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The early use of botulinum
toxin in post stroke spasticity:
developing a new approach to
contracture management

Cameron Lindsay

Doctor of Philosophy

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Keele University

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Abstract

Introduction

Patients surviving a severe stroke are at risk of developing contractures.

Evidence suggests that spasticity may be a cause of contractures, particularly in patients who have not recovered functional movement. The relationship and the time course of spasticity and contractures remain unclear.

This thesis aims to identify when spasticity can be identified and investigate whether treating spasticity at onset using botulinum-toxin, might slow contracture development.

Methods

A double blind randomised placebo-controlled trial with an initial six-week screening phase was conducted in an acute NHS hospital.

Patients with no arm function (Action Research Arm Test grasp-score<2) within six-weeks of stroke were eligible for screening. Screening for spasticity was carried out using a neurophysiological method. Patients who developed spasticity were randomly assigned to receive intra-muscular injections of 0.9% sodium chloride solution or onabotulinumtoxinA.

Measures of spasticity and contracture development (reduced passive range of motion (PROM) and increased stiffness) were taken at the wrist and elbow at baseline, weeks-two, four, six and twelve post injection and six-months post stroke.

Results

Over a 23-month period, 1143 patients were admitted with stroke and 120 consented to study participation. Of these, 100 developed spasticity without functional recovery 84%(95% confidence interval(95%CI):76%-89%). Mean time of spasticity onset was 13.5-days(SD:8.5).

Of the 100 eligible for randomisation 93 were included in intention to treat analysis. At six-weeks, treatment results in a reduction in wrist spasticity (mean difference(MD):4.8 μ V;95%CI:1.2to8.4;p=0.009), stiffness (MD=4.2mN/deg;95%CI:0.7to7.7;p=0.02) and PROM (MD=13.8°;95%CI:6.1to21.6;p=0.01). At the elbow; four-weeks spasticity (MD=9.8 μ V;95%CI:4.3to15.4;p=0.001), four-week stiffness (MD=4.8mN/deg;95%CI:-0.1to9.6;p=0.056) and twelve-weeks PROM– (MD=6.5°;95%CI:0.6to12.3;p=0.03). These changes were not maintained at the six-month follow-up assessment.

Conclusion

Spasticity occurs earlier and is more common than previously reported.

Treating spasticity early with onabotulinumtoxinA can reduce the rate of contracture formation. Further work is required to elucidate who is at greatest risk of contractures and to explore if these treatment effects can be sustained with adjunct therapies.

Activities and personnel involved in the study

This study could not have been achieved without support and assistance being provided to the candidate. This section clarifies what contribution the candidate made to the study. Activities have been divided in to intellectual and practical tasks as suggested by Wade (2010).

Intellectual tasks

Specifying the question

This PhD is slightly unusual in that the candidate came with a specific clinical question that they wanted to answer. In order to investigate that question three unsuccessful grant applications to various funders were submitted by the candidate with gradually reducing advice from Anand Pandyan (ADP). This led to an iterative process whereby feedback from unsuccessful grant applications led to a refining of the study question. The candidate also entirely independently organised a patient and public involvement event. Information from this event informed the grant application and was important in identifying some of the objective measures that needed to be included.

The successful National Institute for Health Research (Research for Patient Benefit) grant application which awarded £245,000 for the study was written and submitted by the candidate on behalf of Sandwell and West Birmingham NHS Trust. ADP advised on the application form and helped to write section ten (Background) and eleven (Research plan and methodology).

The candidate was advised to submit the initial literature review protocol to the Cochrane Library. This protocol was accepted by the Cochrane library and the subsequent Cochrane systematic review has been published.

Designing the Study

Although the grant application specified a general research plan and methodology, this was not sufficient to produce a protocol.

The candidate was initially advised that this study did not require Medical and Healthcare Regulatory Authority (MHRA) approval. Having independently established that this was incorrect the candidate wrote the study protocol and applications for research ethics committee and MHRA approval. This included writing patient, legal representative and GP information sheets, legal representative and family consent forms, sample diary forms and providing the summary of product characteristic for onabotulinumtoxinA. Steve Sturman (consultant neurologist and Principal Investigator) advised on the protocol and ethics and MHRA application forms. ADP was asked to assist with specific questions relating to the scientific methodology to ensure quality of the study.

During the writing of the protocol, the candidate persuaded Steve Sturman (SS) the Principal Investigator, that it was essential to use a localisation technique while injecting to be able to categorically state that the appropriate muscles were injected, and this was included in the protocol.

Following advice from Professor Christine Roffe the candidate wrote and submitted the protocol for publication in a peer reviewed journal and ensured that the protocol was registered with clinicaltrials.gov.

A further issue occurred after the first five patients had been randomised. SS became worried that the agreed doses were too large. Although there is no evidence that the small doses used could cause dysphagia, SS was still worried and the candidate wrote a substantial amendment to the protocol.

Once the PhD began the candidate wrote the pharmacy standard operating procedures (SOPs) which included: dispensing and preparation SOPs, emergency unblinding SOP, and forms for safe injection of the blinded preparation. Julie Simpson (JS) provided very useful advice and helped in completing these SOPs.

Identifying essential data

ADP identified the tools to collect the contracture and spasticity data based on his having developed and used these methods previously.

ADP advised that only EMG measurements should be taken as a measure of spasticity. The candidate strongly felt that a clinical measure had to be used as the long term aim was to change clinical practice. The Tardieu scale was therefore taken for every measurement.

Both ADP and SS were unsure whether the candidate would be overly burdened by attempting to take outcome measures at five time points following randomisation – they both suggested 6, 12 and 24 weeks. The candidate however, felt that measurements at two and four weeks would be useful in identifying the contracture development and this was agreed.

As documented already, the candidate independently organised a patient and public involvement event. This event identified that pain should be included as

an outcome measure and that a way of identifying how difficult caring for the patient was, should be measured.

Analysing Data

Following the end of recruitment, data that had been collected was reviewed. ADP wrote a bespoke programme of functions within Mathcad 15 to allow analysis of the data files. The candidate was required to have a good understanding of this programme as each of the files required manual input of data to ensure the correct time-points could be analysed. During this process the candidate identified issues in the initial formulae which meant data points were not being appropriately identified. In order to ameliorate this problem ADP showed the candidate how to identify the middle 70% of a movement. Having further analysed the data the candidate changed the formulae so that the middle 80% of the movement was analysed.

Over 8000 data files had to be converted from a text file to a Mathcad file before being analysed. Once the candidate had ensured data had been appropriately converted and then analysed, it was then transferred to an excel spreadsheet.

The candidate cleaned the data on the Excel spreadsheet before transferring it to SPSS. ADP provided teaching and training on statistical analysis and the use of SPSS and advised on how best to analyse the data statistically. The data was then all analysed by the candidate.

At one conference the candidate was approached by a team from Australia who introduced him to different ways of analysing serial measurements. This has

led him to further review how the data may be analysed in future papers; the results are not presented in this thesis.

Interpreting data analysis

The candidate was pro-active in presenting data to audiences and identified potential conferences that may be appropriate. The candidate wrote, submitted and presented nine abstracts to national or international conferences. ADP reviewed all the abstracts and provided feedback on drafts.

Presenting these abstracts subjected the candidate to criticism and forced him to defend both the methodology and interpretation in both one to one and group settings. One example occurred at the International Society of Physical and Rehabilitation Medicine Conference in 2015 where the presentation of this study's results directly contradicted the previous speaker's results (data from the Sunnerhagen group which investigated spasticity development using the Ashworth Scale as an outcome measure).

Practical Tasks

Patient Selection and Monitoring

Once the trial began patients were generally identified by the physiotherapy team. Once patients were identified the candidate approached and provided information to all patients who fulfilled the entry criteria for screening. Having ensured that the patient had capacity to make a decision the candidate attained consent from the patient or assent from the relative.

All screening and blinded assessments were carried out by the candidate.

During screening, if the patient fulfilled criteria for randomisation the candidate

re-assessed capacity, formally co-ordinated a medical consultant, research pharmacy technician, trained clinician to reconstitute and injector to complete the injection.

Julie Simpson (JS) was also the named pharmacist who held the randomised list at the hospital. Peter Jones (Keele University) produced the randomisation list and provided this to JS.

The day after injection the candidate checked for bruising and provided the patient and or carer with training on use of the electrical stimulation. The candidate ordered, set up, maintained and kept a register of the electrical stimulation machines. The ward physiotherapist continued to provide this to all in-patients on the programme.

Once discharged the candidate made all appointments and carried out all follow-up assessments. Due to patients' personal circumstances some of these appointments were carried out in unexpected environments such as a Gurdwara and homeless shelter.

As the candidate was the blinded assessor he was able to identify and document all adverse events and these were fed back to the Principal Investigator as per the protocol. SS was succeeded by Sissi Ispoglou as the Principal Investigator for the study in August 2012.

Management of the Grant

The candidate wrote three substantial amendments to the protocol following discussion at the steering committee which all required ethical approval.

The candidate ordered all the necessary equipment for the trial and ensured the grant funding was used appropriately. He assisted the R&D accountant to provide the annual statements to the NIHR and also wrote an unpaid extension request application to the NIHR.

The candidate also wrote the annual report to the NIHR with SS.

The candidate was encouraged to establish two other clinical trial sites (University Hospitals Birmingham (UHB) and at Royal Wolverhampton). This required a great amount of time to alter documents and establish contacts with the R&D departments at both sites and establish clinical links to ensure the logistics of additional electrical stimulation and injections would be possible. Unfortunately no patients were recruited from these sites.

Jocelyn Bell as head of the Sandwell and West Birmingham Research and Development Office and her team ensured good clinical practice was maintained and protocols were adhered to. This was the first occasion that the NHS Trust had acted as a sponsor of a clinical trial involving a medical product. The candidate maintained the Trial Master Folders and these were presented for internal audit inspection on two separate occasions.

Keele University was subject to an MHRA inspection subsequent to the initial PhD submission for which all the trial information from this trial was inspected. Since the candidate had been in control of all the tasks involved in ensuring good clinical practice and documenting data it was gratifying to hear that no major concerns were raised by the MHRA inspection.

In loving memory of:

Dr D. Cameron Lindsay OBE FREng

12 December 1920 – 07 September 2014

Personal Acknowledgments

A PhD is a very personal and lonely journey but it is dependent on a huge team and I wish to thank just some of those who have had a bearing on this voyage of discovery. Some would argue that the acknowledgements section should be brief and succinct but I have carefully kept the other 204 pages of sober scientific prose concise so I hope you will forgive me as I briefly wallow in reflection and gratitude.

My first thank you is to the three people who have been there from the start - my Mum and Dad (Gillian and Cameron) and sister (Kirsten). The determination, work ethic and commitment I saw in each of you as I grew up remains with me. You will never know how much you have each inspired me. You have taken such great care in nurturing and guiding me to be the best I can be and in supporting me to achieve more than I ever thought possible. Thank you for providing me with such a stable and strong foundation and continuing to provide unerring assistance.

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Some teachers leave a lasting influence on their students and, given this academic endeavour, it is only appropriate to identify three that have done so for me. Malcolm Peckover was one such teacher whose love of science was infectious. Thank you for seeing in me intrigue, something that others took for teenage impudence.

Brin Helliwell is someone I initially met as my Sixth Form Biology Lecturer. It has been my honour and privilege to then treat him and finally become a colleague as he took on the patient and public involvement role on the trial steering committee. You have inspired and taught me even more since your stroke than you did at Sixth Form.

The final academic professional I wish to thank is Barby Singer. The post-graduate diploma at University of Western Australia serves as the key milestone in my career. You provided me with the encouragement, guidance and self-confidence to proceed to a PhD.

I never worked clinically with Barby but there are two particular Physiotherapists for whom I have the greatest admiration. They have both shown the importance of building the scientific evidence in neurological physiotherapy and transferring this in to every day practice. As a junior rotational Physio, my senior, Michelle Watson (nee Marr) was instrumental in developing the neurophilia bug (careful

with predictive text). Peter Harding saw the potential in me and offered me a senior role at the tender age of 25 where he developed my clinical experience in spasticity management. Peter, you have opened so many doors for me – I will always be indebted to you.

There is a huge team of Health professionals at Sandwell and West Birmingham NHS Trust that I also wish to thank. The Stroke and Neuro Rehab Physiotherapy team led by Dawn Hicklin have been truly awesome. Thank you to each and every one of you for going the extra mile, being so willing to get involved in this adventure and being so supportive especially when I began to lose the will. Thank you also to Steve Sturman and Sissi Ispoglou. Without your willingness and agreement to act as clinical PI this whole venture would never have happened.

Then there are the 120 marvellous stroke survivors - amazing individuals who endured a severe stroke - and their wonderful relatives. I was always keenly aware that I intruded into some of the darkest days of your life. Your altruism and support were miraculous. Thank you for allowing me to be an interloper in your life for six months. I am so grateful to every single one of you.

Finally to those three people who have had to forsake so much as a direct result of my selfishness.

Cameron Óg and Cian, I may have been there physically more than other Daddies but I am sorry that I feel I have not always been there consciously - the omnipresent cloud of a clinical trial and PhD has followed me throughout your young lives (An early version of section 1.2.1 was written in Birmingham Maternity Hospital). Seeing your smiles every day, first landmark achievements and your developing characters have broken that cloud to let the sunshine in on many occasions. I thank you both for reminding me what is truly most important in life.

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Thank you for being there when my confidence had gone, providing hugs after a frustratingly fruitless 16 hour day and putting up with my grumpiness in the lead up to major events and presentations. I would never have achieved this without your support and I can never thank you enough.

1. Introduction

More people are living longer following a stroke and also surviving much more severe strokes (Feigin et al 2014, Crichton et al 2016, Minnerup et al 2015).

While these facts are positive, the residual impairments following a total anterior circulatory stroke can make the survivor almost entirely dependent on others.

With the aim of optimising participation in society, and minimising distress and discomfort, the process of rehabilitation is important in improving survivors' outcomes following stroke (Wade 2015).

Spasticity and contracture are two impairments that cause distress and discomfort to patients following stroke (Esquenazi 2011). In order to optimise the process of stroke rehabilitation it is important to identify when spasticity develops. Although this remains unclear, there is a theoretical argument that by treating spasticity earlier in the rehabilitation process than is currently the case, contracture development may be slowed (Cousins et al 2010).

This thesis will aim to investigate these issues within the specific context of the arm following a stroke. This introductory chapter will review the definition of spasticity, briefly introduce its pathophysiology and identify how spasticity can be measured. It will then review the development of contractures in animal models and in humans following a stroke before discussing the evidence for the role of spasticity in contracture development. Current treatments in the management of spasticity will then be reviewed before presenting the research questions.

1.1 Definition of spasticity

Spasticity is poorly defined in the published literature. In a review of 250 papers where reduction of spasticity was used as a stated outcome the definition of spasticity was examined (Malhotra et al 2009). Malhotra (et al 2009) concluded that the papers could be split into three, with one third providing no definition, one third considering it increased muscle tone, and one third using the Lance (1980) definition (Malhotra et al 2009). The following section will introduce current terminology and definitions.

1.1.1 Tone

Defining spasticity as increased tone or hypertonia is problematic as the term tone has been used variably. The term tone/tonus was first used by Galen (131 – 201 A.D.) to describe the shoulder being held at 90 degrees (cited in Fulton 1926). In this context tonus clearly meant isometric contraction. Johannes Müller in 1838 has been identified by Fulton (1926) and Rushworth (1960) as the scientist who altered the word's usage to describe the 'slight contractile tension' of normal skeletal muscle at rest.

Tone continues to have two divergent definitions within the scientific literature. One definition taken to its basic level refers to whether the muscle is innervated - a muscle's "readiness to move" Bernstein (1967). Tone in this context, is not related to spasticity at all but refers to paresis (i.e weakness) of a muscle. In cases where a muscle is entirely paretic the term hypotonia has been used.

Tone in the context of spasticity has been variably defined. Two definitions of (spasticity-related) tone are 'the sensation of resistance that is encountered as a

joint is passively moved through a range of motion' (Morris 2002, p54) or 'the resistance of resting muscle to passive movements' (Kheder and Nair 2012, p289). Both of these definitions are similar to "the slight steady enduring tension so characteristic of muscles..." described by Sherrington (1915, p192). It is worth noting that Sherrington (1915) was describing some patients with what would now be diagnosed as dystonia. All three of these definitions of tone describe stiffness which can be assessed quantitatively as Cobb and Wolff highlighted as early as 1932.

In summary, the term tone has become intertwined with spasticity over many decades to the extent that a continuum from hypotonia through normal tone to hypertonia has developed. The hypotonia relates to the Bernstein (1967) definition, hypertonia relates to the Morris (2002) definition. These two definitions describe entirely different pathophysiological processes and should not be confused as two opposing ends of a scale. Such confusion makes it understandable why Cobb and Wolff (1932, p673) made a plea that the term tone be "discarded or returned to its former home in smooth muscle".

1.1.2 Lance definition

The Lance definition of spasticity is a 'motor disorder characterized by a velocity-dependent increase in the tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the upper motor neurone syndrome' (Lance 1980, p485). Lance's definition has some problems. Firstly, it includes 'muscle tone' which has already been discussed and concluded to be an inappropriate term. The definition is also very specific, and it excludes some well accepted clinical

presentations of spasticity (Pandyan et al 2005). It also classifies spasticity as a purely motor disorder, but spasticity is also dependent on changes to the processing of sensory input as will be described later in this thesis.

1.1.3 Recent definitions of spasticity

In an effort to improve on the Lance (1980) definition, two more recent definitions have been developed through consensus. Sanger et al (2003) were a group of North American paediatricians who used the Lance definition as a basis for development. They defined spasticity “as hypertonia in which one or both of the following signs are present: 1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement, and/or 2) resistance to externally imposed movement rises rapidly above a threshold speed or joint angle” (p91 Sanger et al 2003).

