NCCHTA

21 August 2007

What is the clinical effect and cost effectiveness of treating upper limb spasticity due to stroke with botulinum toxin?

Study Protocol/Investigator's Brochure

Sponsor's code number: 2602
EudraCT number: 2004-002427-40
ISRCTN number: ISRCTN78533119
CTA Number: 01511/0266/001-0001

Version 8: 1st May 2007

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PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the final version of the protocol, dated (Version 8) 1 May 2007 and entitled "What is the clinical effect and cost effectiveness of treating upper limb spasticity due to stroke with botulinum toxin?" I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP)[1], research governance and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

Investigator Name: **Title:**

Signature: **Date:**

Affiliation:

On behalf of the Sponsor:

Name: **Dr Helen Rodgers** **Title:** **Reader in Stroke Medicine**

Signature: **Date:**

[1] ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

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GLOSSARY

Abbreviation	Definition
AE	Adverse Event
ADL	Activity of Daily Living
AMTS	Abbreviated Mental Tests Score
ARAT	Action Research Arm Test
BI	Barthel Index
COPM	Canadian Occupational Performance Measure
DMEC	Data Monitoring and Ethics Committee
DS	Dressing Sleeve
EMG	Electromyogram
EQ-5D	Euroquol-5D scale
FM	Fugl Meyer score
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
MAS	Modified Ashworth Scale
MHRA	Medicines and Healthcare Regulatory Authority
NHS	National Health Service
QALY	Quality Adjusted Life Year
QoL	Quality of Life
R&D	Research and Development
REC	Research Ethics Committee
RMA	Rivermead Motor Assessment
ROM	Range of Motion
SAE	Serious Adverse Event
SIS	Stroke Impact Scale
SPC	Summary of Product Characteristics
SUSAR	Serious Unexpected Suspected Adverse Reaction
TSC	Trial Steering Committee
UL	Upper Limb

BACKGROUND INFORMATION

Upper limb problems following stroke

Upper limb impairment affects 85% of stroke patients, 55-75% of whom still experience problems 3-6 months later.[1,2] In contrast, around 80% of stroke survivors are able to walk again.[3] Stroke patients often feel that insufficient attention was paid to upper limb recovery and that rehabilitation focused upon mobility.[4]

Upper limb spasticity

Spasticity can occur following stroke and is a motor disorder characterised by a velocity dependent increase in the tonic stretch reflex with exaggerated tendon reflexes.[5] Put more simply it is over activity of muscles as a result of damage to the brain or spinal cord. Spasticity can cause pain, deformity and spasms and in the longer term may lead to the development of contractures.[6]

Upper limb spasticity can lead to reduced function and problems with ease of hygiene. Effective management of spasticity requires a coordinated multidisciplinary team approach.

Randomised controlled trials of botulinum toxin in the treatment of upper limb spasticity following stroke

Botulinum toxin when injected causes local paralysis of muscles as a result of blocking cholinergic transmission at the neuromuscular junction and the treatment effect lasts for 3-4 months. Botulinum toxin reduces the over activity of spastic muscles and allows for muscles to be stretched (thereby preventing contracture) and facilitates physiotherapy aimed at regaining active function or improving comfort.[7] Botulinum toxin is being increasingly used and while it does reduce spasticity[8] data regarding the subsequent effects on upper limb function following stroke are limited.[9] Our initial literature search and the Intercollegiate Stroke Guidelines Group[10] identified seven published randomised controlled trials of botulinum toxin therapy for upper limb spasticity after stroke (Table 1).[11-17] A systematic review published subsequent to commencing the study identified nine trials comparing botulinum toxin type A with placebo in patients after stroke.[18]

Previous studies have reported a measurable reduction in resistance to passive movement on the modified Ashworth Scale within 6 weeks, which then reduces towards 12-16 weeks, often losing statistical significance at this time. The modified Ashworth scale is frequently used to measure muscle tone in clinical practice but its reliability has been debated[19-22] and it has been suggested that assessment of muscle tone should include alternative measures.[21, 23] No improvement in active upper limb function has been reported, and the main benefits appear to be in terms of global ratings and itemised passive disability scores (notably hand hygiene). Although transient muscle weakness at higher doses of botulinum toxin is well recognised, no unexpected adverse events were reported, although the reporting system for these was often unclear. The 2005 systematic review concluded that long term patient specific goal focused outcomes are needed to further define clinically meaningful improvements in therapeutic outcomes.[18]

No study has considered the effects of treatment beyond 16 weeks, the impact of repeat injections, the clinical application of EMG recording, or the cost-effectiveness of treatment. There have been no attempts to standardise UL therapy. The time between stroke and study

enrolment was longer than would be expected for the development of problematic spasticity according to natural history studies.

Table 1

Study	N	Inclusion	Significant outcomes (median botulinum toxin effect)	Non-significant outcomes	Comments
Bakheit[11]	83	Average 62 yrs > 3m post-stroke MAS>=2 No EMG used	MAS (-1)	ROM Pain RMA BI DS / hand hygiene / nail care	4-16 weeks follow up Dose finding study (4 groups) 4 weeks primary outcome
Bakheit[12]	59	Average 66 years > 3m post-stroke MAS>= 2 No EMG used	MAS (–1) Global improvement	ROM Pain BI DS /hand hygiene / nail care Goal attainment	4-16 weeks follow up 4 weeks primary outcome Elbow MAS not significant at 16w Baseline BI high
Bhakta[13]	40	Average 57 years 3.1 yrs post-stroke MAS >2 No EMG used	MAS (-1 elbow at 6w) 8 item disability	ROM Pain MRC power	2, 6,12 weeks follow up No UL function only Disability gain mainly through hand hygiene
Brashear[14]	122	Average 61 years 4.7 yrs post-stroke MAS > 2 No EMG used	MAS (-1) Physician global rating Caregiver global rating Goal attainment	None reported	4,6,8,12 weeks follow up Pain / DS / hand hygiene / limb position outcomes not presented separately
Hesse[15]	24	Average 52 years 7m post-stroke MAS > 2 EMG used	MAS (-1) Hand hygiene (only with electrical stimulation at 12w)	UL position Nail care DS	2,6,12 weeks follow up Four groups as trial of botulinum and electrical stimulation for 3 days
Simpson[16]	37	Average 59 years 37m post-stroke MAS > 2 EMG used	MAS (-1) Physician global rating Subject global rating only at < 10 weeks	MAS > 6 weeks Global ratings > 6weeks Pain FM Health status	2,4,6,10,16 weeks follow up Dose finding study (4 groups)
Brashear [17]	15	Average 55 years >6 months post stroke	MAS (-1.5) at wrist at 2 weeks	Global assessment Goniometry measurements	2-16 week follow up Double blind Then 12 week open label

Abbreviations – BI Barthel Index; DS dressing sleeve; FM Fugl Meyer score; MAS Modified Ashworth Scale; RMA Rivermead Motor Assessment; ROM range of movement; EMG electromyogram.

Participants in previous studies were significantly younger (average age 52-66 years) than typical stroke patients (whose average age is 75 years) and studies to date have been undertaken in specialist rehabilitation centres. Multidisciplinary care on a stroke unit is currently the gold standard for stroke rehabilitation and benefits are seen regardless of age or stroke severity.[24] We feel that evaluations of botulinum toxin should recruit participants of all ages from stroke units rather than tertiary referral centres. If botulinum toxin is effective in improving upper limb function or comfort then every district general hospital and primary care

trust will have a number of potential participants who may benefit from this treatment and services will need to be provided locally and involve collaboration between local stroke services and regional rehabilitation centres.

Botulinum toxin

There are currently two preparations of Botulinum A toxin-haemagglutinin complex – Botox (Allergan) and Dysport (Ipsen). This study will use Dysport. Dysport vials consist of 500 units *Clostridium botulinum* type A toxin-haemagglutinin complex and 125 mcg albumen solution 20 % and 2.5 mg lactose. Dysport has a licence for the treatment of upper limb spasticity in Australia, Ireland and in the UK.

Clostridium botulinum type A toxin-haemagglutinin complex blocks peripheral cholinergic transmission at the neuromuscular junction by a presynaptic action at a site proximal to the release of acetylcholine. The toxin acts within the nerve ending to antagonise those events that are triggered by Ca^{2+} which culminate in transmitter release. It does not affect postganglionic cholinergic transmission or postganglionic sympathetic transmission.

The action of toxin involves an initial binding step whereby the toxin attaches rapidly and avidly to the presynaptic nerve membrane. Secondly, there is an internalisation step in which toxin crosses the presynaptic membrane, without causing onset of paralysis. Finally the toxin inhibits the release of acetylcholine by disrupting the Ca^{2+} mediated acetylcholine release mechanism, thereby diminishing the endplate potential and causing paralysis.

Recovery of impulse transmission occurs gradually as new nerve terminals sprout and contact is made with the post synaptic motor endplate, a process which takes 6 - 8 weeks in the experimental animal. Pharmacokinetic studies with botulinum toxin pose problems in animals because of the high potency, the minute doses involved, the large molecular weight of the compound and the difficulty of labelling toxin to produce sufficiently high specific activity.

Studies using I^{125} labelled toxin have shown that the receptor binding is specific and saturable, and the high density of toxin receptors is a contributory factor to the high potency. Dose and time responses in monkeys have shown that at low doses there was a delay of 2 - 3 days with peak effect seen 5 - 6 days after injection. The duration of action, measured by changes of ocular alignment and muscle paralysis, varied between 2 weeks and 8 months. This pattern is also seen in man, and is attributed to the process of binding, internalisation and changes at the neuromuscular junction.

Potential risks to human subjects

Side effects of botulinum toxin are rare.[25] Side effects 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 post injection, dry mouth and pain at the injection site 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. There is no specific antidote; antitoxin should not be expected to be beneficial and general supportive care is advised.

Potential benefits to human subjects

Upper limb spasticity after stroke can cause spasm, pain, and reduce functional ability. If botulinum type A is effective in reducing spasticity there is the potential to reduce upper limb pain, comfort and for some function to be regained.

