Botulinum Toxin for the Upper Limb After Stroke (BoTULS) Trial
Effect on Impairment, Activity Limitation, and Pain

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Background and Purpose—Botulinum toxin is increasingly used to treat upper limb spasticity due to stroke, but its impact on arm function is unclear. We evaluated botulinum toxin for upper limb spasticity and function poststroke.

Methods—Three hundred thirty-three patients with stroke with upper limb spasticity and reduced arm function participated in a multicenter randomized controlled trial. The intervention group received botulinum toxin type A injection(s) plus a 4-week therapy program. The control group received the therapy program alone. Repeat injection(s) and therapy were available at 3, 6, and 9 months. The primary outcome was upper limb function at 1 month (Action Research Arm Test). Secondary outcomes included measures of impairment, activity limitation, and pain at 1, 3, and 12 months. Outcome assessments were blinded and analysis was by intention to treat.

Results—There was no significant difference in achievement of improved arm function (Action Research Arm Test) at 1 month (intervention group: 42 of 167 [25.1%], control group 30 of 154 [19.5%]; P=0.232). Significant differences in favor of the intervention group were seen in muscle tone at 1 month; upper limb strength at 3 months; basic arm functional tasks (hand hygiene, facilitation of dressing) at 1, 3, and 12 months; and pain at 12 months.

Conclusions—Botulinum toxin type A is unlikely to be useful for improving active upper limb function (eg, reaching and grasping) in the majority of patients with spasticity after stroke, but it may improve basic upper limb tasks (hand hygiene, facilitation of dressing) and pain. (Stroke. 2011;42:1371-1379.)

Key Words: botulinum toxin • randomized controlled trial • spasticity • stroke • upper limb

Upper limb spasticity affects up to 30% of patients after stroke and may cause deformity, reduced function, and pain. When given by intramuscular injection, botulinum toxin causes temporary local muscle paresis by blocking cholinergic transmission at the neuromuscular junction. Botulinum toxin is increasingly used to treat spasticity due to stroke. Treatment has been shown to reduce muscle tone and improve basic upper limb activities such as hand hygiene and facilitation of dressing. However, the impact on active function (eg, reaching and grasping) and the efficacy of repeat injections is unclear.

The Botulinum Toxin for the Upper Limb after Stroke (BoTULS) trial was a pragmatic multicenter randomized controlled trial to evaluate the clinical and cost-effectiveness of giving botulinum toxin type A in addition to a standardized upper limb therapy program for the treatment of poststroke upper limb spasticity. This article reports the effect on impairment, activity limitation, and pain.

Methods

Study Design
The study objectives and design have been reported previously. This multicenter parallel group randomized controlled trial was undertaken by 12 stroke services and a tertiary spasticity service. Adults with a stroke >1 month previously who had spasticity at the elbow (Modified Ashworth Scale >2) and/or spasticity at shoulder, wrist, or hand; reduced upper limb function (Action Research Arm Test [ARAT]) 0 to 56); and who were able to comply with the requirements of the protocol were eligible to participate provided there was no other significant upper limb problem, contracture, or contraindication to botulinum toxin. Participants were recruited from hospital inpatient and outpatient services, community rehabilitation teams,
day centers, and stroke clubs. Initial assessments were completed once informed consent was obtained. Randomization was by a secure independent Web-based service and participants were stratified according to research site and level of upper limb function (strata: ARAT 0 to 3, 4 to 28, 29 to 56). Outcomes were measured at 1, 3, and 12 months. Upper limb impairment and activity limitation were assessed by: Modified Ashworth Scale, Motricity Index, grip strength (dynamometer), ARAT (Figure 1), 9-hole peg test, basic upper limb functional activity questions (ability to dress a sleeve, open the hand for cleaning the palm, open the hand for cutting the fingernails, ability to use cutlery, scored on a Likert scale from 1 [unable to perform activity] to 5 [no difficulty]), and Barthel Activities of Daily Living Index. Upper limb pain was assessed by verbal (none, mild, moderate, severe, excruciating) and numeric (0 to 10) rating scales.9 The basic upper limb functional activity questions and Barthel Activities of Daily Living Index were collected by self-completion postal questionnaire. Other measures were collected by a blinded assessor. Multicenter research ethics committee, Medicines and Healthcare Products Regulatory Agency and local National Health Service approvals were granted.