This definition is immediately confused by the assertion that “spasticity is hypertonia”. This means that a prior definition of hypertonia is required. Sanger et al (2003) provide a definition of hypertonia as “abnormally increased resistance to externally imposed movement about a joint.” This once again describes stiffness.

Another concern regarding the Sanger et al (2003) definition highlighted by Malhotra et al (2009) was the addition that “resistance... rises rapidly above a threshold speed”. This rapid rise in resistance is later described as a “spastic catch” by Sanger et al (2003) in their explanation. This issue, and the arbitrary velocity threshold that is described, make this definition no improvement on the initial Lance (1980) definition, a conclusion that was also made by Malhotra et al (2009). Arguably, the main flaw, which does not appear to have been

highlighted before, is that the authors have attempted to define a physiological symptom based on the “features of the clinical examination”. If the clinical examination involved in assessing spasticity relied on a clear objective (interval data or ratio data level) outcome measure then this might well be acceptable, but spasticity measurement is not that straightforward.

Another definition which does not appear to be limited by previous definitions, terminology or clinical measurements has also been reported. A European consensus group of clinicians and researchers proposed that spasticity could be defined as “disordered sensory-motor control, resulting from an upper motor-neuron lesion, presenting as intermittent or sustained involuntary activation of muscles” SPASM group (Pandyan et al 2005 p5).

This SPASM definition is potentially too general and, on initial reading (and to clinicians in particular), makes measurement difficult to perform. It can also be argued that such a definition would include clinical presentations that are not traditionally considered as spasticity, such as clonus, spasms and perhaps dystonic posturing. These presentations are certainly consistent with the definition and, in clinical practice are very often called spasticity. This is perhaps because the main treatments are similar for all of them. Such an argument does not therefore harm the definition, but taken to its very limits such a general definition could become problematic. This definition could potentially include seizure activity (intermittent involuntary activation of muscles) during an epileptic seizure (upper motor neuron lesion) and at this point the definition does appear to become too general. The phrase disordered sensory-motor control could feasibly prevent seizure activity from being included since an epileptic seizure is

“abnormal excessive or synchronous neuronal activity in the brain” (Fischer et al 2005 p470).

By accepting the SPASM (Pandyan et al 2005) definition, understanding of the clinical problem is clarified. Fundamentally, the result of a lesion in the central nervous system causes abnormally increased involuntary muscle activity.

The phrase ‘abnormally increased muscle activity’ explains that the muscle is active when it should not be, in much the same way as Gracies (2005) defines muscle over-activity as ‘increased involuntary motor unit recruitment’. The Gracies (2005) phrase ‘muscle over activity’ however, does not make clear the important abnormal element to the muscle activity. Another key benefit of using the SPASM definition is that the term tone is then removed entirely from the vocabulary.

Although it still has weaknesses, this thesis will use the SPASM group definition (Pandyan et al 2005) as it is currently the only definition that is not confounded by describing stiffness of muscle. The pathophysiology of spasticity, which will be reviewed presently, is purely a nervous system disorder so the definition should clearly indicate this.

1.1.4 Pathophysiology of spasticity

Having defined spasticity, it is important to provide some background to the current understanding of its pathophysiology. Spasticity is the result of disinhibited cortical and spinal networks that produce an overall increase in the activity of spinal reflexes.

In order to describe spasticity, it is first necessary to understand the normal spinal reflex system. Essentially, there are two systems (an excitatory system and an inhibitory system) which normally act together to balance the control of the spinal reflexes (Sheean 2002).

The medial reticulospinal tract and vestibulospinal tract make up the excitatory system. These tracts arise in the brainstem (tegmentum of the midbrain and pontine, and reticular formation and in the vestibular nucleus respectively) and generally cause an increase in spinal reflexes (Sheean 2008).

The inhibitory system is under much greater cortical control (Dietz and Sinkjaer 2007). Cortico-reticular tracts from the pre-motor and supplementary motor areas descend through the internal capsule to the ventromedial reticular formation (Sheean 2008). The resulting dorsal reticulospinal tract provides the main inhibition to the spinal reflex activity (Sheean 2002).

Following a stroke, it is this inhibitory system that can become reduced (or disinhibited), leading to exaggerated spinal reflex activity which results in increased activity at the affected muscle.

The reduced inhibition on the spinal reflexes (stretch, proprioceptive or cutaneous reflexes) manifests in an increased propensity of activation to a

stimulus (Dietz and Sinkjaer 2007). The Pandyan et al (2005) definition of spasticity encompasses abnormal muscle activity as a result of either a disinhibited stretch reflex or cutaneous reflex. This means that the presentations of clonus, spasm and stretch reflex can all be included under this definition of spasticity.

1.1.4.1 Specific mechanisms underlying spasticity

The current study does not intend to investigate the underlying mechanisms of spasticity but, for completeness, it is worthwhile to briefly review the current understanding. There is uniform agreement that the specific mechanisms underlying spasticity are not fully understood (Nielsen et al 2007, Dietz and Sinkjaer 2007, Sheean 2008, Burke et al 2013 and Mottram et al 2014). One inherent difficulty with understanding the mechanisms involved is that there are clear differences in pathophysiology of spasticity between spinal and cerebral lesions (Nielsen et al 2007). Other problems that are yet to be resolved include normal circuitry in humans varies during rest and activity making the assessment of how spasticity interferes with functional movement difficult (Nielsen et al 2007, Dietz and Sinkjaer 2007), and, difficulty in measuring two mechanisms at the same time. Additionally, some studies have been confounded by including patients that may have developed contractures rather than muscle over activity (Burke et al 2013). Burke et al (2013) identify three major mechanisms involved in spasticity. Some of these mechanisms may be the natural neural re-organisation that occurs following injury with the intention of increasing excitation through the system.

1. Changes in the properties of the spinal motor neuron – primarily through persistent inward currents (sustained excitatory drive following minimal excitation) (Gorassini et al 2004)
2. Changes in the afferent input to the spinal motor neuron – three mechanisms suggested by Burke et al (2013); enhanced fusimotor drive via γ motor neuron activation, decreased pre-synaptic inhibition and homosynaptic depression (also termed post-activation depression).
3. Changes in reflex circuits that affect the motor neuron – at least eight reflex circuits have been identified.

(For further detail on the proposed mechanisms and evidence regarding whether these mechanisms are involved in post stroke spasticity please see Appendix 1)

The one mechanism whose presence appears uniformly accepted in the stroke population (although there is not consensus on the name) is homosynaptic / post-activation depression. This mechanism fits into Burke et al's (2003) 2nd mechanism (above) whereby afferent inputs to the spinal motor-neuron are altered.

Post-activation depression was initially described in the cat by Curtis and Eccles (1960) who identified that the size of Ia excitatory postsynaptic potentials (EPSPs) varied with frequency of stimulation. The depression of the Ia EPSPs with longer intervals occurred as a result of previous transmitter release (Grey et al 2008). However, once again the aetiology of this mechanism is not understood (Grey et al 2008). In humans, Aymard et al (2000) found that post activation depression correlated with the amount of spasticity in a population post stroke measured using the H-reflex.

1.1.5 Measurement of spasticity

Spasticity occurs as a result of damage to a part of the brain which disinhibits the spinal reflexes. Spasticity may be characterised as abnormal muscle over-activity which presents as a spasm, clonus or increased stretch reflex. With these essential points in mind, the measurement of spasticity can be clinically or physiologically based.

There are clinical scales that measure spasm (Penn Spasm Frequency scale) (Penn et al 1989), and scales that measure changes in clonus (Tardieu Scale) (Held & Pierrot-Deseilligny 1969). These scales are valid, reliable, provide ordinal level data and are appropriate for recording in both the clinical and research context. Measurement of the increased stretch reflex appears to have been less well developed in the clinical context.

Current clinical methods to assess spasticity include the Ashworth scale (Ashworth 1964) and Tardieu scale (Held & Pierrot-Deseilligny 1969). Both these scales are, to a greater or lesser extent, dependent on the development of stiffness and make the assumption that any change in stiffness is directly attributable to a change in neural activity. While these scales are recognised as being reliable, their reliance on stiffness means that their validity has repeatedly been brought into question (Nielsen and Sinkjaer 1996, Pandyan et al 1999, Patrick and Ada 2006, Fleuren et al 2010 and Naghdi 2014).

Since spasticity is characterised by abnormal muscle activity it seems necessary, and almost fundamental, to measure the activity of the muscle. The method of electromyography (EMG) provides a measure of muscle activity. It records the

electrical activity at the motor end plate where the nerve stimulates the muscle, thereby providing information as to how active the muscle is at any given time.

By providing an input to the sensory system it is possible to identify whether an abnormal output from a muscle occurs. This purely neurophysiological method involves electrical stimulation of the Ia afferent fibres (Burke 2016). This is termed the H-reflex and has been used to investigate various mechanisms including the presence or absence of post-activation depression (Grey et al 2008), the one uniformly recognised mechanism of spasticity in stroke population.

An alternative method involves passively stretching a “relaxed” joint and measuring any resulting muscle activity. The muscle of a person with no upper motor neuron lesion will remain inactive when a muscle is passively stretched through range (Thilmann et al 1991). In patients with severe stroke the muscle becomes overactive when passively stretched, and this increased output can be measured by using surface electrode EMG.

In conclusion, it is established that, with regard to spasticity measurement, there are validity issues identified with current clinical measurements and that carrying out H-reflex measurements are time-consuming and invasive. Accordingly, the method most likely to provide clinically relevant and useful data is to use surface EMG to measure the reflex activation of a relaxed muscle during an imposed passive stretch. This method has been used previously by Burke et al (1970), Ashby and Burke (1971), Powers et al (1989) and Pandyan et al (2001). A similar method has been used by Sorinola et al (2009) and identified that

measuring spasticity using EMG correlated well with muscle weakness and lack of active flexion but not with the Modified Ashworth Scale.

1.2 Contractures

Contractures can be characterised as a combination of increasing stiffness and loss of range of movement at a joint (O'Dwyer et al 1996, Pandyan et al 1997 and Harburn and Potter 1993). The incidence of contractures occurring at any of six joints at six months following a stroke was identified as 52% (Kwah et al 2012). When those of the 200 consecutively sampled patients who had had a very mild stroke (NIHSS<6) were removed from the data the incidence increased to 66% of stroke survivors (Kwah et al 2012) with arms affected much more than legs.

The research indicates that contractures are caused by a combination of two factors acting together following stroke: one factor is the relatively shortened positions that a joint naturally rests in; the other factor is spasticity (Pandyan 2003, Lannin 2007). Studies using animals have greatly enhanced the understanding of the causative nature of these two factors (joint held in a shortened position, and spasticity). The following section will review how contracture development and spasticity might interact and then discuss the evidence for the development in stroke survivors.

1.2.1 Contracture development – joint held in shortened position

In animal models, immobilising a muscle in a shortened position will lead to loss of range at the joint (Williams and Goldspink 1984, and Prado et al 2005). The loss of range is the result of a decrease in both the number of sarcomeres in

series and the length of the sarcomeres (Goldspink et al 1974) which directly results in decreased passive extensibility (Williams and Goldspink 1978). This was clearly shown by Tabary et al (1972) who identified a 40% loss of sarcomeres when a cat soleus muscle was examined after four weeks of immobilisation in a shortened position.

This research group went through an iterative protocol to establish whether other processes played a part in the loss of range in the animal model. Goldspink et al (1974) identified that there was no significant difference in loss of sarcomeres between a muscle that was denervated or innervated. This is an important finding because it suggests that loss of sarcomere is dependent primarily on the position that a muscle is immobilised in rather than the presence or not of paresis. This finding led to the hypothesis that connective tissue was involved in the development of contractures.

The perimysium which surrounds each muscle fascicule (Lieber 2009) is one of the three levels of connective tissue surrounding muscle but most important in contributing to passive stiffness (Williams and Goldspink 1984). The collagen forming the perimysium provides a structural support network for the neuro-vascular anatomy. Perimysium is present in greater quantities in postural muscles such as the soleus compared to the gastrocnemius (Purslow 2002). Purslow (2002) suggests that the variation in quantities might correspond with the increased vasculature required for postural slow twitch muscles compared to fast twitch muscles. The perimysium is made up of loose weaved “crimped” collagen fibres which have been shown to be able to alter and un-crimp as a muscle is lengthened (Purslow 1989). The body replaces collagen constantly and normal loading of muscles causes immature collagen to become aligned

along the direction of the muscle force. If the muscle does not move then this loading does not occur meaning that collagen becomes shortened (i.e. further crimped) and more collagen is laid down (Williams and Goldspink 1984). The end result is that the ability for the collagen to uncrimp may be lost and the capacity for the muscle to comply with a stretch may be limited (Williams and Goldspink 1984). Williams and Goldspink (1984) discovered that an increase in perimysial collagen deposition occurred within 48 hours of a muscle being maintained in a shortened position.

1.2.2 Contracture development – abnormal muscle over activity

The most important experiment in the context of this review was the protocol of De La Tour et al (1979). This study investigated the impact of increased muscle activity on the rate of sarcomere loss. This was achieved through a localised injection of tetanus toxin to the crural muscles (in the Guinea Pig). This study identified that there was a much greater and faster loss of sarcomeres when the joint was immobilised in a shortened position and the muscle was abnormally active than when the joint was immobilised in a shortened position without increased activity. A 45% loss of sarcomeres was seen in six days compared to the immobilised-only group (De La Tour et al 1979). Using a different method to achieve outcome of increased muscle activity Tabary et al (1981) identified that electrically stimulating the sciatic nerve caused a 25% loss in sarcomere numbers in just twelve hours (in the Guinea Pig). No changes in sarcomere length were identified in the shortened and immobilised group within this short timeframe (Tabary et al 1981). Using the same methodology as Tabary et al

(1981), Williams (1988) identified that there was a 47% loss of sarcomeres in seven days (in the rabbit).

Due to the need for invasive experimentation, all these studies have been in animal models. However, when placed in the clinical context, these findings explain why patients who have severe cerebral irritation can lose range in less than 24 hours.

1.2.3 Contracture development in the stroke population

Pandyan et al (2003) identified that loss of range developed within six to eight weeks following stroke in the wrist when there was no arm function immediately after the stroke. The important finding was that those who had some function, and who are therefore able to use the arm in functional tasks, were less likely to lose range of movement at a joint. Due to the study design the cause of contracture was not able to be identified, but, when combined with the work of Ada et al (2006), the evidence becomes stronger and clearer. Ada et al (2006) carried out a longitudinal study with eight assessment points over a year in 27 stroke patients beginning two weeks after stroke. The study objective was to investigate the evolution and interaction of spasticity, strength and contracture at the elbow flexors and their effects on function following stroke. They identified that the main factor causing contracture development over the first four months following stroke was spasticity and lack of strength became more significant between six and nine months (Ada et al 2006).

These two studies clarify that if function is lost, and no functional recovery occurs, then contracture development is highly likely and that spasticity is an important factor in early contracture development. Further studies have

reinforced these conclusions and provide evidence on the rate of contracture development in stroke survivors which will be reviewed in more detail now (Lannin et al 2007, Malhotra 2013).

1.2.4 Rate of contracture development in the stroke population

Lannin et al (2007) investigated splinting the wrist in 62 patients after a stroke and used 21 of these as a control. While the unaffected wrist had a mean maximum extension of 64.5° standard deviation (SD)=10.1 at the point of randomisation (mean 30 days post stroke SD=13.3) the affected wrist had already lost range with mean maximum extension of 56.2° (SD=15.0). At four-week follow up, mean extension was 47.3° (SD=16.9) and two weeks later was 39.4° (17.8). If we make two assumptions: 1, the affected wrist and unaffected wrist both had the same range of movement to begin with and 2, in the 30 days following the stroke there had been no loss of range to the unaffected wrist, then a simple calculation indicates that 25° of range were lost in the first ten weeks post stroke.

Using secondary data from the control group of a randomised controlled trial Malhotra et al (2011) divided the group in to those who did not recover function (measured as ability to pick up a two centimetre cube) and those who did recover function. The 25 patients without function lost a mean 25° in the first twelve weeks whereas those who recovered did not lose any range of movement. The Lannin et al (2007) and Malhotra et al (2011) studies both showed that those without recovery of function in the arm lost range at the wrist, confirming the earlier findings of Pandyan et al (2003) described in section 1.2.3. The Malhotra protocol also measured spasticity and they were able to identify

this in all 25 patients. Importantly, spasticity was also identified in the group of patients who recovered function (n=5) suggesting that spasticity was not the only contributing factor to the development of contracture.

1.2.5 Stiffness

Section 1.2 began by stating that contractures can be characterised as a combination of increasing stiffness and loss of range of movement at a joint. The majority of investigations presented so far have focussed on loss of range rather than the development of stiffness (with the exception of Williams and Goldspink (1984)). Studies investigating stiffness have varied in methodology within the stroke population.

In order to specifically quantify stiffness, some studies have measured the impedance to movement over a small mid-range of available movement (Given et al 1995, Kamper et al 2006). These protocols do not measure the increase in stiffness that can be identified towards the end of range of movement (i.e. torque versus angle displacement curve). In order to identify this end of range stiffness some studies have used a specified torque to measure the range of movement. Most studies that have used this method have employed a within subject standardisation technique (e.g. Moseley et al 1991, Moseley et al 2008 and Kwah et al 2012). This method does not quantify the stiffness but measures the loss of range at a joint as a result of increasing stiffness.

The method described by Pandyan et al (2001) allows for the resistance to passive movement to be measured throughout the passive range. Such a method allows stiffness to be quantitatively measured as the force required to move a joint through range (i.e. force over angle).

From the evidence, it can be concluded that if a person does not recover function in the arm following a stroke then it is likely that they will develop a contracture (Pandyan 2003, Lannin 2007 and Malhotra 2011). Spasticity following stroke appears to be a major factor causing contracture development over the first four months (Ada et al 2006). This evidence in the stroke population is consistent with that identified in animal studies investigating contracture development.