STUDY OBJECTIVES

Primary objective

1. To compare the upper limb (UL) function of participants with spasticity due to stroke who receive botulinum toxin injection(s) to the upper arm and/or forearm flexors/ hand/ shoulder girdle plus a four week evidence based UL therapy programme (intervention group) with subjects who receive the UL therapy programme alone (control group) one month after study entry. UL function will be assessed using the Action Research Arm Test (ARAT). [26]

Secondary objectives

1. To compare the upper limb (UL) function and impairment of participants with spasticity due to stroke who receive botulinum toxin injection(s) to the upper arm and / or forearm flexors/ hand/ shoulder girdle plus a four week evidence based UL therapy programme (intervention group) with subjects who receive the UL therapy programme (control group) 3 and 12 months* after study entry. UL function and impairment will be assessed by: Motricity Index[27], grip strength[28], nine hole peg test[29], modified Ashworth scale[30], and biomechanical measures of spasticity[23,31].
2. To compare attainment of participant-selected UL goals, disability and stroke related quality of life between intervention and control groups at 1,3 and 12 months*. The following measures will be used: disability - Barthel ADL index[32], quality of life - Stroke Impact Scale[33], Euroquol-5D.[34]
3. To seek the experience and views of participants about UL botulinum toxin treatment and the UL therapy programme at 1 and 12 months*.
4. To compare the health and social services resources used by control and intervention groups during the 12 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 UL impairment, time since stroke, and baseline muscle activity (identified by surface electromyographic (EMG) activity) upon the efficacy of the intervention.

Primary outcome measure

- UL function (Action Research Arm Test (ARAT) 1 month after study entry.
  The Action Research Arm Test (ARAT) consists of 19 functional movement tasks which are divided into four domains (grasp, grip, pinch, and gross movement).[25] Each task is awarded a score from 0 – 3 depending upon the degree and speed of completeness. It is a popular scale in stroke rehabilitation studies, and so allows comparison with other interventions.

**Participants recruited after 1st June 2007 will be followed for 3 months only*

Secondary outcome measures

- Motor impairment will be measured by the Motricity Index[27] and grip strength measured by dynamometer.[28] The Motricity Index is a clinical assessment of muscle strength in the arm and leg. For the arm pinch grip, elbow flexion and shoulder abduction are assessed. The strength of ankle dorsiflexion, knee extension and hip flexion are measured for the leg. To measure grip strength subjects will be asked to squeeze a hand held dynamometer.

- UL function will be measured by the ARAT at other assessment points and Nine Hole Peg Test.[29] The Nine Hole Peg Test measures the time taken to insert nine pegs of a standard size into holes in a standard board.

- Clinical and biomechanical measurement of spasticity will be carried out with the modified Ashworth Scale, which is a clinical assessment of muscle tone using a scale of 0-4.[19,30] Given the controversy about the reliability and validity of the modified Ashworth Scale[19-21] we propose to use a biomechanical as well as a clinical measure of spasticity. The biomechanical device was developed by the applicants and allows objective quantification of the resistance to passive motion.[23, 31] The device is attached with straps to the participant's forearm and a therapist flexes and extends the arm. Spasticity is measured by a force transducer and electrogoniometer. This device also contains a surface EMG which will allow us to identify evidence of reflex activity at the biceps brachii during rapid stretch. The value of the modified Ashworth scale, biomechanical measure and EMG in identifying those who benefit from treatment will be addressed.

- UL pain will be measured using a self reported numerical rating scale.[35]

- Participants will select goals with their therapist and attainment of these goals will be measured numerically[13,14].

- Disability will be measured using the Barthel ADL Index.[32] These are self reported scales about functional abilities. The Barthel ADL Index covers the following domains: bathing, stairs, dressing, mobility, transfer, feeding, toilet use, grooming, continence.

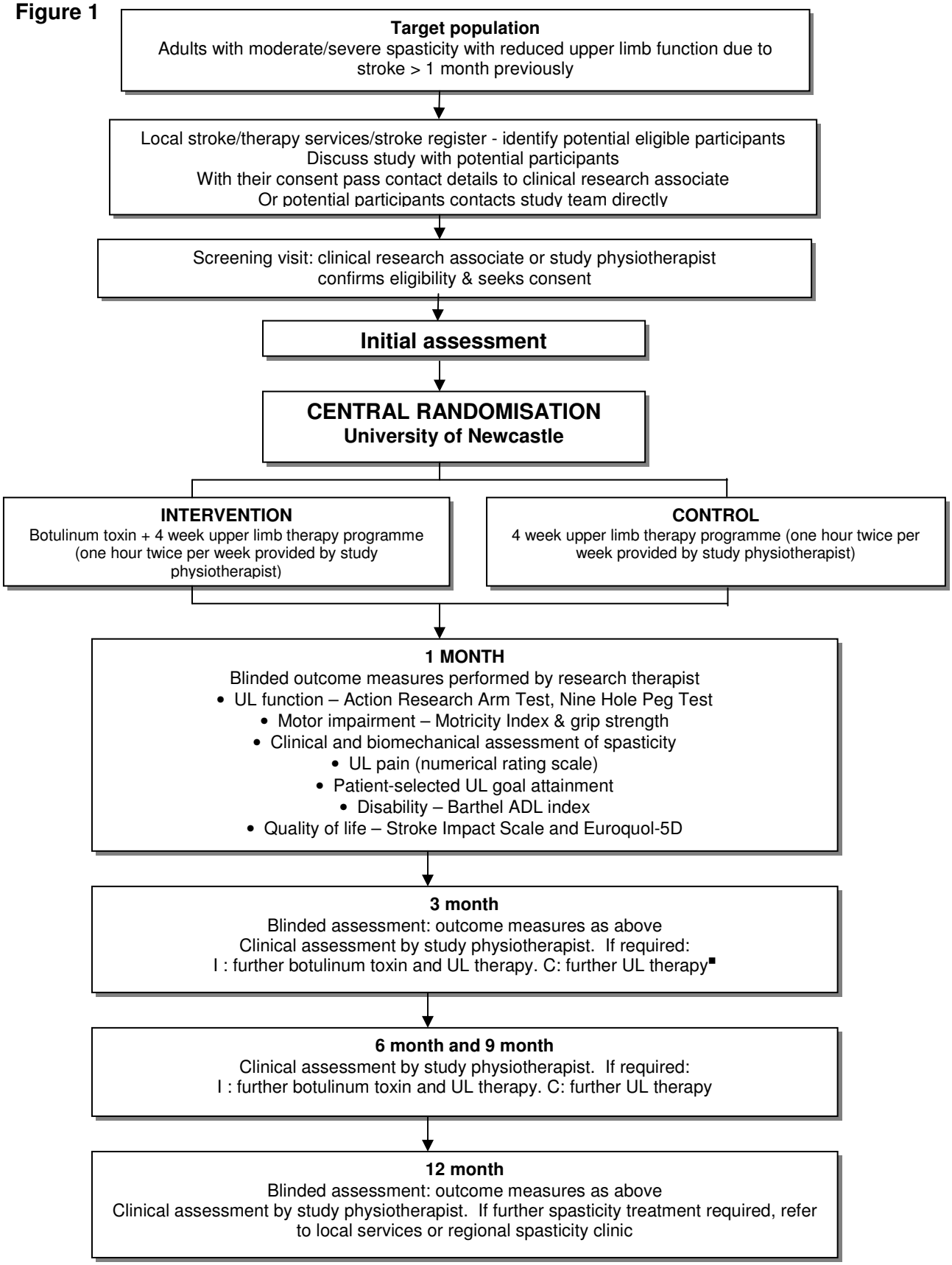
- Quality of life will be measured using the Stroke Impact Scale and Eurolquol-5D which are self completed instruments. [33,34] The Stroke Impact Scale looks at physical problems, memory, mood, activities, mobility and participation in activities.[33] Euroquol-5D consists of five statements about mobility, self care, usual activities, pain/discomfort, anxiety depression, and a visual analogue scale about current health status.[34]

STUDY DESIGN

This is a multi-centre open-label parallel group randomised controlled trial comparing the effectiveness and cost effectiveness of botulinum toxin plus an upper limb therapy programme with the upper limb therapy programme alone in the treatment of upper limb spasticity due to stroke in adults. Outcome assessments will be undertaken by a researcher who is blinded to the randomised group.

Figure 1 outlines the study method.

Figure 1



■*Participants recruited after 1st June 2007 will be followed for 3 months only. If further spasticity treatment required refer to local services or regional spasticity clinic (at 3 months)*

Setting

The study involves a collaborative network of stroke services in the north of England, with expertise in the management of spasticity and use of botulinum toxin being provided by the International Centre for Neuro-Rehabilitation, Walkergate Park, Newcastle. Ten stroke units, the International Neuro-Rehabilitation Centre and outpatient and community-based rehabilitation services which care for stroke patients in the north of England (Newcastle, Gateshead, North Tyneside, Sunderland, South Tyneside, Wansbeck, Hexham, Durham, Bishop Auckland and Carlisle) will participate. Participating stroke units provide organised stroke care to a population of over 1.5 million and admit over 3,000 stroke patients per year. Each stroke service has a stroke register and a structured review process for patients following discharge. The International Centre for Neuro-Rehabilitation, as well as providing specialist care for young stroke patients, runs a regional out-patient and community spasticity service. This service was established in 1990 and has extensive experience in the use of botulinum toxin for a number of clinical conditions. The clinic is the largest in the UK and is rapidly expanding, currently seeing 124 new patients per year with 1356 follow up appointments. We believe that the model which we have developed i.e. stroke units with close links to a specialist spasticity service enables all stroke patients to access specialist care (both in terms of stroke and spasticity management) and this model could be replicated in other NHS settings.

Health technology being assessed

The intervention group will receive botulinum toxin intra-muscular injection(s) to the upper arm/ forearm flexors/ hand/ shoulder girdle according to the pattern of spasticity plus a four week evidence based UL therapy programme. The control group will receive a four week evidence based UL therapy programme.

The study will be conducted in compliance with the protocol, ICH-GCP and the applicable regulatory requirements.

