 27.0) |
| Musculoskeletal | 8 (4.9) | 10 | 13 (7.6) | 16 | 1.5 (0.7 to 3.6) |
| Neurological | 10 (6.2) | 10 | 6 (3.5) | 6 | 0.6 (0.2 to 1.5) |
| Psychiatric | 2 (1.2) | 3 | 5 (2.9) | 4 | 2.4 (0.5 to 12.0) |
| Respiratory | 8 (4.9) | 9 | 12 (7.1) | 13 | 1.4 (0.6 to 3.4) |
| Skin | 11 (6.8) | 12 | 10 (5.9) | 11 | 0.9 (0.4 to 2.0) |
| Urinary tract | 8 (4.9) | 9 | 9 (5.3) | 9 | 1.1 (0.4 to 2.7) |
| Miscellaneous | 32 (19.8) | 42 | 43 (25.3) | 58 | 1.3 (0.9 to 1.9) |

***TABLE 23*** *Adverse events potentially related to botulinum toxin type A or upper limb therapy*

| Event | Potentially related to botulinum toxin type A | Potentially related to upper limb therapy |
|---|---|---|
| ***Gastrointestinal*** | 3 | 0 |
| Diarrhoea | 2 | – |
| Abdominal pain unknown cause | 1 | – |
| ***Musculoskeletal*** | 1 | 3 |
| Muscle sprain | 1 | 1 |
| Frozen shoulder | 0 | 1 |
| Cramp | 0 | 1 |
| ***Neurological*** | 2 | 2 |
| Headache | 2 | 0 |
| Paraesthesia | 0 | 2 |
| ***Respiratory*** | 2 | 0 |
| Chest infection | 1 | – |
| Shortness of breath/cough | 1 | – |
| ***Skin*** | 2 | 0 |
| Rash | 2 | – |
| ***Urinary tract*** | 1 | 0 |
| Urinary frequency/incontinence | 1 | – |
| ***Miscellaneous*** | 17 | 11 |
| General malaise/flu like/cold | 14 | 2 |
| Fall +/– minor injury | 1 | 0 |
| Dizziness | 1 | 0 |
| Perspiration | 1 | 0 |
| Upper limb pain | 0 | 7 |
| Pain – other | 0 | 1 |
| Minor injury | 0 | 1 |

***TABLE 24*** *Estimated 'treatment success' with botulinum toxin adjusting for stratification factors*

| Effects included in logistic regression model[a] | | Estimated effect of botulinum toxin[b] | |
|---|---|---|---|
| **Fixed** | **Random** | **OR[c]** | **95% CI** |
| None | None | 1.39 | 0.82 to 2.36 |
| None | Centre | 1.39 | 0.82 to 2.36 |
| Initial ARAT group | Centre | 1.41 | 0.82 to 2.42 |

a The dependent variable is the primary outcome – for an individual patient whether there has been a clinically important change in the ARAT score; all models include the difference between groups as a fixed effect.
b The parameter estimate corresponding to the difference between groups described above.
c OR = odds ratio (Intervention/Control).

and statistically significant secondary outcomes was addressed.

## Time since stroke

Response to treatment was compared for participants who joined the study within 1 year following stroke ($n = 181$) and those who were recruited after 1 year ($n = 151$).

Fitting a logistic regression model, participants recruited within 1 year of stroke were more likely to experience 'treatment success' than participants recruited more than 1 year after stroke, but the difference was not statistically significant (odds ratio 1.6; 95% CI 0.92 to 2.79; $p = 0.09$). Fitting an interaction between randomised treatment and time since stroke did not improve the fit of the model ($p = 0.69$).

For secondary outcomes (*Table 25*), although there were some significant differences between intervention and control groups within the subgroups, there were no significant differences between the subgroups for any outcome.

## Severity of initial upper limb function

Data were analysed according to baseline ARAT score: no active upper limb function ARAT 0–3 ($n = 184$) and some retained active upper limb function ARAT 4–56 ($n = 145$).

Fitting a logistic regression model, participants with some retained active upper limb function (ARAT 4–56) were more likely to experience 'treatment success' than participants with no retained upper limb function (ARAT 0–3) (odds ratio 2.41; 95% CI 1.40 to 4.14) but on fitting an interaction between randomised treatment and baseline ARAT score, the model was not significant ($p = 0.81$).

For secondary outcomes (*Table 26*), there were no significant differences between the subgroups for the estimated effect of the intervention on changes in muscle tone (1 month), arm strength (3 months), performance of basic upper limb functional activities (1, 3 and 12 months) or pain rating (12 months). However, for the change in ARAT score from baseline to 3 months the estimated effect of the intervention was 0.3 (95% CI –0.5 to 1.1) and 3.6 (95% CI 0.7 to 6.5) in the ARAT 0–3 and ARAT 4–56 subgroups, respectively. The difference in effect between the subgroups was 3.3 (95% CI 0.3 to 6.3).

# Summary

*Table 27* summarises the main results of the RCT.

***TABLE 25*** *Influence of time since stroke on selected secondary outcomes*

| | Control | Intervention | Difference | Difference between subgroups |
|---|---|---|---|---|
| ***Modified Ashworth Score at elbow: mean change 1 month (95% CI)*** | | | | |
| ≤ 1 year | −0.1 (−0.3 to 0.2) | −0.6 (−0.8 to −0.4) | −0.5 (−0.9 to −0.2) | 0.0 (−0.5 to 0.5) |
| > 1 year | 0.0 (−0.3 to 0.2) | −0.6 (−0.8 to −0.3) | −0.5 (−0.9 to −0.2) | |
| ***Motricity Index: mean change 3 months (95% CI)*** | | | | |
| *Arm* | | | | |
| ≤ 1 year | −0.6 (−3.5 to 2.3) | 5.4 (1.9 to 8.7) | 6.0 (1.5 to 10.5) | −5.7 (−12.3 to 1.0) |
| > 1 year | 4.8 (1.2 to 8.5) | 5.1 (1.9 to 8.6) | 0.3 (−4.6 to 5.3) | |
| *Total* | | | | |
| ≤ 1 year | −0.3 (−2.6 to 2.0) | 4.8 (2.1 to 7.6) | 5.1 (1.6 to 8.7) | −4.4 (−9.7 to 0.8) |
| > 1 year | 3.1 (0.0 to 6.2) | 3.8 (1.3 to 6.4) | 0.7 (−3.3 to 4.7) | |
| ***ARAT: mean change 3 months (95% CI)*** | | | | |
| ≤ 1 year | 1.8 (0.7 to 3.1) | 3.5 (1.8 to 5.3) | 1.6 (−0.4 to 3.7) | 0.5 (−2.3 to 3.4) |
| > 1 year | 0.5 (−1.0 to 1.8) | 2.6 (1.4 to 3.9) | 2.1 (0.3 to 4.1) | |
| ***Upper limb functional activities: mean change (95% CI)*** | | | | |
| *Put arm through sleeve* | | | | |
| 1 month | | | | |
| ≤ 1 year | −0.1 (−0.4 to 0.2) | 0.4 (0.2 to 0.7) | 0.5 (0.2 to 0.9) | −0.4 (−0.9 to 0.1) |
| > 1 year | 0.2 (0.0 to 0.4) | 0.3 (0.0 to 0.6) | 0.1 (−0.2 to 0.5) | |
| *Open the hand for cleaning your palm* | | | | |
| 1 month | | | | |
| ≤ 1 year | 0.1 (−0.2 to 0.4) | 0.3 (0.0 to 0.6) | 0.2 (−0.2 to 0.6) | 0.2 (−0.4 to 0.7) |
| > 1 year | 0.2 (−0.2 to 0.5) | 0.5 (0.2 to 0.8) | 0.4 (−0.1 to 0.8) | |
| 3 months | | | | |
| ≤ 1 year | 0.1 (−0.3 to 0.5) | 0.2 (−0.2 to 0.6) | 0.1 (−0.4 to 0.6) | 0.4 (−0.3 to 1.2) |
| > 1 year | −0.2 (−0.5 to 0.2) | 0.4 (0.1 to 0.7) | 0.5 (0.1 to 1.0) | |
| 12 months | | | | |
| ≤ 1 year | 0.0 (−0.5 to 0.5) | 0.2 (−0.3 to 0.8) | 0.3 (−0.5 to 1.0) | 0.5 (−0.5 to 1.4) |
| > 1 year | −0.2 (−0.6 to 0.3) | 0.6 (0.1 to 1.0) | 0.7 (0.1 to 1.4) | |
| *Open the hand for cutting fingernails* | | | | |
| 1 month | | | | |
| ≤ 1 year | 0.1 (0.0 to 0.2) | 0.2 (0.0 to 0.4) | 0.1 (−0.1 to 0.3) | −0.1 (−0.4 to 0.3) |
| > 1 year | 0.1 (−0.1 to 0.3) | 0.2 (0.0 to 0.4) | 0.1 (−0.2 to 0.3) | |
| 3 months | | | | |
| ≤ 1 year | 0.2 (0.0 to 0.4) | 0.3 (0.2 to 0.5) | 0.1 (−0.2 to 0.4) | −0.1 (−0.5 to 0.3) |
| > 1 year | 0.1 (−0.2 to 0.3) | 0.1 (−0.1 to 0.3) | 0.1 (−0.3 to 0.4) | |
| 12 months | | | | |
| ≤ 1 year | −0.1 (−0.4 to 0.3) | 0.3 (−0.1 to 0.6) | 0.3 (−0.2 to 0.8) | −0.1 (−0.7 to 0.5) |
| > 1 year | −0.1 (−0.3 to 0.2) | 0.2 (0.0 to 0.4) | 0.2 (−0.1 to 0.6) | |
| ***Pain description: mean change 12 months (95% CI)*** | | | | |
| ≤ 1 year | 0.4 (−0.1 to 0.8) | 0.9 (0.5 to 1.3) | 0.5 (−0.1 to 1.2) | −0.2 (−1.0 to 0.6) |
| > 1 year | 0.4 (0.0 to 0.7) | 0.7 (0.4 to 1.1) | 0.4 (−0.1 to 0.9) | |
| ***Pain score (0–10): mean change 12 months (95% CI)*** | | | | |
| ≤ 1 year | −0.8 (−2.0 to 0.4) | −2.4 (−3.4 to −1.3) | −1.5 (−3.2 to 0.1) | 0.4 (−1.7 to 2.4) |
| > 1 year | −0.8 (−1.6 to 0.0) | −2.0 (−3.0 to −1.0) | −1.2 (−2.5 to 0.1) | |

***TABLE 26*** *Influence of severity of initial upper limb function on selected secondary outcomes*

| | Control | Intervention | Difference | Difference between subgroups |
|---|---|---|---|---|
| ***Modified Ashworth Score at elbow: mean change 1 month (95% CI)*** | | | | |
| 0–3 | 0.2 (–0.1 to 0.4) | –0.5 (–0.8 to –0.3) | –0.7 (–1.0 to –0.3) | 0.3 (–0.2 to 0.8) |
| 4–56 | –0.3 (–0.6 to –0.1) | –0.7 (–0.9 to –0.4) | –0.4 (–0.7 to 0.0) | |
| ***Motricity Index: mean change 3 months (95% CI)*** | | | | |
| *Arm* | | | | |
| 0–3 | –0.2 (–3.4 to 3.0) | 5.5 (2.2 to 9.0) | 5.7 (1.1 to 10.4) | –5.1 (–11.7 to 1.5) |
| 4–56 | 4.3 (1.1 to 7.6) | 4.9 (1.6 to 8.2) | 0.6 (–4.1 to 5.3) | |
| *Total* | | | | |
| 0–3 | –0.2 (–2.5 to 2.1) | 4.8 (2.2 to 7.4) | 5.0 (1.5 to 8.5) | –4.2 (–9.6 to 1.3) |
| 4–56 | 3.0 (–0.1 to 6.1) | 3.8 (1.2 to 6.4) | 0.8 (–3.2 to 4.9) | |
| ***ARAT: mean change 3 months (95% CI)*** | | | | |
| 0–3 | 0.8 (0.4 to 1.3) | 1.1 (0.6 to 1.8) | 0.3 (–0.5 to 1.1) | **3.3 (0.3 to 6.3)** |
| 4–56 | 1.8 (–0.1 to 3.7) | 5.4 (3.3 to 7.6) | 3.6 (0.7 to 6.5) | |
| ***Upper limb functional activities mean change (95% CI)*** | | | | |
| *Put arm through sleeve 1 month* | | | | |
| 1 month | | | | |
| 0–3 | –0.1 (–0.4 to 0.1) | 0.3 (0.0 to 0.5) | 0.4 (0.0 to 0.8) | –0.1 (–0.6 to 0.4) |
| 4–56 | 0.2 (0.0 to 0.4) | 0.5 (0.2 to 0.7) | 0.3 (0.0 to 0.6) | |
| *Open the hand for cleaning your palm* | | | | |
| 1 month | | | | |
| 0–3 | 0.1 (–0.3 to 0.4) | 0.3 (0.0 to 0.6) | 0.3 (–0.2 to 0.7) | 0.0 (–0.5 to 0.6) |
| 4–56 | 0.2 (–0.1 to 0.5) | 0.5 (0.2 to 0.8) | 0.3 (–0.1 to 0.7) | |
| 3 months | | | | |
| 0–3 | –0.1 (–0.5 to 0.3) | 0.2 (–0.2 to 0.5) | 0.2 (–0.3 to 0.8) | 0.2 (–0.6 to 0.9) |
| 4–56 | 0.0 (–0.3 to 0.4) | 0.4 (0.1 to 0.8) | 0.4 (–0.1 to 0.9) | |
| 12 months | | | | |
| 0–3 | –0.2 (–0.7 to 0.3) | 0.4 (–0.2 to 1.1) | 0.7 (–0.1 to 1.5) | –0.3 (–1.3 to 0.6) |
| 4–56 | 0.1 (–0.4 to 0.5) | 0.4 (0.1 to 0.8) | 0.3 (–0.2 to 0.9) | |
| *Open the hand for cutting fingernails* | | | | |
| 1 month | | | | |
| 0–3 | 0.1 (–0.1 to 0.2) | 0.0 (–0.2 to 0.2) | –0.1 (–0.3 to 0.2) | 0.3 (0.0 to 0.7) |
| 4–56 | 0.1 (0.0 to 0.3) | 0.4 (0.2 to 0.6) | 0.3 (0.0 to 0.5) | |
| 3 months | | | | |
| 0–3 | 0.0 (–0.2 to 0.3) | 0.1 (–0.1 to 0.2) | 0.0 (–0.2 to 0.3) | 0.0 (–0.4 to 0.5) |
| 4–56 | 0.3 to 0.1 to 0.6) | 0.4 (0.2 to 0.6) | 0.1 (–0.2 to 0.4) | |
| 12 months | | | | |
| 0–3 | –0.2 (–0.5 to 0.0) | 0.2 (0.0 to 0.5) | 0.4 (0.1 to 0.8) | –0.4 (–1.0 to 0.1) |
| 4–56 | 0.2 (–0.2 to 0.5) | 0.2 (–0.1 to 0.4) | 0.0 (–0.4 to 0.4) | |
| ***Pain description: mean change 12 months (95% CI)*** | | | | |
| 0–3 | 0.3 (–0.1 to 0.7) | 0.8 (0.3 to 1.2) | 0.5 (–0.1 to 1.1) | –0.1 (–0.9 to 0.7) |
| 4–56 | 0.5 (0.1 to 0.8) | 0.9 (0.5 to 1.2) | 0.4 (–0.1 to 0.9) | |
| ***Pain score (0–10): mean change 12 months (95% CI)*** | | | | |
| 0–3 | –0.5 (–1.5 to 0.5) | –2.1 (–3.2 to –1.0) | –1.6 (–3.1 to –0.2) | 0.6 (–1.4 to 2.8) |
| 4–56 | –1.3 (–2.4 to –0.2) | –2.2 (–3.2 to –1.3) | –1.0 (–2.4 to 0.5) | |

***TABLE 27*** *Summary of RCT results*

| | 1 month | 3 months | 12 months |
|---|---|---|---|
| **Modified Ashworth Scale at elbow** | ✓ | × | × |
| **Motricity Index** | | | |
| Arm | × | ✓ | × |
| Total | × | ✓ | × |
| **Grip strength (kg)** | × | × | × |
| **ARAT predefined success** | × | × | × |
| **ARAT change from baseline** | × | ? | × |
| **Nine-Hole Peg Test (pegs placed in 50s)** | × | × | × |
| **Upper limb functional activities** | | | |
| Put arm through sleeve | ? | × | × |
| Open the hand for cleaning your palm | × | ? | ? |
| Open the hand for cutting fingernails | × | × | × |
| Use cutlery | × | × | × |
| **Improvement on upper limb functional activities of ≥ 1** | | | |
| Put arm through sleeve | ✓ | × | × |
| Open the hand for cleaning your palm | ✓ | ✓ | ✓ |
| Open the hand for cutting fingernails | ✓ | ✓ | ✓ |
| Use cutlery | × | × | × |
| **Barthel ADL Index** | × | × | × |
| **Stroke Impact Scale domains** | | | |
| Strength | × | × | × |
| Memory | × | × | × |
| Emotion | × | × | × |
| Communication | × | × | ? |
| ADL | × | × | × |
| Mobility | × | × | × |
| Hand function | × | × | × |
| Participation / Handicap | × | × | × |
| Physical domain | × | × | × |
| Stroke recovery | × | × | × |
| **EQ-5D** | | | |
| Mobility | × | × | × |
| Self-care | × | × | × |
| Usual activities | × | × | × |
| Pain / discomfort | × | ? | × |
| Anxiety / depression | × | × | ? |
| Good/bad health scale | × | × | × |
| **Oxford Handicap Scale** | × | ? | ? |
| **Pain description** | × | × | ✓ |
| **Pain score (0–10)** | × | × | ✓ |

✓ Statistically and clinically significant difference in favour of intervention group.
× No statistical difference between groups.
? Statistically significant difference in favour of intervention group but of doubtful clinical importance.

# Chapter 4
# Economic evaluation

The aim of the economic evaluation was to assess the cost-effectiveness of botulinum toxin type A injection(s) plus upper limb therapy relative to upper limb therapy alone. The economic evaluation follows the technology appraisal guidelines used by the National Institute for Health and Clinical Excellence (NICE) and as such adopts the perspective of the UK National Health Service and Social Services.[108] The time horizon for the analysis was 3 months from randomisation, with all costs reported in 2007 prices.

## Assessment of costs

Participants' use of resources was categorised under four general headings: (1) upper limb therapy sessions with or without botulinum toxin type A; (2) other antispasticity medication; (3) management of adverse events attributable to botulinum toxin type A and/or upper limb therapy requiring a hospital contact; and (4) other health-care and social services resource use. A breakdown of the individual items of resource use under these headings and their unit costs are presented in *Table 28*.

With respect to therapy sessions and botulinum toxin type A, data were collected in the study case record forms on the number of therapy sessions each participant received and the number of 500-unit vials of botulinum toxin type A they used. Each therapy session was staffed by one therapist and lasted for 1 hour. Unit cost data were obtained from Curtis 2007[109] and the *British National Formulary* (BNF).[110]

Data on other antispasticity medication were collected in the study case record forms. The forms recorded which drugs the participants were on at baseline, 1 and 3 months. For most participants, the length of time they spent taking a particular drug was straightforward to calculate insofar as if no changes to medications were noted, they were assumed to be taking the drug until such time as a change was noted. Problems arose when, for example, a participant was not taking a drug at baseline, but was noted as taking a drug at a later follow-up time point. Since the precise time at which the participant began taking the drug was not recorded, it was assumed that such participants began taking the drug at the mid-point between baseline and the time at which it was first noted they were taking the drug, i.e. 2 weeks for the 1-month follow-up, and 2 months for the 3-month follow-up. In the few cases where follow-up data were missing, it was assumed that participants remained on the drugs they were taking at baseline.

Another problem regarding antispasticity medication was failure to record the drug dosage that participants were taking. To deal with this, it was assumed that participants were taking the standard dose stipulated in the BNF 2007.[110] If a standard dose was not stated, then it was assumed that participants were taking the maximum recommended dose.

Data on adverse events attributable to botulinum toxin type A and/or therapy which led to a hospital contact were obtained from the study adverse event monitoring forms and from participant responses to specific resource use questions included in the participant assessment questionnaires. A distinction was made between outpatient attendances and events requiring an inpatient stay. Although there were cases of participants encountering hospital services as a consequence of their initial stroke, clinical review showed that none of the hospital contacts were attributable to either therapy or botulinum toxin type A. As a result, hospital resource use due to adverse events did not form part of the cost-effectiveness analysis.

Data on other health-care and social services resource use were obtained from the participant assessment questionnaires, which were administered at baseline, 1 and 3 months. These included questions on participants' use of health-care and social services, such as day hospitals and day centres, and health-care and social services professional contacts, such as general practitioners and social workers. Unit cost data were mainly obtained from Curtis 2007.[109] Where unit cost data were not available, assumptions were made (see notes accompanying *Table 28*).

***TABLE 28*** *Breakdown of resource use and corresponding unit cost data*

| Resource | Unit cost (2007 prices) | Source of unit cost data |
|---|---|---|
| ***Upper limb therapy and botulinum toxin*** | | |
| Therapist | £40 per session | Curtis (2007)[109] |
| Botulinum toxin | £153.21 per 500-unit vial | BNF (2007)[110] |
| ***Other antispasticity medication*** | | |
| Gabapentin | £96.73 per month | BNF (2007)[110] |
| Baclofen | £9.13 per month | BNF (2007)[110] |
| Tizanidine | £74.83 per month | BNF (2007)[110] |
| Dantrolene | £33.76 per month | BNF (2007)[110] |
| Methocarbamol | £7.60 per month | BNF (2007)[110] |
| ***Other health-care and social services*** | | |
| Day hospital | £83 per place per day | Curtis (2007)[109] |
| Home care services | £19 per contact[a] | Curtis (2007)[109] |
| Private home help | £11.33 per contact[a] | Curtis (2007)[109] |
| Day centre | £147 per attendance | Curtis (2007)[109] |
| Meals on wheels | £3.63 per meal | Curtis (2007)[109] |
| Laundry service | £3 per wash | Assumption[b] |
| General practitioner | £36 per consultation | Curtis (2007)[109] |
| Practice nurse | £9 per consultation | Curtis (2007)[109] |
| District nurse | £24 per home visit | Curtis (2007)[109] |
| Health visitor | £36 per home visit | Curtis (2007)[109] |
| Physiotherapist | £40 per contact[a] | Curtis (2007)[109] |
| Occupational therapist | £40 per contact[a] | Curtis (2007)[109] |
| Speech and language therapist | £40 per contact[a] | Curtis (2007)[109] |
| Dietician | £32 per contact[a] | Curtis (2007)[109] |
| Chiropodist | £18 per contact[a] | Curtis (2007)[109] |
| Social worker | £34 per contact[a] | Curtis (2007)[109] |
| Clinical psychologist | £67 per contact[a] | Curtis (2007)[109] |
| Continence advisor | £24 per home visit | Curtis (2007)[109] |
| Bath attendant | £11.33 per contact[a] | Assumption[c] |
| Orthotist | £40 per contact[a] | Assumption[d] |

a Assumes 1 hour per contact.
b Based on local council fees of £3 per wash.
c Assumed same rate as private home help.
d Assumed Agenda for Change Band 5.

The resource use questions asked participants to report resource use for the 1-month period prior to completion of the questionnaire. This means that participant-reported resource use data were comprehensive for months 1 and 3, but that extrapolations had to be made for month 2. The extrapolation method adopted in the base-case analysis was to assume resource use in month 2 was the same as that in month 3. The impact on the results of alternatively assuming that resource use in month 2 is the same as in month 1 is investigated in the sensitivity analysis.

## Assessment of outcome

Participant health-related quality of life was assessed using the EQ-5D,[111] which was included in the participant assessment questionnaires. Differences between the randomisation groups

at follow-up with respect to EQ-5D scores were investigated using multiple regression analysis of covariance. The average follow-up score of the EQ-5D (the mean of the 1-, 3- and 12-month assessments) was estimated and included as the dependent variable in a linear regression model. Covariates in the model were the 'baseline EQ-5D score' and the 'randomisation group' (coded 0 for therapy alone and 1 for botulinum toxin type A plus therapy). The regression coefficient estimate for randomisation group represents the difference in mean EQ-5D follow-up scores between the therapy alone and the botulinum toxin plus therapy groups after adjustment for baseline EQ-5D values.