1.3 Current rehabilitation strategies in the management of spasticity and contractures

Following a stroke that results in loss of arm function, the general position that is taken up by the arm is one of flexion. In some cases, the patient may pick the paretic arm up and place it in front of them so that they can visualise where it is due to decreased sensation. In other cases, patients may be placed in a chair and the arm left in a flexed position. Because of paresis, the arm does not move and so the joint is maintained in prolonged immobilisation with the flexor muscles at a shortened length.

While this prolonged immobilisation in the general population might not be enough to cause contracture, the acceleratory effect of spasticity on the development of contractures (evidenced by Tabary et al 1981) places surviving stroke patients at a much higher risk of contracture development, as indicated by the work of Ada et al (2006) and Malhotra et al (2012). The following section will critically review current strategies for treating spasticity. This will include the separate work on contracture development in animals and the impact on treatment regimens for patients as well as the use of systemic and localised medications.

The current methods for treating spasticity have been promoted in scholarly articles, clinical guidelines and textbooks and involve a hierarchical stepped approach (Ward and KoKo 2001, Bogey et al 2004, Rekand 2010 and Australian Government – Department of Health 2015). In an educational supplement for Archives of Physical Medicine and Rehabilitation, Bogey et al (2004) present five steps;

1. Remove nociceptive input.
2. Begin therapeutic modalities.
3. Introduce oral anti-spasticity medications.
4. Give focal injections.
 - a. Motor neuro-muscular transmission blocks such as botulinum toxin and/or
 - b. Nerve blocks such as phenol.
5. Surgical procedures.
 - a. Intrathecal baclofen
 - b. Tendon release or lengthening
 - c. Tendon transfers.

These have been described in further more recent reviews of spasticity management by Rekand (2010) and Kheder and Nair (2012). Steps one and two are sometimes combined and termed physical modalities. This stepped approach means that only when the previous step does not help should the next step be attempted.

National guidelines are vague on any specific formalised approach beyond physical modalities. The National Institute of Clinical Excellence in the UK guidelines for stroke rehabilitation do not mention spasticity management (NICE, 2013). The Canadian Guidelines and the UK RCP Guidelines suggest if spasticity is generalised then a systemically acting drug should be used (specifically Tizanidine in the Canadian guidelines) but if a specific area is involved then botulinum toxin should be used (Lindsay et al 2010 and ISWP

2016). The US Guidelines merely list systemically and locally acting drugs that might be of benefit (Miller et al 2010). The Australian guidelines are the clearest regarding a formalised approach. The clinical criteria for using Botulinum Toxin in Australia are stated as “The treatment must be used as second line therapy when standard management has failed (e.g. physiotherapy and/or oral spasticity agents) or as an adjunct to physical therapy.” Further to these criteria is the additional criterion that “Treatment should not be initiated until 3 months post-stroke in patients who do not have established severe contracture.” (Australian Government – Department of Health 2015).

No investigations in to current practice of spasticity management have been made. An international survey has gathered data about the use of botulinum toxin for arm spasticity (Bakheit et al 2010). The treatment of 974 patients from 122 centres in 31 countries was included in this cross-sectional survey of current medical practice with 72% having had a stroke.

This survey identified that 75.4% of patients were being treated a year after the initial event and less than 15% of the group had been treated within six months of the event. Furthermore, the timing of treatment was found to closely correlate with the specified main objective: active function was the primary goal in those treated within three months; passive function was the main objective after the first three months

This survey may not be entirely representative of current practice, as it was sponsored by one manufacturer of botulinum toxin, meaning that responses may relate to those who use this particular drug. The survey results do not prove that

the hierarchical approach continues to be used, but it does show that treatment with focal injections appears to be delayed.

1.3.1 Physical treatments and modalities to treat spasticity

There are no well-investigated physical treatments that have decreased spasticity although attempts have included vibration (Murillo et al 2011), which appeared to decrease spasticity for a very short period, transcranial magnetic stimulation (Galvao et al 2014) and electrical stimulation (Dewald et al 1996).

While national guidelines for spasticity in the UK (Royal College of Physicians Guidelines) state that a stretching programme should be in place for all patients with spasticity (Turner-Stokes et al 2009) there is limited evidence that the programme is effective. Bovend'Eerd et al (2008) systematically reviewed the research to identify whether stretching specifically affected spasticity. From a potential 38 studies only ten were identified as adequately controlled trials. The stretching interventions varied in these ten trials from clinical practice (holding at end of range) to mechanical interventions. Another factor was the difficulty in distinguishing between treatments that purely held the joint at end of range and treatments that moved the joint through range passively and cyclically. Perhaps unsurprisingly, given these problems, no conclusions were able to be made. Bovend'Eerd et al (2008) did note that there was no evidence of an effect other than immediately after the stretch was stopped.

Given the current understanding of pathophysiology of spasticity it is perhaps not surprising that no effect was noted from stretching. However, the hypothesis that

stretching might help prevent contractures is based on a stronger pathophysiological foundation and supported by animal models.

1.3.1.1 Stretching to prevent contracture in the animal model

A brace of important experiments by Williams investigating the effect of intermittent stretching on the ankle and soleus muscle of mice provide evidence to support stretching. Williams (1988) maintained the ankle in full plantarflexion (with soleus in a shortened position) for ten days in two groups of mice, but provided an intermittent passive stretch to one of these groups. These two groups were compared to a third control group which had forced shortening of soleus. Using the intermittent stretch method (15 minutes every two days) prevented change in the proportion of connective tissue (collagen) to muscle tissue present (i.e. the constantly immobilised group had a significantly greater ($p<0.01$) proportion of connective tissue (4.9% standard error (SE)=0.4) but there was no difference between the control group (3.4% SE=0.1) and intermittent stretch group (3.5% SE=0.9)). Despite no significant increase in connective tissue being identified there was still a significant loss of serial sarcomeres in number and passive range of movement at the joint between the intermittent stretch group and control group. Additionally, the loss of sarcomeres in series between the constantly immobilised and intermittent stretch group was not significant despite the range of movement between the groups being significantly different.

In a progression of this experiment (Williams 1990) the control and constantly immobilised groups were treated using the same methodology as the Williams

(1988) study (again using the soleus of the mouse). The Williams (1990) experiment used four 'treatment groups' that received intermittent stretch on a daily basis for 15, 30, 60 or 120 minutes.

This study identified that half hourly stretching prevented loss of range at the joint and prevented loss of sarcomeres in series compared to the immobilised or 15 minutes per day stretching protocol. There was however a significant ($p < 0.05$) loss of muscle weight when compared to the control group (Williams 1990) suggesting some change in the muscle morphology.

The groups that received 60 or 120 minute daily stretches also showed no change in range of movement and maintained muscle weight. These two groups showed significantly ($p < 0.01$) greater numbers of sarcomeres in series (Williams 1990).

1.3.1.2 Stretching to prevent contracture in stroke survivors

Based on the findings from these two animal models by Williams (1988 & 1990) many human studies have used a thirty-minute stretching protocol. Horsley et al (2007) investigated whether daily stretching to the wrist lasting 30 minutes for four weeks was effective in preventing contractures in a group of stroke survivors. The patients were recruited and began independent stretching a mean 30 days after stroke and there was no significant evidence of benefit at either end of treatment stage or follow up. When the Horsley et al (2007) control group data is reviewed it was apparent that they did not develop contractures at the same rate as has been identified by Lannin et al (2007) or Malhotra et al

(2011). Although no measures of function were taken in the Horsley et al (2007) study, their inclusion criterion that people could only participate if they did not have enough strength to actively bring their wrist to neutral suggests that those included were less likely to develop contractures in the first place. This is based on the evidence that active movement appears to be preventative (Pandyan et al 2003).

Other studies such as de Jong et al (2006) and Ada et al (2005) have used prolonged stretches (two times 30 minutes/day, five days a week for five and four weeks respectively) to the shoulder with or without the elbow but not the wrist. These studies both identified statistically significant reductions of contractures in a single shoulder plane but not in all planes. Contracture development of internal rotation was slowed but not shoulder flexion by Ada et al (2005). This is different to de Jong et al (2006) where shoulder adduction contracture was slowed but not shoulder flexion, abduction, elbow extension or supination. One argument that might be made for lack of efficacy could be that the stretch was too short a duration (de Jong et al 2006) although there was also no measurement of muscle activity.

While the evidence does not support such interventions as being effective, there are further concerns. Such activities are time consuming (one hour during a day) and take focus away from the main objective of physiotherapy which is to provide high intensity, repetitive, task specific treatments with the aim of achieving functionally meaningful objectives within the whole process of rehabilitation (Langhorne et al 2011).

1.3.1.3 Splinting and neuro-muscular electrical stimulation to prevent contractures

The above studies employed a stretch and hold technique to provide a stretch and such methods are time-consuming. Other strategies to achieve prolonged stretches include splinting and casting. The Lannin et al (2007) paper that has already been introduced investigated whether splinting the wrist in end-range or mid-range extension for a mean nine hours could prevent contracture. This study found no evidence for splinting the wrist in either position. This is somewhat counterintuitive given the animal models but is in keeping with other studies of prolonged stretch in patients with varied acquired neurological injury (Lannin et al 2007). Indeed, methods to treat contracture in the stroke population are the same as those used in other populations at risk of developing contracture. A Cochrane Systematic Review of stretching to prevent contractures in all populations failed to identify any benefit (Katalinic et al 2010). Seven of the studies were stroke specific and meta-analysis of these trials showed the immediate effect of splinting provided a mean difference of 2.2 degrees (95%CI=-1.6 to 6.0 degrees). Three studies assessed the efficacy between one and seven days and the mean difference between the control and stretching group was 0.1 degree (95%CI=-3.6 to 3.4 degrees) in favour of the control (Katalinic et al 2011). Heterogeneity of the studies was high in both the immediate and short-term effects analyses which are likely to be the result of varying protocols.

Cyclical neuro-muscular (or transcutaneous) electrical stimulation to the antagonist muscle is another physical modality that can provide a cyclical stretch. Dewald et al (1996) investigated how electrical intensities below motor

threshold over the upper arm affected torque in a group of nine patients post stroke. This study identified that there was an immediate decrease in stiffness in seven patients but that this was not maintained (Dewald et al 1996). An example of a more physiologically based protocol for using cyclical electrical stimulation is that of Malhotra et al (2012). This study used cyclical transcutaneous electrical stimulation to the forearm extensors with the objective of passively moving the wrist from neutral to full extension and back with a three second hold at end of range. The study found the control group had lost 0.8° (SD=-1.1 to -0.5) per week during the entire study but the treatment group lost 0.3° (SD=-0.6 to 0.06) per week in the same time ($p=0.04$). While the low compliance rate (mean 28%) suggests other factors may have impacted these results other analyses tend to confirm that it was the electrical stimulation. Secondary analysis showed that there was a statistically significant difference in both extensor and grip strength, presumably as a result of the electrical stimulation protocol (Rosewilliam et al 2012). In a randomised controlled trial combining these two approaches (i.e. using electrical stimulation and splinting together) did not show a clear effect when assessed against splinting alone (Leung et al 2012).

It can be concluded from this review of the literature that there is a lack of evidence on the best physical method to prevent contracture development. This conclusion was also made in the NICE accredited UK Practice Guidelines on Splinting (Kilbride et al 2015).

There are other factors in deciding which treatment option may be more useful. While the static stretches provided by splinting and holding at end of range are purely passive, neuro-muscular electrical stimulation has been shown to produce additional benefits other than slowing contracture development. Electrical

stimulation to the arm results in muscle strengthening. Nascimento et al (2014) pooled data from 11 trials (n=359) of electrical stimulation to the arm following stroke and identified a standardised mean difference of 0.47 (95%CI 0.26 to 0.68) versus placebo. When the trials were grouped according to time post stroke those treated within six months following stroke had a greater effect size than those treated later (Nascimento et al 2014). This same systematic review identified data from four trials (n=198) that electrical stimulation provided improvements at an activity level beyond the intervention period effect size=0.39 (95%CI 0.09 to 0.66) (Nascimento et al 2014). A further positive effect of electrical stimulation is that it induces changes in the corticospinal pathways which might be important in motor re-learning (Golaszewski et al 2010).

Given the lack of evidence pertaining to prevention of contractures the additional benefits that can be provided by electrical stimulation make this the best overall option.

1.3.2 Systemically acting drugs

As part of this thesis a Cochrane systematic review was carried out “Pharmacological interventions other than botulinum toxin for spasticity after stroke” (Lindsay et al 2016). The objective was to assess if pharmacological interventions for spasticity are more effective than no intervention, normal practice, or control at improving function following stroke.

The Cochrane Stroke Group Trials Register (May 2016), the Cochrane Central Register of Controlled Trials (CENTRAL, 2016, Issue 5), MEDLINE, Embase, CINAHL, AMED (all to May 2016), and eight further databases and trial registers were searched. In an effort to identify further studies, hand searches of reference

lists and study authors and commercial companies were undertaken by the PhD candidate.

Randomised controlled trials (RCTs) that compared any systemically acting or locally acting drug versus placebo, control, or comparative drug with the aim of treating spasticity were included.

Two review authors (one being the PhD candidate) independently assessed the studies for inclusion and extracted the data. They assessed the included studies for both quality and risk of bias. The PhD candidate contacted study authors to request further information when necessary.

Seven RCTs with a total 403 participants were included. A high risk of bias in all but one RCT was identified. Two of the seven RCTs assessed a systemic drug versus placebo. An indirect measure of spasticity (160 participants) from these two studies were pooled but found no significant effect (odds ratio (OR) 1.66, 95% confidence interval (CI) 0.21 to 13.07; $I^2 = 85\%$) (Figure 1a). There was a significant risk of adverse events per participant occurring in the treatment group versus placebo group (risk ratio (RR) 1.65, 95% CI 1.12 to 2.42; 160 participants; $I^2 = 0\%$) (Figure 1b). Only one of these studies used a functional outcome measure, and there was no significant difference between groups.

Of the other five studies, two assessed a systemic drug versus another systemic drug, one assessed a systemic drug versus local drug, and the final two assessed a local drug versus another local drug.

This Cochrane review has shown that there is very little evidence to continue using oral anti-spasmodics in the treatment of spasticity and that there is a high prevalence of side effects.

Figure 1a: Meta-analysis of data from two studies that assessed a systemically acting drug against a placebo on spasticity

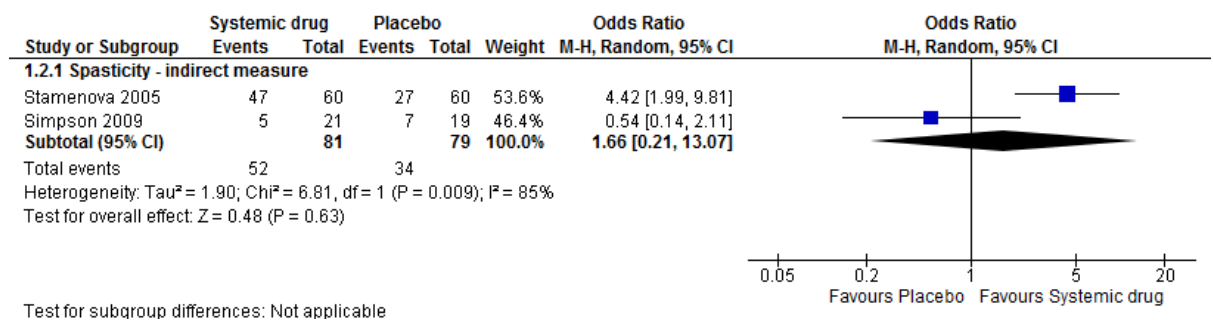
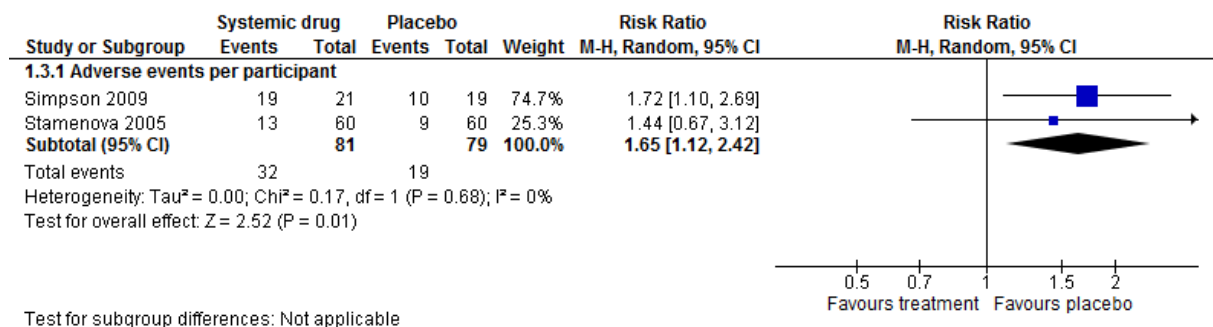


Figure 1b: Meta-analysis of data from two studies that assessed a systemically acting drug against a placebo on risk of adverse events



The side effect profiles of these drugs are reflected in a retrospective analysis of compliance with systemic drugs (Halpern et al. 2013). This study reviewed data from a US health insurance company to identify adherence as a percentage of the expected prescribed drug dose. Out of 285 stroke patients; 199 were on baclofen, 75 on tizanidine and eleven on dantrolene and adherence was 49% (SD35%), 44% (SD28%) and 52% (SD39%) respectively. The numbers of

people taking the prescribed medication was dichotomised at the 80% compliance point and all three drugs showed only around 30% of people adhering at this level. This study may have been negatively affected by the self-selective cohort. It should also be viewed in the knowledge that the study was funded by a botulinum toxin company that had potential benefit from negative results.