Study Treatments
Participants in the intervention group received botulinum toxin type A (Dysport, 100 U or 200 U/mL) injection(s) plus a 4-week standardized, evidence-based program of upper limb therapy. The control group received the therapy program alone. Repeat botulinum toxin type A injections and/or therapy were available at 3, 6, and 9 months if considered necessary after reassessment. The range of muscles and dosages injected was as recommended previously.10 All injectors were clinicians experienced in the use of botulinum toxin. The therapy program was provided by trained study therapists and each participant received 1 hour per day, 2 times per week for 4 weeks. The therapy was delivered as 2 menus in which menu 1 was designed for participants with no active function at baseline (ARAT 0 to 3) and consisted of stretching (20 minutes), positioning (10 minutes), and passive/active, assisted upper limb activity (20 minutes). Menu 2 was designed for participants with some retained function at baseline (ARAT >3) and consisted of stretching (10 minutes) and task-oriented practice (40 minutes). Participants were also given a home exercise program to carry out on days they were not attending therapy. The therapy program started immediately after study entry. Antispasticity medication and physical aids were permitted during the study and changes were recorded at each outcome assessment.

Statistical Analysis
Analyses were undertaken on an “intention-to-treat” basis. All available data were analyzed; missing data were not imputed. The primary end point was the ARAT score at 1 month. It is suggested that the minimal clinically important difference for the ARAT is 10% of its range (6 points)11; however, for patients with poor initial upper limb function, we estimated that a smaller improvement would be clinically beneficial. A “successful outcome” was defined as: (1) a change of ≥3 points on the ARAT scale for a participant whose baseline score was between 0 to 3; (2) a change of ≥6 points for a baseline ARAT score between 4 to 51; and (3) a final ARAT score of 57 for a baseline score between 52 to 56. The proportion of “successes” in each group was compared using the Fisher exact test and an interval estimate of the effect of the intervention was calculated. Inflated to allow for 10% attrition, a sample of 332 participants was needed to provide 80% power to detect a 15% difference in “successful” outcomes assuming a 2-tailed test and a significance level of 5%.

Secondary outcomes providing binary data were compared using the Fisher exact test (or χ² 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 probability values are reported. All secondary outcomes were analyzed using change in scale score from baseline to follow-up. To understand the clinical significance of some of the
results obtained from the Mann-Whitney U test, resampling methods were used to give an interval estimate of the effect of the intervention for each of the outcomes.

There were 2 prespecified subgroup analyses. Logistic regression modeling was used to compare response to treatment (ARAT “success”) for (1) participants who had a stroke 1 year ago and those who had a stroke \( > 1 \) year ago; and (2) participants with no initial active upper limb function at baseline (ARAT 0 to 3) and participants with some initial upper limb function (ARAT 4 to 56).

**Results**

Between July 2005 and March 2008, 333 participants were recruited. From July 2007, newly recruited participants were followed for 3 months only because the trial was behind schedule and 12-month follow-up was curtailed. Two hundred eight participants (62.5%) were enrolled for 12-month follow-up and 125 (37.5%) for 3-month follow-up only. Figure 2 shows participant flow through the trial. Baseline data are presented for 332 participants because 1 participant asked for their data to be excluded. Randomization groups were well matched at baseline with regard to demography, stroke characteristics, comorbidity, and upper limb problems (Table 1).

**Primary Outcome**

There was no significant difference in the proportion of participants achieving improved upper limb function (ARAT “successful outcome”) at 1 month: intervention group 42 of 167 (25.1%) and control group 30 of 154 (19.5%); \( P = 0.232 \). The relative risk of having a “successful outcome” in the intervention group compared with the control group was 1.3 (95% CI, 0.9 to 2.0).

**Secondary Outcomes**

**Upper Limb Impairment**

At 1 month, the median change in muscle tone at the elbow (Modified Ashworth Scale) in the intervention group was \(-1\) compared with 0 in the control group \( (P < 0.001) \). The corresponding differences in change in muscle tone between intervention and control groups at 3 and 12 months were not statistically significant. At 3 months, upper limb strength (Motricity Index) had improved by a mean of 3.5 (95% CI, 0.1 to 6.8) in the intervention group relative to the control group. The differences between the groups for change in upper limb strength from baseline to 1 or 12 months were not significant. There were no significant differences between intervention and control groups for change in grip strength at any assessment (Table 2).