Participant responses to the EQ-5D questionnaire were converted to health-state utility values using the UK tariff values.[112] These values were then multiplied by duration in each health state to estimate quality-adjusted life-years (QALYs). QALYs were estimated using an area under the curve (AUC) approach.[113] To illustrate this approach, consider an individual whose baseline and 3-month quality of life weights are 0.6 and 0.8, respectively. When located on a two-dimensional plane where the *y*-axis corresponds to the quality of life weight and the *x*-axis corresponds to time in years, the AUC that joins these two points defines a trapezium, the area of which is equal to the number of QALYs enjoyed by the patient in the 3 months since randomisation. The area of a trapezium with a base width of 3 months (one-quarter of a year) and whose sides are defined as $a$ and $b$ is equal to $\frac{1}{2} \times \frac{1}{4} (a + b)$. In this example, $a = 0.6$ and $b = 0.8$. Hence, the AUC corresponds to 0.175 QALYs.

To estimate QALYs, participant responses at baseline and 3 months were used to map out the AUC. An alternative approach would be to use the baseline, 1-month and 3-month points. Although this latter approach provides a more precise estimate of QALYs, the inclusion of the 1-month values increases missing values and consequently decreases the number of participants on which the estimation is based. Therefore, the first approach was used in the base-case analysis, with the possible impacts on the results of the second approach being investigated in the sensitivity analysis.

## Assessment of cost-effectiveness

To assess the relative cost-effectiveness of botulinum toxin type A plus upper limb therapy relative to upper limb therapy alone, data on cost and outcome were brought together to estimate an incremental cost-effectiveness ratio (ICER). Specifically, the incremental cost per QALY gained of botulinum toxin type A plus therapy relative to therapy alone was estimated.

The ICER for botulinum toxin type A plus therapy can be located on the cost-effectiveness plane (*Figure 6*), which is a two-dimensional space in which the origin represents the comparator intervention – in this case therapy alone. The *x*-axis represents the average difference in effectiveness per participant between botulinum toxin type A plus therapy and therapy alone, while the *y*-axis represents the average difference in cost per participant between the interventions. The four quadrants are conventionally referred to as points on the compass, namely north-west (NW), north-east (NE), south-west (SW) and south-east (SE). The ICER can be plotted as a point on this plane, with the slope of the line from the origin to the ICER representing the value of the ICER. Treatments with ICERs located in the NW quadrant (more costly, less effective) are said to be dominated by the comparator treatment, whereas treatments with ICERs located in the SE quadrant (less costly, more effective) are said to dominate the comparator treatment. In practice, most new treatments locate in the NE quadrant where increased effectiveness is achieved at increased cost. In this instance the decision to adopt the new treatment will depend upon whether the ICER lies below the acceptable ceiling ratio of the decision-maker. If the decision-maker's willingness to pay for a unit of effectiveness ($\lambda$) is greater than the ICER, then on efficiency grounds the treatment should be recommended for adoption.

The point estimate of the ICER is subject to uncertainty and it is therefore important that this uncertainty is taken into account. Because of the problems associated with estimating CIs for ratio statistics, the approach of non-parametric bootstrapping is adopted to represent the uncertainty surrounding the ICER estimate.[114] A cost-effectiveness acceptability curve (CEAC), which summarises the evidence in support of botulinum toxin type A plus therapy being cost-effective for a range of values of $\lambda$, is also presented. The probabilistic interpretation of this curve should be from a Bayesian perspective. In effect, the CEAC provides information to decision-makers on the level of uncertainty associated with a potential decision to recommend the use of a new or additional intervention. For example, a 0.82 probability of an intervention being cost-effective at a ceiling ratio of £20,000 per QALY implies an error probability (i.e. the probability of making

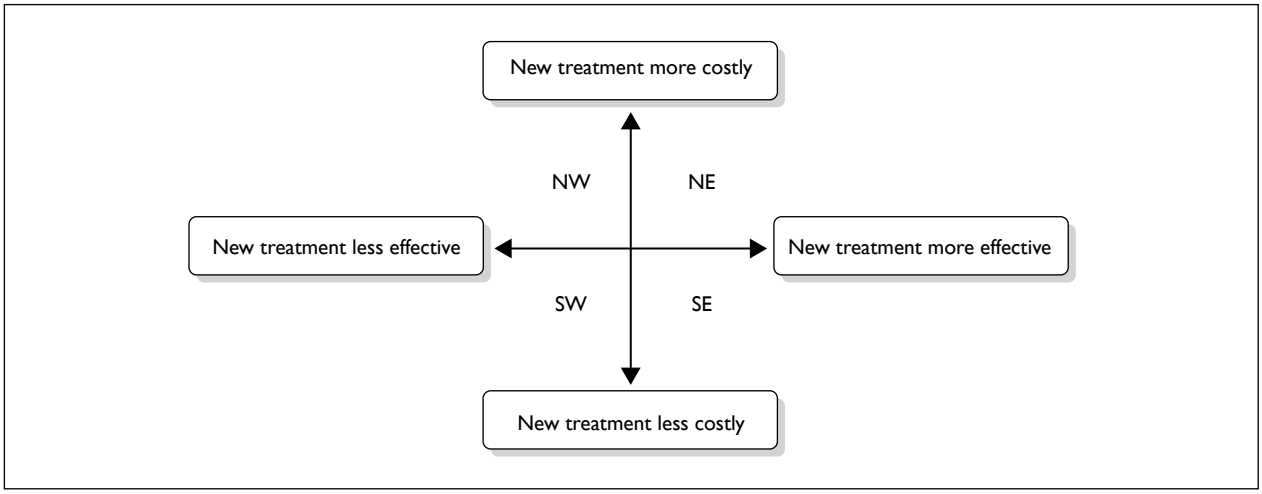


***FIGURE 6*** *The cost-effectiveness plane.*

a wrong decision) of 0.18 (1 – 0.82). In making a decision regarding the potential recommendation of a new intervention, the decision-maker must weigh up these probabilities against one another. Alternatively, instead of deciding whether or not to recommend the new intervention on the basis of the currently available evidence, the decision-maker may demand an expected value of perfect information analysis to compare the expected cost of the uncertainty with the value of conducting further research to reduce the uncertainty (see Claxton *et al.*[115] for more details on expected value of perfect information analysis).

In addition to addressing the uncertainty surrounding the point estimate of the ICER, sensitivity analysis was undertaken to investigate the impact on the results of making alternative assumptions and varying key parameters. As part of the sensitivity analysis, to take into account missing data, an additional set of analyses were carried out using the technique of multiple imputation in which missing data were imputed using the NORM package[116]. Five data sets were imputed using age, sex, place of residence, Barthel ADL score and time between stroke and randomisation as explanatory variables. A point estimate of the ICER and the accompanying CEAC for botulinum toxin type A plus therapy were estimated.

## Results of the outcome assessments

*Table 29* shows the mean EQ-5D scores over time for the botulinum toxin type A plus therapy and therapy alone groups.

Regression analysis of covariance indicated that there was no significant difference between the groups with respect to mean follow-up EQ-5D scores after adjusting for baseline values.

## Results of the cost-effectiveness analysis

The base-case analysis was based on 283 participants who provided EQ-5D responses at baseline and 3 months, of whom 150 were in the intervention group and 133 were in the control group.

There was no significant difference in the mean number of upper limb therapy sessions received by participants in the botulinum toxin type A plus therapy and therapy alone groups (7.64 versus 7.56, respectively; $p = 0.46$). With respect to use of botulinum toxin type A, the average number of vials used by each patient in the intervention group was 1.01. The numbers of participants taking other antispasticity drugs were 38 in the botulinum toxin type A plus therapy group and 31 in the therapy alone group, with the difference between the groups not being significant ($\chi^2 = 0.157$; $p = 0.692$).

A breakdown of other health-care and social services resource use among participants is presented in *Table 30*.

Chi-squared tests of differences in the proportion of participants in each randomisation group reporting a contact reveal significantly more practice nurse and social worker contacts among participants in the botulinum toxin type A plus

***TABLE 29*** *Mean EQ-5D scores over time for the botulinum toxin type A plus therapy and therapy alone groups*

| | Mean (SD) EQ-5D scores and number of participants providing a response (*n*) | | | |
|---|---|---|---|---|
| | Therapy alone | | Botulinum toxin type A plus therapy | |
| Time point | Mean (SD) | *n* | Mean (SD) | *n* |
| Baseline | 0.3322 (0.2962) | 162 | 0.3206 (0.2964) | 170 |
| 1 month | 0.3041 (0.2992) | 134 | 0.3245 (0.2956) | 144 |
| 3 months | 0.3206 (0.2963) | 133 | 0.3478 (0.2920) | 150 |
| 12 months | 0.2727 (0.3078) | 86 | 0.3195 (0.2942) | 88 |

SD, standard deviation.

***TABLE 30*** *Breakdown of other health-care and social services resource use*

| | Mean (SD) number of contacts among patients reporting a contact (*n*) | | | | |
|---|---|---|---|---|---|
| | Therapy alone | | Botulinum toxin type A plus therapy | | Mean difference in number of contacts (95% CI of difference) |
| Item of resource use | Mean (SD) | *n* | Mean (SD) | *n* | |
| Day hospital | 9.4 (9.0) | 25 | 3.1 (2.7) | 21 | 6.3 (2.4 to 10.2) |
| Home-care services | 87.5 (75.7) | 45 | 114.6 (76.5) | 56 | −27.1 (−57.3 to 3.2) |
| Private home help | 32.7 (53.5) | 17 | 38.9 (60.1) | 16 | −6.2 (−46.6 to 34.1) |
| Day centre | 16.3 (8.3) | 25 | 14.1 (10.3) | 24 | 2.2 (−3.1 to 7.6) |
| Meals on wheels | 6.0 | 1 | 56.0 (38.6) | 3 | −50.0 (−241.7 to 141.7) |
| Laundry service | 14.7 (18.5) | 3 | 18.0 (11.1) | 3 | −3.3 (−38.0 to 31.3) |
| General practitioner | 2.8 (1.4) | 60 | 2.8 (1.9) | 86 | 0.0 (−0.6 to 0.6) |
| Practice nurse | 2.6 (1.8) | 24 | 2.9 (2.9) | 44 | −0.3 (−1.6 to 1.0) |
| District nurse | 8.3 (14.6) | 27 | 4.0 (5.0) | 30 | 4.3 (−1.8 to 10.2) |
| Health visitor[a] | | 1 | 1.0 | 1 | |
| Physiotherapist | 13.3 (12.7) | 74 | 12.0 (10.5) | 87 | 1.3 (−2.46 to 4.8) |
| Occupational therapist | 8.2 (8.8) | 26 | 8.5 (9.1) | 38 | −0.3 (−4.9 to 4.2) |
| Speech and language therapist | 4.6 (5.3) | 28 | 8.9 (9.7) | 20 | −4.3 (−9.2 to 0.6) |
| Dietician | 2.2 (1.2) | 6 | 13.0 (15.6) | 2 | −10.8 (−149.5 to 127.8) |
| Chiropodist | 2.0 (1.2) | 24 | 2.3 (1.1) | 40 | −0.3 (−0.9 to 0.3) |
| Social worker | 2.8 (1.7) | 17 | 2.5 (2.0) | 35 | 0.3 (−0.8 to 1.5) |
| Clinical psychologist | 3.1 (2.5) | 8 | 2.5 (1.3) | 4 | 0.6 (−2.4 to 3.7) |
| Continence advisor | 1.8 (1.0) | 4 | 1.0 | 1 | 0.8 (−2.7 to 4.2) |
| Bath attendant | 19.5 (18.9) | 13 | 18.2 (11.4) | 13 | 1.3 (−11.3 to 14.0) |
| Orthotist | 1.00 | 1 | 2.7 (1.2) | 3 | −1.7 (−7.4 to 4.1) |

SD, standard deviation.
a The one patient in the therapy-alone group who reported a health visitor contact did not indicate the number of contacts.

therapy group ($\chi^2 = 5.115$; $p = 0.024$ and $\chi^2 = 4.586$; $p = 0.032$, respectively) and significantly more continence advisor contacts among participants in the therapy alone group ($\chi^2 = 4.319$; $p = 0.038$).

The only significant difference in the mean number of contacts among participants reporting a contact is with respect to day hospital contacts, with participants in the therapy alone group having significantly more contacts on average (9.4 versus 3.1, respectively; 95% CI of the difference, 2.42 to 10.19).

*Table 31* shows the contribution of botulinum toxin type A costs, upper limb therapy costs, other antispasticity medication costs, and other health-care and social services costs to the overall mean cost per participant.

The overall mean cost per participant was higher in the botulinum toxin type A plus therapy group, although the difference was not significant. There were also no significant differences between the groups with respect to upper limb therapy costs, antispasticity medication costs and other health-care and social services costs. The biggest contributor to total costs for both groups was the cost of other health-care and social services contacts, accounting for 81% in the therapy alone group and 77% in the botulinum toxin type A plus therapy group.

*Table 32* shows the point estimate of the ICER of botulinum toxin type A plus therapy relative to therapy alone.

Botulinum toxin type A plus therapy was associated with an incremental cost of £374 and an incremental QALY gain of 0.004, compared with therapy alone. When combined, these data gave an ICER for botulinum toxin type A plus therapy of £93,500 per QALY gained.

Bootstrapping the point estimate of the ICER for botulinum toxin type A plus therapy resulted in 27% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), 21% being located in the SE quadrant (less costly, more effective), and 7% being located in the SW quadrant (less costly, less effective). The largest proportion of the replications (45%) is located in the NW quadrant, where botulinum toxin type A plus upper limb therapy is more costly and less effective, and therefore dominated by, upper limb therapy alone.

*Figure 7* shows the CEAC for botulinum toxin type A plus therapy relative to therapy alone. The probabilities that botulinum toxin type A plus therapy is cost-effective at ceiling ratios of £10,000, £20,000, £50,000 and £100,000 per QALY are 0.29, 0.36, 0.41 and 0.42, respectively.

## Sensitivity analysis

The impact on the results of the following sensitivity analyses were explored:

- making an alternative extrapolation assumption for participant reported resource use

***TABLE 31*** *The contribution of botulinum toxin type A costs, upper limb therapy costs, other antispasticity medication costs, and other health-care and social services costs to overall mean cost per participant*

| Breakdown of overall mean cost per participant | Mean (SD) cost per participant (£) | | |
|---|---|---|---|
| | Therapy alone | Botulinum toxin type A plus therapy | Mean difference in costs (£) (95% CI of difference) |
| Overall | 1796 (1944) | 2170 (2007) | −374 (−837 to 90) |
| Botulinum toxin | 3[a] (23) | 154 (28) | −151 (−157 to −145) |
| Upper limb therapy | 300 (45) | 303 (41) | −3 (−13 to 7) |
| Antispasticity medication | 37 (93) | 38 (90) | −1 (−22 to 21) |
| Other[b] | 1456 (1923) | 1675 (2001) | −219 (−679 to 242) |

SD, standard deviation.
a EQ-5D data were complete for three of four participants in the control group who received botulinum toxin.
b Other health-care and social services costs.

***TABLE 32*** *Incremental cost-effectiveness ratio of botulinum toxin plus therapy*

| Intervention | Cost (£) | QALYs | Incremental cost (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|
| Therapy alone | 1796 | 0.081 | – | – | – |
| Botulinum toxin plus therapy | 2170 | 0.085 | 374 | 0.004 | 93,500 |

- rerunning the analysis using data from participants with complete EQ-5D data at baseline and at 1 and 3 months
- allowing the cost of botulinum toxin type A to fall to zero
- a best–worst QALY analysis in which the impact of alternative assumptions regarding the timing of health-state changes is explored
- rerunning the analysis following multiple imputation of missing data.

The impact on the results of assuming that participant-reported resource use in month 2 is the same as that in month 1 was minimal. Under this assumption the incremental cost of botulinum toxin type A plus therapy increased by £14 to £388, which resulted in the point estimate of the ICER increasing from £93,500 per QALY gained to £97,000 per QALY gained.

The results of the remaining sensitivity analyses, along with those of the base-case analysis, are summarised in *Table 33*.

## Complete EQ-5D data

Rerunning the analysis to include only those participants for whom complete EQ-5D data were available (i.e. responses at baseline and at 1 and 3 months) had little impact on the results. The numbers of participants included were 248, of whom 116 were in the botulinum toxin type A plus therapy group and 132 were in the therapy alone group. The average cost per patient and QALYs enjoyed for therapy alone were £1773 and 0.079 QALYs, respectively. The corresponding figures for botulinum toxin type A plus therapy were £2255 and 0.086 QALYs, respectively. Hence, compared to the base-case analysis, botulinum toxin type

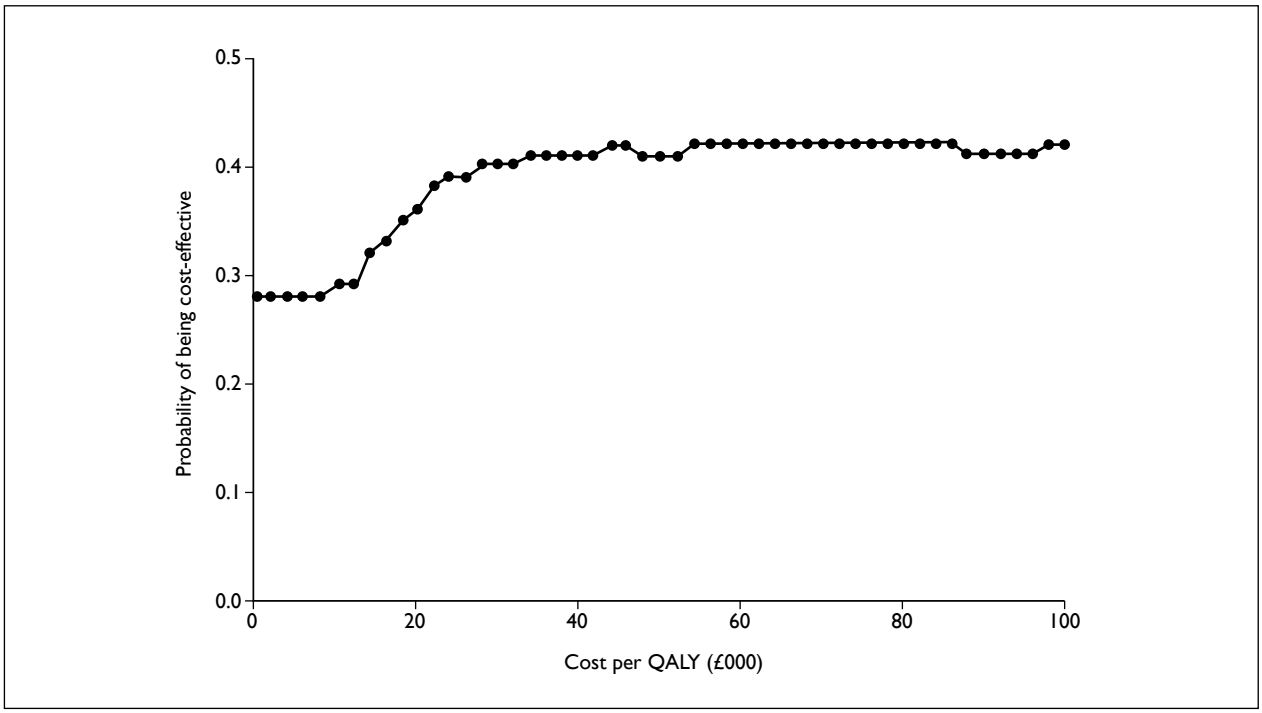


***FIGURE 7*** *Cost-effectiveness acceptability curve for botulinum toxin type A plus therapy relative to therapy alone.*

***TABLE 33*** *Summary of cost-effectiveness results for botulinum toxin type A plus therapy for alternative scenarios*

| Cost-effectiveness analysis scenario | IC (£) | IQ (QALYs) | ICER (£) | Probability that botulinum toxin type A plus therapy is cost-effective at threshold ratio: | | | |
|---|---|---|---|---|---|---|---|
| | | | | £10,000 | £20,000 | £50,000 | £100,000 |
| Base-case data[a] | 374 | 0.004 | 93,500 | 0.29 | 0.36 | 0.41 | 0.42 |
| Complete EQ-5D data[b] | 482 | 0.007 | 68,857 | 0.29 | 0.34 | 0.40 | 0.43 |
| Base-case data and zero cost for botulinum toxin | 223 | 0.004 | 55,750 | 0.31 | 0.39 | 0.42 | 0.43 |
| Base-case data and best–worst QALY assumptions | 374 | 0.006 | 62,333 | 0.29 | 0.35 | 0.43 | 0.45 |
| Missing data imputed using multiple imputation | 430 | 0.005 | 86,000 | 0.34 | 0.39 | 0.42 | 0.46 |

IC, incremental cost; IQ, incremental QALYs.
a EQ-5D responses at baseline and 3 months.
b EQ-5D responses at baseline, 1 month and 3 months.

A plus therapy was associated with a higher incremental cost (£482 versus £374) and a bigger incremental QALY gain (0.007 versus 0.004), compared with therapy alone. The resultant ICER from combining these data was lower than that in the base-case analysis (£68,857 versus £93,500 per QALY gained, respectively).

Bootstrapping the point estimate of the ICER for botulinum toxin type A plus therapy resulted in 27%, 20%, 7% and 46% of the replications being located in the NE, SE, SW and NW quadrants of the cost-effectiveness plane, respectively.

*Figure 8* shows the CEAC for botulinum toxin type A plus therapy relative to therapy alone for participants with complete EQ-5D data at 3 months. The probabilities that botulinum toxin type A plus therapy is cost-effective at ceiling ratios of £10,000, £20,000, £50,000 and £100,000 per QALY are 0.29, 0.34, 0.40 and 0.43, respectively.

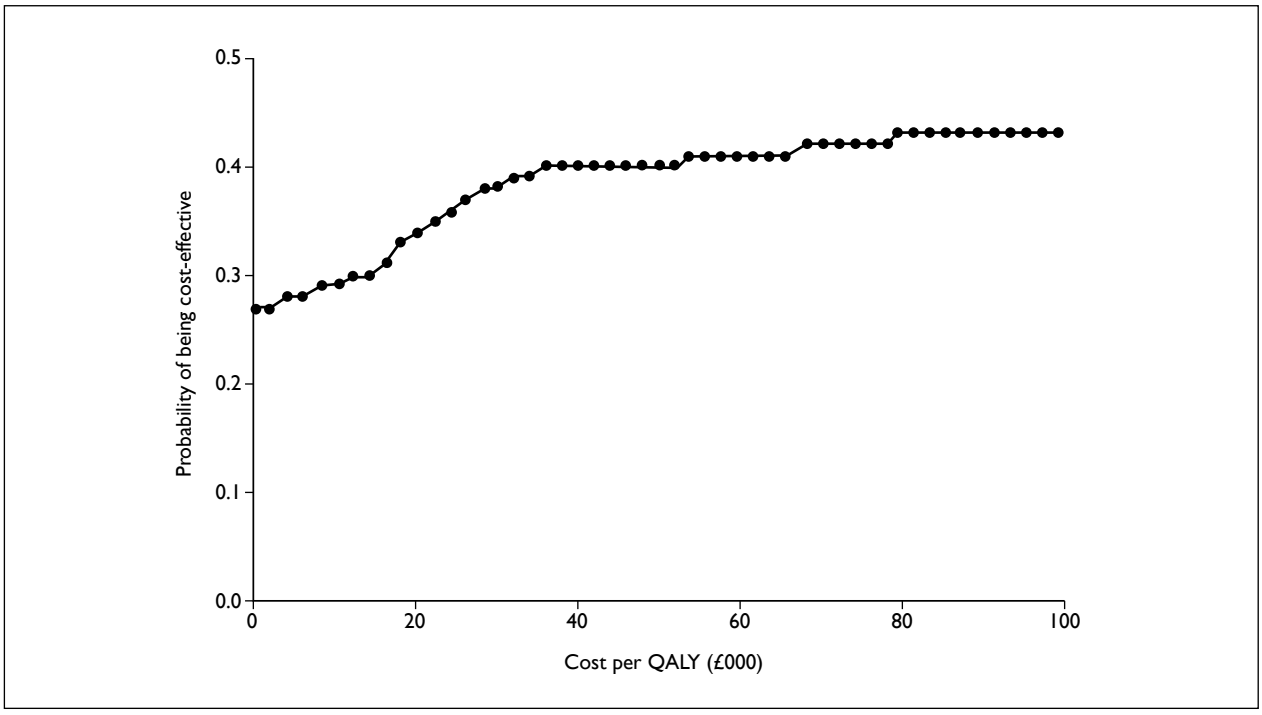


***FIGURE 8*** *Cost-effectiveness acceptability curve for botulinum toxin type A plus therapy relative to therapy alone for participants with complete EQ-5D data at 3 months.*

## Base-case data and zero cost for botulinum toxin

The impact on the results of allowing the cost of botulinum toxin type A to fall was investigated by considering the extreme assumption that the cost of botulinum toxin type A was zero. Under this assumption the average cost per patient and QALYs enjoyed for therapy alone were £1793 and 0.081 QALYs, respectively. The corresponding figures for botulinum toxin type A plus therapy were £2016 and 0.085 QALYs, respectively. Hence, despite the extreme assumption of a zero cost of botulinum toxin type A, botulinum toxin type A plus therapy still had a positive ICER compared with therapy alone, with the ICER having fallen from a base-case value of £93,500 to £55,750.