The other important issue raised in the Cochrane Review is the potential deleterious effect of oral systemic anti-spasmodics on motor learning. It is possible to relate all physiotherapy based treatments to neuroplasticity (whether peripherally or centrally). Neuroplastic changes must occur for any motor learning to occur (Langhorne et al 2011). Following a stroke or any neurological lesion the main objective of physiotherapists is to optimise these neuroplastic changes to achieve appropriate functional activities with the patient. For motor learning to occur in any human a downregulation of GABAergic inhibition is necessary. With this basic science knowledge, some therapeutic approaches have attempted to harness this in order to drive neuroplastic changes following stroke (e.g. Transcranial Magnetic Stimulation, transcranial direct-current stimulation).

What appears to have been overlooked is that the mechanism by which the most commonly used anti-spasmodic (baclofen) decreases spasticity is by upregulation of GABAergic inhibition.

Willerslev-Olsen et al (2011) investigated how baclofen and another GABAergic drug (diazepam) affected visual-motor learning in sixteen healthy young adults. Participants were randomly assigned to placebo, baclofen or diazepam for each

of three individual sessions separated by at least four weeks. A training session consisted of ten three minute sessions where a visual-motor task was practiced. This task involved dorsiflexion movements that corresponded to a screen cursor. The study used a seemingly overly complicated methodology which measured training-induced changes in motor evoked potentials and reductions in intramuscular coherence as well as the primary visual-motor tracking task.

The study is important as it is the only study that has investigated the impact of anti-spasticity medication on motor learning - which is the main basis for recovery of function post stroke (Langhorne et al 2011). The results showed that only the placebo group achieved significant within session improvements in the task ($p=0.05$) (Willerslev-Olsen et al 2011). These within session improvements were reflected in a significant difference ($p<0.05$) between placebo and participants who had received diazepam and baclofen at final session assessment. Willerslev-Olsen et al (2011) highlighted that the changes could be down to increased drowsiness in the drug groups rather than the result of decreased plasticity. The finding that motor evoked potentials threshold in the placebo group reduced in line with previous studies which did not occur in the drug groups suggests plastic changes had occurred.

Although the numbers in each group were small in this study, these findings correlate with the current understanding of how neuroplasticity occurs (Willerslev-Olsen et al 2011). The evidence suggests that this family of antispasticity drugs, that are based on up regulation of GABAergic inhibition, are detrimental to neuroplasticity. Neuroplasticity is the basis upon which neuro-rehabilitation science is based (Langhorne et al 2011) and so it can be concluded that the use of these drugs would not be appropriate in this Trial.

1.3.3 Botulinum Toxin

Botulinum toxin is an injectable drug that acts at the neuromuscular junction on the peripheral cholinergic nerve endings to inhibit the release of acetylcholine and so reduce muscle contraction (Barnes and Davis 2008). Many large, international multi-centre and well organised randomised controlled trials investigating botulinum toxin have been conducted that clearly indicate that the stiffness measured by Ashworth scale can be decreased (Wissel et al 2009). Rosales and Chua-Yap (2008) carried out meta-analysis of the efficacy in post stroke spasticity in five out of nine identified studies that presented Modified Ashworth change as improving by one point. This same study identified an odds ratio of 4.5 (2.79 to 7.25) in favour of botulinum toxin to reduce stiffness.

There are two major problems with the majority of botulinum toxin studies, and indeed all the studies in the included meta-analysis above. The first is the use of the Modified Ashworth Scale, while the second is that many trials exclude participants that had a stroke within the last six months.

The Modified Ashworth Scale is an indirect measure of spasticity which is dependent on the perception of stiffness (Fleuren et al 20010). This makes it impossible to state categorically that spasticity was treated as there is no evidence that the abnormal muscle activity was decreased. It also means that the very impairment that is ideally trying to be prevented (i.e. contracture development) has already started by the time the drug is initiated.

In regard to the second problem, the systematic review of botulinum toxin post stroke by Rosales and Chua-Yap (2008) identified nine randomised controlled trials that had presented Ashworth Scale data as mean and standard deviation.

These nine papers (Table 1.1) have been reviewed again to identify the specified time post stroke for inclusion to the trial and the mean time post stroke.

None of the studies explained why they had specified a minimum time from stroke. General comments that spasticity occurred late in the life time of stroke or that natural recovery should have completed by the time the patients were being investigated point to some of the rationale used. Moreover, in the seven studies that reported the actual mean time from stroke, it was greater than 24 months (2 years) with the exception of Hesse et al (1998) who had a six-month inclusion window of six to twelve months from stroke.

Table 1.1 – Mean time from stroke to injection in the nine papers included in Rosales and Chua-Yap (2008) systematic review

Author	Date	Inclusion criteria	Mean time from stroke (Months)
Bakheit et al	2000	> 3 months post stroke	Not reported
Bakheit et al	2001	> 3 months post stroke	Not reported
Brashear et al	2002	> 6 months post stroke	55.2 months *
Burbaud et al	1996	Spasticity > 3 months	Mean duration of spasticity 23.5 months (SD - 33.8) (range 3.5 to 120)
Childers et al	2004	>6 weeks post stroke	25.8 months (range 0.9 to 226.9)
Hesse et al	1998	6-12 months post stroke	7.45 months (range 6–11)
Pittock et al	2003	>3 months post stroke	33.6 months (SD – 37.2) *
Smith et al	2000	>1 year post stroke	24 months (SD – 19.2) *
Simpson et al	2009	>9 months post stroke	37 months (range 9 to 133)

*Data was only provided in groups (presented data was the group with smallest mean)

There are studies that have investigated botulinum toxin injection within the early stages post stroke (Cousins et al 2010, Rosales et al 2012, Hesse et al 2012, and Fietzek 2014). The first three investigated only the arm whereas the Fietzek paper investigated equinovarus.

An important point to make is that only Cousins et al (2010) measured the abnormal muscle activity indicative of spasticity. The other three depended on the development of clinically perceived stiffness to initiate treatment (using the (Modified) Ashworth scale) and used this as the primary outcome measure. A recent meta-analysis combined mean Ashworth scale data with the mean EMG data of these three studies and identified a standard mean difference (SMD) of -1.53 (95%CI: -2.47 to -0.58 $p=0.002$) (Rosales et al 2016). This result is problematic since combining nominal data with continuous data in a meta-analysis is not appropriate. Only continuous data should be presented using SMD summary statistics as per the 'Cochrane Review Handbook' (Higgins et al 2011). Discussion with the stroke editorial team of the Cochrane review group confirmed that data from the Ashworth scale should only be presented as odds ratio.

The Cousins et al (2010) study was able to prove that the abnormal muscle activity had been significantly decreased in the two treatment groups when compared to a placebo group. Additionally, in those patients with no arm function at randomisation there appeared to be a benefit in functional outcome at final follow-up in the treatment groups compared to the placebo group. The study was underpowered but these results are clearly worth investigating further. The method used by Cousins et al (2010) used measuring techniques similar to

those proposed for this study and provided a base reference that such an intervention was safe to use.

1.4 Conclusions

Patients who are admitted to hospital following a stroke will present with a wide variety of impairments including weakness of the muscles. If this muscle weakness is sufficiently severe, the patient will be unable to move the joint against gravity which will prevent recovery of function. People who do not recover function are at very high risk of developing contractures. Two catalysts to the development of contractures have been identified in animal experiments.

- Muscles that are experimentally made over-active develop contractures faster than those that do not have abnormal muscle activity.
- Muscles held in shortened positions develop contractures faster than those held in a neutral or a stretched position.

If these two known precipitators to the development of contractures in animals (and which are also present in some stroke survivors) could be removed then prevention or at least the slowing of contracture development may be achieved.

The first catalyst, abnormal muscle activity, occurs as a result of the brain losing its inhibitory effect at the spinal cord level following stroke. In stroke patients, the time at which this abnormal muscle activity develops following a stroke has not been identified. A study using a neurophysiological measure to determine when the abnormal muscle activity occurs is likely to provide further insight. This could also allow earlier treatment of spasticity to be initiated.

The second catalyst, when the muscle is maintained in a shortened position for prolonged durations, also presents in humans. The normal posture for the arm while resting in bed or in a chair at rest is one of flexion at the elbow, wrist and

fingers. In people who present with the most severe strokes, weakness will prevent them moving out of this position and so the person's muscle will be immobilised in a shortened position for prolonged periods.

Animal models suggest that prevention of contracture development might be achieved through stretching of the muscle for longer than 30 minutes, but previous studies using splinting have not shown this to be transferable to the population of stroke survivors. There is some evidence that contracture formation is reduced in stroke survivors receiving therapeutic neuromuscular electrical stimulation to the wrist extensors which provides a cyclical extension to the wrist and fingers.

It is possible that using botulinum toxin to the arm flexors (to reduce abnormal muscle activity) in conjunction with electrical stimulation to the wrist extensors (to passively move the wrist and fingers) might be effective in preventing or slowing down contracture development.

1.5 Research Questions

1. When does spasticity in the arm develop following stroke in patients who initially have no arm function, and can the Tardieu scale identify this?
2. Is it possible to prevent or delay contracture development by treating spasticity early with botulinum toxin?
3. Do patients who have spasticity treated early have better recovery of function compared to those who are not treated?
4. Does the sub-group of patients identified as least likely to recover function benefit from early treatment of spasticity more than others?

1.6 Secondary objectives

The secondary objectives of research question one were to:

- identify the proportion of participants who recovered function in the first 6 weeks (measured as scoring greater than 2 on the Grasp sub-section of the Action Research Arm Test (ARAT)).
- identify if there were any variations in EMG pattern activity and if these are the same at the elbow and wrist.
- identify any variations between the Tardieu scale (Held & Pierrot-Deseilligny 1969) and the abnormal muscle activity identified on EMG.

A secondary objective of research question two was to:

- identify whether there was a significant difference in spasticity between the group treated with botulinum toxin and the placebo group and how long this lasted.

There were no secondary objectives for research question three.

Secondary objectives of research question four were to:

- identify whether the clinical measures used to predict recovery of arm function at baseline were able to detect two significantly different groups at six-month follow-up.
- identify whether there was a significant difference in spasticity in treatment and placebo arms of the sub-group and how long this lasted.
- identify whether those patients in the sub-group who have spasticity treated early have better recovery of function compared to those who are not treated?

2. Method

2.1. Trial design

Clinical studies can be divided in to two forms; observational (i.e. one where the researcher does not interfere) and interventional (i.e. one where the researcher alters a particular variable or variables) (Bland 2015). To allow the investigation of all four research questions within the framework of a single study an initial screening phase (observational study) was followed by a single centre randomised controlled trial (interventional study).

Using this combined methodology ‘time of onset’ was answered by analysing the screening phase data. The other research questions were answered through analysis of between group variations in the placebo and treatment groups. In order to answer a particular question, specific outcome measurements were analysed, or in the case of question four, a sub-group of the participating participants were analysed.

In order to prevent duplicating the protocol methods four times, the protocol relating to the screening phase will be presented first (Section 2.7). This will answer research question one in the form of a prospective longitudinal study.

Subsequently the protocol relating to the randomised controlled trial is presented (Sections 2.8 to 2.10). This will answer research questions two to four. All participants who were involved in the randomised controlled trial phase had gone through the screening phase protocol prior to randomisation.

The outcome measures taken at each time point and the process involved in collecting the measurements are described. Finally, the planned data analysis is described.

2.2. Trial registration, funding and sponsorship

The trial was funded by the National Institute of Health Research – Research for Patient Benefit programme (PB-PG-0808-16319). An unrestricted grant from Allergan Ltd. provided funding to purchase equipment and they also provided the clinical trial drug.

The study was approved by a local Research Ethics Committee (Greater Manchester South - 10/H1003/111) (Appendix 2). No drug was requested until written research ethics committee authorisation had been received. The Medicines and Healthcare Regulatory Authority (MHRA) acting as the national legal authority for the European Union provided legal authorisation for the clinical trial to commence (EudraCT number: 2010-021257-39) (Appendix 3). The protocol has been published (Lindsay et al 2014) and also registered with clinicaltrials.gov (NCT01882556).

Sandwell and West Birmingham NHS Trust and Keele University were co-sponsors for this trial and as such an agreement between both sponsors was signed to ensure all Sponsor roles were covered. Regulatory approvals were checked by both co-sponsors prior to the trial beginning. Approval was received from the Research and Development department of SWBH NHS Trust on behalf of the sponsors to approve trial commencement (Appendix 4).

2.3. Sample Size Calculations

Preliminary sample size calculations were identified using data from the study by Cousins et al (2010). With an effect size of 0.5 (using the Action Research Arm Test (ARAT)) and at 80% power and a 0.05 significance level, 126 patients were calculated to be required. With an effect size of 0.6 and at 80% power (0.05) significance level, 88 patients were calculated to be required. This study aimed to recruit 120 patients to a randomised controlled trial in 2 years.

2.4. Study setting and eligibility

All stroke patients admitted to Sandwell and West Birmingham National Health Service Trust (SWBH NHS Trust) were eligible to participate if they satisfied the study inclusion and exclusion criteria. The aim was to recruit 150 patients in total. Potential participants were recruited from the clinical case load of clinicians caring for them.

2.4.1. Eligibility criteria

Patients had to fulfil specific inclusion and exclusion criteria to be eligible to participate in the screening phase and further inclusion criteria to participate in the randomised controlled trial. In order to prevent recruitment of people who would not be able progress to the randomisation phase the same exclusion criteria were used to identify eligibility for participation in the screening phase. The exclusion criteria therefore reflect contraindications to the trial drug.

2.4.1.1. Inclusion criteria (Screening Phase)

- Over 18 years of age
- Patients admitted to hospital with a diagnosis of stroke (between day 1 and day 42 after onset) due to a primary cerebral haemorrhage/infarction, subarachnoid haemorrhage producing an upper motor syndrome affecting one body side which results in a hemiparesis
- Capable of providing informed consent directly or indirectly, or, assent obtainable from next of kin
- No useful arm function (i.e. less than or equal to 2 on the grasp subsection of the Action Research Arm Test) at the stroke onset (Lyle 1981)

2.4.1.2. Inclusion criteria for randomisation treatment phase

- Evidence of upper limb spasticity demonstrated by surface EMG activity (Pandyan et al 2001)

2.4.1.3. Exclusion criteria

- Significant musculoskeletal conditions that affected upper limb function prior to the stroke
- Unconscious or moribund during the screening period, or scheduled to have palliative care only
- Recovery of useful arm function (a score of 3 or more in the grasp section of the Action Research Arm Test) prior to injections (Lyle 1981)

- Patients with contraindications to electrical stimulation including active implants (e.g. cardiac assist devices), metal implants at site of stimulation, scar tissue/cancerous tissue at site of stimulation, uncontrolled epilepsy, deep vein thrombosis in limb / muscle being stimulated
- Previous spasticity due to multiple sclerosis, spinal cord injury or other neurological disorder
- Patients with a known hypersensitivity to any botulinum toxin or to any of the excipients of Botox® (i.e. Human serum albumin)
- Patients with myasthenia gravis or Eaton Lambert Syndrome or other neuromuscular junction or myopathic disorder
- Patients with infection at the proposed injection site(s)
- Patients who were pregnant or may become pregnant at the time of the proposed injections and for the duration of the study
- Current treatment with any anti-spasticity agent or previous injection with botulinum toxin

2.4.2. Withdrawal of patients

Patients were able to withdraw from the study at any stage: in the screening phase prior to injection of Botox® or placebo: after injection either through personal choice (or at the request of their next of kin) or for a pre-determined list of clinical reasons. Patients who withdrew from the study following injection were included in the intention to treat analysis unless they requested that all their data be removed from analysis.

2.5. Recruitment

A screening log was used to track the number of patients who were approached to participate. If the patient was ineligible or refused to participate, the reason was recorded in the log if they chose to provide this information. Any patient who indicated willingness to consider study participation was provided with all the study details and a patient information sheet to review (See Appendix 5). Assessments were only performed after valid consent was obtained and a study code was allocated. A demographic pro-forma was completed after consent to gain all the demographic data necessary for the clinical trial (See Appendix 6) and acted as a secondary verification of eligibility to recruitment.

These included:

- Past and presenting relevant medical history.
- Pre-admission Barthel Index based on discussion with patient and carers (Collin et al (1988).
- Features of the stroke (National Institute of Health Stroke Severity (NIHSS) scale (Brott et al 1989). The NIHSS scale was completed by a consultant stroke physician or neurologist within 24 hours of a stroke and prior to any thrombolysis treatment – in cases where there was a significant deterioration in NIHSS post thrombolysis then the more severe NIHSS at 24 hours was used.
- Classification of stroke using the Oxford community stroke project classification system (Bamford et al 1991).
- Any relevant complications of stroke.

2.6. Consent

For each trial patient, written valid consent was obtained prior to any protocol related activities. The research therapist explained verbally and provided the information in writing regarding the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient and/or carers were aware of the potential risks, inconveniences, or adverse events that might occur. The patient and/or carers were informed that the patient may withdraw from the study at any time. They received all information that is required by local regulations and ICH GCP guidelines (NIHR 2010). See Appendix 7 which is an example of the consent sheet used that was accepted by the Research Ethics Committee.

In cases where the patient was deemed to lack capacity the next of kin was able to provide consent for the patient to participate in the study.

2.7. Screening Assessments

From the date of consent, patients who were enrolled in the study were monitored for a period of up to six weeks from stroke onset by the research therapist (the candidate). Monitoring was normally carried out on a Monday, Wednesday and Friday. The frequency was increased to daily if clinically indicated (i.e. there was apparent developing spasticity or functional recovery on one day but confirmation to establish certainty was required the next day).

For monitoring purposes, the study therapist conducted two simple bedside tests which took a maximum of ten minutes.

- Function - The grasp subsection of the Action Research Arm Test (ARAT) (Minimum score=0 and maximum score=3) (Lyle 1981) to assess for functional recovery, using the protocol by Yozbatiran et al (2008).
- Spasticity - The surface EMG response of the wrist and elbow flexors to an externally imposed perturbation (Pandyan et al 2001). Presence of spasticity was a related increase in muscle activity observed on EMG during a passive movement.