**Upper Limb Activity Limitation**

There was no significant difference in the proportion of participants achieving a “successful outcome” on the ARAT at 3 or 12 months. At 3 months, “success” was achieved by 54 of 161 (33.5%) participants in the intervention group and 37 of 151 (24.5%) in the control group \( (P = 0.083) \). At 12 months, it was 36 of 97 (37.1%) in the intervention group and 27 of 92 (29.3%) in the control group \( (P = 0.282) \). No significant differences were seen in dexterity (9-hole peg test).
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n=162)‡</th>
<th>Intervention (n=170)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex: n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>115 (71.0)</td>
<td>110 (64.7)</td>
</tr>
<tr>
<td>Female</td>
<td>47 (29.0)</td>
<td>60 (35.3)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>66 [59.8–72.3]</td>
<td>67 [58.8–74]</td>
</tr>
<tr>
<td>Range</td>
<td>36–86</td>
<td>30–92</td>
</tr>
<tr>
<td><strong>Stroke subtype: n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total anterior circulation stroke</td>
<td>68 (42.0)</td>
<td>75 (44.1)</td>
</tr>
<tr>
<td>Partial anterior circulation stroke</td>
<td>61 (37.7)</td>
<td>57 (33.5)</td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>26 (16.0)</td>
<td>33 (19.4)</td>
</tr>
<tr>
<td>Posterior circulation stroke</td>
<td>3 (1.9)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>4 (2.5)</td>
<td>3 (1.8)</td>
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<tr>
<td><strong>Time from stroke to randomization</strong></td>
<td></td>
<td></td>
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<tr>
<td>Median [IQR] days</td>
<td>280 [148.8–1145.8]</td>
<td>324 [128.5–1387.5]</td>
</tr>
<tr>
<td><strong>Comorbidity: n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>48 (29.6) (n=162)</td>
<td>49 (28.8) (n=170)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>36 (22.4) (n=161)</td>
<td>39 (23.1) (n=169)</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>8 (5.0) (n=160)</td>
<td>6 (3.6) (n=168)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (13.6) (n=162)</td>
<td>22 (13.1) (n=168)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>119 (73.5) (n=162)</td>
<td>124 (74.3) (n=167)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>103 (64.4) (n=160)</td>
<td>111 (65.7) (n=169)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21 (13.3) (n=158)</td>
<td>24 (14.5) (n=166)</td>
</tr>
<tr>
<td><strong>Distribution of spasticity: n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder and elbow</td>
<td>9 (5.6)</td>
<td>15 (8.8)</td>
</tr>
<tr>
<td>Elbow and wrist</td>
<td>8 (4.9)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Wrist and hand</td>
<td>5 (3.1)</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Shoulder and elbow and wrist</td>
<td>1 (0.6)</td>
<td>9 (5.3)</td>
</tr>
<tr>
<td>Shoulder and elbow and hand</td>
<td>4 (2.5)</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Elbow and wrist and hand</td>
<td>47 (29.0)</td>
<td>43 (25.3)</td>
</tr>
<tr>
<td>Shoulder and elbow and wrist and hand</td>
<td>80 (49.4)</td>
<td>81 (47.6)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (4.9)</td>
<td>12 (7.1)</td>
</tr>
<tr>
<td><strong>Modified Ashworth Scale at elbow</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(scale range, 0, 1, 1+, 2, 3, 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>2 [1 + –2]</td>
<td>2 [1 + -2]</td>
</tr>
<tr>
<td><strong>Motricity Index arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(scale range, 0–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grip strength, kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(scale range, 0–90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>1.8 [0.0–6.0]</td>
<td>0.7 [0.0–5.0]</td>
</tr>
<tr>
<td><strong>ARAT</strong></td>
<td></td>
<td></td>
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<tr>
<td>(scale range, 0–57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3 [3–16]</td>
<td>3 [3–13]</td>
</tr>
<tr>
<td>Grasp</td>
<td>0 [0–5]</td>
<td>0 [0–5]</td>
</tr>
<tr>
<td>Grip</td>
<td>0 [0–4]</td>
<td>0 [0–3]</td>
</tr>
<tr>
<td>Pinch</td>
<td>0 [0–0]</td>
<td>0 [0–0]</td>
</tr>
</tbody>
</table>

(Continued)
or the Barthel Activities of Daily Living Index at any assessment (Table 2).