Bootstrapping the new point estimate of the ICER for botulinum toxin type A plus therapy resulted in 26%, 22%, 8% and 44% of the replications being located in the NE, SE, SW and NW quadrants of the cost-effectiveness plane, respectively.

*Figure 9* shows the CEAC for botulinum toxin type A plus therapy relative to therapy alone assuming a zero cost for botulinum toxin type A. The probabilities that botulinum toxin type A plus therapy is cost-effective at ceiling ratios of £10,000, £20,000, £50,000 and £100,000 per QALY are 0.31, 0.39, 0.42 and 0.43, respectively.

## Base-case data and best–worst QALY assumptions

The AUC approach to estimating QALYs described above assumes that the rate of change in health status between any two points (in this case, EQ-5D tariff values) is linear. For example, if the baseline value is 0.5 and the 3 months value is 0.8, then it is assumed that after 1 month, the health-state value is 0.6, and after 2 months it is 0.7. This is the method most commonly employed in AUC analyses in the literature.[113] However, many other assumptions could be made, each of which may have an impact on the results. In light of the relatively high ICERs associated with botulinum toxin type A plus therapy, it was decided to investigate the impact on the results of the timing of the health-state changes favouring the use of botulinum toxin type A. Specifically, it was assumed in the botulinum toxin type A plus therapy group that participants moved into the health-state value reported at 3 months almost immediately (approximately 3 days or 0.1 of a month) after baseline. This can be regarded as a best-case outcome scenario for botulinum toxin

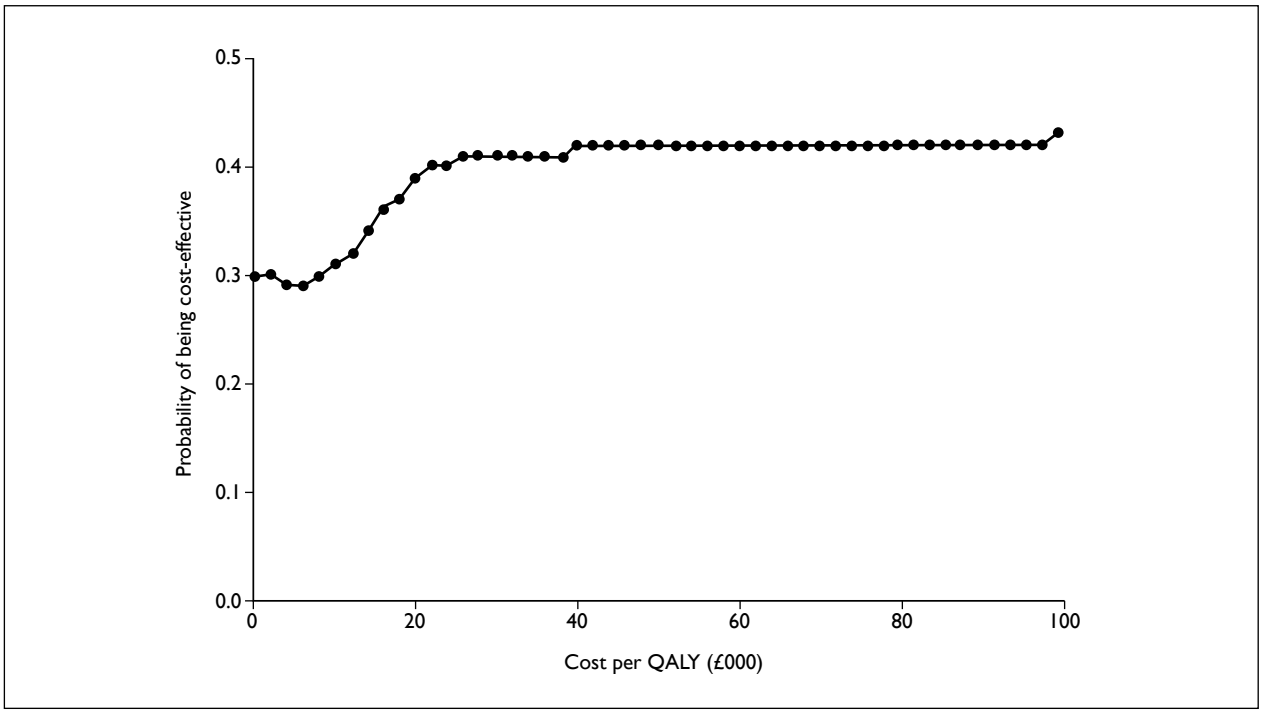


***FIGURE 9*** *Cost-effectiveness acceptability curve for botulinum toxin type A plus therapy relative to therapy alone assuming a zero cost for botulinum toxin type A.*

type A. On the flip side, a worst-case outcome scenario for the therapy alone group was defined whereby it was assumed that participants in this group remained in their baseline reported health state for 2.9 months, at which point they moved into the health state value reported at 3 months. The results of these assumptions were that the average number of QALYs enjoyed by botulinum toxin type A plus therapy participants increased from 0.085 in the base case to 0.087, while the average number of QALYs enjoyed by participants in the therapy alone group remained at 0.081. Combining the incremental QALY gain of 0.006 with the incremental cost of £374 gives a best–worst QALY scenario ICER for botulinum toxin type A plus therapy of £62,333.

Bootstrapping the point estimate of the ICER for botulinum toxin type A plus therapy resulted in 30%, 19%, 9% and 42% of the replications being located in the NE, SE, SW and NW quadrants of the cost-effectiveness plane, respectively.

*Figure 10* shows the CEAC for botulinum toxin type A plus therapy relative to therapy alone for the best–worst QALY scenario. The probabilities that botulinum toxin type A plus therapy is cost-effective at ceiling ratios of £10,000, £20,000, £50,000 and £100,000 per QALY are 0.29, 0.35, 0.43 and 0.45, respectively.

## Missing data imputed using multiple imputation

Imputing missing data using multiple imputation resulted in estimates of average cost per patient and QALYs enjoyed for therapy alone of £1807 and 0.077 QALYs, respectively. The corresponding figures for botulinum toxin type A plus therapy were £2237 and 0.082 QALYs, respectively. Compared with the base-case analysis, therefore, botulinum toxin type A plus therapy was associated with a higher incremental cost (£430 versus £374) and a bigger incremental QALY gain (0.005 versus 0.004), compared with therapy alone. The resultant ICER from combining these data was lower than that in the base-case analysis (£86,000 versus £93,500 per QALY gained, respectively).

Bootstrapping the point estimate of the ICER for botulinum toxin type A plus therapy over the five imputed data sets resulted in 28%, 20%, 11% and

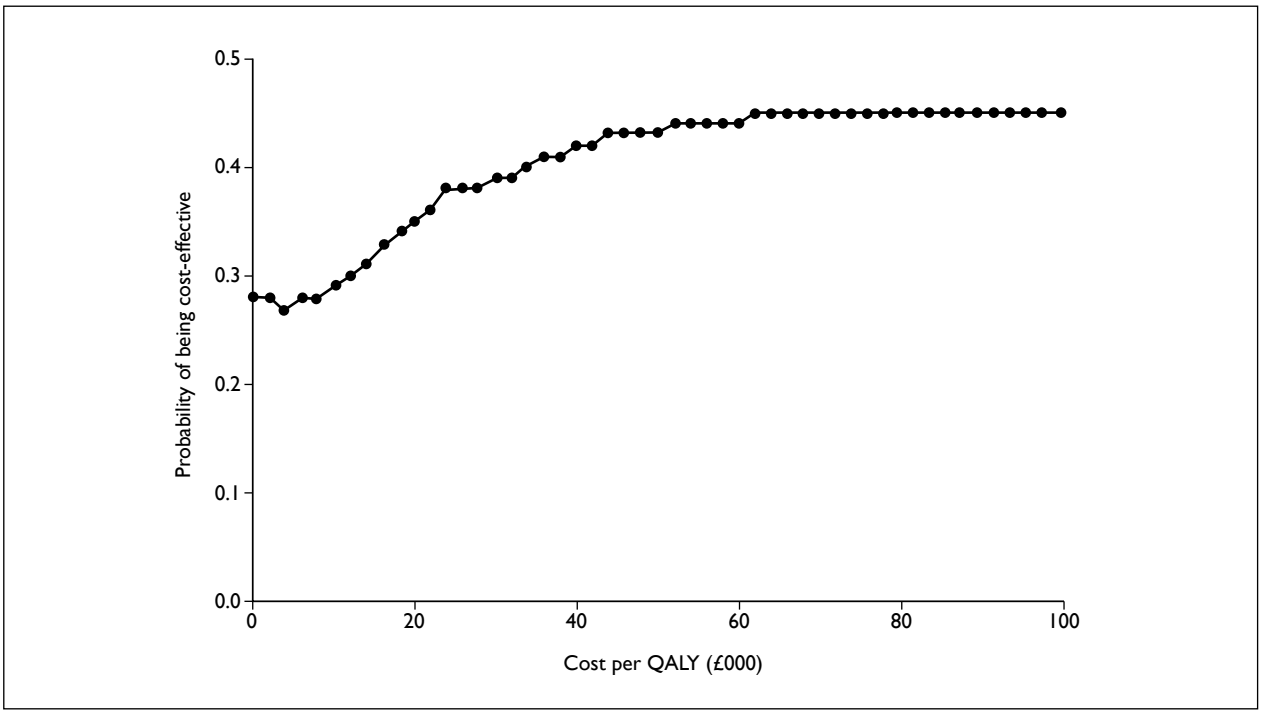


***FIGURE 10*** *Cost-effectiveness acceptability curve for botulinum toxin type A plus therapy relative to therapy alone for the best-worst QALY scenario.*

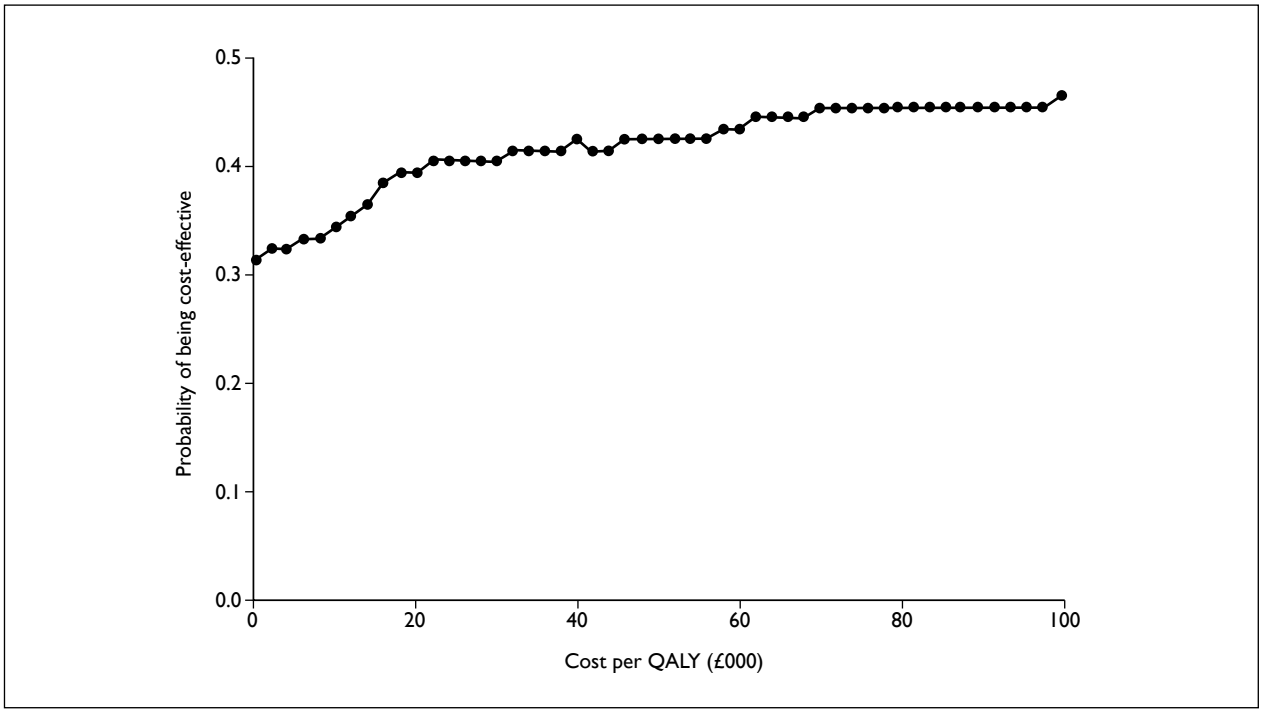


***FIGURE 11*** *Cost-effectiveness acceptability curve for botulinum toxin type A plus therapy relative to therapy alone following multiple imputation of missing data.*

41% of the replications being located in the NE, SE, SW and NW quadrants of the cost-effectiveness plane, respectively.

*Figure 11* shows the CEAC for botulinum toxin type A plus therapy relative to therapy alone when missing data have been imputed. The probabilities that botulinum toxin type A plus therapy is cost-effective at ceiling ratios of £10,000, £20,000, £50,000 and £100,000 per QALY are 0.34, 0.39, 0.42 and 0.46, respectively.

# Chapter 5
# Discussion

## Key findings

### Primary outcome measure

Patients with upper limb spasticity due to stroke who were treated with botulinum toxin type A plus an upper limb therapy programme achieved similar levels of improvement in upper limb function to those who were treated with the upper limb therapy programme alone at 1 month after study entry. Improved arm function (predefined success on the Action Research Arm Test) was achieved by 19.5% of participants in the control group and 25.1% in the intervention group ($p = 0.232$). The relative risk of having a 'successful treatment' in the intervention group compared with the control group was 1.3 (95% CI 0.9 to 2.0). There was no significant improvement in 'treatment success' with botulinum toxin when the analysis was adjusted for randomisation strata factors (research site and baseline upper limb function).

### Secondary outcome measures

#### *Impairment*

Botulinum toxin type A plus the upper limb therapy programme reduced muscle tone at the elbow by one point on the Modified Ashworth Scale at 1 month, but no significant differences were seen between the randomisation groups at 3 or 12 months. The reduction in muscle tone is consistent with previous studies, which reported that botulinum toxin reduced muscle tone at the elbow by one point on the Modified Ashworth Scale and the treatment lasted for approximately 3–4 months.[36,39–41,44,45] A reduction of one point on this scale is generally accepted as a clinically important difference.

Participants who were treated with botulinum toxin showed improvement in upper limb strength (Motricity Index) at 3 months, but no differences between the randomisation groups were found at other time points. This is the first time that improvement in upper limb strength has been demonstrated in an RCT of treatment of upper limb spasticity due to stroke with botulinum toxin.

No differences were seen in grip strength between randomisation groups. Improved grip strength was reported in one study with a dose of 75 units of botulinum toxin (Botox).[36] Reduced grip strength was reported in one trial following treatment with 1000 units of botulinum toxin (Dysport), which was a much higher dose than used in our study.[40]

#### *Upper limb function and activity limitation*

BoTULS included a number of measures of upper limb function and activity limitation at each assessment. Results suggest that treatment with botulinum toxin type A is unlikely to improve active arm function in the majority of patients after stroke, but may improve the ability to carry out specific basic upper limb functional activities.

No differences in predefined success on the ARAT were seen at 3 or 12 months. However, at 3 months, although the median change in ARAT from baseline was zero in both randomisation groups, this result was statistically significant. The mean difference was 1.8 (95% CI 0.4 to 3.3) in favour of those treated with botulinum toxin. Although this does demonstrate improved active arm function following treatment with botulinum toxin, the magnitude of change is small and unlikely to be clinically meaningful.

A small trial[45] ($n = 50$) published after BoTULS commenced found no improvement in upper limb function measured by the ARAT when a dose of 350 units of botulinum toxin (Dysport) was used. A dose of 500 units was associated with an improvement of 9.27 points at 8 weeks ($p = 0.024$) and 10.0 points at 24 weeks ($p = 0.019$) compared with placebo. The study also found that a higher dose of botulinum toxin (1000 units) significantly reduced active upper limb function, presumably as a result of weakness.

The relative contributions of spasticity and motor weakness to reduced function are debated.[12,13] Although there are those who advocate spasticity as an important component of reduced upper limb function, others believe that the main

problem is motor weakness. As we have not shown improvement in active function despite improvement in muscle tone at 1 month, and only a small change in active function at 3 months, this study supports the argument that spasticity is of less importance. However, we may have failed to detect important differences because the impact of treatment may relate to practising activities over a longer period. Lack of sustained improvement at 12 months may be because a significant proportion of participants did not receive repeated botulinum toxin type A or upper limb therapy, or lack of power for detecting change at this time point.

Improvements in some specific basic upper limb activities in favour of those who received botulinum toxin type A were seen at 1, 3 and 12 months. When change in score from baseline was analysed, improvements were seen in dressing the sleeve at 1 month and opening the hand to clean the palm at 3 and 12 months. These differences were small and of uncertain clinical significance. To further understand these data and to enable comparison with other studies, we compared the proportion of participants who improved by one or more points from baseline at 1, 3 and 12 months. This showed a clear benefit in favour of the intervention group for opening the hand to clean the palm and opening the hand to cut nails at all time points. Improvement in dressing the sleeve was only seen at 1 month and no differences were seen between randomisation groups in terms of using cutlery at any time point.

Six previous RCTs have assessed similar upper limb functional activities and four reported improvements in participants receiving botulinum toxin.[37,40,42,51] Two studies reported magnitude of change from baseline in activities which was similarly small, but concluded that these were clinically important findings.[40,42] Two studies reported the proportion of participants who had improved by one point or more and demonstrated improvement with botulinum toxin for these tasks.[42,51]

As spasticity is believed to limit activities such as opening the hand and dressing a sleeve,[10] it follows that decreasing spasticity with botulinum toxin should result in improvement. It may seem inconsistent that such activities showed improvement when arm function measured by the ARAT did not improve. However, the measurement tool used to assess the basic upper limb activities asked about ability to undertake tasks but did not distinguish whether they were performed by the affected arm, with assistance from the non-affected arm, or by a carer. This means that the questions may measure passive and/or active function, whereas the ARAT measures only active function. The improvement in the specific upper limb activities demonstrated in this trial is likely to reflect a combination of improvement in both passive and/or active function. The lack of improvement in the use of cutlery may be because this requires improvement in active function.

No differences were seen in dexterity (Nine-Hole Peg Test) or ADL (Barthel ADL Index) at any time point. Four previous studies have used the Barthel ADL Index to measure activity limitation.[39,41,45,49] One reported significant improvements at 8 and 24 weeks in patients who received 350 or 500 units of botulinum toxin (Dysport).[45] Compared with placebo, participants who received 350 units of botulinum toxin improved by 7.0 points at 8 weeks ($p = 0.012$) and 14.0 points at 24 weeks ($p < 0.001$). Those who received 500 units improved by 20.6 points and 28.3 points at 8 ($p < 0.001$) and 24 weeks ($p < 0.001$), respectively.

### *Stroke-related quality of life/ participation restriction*

There were statistically significant improvements in the Oxford Handicap Scale at 3 and 12 months in favour of those who had received botulinum toxin. However, the differences were small and of doubtful clinical significance. In addition, those who received botulinum toxin type A had improved scores on the anxiety/depression component of EQ-5D, but this change was also small and of doubtful clinical significance.

Four previous trials have assessed quality of life/ participation restriction, but no improvements were demonstrated after treatment of upper limb spasticity with botulinum toxin.[36,44,49,51]

### *Pain*

Our results suggest that botulinum toxin type A can reduce pain in patients with upper limb spasticity due to stroke. Those who received botulinum toxin type A experienced less pain at 3 months, as measured by the EQ-5D, but this difference was small and of doubtful clinical significance. However, a clinically important decrease in pain was found at 12 months.

Previous studies have shown that botulinum toxin reduces upper limb pain at 8 and 24 weeks[45] and that it can also be used to treat shoulder pain associated with spasticity.[46,47]

Upper limb pain is common after stroke and it is not unusual for sites and intensity to fluctuate, especially during the first 6 months. Identification of a single cause is often difficult.[117] As spasticity is believed to cause pain, decreasing spasticity may relieve pain. In addition, recent evidence suggests that botulinum toxin may have a direct analgesic effect by blocking transmission of neurotransmitters involved in pain pathways.[27] BoTULS found that pain was decreased at 12 months but not at 1 or 3 months, whereas muscle tone at the elbow was decreased at 1 month but not at 3 or 12 months. Hence, pain was decreased in the absence of a decrease in muscle tone. This suggests that pain reduction may be through a mechanism other than spasticity reduction, or alternatively, as muscle tone was only evaluated at the elbow, it is possible that spasticity was decreased at other joints but this was not recorded. It may be also be the result of the avoidance of late complications of spasticity, such as spasm and contracture.

#### *Patient-selected goals*

Treatment with botulinum toxin type A did not lead to improvement in achieving upper limb rehabilitation goals. Two previous trials asked participants to select and score a principle target of treatment from a list of upper limb functional activities (including dressing a sleeve, opening the hand for cleaning the palm) and demonstrated improvement in this activity after botulinum toxin treatment.[42,51] Two previous trials asked participants to identify individual treatment goals[41,51] and one demonstrated improved achievement of the goals following treatment with botulinum toxin.[51]

## Adverse events

There were no significant differences in the number and type of serious adverse events between participants who received botulinum toxin type A and those who did not receive botulinum toxin type A injections. Only one serious adverse event (dysphagia) was potentially related to botulinum toxin type A. Although the number of adverse events was similar between participants who received botulinum toxin type A and those who did not receive injections, there was a higher incidence of general malaise/flu-like/cold symptoms in those who received botulinum toxin type A with a relative risk of 7.6 (95% CI 1.8 to 32.3).

Although the overall numbers of serious adverse events and adverse events reported in this study were higher than in other trials, this probably reflects the robust reporting system employed in line with the *Medicines for Human Use (Clinical Trials) Regulations*.[100] The few events likely to be related to botulinum toxin type A were in keeping with those reported in other studies and data compiled by the manufacturing company.[32]

## Subgroup analyses

#### *Time since stroke*

There were no significant differences between patients treated within 1 year of stroke and those treated more than 1 year after stroke for the estimated effect of the intervention on any outcome. The hypothesis that time after stroke to treatment with botulinum toxin type A may influence effectiveness was therefore not supported. However, the study was not powered for subgroup analyses and we may have failed to detect important differences.

#### *Severity of initial upper limb function*

Participants with some retained function at baseline who were treated with botulinum toxin type A (ARAT 4–56) had a significantly greater improvement in ARAT score at 3 months (change from baseline) when compared with those with no retained function at baseline. This suggests that the improvement in ARAT score at 3 months in the main analysis was predominantly due to participants in the 4–56 group. However, the magnitude of difference between the subgroups (3.3; 95% CI 0.3 to 6.3) was small and this finding is of uncertain clinical significance. It is possible that there is a small group of patients for whom botulinum toxin type A and upper limb therapy can improve active arm function, but we have not been able to demonstrate this convincingly.

There were no other differences between participants with some retained function at baseline and those with no retained function for the estimated effect of botulinum toxin type A on other outcomes.

## Economic evaluation

The base-case ICER for botulinum toxin type A plus therapy was £93,500, which is well in excess of the £20,000 threshold value used by NICE.[118] Estimation of the CEAC for botulinum toxin type A plus therapy indicated that there was only a 0.36 probability of its being cost-effective at a ceiling ratio of £20,000 per QALY.