To measure the grasp subsection of the ARAT a 2.5cm cube was placed on a table in front of the patient and they were asked to pick it up and place it on a shelf 37cm above the table (Lyle 1981). If they were unable to achieve this task they scored zero or only partly able to achieve this task then they scored one and so screening continued. If they scored greater than two (i.e. they were able to place it on the cube on the shelf) on this task then they were deemed to have recovered function.

To measure spasticity, non-invasive EMG electrodes (SX230 active surface electrodes for bipolar recording of muscle activity, Biometrics Ltd, UK) were placed on the elbow flexors and wrist flexors (See figure 2.1 for equipment). The joint was moved from full flexion to extension a maximum of six times from a position of rest. Patient positioning was documented as sitting or half lying and these tests took a maximum of ten minutes. (A more in-depth explanation of this assessment process is provided in Section 2.11.1). Presence of spasticity was a movement related increase in muscle activity observed on EMG during a passive

movement (Pandyan et al 2001). If no abnormal muscle activity was observed on EMG during the passive movement then screening continued.

All patients who completed the screening phase could be classified in to one of four groups. They either developed: spasticity with functional recovery, no spasticity with functional recovery, no spasticity with no functional recovery or spasticity with no functional recovery.

Figure 2.1 – Equipment used during screening assessment and trial



MWX8 (Biometrics Ltd, UK)

1. MyoMeter M550, (Biometrics Ltd, UK)
2. SX230 surface electrodes, (Biometrics Ltd, UK)
3. SG 110 electrogoniometer, (Biometrics Ltd, UK)
4. DataLOG

If a participant scored greater than two on the grasp sub-section of the ARAT then they were deemed to have recovered function and, irrespective of their spasticity, the screening phase stopped. They had baseline assessment measurements taken and were then followed up at three and six months.

If a patient did not develop spasticity in the first 42 days following stroke then baseline measures were taken on day 42 and they were followed up at three months and six months following stroke.

If a participant satisfied the inclusion criteria for the randomised control trial (i.e. developed spasticity with no functional recovery) they immediately progressed to have the baseline assessment measurements taken and were randomised to either active treatment or placebo.

2.8. Randomisation

Randomisation was carried out by a statistician at Keele University using computer generated random permuted blocks in a pseudorandom sequence. They were stored in a sealed envelope and held securely at SWBH NHS Trust in the Pharmacy Department. The research therapist contacted pharmacy and the research pharmacist was asked to randomise the patient (by opening the next sealed opaque envelope in the randomisation pack). The pharmacist gave the research therapist the study identification number but did not disclose the allocated treatment to the injecting clinician or the research therapist. Please see Appendix 8 for the delegation log.

2.9. Interventions

2.9.1. Details of treatment groups

There were two treatment groups: the treatment group received injections of the investigational medicinal product (BOTOX®/ onabotulinumtoxinA) and the placebo group received injections of 0.9% sodium chloride solution. The investigational medicinal product was supplied to the site by Allergan Ltd. All participants received standardised physiotherapy in addition to their normal routine physiotherapy and occupational therapy.

2.9.2. Investigational Medicinal Product

There are three preparations of botulinum toxin type A available in the United Kingdom. Although the active substance in all three preparations is the same due to production processes there is variation in the dose/units. Allergan manufacture Botox® (onabotulinumtoxinA), Ipsen manufacture Dysport® (abobotulinumtoxinA) and Merz manufacture Xeomin® (incobotulinumtoxinA). The active substance is a neurotoxin obtained from cultures of *Clostridium botulinum* (gram-positive anaerobic bacteria) and works by temporarily inhibiting the release of acetylcholine at the pre-synaptic nerve endings of the motor end plate, thus temporarily inhibiting muscle force production (Black and Dolly 1986). In this study Botox® was used as the injecting team had the most experience of using this product.

2.9.3. Dispensing investigational medicinal product

The research therapist identified which muscles required injection and completed the Study Medicines Request/Prescription Form (See Appendix 9). The form was then given to one of the medically qualified Clinical Investigators who would sign the form only after they were satisfied that there were no contra-indications or cautions why the patient could not receive the study medications and all exclusion and inclusion criteria had been checked. This form was then sent to pharmacy. Copies of this were held in the patient's medical notes and the patient's Trial folder.

The trial pharmacist dispensed either one or two vials of Botox®, and one 5ml ampoule of 0.9% Sodium Chloride solution (Treatment group) or only the one

5ml ampoule of 0.9% Sodium Chloride solution (Placebo group) depending on the randomisation. The agents dispensed were listed in a Dispensing Pro-forma. This form was held securely in the pharmacy with the randomisation envelopes in the Trial Folder. Had unblinding been necessary on clinical grounds then this form could be accessed 24 hours per day by the on-call pharmacist. A standard operating procedure for emergency unblinding of a patient who has been randomised (e.g. in the event of a serious adverse event) was written (See Appendix 10).

The dispensed medicines were passed to an independent clinician in a sealed opaque container. These clinicians (either a physiotherapist or nurse) had to have completed training in reconstitution of Botulinum Toxin and their competencies recorded in the trial folder. Because they were unblinded to the treatment group, they were not involved in the day to day rehabilitation therapy of the patient being injected.

2.9.4. Reconstitution and masking

The syringe was filled by the independent clinician with either the reconstituted botulinum toxin in 0.9% sodium chloride (NaCl) solution or NaCl solution alone if the patient is randomised to placebo treatment to the exact requirements as documented in the study medication request/prescription form filled out by the research therapist. In particular, care was taken to ensure when the toxin or saline was drawn up into the syringe, that the syringes always contained exactly 2.0ml of solution. This was to avoid the risk of any difference in appearance of the syringe containing active toxin or saline alone which might have allowed unblinding to occur.

A second trained clinician unrelated to the trial was (a pharmacist or pharmacy assistant) in attendance throughout this activity and signed, in duplicate, the reconstitution pro-forma to confirm that the syringe was filled with the dispensed medicinal product.

Once the syringe was ready it was placed in a mobile sharps tray with attached sharps bin and given to the injecting clinician outside the preparation room with the signed reconstitution pro-forma for review by the injecting clinician.

The research pharmacist or pharmacy assistant then took the reconstitution pro-forma and the used vials/ampoules back to pharmacy in the container. One copy of the reconstitution pro-forma was filed by pharmacy in the Trial folder. The second copy of the reconstitution pro-forma was filed in the patient's notes with the drug chart which was signed by the injecting clinician once the medication has been administered.

This procedure ensured that the independent reconstituting clinician and certifying pharmacy colleague were the only persons who knew whether a patient received a treatment or placebo injection. None were involved in any other part of the study.

2.9.5. Injections

The patient received the intra muscular injection of either BOTOX® or placebo within 48 hours of the baseline assessment. Because the injector was blinded even if the patient was allocated to receive placebo, the volume in the vial(s) and location of the injections was the same as if the patient were receiving BOTOX®.

2.9.5.1. Total dose and injection sites

All eligible patients randomised to receive intra muscular injections of Botox® or 0.9% Sodium Chloride solution were injected in six muscles of the affected arm in predetermined doses. Muscles injected were flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), flexor carpi ulnaris (FCU), flexor carpi radialis (FCR), biceps and brachialis. The volume to be injected was calculated on the number of units per ml that the injection solution would contain if it contained Botox®. Table 2.1 shows the Botox® units administered to each muscle. In patients with a substantial lack or excess of muscle bulk or where there was excessive muscle activity leading to clonus, the research therapist adjusted the concentration of dosage.

Table 2.1 – Muscles and dosage of Botox® Units to be injected

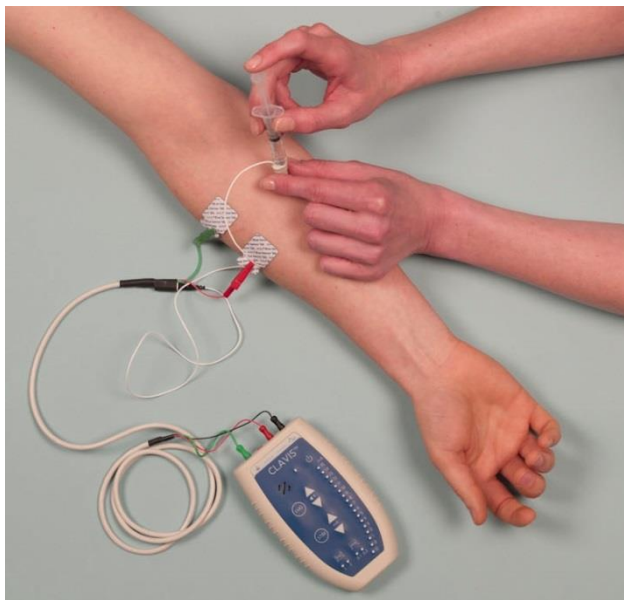
Muscle	Units (-25%)	Main Dose units	Units (+25%)
Biceps	30	40	50
Brachialis	30	40	50
Flexor digitorum superficialis	20	25	30
Flexor digitorum profundus	20	25	30
Flexor carpi ulnaris	10	15	20
Flexor carpi radialis	10	15	20

Maximum dose / person: 200 Botox® Units

2.9.5.2. Method of administration

Reconstituted Botox® and placebo was injected using a sterile 27- gauge electrical stimulation needle for muscles. Localisation of the involved muscles were determined clinically by superficial anatomical landmarks and using electrical stimulation techniques using the techniques presented by Harding et al (2013) (Please see figure 2.2 which shows the electrical stimulation equipment being used to identify flexor digitorum superficialis from Harding et al (2013)). Where localisation of the muscles for injection proved to be difficult using surface anatomy and EMG then ultrasound was employed to guide the injection procedure and check accuracy of placement of the needle in the specified muscles.

Figure 2.2 – Injection placement in to flexor digitorum superficialis using electrical stimulation (with permission from Harding et al (2013))



2.9.5.3. Standardised physiotherapy treatment

The current Royal College of Physicians recommendation is that injections of botulinum toxin should be followed by a period of targeted rehabilitation therapy (Turner-Stokes 2009), although there is little guidance on what the content or duration of this therapy should be.

This study standardised part of the patients' overall physiotherapy by providing neuromuscular electrical stimulation to the forearm extensors. On the day following the injections the research therapist reviewed the arm for any adverse events related to the injection and provided an electrical stimulator.

The electrical stimulator (Nature's Gate Ltd) provided the forearm extensors with an electrical stimulation to achieve wrist and finger extension. The stimulation parameters were standardised to have a pulse-width of 400 microseconds and frequency of stimulation of 50Hz. The stimulation was provided for 30 seconds inclusive of a ramp up time of 5 seconds and ramp down time of 5 seconds. A 30 second rest was then provided (Pandyan et al 1997). The machine was set to provide a stimulation intensity that produced a contraction and extended the wrist and fingers against gravity without evoking pain and the treatment lasted 30 minutes. The patient received the electrical stimulation three times a day for the first three months after the injection. Whilst in hospital a physiotherapy assistant provided the electrical stimulation five days a week and the patient and carer were taught how to provide the stimulation independently. On discharge the patient and or carer were asked to continue to provide the treatment three times a day until the three-month assessment. A diary to tick when the treatment was carried out was completed to assess compliance of this treatment. Because this treatment was primarily aimed at providing a passive movement to the wrist and

finger joints, patients who subsequently recovered a grade of three on the MRC scale discontinued the electrical stimulation in order to concentrate on more appropriate active functional task training as prescribed by the treating physiotherapist. All other physiotherapy and occupational therapy was provided as appropriate by clinicians not directly involved in the study. Content and quantity of therapy was monitored using a bespoke tick sheet documentation developed with the specific team.

2.10. Outcome Measures

The standard format to describe the outcomes is to state the primary outcome followed by any secondary outcomes. Because this study reports a number of research questions, the primary outcome measures vary depending on the question. The research therapist carried out assessments at baseline (prior to randomisation), two, four and six weeks after the injections, three months after the injections and then at six months following stroke. This section reports all the outcome measures taken at each time point from baseline through to final follow-up assessment in a chronological format. See table 2.2.

2.10.1. Baseline assessments

Once patients had either: developed spasticity without recovery of arm function (i.e. fulfilled the inclusion criteria for entry to the randomised controlled trial and prior to randomisation), recovered arm function, or reached the end of the six-week screening phase baseline measurements were taken. Baseline assessments were:

- Arm function (Action Research Arm Test - ARAT) (Lyle 1981) using the protocol by Yozabatiran et al (2008) – minimum score=0 and maximum score = 57.
- Spasticity in the wrist and elbow flexor muscles measured using protocol by Pandyan et al (2001) and the Tardieu Scale (Held & Pierrot-Deseilligny 1969 and Morris 2002)

- Stiffness – the resistance encountered during a slow passive extension of the elbow and wrist measured using the protocol by Pandyan et al (2001) and Cousins et al (2010)
- Passive range of movement – the maximum passive extension achieved during a slow passive extension of the elbow and wrist measured using the protocol by Pandyan et al (2001) and Cousins et al (2010)
- Pain - measured using a visual analogue scale from 0-100 (Gallagher et al 2001).
- Muscle function
 - Isometric strength at midrange of movement using a dynamometer for elbow flexion, elbow extension, wrist flexion and wrist extension. (MyoMeter M550, Biometrics Ltd, UK) (Cousins et al 2010).
 - Fatigue - Derived from the above measurement of isometric strength by estimating the time taken for the force generation to drop to 70% of the maximum isometric strength measurement).
 - Grip strength was measured using a grip dynamometer (Precision Dynamometer G200, Biometrics Ltd, UK).
- A measure of activities of daily living was carried out - Barthel Index Score described by Collin et al (1988) (minimum score=0 and maximum score = 20).

Please see Appendix 11 for the Baseline Assessment Pro-forma used.

2.10.2. Assessments at two, four and six weeks following injection

- Grasp subsection of the ARAT
- Spasticity in the wrist and elbow flexor muscles
- Stiffness
- Passive range of movement

2.10.3. Midpoint assessment

At the midpoint assessment - which was standardised as three months post injection ± 7 days - all the baseline measurements were repeated and three additional measurements were taken. These are:

- Quality of life – measured using the EQ5D-5L (Herdman et al 2011)
- Carer burden – measured using the Caregiver Strain Index (Robinson 1983)
- Patient satisfaction of how their arm was recovering was measured using a Likert scale (0 – 5)

2.10.4. Endpoint assessment

At the endpoint assessment - which was standardised as six months following stroke ± 7 days - all measurements taken at the midpoint assessment were reassessed at this point with the addition of one further assessment:

- Level of dependence -- As measured using the Modified Rankin Scale.
Minimum score = 0 and maximum score = 6 (van Swieten et al 1988)

Table 2.2 (on page 62) indicate the occasions and approximate durations of contact between patient and research therapist. The time durations for the ARAT and isometric testing were dependent on the participant's capability to attempt and/or complete these activities.

Table 2.2 – Activities involved in the study with approximate duration of activity at each time-point

	Person	Approximate time	Stroke diagnosis	Pre-study - consent	Screening phase (repeated Mon, Wed, Fri) for up to 6 weeks	Baseline	Randomisation/ injection	Week 2 assessment	Week 4 assessment	Week 6 assessment	Midpoint assessment	Final assessment
Screened	CL	5 mins	X									
Provision of trial information	CL	10-20 mins		X								
Consent	CL	10 mins		X								
Grasp sub-section of ARAT	CL	2 mins			X			●	●	●		
EMG - Spasticity	CL	10 mins			X	X		●	●	●	X	X
ARAT	CL	1 to 20mins				X					X	X
Stiffness	CL	With EMG				X		●	●	●	X	X
PROM	CL	With EMG				X		●	●	●	X	X
Pain	CL	2 mins				X					X	X
Isometric strength	CL	1-30 mins				X					X	X
Barthel Index	CL	5 mins				X					X	X
Randomisation	CL						●					
Injection	CL	20 mins					●					
EQ5D	CL	10 mins									X	X
CGSI	CL	10 mins									X	X
Patient satisf	CL	2 mins									X	X
Modified Rankin	CL	3 mins										X

X – Indicates activities that all recruited patients participated in.

● – Indicates activities that only those involved in the randomised controlled trial participated in.

2.11. Data collection

The following section describes the process for collecting data for all the outcome measures in greater detail. In order to allow the reader to understand the process that the patient went through this section is presented in the order that measurements were carried out at the six-month (final) assessment rather than in the order presented in section 2.10.

2.11.1. Spasticity, stiffness and passive range of movement

Data for spasticity, stiffness, and passive range of movement were all measured in the same procedure which has previously been used by Cousins et al (2010). The patient was positioned in either supported sitting or half lying. A flexible electrogoniometer (SG 110 electrogoniometer, Biometrics Ltd, UK) was placed on the lateral border across the wrist or elbow depending on the joint being tested. Surface EMG electrodes (SX230 active surface electrodes for bipolar recording of muscle activity, Biometrics Ltd, UK) were positioned in accordance with European recommended sites (SENIAM) for the biceps and long head of triceps (Hermens et al 1999). There are no such recommendations for placement of electrodes on the forearm. A standardised format to ensure uniform placement at the forearm was used. To place the electrode on the forearm flexor muscles a line between the medial epicondyle of the humerus and medial border of the biceps tendon was visualised. From the mid-point of this line the electrodes were attached approximately one-third of the length of the forearm in line with the radial styloid. To place the electrode on the forearm extensors the arm was placed in full pronation and the electrode is placed one-third of the distance between the lateral epicondyle of the humerus and the radial styloid.