Basic upper limb functional activity questions (Table 3) were analyzed by comparing the proportion of participants in each randomization group who had improved by ≥1 points on the scale from baseline. For the ability to dress a sleeve, this improvement was seen for 65 of 144 (45.1%) of participants in the intervention group compared with 38 of 125 (30.4%) in the control group at 1 month (P=0.017). For opening the hand to clean the palm and opening the hand to cut fingernails, significant differences in favor 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.

**Upper Limb Pain**
No significant differences were found in change in pain rating on either pain scale from baseline to 1 or 3 months. However, there was a significant decrease in pain rating from baseline to 12 months in the intervention group compared with the control group on both pain scales (Table 2).

**Blinding of Outcome Assessments**
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) of participants, respectively, at 1, 3, and 12 months.

**Prespecified Subgroup Analyses**
Fitting a logistic regression model, participants recruited within 1 year of stroke were more likely to experience a “successful outcome” than participants recruited >1 year after stroke but the difference was not statistically significant (OR, 1.6; 95% CI, 0.92 to 2.79; P=0.09). Fitting an interaction between randomized treatment and time since stroke did not improve the fit of the model (P=0.69). Participants with some retained active upper limb function (ARAT 4 to 56) were more likely to experience a “successful outcome” than participants with no retained upper limb function (ARAT 0 to 3); (OR, 2.41; 95% CI, 1.40 to 4.14) but on fitting an interaction between randomized treatment and baseline ARAT score, the model was not significant (P=0.81).

**Botulinum Toxin**
An initial set of injections was received by 164 of 170 (96.5%) of the intervention group participants. At 3, 6, and 9 months, further injections were received by 71 of 105 (67.6%), 64 of 105 (61.0%), and 54 of 105 (51.4%) intervention group participants, respectively. Muscles treated and botulinum toxin type A doses used are shown in Table 4. The median (interquartile range) total botulinum toxin type A doses used are shown in Table 4. The median (interquartile range) total botulinum toxin type A doses used are shown in Table 4.

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**Table 1. Continued**

<table>
<thead>
<tr>
<th>ARAT groups: n (%)</th>
<th>Control (n=162)†</th>
<th>Intervention (n=170)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3</td>
<td>91 (56.2)</td>
<td>93 (54.7)</td>
</tr>
<tr>
<td>4–56</td>
<td>71 (43.8)</td>
<td>77 (45.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nine-hole peg test (pegs placed in 50 seconds; scale range, 0–9)</th>
<th>Median [IQR]</th>
<th>Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial</td>
<td>0 [0–0]</td>
<td>0 [0–0]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basic upper limb functional activities (scale range, 1 (unable) to 5 (no difficulty))</th>
<th>Median [IQR]</th>
<th>Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Put arm through sleeve</td>
<td>3 [2–4] (n=142)</td>
<td>3 [2–4] (n=159)</td>
</tr>
<tr>
<td>Open the hand for cleaning your palm</td>
<td>3 [2–4] (n=142)</td>
<td>3 [2–4] (n=159)</td>
</tr>
<tr>
<td>Open the hand for cutting finger nails</td>
<td>2 [1–4] (n=141)</td>
<td>2 [1–3.3] (n=158)</td>
</tr>
<tr>
<td>Use cutlery</td>
<td>1 [1–1] (n=140)</td>
<td>1 [1–1] (n=155)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Barthel ADL Index (scale range, 0–20)</th>
<th>Median [IQR]</th>
<th>Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain description (excruciating, severe, moderate, mild, none)*</td>
<td>3 (moderate)</td>
<td>3 (moderate)</td>
</tr>
<tr>
<td>Pain score (0–10)†</td>
<td>5 [1–7]</td>
<td>5 [0–7]</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; TIA, transient ischemic attack; ARAT, Action Research Arm Test; ADL, activities of daily living.

*A high score on this scale is less pain.
†A high score on this scale is more pain.
‡n values valid except where alternative n is provided.
3-month assessment, and 8 started treatment between 3 and 12 months.