Sensitivity analysis using participants with complete EQ-5D data at 3 months produced an improved point estimate for the ICER of £68,857, but this was still over three times the NICE threshold value. The CEAC for these participants suggests that the probability of botulinum toxin type A plus therapy being cost-effective at £20,000 per QALY is actually lower than in the base case (0.34 versus 0.36, respectively).

Sensitivity analysis on the cost of botulinum toxin type A revealed that even if the cost of the drug were zero, the point estimate of the ICER still exceeded the NICE threshold value (£55,750 versus £20,000, respectively), and the probability of botulinum toxin type A plus therapy being cost-effective at £20,000 was little changed from the base case (0.39 versus 0.36, respectively).

Altering the assumptions regarding the timing of the health-state changes following treatment so that they favoured botulinum toxin type A plus therapy (best–worst QALY analysis) resulted in a lower ICER than in the base-case analysis (£62,333 versus £93,500, respectively). However, the probability that botulinum toxin plus therapy was cost-effective at £20,000 per QALY was actually lower than in the base-case analysis (0.35 versus 0.36, respectively).

Imputing missing data using multiple imputation resulted in an ICER of £86,000 for botulinum toxin plus therapy and a probability of 0.39 of its being cost-effective at £20,000 per QALY.

In summary, even the lowest point estimate of the ICER for botulinum toxin type A plus therapy was over two and a half times the NICE cost-effectiveness threshold value (£55,750 versus £20,000, respectively), and the probability of its being cost-effective at the threshold value did not exceed 0.39, regardless of the assumptions made. The economic analysis therefore provides no evidence to suggest that botulinum toxin type A plus therapy is a cost-effective alternative to therapy alone.

# Methodological issues

## Study setting

A multicentre RCT is the gold standard study design to assess the effectiveness of an intervention and increase the generalisability of the results. Of the previous 16 trials which have evaluated the effectiveness of using botulinum toxin to treat upper limb spasticity due to stroke, seven were multicentre studies.[36,38,39,41,42,44,51] In BoTULS, for logistical reasons, all centres were in the north of England, but the range of stroke services involved was typical of stroke care across the UK. The majority of botulinum toxin type A injections were given at a single clinic at the regional rehabilitation centre, with a small number being given at one study site. This does have an impact upon the generalisability of results although both clinics followed national guidelines for the range of muscles and dosages of botulinum toxin injected.[9] We had originally intended that botulinum toxin type A injections would be given at each study site by a local clinician or the study clinical research associate, but only two clinicians had training and expertise in giving botulinum toxin and most preferred to refer patients centrally. This involved study participants travelling to the regional rehabilitation centre, which is the usual service model currently used to deliver botulinum toxin treatment in the UK.

## Case ascertainment

Unfortunately, it was not possible to describe the proportion of stroke patients who were screened for the study because this was undertaken in a number of settings by a large number of clinicians. Referral to the study was on an ad hoc basis so it was not possible to identify and screen the prevalent population of stroke patients for upper limb spasticity across such a large geographical area. Screening logs were kept but it was not possible to keep an accurate record. To have achieved this would have required significant resource and would have contributed relatively little to our findings, although it would have helped to identify the proportion of prevalent stroke patients who may have benefitted from treatment.

Study therapists had close links with clinical services and we feel that our notification systems enabled us to identify the majority of patients with upper limb spasticity who were in contact with stroke and rehabilitation services. As long-term follow-up and support for stroke patients is limited,[1] there were likely to be a number of patients with upper limb spasticity who were not in contact with stroke or rehabilitation services who did not have the opportunity to take part in the study.

## Study participants

Recruitment of participants from stroke services avoided a potential participant selection bias, which may have occurred if participants were recruited from specialist rehabilitation services. For 8/16 previously published studies[37,38,40,43,45,47,48,51] recruitment was from rehabilitation clinics and for the other 8/16 studies[36,39,41,42,44,46,49,50] the setting was unclear. None recruited participants from the wider stroke population.

As there was uncertainty about which patients with upper limb spasticity due to stroke may benefit from botulinum toxin our eligibility criteria were broad and inclusive. Although the incidence and prevalence of upper limb spasticity post stroke is unclear, we feel that study participants were typical of stroke patients who experience upper limb spasticity post stroke in the UK. Study participants may have had less severe spasticity than patients who participated in previous studies (Modified Ashworth Score at the elbow at baseline was two in BoTULS compared with more than two in most previous studies). As we were keen to include participants with retained active upper limb function, this was not surprising as it is unusual to see severe spasticity in this group of patients. The pattern of upper limb spasticity was similar to that seen in clinical practice and described in published studies.

The study design did not include an upper limit of time since stroke because we were keen to have inclusion criteria that reflected the spectrum of patients with upper limb spasticity following stroke seen in clinical practice. In terms of time since stroke, the study population was therefore heterogeneous. As we hypothesised that the effect of treatment may be influenced by time since stroke the study design included a preplanned subgroup analysis of this variable. Previous studies also recruited some patients a number of years after stroke and some have shown benefit.[38,40,42,44,49]

Study participants were well matched at baseline with respect to all key variables. The median age of study participants was 67 years, which is younger than the median age at which stroke occurs (74 years[64]). The higher proportion of male participants recruited (67.8%) may reflect the higher prevalence of stroke in males compared to females.[119,120].

## Measurement of spasticity

Spasticity is difficult to define and measure.[18] Although the Modified Ashworth Scale is used to measure spasticity in clinical practice and research studies, it measures muscle tone rather than spasticity. The scale has been validated to measure muscle tone at the elbow[121] and although it has been used in some studies to measure tone at other upper limb joints it is unclear how this was undertaken. As there is no validated measure of spasticity at the shoulder, wrist, or fingers, study therapists, who all had extensive experience of stroke rehabilitation, used their clinical judgement to determine the presence of spasticity at joints other than the elbow. As no validated measure exists, the severity of spasticity at these joints was not rated.

Neurophysiological techniques[22] and biomechanical measures[21] of spasticity have been developed, but are not yet at the stage where they can be used in routine clinical practice or multicentre studies.

## Randomisation

One of the strengths of BoTULS is that the methods of randomisation and group allocation concealment employed were robust. Randomisation and allocation concealment were adequately reported in only 8/16 previous studies.[40,41,43,44,46–48,51]

## Botulinum toxin

In contrast to several other trials evaluating the use of botulinum toxin to treat upper limb spasticity after stroke, the dose and pattern of botulinum toxin type A injections delivered were according to the spasticity pattern of participants and determined by the injecting clinician rather than fixed in a trial protocol. The doses for individual muscles or muscle groups used were in accordance with published guidelines,[9] which were developed by an expert panel. Some previous studies have been criticised for using fixed injection protocols, which may not target the most appropriate muscles for treatment gain.[11] By allowing an experienced clinician to determine the dosage and pattern of use of botulinum toxin type A for individual patients we have evaluated how botulinum toxin type A is currently used in clinical practice. Studies of inter- or intra-clinician use of botulinum toxin dosages or patterns of use of botulinum toxin in clinical practice are not available.

Localisation of muscle for injection was by surface anatomy. Although electromyography can be used to identify muscles for treatment, injection site placement by surface anatomy is considered acceptable as botulinum toxin spreads locally to active muscles.[63] Only five of the 16 previously published studies report use of electromyography.[36,37,43,46,47]

Our median initial dose of botulinum toxin type A (Dysport) was 200 units (IQR 100–300). This compares with doses of 500–1500 units of botulinum toxin (Dysport) used in previous studies. The dosages of Dysport and Botox are not interchangeable and studies that have used Botox have used dosages ranging from 50 to 360 units. Our study could be criticised for not having used a high enough dose of botulinum toxin type A, but although dosages used were lower than in previous studies, the same level of reduction in spasticity (as measured by the Modified Ashworth Scale at the elbow) was achieved. We can therefore be confident that sufficient botulinum toxin was given to achieve a reduction in muscle tone. The lower dosage of botulinum toxin type A in BoTULS compared with previous studies is likely to reflect the fact that patients with less severe levels of spasticity were included. Guidelines recommend dose adjustment according to the level of spasticity.[9] The pattern of muscles injected was in keeping with common spasticity patterns in the post-stroke upper limb and was similar to published studies.[36,37,39–45,49]

Participants in the intervention group were assessed by a study therapist to decide whether they should be referred for further botulinum toxin type A injections at 3, 6 and 9 months. All study therapists were experienced in stroke rehabilitation and had experience in treating patients with spasticity. As spasticity is a chronic condition it was surprising that not all participants received repeat injections and unfortunately we did not record the reasons for this decision. In retrospect, clear criteria for repeat injections should have been developed. We did consider reviewing all participants at the regional spasticity clinic at 3, 6 and 9 months, but this would not have been practical. Failure to show sustained benefit from botulinum toxin type A treatment may be because a significant proportion of participants did not receive 3-monthly repeat injections.

The median dosage of botulinum toxin type A was higher for repeat injections. This may be because participants with more severe spasticity were referred for repeat injections [the median Modified Ashworth Scale score at elbow at 3 months for participants receiving repeat injections was 2 (IQR 1+ to 2) compared with 1+ (IQR 1–2) for those who did not receive injections]. A clear dose–response for treating upper limb spasticity due to stroke with botulinum toxin has not been established and in clinical practice where minimal benefit is obtained from the initial injections a higher dose is usually subsequently used. Uncontrolled studies of repeat injections have used up to 1000 units of Dysport or 50–400 units of Botox.

Although the study protocol did allow for participants with an unacceptable degree of symptomatic spasticity to be referred for treatment with botulinum toxin during the study period, the crossover rate was low.

## Upper limb therapy

A standardised therapy programme is one of the strengths of BoTULS as most previous studies have neither described nor quantified the amount of therapy received. The programme was based upon best available evidence and a manual and training programme were developed. Unlike many rehabilitation studies we were able to describe the amount and type of treatment received. As study therapists were trained centrally, delivery and content of the programme should not have differed across the study sites. The therapy programme was provided 2 hours per week for 1 month and for most participants this was likely to be more therapy than they would have received with 'usual care'. Further upper limb therapy was available at 3, 6 and 9 months at the discretion of the study therapists. As with repeat botulinum toxin injections, we feel that specific criteria for repeat therapy would have been useful and informative. It was unfortunate that data regarding the amount and content of therapy at 3, 6 and 9 months were not suitable for analysis and this was a study limitation.

There was considerable debate in establishing the study about whether upper limb therapy should be 'usual care' or a standardised upper limb therapy programme. We felt that to maximise the potential effectiveness of botulinum toxin type A, a standardised therapy programme should be provided. 'Usual care' is very variable and difficult to measure and if we had adopted this approach and the study results had been neutral then we could be criticised for not evaluating best practice in relation to botulinum toxin type A and uncertainty would remain about the effectiveness

of treating upper limb spasticity due to stroke with botulinum toxin. We did collect information about contact with rehabilitation services at each assessment but as with most rehabilitation RCTs we did not collect detailed information about the therapy received in addition to the study upper limb therapy programme. As this treatment could have been provided by a number of services within each study site it would have been impossible to collect reliable data without intensive effort and significant additional resource.

In designing the study we did consider a factorial design of botulinum toxin type A versus no botulinum toxin type A and enhanced therapy versus 'usual care'. However, the sample size required to address this issue was over 1000 and we did not feel that this was achievable.

Participants in both intervention and control groups made positive comments about the programme and 44.8% felt that they had gained benefit in terms of upper limb function as a result of the therapy programme. Most found that the upper limb therapy programme met their needs and expectations although it was too easy or too difficult for a small number of participants. Aspects of the programme may need to be modified as 13% experienced pain during stretching or exercises, although discomfort may be unavoidable in some cases and indeed may lead to longer-term benefit. The predominant negative comment about the programme was that it was too short and many participants were keen to have further additional treatment.

Improvements in several outcomes were seen for both intervention and control groups. At 1, 3 and 12 months predefined ARAT success was achieved by 19.5%, 24.2% and 29.3% of participants in the control group, respectively. This improvement was higher than anticipated and may reflect benefit from the upper limb therapy programme, which incorporated repetitive task-specific practice. However, a recent systemic review examining the effects of repetitive task practice on functional ability after stroke showed that improvement in upper limb function did not reach statistical significance.[122]

## Outcome measures

As the focus of BoTULS was to look at the effect of botulinum toxin type A upon upper limb function in patients with upper limb spasticity due to stroke, the ARAT was selected as the primary outcome measure. The ARAT has been widely used in rehabilitation research and has been shown to be valid, reliable and sensitive to change in stroke patients.[123,124] Previous studies have predominantly assessed specific basic functional activities, e.g. putting the arm through a sleeve, or used global disability scales as functional outcomes measures. Of the 16 previous studies only nine defined a primary outcome measure[38–41,43,44,47,50,51] and only one was a functional assessment.[40]

Defining a clinically meaningful change in arm function is difficult and the judgements upon which the decision is based can always be challenged. Improvement in arm function is influenced by a number of parameters including time since stroke and severity of the initial neurological deficit and the perspectives of patients, carers and clinicians may differ. More recovery would be expected for participants randomised early after stroke and for those who had some active upper limb function at baseline. Initially, BoTULS included only participants with some active upper limb function and treatment success was based upon an improvement of the ARAT score by six points, which has been suggested as the minimal clinically important change for the ARAT.[101] When the eligibility criteria were widened to include patients with no active upper limb function (ARAT 0–3) we felt that an improvement of three points would be a meaningful clinical improvement in this group because they have a poorer prognosis for recovery of active function.

It can also be argued that the ARAT is not the optimum instrument to measure outcome in patients with no active upper limb function as many patients might be expected to show little improvement. Of participants who had no active upper limb function at baseline (ARAT 0–3), 67.4% in the control group and 77.2% in the intervention group demonstrated no change on the ARAT at 1 month. Assessment of specific basic upper limb functional activities, e.g. putting hand into a sleeve, opening the hand for washing, may be a more appropriate primary outcome measure for this group. Measures of these basic upper limb functional activities were included as secondary outcomes and we were able to demonstrate improvement for a number of these. In clinical practice and research an outcome measure needs to be able to measure change across the spectrum of patients to whom treatment is given and we do not feel that current measures of upper limb function fulfil this criterion.

The secondary outcome measures chosen are widely used in rehabilitation research. The COPM was included as an outcome measure because of the recognition that improvement in patient-selected goals may provide a more meaningful treatment evaluation than standard outcome measures.[54] However, the goals set may or may not have been realistic and achievable.

## Timing of outcome measurements

Botulinum toxin type A takes approximately 1 week to achieve maximal effect and wears off after 3–4 months. Therefore, the 1-month outcome assessment should have captured a maximal treatment effect directly due to the botulinum toxin type A. At 3 months the effects of the initial injection would be wearing off so any benefit that relied upon a direct treatment effect of botulinum toxin type A may have been reduced. As injections could be repeated at 3, 6 and 9 months, then the 12-month outcome assessment may also have been at a time when any treatment effect was declining. As there may be benefits that are sustained when the effect of the toxin wears off, it was not unreasonable to look at the intermediate and long-term effects at these times. It would have been useful to have included further assessments at 4 months, 7 months and 10 months to study the effects of repeat injections because at these times the treatment effect would likely be greater; however, this would have needed additional resources and increased participant burden.

## Blinding

BoTULS did not use placebo injections so participants and the study therapists who delivered the upper limb therapy programme were not blinded to the randomisation group, which was a source of potential bias. Some participants were disappointed that they did not receive botulinum toxin and may have felt disadvantaged. Although therapists were trained to deliver a standard therapy programme it is possible that there were inadvertent differences in content between participants in the intervention and control groups. Every effort was made to ensure that the study therapists who undertook outcome assessments were blinded to the patients' randomisation group. As participants were unblinded, it was possible for outcome assessors to become unintentionally unblinded during conversation. The assessor was unblinded for 36.1% of primary outcome assessments and it is difficult to know how this could have been reduced because participants were asked not to mention the treatment they had received at each outcome assessment.

In planning the study, the use of placebo injections was discussed at length. It was decided that they should not be used because the study was a pragmatic trial and because it was felt unethical to subject participants to sham injections.

## Study dropout and data quality

One of the strengths of this study is the quality of the data. Follow-up levels were high at all assessment points and levels of missing data were low.

## Statistical considerations

The study achieved the prespecified sample size of 332 participants so we can be confident that we have not missed an important treatment effect upon our primary outcome measure. However, it could be argued that our prespecified level of successful treatment was too ambitious.

BoTULS is the largest RCT to evaluate the role of botulinum toxin in the treatment of upper limb spasticity due to stroke undertaken to date. Sample sizes of previous RCTs range from 15 to 126 participants (median $n = 39$) and the total number of participants who have been randomised in studies of botulinum toxin in the treatment of upper limb spasticity due to stroke is 785. This rises to 1118 with our data. Only 9/16 of the previous studies reported a power calculation[39–42,44,46–48,51] and seven achieved their prespecified sample size.[39–42,44,47,51]

Due to the nature of the data collected in the study many statistical comparisons were made during the analyses. As multiple statistical testing could have been responsible for some of the statistically significant findings, we have been cautious in the interpretation of the results. Sample size calculations were not undertaken for secondary outcome measures or for subgroup analyses so we may have failed to detect some important treatment effects. In addition, as 12-month follow-up was curtailed, 12-month outcomes were available for 57% of participants and therefore we may have failed to detect an important treatment effect because of the reduced sample size at this stage.

We have undertaken an intention-to-treat analysis as described in our protocol. We have not undertaken an on-treatment analysis because 96.5% of participants in the intervention group received treatment with botulinum toxin type A as planned.

## Economic evaluation

The main limitation of the cost-effectiveness analysis was the relatively short time horizon over which it was conducted. The rationale for adopting a 3-month time horizon rather than 12 months was the loss of participant responses due to curtailment of 12-month follow-up. The proportion of participants providing EQ-5D data at 12 months was 52.4%. This is considerably lower than the corresponding figures for baseline, 1 month and 3 months, which were 100%, 83.7% and 85.2%, respectively.

One option would have been to impute the missing 12-month data, but this would have meant that even if the estimation of QALYs was restricted to the baseline and 12-month EQ-5D values only, data would have to be imputed for almost half the sample. If the intermediate EQ-5D values were also used in the QALY estimation, then data for more than half the sample would need to be imputed. For these reasons, a decision was made to conduct the analysis over 3 months where levels of missing data were much lower. This is not to say that there would not be benefits in extrapolating costs and outcomes over a longer time period. This could be done using economic modelling, which would incorporate data from the trial and other relevant sources to estimate cost-effectiveness beyond the time horizon of the trial. Although such an exercise is beyond the scope of this study, it would be a potentially worthwhile piece of future research.

# Chapter 6
# Conclusions

The addition of botulinum toxin type A to an upper limb therapy programme to treat spasticity due to stroke did not enhance improvement in upper limb function when assessed by the prespecified primary outcome measure.

Botulinum toxin type A reduced muscle tone and the level of reduction was similar to that in previous studies.

Treatment with botulinum toxin type A was associated with increased upper limb strength at 3 months but this was not sustained until 12 months.

Treatment with botulinum toxin type A resulted in improvements in basic upper limb functional activities related to specific tasks, e.g. dressing a sleeve, opening the hand for cleaning the palm or opening the hand for cutting fingernails, which were sustained until 12 months for some activities.

Participants treated with botulinum toxin type A demonstrated a small improvement in active upper limb function at 3 months when this was analysed as change in ARAT score from baseline. This was predominantly because of improvement in participants with some retained function at baseline. However, the size of the improvement was small and this finding is of uncertain clinical significance. Improvement in upper limb function was not sustained at 12 months.

It is of interest that participants in both randomisation groups made improvements in upper limb function over a 12-month period.

Treatment with botulinum toxin type A did not result in any important improvements in stroke-related quality of life.

Botulinum toxin type A appeared to have a long-term benefit in terms of pain reduction for patients with upper limb spasticity due to stroke.

Failure to show sustained benefit at 12 months may have been because a significant proportion of participants did not receive 3-monthly repeat injections, the timing of outcome measurement in relation to repeat injections, or lack of power to detect change at this time.

The side effects of botulinum toxin type A were minor and predominantly of flu-like illness.

The addition of botulinum toxin type A to an upper limb therapy programme for the treatment of upper limb spasticity due to stroke was not cost-effective at 3 months.

## Implications for clinical practice

National clinical guidelines for the management of spasticity in adults using botulinum toxin were updated in January 2009.[63] Our study has followed the guidelines by ensuring that botulinum toxin was not used in isolation, but was part of a multidisciplinary approach to the management of spasticity.

Our results will help to inform clinicians regarding the outcomes that may be improved by treating upper limb spasticity due to stroke with botulinum toxin type A. Management of spasticity should include clearly agreed goals for treatment and for our study the primary goal was improvement in upper limb function. The guidelines suggest that active functional gain is an appropriate goal in some cases. However, our primary analysis and preplanned subgroup analyses did not find any significant clinical improvement in active upper limb function. Other goals suggested in the guidelines include improvement of basic upper limb tasks and pain reduction, and our results support these choices. Although repeated treatment is commonly used in clinical practice and suggested in the guidelines, our study was not able to demonstrate sustained improvement for all outcomes.

Guidelines suggest that botulinum toxin 'has the potential to reduce the overall cost of ongoing care in people with severe spasticity through the prevention of contracture and deformity, and improved ease of care and handling'. Botulinum toxin type A was not a cost-effective treatment

for the patients included in our study, but we acknowledge that we did not examine the longer-term consequences.

## Implications for research

We have demonstrated that it is possible to undertake an investigator-led multicentre study of an investigational medicinal product and standardised therapy programme in the UK. Only a small number of multicentre stroke rehabilitation studies have been published to date, although since the Stroke Research Network was established in 2005 numbers are increasing.

Further research is needed to increase our understanding of the natural history and clinical impact of spasticity following stroke, and to explain the relationship between spasticity and functional limitation. Studies are needed to improve the measurement of spasticity and to develop valid measures for all upper limb joints.

Further work is required to establish the optimum dosage and pattern of injections of botulinum toxin type A to treat upper limb spasticity due to stroke and to define the efficacy of repeat injections. The timing of outcome measures should relate to the time when botulinum toxin type A is likely to be optimally effective and measure outcome in the longer term.

There is a need for patients, clinicians and the research community to clearly define important clinical outcomes for patients with upper limb impairment. Further work is needed to develop robust person-centred outcome measures that can be used in national or international multicentre studies.

A national register to record the clinical details of patients who receive treatment with botulinum toxin, their goals and outcomes would be helpful to assist the development of RCTs to identify which patients benefit from this treatment.

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## Contribution of authors

Dr Lisa Shaw (Clinical Research Associate) was responsible for day-to-day management of the study, delivery of botulinum toxin type A injections and drafting the report. Professor Helen Rodgers (Professor of Stroke Care and chief investigator) designed the RCT and was responsible for the overall management of the study and drafting the report. Dr Christopher Price (Consultant Stroke Physician and Clinical Senior Lecturer) designed the RCT and undertook the initial literature review. Dr Frederike van Wijck (Senior Lecturer, Physiotherapy) contributed to the design of the RCT, designed the upper limb therapy programme, and trained the research therapists. Dr Phil Shackley (Senior Lecturer, Health Economics) designed and conducted the economic analyses. Dr Nick Steen (Principle Research Associate, statistics) was responsible for the trial statistics. Professor Michael Barnes (Professor of Neurological Rehabilitation) contributed to the design of the RCT and provided expertise in spasticity management and

the use of botulinum toxin. Professor Gary Ford (Professor of Clinical Pharmacology) contributed to the design of the RCT. Dr Laura Graham (Consultant in Rehabilitation Medicine) provided expertise in spasticity management and the use of botulinum toxin, and was involved in delivery of botulinum toxin type A injections. All authors have contributed to analyses, interpretation of results and drafts of the report.

# References


1. National Audit Office. *Reducing brain damage: faster access to better stroke care*. London: National Audit Office; 2005.

2. Heller A, Wade DT, Wood VA, Sunderland A, Hewer RL, Ward E. Arm function after stroke: measurement and recovery over the first three months. *J Neurol Neurosurg Psychiatry* 1987;**50**:714–19.

3. Skilbeck CE, Wade DT, Hewer RL, Wood VA. Recovery after stroke. *J Neurol Neurosurg Psychiatry* 1983;**46**:5–8.

4. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJ. The long-term outcome of arm function after stroke: results of a follow-up study. *Disab Rehab* 1999;**21**:357–64.