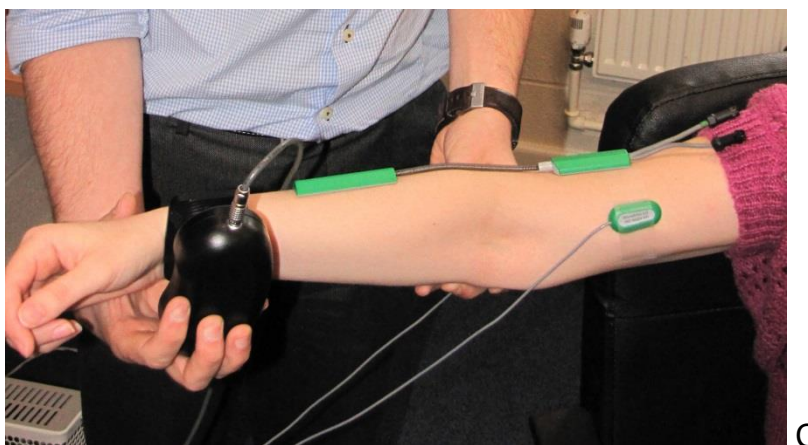
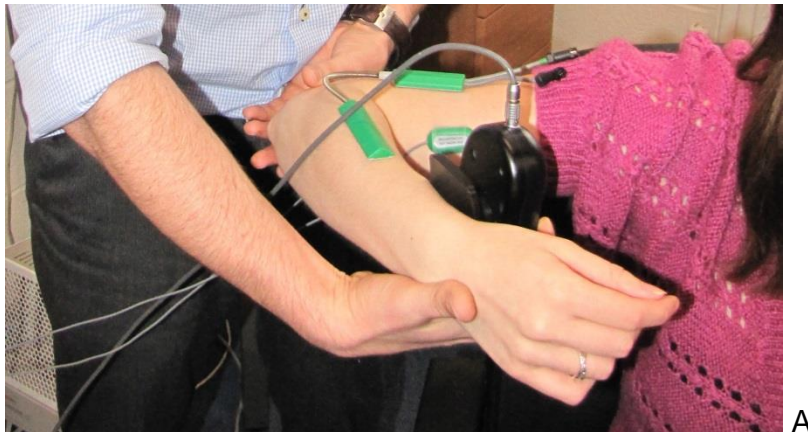
Using a hand-held force transducer, (MyoMeter M550, Biometrics Ltd, UK) the research therapist then moved the joint from full flexion to full extension, using two manually controlled velocities (i.e. high velocity and low velocity), a maximum of six times. The assessor documented the passive range of movement during the low velocity movement as well as the angle at which any catch of the muscle was perceived during the high velocity movement to allow a spasticity angle to be calculated (described first by Tardieu et al 1954). The assessor also graded the quality of muscle reaction during the high velocity movement using the Tardieu Scale (Held and Pierrot-Deseilligny 1969) and first described in English by Boyd and Graham (1999).

1. No resistance throughout the course of the passive movement
2. Slight resistance throughout the course of passive movement, no clear 'catch' at a precise angle
3. Clear catch at a precise angle, interrupting the passive movement, followed by release
4. Fatiguable clonus (c 10 s when maintaining the pressure) appearing at a precise angle
5. Unfatiguable clonus (> 10 s when maintaining the pressure) at a precise angle

The EMG electrodes, electrogoniometer and, myometer transducers were sampled at 1000Hz using a MWX8 DataLOG (Biometrics Ltd, UK.) and stored for post hoc analysis. The data was later extracted from the data files using a customised programme (Mathcad 15, PTC, USA.). The current method is very similar to the method described by Burke et al (1970) and Ashby and Burke(1971) but has not been investigated for reliability.

(See figure 2.3 for a pictorial presentation of the elbow being moved from full flexion to full extension using the equipment)

Figure 2.3 – Method employed to assess for spasticity at the elbow - (A) full flexion phase, (B) mid-position phase and (C) full extension phase.



2.11.2. Pain

Pain was assessed according to how the patient was able to communicate.

Patients who were able to communicate were asked whether they had any pain in the paretic arm at rest and any pain on movement of the arm. They were then asked to indicate the severity on a visual analogue scale from 0 being no pain at all to 100 being the worst pain imaginable (Gallagher et al 2001). This scale was recommended by an international consensus statement on the assessment of pain in older patients (Hadjistavropoulos et al 2007). In patients who had communication impairments any evidence of pain during the passive movements described above such as grimacing or rubbing the arm afterwards were used to indicate that the patient had pain so that in these patients a dichotomous variable was identified.

2.11.3. Barthel ADL Index

The patient's main carer (and in most cases the patient themselves) was asked how much assistance they required in ten specific tasks (feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility and stairs) and a number assigned according to their response. The original Barthel Index scored from 0-100 (Mahoney and Barthel 1965) however a change in the format to provide a score of 0-20 was tested for reliability by Collin et al (1988). A score of 0 indicates that they are fully dependent on others and a score of 20 indicates that they are fully independent.

With the exception of the variation in numbers, the original Barthel Index and Collin et al (1988) versions are identical in all other ways meaning that the psychometrics are equivalent (Quinn et al 2011). Wade and Collin (1988)

recommended that the Barthel Index be adopted as the standard measure of physical disability and that future indices should be compared against this. Quinn et al (2011) reaffirm this statement for studies in stroke. Wade and Collin (1988) advised “*temptation to use variations on the standard Barthel Index should be resisted.*” Unfortunately, this advice was not taken. Since then there have been a number of modifications to the original index which will have altered the psychometrics, Shah et al (1989) attempted to increase sensitivity by adding sub-units, Schönle (1995) extended the Barthel Index adding categories for tracheostomy and ventilation to reflect areas in early neuro-rehabilitation while others have truncated the original Barthel Index (Hobart and Thompson 2001). As a result of this proliferation in heterogeneous Barthel Indices Quinn et al (2011) repeated the advice made by Wade and Collins (1988) and urged a consistent single version of the Barthel Index be adopted for stroke trials. While Quinn et al (2011) suggest the original Mahoney and Barthel (1965) the fact that there are no psychometric differences between the original and Collin et al (1988) version make both acceptable.

The 20-point version has been used at the recruiting hospital for many years and was therefore used in this trial. This form of the Barthel Index has good test-retest reliability and inter-observer reliability (Wade and Collin 1988). Concurrent validity – assessed by associating the amount of nursing time required for patients – has been shown to be good (Novak et al 1996). The one psychometric concern regarding the Barthel Index is how responsive it is. A lack of sensitivity to changes at the extreme high and low ends of the scale have been identified (Cano et al 2006). It was expected that the current trial would recruit severe stroke survivors who were likely to have very low Barthel scores.

This floor effect may be detrimental to identifying changes in this group. To improve sensitivity to changes in stroke survivors at this severe level in stroke trials Quinn et al (2011) recommend using the Barthel Index in conjunction with the modified Rankin Scale. Both of these outcome measures were used in the present study,

2.11.4. Isomeric muscle strength testing

Using the same surface EMG electrodes (SX230 active surface electrodes for bipolar recording of muscle activity, Biometrics Ltd, UK) placed as described in section 2.11.1 and the hand-held force transducer (MyoMeter M550, Biometrics Ltd, UK) also described in section 2.11.1 strength of the elbow flexors, elbow extensors, wrist flexors and wrist extensors was assessed.

In order to assess elbow flexion strength, the shoulder was abducted to 90 degrees and maintained in this position by the research therapist (or as much abduction as possible without evoking pain in cases where shoulder pain was reported) and the myometer was placed at the distal end of the ulnar and radius on the palmar side. With the elbow in 90 degrees of flexion and the wrist supinated, the patient was then asked to bend their elbow as hard as possible and hold for as long as possible. After a two-minute rest the trial was repeated again, and, following a further two-minute rest, the patient was assessed for a third time.

In order to assess elbow extension strength, the same position was assumed by both the assessor and patient with the only change being the placement of the myometer being on the dorsal side of the wrist. The patient was asked to straighten their elbow as hard as possible and hold for as long as possible. They repeated this exercise three times with a two-minute rest in between each trial.

Wrist flexion and extension were assessed with the shoulder in neutral, the elbow in 90 degrees and the forearm resting on a table. The patient's forearm was held in position by the assessor and the myometer was placed across the metacarpal phalangeal joints (on either the dorsal or palmar side). The patient was then asked to either bend or extend the wrist. The assessor ensured that shoulder internal or external rotation did not become involved by maintaining the forearm position with their second hand. They repeated this three times with a two-minute rest in between each trial.

The final muscle function test used a grip dynamometer to assess the patient's grip strength. With the patient in the same position as for the wrist strength testing, the patient was asked to grip the dynamometer as tight and for as long as possible. The assessor took the weight of the dynamometer so that even those patients unable to hold the weight of the dynamometer could be assessed. The wrist was maintained in neutral throughout by the assessor maintaining the position of the dynamometer.

Bohannon (1986) identified that there was good test-retest reliability of this technique during a single session across various muscle groups of the arm in neurological patients. Bertrand et al (2007) also found good reliability for use of the technique in strength ratio testing whereby the difference between the paretic and non-paretic arm are assessed. Martins et al (2015) investigated the psychometrics of using hand held dynamometry in neurological patients. Four studies had assessed reliability using intra-class correlation coefficients and identified excellent reliability.

2.11.5. Action Research Arm Test

The Action Research Arm Test (ARAT) is a measure of arm function first described by Lyle (1981). With the patient in a sitting position, a bespoke table with shelf was brought in front of them and they were asked to perform 19 separate tasks. The 19 tasks are divided into four sub-scales; grasp, grip, pinch and gross movement. For each of these tasks an ordinal four-point scale from zero to three was given by the research therapist meaning the minimum score was 0 and the maximum score could be 57 (Lyle 1981).

0 - no movement

1 - the movement task is partially performed

2 - the movement task is completed but takes abnormally long

3 - the movement is performed normally

The standardised protocol described by Yozbatiran et al (2008) was used to ensure that both scoring and placement of objects was consistent during all tests. The grasp subscale involved six tasks with various items that had to be picked up from the table and placed on the shelf 37cm above the table. If the person was able to pick up the largest wooden cube (10cm^3) and place on the shelf in less than five seconds then they automatically scored 18 for the subscale and moved on to the next subscale Yozbatiran et al (2008). If they scored less than three then they were asked to pick up the smallest cube. In cases where the patient was unable to perform any part of picking up the smallest wooden cube (2cm^3) they scored zero for the whole subscale (Yozbatiran et al 2008). In patients who did not score zero for the smallest cube they were asked to pick up a 5cm^3 wooden block, 7.5cm^3 wooden block, cricket ball and sharpening stone

measuring 10cm×2.5cm×1cm. They were then scored on each of these tasks and a score out of 18 identified.

The grip subscale involves four tasks with the most difficult being pouring water from one glass to another and the easiest being to pick up a 2.25cm wide alloy tube from one side of the table and place it on a stand 30cm in front.

The pinch subscale involved six tasks all of which required the patient to pick up and place various sized balls. The easiest task involved picking a marble up between index finger and thumb and placing it on the shelf above while the hardest task involved picking up a 6mm ball bearing between ring finger and thumb and placing it on the shelf.

A gross movement subscale involved three tasks with the hardest being to place the hand behind the head and the easiest being to place the hand on top of the head.

The ARAT has repeatedly been found to be both valid and reliable to assess arm function in stroke survivors (Lyle 1981, Hsieh et al 1998, Hsueh and Hsieh 2002). Lin et al (2009) concluded the same and also identified that, based on inherent errors in assessment, the minimal detectable change (MDC) for the ARAT was four. As a result of the improvement in the assessment protocol by Yozbatiran et al (2008) it is possible that this MDC might have become less. While the MDC indicates the change needed to be confident that a change in the score is real the minimal clinically important difference (MCID) indicates the change needed to for a patient to actually perceive a benefit. Lang et al (2008) investigated what the MCID was for a number of different measures of arm function. They estimated for the ARAT that a change of 12 for the dominant

hand and 17 for the non-dominant hand needed to occur for patients to perceive a benefit from any given treatment (Lang et al 2008).

2.11.6. EQ-5D

In order to assess the patient's perceived health related quality of life a questionnaire called the EQ-5D-5L was completed (Herdman et al 2011). This questionnaire is a descriptive classification system developed by the EuroQoL Group which initially had three levels but was further developed to have five levels (Janssen et al 2013). The five dimensions are: Mobility, Self-Care, Usual Activities, Pain/Discomfort and, Anxiety/Depression, and patients were able to respond with; no problems, slight problems, moderate problems, severe problems and, unable to/extreme problems for each dimension. Finally, the patient was asked to rate how good or bad they considered their health to be on a scale with 0 being the worst imaginable health and 100 being the best imaginable health.

The EQ-5D-5L has been found to be superior to the original EQ-5D-3L as it had a reduced ceiling effect and improved discriminatory power in the general population (Janssen et al 2012). Golicki et al (2015) found that the 3L was more responsive in a stroke population when assessed longitudinally however they used a cross-walk technique to measure the difference between the two questionnaires. Another study identified that EQ-5D-5L had good concurrent validity with the Functional Independence Measure and Stroke Impact Scale (Chen et al 2016). This same study also estimated the MCID to be 0.1 (Chen et al 2016).

2.11.7. Caregiver strain index

In order to assess the impact of the stroke and subsequent treatment on people who were providing care or support to the patient, the most appropriate person was asked to complete a questionnaire. This was completed entirely separately to the other parts of the study and it was made clear to the care giver that it was entirely up to them whether they wished to complete it.

The Caregiver Strain Index (CSI) was developed by Robinson (1983) and, although initially validated in carers of patients who had received treatment for hip surgery or heart problems, it is the most commonly used measure of caregiver burden in stroke (Rigby et al 2009). Clinical validity and reliability of the CSI is good in the caregivers of stroke survivors (van Exel et al 2005) and it also has good reproducibility and moderate responsiveness (Post et al 2007).

2.11.8. Patient satisfaction

A simple five-point Likert scale to check patient's satisfaction with trial participation was used. Patients were asked how much they agreed with the statement "I am happy that I participated in this trial" with answers ranging from strongly disagree to strongly agree. This was asked by the research therapist as a final question and the results of this question were not intended to be investigated or further analysed.

2.11.9. Modified Rankin scale

The modified Rankin scale was completed by the research therapist during the final review. The original Rankin Scale (Rankin 1957) had a range from one to five with one identified as "*no significant disability: able to carry out all usual activities*" and five indicating "*Severe Disability: bedridden, incontinent and requiring constant nursing care and attention*". van Swieten et al (1988) altered

the scale from five grades to seven by adding zero and seven indicating no symptoms at all and death respectively. The only other variation from the original was to clarify that a grade of one indicated continuing symptoms which did not impact on function.

The modified Rankin Scale has been used extensively in stroke research and Banks and Marotta (2007) carried out a literature review and synthesis of the clinometric properties of the scale. This study identified 224 articles and carried out detailed assessment of 50. They identified that there was excellent consistency with test-re-test reliability, construct validity had been confirmed in relation to lesion volume, location and type of stroke and that convergent validity had been identified with various other disability scales (including the Barthel Index, Stroke Impact Scale and Functional Independence Measure) (Banks and Marotta 2007). While reliability and validity are good, Dromerick et al (2003) identified that sensitivity was not as good as the Barthel Index in a group of 95 consecutive stroke rehab patients. A further limitation was the negative effect that co-morbidities may have had when scoring the modified Rankin scale (Banks and Marotta 2007). Since many stroke patients have multiple co-morbidities this may be an important factor.

2.12. Data extraction

Data from the myometer, electrogoniometer and surface EMG electrodes were sampled at 1000Hz and stored in a password protected personal computer.

Data was then processed and analysed using a bespoke programme written in specialised software (Mathcad 15, PTC, USA). The raw electromyography data was notch filtered at 50Hz and smoothed using a low-pass filter at 10Hz.

Data from both the low velocity and high velocity passive movements were identified. Passive range of movement was identified from the first low velocity movement (i.e. greatest angle at flexion and extension during this movement).

The first and last 10% of the movement was removed from subsequent analysis. Mean velocity and EMG activity was then able to be calculated. Stiffness was calculated as the slope of the force angle curve using standard linear regression techniques. Spasticity was quantified as the mean muscle activity of the flexors throughout the movement.

2.13. Data analysis

In order to answer the four research questions in this thesis not all the outcome measures collected needed to be analysed. Only descriptions of the analyses of the impairment measures of spasticity, stiffness, passive range of movement, and activity measure of arm function, are included in this section. All other data has been analysed but is not pertinent to the research questions. Statistical analysis of data was carried out using IBM SPSS Statistics for Windows Version 19 (IBM, USA).

2.13.1. Data analysis for research question one - When does abnormal muscle activity in the arm develop following stroke in patients who initially have no arm function and can the Tardieu scale identify this?

Spasticity was deemed to be present when there was evidence of abnormal muscle activity on EMG during a passive movement. Presence or lack of spasticity was dichotomised and presence or lack of function was dichotomised as previously described using the grasp sub-scale of the ARAT.

This meant patients were placed into one of four groups: those with spasticity and function, spasticity and no function, no spasticity and function, and no spasticity and no function. Population proportion and 95%CI is presented for each group (Daniel and Cross 2013).

The time at which spasticity occurs is presented as the median days with IQR.

The Tardieu scale is presented as a scale – specificity and sensitivity were analysed against the abnormal muscle activity by dichotomising the Tardieu scale to be 0=no spasticity and 1=Tardieu scale greater or equal to one.

Visual analysis of the electromyography after data extraction was used to identify any variations in the patterns of EMG activity.

2.13.2. Data analysis for research question two - Is it possible to prevent or delay contracture development by treating spasticity early with botulinum toxin?

Spasticity - Surface EMG activity - Raw data and the calculated mean difference from baseline data were calculated and presented with the mean difference and the 95%CI between the treatment and placebo groups reported.

The presence of contracture was measured using both loss of range and development of stiffness.

Passive range of movement - Raw data and the calculated mean difference from baseline data were calculated and presented with the mean difference and the 95%CI between the treatment and placebo groups reported.

Stiffness - Raw data and the calculated mean difference from baseline data were calculated and presented with the mean difference and the 95%CI between the treatment and placebo groups reported.