**Upper Limb Therapy**
Initial therapy was received by 327 of 333 (98.2%) participants. A median of 8 treatment sessions was received by participants in both groups in the 4 weeks postrandomization. Further therapy assessments were completed by 193 of 208 (92.8%) at 3 and 6 months and 189 of 208 (90.9%) at 9 months. Unfortunately, data regarding the amount and content of therapy received at 3, 6, and 9 months were limited and not suitable for analysis. There were no significant differences between the groups for the use of physical aids or antispasticity medication.

**Trial Safety Evaluation**
An on-treatment safety analysis was performed. Fifty-two serious adverse events were reported from the “received botulinum toxin” group and 50 from the “no botulinum toxin” group. There were no significant differences between the groups for event type (cardiac, respiratory, etc). Only 1 serious adverse event (dysphagia of unknown cause) was believed potentially related to botulinum toxin type A.

One hundred forty-seven adverse events were reported from the “received botulinum toxin” group. There was a higher incidence of general malaise/flu-like/cold symptoms in the “received botulinum toxin” group (relative risk, 7.6; 95% CI, 1.8 to 32.3).

**Discussion**
In this trial, the addition of botulinum toxin type A to an upper limb therapy program to treat spasticity due to stroke did not enhance improvement in active upper limb function. Although spasticity is believed to contribute to reduced active function, the precise relationship between spasticity and
motor performance is debated.\textsuperscript{12,13} Although there are those that advocate spasticity as an important component of reduced upper limb function, others believe the main problem is motor weakness. Because this study did not demonstrate improved active function, it supports the argument that spasticity is of less importance. Only 1 small previous randomized controlled trial has demonstrated improvement in active upper limb function after treatment with botulinum toxin.\textsuperscript{14} This study demonstrated that botulinum toxin type A reduced muscle tone at the elbow and the level of reduction was similar to previous studies.\textsuperscript{8} Treatment with botulinum toxin type A was also associated with increased upper limb strength (Motricity Index) at 3 months but this was not sustained at 12 months. This is the first randomized controlled trial to report improvement in upper limb strength.

Botulinum toxin type A treatment resulted in enhanced performance of specific basic upper limb functional activities and improvement was sustained until 12 months for some activities. Previous trials have also reported improvement in these activities after treatment with botulinum toxin.\textsuperscript{5–7} Although it may seem inconsistent that such activities showed improvement when arm function measured by the ARAT did not improve, the basic upper limb functional activity questions ask about the ability to undertake a specific task and do not distinguish whether the activities are performed by the affected arm, with assistance from the nonaffected arm or by

### Table 3. Improvement in Basic Upper Limb Functional Activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Control</th>
<th>Intervention</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing sleeve improvement by ( \geq 1 )</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>38 (30.4) (n = 125)</td>
<td>65 (45.1) (n = 144)</td>
<td>0.017</td>
</tr>
<tr>
<td>3 months</td>
<td>39 (32.0) (n = 122)</td>
<td>62 (43.7) (n = 142)</td>
<td>0.057</td>
</tr>
<tr>
<td>12 months</td>
<td>32 (40.5) (n = 79)</td>
<td>30 (34.9) (n = 86)</td>
<td>0.521</td>
</tr>
<tr>
<td>Opening hand for cleaning palm improvement of ( \geq 1 )</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>41 (33.1) (n = 124)</td>
<td>65 (45.5) (n = 143)</td>
<td>0.045</td>
</tr>
<tr>
<td>3 months</td>
<td>34 (27.9) (n = 122)</td>
<td>64 (45.1) (n = 142)</td>
<td>0.005</td>
</tr>
<tr>
<td>12 months</td>
<td>25 (31.6) (n = 79)</td>
<td>41 (47.7) (n = 86)</td>
<td>0.040</td>
</tr>
<tr>
<td>Ability to use cutlery improvement of ( \geq 1 )</td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>22 (17.9) (n = 123)</td>
<td>31 (22.0) (n = 141)</td>
<td>0.444</td>
</tr>
<tr>
<td>3 months</td>
<td>25 (20.8) (n = 120)</td>
<td>31 (22.1) (n = 140)</td>
<td>0.880</td>
</tr>
<tr>
<td>12 months</td>
<td>10 (13.0) (n = 77)</td>
<td>17 (20.5) (n = 83)</td>
<td>0.291</td>
</tr>
</tbody>
</table>