Appendix 1 provides an overview of project timeline and milestones.

Botulinum toxin use

The intervention group will receive botulinum toxin type-A (Dysport®). Appendix 2 provides a summary of product characteristics (SPC). Study medication will be supplied by Ipsen for use during the study. Dysport is presented as a white lyophilised powder for reconstitution containing 500 units of *Clostridium botulinum* type A toxin-haemagluttinin complex together with 125 mcg albumen solution 20 % and 2.5 mg lactose in a clear glass vial.

Although it is generally accepted that it is not desirable for individuals to be injected according to standard sites and in standard dosage[6], a recent document recommends a range of muscles and dosages that should be injected in the context of spasticity of the upper limb.[7] These guidelines will be adhered to. Appendix 3 gives details of dosage and injection sites.

The majority of injections will be confined to the forearm flexor compartment (for finger and wrist flexion spasticity) and the biceps and brachioradialis (for elbow flexion spasticity) but occasionally the shoulder musculature will be injected for shoulder spasticity. All injectors will be clinicians properly qualified and trained in the assessment and injection of botulinum toxin in the context of upper limb spasticity. The dosage and injection sites will be properly

recorded by the injecting clinician. The maximum dose of Dysport that will be administered at any one time point will be 1000 units.

The use of aminoglycosides will be prohibited during the study as they enhance the effects of botulinum toxin thereby increasing the risk of toxicity. Muscle relaxants should be used with caution as the effects of botulinum toxin are enhanced by non depolarising muscle relaxants. The INR of participants taking warfarin will be checked prior to injection. The notes of each participant will be clearly marked to indicate that they have had botulinum toxin and that aminoglycosides should not be used and non depolarising muscle relaxants should be used with caution. This information will also be included in the information sheet for general practitioners. Study outcomes will be assessed at one, three and twelve months✳. Changes in concomitant medications taken during the study will be documented. Side effects and adverse events will be recorded. In addition, participants will be reviewed at six and nine months by the study therapist✳.

If the clinician decides that further treatment is necessary at three, six or nine months✳ a further injection plus upper limb rehabilitation will be provided to those in the intervention group and a further period of therapy to those in the control group. Our current experience suggests that 60% may need a repeat injection at three months, with 40 % needing three monthly injections thereafter. At the 12-month◆ review individuals in both the intervention and control groups who require botulinum toxin will be referred to the spasticity clinic. At each visit a letter will be sent to the participant's stroke physician, general practitioner and physiotherapist.

If during the course of the study the study clinician decides that a participant in the control group has an unacceptable degree of symptomatic spasticity he/she will discuss the participant with their stroke physician, physiotherapist, and/or a member of the local or regional spasticity team and the participant may then be referred to the spasticity service for botulinum toxin. We anticipate that this will happen infrequently and analysis will be on an intention to treat basis.

Study treatment labelling

The core label texts for all packaging units will comply with the requirements of Annexe 13 of the Rules Governing Medicinal Products in the European Union, and the national laws in force in the UK.

Reconstitution of study treatment

Reconstitution will be with normal (0.9 %) saline. Instructions for the reconstitution of botulinum toxin type-A (Dysport) are as follows:

- Using a 5 ml syringe, fitted with a 25 gauge needle, draw up 2.0 ml of 0.9 % preservative free, sterile saline.
- Inject all 2.0 ml into the study medication vial.
- Remove the needle and syringe and gently invert the vial. DO NOT SHAKE.
- Using a 5 ml syringe, fitted with a 25 gauge needle, draw up 3 ml of 0.9 % preservative free, sterile saline.

✳*Participants recruited after 1st June 2007 will be followed for 3 months only*
◆*This will occur at the 3 month review for those participants recruited after 1st June 2007*

- Into the 5 ml syringe (with saline) draw up 2.0 ml of reconstituted study treatment making 5 ml of reconstituted study treatment (100 units in 1 ml). Invert syringe gently to mix prior to administration.

Study treatment storage and accountability

Unopened vials will be maintained at temperatures between 2 and 8 degrees centigrade. Dysport will be stored in a refrigerator at Walkergate Park Hospital or Cumberland Infirmary and taken by the administering clinician to clinics in each participating hospital in a cool bag. The shelf life of the packaged product is 12 months. Immediately after treatment of the participant, any residual Dysport which may be present in either vial or syringe will be inactivated with dilute hypochlorite solution (1% available chlorine). Thereafter, all items will be disposed of in accordance with standard hospital practice. Spillages of Dysport will be wiped up with an absorbent cloth soaked in dilute hypochlorite.

The investigator, or an approved representative (e.g. pharmacist), will ensure that all study drug is stored in a secured area, under temperature monitored storage conditions, in accordance with applicable regulatory requirements, and will be dispensed by qualified members of staff. Records will be maintained of the accountability of the study treatment.

The UL rehabilitation programme

Guidelines highlight that it is important that botulinum toxin is not used in isolation but is part of a comprehensive UL therapy programme.[6, 7, 10] Focal reductions in UL 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 UL therapy programme has been developed based upon current research evidence and consists of two menus.[10, 36-50] Participants with ARAT 0-3 will receive menu 1 which is designed specifically for participants with no active hand function and focuses on stretching and passive UL movement along with hand hygiene and positioning.[44-49] Menu 2 is for participants with some retained active UL movement (ARAT 4-56) and has been piloted in a previous study.[51] This menu specifically addresses stretching of soft tissues affected by spasticity followed by intensive task-orientated practice aimed at patient-centred goals. Goals will be measured by the Canadian Occupational Performance Measure (COPM).[52] Manuals and training programmes have been developed for both UL therapy menus. The UL therapy programme will be provided by study physiotherapists and each participant will receive one hour per day, two times per week for four weeks, in addition to their other rehabilitation needs. The study physiotherapist may transfer participants between menu 1 and menu 2 according to their clinical opinion.

Participants will be given a written exercise programme to carry out by themselves or with a carer (following training), on the weekdays they are not attending therapy. The participants will be requested to complete a log to monitor compliance with the programme. If the participant is currently receiving rehabilitation, then the UL therapy programme will be delivered in that setting e.g. stroke unit, out-patients, day hospital or home. In each case, the study therapist will liaise closely with the rehabilitation team to ensure the participant's needs are addressed and well co-ordinated. An UL therapy log will be used to document (i) each category of UL intervention being carried out (in coded form) and (ii) the amount of time spent on each activity. At the end of the four week intervention period patients will be given advice by the study physiotherapist regarding maintaining UL function.

**Participants recruited after 1st June 2007 will be followed for 3 months only*
◆This will occur at the 3 month review for those participants recruited after 1st June 2007

Participants will be reviewed by the clinical team every three months*. If further therapy is required, this will be provided by a study physiotherapist. Those in the intervention group may also receive a further botulinum injection. Participants in both the intervention and control group who have symptomatic spasticity at the 12 month◆ follow up appointment will be referred to the Spasticity Clinic at the regional or local Rehabilitation Centre.

Some participants will make a good recovery prior to completing the four week UL therapy programme. These participants will be discharged from the programme provided that they can achieve maximum score on the ARAT and have achieved their UL goals.

We will record the use of antispasticity medication, upper limb analgesia, splints, additional physiotherapy throughout the study period. Data will be sought from participants, therapists and medical and therapy records.

Case ascertainment

There are three methods to identify potential participants; 1. by members of clinical services, 2. from hospital based stroke registers, and 3. by contact with local stroke clubs.

1. By seeking participants within stroke services we will be including a more representative stroke population than previously published trials. Potential participants will be identified from a number of sources in each study centre (stroke unit, out-patients, day hospital, community rehabilitation teams). He/she will be given an information leaflet and have an opportunity to discuss the study with a member of the clinical team (training will be given to clinical teams about the project and research governance). The research team will then be notified of potential participants by telephone or confidential fax and potential participants will be contacted by a member of the research team who will arrange to see him/her to discuss the study and seek consent at a screening visit.

2. Subject to Caldicott approvals we will use stroke registers in participating centres to identify potential participants who have been discharged from follow-up. This group will receive a letter informing them about the study signed by their stroke consultant inviting them to contact the study team if they would be interested in taking part in the study.

3. There may be some potential participants who are not currently in contact with rehabilitation or stroke services. We will contact local community stroke clubs and day centres by letter and offer to present information on the study to their members. We will also provide posters and flyers about the study.

A log will be kept with details of who has been invited to participate in the study to ensure that potential participants are only approached once.

Inclusion criteria

Adults with a stroke greater than 1 month previously who have moderate/severe spasticity and reduced UL function who fulfil the all of following criteria will be eligible:

- Age over 18 years.
- At least 1 month since stroke.
- Upper limb spasticity (modified Ashworth scale > 2 at the elbow [30] and/or spasticity at wrist or shoulder (there is no validated measure of spasticity at these sites).
- Reduced UL function (ARAT score 0-56)[26].
- Able to comply with the requirements of the protocol and UL therapy programme.
- The participant or legal representative must give informed consent before completing any study-related procedure, which means any assessment or evaluation that would not have formed part of their normal care.

Exclusion criteria

- Significant speech or cognitive impairment which will impede ability to perform the ARAT assessment.
- Other significant upper limb impairment e.g. fracture or frozen shoulder within six months, severe arthritis, amputation.
- Evidence of fixed contracture.
- The participant is pregnant or lactating (female participants who are at risk of pregnancy (i.e. who are not surgically sterile or at least 1 year post menstrual period) must have a negative pregnancy test on the day of randomisation and prior to any subsequent botulinum injection if in the intervention group).
- The participant is a female at risk of pregnancy who is not willing to take adequate precautions against pregnancy for the duration of the study.
- 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 contains human albumen).
- Contraindications to botulinum toxin which include bleeding disorders, myasthenia gravis and concurrent use of aminoglycosides.
- Use of botulinum toxin to the upper limb in the previous three months.
- Known allergy or hypersensitivity to any of the test compounds.
- Previous enrolment in this study.