In order to study the rate of change in contractures the rate in the change of angle over time was estimated using least square estimate and the change in the control group was compared with that of the treatment group (Matthews et al 1990).

2.13.3. Data analysis for research question three - Do patients who have spasticity treated early have better recovery of function compared to those who are not treated?

The Action Research Arm Test – Raw data is presented as mean and standard deviation and was used to calculate the mean difference and the 95%CI between the treatment and placebo groups.

Using the pre-specified cut off point of greater than 2 on the grasp sub-scale of the ARAT, data was dichotomised to identify those who had recovered function against those who had not recovered function. Odds Ratio with 95%CI was presented to identify differences between the treatment and placebo groups.

2.13.4. Data analysis for research question four - Does the sub-group of patients identified as least likely to recover function benefit from early treatment of spasticity more than others?

Those stroke survivors least likely to recover function are likely to be at most risk of contracture development. It is likely that these people are most likely to benefit from intervention. A planned sub-group analysis of those patients who were least likely to recover function at any point over the first six months was carried out. Current studies attempting to clearly differentiate patients who are least likely to recover post stroke function have been able to identify some predictors but are dependent on expensive scanning and remain incomplete (Winters et al 2014 and Stinear et al 2013). The two clearest predictors remain severity of the stroke and recovery in the first two weeks of stroke Winters et al (2014).

There is clear evidence that a more severe stroke will result in less likelihood of recovery (Winters et al 2014 and Byblow et al 2015). Brott et al (1989) identified that those with an NIHSS score of greater than 15 had sustained severe strokes.

The Barthel Index is a measure of function and indicates motor recovery that has translated in to functional improvements. No change in this index, or deterioration, provides evidence that the person is not recovering function.

Entry to this sub-group was restricted to patients who had an initial NIHSS score of 15 or greater and had no improvement in the Barthel index.

Analyses of the baseline measures between those included in this sub-group and the rest of the patients were carried out and the mean difference and 95%CI is presented. Between group analysis of this sub-group and the rest of the population at six months was also investigated with the mean difference and 95%CI presented for each group and the mean difference and 95%CI between groups.

For measurement of EMG, loss of range, and stiffness, the raw data and the calculated mean difference from baseline data were calculated and presented with the mean difference and the 95%CI between the treatment and placebo groups reported in the same way as question two. Function between the two groups was also presented in the same way as question three.

2.14. Adverse events

All adverse events that occurred between the signing of the informed consent form and the last visit were reported in the case report forms. Adverse events were followed up routinely.

For all adverse events, the research therapist obtained information to determine the outcome of the adverse event and to assess whether it met the criteria for classification as a serious adverse event, requiring immediate notification. The start date, duration, intensity, relationship to the study medication, actions taken and outcome were documented.

All serious events, reactions or unexpected reactions that occurred between the signing of the informed consent form and the last visit were reported immediately upon knowledge of the event occurring to both the Chief Investigator and sponsors. It was also reported in the case report form and outcomes were tracked and followed up.

Causality and expectedness were assessed by the research therapist in the first instance and later by both the Chief investigator and the Sponsors. The research therapist kept detailed records of all serious adverse events relating to the trial. Had any suspected unexpected severe adverse reaction occurred, it would have been reported to the Medicines and Healthcare products Regulatory Agency (MHRA) in keeping with MHRA legal requirements and the local ethics committee.

3. Results

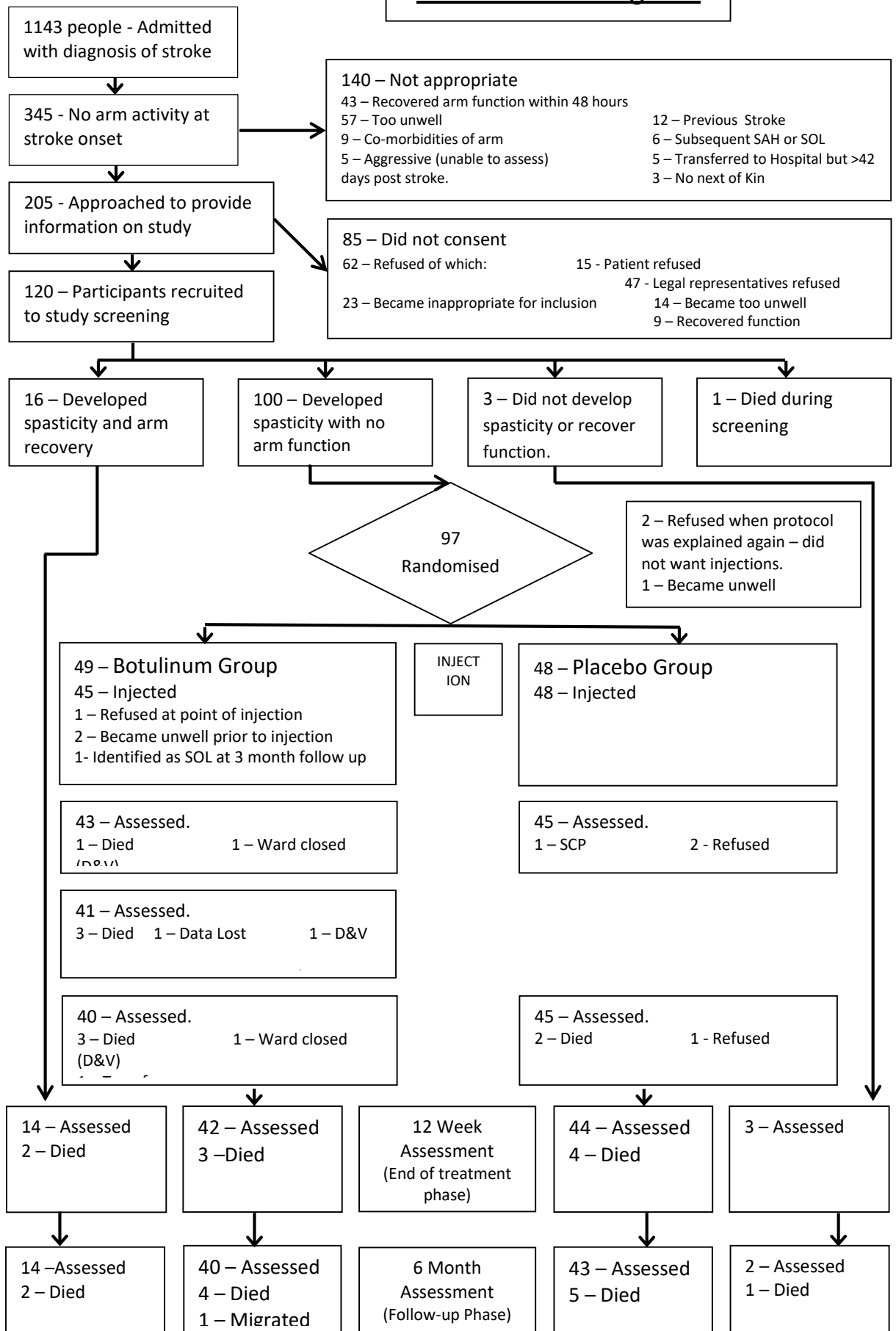
3.1. When does spasticity in the arm develop following stroke in patients who initially have no arm function, and can the Tardieu scale identify this?

Between January 2012 and December 2013, 1143 patients were admitted with a diagnosis of stroke to either City Hospital Birmingham or Sandwell Hospital (both part of Sandwell and West Birmingham NHS Trust) of whom 345 had no arm function at stroke onset (95% confidence interval for population proportion (95CI) between 28% and 33%). The CONSORT diagram of recruitment for participants who were admitted with a stroke through the trial is presented on page 83. One hundred and twenty patients consented to trial participation. The median days from stroke to screening was eight (IQR=5-14) (mean=10.6 SD=8.2), median age was 71 years (IQR=56-80) (mean=68.2 SD=15.7), and median NIHSS score was 16 (IQR=10-20) (mean=15.4 SD=6.0).

Of the 120 participants who consented, one died during the screening phase. At the end of the screening phase the remaining 119 participants could be classified in to one of four potential categories.

- No function and developed spasticity – n=100 (84% 95CI between 76% and 89%).
- No function and no spasticity – n=3 (2.5% 95CI between 0.8% and 7%).
- Recovered function and developed spasticity – n=16 (13.5% 95CI between 8% and 21%).
- Recovered function and no Spasticity – n=0

CONSORT Diagram



Key – D&V = Diarrhoea and vomiting, SOL = Space occupying lesion, SCP=Supported care pathway (palliative care approach), UTC = Unable to contact

3.1.1. When does spasticity in the arm develop?

Out of the 100 participants who did not recover function but developed spasticity, 54 were identified as having spasticity on the first day that screening was able to commence - a median 11 days post stroke (IQR=7.5-19) (mean=14.0 SD=9.5). The remaining 46 participants were screened for a number of days before spasticity was identified. In this group, spasticity was identified a median 12 days post stroke (IQR=8-19) (mean=14.5 SD=7.2). The group of 16 who recovered function but developed spasticity did so a median of 7.5 days post stroke (IQR=6-10). All of these subjects developed spasticity on the same day, or the day before, they recovered function.

3.1.2. Can spasticity be identified using the Tardieu scale at this early stage?

In order to investigate whether the Tardieu scale was able to identify the abnormal muscle activity indicative of spasticity, data from all 119 subjects was analysed. By dichotomising all patients in to those who scored greater than or equal to one on the Tardieu scale and those who presented with or without abnormal activity on EMG (see table 3.1), it was possible to investigate the specificity and sensitivity of the Tardieu at this early point in spasticity.

Three patients had no abnormal muscle activity and all scored zero on the Tardieu scale meaning that the specificity of the Tardieu scale is 1.0 at both elbow and wrist. The sensitivity of the Tardieu scale was identified to be 0.53 ($61 / (61+55)$) at the elbow and 0.49 ($57 / (57+59)$) at the wrist.

Table 3.1 – Variations between EMG and Tardieu in identifying spasticity at elbow and wrist at baseline

Elbow (Wrist)	EMG Positive	EMG Negative
Tardieu Positive	61 (57)	0 (0)
Tardieu Negative	55 (59)	3 (3)

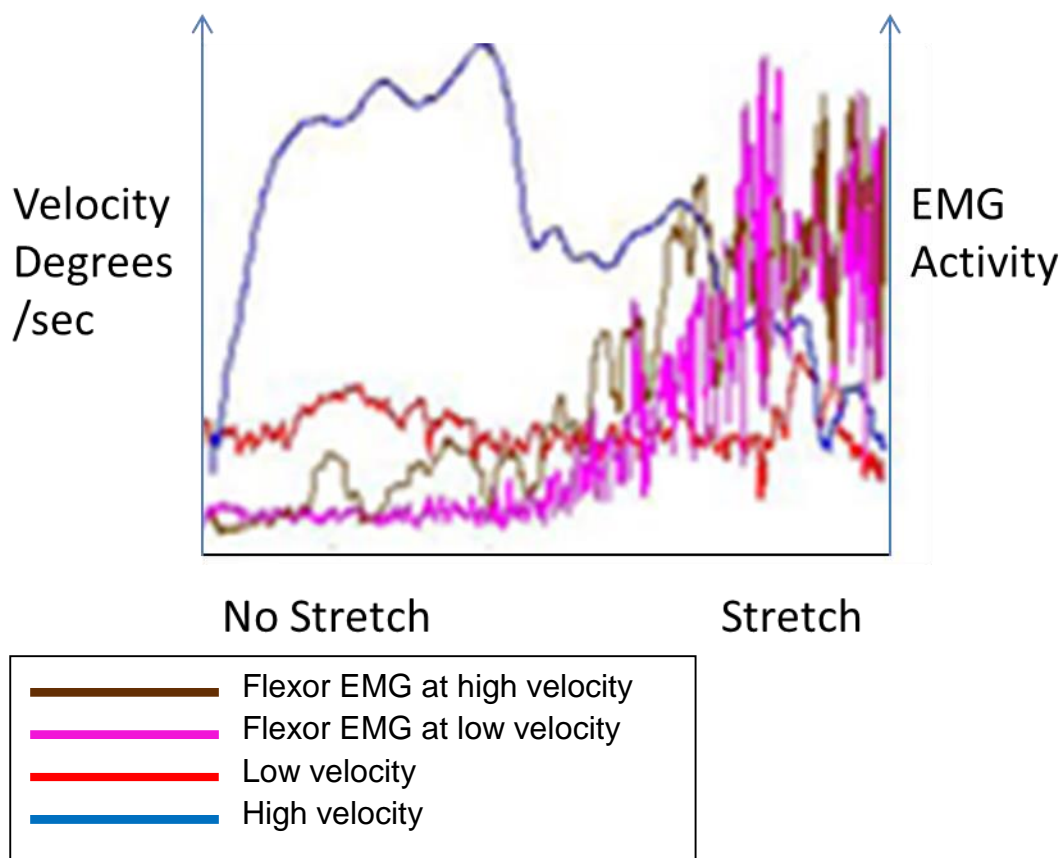
The number of participants who scored 0 on the Tardieu Scale (no resistance/spasticity) made up around 50% of all people identified with spasticity on EMG. When a score of greater than one is used which appears to best represent clinical spasticity, those presenting with spasticity were 20% (23) and 13% (15) in the elbow and wrist respectively.

3.1.3. Patterns of abnormal muscle activity observed on EMG

The pattern of EMG activity was reviewed and two patterns identified. Subjects either showed a combination of position and velocity dependent activity (figure 3.1) or pure velocity dependent activity (figure 3.2). These figures are representative of the two patterns as either an elbow or wrist is passively moved from full flexion (no stretch) to full extension (full stretch). The EMG activity when the elbow is moved at high and low velocities are indicated by the brown and mauve coloured lines (respectively). The blue and red lines indicate the speed at which the elbow was passively extended and is presented to clearly show the difference between the high and low velocity movements. The mean velocity to passively move the joint at slow speed was 30.5 degrees/sec (deg/s)

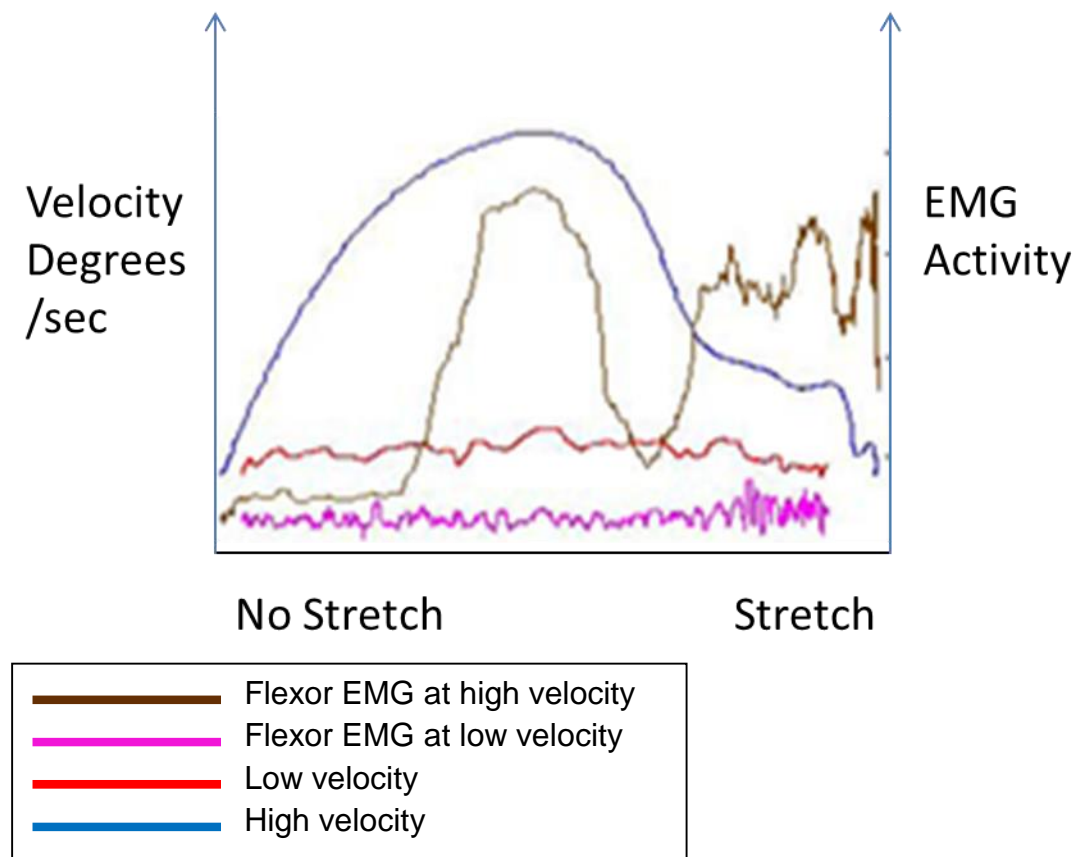
SD=19.6deg/s and at high speed was 258deg/s SD=101.5deg/s. These patterns were not uniform at the elbow and wrist joint within participants.

Figure 3.1 – Representative diagram of position and velocity dependent spasticity



In this presentation of position and velocity dependent activity, the muscle becomes active during movement and continues to remain active on cessation of movement. The muscle became active at both slow and fast passive movements although the angle at which muscle becomes activated was usually earlier with high velocity movement.

Figure 3.2 –Representative diagram of velocity dependent spasticity



In this presentation the muscle becomes active during high velocity movement only and stops on cessation of movement. There is no increase muscle activity during slow passive movement.