5. Wade D. Editorial. *Clin Rehab* 1997;**11**:91–2.

6. Friedman P. Gait recovery after hemiplegic stroke. *Int Disab Stud* 1990;**12**:119–22.

7. Lance JW. Symposium Synopsis. In Feldman RG, Young RR, Koella WP, editors. *Spasticity: Disordered Motor Control*. Chicago, IL: Symposium Specialists Inc.; 1980.

8. Pandyan AD, Gregoric M, Barnes MP, Wood D, Van Wijck F, Burridge J, *et al*. Spasticity: clinical perceptions, neurological realities and meaningful measurement. *Disab Rehab* 2005;**27**:2–6.

9. Barnes MP, Bhakta BB, Moore P, Richardson D, Salisbury C, Thornton H, *et al*. *The management of adults with spasticity using botulinum toxin: a guide to clinical practice*. London: Radius Healthcare 2001.

10. Mayer NH, Esquenazi A, Childers MK. Common patterns of clinical motor dysfunction. *Muscle Nerve* 1997;**20**(Suppl. 6):s21–s35.

11. Sheean GL. Botulinum treatment of spasticity: why is it so difficult to show a functional benefit? *Curr Opin Neurol* 2001;**14**:771–6.

12. Ada L, O'Dwyer N, O'Neill E. Relation between spasticity, weakness and contracture of the elbow flexors and upper limb activity after stroke: an observational study. *Disab Rehab* 2006;**28**:891–7.

13. Leonard CT, Gardipee KA, Koontz JR, Anderson J-H, Wilkins SA. Correlation between impairment and motor performance during reaching tasks in subjects with spastic hemiparesis. *J Rehab Med* 2006;**38**:243–9.

14. Brashear A, Mayer NH. *Spasticity and other forms of muscle overactivity in the upper motor neuron syndrome*. New York, NY: We Move; 2009.

15. Watkins CL, Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK. Prevalence of spasticity post stroke. *Clin Rehab* 2002;**16**:515–22.

16. Sommerfeld DK, Eek EUB, Svensson A-K, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke* 2004;**35**:134–9.

17. Intercollegiate Stroke Working Party. *National clinical guideline for stroke*, 3rd edn. London: Royal College of Physicians; 2008.

18. Burridge JH, Wood DE, Hermens HJ, Voerman GE, Johnson GR, van Wijck F, *et al*. Theoretical and methodological considerations in the measurement of spasticity. *Disab Rehab* 2005;**27**:69–80.

19. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Physical Ther* 1987;**67**:206–7.

20. Johnson GR. Measurement of spasticity. In Barnes MP, Johnson GR, editors. *Upper motor neurone syndrome and spasticity*, 1st edn. Cambridge: Cambridge University Press; 2001.

21. Wood DE, Burridge JH, van Wijck FM, McFadden C, Hitchcock RA, Pandyan AD, *et al*. Biomechanical approaches applied to the lower and upper limb for the measurement of spasticity: a systematic review of the literature. *Disab Rehab* 2005;**27**:19–32.

22. Voerman GE, Gregoric M, Hermens HJ. Neurophysiological methods for the assessment of spasticity: the Hoffmann reflex, the tendon reflex, and the stretch reflex. *Disab Rehab* 2005;**27**:33–68.

23. Collins MD, East AK. Phylogeny and taxonomy of the food-borne pathogen *Clostridium botulinum* and its neurotoxins. *J Appl Microbiol* 1998;**84**:5–17.

24. Goonetilleke A, Harris JB. Clostridial neurotoxins. *J Neurol Neurosurg Psychiatry* 2004;**75**(Suppl. 3):35–9.

25. Sobel J. Botulism. *Clin Infect Dis* 2005;**41**:1167–73.

26. Erbguth FJ. From poison to remedy: the chequered history of botulinum toxin. *J Neural Transm* 2008;**115**:559–65.

27. Dolly JO, Aoki KR. The structure and mode of action of different botulinum toxins. *Eur J Neurol* 2006;**13**(Suppl. 4):1–9.

28. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. *Neurotoxicology* 2005;**26**:785–93.

29. Mense S. Neurobiological basis for the use of botulinum toxin in pain therapy. *J Neurol* 2004;**251**(Suppl. 1):I1–7.

30. Rossetto O, Montecucco C. How botulinum toxins work. In Moore P, Naumann M, editors. *Handbook of botulinum toxin treatment*, 2nd edn. Oxford: Blackwell Science Ltd; 2003. pp. 9–27.

31. Naumann M, Toyka KV, Moore P. History and current applications of botulinum toxin – from poison to remedy. In Moore P, Naumann M, editors. *Handbook of botulinum toxin treatment*, 2nd edn. Oxford: Blackwell Science Ltd; 2003. pp. 3–8.

32. Electronic medicines compendium. URL: www.emc.medicines.org.uk.

33. Dressler D, Benecke R. Pharmacology of therapeutic botulinum toxin preparations. *Disab Rehab* 2007;**29**:1761–8.

34. Naumann M, Albanese A, Heinen F, Molenaers G, Relja M. Safety and efficacy of botulinum toxin type A following long-term use. *Eur J Neurol* 2006;**13** (Suppl. 4):35–40.

35. Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve Suppl* 1997;**6**:S146–68.

36. Simpson DM, Alexander DN, O'Brien CF, Tagliati M, Aswad AS, Leon JM, *et al*. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996;**46**:1306–10.

37. Hesse S, Reiter F, Konrad M, Jahnke MT. Botulinum toxin type A and short-term electrical stimulation in the treatment of upper limb flexor spasticity after stroke: a randomized, double-blind, placebo-controlled trial. *Clin Rehab* 1998;**12**:381–8.

38. Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin Rehab* 2000;**14**:5–13.

39. Bakheit AM, Thilmann AF, Ward AB, Poewe W, Wissel J, Muller J, *et al*. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. *Stroke* 2000;**31**:2402–6.

40. Bhakta BB, Cozens JA, Chamberlain MA, Bamford JM. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. *J Neurol Neurosurg Psychiatry* 2000;**69**:217–21. [Erratum appears in *J Neurol Neurosurg Psychiatry* 2001;**70**:821.]

41. Bakheit AM, Pittock S, Moore AP, Wurker M, Otto S, Erbguth F, *et al*. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. *Eur J Neurol* 2001;**8**:559–65.

42. Brashear A, Gordon MF, Elovic E, Kassicieh VD, Marciniak C, Do M, *et al*. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002;**347**:395–400.

43. Brashear A, McAfee AL, Kuhn ER, Fyffe J. Botulinum toxin type B in upper-limb poststroke spasticity: a double-blind, placebo-controlled trial. *Arch Physical Med Rehab* 2004;**85**:705–9.

44. Childers MK, Brashear A, Jozefczyk P, Reding M, Alexander D, Good D, *et al*. Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke. *Arch Physical Med Rehab* 2004;**85**:1063–9.

45. Suputtitada A, Suwanwela NC. The lowest effective dose of botulinum A toxin in adult patients with upper limb spasticity. *Disab Rehab* 2005;**27**:176–84.

46. Yelnik AP, Colle FM, Bonan IV, Vicaut E. Treatment of shoulder pain in spastic hemiplegia by reducing spasticity of the subscapular muscle: a randomised, double blind, placebo controlled study of botulinum toxin A. *J Neurol Neurosurg Psychiatry* 2007;**78**:845–8.

47. Marco E, Duarte E, Vila J, Tejero M, Guillen A, Boza R, *et al*. Is botulinum toxin type A effective in the treatment of spastic shoulder pain in patients after stroke? A double-blind randomized clinical trial. *J Rehab Med* 2007;**39**:440–7.

48. Kong K-H, Neo J-J, Chua KS. A randomized controlled study of botulinum toxin A in the treatment of hemiplegic shoulder pain associated with spasticity. *Clin Rehab* 2007;**21**:28–35.

49. Jahangir AW, Tan HJ, Norlinah MI, Nafisah WY, Ramesh S, Hamidon BB, *et al*. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after stroke. *Med J Malaysia* 2007;**62**:319–22.

50. de Boer KS, Arwert HJ, de Groot JH, Meskers CGM, Mishre ADR, Arendzen JH. Shoulder pain and external rotation in spastic hemiplegia do not improve by injection of botulinum toxin A into the subscapular muscle. *J Neurol Neurosurg Psychiatry* 2008;**79**:581–3.

51. McCrory P, Turner-Stokes L, Baguley IJ, De Graaff S, Katrak P, Sandanam J, *et al*. Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomized placebo-controlled study of the effects on quality of life and other person-centred outcomes. *J Rehab Med* 2009;**41**:536–44.

52. van Kuijk AA, Geurts ACH, Bevaart BJW, van Limbeek J. Treatment of upper extremity spasticity in stroke patients by focal neuronal or neuromuscular blockade: a systematic review of the literature. *J Rehab Med* 2002;**34**:51–61.

53. Cardoso E, Rodrigues B, Lucena R, Oliveira IR, Pedreira G, Melo A. Botulinum toxin type A for the treatment of the upper limb spasticity after stroke: a meta-analysis. *Arquiv Neuro-Psiquiatria* 2005;**63**:30–3.

54. Garces K, McCormick A, McGahan L, Skidmore B. *Botulinum toxin A for upper and lower limb spasticity: a systematic review* (Technology report no. 51). Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005.

55. Rosales RL, Chua-Yap AS. Evidence-based systematic review on the efficacy and safety of botulinum toxin-A therapy in post-stroke spasticity. *J Neural Transm* 2008;**115**:617–23.

56. Elia A, Filippini G, Calandrella D, Albanese A. Botulinum neurotoxins for post stroke spasticity in adults: a systematic review. *Movement Disord* 2009;**24**:801–12.

57. Rodriquez AA, McGinn M, Chappell R. Botulinum toxin injection of spastic finger flexors in hemiplegic patients. *Am J Physical Med Rehab* 2000;**79**:44–7.

58. Lagalla G, Danni M, Reiter F, Ceravolo MG, Provinciali L. Post-stroke spasticity management with repeated botulinum toxin injections in the upper limb. *Am J Physical Med Rehab* 2000;**79**(4):377–84; quiz 391–4.

59. Gordon MF, Brashear A, Elovic E, Kassicieh D, Marciniak C, Liu J, *et al*. Repeated dosing of botulinum toxin type A for upper limb spasticity following stroke. *Neurology* 2004;**63**:1971–3.

60. Bakheit AMO, Fedorova NV, Skoromets AA, Timerbaeva SL, Bhakta BB, Coxon L. The beneficial antispasticity effect of botulinum toxin type A is maintained after repeated treatment cycles. *J Neurol Neurosurg Psychiatry* 2004;**75**:1558–61.

61. Cardoso E, Pedreira G, Prazeres A, Ribeiro N, Melo A. Does botulinum toxin improve the function of the patient with spasticity after stroke? *Arquiv Neuro-Psiquiatria* 2007;**65**:592–5.

62. Elovic EP, Brashear A, Kaelin D, Liu J, Millis SR, Barron R, *et al*. Repeated treatments with botulinum toxin type a produce sustained decreases in the limitations associated with focal upper-limb poststroke spasticity for caregivers and patients. *Archiv Physical Med Rehab* 2008;**89**:799–806.

63. Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy, Association of Chartered Physiotherapists Interested in Neurology. *Spasticity in adults: management using botulinum toxin. National guidelines.* London: Royal College of Physicians; 2009.

64. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, *et al*. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004;**363**:1925–33.

65. Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2007; Issue 1, Art. No. CD000197.

66. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehab Res* 1981;**4**:483–92.

67. Sharpless JW. The nine hole peg test of finger hand coordination for the hemiplegic patient. In *Mossman's A problem-orientated approach to stroke rehabilitation*, 2nd edn. Illinois: Charles C Thomas, 1982.

68. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. *Eur Neurol* 1980;**19**:382–9.

69. Sunderland A, Tinson D, Bradley L, Hewer RL. Arm function after stroke. An evaluation of grip strength as a measure of recovery and a prognostic indicator. *J Neurol Neurosurg Psychiatry* 1989;**52**:1267–72.

70. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Maryland State Med J* 1965;**14**:61–5.

71. Law M, Baptiste S, McColl M, Opzoomer A, Polatajko H, Pollock N. The Canadian Occupational Performance Measure: an outcome measure for occupational therapy. *Can J Occup Ther – Rev Can Ergother* 1990;**57**:82–7.

72. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* 1994;**56**:217–26.

73. Duncan PW, Bode RK, Min Lai S, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. *Arch Physical Med Rehab* 2003;**84**:950–63.

74. Euroquol Group. Euroquol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–290.

75. Bamford JM, Sandercock PA, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989;**20**:828.

76. Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age and Ageing* 1972;**1**:233–9.

77. Al-Khawaja I, Wade DT, Collin CF. Bedside screening for aphasia: a comparison of two methods. *J Neurol* 1996;**243**:201–4.

78. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;**337**:1521–6.

79. Royal College of Physicians. *Guidelines for the use of botulinum toxin (BTX) in the management of spasticity in adults*. London: Royal College of Physicians; 2002.

80. Intercollegiate Stroke Working Party. *National clinical guideline for stroke*, 2nd edn. London: Royal College of Physicians; 2004.

81. Wade D. Goal planning in stroke rehabilitation: evidence. *Topics Stroke Rehab* 1999;**6**:37–42.

82. Pomeroy V, Tallis R. Restoring movement and functional ability after stroke: now and the future. *Physiotherapy* 2002;**88**:3–17.

83. van der Lee JH, Snels IA, Beckerman H, Lankhorst GJ, Wagenaar RC, Bouter LM. Exercise therapy for arm function in stroke patients: a systematic review of randomized controlled trials. *Clin Rehab* 2001;**15**:20–31.

84. Kwakkel G, Wagenaar R, Twisk J, Lankhorst G, Koetsier J. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. *Lancet* 1999;**354**:191–6.

85. Dean CM, Richards CL, Malouin F. Task-related circuit training improves performance of locomotor tasks in chronic stroke: a randomized, controlled pilot trial. *Arch Physical Med Rehab* 2000;**81**:409–17.

86. Dean CM, Shepherd RB. Task-related training improves performance of seated reaching tasks after stroke. A randomized controlled trial. *Stroke* 1997;**28**:722–8.

87. Carr J, Shepherd RB. *Stroke Rehabilitation. Guidelines for exercise training to optimise motor skill.* London: Butterworth Heinemann; 2003.

88. Barnes MP, Johnson GR. *Upper motor neurone syndrome and spasticity*, 1st edn. Cambridge: Cambridge University Press; 2001.

89. Barnes M, Dobkin B, Bogousslavsky J. *Recovery after stroke*. Cambridge: Cambridge University Press; 2005.

90. Edwards S. *Neurological physiotherapy*, 2nd edn. Edinburgh: Churchill Livingstone; 2002.

91. Lannin NA, Herbert RD. Is hand splinting effective for adults following stroke? A systematic review and methodologic critique of published research. *Clin Rehab* 2003;**17**:807–16.

92. Scottish Intercollegiate Guidelines Network (SIGN). *Guidelines on stroke*. www.sign.ac.uk (accessed 9 November 2005).

93. Stokes M. *Physical management in neurological rehabilitation*, 2nd edn. Edinburgh: Elsevier Mosby; 2005.

94. Van Peppen RPS, Kwakkel G, Wood-Dauphinee S, Hendriks HJM, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clin Rehab* 2004;**18**:833–62.

95. Hanlon RE. Motor learning following unilateral stroke. *Arch Phys Med Rehab* 1996;**77**(8):811–15.

96. Magill RA. *Motor learning: concepts and applications*. Boston, MA: McGraw Hill; 2001.

97. Shea JB, Morgan RL. Contextual interference effects on the acquisition, retention and transfer of a motor skill. *J Exp Psychol: Learn Mem Cogn* 1979;**5**:179–87.

98. Duncan PW. Synthesis of intervention trials to improve motor recovery following stroke. *Topics Stroke Rehab* 1997;**3**:1–20.

99. van Wijck F, Mackenzie J, Hooper J, Barnes M, Johnson G. Improving arm function in patients with chronic spasticity: combining botulinum toxin with a task orientated motor learning programme. *Int J Rehab Res* 2004;**27**(Suppl. 1):109.

100. *Medicines for Human Use (Clinical Trials) Regulations*; 2004. URL: www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm.

101. van der Lee JH, Wagenaar RC, Lankhorst GJ, Vogelaar TW, Deville WL, Bouter LM. Forced use of the upper extremity in chronic stroke patients: results from a single-blind randomized clinical trial. *Stroke* 1999;**30**:2369–75.

102. Mendelow AD, Gregson BA, Fernandes HM, Murray GD, Teasdale GM, Hope DT, *et al*. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet* 2005;**365**:387–97.

103. Fleiss JL. *Statistical methods for rates and proportions*. New York, NY: Wiley; 1981.

104. International Conference on Harmonisation. *Harmonised Tripartite Guideline for Good Clinical Practice*. URL: www.ich.org.

105. Department of Health. *Research Governance Framework for Health and Social Care*, 2nd edn. London: HMSO; 2005.

106. MRC. *Guidelines for good clinical practice in clinical trails*. London: Medical Research Council; 1998.

107. Pandyan AD, Vuadens P, van Wijck FMJ, Stark S, Johnson GR, Barnes MP. Are we underestimating the clinical efficacy of botulinum toxin (type A)? Quantifying changes in spasticity, strength and upper limb function after injections of Botox to the elbow flexors in a unilateral stroke population. *Clin Rehab* 2002;**16**:654–60.

108. National Institute for Clinical Excellence. *Guide to the methods of technology appraisal*. London: National Institute for Clinical Excellence; 2004.

109. Curtis L. *Unit costs of health and social care*. Canterbury: PSSRU, University of Kent; 2007.

110. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. No. 53. London: BMJ Publishing Group Ltd and RPS Publishing; 2007.

111. Brooks R. EuroQol: the current state of play. *Health Policy* 1996;**37**:53–72.

112. Dolan P. Modeling valuations for EuroQol health states. *Medical Care* 1997;**35**:1095–108.

113. Richardson G, Manca A. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. *Health Econ* 2004;**13**:1203–10.

114. O'Brien B, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods. *Stat Meth Med Res* 2002;**11**:455–68.

115. Claxton K, Fenwick E, Sculpher M. Decision-making with uncertainty: the value of information. In Jones A, editor. *The Elgar companion to health economics*. Cheltenham: Edward Elgar Publishing; 2006.

116. Schafer JL. *Analysis of incomplete multivariate data*. London: Chapman and Hall; 1997.

117. Price C. Treatment of shoulder and upper limb pain after stroke: an obstacle course for evidence based practice. *Rev Clin Gerontol* 2003;**13**:321–33.

118. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. *BMJ* 2004;**329**:224–7.

119. Geddes JML, Fear J, Tennant A, Pickering A, Hillman M, Chamberlain MA. Prevalence of self reported stroke in a population in northern England. *J Epidemiol Commun Health* 1996;**50**:140–3.

120. O'Mahony PG, Thomson RG, Dobson R, Rodgers H, James OFW. The prevalence of stroke and associated disability. *J Publ Health Med* 1999;**21**:166–71.

121. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehab* 1999;**13**:373–83.

122. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, *et al*. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev* 2007; Issue 4, Art No. CD006073.

123. Platz T, Pinkowski C, van Wijck F, Kim I-H, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the Fugl–Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. *Clin Rehab* 2005;**19**:404–11.

124. Lang CE, Wagner JM, Dromerick AW, Edwards DF. Measurement of upper extremity function after stroke: properties of the Action Research Arm Test. *Arch Phys Med Rehabil* 2006;**87**:1605–10.

125. SIGN. *Methodology checklist 2: randomised controlled trials*; 2004. URL: www.sign.ac.uk.

# Appendix 1

# Additional literature review documents

## Literature search strategy

Literature search strategy for studies of botulinum toxin for treatment of upper limb spasticity following stroke.

The following databases were accessed:

- MEDLINE (1950 to July 2009) via Ovid
- PubMed
- EMBASE (1980 to July 2009) via Ovid
- CINAHL (1982 to July 2009) via Ovid
- EBM reviews via Ovid.

The following search terms were used and combined as the databases allowed:

- stroke/cerebrovascular accident
- upper limb/arm
- spasticity
- botulinum toxin.

The limits 'human' and 'english' were applied.

Database results were manually scanned and potentially relevant abstracts were reviewed. Full papers were selected from potentially relevant abstracts and were fully reviewed to determine appropriateness of inclusion. References of retrieved studies were also reviewed and any further potentially relevant papers were obtained and assessed.

## Methodological appraisal of randomised controlled trials

Randomised controlled trials were methodologically appraised using the Scottish Intercollegiate Guidelines Network (SIGN) checklist for RCTs.[125] Each methodological question was answered with one of the following:

- well covered
- adequately addressed
- poorly addressed
- not reported (mentioned, but insufficient detail to allow assessment to be made)
- not addressed (not mentioned or indicated this aspect of study design was ignored)
- not applicable.

Results are shown in *Table 34*.

## Overview of randomised controlled trials

An overview of each trial is shown in *Table 35*.

## Summary of systematic reviews

***van Kuijk* et al. *2002*[52]**

This systematic review was about the use of any focal treatment for upper limb spasticity after stroke. Four RCTs evaluating the effect of botulinum toxin injections were included.[36–39] No meta-analysis was performed. The authors concluded that there was evidence to support a decrease in muscle tone and increase in passive range of movement following botulinum toxin treatment.

***Cardoso* et al. *2005*[53]**

This systematic review included five RCTs evaluating the effect of botulinum toxin as a treatment for post-stroke upper limb spasticity.[36,38,39,41,42] Modified Ashworth Scale scores and patient/physician global assessment scale scores were combined as possible for meta-analysis. The authors concluded that there was evidence to support improvement in both muscle tone and global response following treatment.

***Garces* et al. *2005*[54]**

This systematic review was about the use of botulinum toxin in both upper and lower limb spasticity in various conditions. Six RCTs[36,37,39–42] and three published abstracts regarding botulinum toxin for upper limb spasticity after stroke were included. Muscle tone scores and range of movement evaluations were combined where possible for meta-analysis. Effects on function/disability (including patient and carer disability scales, global assessment scales) and pain were also reviewed, but data could not be combined. The meta-analysis showed that muscle tone was reduced after treatment, but there was no improvement in range of movement. There was no evidence to support pain decrease after treatment but trials had shown function/disability was improved after treatment.

### *Rosales and Chua-Yap 2008*[55]

This systematic review examined botulinum toxin for the upper and lower limb after stroke. Seven upper limb studies were included.[36–39,41,42,44] Modified Ashworth Scale scores and global assessment scale scores from both upper and lower limb studies were extracted for a combined meta-analysis. Both muscle tone and global assessment were improved after botulinum toxin treatment. Other outcome measures were not analysed.

### *Elia et al. 2009*[56]

The effect of botulinum toxin on muscle tone, global ratings, functional disability, pain, quality of life and adverse events in both upper and lower limb spasticity following stroke were evaluated in this systematic review. Ten upper limb RCTs were included.[36–45] Muscle tone scores and global rating scores were combined for meta-analysis and improvements were demonstrated after botulinum toxin treatment. The remaining outcome measures could not be combined. The authors concluded that botulinum toxin can reduce upper limb spasticity, but effects on functional ability are unclear.

## Overview of uncontrolled studies of repeated botulinum toxin injections

An overview of each study is shown in *Table 36*.