Informed consent

The potential participant must give informed consent before completing any study-related procedure, which means any assessment or evaluation that would not have formed part of their normal care. For those participants unable to sign the consent form personally or who are incapable adults, a legal representative would be sought to perform this duty. The study will follow the conditions and principles as listed in part 5 of Schedule 1 to the Clinical Trials Regulations and implement Article 5 of the EU Directive. The legal representative can be defined as follows: a personal legal representative is a person not connected with the conduct of the study who is; a) suitable to act as the legal representative by virtue of their relationship with the adult and b) willing and able to do so. A professional legal representative is a person not connected with the conduct of the study who is; a) the doctor primarily responsible for the adult's medical treatment, or b) a person nominated by the relevant health care provider. A professional legal representative may be approached if no suitable personal legal representative is available.

At the screening visit the clinical research associate or research physiotherapist will further explain the benefits and risks of participation in the study to each participant and obtain written informed consent or proxy consent for participants. Each participant's original consent form will be retained by the Principal Investigator. A copy of the signed consent form will be placed in the medical notes and a copy sent to the Chief Investigator. The clinical research associate or research physiotherapist will supply all enrolled participants with a copy of the signed informed consent and the patient information. The clinical research associate will with the consent of the participant, inform the participant's GP, stroke consultant and physiotherapist (if appropriate) about their participation in the clinical trial and send him/her a copy of the patient information sheet.

The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the participant. In this instance main REC approval will be sought and existing participants informed of the changes.

Screening visit

Having sought consent we will complete the screening assessment. The assessment will consist of demographic details, review of medical history and medication; handedness; Abbreviated Mental Test Score[53] , Sheffield Aphasia Screening Test.[54] ,pre-stroke function (Oxford Handicap Scale)[55]; time since stroke; stroke type and subtype [56]; self reported current neurological impairment and function (Barthel ADL Index)[32]; quality of life (EQ-5D[34]). Details of current and anti-spasticity treatment received within the previous 3 months and concomitant medications will be recorded.

Baseline assessment

The baseline visit will be within 2 weeks after the screening visit. The inclusion / exclusion criteria will be reviewed to ensure that the participant is still eligible for the trial. The baseline assessment will be noted on a standard proforma. Participants undergo a clinical assessment and will be asked to complete a battery of assessments including: Action Research Arm Test [26]; Stroke Impact Scale[33] ;Motricity Index [27]; grip strength[28]; Nine Hole Peg Test[29]; modified Ashworth Scale [30] ; upper limb pain [35]; biomechanical measurement of spasticity.[22, 29] Patient selected upper limb goals will also be identified.[13,14]

Details of the participant's medical history will be checked as will prior and concomitant medications / therapies. Female participants of child-bearing potential (i.e. those who are not either surgically sterile or at least 1 year post-last menstrual period) will have a urine pregnancy test, the result of which must be negative for the participant to be included in the study. Such participants must agree to use adequate contraception throughout the study if they are randomised to receive botulinum toxin.

Randomisation

Randomisation will be by a central independent randomisation service from the Clinical Trials Unit, Centre for Health Services Research, University of Newcastle upon Tyne. The researcher will contact the project secretary who will then use a web based randomisation service. Subjects will be stratified according to level of UL function (ARAT).

Prior to the study a master randomisation list will be produced using a computer random number generator. Participants will be randomised to the two study treatments, botulinum

toxin plus upper limb therapy programme or upper limb therapy programme alone in a 1:1 ratio. This list will be prepared by an individual who is completely independent of the study.

Outcome assessments

Outcomes will be measured by an assessor who is blinded to the randomisation group one month (+/-3 days), three months (+/-5days) and twelve months* (+/- 5 days) after the baseline visit. Before contacting the participant a member of the research team will check with their general practice or stroke unit that they are still alive and at their current address. We will review the medical records of participants who have died to seek details of the cause and circumstances of death, resource utilisation data, and any potential side effects from botulinum toxin. We do not anticipate significant loss to follow up as in our previous studies of stroke rehabilitation 90% of survivors completed at the six month assessment. A member of the research team will organise outcome assessment appointments with participants. Each outcome assessment will consist of two stages – stage 1 outcome assessment will be a self completion postal questionnaire (Barthel ADL Index [32], quality of life (Stroke Impact Scale [33], EQ-5D [34]), upper limb pain[35], goal attainment[52], resource utilisation[58-62] which will be sent to participants one week prior to stage 2. This will take 40 minutes to complete and participants will be asked to bring the completed proforma to their Stage 2 appointment.

Stage 2 outcome assessments will consist of assessment of upper limb impairment and function (ARAT [26], Motricity Index [27], grip strength [28], Nine Hole Peg Test [29], and assessment of spasticity [23, 30, 31]) and face to face interview seeking participants experience and views of the treatment received as part of the study. We will also seek information about side effects, use of other antispasticity treatment and analgesia for post stroke upper limb pain. Any changes in the participant's concomitant medications since the previous visit will be noted. Any new adverse events or changes in existing adverse events that have occurred since the previous visit will be sought. Stage 2 assessments will take 30-45 minutes and we will also check the stage 1 questionnaire for completeness. Stage 2 assessments will take place in hospital if the participant is well enough to travel and happy to do so. Transport will be provided if required. Participants who do not wish to or who are unable to travel to hospital will be assessed in their own home.

At 12 months◆ we will review all participant's primary and secondary care medical and rehabilitation records for details of upper limb spasticity treatment and resource utilisation.

**Participants recruited after 1st June 2007 will be followed for 3 months only*

◆This will occur at the 3 month review for those participants recruited after 1st June 2007

Study Schedule

Time point	**Screening** < 2 weeks	**Baseline** Day 0	**Visit 3** Month 1[1]	**Visit 4** Month 3[2]	**Visit 5**✳ Month 6	**Visit 6**✳ Month 9	**Visit 7**✳ Month 12[2]
Informed consent	X						
Record demographics & handedness	X						
Review inclusion/exclusion criteria	X	X					
Review medical history	X	X					
Details of stroke	X						
Pre stroke function (inc Oxford Handicap Scale [(55)])	X						
Abbreviated Mental Test Score (AMTS) [(53)]	X						
Sheffield Aphasia Screening Test [(54)]	X						
Action Research Arm Test (ARAT) [(26)]		X	X	X			X
Motricity Index [(27)]		X	X	X			X
Grip strength [(28)]		X	X	X			X
Nine Hole Peg Test [(29)]		X	X	X			X
Modified Ashworth Scale [(30)]		X	X	X			X
Self rating of severity		X	X	X			X
Biomechanical assessment of spasticity (incl. EMG) [(23,31)]		X	X	X			X
UL pain (numerical rating scale)[3]		X	X	X			X
Patient selects UL goals		X		X	X	X	
Review UL goal attainment[3]			X				
Barthel ADL Index	X		X[3]	X[3]			X[3]
QoL – Stroke Impact Scale[3]	X		X[3]	X[3]			X[3]
QoL – EQ-5D[3]	X		X[3]	X[3]			X[3]
Resource utilisation questions[3]	X		X	X			X
Pregnancy test[4]		X	?[6]	?[6]	X[6]	X[6]	
Randomisation		X					
Treatment with Dysport[5]		X		X[7]	X[7]	X[7]	
Commencement of 4 week UL therapy programme		X		X[7]	X[7]	X[7]	
Clinical assessment by study physiotherapist		X	X	X	X	X	X
Concomitant medications (inc anti-spasticity treatment)	X	X	X	X			X
Adverse Events		X	X	X			X
Participants views and experience			X				X

1. Visit window is +3 days.
2. Visit window is +5 days.
3. Questionnaires will be sent to the participant for completion 1 week prior to the visit. Participants will bring completed forms to the visit. Patient selected UL goals will only be undertaken if further therapy is required.
4. For female participants at risk of pregnancy.
5. Participants in the intervention group only.
6. Pregnancy test to be performed prior to any additional Dysport injections.
7. Additional Dysport injections/UL therapy to be provided if clinically appropriate.

✳*Participants recruited after 1st June 2007 will be followed for 3 months only*

Resource utilisation and economic evaluation

Health and social service resource use associated with botulinum toxin therapy will be costed according to established methods.[58-62] Measurement and valuation of resource use will be undertaken using a combination of routine administrative data and primary data collection methods devised specifically for the study. Costs to be measured and valued include the costs of the drugs, costs of the upper limb rehabilitation programme (e.g. staff time) and costs associated with any adverse side effects associated with the administration of the drugs (e.g. general practitioner or other health care contacts, contacts with social services, out of pocket payments by participants for pain relieving drugs).The costs of the drugs will be ascertained from suppliers. Staff time will be recorded and costed using gross hourly wage rates derived from the mid-point of appropriate salary scales. Costs of rehabilitation equipment e.g. UL splinting will be obtained from routine data. The frequency of participant contacts with health professionals and social services will be ascertained through the administration of a participant questionnaire at the 1, 3 and 12 month* outcome assessments. Participants will be asked about any contacts they have had with health care professionals and social services since their last assessment (including repeat injections and therapy) and to indicate any out of pocket expenditure they have incurred for medication. As the study period is 12 months, there will be no need to discount costs. Sensitivity analysis will be undertaken to investigate the impact of any uncertainties in the methods and/or data used. The economic evaluation will combine the cost data with data on outcomes from the Euroquol-5D.[34] The type and extent of economic evaluation will crucially depend upon the clinical outcome of the trial: (a) if intervention and control group outcomes are equally effective, the preferred option will be that which is less costly; (b) if intervention is both more effective and less costly than control, botulinum toxin plus upper limb therapy can be unambiguously recommended; (c) if intervention is both more effective and more costly, an incremental costs per quality adjusted life year (QALY) will be estimated to aid a decision about whether the additional effectiveness gained from botulinum toxin is worthwhile.

Participant withdrawal criteria

No specific withdrawal criteria have been defined for this study. If a participant discontinues from the study prematurely (i.e. prior to completion of the protocol), the primary reason for discontinuation will be determined and recorded. In all cases the investigator will ensure that the participant receives medical follow-up as necessary. Withdrawn participants will not be replaced.