*Fisher exact test.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Participants Injected No. (%)</th>
<th>Dose, U Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor digitorum superficialis (FDS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>90 (54.9) (n = 164)</td>
<td>100 [50–100]</td>
</tr>
<tr>
<td>3 months</td>
<td>50 (70.4) (n = 71)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>6 months</td>
<td>46 (71.9) (n = 64)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>9 months</td>
<td>39 (72.2) (n = 54)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>Flexor digitorum profundus (FDP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>63 (38.4) (n = 164)</td>
<td>100 [50–100]</td>
</tr>
<tr>
<td>3 months</td>
<td>37 (52.1) (n = 71)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>6 months</td>
<td>39 (60.9) (n = 64)</td>
<td>100 [100–120]</td>
</tr>
<tr>
<td>9 months</td>
<td>35 (64.8) (n = 54)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>Flexor pollicis longus (FPL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>6 (3.7) (n = 164)</td>
<td>100 [72.5–112.5]</td>
</tr>
<tr>
<td>3 months</td>
<td>5 (7.0) (n = 71)</td>
<td>80 [50–100]</td>
</tr>
<tr>
<td>6 months</td>
<td>7 (10.9) (n = 64)</td>
<td>50 [50–100]</td>
</tr>
<tr>
<td>9 months</td>
<td>7 (13.0) (n = 54)</td>
<td>50 [50–80]</td>
</tr>
<tr>
<td>Forearm flexors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>17 (10.4) (n = 164)</td>
<td>200 [200–300]</td>
</tr>
<tr>
<td>3 months</td>
<td>7 (9.9) (n = 71)</td>
<td>300 [300–300]</td>
</tr>
<tr>
<td>6 months</td>
<td>4 (6.3) (n = 64)</td>
<td>200 [100–300]</td>
</tr>
<tr>
<td>9 months</td>
<td>0 (0.0) (n = 54)</td>
<td>0 [0–0]</td>
</tr>
<tr>
<td>Flexor carpi ulnaris (FCU)</td>
<td></td>
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</tr>
<tr>
<td>Initial</td>
<td>57 (34.8) (n = 164)</td>
<td>100 [50–100]</td>
</tr>
<tr>
<td>3 months</td>
<td>29 (40.8) (n = 71)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>6 months</td>
<td>31 (48.4) (n = 64)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>9 months</td>
<td>29 (53.7) (n = 54)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>Flexor carpi radialis (FCR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>10 (6.1) (n = 164)</td>
<td>50 [28.8–100]</td>
</tr>
<tr>
<td>3 months</td>
<td>3 (4.2) (n = 71)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>6 months</td>
<td>1 (1.6) (n = 64)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>9 months</td>
<td>1 (1.9) (n = 54)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>125 (76.2) (n = 164)</td>
<td>100 [50–100]</td>
</tr>
<tr>
<td>3 months</td>
<td>55 (77.5) (n = 71)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>6 months</td>
<td>47 (73.4) (n = 64)</td>
<td>100 [100–150]</td>
</tr>
<tr>
<td>9 months</td>
<td>41 (75.9) (n = 54)</td>
<td>100 [100–175]</td>
</tr>
<tr>
<td>Brachioradialis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>25 (15.2) (n = 164)</td>
<td>100 [50–100]</td>
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<tr>
<td>3 months</td>
<td>13 (18.3) (n = 71)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>6 months</td>
<td>8 (12.5) (n = 64)</td>
<td>100 [100–100]</td>
</tr>
<tr>
<td>9 months</td>
<td>5 (3.3) (n = 54)</td>
<td>100 [100–150]</td>
</tr>
</tbody>
</table>

(Continued)
a caregiver. They may measure passive (activities performed with assistance\textsuperscript{14}) and/or active function, and changes in both were possible after treatment with botulinum toxin.

Botulinum toxin type A appeared to have a long-term benefit in terms of pain reduction in which decreased pain rating was seen at 12 months but not at 1 or 3 months. Because muscle tone was not decreased at 12 months, the effect on reducing pain may be through a mechanism other than spasticity reduction. Botulinum toxin may have a direct analgesic effect by blocking transmission of neurotransmitters involved in pain pathways.\textsuperscript{3} It could also be due to the avoidance of complications of spasticity such as spasm and contracture. One previous trial has shown that botulinum toxin reduces upper limb pain up to 24 weeks\textsuperscript{15} but no trial has reported a reduction in pain in the longer term.