***TABLE 34*** *Methodological appraisal of RCTs*

| | Simpson 1996[36] | Hesse 1998[37] | Smith 2000[38] | Bakheit 2000[39] | Bhakta 2000[40] | Bakheit 2001[41] | Brashear 2002[42] | Brashear 2004[43] |
|---|---|---|---|---|---|---|---|---|
| Appropriate and clearly focused question | Well covered | Well covered | Well covered | Well covered | Well covered | Well covered | Well covered | Well covered |
| Randomisation method | Not reported | Not reported | Not reported | Not reported | Well covered | Well covered | Not reported | Well covered |
| Adequate concealment method | Not addressed | Not addressed | Not addressed | Not addressed | Well covered | Well covered | Not addressed | Well covered |
| Blinded subjects and investigators | Adequately addressed | Adequately addressed | Adequately addressed | Adequately addressed | Well covered | Well covered | Adequately addressed | Well covered |
| Groups are similar at baseline | Adequately addressed | Adequately addressed | Well covered | Adequately addressed | Adequately addressed | Well covered | Adequately addressed | Adequately addressed |
| Only difference between groups is the intervention | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Not addressed | Not addressed | Poorly addressed |
| Relevant outcomes measured in a valid and reliable way | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Adequately addressed | Poorly addressed |
| % recruited dropped out before study completed | 5% | Not addressed | Not addressed | 1% | 7% | 1% | 3% | 6% |
| Intention-to-treat analysis | Not addressed | Not addressed | Not addressed | Well covered | Not addressed | Well covered | Not addressed | Not addressed |
| Results comparable for all sites | Not addressed | Not applicable | Not addressed | Not addressed | Not applicable | Not addressed | Not addressed | Not applicable |
| How well does study minimise bias | – | – | – | – | + | + | – | – |
| Does methodology mean overall effect due to the intervention? | Possibly | Possibly | Possibly | Possibly | Probably | Probably | Possibly | Possibly |

*continued*

***TABLE 34*** *Methodological appraisal of RCTs (continued)*

| | **Childers 2004[44]** | **Suputtitada 2005[45]** | **Yelnik 2007[46]** | **Marco 2007[47]** | **Kong 2007[48]** | **Jahangir 2007[49]** | **de Boer 2008[50]** | **McCrory 2009[51]** |
|---|---|---|---|---|---|---|---|---|
| Appropriate and clearly focused question | Well covered | Adequately addressed | Well covered | Well covered | Well covered | Well covered | Well covered | Well covered |
| Randomisation | Well covered | Poorly addressed | Well covered | Well covered | Well covered | Not reported | Not reported | Well covered |
| Adequate concealment method | Well covered | Not addressed | Well covered | Well covered | Well covered | Not addressed | Not addressed | Well covered |
| Blinded subjects and investigators | Well covered | Poorly addressed | Not reported | Well covered | Well covered | Poorly addressed | Poorly addressed | Well covered |
| Groups are similar at baseline | Well covered | Adequately addressed | Adequately addressed | Adequately addressed | Adequately addressed | Adequately addressed | Poorly addressed | Well covered |
| Only difference between groups is the intervention | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed | Poorly addressed |
| Relevant outcomes measured in a valid and reliable way | Adequately addressed | Adequately addressed | Adequately addressed | Adequately addressed | Adequately addressed | Adequately addressed | Adequately addressed | Adequately addressed |
| % recruited dropped out before study completed | 15% first cycle; ? second cycle | Not addressed | 0% | 0% | 0% | Not addressed | 4% (one participant) | 6% |
| Intention-to-treat analysis | Not addressed | Not addressed | Not addressed | Well covered | Adequately addressed | Not addressed | Not addressed | Well covered |
| Results comparable for all sites | Not addressed | Not applicable | Not applicable | Not applicable | Not applicable | Not applicable | Not applicable | Not addressed |
| How well does study minimise bias | + | – | + | + | + | – | – | + |
| Does methodology mean overall effect due to the intervention? | Probably | Possibly | Probably | Probably | Probably | Possibly | Possibly | Probably |

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***TABLE 35*** *Overview of randomised controlled trials*

| Author and year | Purpose of study | Eligibility | Exclusions | Number of participants | Intervention/ Control | Outcome measures | Follow-up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Simpson 1996[36] | To evaluate effectiveness of botulinum toxin in treating upper extremity spasticity in chronic stroke patients | At least 9 months post stroke<br>Mean 2.5 on AS at elbow and wrist with minimum 2 at either joint<br>Stable clinical course for 2 months before study<br>Willing to maintain ongoing spasticity treatment | Fixed contracture<br>Previous treatment with botulinum<br>Neurolytic or surgical procedures in the study limb<br>Neuromuscular disease | 39 | 10 placebo<br>9, 75 u Botox<br>9, 150 u Botox<br>9, 300 u Botox<br>(only give numbers analysed)<br>All had biceps, FCU, FCR | AS, FIM, Rand 36-Item Health Survey, Fugl–Meyer Scale, caregiver dependency, function and pain assessment, motor task/ function rating scale, grip strength, Global Assessment of Spasticity Scale | 2, 4, 6, 10, 16 weeks | Decreased AS score at elbow and wrist at weeks 2, 4, 6 in high-dose group compared with placebo<br>Decreased AS at wrist at week 6 in low-dose group compared with placebo<br>Improvement on physicians and patients global assessment in the high- and low-dose groups at weeks 4 and 6<br>Increased grip strength in low-dose group at weeks 6 and 16 |
| Hesse 1998[37] | To investigate whether the combined approach of botulinum toxin and electrical stimulation was more effective than botulinum toxin alone in the treatment of chronic upper limb spasticity after stroke | 6–12 months post stroke<br>MAS at least 3 at elbow, wrist and fingers<br>No function of study arm | Fixed contracture<br>Previous treatment with botulinum<br>Neurolytic or surgical procedures in the study limb<br>Severe impairments of cognition and communication | 24 | 6 placebo<br>6 placebo + ES<br>6, 1000 u Dysport<br>6, 1000 u Dysport + ES<br>All had biceps, brachioradialis, FCU, FCR, FDP, FDS | MAS, limb position at rest, 3 functional activities, pain | 2, 6, 12 weeks | Cleaning the palm better in BTX + ES group compared with BTX alone or placebo alone at all time points |

*continued*

***TABLE 35*** *Overview of randomised controlled trials (continued)*

| Author and year | Purpose of study | Eligibility | Exclusions | Number of participants | Intervention/ Control | Outcome measures | Follow-up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Smith 2000[38] | To assess dose–response relationships to a single dose of botulinum toxin in upper limb spasticity associated with stroke or head injury | At least 1 year post stroke or head injury<br>Significant disabling spasticity<br>Non function or partial function of study arm | Fixed contracture | 21 | 6 placebo<br>6, 500 u Dysport<br>7, 1000 u Dysport<br>6, 1500 u Dysport<br>(25 in total as four people re randomised at end of follow-up period)<br>Muscles injected according to spasticity | MAS, passive and active range of movement, time to dress upper body, FAT, finger curl, global clinical assessment score, gait (if mobile) | 2, 6, 12 weeks | Decreased wrist and finger MAS score, increased passive range of movement and greater number of patients improved on global assessment at week 6 when all botulinum toxin groups combined and compared to placebo<br>Individual groups: 500 u group MAS score decreased compared to placebo at week 6. 1500 u group passive range of movement better at weeks 6 and 12 |
| Bakheit 2000[39] | To define an effective and safe dose of Dysport for the treatment of upper limb spasticity in stroke patients | At least 3 months post stroke<br>MAS 2 or more at elbow, wrist, fingers | Muscle contracture<br>Previous treatment with botulinum, phenol or alcohol nerve blocks | 83 | 20 placebo<br>22, 500 u Dysport<br>22, 1000 u Dysport<br>19, 1500 u Dysport<br>All had biceps, FDS, FDP, FCU, FCR | MAS, range of movement, pain, Rivermead Motor Assessment, Barthel ADL index, three functional activities | 2, 4, 8, 12, 16 weeks | Decreased MAS score at any joint in all BTX groups compared with placebo at week 4<br>Decreased MAS score over 16 weeks for elbow and wrist in all BTX groups and fingers in 1000 u group |

| Author and year | Purpose of study | Eligibility | Exclusions | Number of participants | Intervention/ Control | Outcome measures | Follow-up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Bhakta 2000[40] | To investigate whether reduction in spasticity after botulinum toxin treatment translates into reduction in disability and carer burden | At least 6 months post stroke<br>Elbow or finger MAS >2<br>Non-function of study arm<br>Moderate difficulty with two out of eight items on the disability scale | Functionally useful arm<br>Previous botulinum toxin or phenol treatment | 40 | 20 placebo<br>20, 1000u Dysport<br>Muscles injected according to spasticity | Patient disability scale, carer burden scale, MAS, range of movement, pain, muscle power, grip strength | 2, 6, 12 weeks | Improved patient disability scale score in BTX group at 2 and 6 weeks compared with placebo. Improved carer burden out to 12 weeks<br>Decreased MAS score at fingers at all time points in BTX group compared with placebo and decreased MAS at elbow at week 2<br>Decreased grip strength in BTX group compared with placebo at week 6 |
| Bakheit 2001[41] | To study the efficacy and safety of botulinum toxin in the treatment of upper limb spasticity caused by stroke | At least 3 months post stroke<br>MAS 2 or more in at least two of elbow, wrist, fingers and 1+ in remaining area | Muscle contracture<br>Previous treatment with alcohol or phenol nerve blocks<br>Treatment with BTX in previous 6 months | 59 | 32 placebo<br>27, 1000u Dysport<br>All had biceps, FDS, FDP, FCU, FCR | MAS, range of movement, pain, Barthel ADL index, three functional activities, goal attainment and subjective global assessment | 4, 8, 12, 16 weeks | Decreased MAS score at any joint in BTX group compared with placebo at week 4. Decreased MAS score over 16 weeks for fingers and wrist in BTX group compared with placebo<br>Improved passive range of movement at the elbow over 16 weeks in BTX group compared with placebo<br>Numbers improving on global assessment greater in BTX group at all time points compared with placebo at week 16 |

*continued*

***TABLE 35*** *Overview of randomised controlled trials (continued)*

| Author and year | Purpose of study | Eligibility | Exclusions | Number of participants | Intervention/ Control | Outcome measures | Follow-up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Brashear 2002[42] | Assess the effects of one set of injections of botulinum toxin on muscle tone and measures of disability with respect to self-care, limb position, pain | At least 6 months post stroke<br>Wrist AS 3 or more, fingers AS 2 or more<br>2 or 3 on disability assessment scale | Fixed contracture<br>Profound muscle atrophy<br>Previous or planned treatment of limb with botulinum, alcohol, phenol, surgery<br>Intrathecal baclofen<br>Change in medication for spasticity in previous 3 months<br>Pregnancy | 126 | 62 placebo<br>64, 200–200 u Botox<br>All had FCU, FCR, FDP, FDS and some FPL, AP | AS, disability assessment scale, global assessment scale | 1, 4, 6, 8, 12 weeks | Disability assessment scale principle target score improved in BTX group than placebo at all time points<br>Greater number of patients improved by at least one point on the disability scale in BTX group compared with placebo week 6<br>Decreased AS score in BTX group compared with placebo at all time points<br>Greater number of patients improving by at least one point on global assessment in BTX group at all time points |
| Brashear 2004[43] | To determine whether botulinum toxin type B is effective in controlling upper limb spasticity | At least 6 months post stroke<br>AS 2 or more at elbow, wrist and fingers | Unstable medical illness<br>Previous treatment with botulinum, phenol or surgery to the affected limb | 15 | 5 placebo<br>10 botulinum toxin type B<br>All had biceps, FCU, FCR, FDS, FDP | AS, physician, patient and therapist global assessment of change, range of movement, nine-hole peg test, Jebsen test of hand function | 2, 4, 8, 12, 16 weeks (+ 12 weeks further open label) | Decreased AS score at wrist at week 2 compared with placebo<br>All MAS and global scores improved in the open label f/u |

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| Author and year | Purpose of study | Eligibility | Exclusions | Number of participants | Intervention/ Control | Outcome measures | Follow-up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Childers 2004[44] | To test the hypothesis that intramuscular botulinum toxin reduces excessive muscle tone in a dose-dependent manner in the elbow, wrist and fingers after stroke | At least 6 weeks post stroke<br>Wrist AS 3 or more, elbow AS 2 or more | Fixed contracture<br>Profound muscle atrophy of affected limb<br>Previous treatment with botulinum, phenol or surgery<br>Plaster casting for spasticity<br>FEV1 <65% predicted<br>Diagnosis myasthenia gravis or other condition that could interfere with study<br>Sensitivity to components of botulinum<br>Pregnancy | 91 | 26 placebo<br>21, 90u Botox<br>23, 180u Botox<br>21, 360u Botox<br>All had biceps, FCU, FCR, FDP, FDS<br>second injection given at >12 weeks if AS 2 or more at wrist and/or elbow<br>same dose given as first injection | Trial's own MAS, pain score and functional disability measure. SF-36, FIM, physician and patients global assessment | 1, 2, 3, 4, 5, 6, 9, 12, 18, 24 weeks | *After first injection*<br>Decreased AS score at wrist in all BTX groups compared with placebo at most time points out to week 9<br>Decreased AS score at elbow in the BTX group compared with placebo out to week nine<br>Global response score higher in 360u and 180u groups compared with placebo at some time points<br>*After second injection*<br>Number of participants to decrease AS score by a least one point higher in the 360u group compared with placebo at weeks 18 and 24 |
| Suputtitada 2005[45] | To define the lowest effective dose and safety of botulinum toxin in the treatment of adult patients with upper limb spasticity | Any cause spasticity (but only stroke included)<br>Upper limb spasticity<br>Medically stable<br>No cognitive deficits<br>Not independent ADLs<br>Had already had rehabilitation programme for 6 weeks | Fixed contracture<br>Complete plegia<br>Previous phenol or surgery to affected muscles<br>Hypersensitivity to BTX<br>Myasthenia gravis or other disorders where BTX contraindicated<br>Aminoglycoside use<br>Pregnancy | 50 | 15 placebo<br>15, 350u Dysport<br>15, 500u Dysport<br>5, 1000u Dysport<br>All had biceps, FCU, FCR, FDP, FDS | MAS, ARAT, Barthel ADL index, visual analogue pain scale | 2, 4, 8, 16, 24 weeks | Mean MAS score decreased in all botulinum toxin groups at week 8 compared with placebo<br>Improved VAS score compared with placebo at weeks 8 and 24<br>Improved ARAT score in 500u group compared with placebo at weeks 8 and 24. Decreased ARAT score in 1000u compared with placebo at weeks 8 and 24<br>Increased Barthel ADL Index in 350 and 500u groups at weeks 8 and 24 |

*continued*

***TABLE 35*** *Overview of randomised controlled trials (continued)*

| Author and year | Purpose of study | Eligibility | Exclusions | Number of participants | Intervention/ Control | Outcome measures | Follow-up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Yelnik 2007[46] | To assess the beneficial effect of injection of botulinum toxin into the subscapularis muscle on shoulder pain | Any time limit after stroke<br>MAS at least 1+ at shoulder and elbow<br>Shoulder external rotation > 30° | Retraction of muscle at elbow, wrist or fingers<br>Previous traumatic or neurological disease of the shoulder<br>Previous BTX or alcohol to subscapularis<br>Myasthenia gravis<br>Pregnancy | 20 | 10 placebo<br>10, 500 u Dysport<br>All had subscapularis | 10-point pain VAS, MAS, passive range of movement | 1,2, 4 weeks | Decreased pain in BTX group compared with placebo at week 4<br>Improved lateral rotation compared with placebo at weeks 2 and 4<br>Decreased MAS at fingers compared with placebo at week 4 |
| Marco 2007[47] | To determine the efficacy of botulinum toxin type A for the treatment of spastic shoulder pain in patients after stroke | > 18 years old<br>> 3 months post stroke<br>MAS at least 3 but limb area/s unclear<br>Pain VAS at least 40 mm | Mild hemiparesis<br>Concomitant shoulder pathology<br>Pacemaker<br>Peripheral nervous system disease<br>Hypersensitivity to botulinum toxin<br>Pregnancy | 31 | 15 placebo<br>16, 500 u Dysport<br>All had pectoralis major<br>All had TENS machine | 100-point pain VAS, MAS, passive range of movement | 1, 3, 12, 24 weeks | Decreased pain compared with placebo at all time points<br>Improved external rotation compared with placebo at all time points |
| Kong 2007[48] | To assess the effects of botulinum toxin type A on hemiplegic shoulder pain associated with spasticity | Aged 18–80<br>> 3 months post stroke<br>MAS at least 2 at shoulder and elbow<br>Pain VAS at least 4 | Shoulder pain or surgery before stroke<br>Aphasia/cognitive impairment<br>Reflex sympathetic dystrophy<br>Post-stroke central pain<br>Neuromuscular disease<br>Previous treatment BTX | 17 | 9 placebo<br>8, 500 u Dysport<br>All had pectoralis major and biceps | 10-point pain VAS, MAS, passive range of movement | 4, 8, 12 weeks | Decreased MAS score at shoulder and elbow compared with placebo at week 4 |

| Author and year | Purpose of study | Eligibility | Exclusions | Number of participants | Intervention/ Control | Outcome measures | Follow up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Jahangir 2007[49] | To assess the effectiveness, safety and impact of botulinum toxin on activities of daily living and quality of life in post-stroke hand spasticity in Malaysian patients | >21 years old<br>At least 1 year post stroke<br>MAS at least 2 at wrist and fingers | Fixed contracture<br>Profound muscle atrophy<br>Prior BTX or nerve blocks<br>Treatment agents affecting neuromuscular transmission<br>Neuromuscular disease<br>Injection site infection<br>Systemic infection<br>Pregnancy or lactation | 52 | 25 placebo<br>27, 80 u Botox<br>All had FCR, FCU, FDS, FDP | MAS, Barthel ADL Index, Euroqol EQ-5D | 1, 12 weeks | Decreased MAS score at wrist and fingers compared with placebo at 1 and 12 weeks |
| de Boer 2008[50] | To study the effect of botulinum toxin type A in the subscapular muscle on shoulder pain and humerus rotation | > 18 years old<br>Any time after stroke<br>MAS at least 1 at elbow<br>Pain VAS at least 40<br>50% restricted external rotation relative to unaffected arm | Inability to complete VAS<br>INR > 3<br>Glenohumeral infiltration in last 4 weeks<br>Shoulder pathology | 21 | 11 placebo<br>10, 50 u Botox<br>All had subscapular muscle | 100-point pain VAS, passive range of movement | 6, 12 weeks | Nil |

*continued*

***TABLE 35*** *Overview of randomised controlled trials (continued)*

| Author and year | Purpose of study | Eligibility | Exclusions | Number of participants | Intervention/ Control | Outcome measures | Follow up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| McCrory 2009[51] | To examine the effect of botulinum toxin type A on quality of life and person-centred outcomes in patients with upper limb spasticity following stroke | >18 years old<br>>6 months post stroke<br>MAS at least 2 in two out of three of elbow, wrist, fingers and 1+ remaining area<br>Cognitive and communicative ability to give written consent | Severe contracture<br>Other neurological impairment<br>Concurrent treatment with aminoglycoside antibiotics<br>Botulinum toxin within last 4 months<br>Previous with phenol or intrathecal baclofen for arm spasticity | 96 | 42 placebo<br>54, 750–1000 u Dysport<br>Muscles injected according to spasticity pattern<br>Second injections given at week 12, muscles and dosages according to response to first injection | Assessment of quality of life measure<br>100-point pain VAS, Hospital Anxiety and Depression rating scale, goal attainment, MAS, Modified Motor Assessment Scale, patient disability and carer-burden scale (with a principal target of treatment), global assessment of benefit | 8, 20 weeks<br>(global benefit only 12, 24 weeks) | Decreased MAS score across all joints at weeks 8 and 20 in BTX group compared with placebo<br>Higher proportion of participants with improved score for principle target of treatment at weeks 8 and 20.<br>Goal attainment score higher at week 20<br>Higher proportion of participants with global benefit at week 12, 24 |

AP, adductor pollicis; AS, Ashworth Scale; BTX, botulinum toxin; DAS, Disability Assessment Scale; ES, electrical stimulation; FAT, Frenchay Arm Test; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; FIM, Functional Independence measure; FPL, flexor pollicis longus; f/u, follow up; INR, international normalised ratio; MAS, Modified Ashworth Scale; ROM, range of movement; SF-36, Short Form questionnaire-36 items; TENS, transcutaneous electrical nerve stimulation; u, units; VAS, visual analogue scale.

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***TABLE 36*** *Overview of uncontrolled repeat injection studies*

| Author and year | Purpose of study | Eligibility | Exclusions | Number of subjects | Treatment | Outcome measures | Follow up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Rodriquez 2000[57] | Assess the outcomes of botulinum toxin injection of spastic finger flexors followed by intensive training of finger extensors | Chronic hemiplegia (all were stroke)<br>Clinical spasticity of long fingers flexors<br>Trace finger extension when wrist flexed<br>Full passive range of movement of finger flexors<br>Adequate cognition for home programme<br>No lower motor neurone disease | None given | 14 | 50 mouse u into FDS and FDP. Preparation of botulinum not detailed<br>No criteria given for repeat injections<br>Six participants given second injection at mean 5.7 months after first injection<br>Two participants given third injection at mean 5.5 months after second | MAS<br>Grip strength<br>Clonus score<br>Finger extension (by video) | Mean 3.5 days after first injection.<br>Mean 1.7 days after second injection<br>Mean 1 day after third | Improved MAS, clonus and video of finger extension after first injections<br>No significant differences after second injections |
| Lagalla 2000[58] | Evaluate long-term ability of repeated botulinum treatment of upper limb spasticity after stroke to accomplish technical, functional and caregiver objectives | Spasticity after stroke present for at least 6 months<br>Lack of efficiency of drug treatment | Fixed contracture<br>Previous treatment with alcoholic neurolytic agents<br>Concurrent treatment with antispastic drugs<br>Severe concomitant disease | 34 | 50–300 u Botox depending on size of muscles and severity of spasticity. Muscles injected according to spasticity pattern<br>Repeat injections given when tone and ROM returned to baseline | MAS ROM<br>FAT<br>Pt/carer goals assessment | 4 weeks following injection<br>Minimum six injection cycles | Improved MAS at elbow, wrist and fingers compared with baseline after each injection<br>Improved ROM at each joint after each injection compared with baseline<br>No difference between scores across injection cycles |

*continued*

***TABLE 36*** *Overview of uncontrolled repeat injection studies (continued)*

| Author and year | Purpose of study | Eligibility | Exclusions | Number of subjects | Treatment | Outcome measures | Follow up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Gordon 2004[59] | Evaluate long-term efficacy and safety of botulinum in post-stroke spasticity (follow-up of patients involved in Brashear *et al.* 2002 study[42]) | At least 6 months post stroke<br>Wrist AS 3 or more, fingers AS 2 or more<br>2 or 3 on disability assessment scale | Fixed contracture<br>Profound muscle atrophy<br>Previous or planned treatment of limb with botulinum, alcohol, phenol, surgery<br>Intrathecal baclofen<br>Change in medication for spasticity in previous 3 months<br>Pregnancy | 111 | 200–240 u Botox distributed between FCU, FCR, FDP, FDS in all participants with some having additional FPL and AP<br>Repeat injections given once 12 weeks had passed and wrist AS 2 or more, finger AS 1 or more. Same muscles injected and doses used | Disability assessment scale<br>AS, botulinum antibody level. | Every 6 weeks for 42 weeks<br>Up to 4 injection cycles | Improved DAS and AS scores compared with baseline after each injection cycle<br>No differences in scores across the cycles |
| Bakheit 2004[60] | To study the efficacy, safety and incidence of botulinum antibody formation with repeated treatments with botulinum in post-stroke upper limb spasticity | At least 3 months post stroke<br>MAS 2 or more in at least 2 of elbow, wrist, fingers and 1+ in remaining area<br>10 or more on disability and carer burden rating scale | Muscle contracture<br>Previous treatment with alcohol or phenol nerve blocks<br>Treatment with BTX in previous 3 months<br>Treatment with intrathecal baclofen | 51 | 1000 u Dysport distributed between biceps, FCR, FCU, FDS and FDP for initial injections<br>Repeat injections at week 12 if MAS back to baseline, otherwise at week 16. Same muscles injected but dose at discretion of clinician | MAS<br>ROM<br>Pain<br>Disability and carer burden rating scale<br>Global assessment<br>Goal attainment scale<br>Antibody level | 4 weeks after each injection<br>3 injection cycles | Decrease of at least one point on the MAS across at least one joint achieved by 100%, 98% and 98% of participants following first, second and third injections, respectively<br>Improvements on disability and carer scale after each injection<br>Improvements in ROM after each injection<br>Approx 50% of patients achieved their goals after each injection<br>90% of patients reported global benefit |

| Author and year | Purpose of study | Eligibility | Exclusions | Number of subjects | Treatment | Outcome measures | Follow up | Statistically significant results |
|---|---|---|---|---|---|---|---|---|
| Cardoso 2007[61] | To establish whether individualised botulinum toxin type A injections improve upper limb function in post-stroke patients | >18 years old<br>Between 6 months and 5 years post stroke<br>Spastic hemiparesis | Fibrotic retraction of affected muscles<br>Liver, blood or kidney disease<br>Aphasia or dementia<br>Pregnancy or lactation | 20 | Dysport dosed and delivered according to spasticity pattern<br>Repeat injections at week 16. No criteria given | Fugl–Meyer Scale<br>MAS<br>FIM<br>Passive range of movement | 16, 32 weeks | Improved MAS scores at both 16 and 32 weeks<br>Improved ROM at both 16 and 32 weeks<br>Arm sections of Fugl–Meyer and FIM improved at both 16 and 32 weeks |
| Elovic 2008[62] | To assess the safety and effects of repeated administration of botulinum toxin type A in patients with post stroke spasticity | >21 years old<br>>6 months post stroke<br>'Need' for a minimum of 200 u Botox into wrist or finger flexors | Fixed contracture<br>Profound atrophy affected arm<br>Neuromuscular disorders<br>Infection/ dermatological condition at injection site<br>Inflammation of study limb limiting movement<br>Past/planned treatment with phenol, alcohol, surgery, intrathecal baclofen, casting<br>Hypersensitivity to botulinum toxin | 279 | 200–400 u Botox distributed at discretion of study investigators<br>Repeated treatments at minimum of 12-weekly intervals if 'need' for at least 200 u Botox into wrist or finger muscles | DAS<br>MAS<br>Stroke-adapted sickness impact profile, EQ-5D VAS<br>Botulinum toxin antibody level | Every 6 weeks for 54 weeks | Improved DAS 'principal target' scores from baseline at all time points<br>Improved MAS scores at the wrist, fingers and thumb from baseline at all time points<br>Improved MAS scores at the elbow in participants receiving at least 250 u at all time points<br>Improved scores on the stroke-adapted sickness impact profile and EQ-5D at all time points from baseline |

AP, adductor pollicis; BTX, botulinum toxin; AS, Ashworth Scale; DAS, Disability Assessment Scale; FAT, Frenchay Arm Test; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; FIM, Functional Independence measure; FPL, flexor pollicis longus; MAS, Modified Ashworth Scale; ROM, range of movement; u, units; VAS, visual analogue scale.