Study completion/early termination visit

Participants will return to the clinic 12 months* after the baseline visit for the study completion visit. Study completion is the last visit of the participant. If a participant discontinues from the study prematurely, every effort will be made to perform an early termination visit, including: function (Barthel ADL Index [32]); quality of life (Stroke Impact Scale [33], EQ-5D [34]); upper limb pain[35]; goal attainment[52]; resource utilisation[58-62]; upper limb impairment and function (ARAT[26], Motricity[27], grip strength [28] , nine hole peg test[29], and assessment of spasticity[23, 30, 31]); views of the treatment received as part of the study. We will also seek information about side effects, use of other antispasticity treatment and analgesia for post stroke upper limb pain. Female participants of child-bearing potential (i.e. those who are not either surgically sterile or at least 1 year post-last menstrual period) in the intervention group will have a urine pregnancy test. At the participant's last study visit details of their completion of the study/withdrawal from the study will be recorded.

Participants recruited after 1st June 2007 will be followed for 3 months only

Safety evaluation

The safety of Dysport in the treatment of participants with upper limb spasticity post stroke will be evaluated by examining the occurrence of all adverse events, abnormal laboratory findings, the use of concomitant medications and physical examination findings. Follow-up of each adverse event should continue until the event or its sequelae resolve or stabilise at a level that is acceptable to the investigator.

Safety criteria

An "adverse event" (AE) is any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. In order to elicit details of any AEs, at each visit the participant will be asked a non-leading question: "Do you feel different in any way since the since the last assessment/visit?"

An "adverse reaction" is an untoward or unintended response to an investigational medicinal product (IMP) related to any dose administered.

For "serious adverse event" description, see note below.

Intensity classification:

Mild:	Symptoms do not alter participant's normal functioning
Moderate:	Symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the participant
Severe:	Symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

Causality classification:

Probable:	Reports including good reasons and sufficient information to assume a causal relationship in the sense that it is plausible, conceivable, or likely.
Possible:	Reports containing sufficient information to indicate the possibility of a causal relationship in the sense of it not being impossible and not unlikely, although the connection may be uncertain or doubtful (eg due to missing data, insufficient evidence etc)
Unlikely:	Reports of a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Not related:	Reports excluding the possibility of a relationship between the event and the drug treatment, i.e., no reasonable suspected causal relationship to study drug administration.
Unclassified:	Reports of a clinical event, including laboratory abnormality, reported as an adverse event, about which more data are essential for a proper assessment or the additional data are under examination.

Serious adverse events

All serious adverse events regardless of treatment group or suspected relationship to study drug will be reported immediately (within 24 hours) by telephone to the contact person at Ipsen Ltd (refer to the contact details on the cover of this protocol). Serious adverse events should also be reported immediately to the chief investigator (Dr Helen Rodgers), the representative of the sponsor (Mrs Amanda Tortice) and the Director of Research and Development of the Trust where principal investigator is based. Immediate report should be followed by detailed written reports to these four individuals.

A serious adverse event is any adverse drug experience occurring at any dose that:

1. Results in death;
2. Is life-threatening;
3. Results in in-patient hospitalisation or prolongation of existing hospitalisation;
4. Results in a persistent or significant disability/incapacity; or
5. Results in congenital anomaly/birth defect.
6. Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious adverse drug experiences when, based upon appropriate medical judgement, they may jeopardise the participant/subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include pregnancy, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

Expected adverse reactions

Side effects of Dysport 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 post injection, dry mouth and pain at the injection site 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. Appendix 2, Dysport Summary of Product Characteristics.

Regardless of the above (serious) criteria, any additional adverse experiences which an investigator considers serious will be immediately (within 24 hours of the investigator becoming aware of the event) reported. SAEs will be included in the Ipsen corporate serious adverse events database system.

The minimum information required from the investigator when reporting an SAE is as follows:

1. Protocol identification number.
2. Investigator's identification (name and centre number).
3. Subject identification number.
4. Serious Adverse Event description including criteria for seriousness and the immediate outcome.

The chief investigator and sponsor will report all SAEs to the MHRA, REC, Eudravigilance component of the EudraCT data base within the required reporting timelines. A written acknowledgement is required from the ethics committee to confirm that they have received this notification.

SUSAR

In accordance with the EU directive the principal investigator will report SUSARs (Suspected Unexpected Serious Adverse Reactions) to Ipsen, the chief investigator, his/her local Trust R&D department and the sponsor within 24 hours of becoming aware of the event. The chief investigator and sponsor will report SUSARs to the MRHA, REC, Eudravigilance component of the EudraCT data base within 7 days if the event was fatal or life threatening or 15 days if the event was not fatal or life threatening.

Ethical arrangements

We believe that a number of potential participants who would not otherwise receive treatment for UL spasticity will be recruited as spasticity is a clinical problem which is currently under diagnosed and under treated. Detailed patient information sheets and consent sheets will be developed which will be checked for clarity and readability by service users, including stroke patients who have had botulinum injections. All participants will have ample opportunity to discuss the study with members of the clinical services and research team prior to giving consent. Participants will have at least 24 hours to decide whether or not to participate to allow time to reflect and discuss the study with their families. All participants will be required to give written informed consent. The study will be conducted according to the ICH-GCP, Research Governance Framework for Health and Social Care.

Ethical committee approval will be sought and the study will be registered with the Data Protection Act. Documents will be held securely for 10 years following completion of the study. On completing the study we will prepare a report for study participants.

Pilot study

We have not undertaken a pilot study as we have extensive experience of using the dosage regime and assessment tools. We have undertaken four stroke rehabilitation randomised controlled trials using the proposed methods of randomisation, follow up and outcome assessment.[63-65] The UL therapy programme has been piloted in a small RCT at the Regional Neurorehabilitation Centre.[51]

Links with clinical services

To develop robust systems of case ascertainment, close links between the research team and clinical services in each centre are essential. We have met with teams in each location and we will produce study posters and information leaflets for clinical teams and key individuals. Prior to commencing the study further meetings will be held to discuss implementation and training issues for clinical staff to ensure that they are comfortable and confident about the research and service aspects of the study. The research team will maintain weekly contact with a link person from each component of the stroke service in each participating centre to discuss issues relating to the project. Three monthly newsletters which will include details of recruitment rates of individual centres will be produced. On completing the study, members of the clinical services will be invited to a meeting where the results will be presented and discussed.

Statistical Analysis

Primary Analysis

The primary endpoint will be the ARAT score at 1 month. The analysis will be undertaken on an "intention to treat" basis; participants will analysed in the group to which they were randomised.

For each participant we will determine whether there has been a significant improvement in function based on the change in ARAT score. A successful outcome will be defined as:

(i) a change of 3 or more points on the ARAT scale for a participant whose baseline ARAT score is between 0 and 3 inclusive
(ii) a change of 6 or more points on the ARAT scale for a participant whose baseline ARAT score is between 4 and 51
(iii) a final ARAT score of 57 for a participant whose baseline ARAT score is 52 or greater.

The proportion of "successes" in each group will then be compared using Fisher's exact test. An interval estimate of the relative odds of a successful outcome in each group will also be calculated. This interval estimate of effect size will be taken forward into the economic evaluation.

Secondary Analysis

In the primary analysis we have specified a dichotomous measure of outcome. To some extent this does not make full use of all the information in the data. In previous studies where the ARAT has been used to assess outcome the distribution of scores has been very non-normal. The standard approach to compare two groups of participants has been to use a non-parametric test such as the Mann-Whitney U test to compare final ARAT scores at follow-up. To be consistent with these previous studies we will undertake an exact form of this test.

Upper limb function will also be compared at 3 months and 12 months using both the methods specified above.

As a further pre-specified sub group analysis we will consider the effect of time since stroke as a covariate. It is hypothesised that participants who have recently had a stroke will have a better response to treatment than those who had a stroke some time ago.

Although the distribution of ARAT scores at any one time point is not normal it may be possible to investigate changes over time in the two groups using a repeated measures analysis of variance procedure but including the baseline ARAT score as a covariate. The feasibility of this approach will be investigated.

Secondary outcomes will be analysed on an intention to treat basis. Participants randomised to each arm of the trial will be treated as two independent samples and for each outcome a test appropriate to that type of variable will be undertaken.

Sample size

The power calculation uses prognosis based methodology.[66] If we define a clinically important treatment effect as being a difference in good outcomes between intervention and control groups of 15% and expect to see 20% of the control group achieve good outcomes and 35% of the intervention group achieve good outcomes then allowing for 10% attrition the sample size for 80% power is 332 participants (to detect a mean difference of 6 points on the ARAT scale in the ARAT 4-56 group and 3 points in the ARAT 0-3 group). We aim to recruit 50% of the sample from the ARAT 0-3 group and 50% from the ARAT 4-56 group.

Interim Analysis

Interim analyses will be carried out as requested by the Data Monitoring and Ethics Committee. Results will not be disclosed to anyone outside the DMEC unless the DMEC have concerns about the advisability of continuation of the study.

Independent supervision of trials

We will establish a Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) following MRC guidelines.[67] The TSC will comprise an independent chairman - Professor Peter Langhorne (Glasgow), Professor Anne Forster (Bradford), Professor Bipin Bhakta (Leeds) all of whom have expertise in rehabilitation research and Professor Bhakta has clinical and research experience in the use of botulinum toxin. Consumer representatives (Mrs Beryl Fairless and Mr Jonathan Cleland) will also be members of this committee. Dr Rodgers, Professor Ford and Professor Barnes will represent the project team and a member of the NHS R&D Programme will be invited to attend TSC meetings. The DMEC will be chaired by Professor Martin Dennis (Edinburgh) and also includes Professor Ian Ford (Glasgow), Dr Marion Walker (Nottingham) and the study statistician (Dr Nick Steen). The TSC and DMEC will meet independently prior to the start of the study. The DMEC will agree terms of reference and will monitor unblinded data and the conduct of the study. Only the DMEC will have access to unblinded data until the final outcome assessment has been completed. The DMEC will recommend discontinuation of the study if significant ethical or safety concerns arise or if there is very clear evidence of benefit (clinical or statistical) prior to completion of the study.