Although it was hypothesized that time since stroke and severity of initial upper limb function may influence effectiveness of botulinum toxin type A, there were no significant differences for improvement in arm function (ARAT “success”) between our prespecified subgroups.

This is the largest and most comprehensive trial evaluating the use of botulinum toxin type A for poststroke upper limb spasticity. Recruitment of participants from stroke services avoided a potential selection bias, which may have occurred if participants were recruited from specialist rehabilitation services. Because there was uncertainty about which patients with upper limb spasticity due to stroke may benefit from botulinum toxin, the eligibility criteria were broad and inclusive and we believe participants were typical of patients with stroke who experience upper limb spasticity poststroke. Some participants may have had less severe spasticity than those included in previous studies, but this was unsurprising because we were keen to include patients with retained active function and it is unlikely to see severe spasticity in this group of patients. We did not quantify spasticity at joints other than the elbow because the Modified Ashworth Scale has only been validated at the elbow.\textsuperscript{16}

Some previous studies have been criticized for using fixed botulinum toxin injection protocols that may not target the most appropriate muscles for treatment gain.\textsuperscript{14} The dose and pattern of botulinum toxin type A injections delivered in this study were according to the spasticity pattern of participants and determined by the treating clinician. Localization of muscles was by surface anatomy, which is considered acceptable as botulinum toxin spreads locally to active muscles.\textsuperscript{2} The median initial dose of botulinum toxin type A (Dysport) was 200 U, which was lower than previous studies; however, the reduction in muscle tone at the elbow was similar to other studies. This lower dosage of botulinum toxin type A is likely to reflect the inclusion of patients with less severe levels of spasticity. The provision of a standardized therapy program in combination with injections is one of the strengths of this study because most previous studies have not described or quantified the amount of therapy received. It was unfortunate that data regarding the content of therapy at 3, 6, and 9 months was not suitable for analysis and this is a study limitation. In addition, we did not collect detailed information about therapy received outside of the study.

Botulinum toxin type A takes approximately 1 week to achieve maximal effect and wears off after 3 to 4 months. The 1-month assessment should have captured a maximal treatment effect directly due to the botulinum toxin type A. At 3 and 12 months, the effects of injections may have been wearing off and any benefit that relied on a direct treatment effect of botulinum toxin type A may have been reduced. However, it is important to look at longer-term effects and because there may be benefits that are sustained when the effect of the toxin wears off, it was not unreasonable to look at effects at these times. Failure to show sustained benefit for some outcomes may have been due to the timing of outcome measurement or because not all participants in the intervention group received repeat injections or therapy. Study therapists assessed participants to determine the need for further treatments and in retrospect clear criteria should have been developed.

Because BoTULS was a pragmatic trial, we did not use placebo injections. Participants and the study therapists who delivered the upper limb therapy program were not blinded to treatment, which is a source of potential bias.

In conclusion, the addition of botulinum toxin to an upper limb therapy program did not enhance improvement in active upper limb function but did show beneficial effects on muscle tone, upper limb strength, ease of performing specific basic functional activities, and pain. These results suggest that botulinum toxin is unlikely to be useful for improving active upper limb function in the majority of patients with spasticity after stroke but it may improve basic upper limb tasks and pain.

**Acknowledgments**

We thank the following for their contribution: the patients who participated in the trial; local investigators (Professor David Barer, Dr David Bruce, Dr Tim Cassidy, Dr Paul Davies, Dr Philip Earnshaw, Dr Akif Gani, Professor Chris Gray, Dr Ali Mehrzad, Dr Jon Scott); study therapists (Lydia Aird, Louise Baxter, Lianne Brkic, Caroline Deacon, Hilary Ford, Heather Hunter, Nina Lishman, Paul McNeillie, Dadirayi Mhiripiri, Janet Nesbitt, Frances Sapsford); coordinating center staff (Jessie Cowe, Katharine Foster, Linda Goulbourne, Anne Harrison, Joseph Hoben, Debbie Jones, Ruth Wood); outpatient staff at the International Centre for Neuromodulation, Newcastle on Tyne; the Data Monitoring and Ethics

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**Table 4. Continued**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Participants Injected No. (%)</th>
<th>Dose, U Median [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pectoralis major</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>9 (5.5) (n=164)</td>
<td>100 [50–100]</td>
</tr>
<tr>
<td>3 months</td>
<td>5 (7.0) (n=71)</td>
<td>100 [50–100]</td>
</tr>
<tr>
<td>6 months</td>
<td>1 (1.6) (n=64)</td>
<td>200 [200–200]</td>
</tr>
<tr>
<td>9 months</td>
<td>2 (3.7) (n=54)</td>
<td>150 [100–200]</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
Committee; the Trial Steering Committee; and Dr Tony Field (deceased) who was involved in designing and planning the study.