# Appendix 2

## List of case record forms

The following case record forms were used in the study:

- patient information sheet
- consent form 1 (potentially interested in study, contact details can be given to study team)
- consent form 2 (consent to take part in study)
- screening visit
- baseline visit
- randomisation (included initial botulinum toxin injection details for intervention group)
- therapy manual and data collection forms menu 1
- therapy manual and data collection forms menu 2
- Canadian Occupational Performance Measure
- 1-month outcome visit
- 1-month questionnaire
- 3-month outcome visit
- 3-month questionnaire
- 12-month outcome visit
- 12-month questionnaire
- clinical review form (review regarding further therapy/botulinum toxin at 3, 6, 9, 12 months)
- end of study form
- withdrawal of consent form
- adverse event form
- serious adverse event form.

Copies of case record forms are available from Professor Helen Rodgers: e-mail: Helen.Rodgers@ncl.ac.uk

# Appendix 3

# Outcome scale scores at follow-up

## Impairment

***TABLE 37*** *Impairment at 1 month; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Modified Ashworth Score at elbow:* n *(%)*** | | | |
| 0 | 7 (4.5) (*n* = 154) | 11 (6.6) (*n* = 167) | < 0.001 |
| 1 | 25 (16.2) (*n* = 154) | 59 (35.3) (*n* = 167) | |
| 1+ | 48 (31.2) (*n* = 154) | 35 (21.0) (*n* = 167) | |
| 2 | 40 (26.0) (*n* = 154) | 47 (28.1) (*n* = 167) | |
| 3 | 33 (21.4) (*n* = 154) | 15 (9.0) (*n* = 167) | |
| 4 | 1 (0.6) (*n* = 154) | 0 (0.0) (*n* = 167) | |
| Median (IQR) | 1+ (1+ to 2) | 1+ (1 to 2) | |
| ***Grip strength: median (IQR)*** | 2.0 (0.0 to 6.5) (*n* = 154) | 1.3 (0.0 to 5.3) (*n* = 167) | 0.092 |
| ***Motricity Index: median (IQR)*** | | | |
| Arm | 46.5 (29 to 66) (*n* = 154) | 40 (26 to 66) (*n* = 167) | 0.790 |
| Leg | 54 (43 to 76) (*n* = 154) | 65 (43 to 76) (*n* = 167) | 0.410 |
| Total | 49 (36.3 to 66.3) (*n* = 153) | 52.5 (33.5 to 71) (*n* = 167) | 0.751 |

***TABLE 38*** *Impairment at 1 month; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Modified Ashworth Score at elbow: mean (95% CI)***[a] | 2.5 (2.3 to 2.6) | 2.0 (1.8 to 2.1) | −0.5 (−0.7 to −0.2) |
| ***Grip strength (kg): mean (95% CI)*** | 4.7 (3.7 to 5.8) | 4.0 (3.1 to 5.0) | −0.7 (−2.1 to 0.7) |
| ***Motricity Index: mean (95% CI)*** | | | |
| Arm | 44.4 (40.4 to 48.4) | 43.9 (39.9 to 47.8) | −0.6 (−6.2 to 5.1) |
| Total | 50.5 (47.2 to 53.8) | 51.1 (47.7 to 54.5) | 0.6 (−4.2 to 5.4) |

a Not true MAS value as scale 0, 1, 1+, 2, 3, 4 became 0, 1, 2, 3, 4, 5 for analysis.

***TABLE 39*** *Impairment at 3 months; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Modified Ashworth Score at elbow:* n *(%)*** | | | |
| 0 | 6 (4.0) (*n* = 151) | 9 (5.5) (*n* = 163) | 0.145 |
| 1 | 30 (19.9) (*n* = 151) | 37 (22.7) (*n* = 163) | |
| 1+ | 37 (24.5) (*n* = 151) | 47 (28.8) (*n* = 163) | |
| 2 | 47 (31.1) (*n* = 151) | 44 (27.0) (*n* = 163) | |
| 3 | 30 (19.9) (*n* = 151) | 23 (14.1) (*n* = 163) | |
| 4 | 1 (0.7) (*n* = 151) | 3 (1.8) (*n* = 163) | |
| Median (IQR) | 2 (1+ to 2) | 1+ (1 to 2) | |
| ***Grip strength: median (IQR)*** | 2.0 (0.0 to 7.0) (*n* = 151) | 2.0 (0.0 to 6.7) (*n* = 163) | 0.874 |
| ***Motricity Index: median (IQR)*** | | | |
| Arm | 40 (29 to 67) (*n* = 151) | 40 (29 to 66) (*n* = 163) | 0.862 |
| Leg | 54 (43 to 76) (*n* = 150) | 65 (43 to 76) (*n* = 162) | 0.093 |
| Total | 47 (35.9 to 70.1) (*n* = 150) | 54.3 (36 to 69.5) (*n* = 162) | 0.256 |

***TABLE 40*** *Impairment at 3 months; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Modified Ashworth Score at elbow: mean (95% CI)***[a] | 2.5 (2.3 to 2.6) | 2.3 (2.1 to 2.4) | –0.2 (–0.4 to –0.1) |
| ***Grip strength (kg): mean (95% CI)*** | 5.0 (3.9 to 6.1) | 5.4 (4.2 to 6.6) | 0.4 (–1.2 to 2.0) |
| ***Motricity Index: mean (95% CI)*** | | | |
| Arm | 43.8 (39.7 to 48.0) | 45.7 (41.6 to 49.7) | 1.9 (–4.0 to 7.7) |
| Total | 49.5 (46.0 to 52.9) | 53.2 (50.0 to 56.6) | 3.8 (–1.0 to 8.5) |

a Not true MAS value as scale 0, 1, 1+, 2, 3, 4 became 0, 1, 2, 3, 4, 5 for analysis.

***TABLE 41*** *Impairment at 12 months; median, Mann Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Modified Ashworth Score at elbow:* n *(%)*** | | | |
| 0 | 6 (6.6) (*n* = 91) | 6 (6.2) (*n* = 97) | 0.508 |
| 1 | 25 (27.5) (*n* = 91) | 21 (21.6) (*n* = 97) | |
| 1+ | 13 (14.3) (*n* = 91) | 22 (22.7) (*n* = 97) | |
| 2 | 22 (24.2) (*n* = 91) | 34 (35.1) (*n* = 97) | |
| 3 | 21 (23.1) (*n* = 91) | 14 (14.4) (*n* = 97) | |
| 4 | 4 (4.4) (*n* = 91) | 0 (0.0) (*n* = 97) | |
| Median (IQR) | 2 (1–3) | 1+ (1–2) | |
| ***Grip strength: median (IQR)*** | 3.0 (0.0 to 8.9) (*n* = 92) | 2.0 (0.0 to 9.8) (*n* = 97) | 0.484 |
| ***Motricity Index: median (IQR)*** | | | |
| Arm | 44 (29 to 66) (*n* = 92) | 48 (29 to 66.5) (*n* = 97) | 0.737 |
| Leg | 54 (38.3 to 76) (*n* = 92) | 62 (46.5 to 76) (*n* = 97) | 0.488 |
| Total | 49.5 (36.1 to 70.3) (*n* = 92) | 54.5 (38.5 to 69.8) (*n* = 97) | 0.535 |

***TABLE 42*** *Impairment at 12 months; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Modified Ashworth Score at elbow: mean (95% CI)***[a] | 2.4 (2.1 to 2.7) | 2.3 (2.1 to 2.5) | −0.1 (−0.5 to 0.3) |
| ***Grip strength (kg): mean (95% CI)*** | 5.8 (4.4 to 7.3) | 5.4 (4.0 to 6.9) | −0.4 (−2.4 to 1.6) |
| ***Motricity Index: mean (95% CI)*** | | | |
| Arm | 45.5(40.6 to 50.6) | 47.1 (42.1 to 52.2) | 1.6 (−5.7 to 8.7) |
| Total | 51.5 (47.1 to 56.0) | 53.0 (48.8 to 57.0) | 1.5 (−4.7 to 7.4) |

a Not true MAS value as scale 0, 1, 1+, 2, 3, 4 became 0, 1, 2, 3, 4, 5 for analysis.

## Upper limb function and activity limitation

***TABLE 43*** *Upper limb function and activity limitation at 1 month; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***ARAT: median (IQR)*** | | | |
| Total | 4 (3 to 18) (*n* = 154) | 3 (3 to 16) (*n* = 167) | 0.754 |
| Grasp | 0 (0 to 6) (*n* = 154) | 0 (0 to 5) (*n* = 167) | 0.979 |
| Grip | 0 (0 to 4.3) (*n* = 154) | 0 (0 to 4) (*n* = 167) | 0.965 |
| Pinch | 0 (0 to 1) (*n* = 154) | 0 (0 to 2) (*n* = 167) | 0.401 |
| Gross | 3 (3 to 5) (*n* = 154) | 3 (3 to 5) (*n* = 167) | 0.485 |
| ***Nine-Hole Peg Test (pegs placed in 50 seconds): median (IQR)*** | 0 (0 to 0) (*n* = 155) | 0 (0 to 0) (*n* = 166) | 0.979 |
| ***Upper limb functional activities: median (IQR)*** | | | |
| Put arm through sleeve | 3 (2 to 4) (*n* = 138) | 3 (2 to 4) (*n* = 152) | 0.255 |
| Open the hand for cleaning your palm | 3 (2 to 4) (*n* = 137) | 3 (2 to 4) (*n* = 151) | 0.538 |
| Open the hand for cutting fingernails | 2 (1 to 4) (*n* = 138) | 3 (1 to 4) (*n* = 151) | 0.480 |
| Use cutlery | 1 (1 to 2) (*n* = 135) | 1 (1 to 2) (*n* = 149) | 0.746 |
| ***Barthel ADL Index: median (IQR)*** | 14 (10 to 17) (*n* = 134) | 14.5 (9 to 17) (*n* = 142) | 0.873 |
| ***Barthel ADL Index groups:*** **n** ***(%)*** | | | |
| 0–4 | 9 (6.7) (*n* = 134) | 10 (7) (*n* = 142) | 0.265 |
| 5–9 | 21 (15.7) (*n* = 134) | 27 (19) (*n* = 142) | |
| 10–14 | 47 (35.1) (*n* = 134) | 34 (23.9) (*n* = 142) | |
| 15–19 | 48 (35.8) (*n* = 134) | 64 (45.1) (*n* = 142) | |
| 20 | 9 (6.7) (*n* = 134) | 7 (4.9) (*n* = 142) | |

***TABLE 44*** *Upper limb function and activity limitation at 1 month; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***ARAT: mean (95% CI)*** | 11.9 (9.5 to 14.3) | 11.5 (9.4 to 13.8) | −0.3 (−3.6 to 2.9) |
| ***Nine-Hole Peg Test (pegs placed in 50s): mean (95% CI)*** | 1.2 (0.8 to 1.6) | 1.1 (0.7 to 1.5) | −0.1 (−0.6 to 0.5) |
| ***Upper limb functional activities: mean (95% CI)*** | | | |
| Put arm through sleeve | 3.0 (2.8 to 3.2) | 3.1 (3.0 to 3.3) | 0.1 (−0.1 to 0.4) |
| Open the hand for cleaning your palm | 3.2 (3.0 to 3.4) | 3.3 (3.1 to 3.5) | 0.1 (−0.2 to 0.4) |
| Open the hand for cutting fingernails | 2.5 (2.3 to 2.8) | 2.6 (2.3 to 2.8) | 0.0 (−0.3 to 0.4) |
| Use cutlery | 1.5 (1.3 to 1.7) | 1.6 (1.4 to 1.7) | 0.0 (−0.2 to 0.3) |
| ***Barthel ADL Index: mean (95% CI)*** | 13.2 (12.3 to 14.0) | 13.2 (12.4 to 14.0) | 0.0 (−1.1 to 1.2) |

***TABLE 45*** *Upper limb function and activity limitation at 3 months; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***ARAT: median (IQR)*** | | | |
| Total | 3 (3 to 18) (*n* = 151) | 4 (3 to 18.5) (*n* = 161) | 0.759 |
| Grasp | 0 (0 to 6) (*n* = 151) | 0 (0 to 6) (*n* = 161) | 0.427 |
| Grip | 0 (0 to 4) (*n* = 151) | 0 (0 to 5) (*n* = 161) | 0.228 |
| Pinch | 0 (0 to 2) (*n* = 151) | 0 (0 to 1.5) (*n* = 161) | 0.663 |
| Gross | 3 (3 to 5) (*n* = 151) | 3 (3 to 5) (*n* = 161) | 0.704 |
| ***Nine-Hole Peg Test (pegs placed in 50 seconds): median (IQR)*** | 0 (0 to 0) (*n* = 151) | 0 (0 to 0) (*n* = 162) | 0.529 |
| ***Upper limb functional activities: median (IQR)*** | | | |
| Put arm through sleeve | 3 (2 to 4) (*n* = 134) | 3 (2 to 4) (*n* = 151) | 0.577 |
| Open the hand for cleaning your palm | 3 (2 to 4) (*n* = 134) | 3 (2 to 4) (*n* = 151) | 0.413 |
| Open the hand for cutting fingernails | 2 (1 to 3) (*n* = 134) | 2 (1 to 4) (*n* = 151) | 0.620 |
| Use cutlery | 1 (1 to 2) (*n* = 132) | 1 (1 to 2) (*n* = 151) | 0.692 |
| ***Barthel ADL Index: median (IQR)*** | 14.5 (10 to 17) (*n* = 130) | 15 (11 to 17) (*n* = 143) | 0.967 |
| ***Barthel ADL Index groups:* n *(%)*** | | | |
| 0–4 | 6 (4.6) (*n* = 130) | 8 (5.6) (*n* = 143) | 0.980 |
| 5–9 | 24 (18.5) (*n* = 130) | 23 (16.1) (*n* = 143) | |
| 10–14 | 35 (26.9) (*n* = 130) | 40 (28.0) (*n* = 143) | |
| 15–19 | 55 (42.3) (*n* = 130) | 62 (43.4) (*n* = 143) | |
| 20 | 10 (7.7) (*n* = 130) | 10 (7) (*n* = 143) | |

***TABLE 46*** *Upper limb function and activity limitation at 3 months; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***ARAT: mean (95% CI)*** | 11.4 (9.2 to 13.7) | 12.5 (10.2 to 15.2) | 1.2 (–2.2 to 4.7) |
| ***Nine-Hole Peg Test (pegs placed in 50s): mean (95% CI)*** | 1.1 (0.7 to 1.5) | 1.4 (1.0 to 1.9) | 0.3 (–0.3 to 0.9) |
| ***Upper limb functional activities: mean (95% CI)*** | | | |
| Put arm through sleeve | 3.1 (2.9 to 3.3) | 3.1 (2.9 to 3.3) | 0.1 (–0.2 to 0.3) |
| Open the hand for cleaning your palm | 3.0 (2.8 to 3.2) | 3.2 (3.0 to 3.4) | 0.2 (–0.2 to 0.5) |
| Open the hand for cutting fingernails | 2.3 (2.0 to 2.5) | 2.4 (2.1 to 2.6) | 0.1 (–0.2 to 0.4) |
| Use cutlery | 1.5 (1.4 to 1.7) | 1.5 (1.4 to 1.7) | 0.0 (–0.2 to 0.2) |
| ***Barthel ADL Index: mean (95% CI)*** | 13.4 (12.6 to 14.2) | 13.4 (12.6 to 14.2) | 0.0 (–1.2 to 1.1) |

***TABLE 47*** *Upper limb function and activity limitation at 12 months; median, Mann–Whitney* U*-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***ARAT: median (IQR)*** | | | |
| Total | 4 (3 to 20) (*n* = 92) | 4 (3 to 23) (*n* = 97) | 0.329 |
| Grasp | 0 (0 to 6) (*n* = 92) | 1 (0 to 6) (*n* = 97) | 0.288 |
| Grip | 0 (0 to 5) (*n* = 92) | 0 (0 to 6) (*n* = 97) | 0.416 |
| Pinch | 0 (0 to 1.8) (*n* = 92) | 0 (0 to 3) (*n* = 97) | 0.319 |
| Gross | 3 (3 to 5) (*n* = 92) | 3 (3 to 5) (*n* = 97) | 0.497 |
| ***Nine-Hole Peg Test (pegs placed in 50 seconds): median (IQR)*** | 0 (0 to 0) (*n* = 92) | 0 (0 to 0) (*n* = 97) | 0.833 |
| ***Upper limb functional activities: median (IQR)*** | | | |
| Put arm through sleeve | 3 (2 to 4) (*n* = 83) | 3 (2 to 4) (*n* = 87) | 0.303 |
| Open the hand for cleaning your palm | 3 (2 to 4) (*n* = 83) | 3 (2 to 5) (*n* = 87) | 0.026 |
| Open the hand for cutting fingernails | 2 (1 to 3) (*n* = 83) | 3 (1 to 4) (*n* = 87 | 0.036 |
| Use cutlery | 1 (1 to 2) (*n* = 83) | 1 (1 to 2) (*n* = 87) | 0.124 |
| ***Barthel ADL Index: median (IQR)*** | 14 (12 to 17) (*n* = 75) | 14 (9 to 17) (*n* = 82) | 0.767 |
| ***Barthel ADL Index groups:*** **n** ***(%)*** | | | |
| 0–4 | 3 (4.0) (*n* = 75) | 3 (3.7) (*n* = 82) | 0.372 |
| 5–9 | 9 (12.0) (*n* = 75) | 19 (23.2) (*n* = 82) | |
| 10–14 | 26 (34.7) (*n* = 75) | 21 (25.6) (*n* = 82) | |
| 15–19 | 33 (44.4) (*n* = 75) | 33 (40.2) (*n* = 82) | |
| 20 | 4 (5.3) (*n* = 75) | 6 (7.3) (*n* = 82) | |

***TABLE 48*** *Upper limb function and activity limitation at 12 months; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***ARAT: mean (95% CI)*** | 11.9 (9.0 to 15.1) | 13.6 (10.6 to 16.5) | 1.6 (–2.7 to 6.1) |
| ***Nine-Hole Peg Test (pegs placed in 50s): mean (95% CI)*** | 1.2 (0.7 to 1.8) | 1.3 (0.7 to 1.9) | 0.0 (–0.7 to 0.8) |
| ***Upper limb functional activities: mean (95% CI)*** | | | |
| Put arm through sleeve | 2.9 (2.6 to 3.1) | 3.1 (2.8 to 3.3) | 0.2 (–0.2 to 0.5) |
| Open the hand for cleaning your palm | 2.9 (2.6 to 3.2) | 3.4 (3.1 to 3.7) | 0.5 (0.1 to 0.9) |
| Open the hand for cutting fingernails | 2.2 (1.9 to 2.5) | 2.7 (2.4 to 3.0) | 0.5 (0.1 to 0.9) |
| Use cutlery | 1.4 (1.2 to 1.5) | 1.6 (1.4 to 1.8) | 0.3 (0.0 to 0.5) |
| ***Barthel ADL Index: mean (95% CI)*** | 13.7 (12.8 to 14.7) | 13.4 (12.4 to 14.4) | –0.3 (–1.7 to 1.1) |

## Stroke-related quality of life/participation restriction

***TABLE 49*** *Stroke-related quality of life/participation restriction at 1 month; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Stroke Impact Scale domains: median (IQR)*** | | | |
| Strength | 34.4 (18.8 to 50.0) (*n* = 138) | 31.3 (18.8 to 50.0) (*n* = 150) | 0.767 |
| Memory | 75.0 (60.7 to 92.9) (*n* = 137) | 75.0 (64.3 to 92.9) (*n* = 152) | 0.981 |
| Emotion | 66.7 (55.6 to 80.6) (*n* = 136) | 66.7 (55.6 to 75.0) (*n* = 151) | 0.413 |
| Communication | 89.3 (64.3 to 100) (*n* = 138) | 85.7 (57.1 to 96.4) (*n* = 152) | 0.156 |
| ADL | 42.5 (30.0 to 57.5) (*n* = 138) | 42.5 (30.0 to 57.5) (*n* = 151) | 0.876 |
| Mobility | 50.0 (29.2 to 63.9) (*n* = 137) | 44.4 (27.8 to 63.9) (*n* = 151) | 0.618 |
| Hand function | 0.0 (0.0 to 25.0) (*n* = 138) | 0.0 (0.0 to 20.0) (*n* = 151) | 0.740 |
| Participation/Handicap | 37.5 (18.8 to 62.5) (*n* = 137) | 34.4 (17.9 to 57.1) (*n* = 151) | 0.452 |
| Physical domain | 34.0 (24.1 to 45.6) (*n* = 138) | 32.4 (20.5 to 45.5) (*n* = 152) | 0.728 |
| Stroke recovery | 40.0 (30.0 to 57.5) (*n* = 137) | 40.0 (25.0 to 50.0) (*n* = 151) | 0.585 |
| ***EQ-5D: median (IQR)*** | | | |
| Mobility | 2 (2 to 2) (*n* = 138) | 2 (2 to 2) (*n* = 151) | 0.746 |
| Self-care | 2 (2 to 2) (*n* = 138) | 2 (2 to 2) (*n* = 151) | 0.540 |
| Usual activities | 3 (2 to 3) (*n* = 138) | 3 (2 to 3) (*n* = 149) | 0.440 |
| Pain/discomfort | 2 (2 to 2) (*n* = 137) | 2 (1 to 2) (*n* = 150) | 0.181 |
| Anxiety/depression | 2 (1 to 2) (*n* = 133) | 2 (1 to 2) (*n* = 149) | 0.377 |
| Good/bad health scale | 50 (40 to 65) (*n* = 135) | 50 (40 to 70) (*n* = 150) | 0.401 |
| ***Oxford Handicap Scale: median (IQR)*** | 3 (3 to 4) (*n* = 137) | 3 (3 to 4) (*n* = 152) | 0.169 |

***TABLE 50*** *Stroke related quality of life/participation restriction at 1 month; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Stroke Impact Scale domains: mean (95% CI)*** | | | |
| Strength | 33.7 (30.4 to 37.0) | 33.7 (30.8 to 36.8) | 0.0 (−4.4 to 4.5) |
| Memory | 74.5 (70.5 to 78.5) | 74.5 (70.9 to 77.8) | −0.1 (−5.2 to 5.1) |
| Emotion | 66.9 (63.9 to 69.7) | 65.2 (62.8 to 67.7) | −1.7 (−5.4 to 2.2) |
| Communication | 78.2 (73.8 to 82.5) | 75.7 (71.4 to 79.8) | −2.5 (−8.5 to 3.6) |
| ADL | 42.5 (39.1 to 45.9) | 43.3 (39.9 to 46.7) | 0.8 (−3.9 to 5.5) |
| Mobility | 48.0 (43.7 to 52.4) | 47.3 (43.3 to 51.4) | −0.7 (−6.6 to 5.4) |
| Hand function | 12.7 (9.6 to 16.1) | 15.2 (11.7 to 19.0) | 2.5 (−2.3 to 7.3) |
| Participation/Handicap | 41.5 (36.7 to 46.3) | 38.3 (33.9 to 42.9) | −3.1 (−9.7 to 3.6) |
| Physical domains | 34.0 (31.2 to 36.8) | 34.5 (31.7 to 37.3) | 0.5 (−3.6 to 4.4) |
| Stroke recovery | 43.1 (39.9 to 46.3) | 40.5 (37.4 to 43.7) | −2.6 (−7.1 to 1.9) |