FUNDING

The study is funded by The Department of Health Research and Development Health Technology Assessment Programme (£686,674). Ipsen will provide the botulinum toxin. Excess treatment costs will be paid by the Department of Health.

INDEMNITY

NHS indemnity arrangements are covered by HSG(96)48: 'Arrangements for Handling Clinical Negligence Claims Against NHS Staff'. The liabilities covered are for clinical negligence, but not for any other liability, such as product liability, employer's liability or liability for NHS Trust Board members.

NHS indemnity applies where:

(a) the negligent health care professional was:

(i) working under a contract of employment and the negligence occurred in the course of that employment,

(ii) not working under a contract of employment, but was contracted to an NHS body to provide services to persons to whom that NHS body owed a duty of care,

(iii) neither of the above, but otherwise owed a duty of care to the persons injured.

(b) persons not employed under a contract of employment, and who may or may not be a health care professional, who owes a duty of care to other persons injured. These include: locums; medical academic staff with Honorary contracts; students; those conducting clinical trials; charitable volunteers; persons undergoing further professional education, training and examinations; students and staff working on income generation projects.

NHS indemnity covers significant harm caused to participants or healthy volunteers in the following circumstances: whenever they are receiving an established treatment, whether or not in accordance with an agreed guideline or protocol; whenever they are receiving a novel or unusual treatment which, in the judgement of the health care professional, is appropriate for that particular participant; whenever they are subjects as participants or healthy volunteers of clinical research.

The financial support arrangements for NHS indemnity is under the Clinical Negligence Scheme for Trusts (CNST) as per EL(95)40.

Honorary contracts with each participating Trust will be sought for study staff.

DISSEMINATION OF RESULTS

The study will be registered with the National Research Register and details of the study will be available on the HTA website. A meeting will be held to present the results to the project team and staff from participating centres. A newsletter will also be sent to study participants and their GPs informing them of the results of the study. The results will be submitted for presentation at national and international meetings and papers will be submitted for publication in peer reviewed journals. Data will also be made available to the Cochrane Collaboration.

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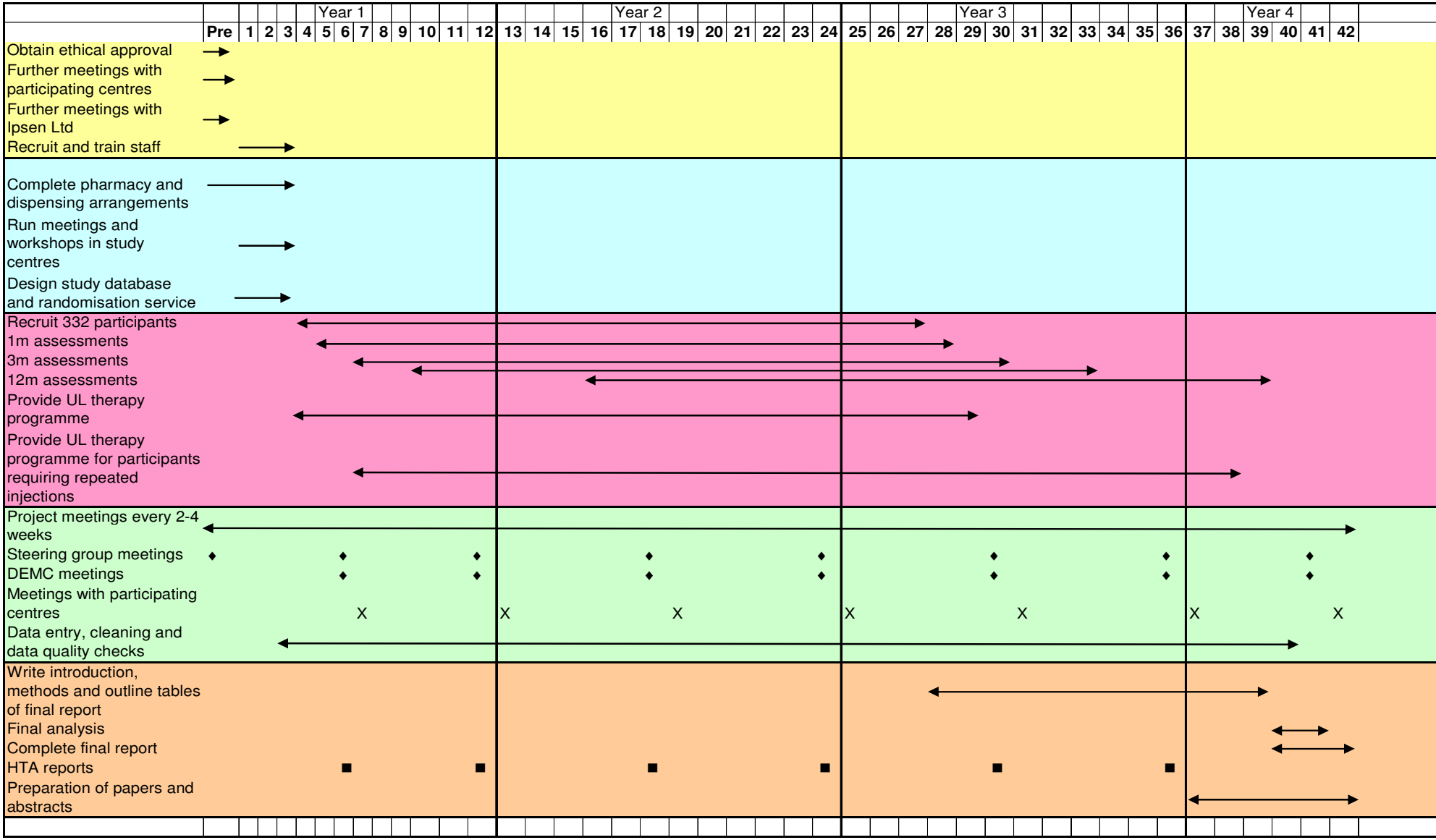
Appendix 1 Original Project Milestones
Study start date 1/02/05 with anticipated participant recruitment over a 2 year period.
Total study duration is 42 months.


Year 1
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Pre 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42
Obtain ethical approval
Further meetings with participating centres
Further meetings with Ipsen Ltd
Recruit and train staff
Complete pharmacy and dispensing arrangements
Run meetings and workshops in study centres
Design study database and randomisation service
Recruit 332 participants
1m assessments
3m assessments
12m assessments
Provide UL therapy programme
Provide UL therapy programme for participants requiring repeated injections
Project meetings every 2-4 weeks
Steering group meetings
DEMC meetings
Meetings with participating centres
Data entry, cleaning and data quality checks
Write introduction, methods and outline tables of final report
Final analysis
Complete final report
HTA reports
Preparation of papers and abstracts

Appendix 2 Summary of Product Characteristics

1.1 Ipsen Ltd

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Telephone:	**+44 (0)1753 627 777**
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Document last updated on the *e*MC: **Tue 30 November 2004**

Dysport

1. NAME OF THE MEDICINAL PRODUCT

Dysport

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

	Per Vial
Active Constituent	
Clostridium botulinum type A toxin-haemagglutinin complex	500U*
Other Constituents	
Albumin solution	125 MCG
Lactose	2.5 MG

* One unit (U) is defined as the median lethal intraperitoneal dose in mice.

3. PHARMACEUTICAL FORM

Injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dysport is indicated for focal spasticity, including the treatment of:
arm symptoms associated with focal spasticity in conjunction with physiotherapy; and
dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy

patients, two years of age or older, only in hospital specialist centres with appropriately trained personnel.
Dysport is also indicated for the following treatments:
Spasmodic torticollis in adults
Blepharospasm in adults
Hemifacial spasm in adults

4.2 Posology and method of administration

The units of Dysport are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.
Training: Dysport should only be administered by appropriately trained physicians. Ipsen can facilitate training in administration of Dysport injections .
The exposed central portion of the rubber stopper should be cleaned with alcohol immediately prior to piercing the septum. A sterile 23 or 25 gauge needle should be used.

Arm spasticity:

Posology

The recommended dose is 1000 units in total, distributed amongst the following five muscles:

Biceps brachii (BB)	**Flexor digitorum profundus (FDP)**	**Flexor digitorum superficialis (FDS)**	**Flexor carpi ulnaris (FCU)**	**Flexor carpi radialis FCR)**	**Total Dose**
300 - 400 units (0.6 - 0.8 ml)	150 units (0.3 ml)	150 - 250 units (0.3 - 0.5 ml)	150 units (0.3 ml)	150 units (0.3 ml)	1,000 units (2.0 ml)

The sites of injection should be guided by standard locations used for electromyography, although actual location of the injection site will be determined by palpation. All muscles except the biceps brachii (BB) should be injected at one site, whilst the biceps should be injected at two sites.
The dose should be lowered if there is evidence to suggest that this dose may result in excessive weakness of the target muscles, such as for patients whose target muscles are small, where the BB muscle is not to be injected or patients who are to be administered multi-level injections. Clinical improvement may be expected within two weeks after injection. Data on repeated and long term treatment are limited.
Children: The safety and effectiveness of Dysport in the treatment of arm spasticity in children have not been demonstrated.

Method of administration

The exposed central portion of the rubber stopper should be cleaned with alcohol immediately prior to piercing the septum. A sterile 23 or 25 gauge needle should be used. Dysport is reconstituted with 1.0 ml of sodium chloride injection B.P. (0.9%) to yield a solution containing 500 units per ml of Dysport. Dysport is administered by intramuscular injection into the five muscles detailed above when treating arm spasticity.
Paediatric cerebral palsy spasticity :

Posology

The initial recommended dose is 20 units/kg body weight given as a divided dose between both calf muscles. If only one calf is affected, a dose of 10 units/kg bodyweight should be

used. Consideration should be given to lowering this starting dose if there is evidence to suggest that this dose may result in excessive weakness of the target muscles, such as for patients whose target muscles are small or patients who require concomitant injections to other muscle groups. Following evaluation of response to the starting dose subsequent treatment may be titrated within the range 10 units/kg and 30 units/kg divided between both legs. The maximum dose administered must not exceed 1000 units/patient.
Administration should primarily be targeted to the gastrocnemius, although injections of the soleus and injection of the tibialis posterior should also be considered.
The use of electromyography (EMG) is not routine clinical practice but may assist in identifying the most active muscles.
Clinical improvement may be expected within two weeks after injection. Injections may be repeated approximately every 16 weeks or as required to maintain response, but not more frequently than every 12 weeks.