Sources of Funding
The BoTULS trial was funded by the UK National Institute for Health Research, Health Technology Assessment (HTA) Programme. It will be reported in full in a HTA monograph. The views and opinions expressed here are those of the authors and do not necessarily reflect those of the UK Department of Health. Additional treatment costs to provide the upper limb therapy program were available from a National Health Service subvention. Ipsen Ltd provided the botulinum toxin type A (Dysport) free of charge. The study was adopted by the UK Stroke Research Network.

Disclosures
Ipsen Ltd provided the botulinum toxin type A (Dysport) used by the study free of charge. They also provided sponsorship for launch meetings at study sites. The design, analysis, and reporting of the study was undertaken independently of Ipsen Ltd. M.P.B. and L.A.G. use botulinum toxin regularly in clinical practice. They have received sponsorship from Ipsen Ltd to attend and teach at conferences and meetings but have no personal financial interest in botulinum toxin or any related product.

References
Botulinum Toxin for the Upper Limb After Stroke (BoTULS) Trial: Effect on Impairment, Activity Limitation, and Pain
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Stroke. 2011;42:1371-1379; originally published online March 17, 2011; doi: 10.1161/STROKEAHA.110.582197

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/5/1371

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/02/28/STROKEAHA.110.582197.DC1

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脳卒中後の上肢痙縮に対するボツリヌス毒素治療（BoTULS試験）—機能障害、活動制限、および疼痛に対する影響

BoTulinum Toxin for the Upper Limb After Stroke (BoTULS) Trial
— Effect on Impairment, Activity Limitation, and Pain

Lisa C. Shaw, MRCP1; Christopher I.M. Price, MD2; Frederike M.J. van Wijck, PhD3; Phil Shackley, PhD4; Nick Steen, PhD4; Michael P. Barnes, MD5; Gary A. Ford, FRCP1,6; Laura A. Graham, MD5; Helen Rodgers, FRCP1,2; on behalf of the BoTULS Investigators

1 Institute for Ageing and Health, Stroke Research Group, Newcastle University, Newcastle upon Tyne, UK; 2 Northumbria Healthcare NHS Foundation Trust, Northumberland, UK; 3 School of Health Sciences, Queen Margaret University, Edinburgh, UK; 4 Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK; 5 International Centre for Neurorehabilitation, Newcastle upon Tyne, UK; and 6 Newcastle upon Tyne Hospitals NHS Foundation Trust Newcastle upon Tyne, UK

表3 基本的な上肢機能活動の改善

<table>
<thead>
<tr>
<th>検査</th>
<th>対照群</th>
<th>介入群</th>
<th>介</th>
<th>p値*</th>
</tr>
</thead>
<tbody>
<tr>
<td>本に腕を通す 1以上の改善</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>数（%）</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1カ月</td>
<td>38 (30.4) (n = 125)</td>
<td>65 (46.1) (n = 144)</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>3カ月</td>
<td>39 (32.6) (n = 122)</td>
<td>62 (43.7) (n = 142)</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>12カ月</td>
<td>32 (40.5) (n = 79)</td>
<td>30 (34.9) (n = 86)</td>
<td>0.521</td>
<td></td>
</tr>
<tr>
<td>手のひらを洗うために手を開く 1以上の改善</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>数（%）</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1カ月</td>
<td>41 (33.1) (n = 124)</td>
<td>65 (45.5) (n = 143)</td>
<td>0.045</td>
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<td>3カ月</td>
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<td>64 (45.1) (n = 142)</td>
<td>0.005</td>
<td></td>
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<tr>
<td>12カ月</td>
<td>25 (31.6) (n = 79)</td>
<td>41 (47.7) (n = 86)</td>
<td>0.040</td>
<td></td>
</tr>
</tbody>
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* Fisher の直接確率検定。