*continued*

***TABLE 50*** *Stroke related quality of life/participation restriction at 1 month; mean, 95% CI (continued)*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***EQ-5D: mean (95% CI)*** | | | |
| Mobility | 2.0 (2.0 to 2.1) | 2.1 (2.0 to 2.1) | 0.0 (–0.1 to 0.1) |
| Self-care | 2.1 (2.0 to 2.2) | 2.1 (2.0 to 2.2) | 0.0 (–0.2 to 0.1) |
| Usual activities | 2.5 (2.4 to 2.6) | 2.5 (2.4 to 2.6) | 0.0 (–0.1 to 0.2) |
| Pain/discomfort | 1.9 (1.8 to 2.0) | 1.8 (1.7 to 1.9) | –0.1 (–0.2 to 0.0) |
| Anxiety/depression | 1.7 (1.6 to 1.8) | 1.6 (1.6 to 1.7) | –0.1 (–0.2 to 0.1) |
| Good/bad health scale | 53.4 (50.1 to 56.8) | 55.0 (52.0 to 58.0) | 1.6 (–2.9 to 6.2) |
| ***Oxford Handicap Scale: mean (95% CI)*** | 3.4 (3.2 to 3.5) | 3.5 (3.3 to 3.7) | 0.1 (–0.1 to 0.3) |

***TABLE 51*** *Stroke-related quality of life/participation restriction at 3 months; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Stroke Impact Scale domains: median (IQR)*** | | | |
| Strength | 31.3 (12.5 to 50.0) (*n* = 130) | 31.3 (18.8 to 43.8) (*n* = 151) | 0.966 |
| Memory | 78.6 (59.8 to 96.4) (*n* = 133) | 78.6 (64.3 to 92.9) (*n* = 152) | 0.668 |
| Emotion | 65.3 (55.6 to 77.8) (*n* = 132) | 63.9 (54.6 to 75.0) (*n* = 149) | 0.422 |
| Communication | 85.7 (60.7 to 100.0) (*n* = 134) | 86.6 (66.1 to 100.0) (*n* = 150) | 0.468 |
| ADL | 42.5 (30.0 to 57.5) (*n* = 134) | 40.0 (28.1 to 55.0) (*n* = 151) | 0.663 |
| Mobility | 52.8 (30.6 to 70.4) (*n* = 133) | 47.2 (30.6 to 67.2) (*n* = 150) | 0.455 |
| Hand function | 0.0 (0.0 to 15.0) (*n* = 134) | 0.0 (0.0 to 20.0) (*n* = 151) | 0.673 |
| Participation/Handicap | 34.7 (15.6 to 62.5) (*n* = 134) | 39.1 (18.5 to 62.5) (*n* = 150) | 0.874 |
| Physical domain | 34.6 (21.8 to 44.9) (*n* = 134) | 31.0 (20.7 to 44.6) (*n* = 152) | 0.683 |
| Stroke recovery | 40.0 (30.0 to 60.0) (*n* = 133) | 40.0 (30.0 to 60.0) (*n* = 152) | 0.844 |
| ***EQ-5D: median (IQR)*** | | | |
| Mobility | 2 (2 to 2) (*n* = 134) | 2 (2 to 2) (*n* = 151) | 0.525 |
| Self-care | 2 (2 to 2) (*n* = 134) | 2 (2 to 2) (*n* = 152) | 0.325 |
| Usual activities | 2 (2 to 3) (*n* = 134) | 3 (2 to 3) (*n* = 151) | 0.605 |
| Pain/discomfort | 2 (2 to 2) (*n* = 133) | 2 (1 to 2) (*n* = 152) | 0.008 |
| Anxiety/depression | 2 (1 to 2) (*n* = 132) | 2 (1 to 2) (*n* = 151) | 0.139 |
| Good/bad health scale | 50 (40 to 70) (*n* = 133) | 50 (40 to 70) (*n* = 149) | 0.734 |
| ***Oxford Handicap Scale: median (IQR)*** | 3 (3 to 4) (*n* = 133) | 3 (3 to 4) (*n* = 151) | 0.928 |

***TABLE 52*** *Stroke-related quality of life/participation restriction at 3 months; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Stroke Impact Scale domain: mean (95% CI)*** | | | |
| Strength | 31.2 (27.2 to 35.2) | 32.1 (28.7 to 35.4) | 0.9 (−4.3 to 6.1) |
| Memory | 73.6 (68.8 to 78.2) | 75.1 (71.6 to 78.6) | 1.5 (−4.3 to 7.5) |
| Emotion | 67.3 (64.5 to 70.2) | 63.9 (61.2 to 66.6) | −3.4 (−7.4 to 0.5) |
| Communication | 76.4 (71.8 to 80.9) | 79.5 (75.5 to 83.2) | 3.0 (−2.8 to 9.1) |
| ADL | 43.0 (39.5 to 46.5) | 43.0 (39.8 to 46.2) | −0.1 (−4.8 to 4.8) |
| Mobility | 50.4 (45.8 to 55.1) | 49.1 (45.0 to 53.2) | −1.3 (−7.6 to 5.0) |
| Hand function | 12.2 (8.6 to 16.0) | 13.4 (10.1 to 16.9) | 1.3 (−3.8 to 6.2) |
| Participation/Handicap | 40.4 (35.7 to 45.1) | 40.8 (36.1 to 45.4) | 0.3 (−6.3 to 7.0) |
| Physical domains | 33.9 (30.7 to 37.0) | 34.0 (31.1 to 36.9) | 0.2 (−4.1 to 4.4) |
| Stroke recovery | 43.8 (40.2 to 47.5) | 43.5 (40.3 to 46.7) | −0.3 (−5.2 to 4.5) |
| ***EQ-5D: mean (95% CI)*** | | | |
| Mobility | 2.0 (1.9 to 2.1) | 2.0 (2.0 to 2.1) | 0.0 (−0.1 to 0.1) |
| Self-care | 2.1 (2.0 to 2.2) | 2.1 (2.0 to 2.2) | −0.1 (−0.2 to 0.1) |
| Usual activities | 2.5 (2.4 to 2.6) | 2.5 (2.4 to 2.6) | 0.0 (−0.1 to 0.1) |
| Pain/discomfort | 1.9 (1.8 to 2.0) | 1.7 (1.7 to 1.8) | −0.2 (−0.3 to 0.0) |
| Anxiety/depression | 1.6 (1.5 to 1.7) | 1.7 (1.6 to 1.8) | 0.1 (0.0 to 0.2) |
| Good/bad health scale | 53.8 (50.2 to 57.5) | 54.3 (51.2 to 57.4) | 0.5 (−4.3 to 5.3) |
| ***Oxford Handicap Scale: mean (95% CI)*** | 3.4 (3.3 to 3.6) | 3.4 (3.2 to 3.5) | −0.1 (−0.3 to 0.2) |

***TABLE 53*** *Stroke-related quality of life/participation restriction at 12 months; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| ***Stroke Impact Scale domains: median (IQR)*** | | | |
| Strength | 25.0 (12.5 to 43.8) (*n* = 80) | 31.3 (12.5 to 43.8) (*n* = 86) | 0.675 |
| Memory | 75.0 (53.6 to 92.9) (*n* = 83) | 82.1 (64.3 to 92.9) (*n* = 87) | 0.328 |
| Emotion | 63.9 (52.8 to 75.7) (*n* = 82) | 66.7 (55.6 to 75.0) (*n* = 87) | 0.964 |
| Communication | 85.7 (60.7 to 100.0) (*n* = 83) | 89.3 (67.9 to 96.4) (*n* = 87) | 0.754 |
| ADL | 45.0 (30.0 to 55.6) (*n* = 83) | 41.3 (30.0 to 57.5) (*n* = 86) | 0.660 |
| Mobility | 52.8 (30.6 to 66.7) (*n* = 83) | 47.2 (27.8 to 69.4) (*n* = 87) | 0.806 |
| Hand function | 0.0 (0.0 to 10.0) (*n* = 83) | 0.0 (0.0 to 25.0) (*n* = 87) | 0.130 |
| Participation/Handicap | 40.6 (18.8 to 61.6) (*n* = 81) | 39.1 (17.9 to 63.3) (*n* = 86) | 0.978 |
| Physical domain | 30.7 (23.1 to 44.1) (*n* = 83) | 32.6 (19.5 to 47.2) (*n* = 87) | 0.648 |
| Stroke recovery | 40.0 (22.5 to 55.0) (*n* = 81) | 40.0 (30.0 to 60.0) (*n* = 87) | 0.266 |
| ***EQ-5D: median (IQR)*** | | | |
| Mobility | 2 (2 to 2) (*n* = 83) | 2 (2 to 2) (*n* = 87) | 0.381 |
| Self-care | 2 (2 to 2) (*n* = 82) | 2 (2 to 2) (*n* = 87) | 0.589 |
| Usual activities | 2 (2 to 3) (*n* = 83) | 2.5 (2 to 3) (*n* = 86) | 0.765 |
| Pain/discomfort | 2 (2 to 2) (*n* = 83) | 2 (2 to 2) (*n* = 87) | 0.588 |
| Anxiety/depression | 2 (1 to 2) (*n* = 81) | 2 (1 to 2) (*n* = 86) | 0.167 |
| Good/bad health scale | 52.5 (40 to 70) (*n* = 80) | 60 (40 to 70) (*n* = 85) | 0.583 |
| ***Oxford Handicap Scale: median (IQR)*** | 3 (3 to 4) (*n* = 83) | 3 (3 to 4) (*n* = 87) | 0.119 |

***TABLE 54*** *Stroke-related quality of life/participation restriction at 12 months' mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| ***Stroke Impact Scale domains: mean (95% CI)*** | | | |
| Strength | 29.7 (25.5 to 34.0) | 31.5 (27.3 to 35.9) | 1.9 (–4.2 to 7.9) |
| Memory | 71.1 (65.8 to 76.3) | 75.0 (70.3 to 79.6) | 3.9 (–3.2 to 11.0) |
| Emotion | 64.7 (60.9 to 68.4) | 63.7 (60.3 to 67.1) | –0.9 (–6.1 to 4.0) |
| Communication | 77.9 (72.3 to 83.2) | 79.1 (73.9 to 84.1) | 1.2 (–6.1 to 8.7) |
| ADL | 41.8 (37.5 to 46.1) | 44.3 (40.3 to 48.3) | 2.5 (–3.4 to 8.4) |
| Mobility | 49.1 (43.9 to 54.2) | 48.1 (42.9 to 53.3) | –1.1 (–8.4 to 6.3) |
| Hand function | 8.3 (5.1 to 11.9) | 15.1 (10.3 to 20.1) | 6.8 (0.8 to 12.7) |
| Participation/Handicap | 41.4 (35.4 to 47.4) | 41.8 (35.6 to 48.0) | 0.4 (–8.3 to 9.1) |
| Physical domains | 31.9 (28.5 to 35.1) | 34.5 (30.8 to 38.4) | 2.7 (–2.2 to 7.7) |
| Stroke recovery | 40.6 (36.0 to 45.1) | 44.0 (39.5 to 48.5) | 3.4 (–3.0 to 9.7) |
| ***EQ-5D: mean (95% CI)*** | | | |
| Mobility | 2.0 (2.0 to 2.1) | 2.1 (2.0 to 2.2) | 0.1 (–0.1 to 0.2) |
| Self-care | 2.1 (2.0 to 2.3) | 2.1 (2.0 to 2.2) | –0.1 (–0.2 to 0.1) |
| Usual activities | 2.5 (2.3 to 2.6) | 2.5 (2.4 to 2.6) | 0.0 (–0.1 to 0.2) |
| Pain/discomfort | 1.9 (1.8 to 2.0) | 1.9 (1.7 to 2.0) | –0.1 (–0.2 to 0.1) |
| Anxiety/depression | 1.8 (1.7 to 2.0) | 1.7 (1.5 to 1.8) | –0.2 (–0.3 to 0.0) |
| Good/bad health scale | 54.2 (48.7 to 59.6) | 57.1 (52.5 to 61.6) | 2.9 (–4.2 to 10.0) |
| ***Oxford Handicap Scale: mean (95% CI)*** | 3.5 (3.3 to 3.7) | 3.3 (3.0 to 3.5) | –0.2 (–0.5 to 0.1) |

## Upper limb pain

***TABLE 55*** *Upper limb pain at 1 month; median, Mann–Whitney U-test*

| | Control | Intervention | *p*-value |
|---|---|---|---|
| Pain description (excruciating, severe, moderate, mild, none): median (IQR) | 4 (mild) (3 to 5) (*n* = 155) | 4 (mild) (3 to 5) (*n* = 167) | 0.066 |
| Pain score (0–10): median (IQR) | 4 (0 to 6) (*n* = 153) | 2 (0 to 6) (*n* = 167) | 0.216 |

***TABLE 56*** *Upper limb pain at 1 month; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| Pain description (excruciating, severe, moderate, mild, none): mean (95% CI) | 3.7 (3.5 to 3.9) | 4.0 (3.8 to 4.1) | 0.3 (0.0 to 0.5) |
| Pain score (0–10): mean (95% CI) | 3.5 (3.0 to 4.0) | 3.0 (2.5 to 3.5) | −0.5 (−1.2 to 0.2) |

***TABLE 57*** *Upper limb pain at 3 months; median, Mann–Whitney U-test*

| | Control (*n* = 151) | Intervention (*n* = 163) | *p*-value |
|---|---|---|---|
| Pain description (excruciating, severe, moderate, mild, none): median (IQR) | 4 (3 to 5) (mild) (*n* = 149) | 5 (3 to 5) (none) (*n* = 163) | 0.068 |
| Pain score (0–10): median (IQR) | 3 (0 to 6) (*n* = 148) | 0 (0 to 5) (*n* = 162) | 0.047 |

***TABLE 58*** *Upper limb pain at 3 months; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| Pain description (excruciating, severe, moderate, mild, none): mean (95% CI) | 3.7 (3.5 to 3.9) | 4.0 (3.8 to 4.1) | 0.3 (0.0 to 0.5) |
| Pain score (0–10): mean (95% CI) | 3.4 (3.0 to 4.0) | 2.7 (2.2 to 3.2) | −0.8 (−1.5 to 0.0) |

***TABLE 59*** *Upper limb pain at 12 months; median, Mann–Whitney U-test*

| | Control (*n* = 92) | Intervention (*n* = 97) | *p*-value |
|---|---|---|---|
| Pain description (excruciating, severe, moderate, mild, none): median (IQR) | 4 (mild) (3 to 5) | 5 (none) (3.5 to 5) | 0.001 |
| Pain score (0–10): median (IQR) | 4 (0 to 7) | 0 (0 to 4) | < 0.001 |

***TABLE 60*** *Upper limb pain at 12 months; mean, 95% CI*

| | Control | Intervention | Difference |
|---|---|---|---|
| Pain description (excruciating, severe, moderate, mild, none): mean (95% CI) | 3.7 (3.4 to 3.9) | 4.2 (4.0 to 4.5) | 0.6 (0.2 to 0.9) |
| Pain score (0–10): mean (95% CI) | 3.6 (2.9 to 4.3) | 1.9 (1.4 to 2.5) | −1.7 (−2.6 to −0.8) |

# Appendix 4

## Site recruitment

Twelve research sites participated in the BoTULS study. For logistical reasons, some sites were joined or divided to create recruitment areas as shown in *Table 61*. There were differences in recruitment from each area because of time of site/area initiation and study therapist availability.

The study was initially planned in four recruitment areas (North Tyneside, Wansbeck area, Newcastle upon Tyne and Sunderland) but because of low recruitment rates the additional sites/areas were added.

***TABLE 61*** *Study research sites and recruitment areas within the UK*

| Research site | Recruitment area | First patient recruited | Total recruitment |
|---|---|---|---|
| Northumbria Healthcare NHS Foundation Trust (North Tyneside General Hospital) | North Tyneside | July 2005 | 37 |
| Newcastle Primary Care Trust | Newcastle upon Tyne | October 2005 | 44 |
| Newcastle upon Tyne Hospitals NHS Foundation Trust | | | |
| Northumberland, Tyne and Wear NHS Trust | | | |
| Northumbria Healthcare NHS Foundation Trust (Wansbeck, Hexham, Morpeth, Blyth, Alnwick hospitals) | Wansbeck, Morpeth, Blyth and Alnwick | November 2005 | 41 |
| | Hexham | April 2007 | 5 |
| City Hospitals Sunderland NHS Foundation Trust | Sunderland | January 2006 | 69 |
| South Tyneside NHS Foundation Trust | South Tyneside | October 2006 | 34 |
| Gateshead Health NHS Foundation Trust | Gateshead | November 2006 | 11 |
| Durham and Darlington NHS Foundation Trust (Durham hospitals) | Durham | November 2006 | 26 |
| North Cumbria University Hospitals NHS Trust | Carlisle | February 2007 | 15 |
| Durham and Darlington NHS Foundation Trust (Bishop Auckland General Hospital) | Bishop Auckland | June 2007 | 25 |
| North Tees and Hartlepool NHS Foundation Trust | Hartlepool | September 2007 | 16 |
| | North Tees | October 2007 | 10 |

# Appendix 5
## Study dissemination

### Protocol

The trial protocol (or summary of protocol) is available from:

- NIHR Health Technology Assessment programme website: http://www.ncchta.org/project/1408.asp.
- ISRCTN website: http://www.controlled-trials.com/ISRCTN78533119/78533119.
- UK Clinical Research Network website: http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=2185.
- *The Lancet* website: http://www.thelancet.com/protocol-reviews/07PRT-5979.

### Study methods

#### *Study method publication*

Rodgers H, Shaw L, Price C, van Wijck F, Barnes M, Graham L, et al. Study design and methods of the BoTULS trial: a randomised controlled trial to evaluate the clinical effect and cost effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. *Trials* 2008;**9**:59. URL: http://www.trialsjournal.com/content/9/1/59.

#### *Study method presentations*

- British Geriatric Society Northern Regional meeting 2005 (poster).
- British Association of Stroke Physicians meeting 2006 (poster).
- European Stroke Conference 2006 (poster).
- World Congress of Rehabilitation 2006 (poster).
- UK Stroke Forum 2006 (poster).
- Stroke Research Network meetings 2007 and 2008 (invited posters).
- North East Stroke Research Network meeting 2007 (invited poster).
- Society for Research in Rehabilitation meeting 2008 (invited presentation).

#### *Botulinum toxin reviews*

Shaw L, Rodgers H. Botulinum toxin type A for upper limb spasticity after stroke. *Expert Rev Neurother* 2009;**9**:1713–25.

Shaw L and Rodgers H. Botulinum toxin to treat spasticity after stroke. *Stroke Matters* 2010;6:12–13.

### Study results

A summary of the results was sent to study participants.

#### *Study results publications*

Shaw LC, Price CIM, van Wijck FMJ, Shackley P, Steen N, Barnes MP, et al. Botulinum Toxin for the Upper Limb after Stroke (BoTULS) Trial: effect upon impairment, activity limitation and pain. *Stroke*, in press.

Shackley P, Shaw LC, Price CIM, van Wijck FMJ, Barnes MP, Graham LA, et al. Cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A: results from the Botulinum Toxin for the Upper Limb after Stroke (BoTULS) trial. Submitted for publication.

#### *Study results presentations*

- Local investigators and study team meeting July 2008.
- World Stroke Congress 2008 (poster).
- Association of North of England Physicians meeting 2008 (platform presentation).
- UK Stroke Forum 2008 (invited presentation).
- North East Stroke Research Network meeting 2009 (invited presentation).
- Society for Research in Rehabilitation meeting 2009 (platform presentation).
- British Geriatric Society Northern Regional meeting 2009 (platform presentation).
- European Stroke Conference 2009 (platform presentation).
- British Society of Rehabilitation Medicine meeting 2009 (platform presentation).
- UK Stroke Forum 2009 (platform presentation).
- Society for Research in Rehabilitation meeting 2010 (platform presentation).
- European Stroke Conference 2010 (poster).

# Health Technology Assessment reports published to date

## Volume 1, 1997

**No. 1**
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

**No. 2**
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

**No. 3**
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

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Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

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A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al.*

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Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

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Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al.*

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Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

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Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

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A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

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Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al.*

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Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

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Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

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When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

## Volume 2, 1998

**No. 1**
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

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Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

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Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al.*

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A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

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Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al.*

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Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

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Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

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A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

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Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

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Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

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Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

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Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

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Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

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Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

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Ethical issues in the design and conduct of randomised controlled trials.

A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

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Qualitative research methods in health technology assessment: a review of the literature.

By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

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The costs and benefits of paramedic skills in pre-hospital trauma care.

By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

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Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.

By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al.*

**No. 19**

Systematic reviews of trials and other studies.

By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

**No. 20**

Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.

A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al.*

## Volume 3, 1999

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Informed decision making: an annotated bibliography and systematic review.

By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al.*

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Handling uncertainty when performing economic evaluation of healthcare interventions.

A review by Briggs AH, Gray AM.

**No. 3**

The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.

By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

**No. 4**

A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.

By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al.*

**No. 5**

Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.

By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

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Assessing the costs of healthcare technologies in clinical trials.

A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

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Cooperatives and their primary care emergency centres: organisation and impact.

By Hallam L, Henthorne K.

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Screening for cystic fibrosis.

A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

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A review of the use of health status measures in economic evaluation.

By Brazier J, Deverill M, Green C, Harper R, Booth A.

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Methods for the analysis of quality-of-life and survival data in health technology assessment.

A review by Billingham LJ, Abrams KR, Jones DR.

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Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.

By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

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Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.

A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al.*

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'Early warning systems' for identifying new healthcare technologies.

By Robert G, Stevens A, Gabbay J.

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A systematic review of the role of human papillomavirus testing within a cervical screening programme.

By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al.*

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Near patient testing in diabetes clinics: appraising the costs and outcomes.

By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

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Positron emission tomography: establishing priorities for health technology assessment.

A review by Robert G, Milne R.

**No. 17 (Pt 1)**

The debridement of chronic wounds: a systematic review.

By Bradley M, Cullum N, Sheldon T.

**No. 17 (Pt 2)**

Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.

By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

**No. 18**

A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.

By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al.*

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What role for statins? A review and economic model.

By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al.*

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Factors that limit the quality, number and progress of randomised controlled trials.

A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al.*

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Antimicrobial prophylaxis in total hip replacement: a systematic review.

By Glenny AM, Song F.

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Health promoting schools and health promotion in schools: two systematic reviews.

By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

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Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.

A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

**Volume 4, 2000**

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The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

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Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al.*

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Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

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Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

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False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

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Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

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Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al.*

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An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

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Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

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Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

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Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

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Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

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The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al.*

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The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

**No. 15**
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

**No. 16**
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al.*

**No. 17**
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

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Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

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Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al.*

**No. 20**
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

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Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

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Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

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Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

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Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al.*

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A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

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Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
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Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

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Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al.*

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Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

**No. 30**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

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A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

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By Williams JE, Louw G, Towlerton G.

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Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

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A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

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Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al.*

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A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

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Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

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The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al.*

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A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

## Volume 5, 2001

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Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al.*

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The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
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Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al.*

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General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
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An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

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Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al.*

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Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
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Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
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Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

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The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

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A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

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Home treatment for mental health problems: a systematic review.
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How to develop cost-conscious guidelines.
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The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

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A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
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The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

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Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al.*

**No. 21**
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al.*

**No. 22**
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

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Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

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A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al.*

**No. 25**
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

**No. 26**
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al.*

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The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al.*

**No. 28**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

**No. 29**
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**No. 30**
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

**No. 31**
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al.*

**No. 32**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

**No. 33**
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

**No. 34**
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

**No. 35**
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al.*

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Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

## Volume 6, 2002

**No. 1**
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

**No. 2**
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al.*

**No. 3**
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al.*

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A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al.*

**No. 5**
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

**No. 6**
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

**No. 7**
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al.*

**No. 8**
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

**No. 9**
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al.*

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***We look forward to hearing from you.***

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