Method of administration

When treating paediatric cerebral palsy spasticity, Dysport is reconstituted with 1.0 ml of sodium chloride injection B.P. (0.9%) to yield a solution containing 500 units per ml of Dysport. Dysport is administered by intramuscular injection into the calf muscles when treating spasticity.

Spasmodic torticollis:

Posology

Adults and elderly: The doses recommended for torticollis are applicable to adults of all ages providing the adults are of normal weight with no evidence of low neck muscle mass. A reduced dose may be appropriate if the patient is markedly underweight or in the elderly, where reduced muscle mass may exist.
The initial recommended dose for the treatment of spasmodic torticollis is 500 units per patient given as a divided dose and administered to the two or three most active neck muscles.
For rotational torticollis distribute the 500 units by administering 350 units into the splenius capitis muscle, ipsilateral to the direction of the chin/head rotation and 150 units into the sternomastoid muscle, contralateral to the rotation.
For laterocollis, distribute the 500 units by administering 350 units into the ipsilateral splenius capitis muscle and 150 units into the ipsilateral sternomastoid muscle. In cases associated with shoulder elevation the ipsilateral trapezoid or levator scapulae muscles may also require treatment, according to visible hypertrophy of the muscle or electromyographic (EMG) findings. Where injections of three muscles are required, distribute the 500 units as follows, 300 units splenius capitis, 100 units sternomastoid and 100 units to the third muscle.
For retrocollis distribute the 500 units by administering 250 units into each of the splenius capitis muscles. This may be followed by bilateral trapezius injections (up to 250 units per muscle) after 6 weeks, if there is insufficient response. Bilateral splenii injections may increase the risk of neck muscle weakness.
All other forms of torticollis are highly dependent on specialist knowledge and EMG to identify and treat the most active muscles. EMG should be used diagnostically for all complex forms of torticollis, for reassessment after unsuccessful injections in non complex cases, and for guiding injections into deep muscles or in overweight patients with poorly palpable neck muscles.
On subsequent administration, the doses may be adjusted according to the clinical response and side effects observed. Doses within the range of 250-1000 units are recommended, although the higher doses may be accompanied by an increase in side effects, particularly dysphagia. Doses above 1000 units are not recommended.
The relief of symptoms of torticollis may be expected within a week after the injection.

Injections should be repeated approximately every 12 weeks or as required to prevent recurrence of symptoms.
Children: The safety and effectiveness of Dysport in the treatment of spasmodic torticollis in children have not been demonstrated.

Method of administration

When treating spasmodic torticollis Dysport is reconstituted with 1.0 ml of sodium chloride injection B.P. (0.9%) to yield a solution containing 500 units per ml of Dysport. Dysport is administered by intramuscular injection as above when treating spasmodic torticollis.

Blepharospasm and hemifacial spasm:

Posology

Adults and elderly: In the treatment of bilateral blepharospasm the recommended initial dose is 120 units per eye.
Injection of 0.1 ml (20 units) should be made medially and of 0.2.ml (40 units) should be made laterally into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of each eye.
For injections into the upper lid the needle should be directed away from its centre to avoid the levator muscle. A diagram to aid placement of these injections is provided. The relief of symptoms may be expected to begin within two to four days with maximal effect within two weeks.
Injections should be repeated approximately every 12 weeks or as required to prevent recurrence of symptoms. On such subsequent administrations the dose may need to be reduced to 80 units per eye - viz -: 0.1 ml (20 units) medially and 0.1 ml (20 units) laterally above and below each eye in the manner previously described. The dose may be further reduced to 60 units per eye by omitting the medial lower lid injection.

In cases of unilateral blepharospasm the injections should be confined to the affected eye. Patients with hemifacial spasm should be treated as for unilateral blepharospasm. The doses recommended are applicable to adults of all ages including the elderly.
Children: The safety and effectiveness of Dysport in the treatment of blepharospasm and hemifacial spasm in children have not been demonstrated.

Method of administration

When treating blepharospasm and hemifacial spasm Dysport is reconstituted with 2.5 ml of sodium chloride injection BP (0.9%) to yield a solution containing 200 units per ml of Dysport. Dysport is administered by subcutaneous injection medially and laterally into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of the eyes.

4.3 Contraindications

Dysport is contraindicated in individuals with known hypersensitivity to any components of Dysport.

4.4 Special warnings and special precautions for use

Dysport should be administered with caution to patients with existing problems in swallowing or breathing as these problems can worsen if toxin spreads to the relevant muscles. Aspiration has occurred in rare cases, and is a risk when treating patients with spasmodic torticollis who have a chronic respiratory disorder.
Careful consideration should be given before the injection of patients who have experienced a previous allergic reaction to a product containing botulinum toxin type A.

The risk of a further allergic reaction must be considered in relation to the benefit of treatment.
Dysport should only be used with caution under close supervision in patients with subclinical or clinical evidence of marked defective neuro-muscular transmission (eg myasthenia gravis). Such patients may have an increased sensitivity to agents such as Dysport which may result in excessive muscle weakness.
There are no reports of any immune response after the local administration of *Clostridium botulinum* type A toxin-haemagglutinin complex in accordance with the doses recommended when treating hemifacial spasm. Antibody formation to botulinum toxin has been noted rarely in patients (approximately 1 in 10, 000 cases) receiving Dysport. Clinically, neutralizing antibodies have been detected by substantial deterioration in response to therapy or a need for consistently increasing doses.
For the treatment of cerebral palsy in children, Dysport should only be used in children over 2 years of age.
As with any intramuscular injection, Dysport should be used only where strictly necessary in patients with prolonged bleeding times, infection or inflammation at the proposed injection site.
This product contains a small amount of human albumin. The risk of transmission of viral infection cannot be excluded with absolute certainty following the use of human blood or blood products.

4.5 Interaction with other medicinal products and other forms of Interaction

Drugs which affect neuromuscular transmission, such as aminoglycoside antibiotics, should be used with caution.

4.6 Pregnancy and lactation

Teratological and other reproductive studies have not been performed with Dysport. The safety of its use in pregnant or lactating women has not been demonstrated.
Dysport should not be used in pregnant or lactating women, unless clearly necessary.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Very common>1/10: Common>1/100, <1/10: Uncommon>1/1000, <1/100: Rare>1/10 000, < 1/1000: Very rare <1/10 000.

General:

A total of approximately 7500 patients were treated with Dysport during a series of clinical trials in patients suffering blepharospasm, hemifacial spasm, torticollis or spasticity associated with cerebral palsy or stroke.
Approximately 2200 patients included in these trials experienced an adverse event.

Nervous system disorders

Rare: Neuralgic amyotrophy

Skin and subcutaneous tissue disorders

Uncommon: Itching
Rare: Skin rashes

General disorders and administration site conditions

Common: Generalised weakness, fatigue, flu-like syndrome, pain / bruising at injection site.

Arm spasticity:

In 5 clinical trials involving 141 patients treated with Dysport the following adverse reactions were reported.

Gastrointestinal disorders

Common: Dysphagia

Musculoskeletal and connective tissue disorders

Common: Arm muscle weakness

Injury, poisoning and procedural complications

Common: Accidental injury/falls

Paediatric cerebral palsy spasticity:

In 14 clinical trials involving approximately 900 patients treated with Dysport, the following adverse reactions were reported:

Gastrointestinal disorders

Common: Diarrhoea, vomiting

Musculoskeletal and connective tissue disorders

Common: Leg muscle weakness

Renal and urinary disorders

Common: Urinary incontinence

General disorders and administration site conditions

Common: Abnormal gait

Injury, poisoning and procedural complications

Common: Accidental injury due to falling
Accidental injury due to falling and abnormal gait may have been due to the over-weakening of the target muscle and / or the local spread of Dysport to other muscles involved in ambulation and balance.

Spasmodic torticollis:

In 21 clinical trials involving approximately 4100 patients the following adverse reactions were reported:

Nervous system disorders

Common: Dysphonia
Uncommon: Headache

Eye disorders

Uncommon: Diplopia, blurred vision

Respiratory, thoracic and mediastinal disorders

Rare: Respiratory disorders

Gastrointestinal disorders

Very common: Dysphagia

Uncommon: Dry mouth

Musculoskeletal and connective tissue disorders

Common: Neck muscle weakness
Dysphagia appeared to be dose related and occurred most frequently following injection into the sternomastoid muscle. A soft diet may be required until symptoms resolve. These side effects may be expected to resolve within two to four weeks.

Blepharospasm and hemifacial spasm:

In 13 clinical trials involving approximately 1400 patients treated with Dysport, the following adverse reactions were reported:

Nervous system disorders

Common: Facial muscle weakness
Uncommon: Facial nerve paresis

Eye disorders

Very common: Ptosis
Common: Diplopia, dry eyes, tearing
Rare: Ophthalmoplegia

Skin and subcutaneous tissue disorders

Common: Eyelid oedema
Rare: Entropion
Side effects may occur due to deep or misplaced injections of Dysport temporarily paralysing other nearby muscle groups.
The profile of adverse reactions reported to the company during post-marketing use reflects the pharmacology of the product and those seen during clinical trials.

