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Information Sheet for Patients – Part 1

## **'A study to test if botulinum toxin can improve the ability of stroke patients to 'let go' of grasped objects'**

**(Predicting Outcome and Measuring Benefit from botulinum therapy in Stroke:PrOMBiS)**

REC reference number: 09/H0714/5, 30th March 2009, version 1.1

We would like to invite you to take part in a research project that is being performed at the Institute of Neurology and at the National Hospital for Neurology and Neurosurgery (NHNN). Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

- Part 1 tells you the purpose of this study and what will happen if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

### **What is the purpose of the study?**

People with stroke often say they cannot use their affected arm and hand. There are many potential causes for this but one problem likely to contribute is a type of muscle stiffness (spasticity) affecting the muscles that flex the wrist and close the hand. Patients with spasticity might experience extra unwanted muscle activity, muscle spasms and tightness or stiffness of the affected muscles.

When this is severe it may prevent any movement of the hand at all, leading to difficulty with cleanliness and comfort. Injections of a drug called botulinum toxin into the muscles of the hand and arm can help by weakening the overactive muscles and allowing movement.

Botulinum toxin is a purified protein derived from the bacteria *Clostridium botulinum*. It works by blocking the signal from the brain to the muscle nerve endings. When Botulinum toxin is injected, it affects the nerves in the immediate area. Usually the effect only spreads for a short distance in the muscle. The Botulinum toxin goes in to the local nerves



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(called motor neurons) that control the muscles, where it prevents release of the chemical at the junction where the nerve connects with the muscle. This stops the nerve impulse from reaching the muscle, so that the muscle supplied by that nerve is temporarily paralysed (the effects wear off after about three months). Whilst the muscle is paralysed there is a “window of opportunity” where other treatments like physiotherapy may be more effective.

We aim to investigate whether injection of Botulinum toxin can help in less severe spasticity by reducing the muscle overactivity so that **active functional use** of the arm and hand can be improved. There have been some reports of success from doctors and patients but there is no current definite proof that it works, and so this expensive drug is not routinely offered to improve active function of the hand and arm.

### **Why have I been chosen?**

You have had a stroke and have difficulty using your arm and hand. We think that you might benefit from treatment with botulinum toxin, but are not certain. In total, we will be investigating 30 similar people with stroke.

### **Do I have to take part?**

It is up to you to decide. We will describe the study and go through this information sheet, which you can keep. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

### **What will happen to me if I take part?**

Sometimes we don't know which way of treating patients is best. To find out, we need to compare a new treatment either against an existing treatment, or a “dummy” (placebo) treatment. The most powerful and reliable way to do this is with a “randomised controlled trial” We randomly allocate people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). In this study there will be an active treatment group and a placebo group. A placebo is a ‘dummy treatment’, which looks like the genuine medicine but contains no active ingredient. You will have a 50% chance of being in either group. This is a ‘double blind trial’ which means neither you nor your doctor will know which treatment group you are in (although, if your doctor needs to find out he can do so). To be clear, you might be injected with botulinum toxin or with a water solution which looks the same.

You will be asked to attend the National Hospital for Neurology and Neurosurgery (NHNN) for assessment and treatment. This will require 11 visits over 5 weeks; one for initial assessment and injection and the other 10 for out-patient physiotherapy treatment. You will then need to return to the NHNN a further three times for follow up assessments. Your participation in the study will last four months. We will contact you three months after your last assessment visit, to repeat the questionnaires one last time. You can choose to do this by telephone or by post and you will not need to visit the hospital again. The whole study will take about 2 years to complete.



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On your first visit you will be assessed by a group of doctors and physiotherapists for suitability for the study. If you decide to take part you will be asked to sign a consent form and then undergo some baseline tests. You will then be given the study drug by Dr Werring which will be given as several injections into the muscles in your hand and arm.