4.9 Overdose

Excessive doses may produce distant and profound neuromuscular paralysis. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. There is no specific antidote; antitoxin should not be expected to be beneficial and general supportive care is advised. Overdose could lead to an increased risk of the neurotoxin entering the bloodstream and may cause complications associated with the effects of oral botulinum poisoning (e.g deglutition and phonation).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clostridium botulinum type A toxin-haemagglutinin complex blocks peripheral cholinergic transmission at the neuromuscular junction by a presynaptic action at a site proximal to the release of acetylcholine. The toxin acts within the nerve ending to antagonise those events that are triggered by Ca2+ which culminate in transmitter release. It does not affect postganglionic cholinergic transmission or postganglionic sympathetic transmission. The action of toxin involves an initial binding step whereby the toxin attaches rapidly and avidly to the presynaptic nerve membrane. Secondly, there is an internalisation step in which toxin crosses the presynaptic membrane, without causing onset of paralysis. Finally the toxin inhibits the release of acetylcholine by disrupting the Ca2+ mediated acetylcholine release mechanism, thereby diminishing the endplate potential and causing paralysis.
Recovery of impulse transmission occurs gradually as new nerve terminals sprout and

contact is made with the post synaptic motor endplate, a process which takes 6 - 8 weeks in the experimental animal.

5.2 Pharmacokinetic properties

Pharmacokinetic studies with botulinum toxin pose problems in animals because of the high potency, the minute doses involved, the large molecular weight of the compound and the difficulty of labelling toxin to produce sufficiently high specific activity. Studies using I125 labelled toxin have shown that the receptor binding is specific and saturable, and the high density of toxin receptors is a contributory factor to the high potency. Dose and time responses in monkeys showed that at low doses there was a delay of 2 - 3 days with peak effect seen 5 - 6 days after injection. The duration of action, measured by changes of ocular alignment and muscle paralysis varied between 2 weeks and 8 months. This pattern is also seen in man, and is attributed to the process of binding, internalisation and changes at the neuromuscular junction.

5.3 Preclinical safety data

There is no further pre-clinical information relevant to the prescribing physician that has not been included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Albumin and Lactose.

6.2 Incompatibilities

None known.

6.3 Shelf life

The shelf life of the packaged product - 15 months at 2 - 8ºC.
The product may be stored for up to 8 hours at 2 - 8ºC following reconstitution.
Since the product does not contain an anti-microbial agent, from a microbiological point of view, it is recommended that the product should be used immediately following reconstitution.

6.4 Special precautions for storage

Unopened vials must be maintained at temperatures between 2°C and 8°C. Dysport must be stored in a refrigerator at the hospital where the injections are to be carried out and should not be given to the patient to store.
Reconstituted Dysport may be stored in a refrigerator (2 - 8ºC) for up to 8 hours prior to use.
Dysport should not be frozen.

6.5 Nature and contents of container

Nature of container/closure:

Type 1 glass vials 3 ml capacity. 13 mm chlorbutyl freeze-drying closures oversealed by 13 mm aluminium overseals with centre hole, crimped over.

Contents of container:

A white lyophilised powder for reconstitution.

6.6 Instructions for use and handling

Immediately after treatment of the patient, any residual Dysport which may be present in either vial or syringe should be inactivated with dilute hypochlorite solution (1% available chlorine). Thereafter, all items should be disposed of in accordance with standard hospital practice.
Spillage of Dysport should be wiped up with an absorbent cloth soaked in dilute hypochlorite solution.

7. MARKETING AUTHORISATION HOLDER

Ipsen Limited
190 Bath Road, Slough
Berkshire, SL1 3XE

8. MARKETING AUTHORISATION NUMBER(S)

PL 6958/0005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9th December 1990

10. DATE OF REVISION OF THE TEXT

September 2004
DYSPORT is a registered trademark.

Appendix 3 Botulinum Toxin Treatment Regimen

Muscle	Origin	Insertion	Action	Dose	Injection Point
Pectoral Girdle					
Trapezius	Occiput down median line to last thoracic vertebra	Lateral third of clavicle, acromion and scapular spine	Scapular elevation and rotation	200-300u	Large muscle between neck and shoulder
Rhomboid	Spinous processes C7-T5	Medial border scapula	Extension of scapulae	200-250u	Superficial between scapula and spine
Supraspinatus	Supraspinatus fossa scapula	Greater tubercle of humerus	Abduction of arm from 0°-15° above 90°	160u	Supraspinous fossa on scapula
Infraspinatus	Posterior aspect scapula below spine	Greater tubercle humerus	External rotation of arm	200u	Infraspinous surface of scapula
Subscapularis	Anterior aspect of scapula	Lesser tubercle of humerus	Internal rotation of arm	200u	Inject under lateral border of scapula
Deltoid	Scapular spine, acromion and clavicle	Deltoid tuberosity of humerus	Arm adduct from 15-90°	200-300u	Inject anterior middle and posterior fibres
Teres major	Dorsum of scapula at inferior angle	Crest of lesser tubercle of humerus	Adducts, medially rotates and extends arm	120u	Lateral aspect lower scapula
Teres minor	Lateral aspect of scapula	Back of greater tubercle of humerus	Adducts and laterally rotates	120u	Lateral aspect scapula above
Latissimus dorsi	Tips lower six thoracic spines, thoracolumbar fascia and iliac crest	Floor of intertubercular groove of humerus	Adducts, retracts and medially rotates upper limb	325u	Find in posterior fold of axilla while asking patient to pull down elevated arm
Serratus anterior	Upper eight ribs in three parts	Medial border scapula	Protracts upper limb	250-275u	Lateral aspect of upper eight ribs
Pectoralis major	Clavicle and 3rd-8th anterior ribs	Greater tubercle of humerus	Adducts and medially rotates	300u	Anterior axillary fold
Pectoralis minor	3rd, 4th and 5th ribs at costo-chondral cartilages	Coracoid process	Draw scapula down and forwards, depresses shoulder	160u	Deep to upper part of pectoralis major
Muscle	**Origin**	**Insertion**	**Action**	**Dose**	**Injection Point**
Arm					
Biceps brachii	Short: coracoid process Long: supra glenoid tubercle scapula	Bicipital aponeurosis	Supination and elbow flexion	300-400u	Anterior aspect of upper arm. Inject both heads.
Triceps brachii	Scapula and humerus	Olecranon	Elbow extension	300-400u	Three heads on post aspect of arm
Coracobrachialis	Coracoid process	Middle medial border humerus	Flexes and adducts upper arms	160u	Medial to upper humerus between it and neurovascular bundle

Brachialis	Front of distal half humerus	Coranoid process of ulna	Flexes elbow	200u	Lower anterior humerus medial and lateral of biceps tendon

Appendix 3 (Cont.)

Muscle	Origin	Insertion	Action	Dose	Injection Point
Extensor Aspect Forearm					
Brachioradialis	Left supracondylar ridge of humerus	Lateral surface distal radius	Elbow flexion	200u	Radial side upper forearm
Supinator	Radial notch of ulna	Shaft of proximal radius	Supinates forearm	120-160u	Extensor aspect of arm below radial neck – deep
Extensor carpi radialis longus	Distal third of lateral supracondylar ridge of humerus	Base of second metacarpal (MC)	Extends and adducts hand at wrist	120-160u	Posterior to brachio radialis on back of forearm
Extensor carpi radialis brevis	Common extensor origin (lateral humeral epicondyle)	Base of 3rd MC	Extends and adducts hand at wrist	75-120u	Posterior and medial to extensor carpi radialis longus
Extensor carpi ulnaris	Common extensor origin	Base of 5th MC	Extends wrist and elbow and adducts hand	120-160u	Most medially placed extensor muscle. Half way down ulna shaft.
Extensor digitorum communis	Common extensor origin	Bases of middle and distal phalanges	Extends wrist and fingers	120-160u	Middle of back of forearm distal to radial tuberosity
Extensor digiti minimi	Common extensor origin	Bases of middle and distal 5th phalanges	Extends 5th finger	120-160u	Medial to extensor digitorum
Extensor pollicis longus	Posterior surface middle third ulna	Base of distal phalanx thumb	Extends all joints of thumb	75-120u	Midway down back of forearm
Extensor pollicis brevis	Posterior surface of radius and interosseous membrane	Base of proximal phalanx of thumb	Extends CMC and MCP joints of thumb	75-100u	Distal third of forearm. Palpat by moving CMC and MCP joints
Adductor pollicis longus	Back of interosseous membrane and both radius and ulna	Base of 1st MC	Adducts thumb and hand		Proximal to ext pollicis brevis on back of forearm. Palpate action
Extensor indicis	Back of distal ulna and interosseous membrane	Extensor expansion of dorsum of 1st phalanx	Extensor forefinger	75-120u	Found medial of most lateral tendon of extensor digit communis

Appendix 3 (Cont.)

Muscle	Origin	Insertion	Action	Dose	Injection Point
Flexor Aspect of Forearm					
Pronator teres	Humeral head medial humeral epicondyle. Ulna head from medial border of ulna coronoid process	Middle of lateral surface of radius	Pronates forearm and flexes elbow	120-160u	Medial border of anterior cubital fossa-medial to brachial artery
Flexor carpi radialis	Medial humeral epicondyle	Base of 2nd metacarpal	Flexes wrist and elbow	150u	Upper forearm just below bicipital aponeurosis and medial to pronator teres
Flexor carpi ulnaris	Humeral head from medial humeral epicondle. Ulna head from olecranon and upper two-thirds of its posterior border	Pisiform bone in wrist	Flexes and adducts hand and wrist	150u	Upper forearm medial aspect of flexor surface below bicipital aponeurosis. Medial to flexor carpi radialisis. Observe action of wrist flexion.
Flexor digitorum superficialis	Humero-ulna head from medial epicondlye and coronoid process. Radial head from upper half of anterior border of radius	Middle phalanges of medial four digits	PIP joint flexor and MCP joint flexor	150-250u	Middle of forearm half way down to either side of palmaris tendon
Flexor digitorum profundus	Proximal two-thirds of ulna	Terminal phalanges of fingers	Flexes all finger joints	150u	Upper third of forearm. Deep muscle above lateral border of ulna.
Flexor pollicis longus	Upper two thirds muscle above lateral border of front radius	Terminal phalanx of thumb	Flexes all joints of thumb	75-120u	Mid forearm over anterior aspect of radius
Pronator quadratus	Front of ulna (distal)	Front of distal radius	Pronates forearm	75-120u	Approach muscle from extensor aspect of forearm just proximal to wrist and advance through interosseous membrane.