The table below explains how often you will need to visit the hospital, what will happen on each visit, and how long each visit will take. We will work at a pace that suits you and if you feel tired we will arrange for a rest break. The different tests are explained in more detail in the text on the next page.

| Date                                 | Event   | Approximate duration    |
|--------------------------------------|---|-------------------------|
| 1 <sup>st</sup> hospital appointment | Assessment by the team for suitability<br>Informed consent  | 30 - 60 minutes         |
|                                      | baseline assessment including the following tests:<br>1. a short questionnaire about daily activities ( <b>Barthel index</b> )<br>2. test of your hand and grip ( <b>ARAT</b> )<br>3. test of your finger movement ( <b>nine hole peg test</b> )<br>4. find out your goal of treatment ( <b>GAS</b> )<br>5. test how you let go of things ( <b>grasp release task</b> )<br>6. measures of muscle, strength, stiffness and spasticity<br>7. short questionnaires about your health ( <b>ArMA and EQ-5D</b> ) | 150 minutes             |
|                                      | Injection   | 10 minutes              |
| Week 1 to week 5                     | Physiotherapy treatment – 10 sessions over 4 weeks<br>You will be given a diary with all your appointment dates & times   | 60 minutes each session |
| week 5                               | immediate outcome assessment including the following tests:<br>1. ARAT<br>2. nine hole peg test<br>3. GAS<br>4. the grasp release task<br>5. measures of muscle strength, stiffness and spasticity<br>6. ArMA and EQ-5D questionnaires  | 120 minutes             |
| week 9                               | one month follow up assessment including the following tests:<br>1. ARAT<br>2. nine hole peg test<br>3. GAS<br>4. the grasp release task<br>5. measures of muscle strength, stiffness and spasticity<br>6. ArMA and EQ-5D questionnaires  | 120 minutes             |
| week 17                              | three month follow up assessment including the following tests:<br>1. ARAT<br>2. nine hole peg test<br>3. GAS<br>4. the grasp release task<br>5. measures of muscle strength, stiffness and spasticity<br>6. ArMA and EQ-5D questionnaires  | 120 minutes             |
| Week 30                              | 6 month follow up: repeat of questionnaires only (by telephone or post) – GAS, ArMA and EQ-5D.  |                         |



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The Barthel index: a short questionnaire about how you well manage everyday tasks like dressing and walking.

The action research arm test (ARAT): a standard test of arm and hand function which includes, for example, picking up different sized wooden blocks and placing them on a shelf in front of you.

The nine hole peg test: a standard test of finger dexterity requiring you to pick up 9 small pegs and place them in holes on a board as quickly as possible.

The goal attainment scale (GAS): this is where we discuss what specific activity you would like to improve with treatment. We will then set a detailed goal so that we can measure how well you achieve your aim at the end of the treatment.

The grasp release task: The task involves repeatedly lifting up a glass and placing it on different targets, rest is provided as required. We will record the movement of the arm using markers that are taped to the arm.

Measures of muscle strength, stiffness and spasticity: Strength is tested using our strength testing equipment. You will be asked to do three different strength tests (wrist, finger and grip strength). Stiffness and spasticity will be measured manually by the therapist and also using a special piece of equipment. You will place your hand in a rest and then relax. The machine will move your fingers and wrist over a small distance at two different speeds. Muscle activity in the arm will be recorded using electrode pads that are taped to the arm. This part of the test only takes about 10 minutes. We will also use a brief electrical stimulus to activate the muscles in the arm.

ArMA and EQ-5D questionnaires: these are two short questionnaires that will take a few minutes to complete. The first asks you about daily activities you can perform with your affected arm and hand (ArMA) and the second asks you about your general health state (EQ-5D).

Physiotherapy treatment: will consist of 10 sessions over 4 weeks. The physiotherapy treatment was developed at this hospital. Each session will last approximately one hour and will include strengthening exercises for specific muscles and task practice for skilled hand use. You will be working under the supervision and instruction of a senior physiotherapist. You will also be expected to do some practice at home on the days you do not have treatment and will be given a diary to record what you practice.

The physiotherapy treatment in this study may differ from what you might receive as part of routine care. This is because your local service may not offer as much as 10, hour long, one to one sessions, and the therapy given in the study will follow a standard protocol which is based on the evidence in the literature for effective practice and includes a standardised programme adjusted for each individual's ability.



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All other tests are not considered part of routine care. No treatment normally given under routine care will be withheld. You will be able to claim back the cost of your travel to the hospital for the appointments.

After the study, any follow up care you require will be provided in Dr Werring's clinic at NHNN.

### **What will I have to do?**

If you decide to take part in this study it is very important that you attend all your scheduled appointments. You should also complete your home exercise programme daily and record this in your exercise diary.

During the study you will not be able to take any new drugs for treating spasticity or increase the dose of any drugs you are already taking for spasticity. You should tell the investigators if any of your medications are changed or you start taking a new medicine. You should also not start any new physical therapy or exercise programme involving the arm and hand other than the one you receive in this study.

The use of some medication (aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission e.g. curare-like muscle relaxants) will also be restricted during the trial. This is because they can interact with the drug being injected. You will be given a 24 hour contact card so that you or your representative can contact the trial doctor if you are concerned or need to check about possible new drugs.

### **What is the drug that is being tested?**

The drug being tested is called botulinum toxin A and is already licensed in the UK for treating muscle spasticity after stroke. We are investigating whether it can be used in people with some active movement to improve their ability to use the arm and hand.

### **What are the alternatives for treatment?**

Standard clinical treatment for difficulty using the arm and hand when some active function is present would be local referral for physiotherapy assessment and treatment. Whilst physiotherapy can help to improve function it is often difficult to get good results when spasticity is also a problem. We think that combining the drug treatment for spasticity (that is botulinum toxin A) with physiotherapy will give the best possible chance for improvement in the use of the arm and hand.

### **What are the possible disadvantages and risks of taking part?**

You may have some mild muscle soreness from the strength tests. This should not last longer than 48 hours. You may also experience some very mild skin redness or irritation from the tape used to attach the electrodes and skin markers to your arm. This should not last longer than a few hours. If you have had a strong reaction in the past to tape or sticking plasters please tell us about it.



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## **What are the side effects of any treatment received when taking part?**

Botulinum toxin A is already licensed for use in people who have had a stroke and is used regularly with few side effects. One in six people in clinical trials for spasticity of the upper limb experienced side effects. In general, side effects occurred within the first few days following injection and were short lasting. In rare cases, they lasted several months or longer. Dr Werring has been involved in specialist spasticity clinics at the National Hospital since 1999, and has been running his own clinics since 2006. There have not been any reports of serious side effects from the injections in that time.

The most commonly reported side effects are local muscle weakness, which is the expected action of the drug and, as for any injection procedure, localised bleeding, pain, tenderness and/or bruising. Fever and flu syndrome have also been reported after injections of botulinum toxin.

If you think you may have had any side effects from participation in the trial, please report them to the doctor or the physiotherapist the next time you attend the hospital.

There are no adequate data from the use of botulinum toxin type A in pregnant or breast feeding women. The potential risk for the unborn child or breast feeding infants is unknown. Botulinum toxin should not be used during pregnancy or breast feeding.

### For women

Please share this information with your partner if it's appropriate.

The treatment might harm the unborn child; therefore you should not take part in this study if you are pregnant, breast-feeding or you may become pregnant during the study period.

If you could become pregnant, you will be asked to have a pregnancy test (urine) before taking part. You must agree to use a reliable form of contraception during the trial, e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom.

This should be continued for at least 6 months and one menstrual cycle after the treatment has finished.

If you do become pregnant during the course of the study, we would ask you to tell your study doctor immediately so we can help decide appropriate action. We would discuss referral for specialist counselling on the possible risks to your unborn baby and arrangements will be offered to monitor the health of both yourself and your unborn baby. We may also request your consent to collect information about your health and that of the baby.

### For men

Please share this information with your partner if it's appropriate.

It is not known if the study medicine will affect sperm or semen and therefore you should not father a child during this study or for a safety period of 6 months after treatment. If your partner might become pregnant you must use reliable forms of contraception during the trial and for 6 months afterwards, e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom.



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If your partner becomes pregnant during the study or within 6 months of stopping treatment, you should inform your study doctor immediately.

As the risk to your partner and baby is unknown, it is desirable for your partner to agree to medical supervision during her pregnancy and for the baby after it is born. Your partner will be invited to sign a consent form to allow medical supervision. We may also request you and your partner's consent to collect confidential information about her health and that of the baby.

### **What are the possible benefits of taking part?**

We hope that the treatment will have positive results for the participants in this study. You will have access to follow up by a specialist team with expertise in treating your condition, and will have the opportunity to ask about any questions or concerns you may have.

However, we cannot promise that the study will help you as an individual, and there is a 50% chance that you will receive dummy injections. Every participant will take part in a specialist physiotherapy programme. You may see some improvement with this.

We expect the information we collect from the study to help improve the future treatment of people with stroke.

### **What happens when the research study stops?**

You will be followed up in Dr Werring's clinic for any further treatment required. We will only be able to tell you what treatment group you were in at the end of the trial.

### **What if there is a problem?**

Any complaint about the way you have been dealt with during this study or any possible harm you might suffer will be addressed. The detailed information about this is given in part 2.

### **Will my taking part in the study be kept confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

**This completes part 1 of the information sheet. If the information in part 1 has interested you and you are considering participation, please continue to read the additional information in part 2 before making any decision.**

***Thank you for the opportunity to invite you to take part in this project***



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## **Information sheet for patients- part 2**

### **Predicting Outcome and Measuring Benefit from botulinum therapy in Stroke (PrOMBIS)**

**REC reference number: 09/H0714/5, 30th March 2009, version 1.1**

#### **What if relevant new information becomes available?**

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an updated consent form.

#### **What will happen if I don't want to carry on with the study?**

Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the trial, or to withdraw once entered, this will in no way affect your future medical care. Participation in this study will in no way affect your legal rights. The data collected will be kept for future analyses in conjunction with this study. If there are more studies proposed using this data then approval of the Regional Ethics Committee will be sought. If you decide to withdraw from the study at any stage we will need to use data collected up to the point of your withdrawal.

#### **What if there is a problem?**

UCL will provide non negligent (no fault compensation) for the trial. This means that any person who is harmed from any procedure carried out in accordance with the study protocol will be eligible to make a claim for compensation. Claims must be made in writing to the Chief Investigator. If you are harmed due to someone's negligence, then you may have grounds for a legal action for compensation against UCLH NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.



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If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure. Details can be obtained from the hospital. The Patient Advice and Liaison Service (PALS) is also available to you on 020 7380 9975. PALS was set up to help patients, and their relatives and carers, find a speedy and effective solution to any problems they may encounter.

### **Will my taking part in this study be kept confidential?**

All information regarding a person's medical records and data collected as part of the trial will be treated as strictly confidential and will only be used for medical purposes. Some parts of your medical records and the data collected as part of the trial may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done so in coded form so that confidentiality is strictly maintained. We will collect basic data about age, sex, and diagnosis, and this data, along with the results of the tests will be used to investigate whether the trial treatment is effective. All electronic data will be stored on a password protected computer server and paper files will be kept in locked filing cabinets during this research project. Dr David Werring will be responsible for security and access to the data during the project. Data will be stored for a period of 15 years after the end of the study and will then be disposed of securely. Publication of the results of this study will not reveal your identity.

### **Will my GP be informed of my participation in this study?**

Your GP will be notified of your participation in this study but we will first ask your permission to do so. If you do not want us to inform your GP you can still take part in the study.

### **What happens to the information that this study generates?**

The results of the study will be published in a peer-reviewed scientific journal and presented at scientific conferences. They will also be presented to interested community groups and sent to each participant. You will not be identifiable when the data is published or presented.

### **Who is organising and funding the research?**

This study has been funded by a research grant from the UK Stroke Association. Your doctor will not be paid for including you in this study.

### **Who has reviewed this study?**

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by the UCLH Research Ethics Committee A.



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### Further information and contact details

You can contact us at the address or telephone number below should you have any questions about the study, if you want to make a complaint, or if you want to tell us about any side effects.

Amanda Wallace, Research Physiotherapist,  
Institute of Neurology, 33 Queen Square, London WC1N 3BG.

Tel: 020 3108 0058  
Email: a.wallace@ion.ucl.ac.uk

Project Supervisor (Principle Investigator):

Dr David Werring d.werring@ion.ucl.ac.uk 020 7829 8753

### Out of hours contact details

In case of any medical problems or, if further urgent information is required outside of normal working hours, please contact the switchboard at the National Hospital:

**020 7837 3611**

Ask to be through to the PrOMBiS trial doctor and switchboard will connect you.

Also, the UK Clinical Research Collaboration (UKCRC) publishes a booklet called 'Understanding Clinical Trials'. It contains information about medical research, and questions you might want to ask. If you'd like to read it, please ask us for a copy or if you have access to the internet you can visit <http://www.ukcrc.org/publications/informationbooklets.aspx>

***If you decide to take part in this study you will be given copies of part 1 & 2 of the information sheet and a copy of the signed consent form to keep.  
Thank you for considering taking part in this project***



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