The population proportion that developed velocity dependent spasticity at the elbow was 29 (25% 95CI between 18% and 34%) and the number who developed this pattern at the wrist was 41 (35% 95CI between 27% and 44%). While there was a significant association ($p < 0.01$) between the spasticity presentation at the elbow and the wrist (tested using the X^2 test) not all patients demonstrated the same pattern between wrist and elbow. (See table 3.1.1)

Table 3.1.1 – Variation in patterns of spasticity between elbow and wrist at baseline

		Wrist joint patterns of spasticity		Total elbow
		Velocity Dependent	Position & Velocity Dependent	
Elbow joint patterns of spasticity	Velocity Dependent	<u>19</u>	10	29
	Position & Velocity Dependent	22	<u>65</u>	87
Total wrist		41	75	116

3.1.4 Patterns of abnormal muscle activity observed on EMG compared to the Tardieu scale

When the score on the Tardieu Scale was analysed against the spasticity patterns there appeared to be some evidence that those presenting with a velocity dependent pattern of muscle activity were less likely to have resistance perceived during the passive movement. This was more evident in the elbow (table 3.1.2) compared to the wrist (table 3.1.3).

Table 3.1.2 – Spasticity identified at the elbow compared to the Tardieu score at baseline

		Baseline Tardieu Score Elbow			Total
		No resistance	Slight resistance no clear catch	Clear catch at angle then release	
Baseline Elbow Flexor Activity Observed	Velocity Dependent	19 (66%)	5 (17%)	5 (17%)	29
	Position & Velocity Dependent	36 (41%)	33 (38%)	18 (21%)	87
Total		55 (47%)	38 (33%)	23 (20%)	116

Table 3.1.3 – Spasticity identified at the wrist compared to the Tardieu score at baseline

		Baseline Tardieu Score Wrist				Total
		No resistance	Slight resistance no clear catch	Clear catch at angle then release	Fatigable Clonus	
Baseline Wrist Flexor Activity Observed	Velocity Dependent	24 (58%)	15 (37%)	2 (5%)	0	41
	Position & Velocity Dependent	35 (47%)	27 (36%)	12 (16%)	1 (1%)	75
Total		59 (51%)	42 (36%)	14 (12%)	1 (1%)	116

3.2. Is it possible to prevent or delay contracture development by treating spasticity early with botulinum toxin?

From the 100 participants who developed spasticity with no arm function, 97 were randomised to either the treatment group or placebo group. Of the three who were not randomised, two refused injections when the protocol was explained to them again prior to randomisation, and one became unwell prior to randomisation occurring.

Following randomisation, four subjects were deemed to be protocol deviations. One refused at point of injection, two developed illness that meant they could not be injected, and one was found not to be a stroke on three-month imaging. This meant that 93 participants were injected, (treatment group n=45 and placebo group n=48) and are included in the intention to treat analysis. Of the 93 participants, 65 had total anterior circulatory strokes, 19 partial anterior strokes, and 9 lacunar strokes. Forty-eight were male and 45 were female with a mean age of 67.5 (SD=15.8) and a mean NIHSS score of 16.2 (SD=6.2).

Baseline demographics are presented as the mean with standard deviation in table 3.2.1. Baseline measures were similar in both groups.

Table 3.2.1 – Baseline demographics for the intention to treat population.

INTENTION TO TREAT		Treatment Group	Placebo Group	P-value (95%CI)	Total
	Numbers	45	48		93
	Age in years	67 (17.1)	68.1 (14.8)	0.75 (-7.6 to 5.5)	67.5 (15.8)
	Sex female (%)	21 (47%)	24 (50%)		45 (48%)
Type of Stroke	Infarct (Thrombolysed)	36 (7)	38 (10)		74 (17)
	Haemorrhage	9	10		19
	NIHSS	16 (6.2)	16.4 (6.2)	0.76 (-2.9 to 2.1)	16.2 (6.2)
NIHSS Sub-Group (Best score = 0)	Arm (0-4)	3.6 (0.6)	3.6 (0.6)	0.9 (-0.2 to 0.3)	3.6 (0.6)
	Leg (0-4)	2.8 (1.0)	2.9 (1.0)	0.58 (-0.5 to 0.3)	2.9 (1.0)
	Sensation (0-2)	1.2 (0.7)	1.2 (0.7)	0.63 (-0.4 to 0.2)	1.2 (0.7)
	Inattention (0-2)	1 (0.8)	1 (0.8)	1(-0.34 to 0.34)	1 (0.8)
Barthel (Best score = 20)	Pre stroke	19.4 (2.7)	19.5 (1.3)	0.58	19.4 (2.1)
	Admission	1.9 (2.9)	1.5 (3.1)	0.62	1.7 (3.0)
	Stroke to Injection (days)	16.8 (8.9)	19.1 (9.5)	0.66	16.0 (9.3)

3.2.1. The effectiveness of botulinum toxin to decrease spasticity

Before presenting the results of research question two it is important to identify that the botulinum toxin treatment was effective in treating spasticity.

In the elbow, spasticity markedly decreased in the treatment group following injection and remained lower than that observed at baseline until six-month follow up. Spasticity continued to increase in the placebo group over the same

period with a slight decrease at six months (Table 3.2.2). There was a significant difference between the groups from week two to week twelve.

Table 3.2.2 – Development of spasticity at the elbow for each time point in the placebo and treatment groups

		Raw results						Calculated mean difference from baseline				
		Baseline (BL)	Week 2	Week 4	Week 6	Month 3	Month 6	Week 2 minus BL	Week 4 minus BL	Week 6 minus BL	Month 3 minus BL	Month 6 minus BL
Elbow EMG at slow stretch (μV)	Placebo	6.9 (8.3)	10.5 (16.4)	10.8 (12.7)	13.1 (14.4)	14.2 (27.9)	11.6 (16.5)	3.4 (13.4)	5.7 (16.0)	7.3 (29.5)	3.5 (13.2)	4.7 (19.1)
	Treatment	8.9 (10.9)	3.4 (2.9)	4.1 (3.0)	3.7 (2.7)	5.8 (5.4)	8.1 (9.3)	-4.5 (10.4)	-4.1 (10.2)	-2.8 (9.4)	-4.2 (10.3)	-0.6 (9.5)
	Mean Diff.	2.0	7.1	6.7	9.4	8.5	3.5	7.8	9.8	10.1	7.8	5.3
	P-Value	0.31	0.007	0.002	<0.001	0.045	0.21	0.003	0.001	0.03	0.002	0.09
	(95% CI)	(-2 to 6)	(-12 to -2)	(-11 to -3)	(-14 to -5)	(-17 to 0)	(-9 to 2)	-12.9 to 2.7	-15.4 to -4.3	-18.9 to -1.3	-12.6 to -2.9	-11.3 to 0.7

Spasticity in the forearm flexors was slightly different to the elbow flexors.

There was no decrease in spasticity following injections in the treatment group (as observed in the elbow flexors) but the rate of spasticity development was significantly slowed compared to the group who received placebo injections for the first six weeks as seen in table 3.2.3.

Table 3.2.3 – Development of spasticity at the wrist for each time point in the placebo and treatment groups

		Raw results						Calculated mean difference from baseline				
		Baseline (BL)	Week 2	Week 4	Week 6	Month 3	Month 6	Week 2 minus BL	Week 4 minus BL	Week 6 minus BL	Month 3 minus BL	Month 6 minus BL
Wrist EMG at slow stretch (μV)	Placebo	4.6 (5.8)	8.5 (7.5)	8.1 (6.0)	10.9 (10.6)	7.8 (6.2)	10.1 (7.3)	3.9 (7.9)	3.4 (7.7)	6.1 (10.5)	2.9 (7.4)	5.0 (8.5)
	Treatment	4 (3.6)	4.1 (3.8)	4.9 (4.7)	5.2 (5.9)	7.5 (7.9)	9.3 (9.2)	0.2 (4.7)	1.2 (5.3)	1.4 (6.3)	3.3 (8)	4.9 (8.8)
	Mean Diff.	0.6	4.4	3.1	5.8	0.3	0.8	3.8	2.2	4.8	0.4	0.1
	P - Value	0.57	0.001	0.01	0.002	0.85	0.58	0.007	0.12	0.009	0.78	0.95
	(95% CI)	-2.5 to 1.4	-7 to -1.8	-5.6 to -0.7	-9 to -2	-3.3 to 2.7	-4.4 to 2.7	-6.4 to -1.1	-5.1 to 0.6	-8.4 to -1.2	-2.6 to 3.5	-3.6 to 3.4

Having identified that spasticity was significantly reduced in the treatment group the effect of this treatment on contracture development can be investigated.

The raw data and calculated mean difference from baseline to each time point is presented for the elbow followed by the wrist.

3.2.2. Contracture development at the elbow

Quantitative measures of contracture are presented as stiffness (force required to move the joint through range) and loss of range of movement lost from the initial baseline measures (Table 3.2.4).

3.2.2.1. Stiffness at the elbow

Elbow stiffness significantly decreased in the treatment group immediately after injection before beginning to increase. Stiffness continued to gradually increase in the initial stages in the placebo group. A significant difference was observed at week two (Mean difference = 4.9mN/deg, $p=0.042$). At three months after injection and six months post stroke there was no significant difference in stiffness identified between groups.

3.2.2.2. Range of movement at the elbow

Both groups gradually lost passive range of movement in the elbow over time. The placebo group lost range 2.9 times faster than the treatment group. At three months, a significant difference between groups was identified (mean difference=6.3° $p=0.03$).

Table 3.2.4 –Development of contractures at the elbow each time point in the placebo and treatment groups

ELBOW		Raw results						Calculated mean difference from baseline(BL)				
		Baseline (BL)	Week 2	Week 4	Week 6	Week 12	Month 6	Week 2 minus BL	Week 4 minus BL	Week 6 minus BL	Week 12 minus BL	Month 6 minus BL
Stiffness at slow stretch (mN/deg)	Placebo	12.7 (10.2)	13.5 (10.1)	13.6 (10.0)	14.3 (11.6)	16.8 (15.0)	19.0 (14.7)	0.8 (12)	1.3 (11.9)	1.5 (13.2)	3.8 (16.4)	6.4 (16.0)
	Treatment	14 (11.0)	9.1 (6.7)	10.3 (12.6)	11.7 (8.2)	14.6 (12.6)	15.9 (16.2)	-4 (11)	-3.5 (10.9)	-1.7 (11.3)	0.9 (13.5)	2.6 (16.6)
	Mean Diff.	1.3	4.4	3.3	2.6	2.2	3.1	4.9	4.8	3.2	2.8	3.8
	P - Value	0.55	0.02	0.21	0.23	0.48	0.34	0.042	0.056	0.21	0.36	0.25
	95% CI	-3.1 to 5.7	-8 to -0.7	-8 to 2	-7 to 2	-7.5 to 3.6	-9.7 to 3.4	-9.5 to -0.2	-9.6 to 0.1	-8.3 to 1.9	-8.9 to 3.3	-10.5 to 2.8
Range of extension at slow stretch (Degrees)	Placebo	-0.4 (3.3)	1.7 (10.0)	3.4 (11.9)	4.4 (11.8)	9.5 (18.9)	9.7 (17.7)	2.3 (9.9)	3.9 (11.5)	4.9 (11.8)	9.9 (18.6)	9.4 (17.7)
	Treatment	-0.6 (4.5)	0.6 (5.2)	0.7 (5.3)	1.4 (7.5)	2.9 (7.6)	5.0 (11.4)	0.1 (4.8)	1.5 (5.5)	2.0 (7.3)	3.4 (7.8)	5.6 (11.0)
	Mean Diff.	0.2	2.2	2.6	3	6.6	4.7	2.2	2.3	2.9	6.5	4.2
	P - Value	0.82	0.19	0.18	0.15	0.028	0.13	0.19	0.24	0.17	0.03	0.17
	95% CI	1.43 to -1.8	1.7 to -1.1	1.4 to -6.7	1.2 to -7.2	-0.7 to -12.6	1.4 to -10.8	-1.1 to 5.5	-1.6 to 6.2	-1.3 to 7.1	0.6 to 12.3	-1.8 to 10.2

3.2.3. Contracture development at the wrist

In the wrist, both measures of contracture (the loss of range and development of stiffness) were significantly slowed in the treatment group when compared to the placebo group for the first six weeks following injections (Table 3.2.5).

3.2.3.1. Stiffness at the wrist

The change in stiffness in the wrist followed a similar pattern to the elbow.

Stiffness reduced from baseline in the treatment group following injections but gradually increased in the placebo group. At six weeks, there was still a significant difference ($p=0.02$) in stiffness between groups of 4.2mN/deg (95%CI=-7.7 to -0.7). By three and six month measurements, there was no significant difference between the groups.

3.2.3.2. Range of movement at the wrist

The rate of loss of range of movement was identified to be 1.7 times faster in the placebo group compared to the treatment group over the first three months.

By six weeks a mean difference in passive range of movement of 13.8° (95%CI= 6.1° to 21.6°) was noted between the two groups ($p=0.001$).

Table 3.2.5 – Development of contractures at the wrist at each time point in the placebo and treatment groups

WRIST		Raw results						Calculated mean difference from baseline				
		Base line (BL)	We ek 2	We ek 4	We ek 6	We ek 12	Mo nth 6	We ek 2 min us BL	We ek 4 min us BL	We ek 6 min us BL	We ek 12 min us BL	Month 6 minus BL
Stiffness at slow stretch (mN/deg)	Placebo	11.8 (5.5)	13.3 (4.8)	13.8 (6.3)	14.8 (9.1)	15.0 (7.6)	20.0 (12.8)	1.4 (4.8)	2.2 (6.5)	2.5 (9.4)	3.2 (9.0)	7.8 (13.5)
	Treatment	13.1 (6.3)	11.8 (8.5)	11.6 (7.1)	11.6 (7)	15.4 (10.6)	17.2 (11.5)	-1.6 (8.4)	-2.2 (7.7)	-1.7 (7.2)	2.3 (10.6)	4.2 (10.7)
	Mean Diff.	1.3	1.6	2.2	3.1	-0.4	2.8	3	4.4	4.2	0.9	3.6
	P - Value	0.29	0.28	0.14	0.07	0.82	0.27	0.04	0.06	0.02	0.68	0.15
	95% CI	-1.1 to 3.7	-4.6 to 1.3	-5.1 to 0.7	-6.8 to 0.3	-3.4 to 4.3	-7.8 to 2.2	-6 to -0.1	-7.5 to -1.3	-7.7 to -0.7	-4.9 to 3.2	-8.7 to 1.4
Range of extension at slow stretch (Degrees)	Placebo	84.4 (10.3)	74.9 (16.3)	72.4 (15.8)	63.8 (19.5)	58.4 (28.5)	56.4 (37)	9.2 (14.8)	12.5 (15.9)	20.2 (20.2)	24 (32.8)	25.3(40.4)
	Treatment	82.2 (11.3)	78.5 (14.1)	78.1 (15.9)	75.6 (18.7)	65.4 (28.6)	65.5 (31.4)	3.6 (11.3)	4.1 (12.5)	6.5 (16.4)	17.2 (23.3)	15.8 (27.1)
	Mean Diff.	2.2	3.6	5.7	11.8	7.1	9.1	5.6	8.4	13.8	6.8	9.5
	P - Value	0.32	0.27	0.11	0.04	0.24	0.2	0.048	0.09	0.01	0.25	0.18
	95% CI	-6.7 to 2.2	-2.8 to 10.0	-1.2 to 12.6	3.8 to 19.8	-4.7 to 18.9	-5.1 to 23.3	0 to 11.2	2.3 to 14.6	6.1 to 21.6	-5.4 to 18.1	-4.6 to 23.6

3.2.4. Serious adverse events

There were no adverse reactions in either group. There were 20 serious adverse events in the treatment group and 25 in the placebo group including four deaths occurring in the treatment and five deaths occurring in the placebo group over the six month period.

3.3. Do patients who have spasticity treated early have better recovery of function compared to those who are not treated?

At baseline, the treatment group had a mean ARAT score of 1 (SD=2.6) which was slightly greater than the placebo group with a mean score of 0.44 (SD=1.7). There was no significant difference between groups ($p=0.23$, 95%CI=-0.36 to 1.45). Both groups showed evidence of recovery in function over the first six months. There were no significant differences in function identified at any time points between groups.

At the end of the treatment phase at 12 weeks the treatment group had a mean ARAT score of 11.9 (SD=19.23) while the placebo group had a mean score of 9.5 (SD=17.95). These were both significant improvements to the corresponding baseline measures but there was a mean difference between groups of 2.4 with no significant difference ($p=0.53$, 95%CI=-5.27 to 10.05).

At six months post stroke, the treatment group had improved to 15.3 (SD=21.6) which was 2.9 points better than the placebo group who had a mean score of 12.4 (SD=20.7). There was no significant difference ($p=0.51$, 95%CI=-5.8 to 11.6).

The odds ratio for the number of people in each group who recovered function at three months (based on scoring greater than 2 on the grasp sub-section of the ARAT) was calculated. 17 out of 45 people injected in the treatment group

recovered this level of function while 12 out of the 48 people in the placebo group did. The odds ratio was therefore calculated as 1.82 but this was not significant with a 95%CI of 0.75 to 4.43. By six months 18 out of 45 injected in the treatment group recovered this level of function while 14 out of the 48 people in the placebo group did. The odds ratio was therefore calculated as 1.62 but this was not significant (95%CI 0.68 to 3.83).

3.4. Does the sub-group of patients identified as least likely to recover function benefit from early treatment of spasticity more than others?

Patients who had an NIHSS score of 15 or more on stroke admission and who had not recovered any function as measured by the Barthel Index between admission and randomisation were included in this sub group analysis.

Out of the 93 patients included in the intention to treat analysis, 38 participants fulfilled the criteria for inclusion into this sub-group analysis. Seventeen were in the treatment group and 21 were in the placebo group.

3.4.1. Differences between those included in the sub-group analysis and those excluded

Analysis between the 38 participants deemed less likely to recover (and included in the sub-group) was made against the other 55 participants who were included in the intention to treat analysis. These 55 participants were deemed to have a higher potential to recover function at baseline, while those in the sub-group had less potential. These groups are respectively labelled as 'Good' and 'Poor' in the column labelled 'potential to recover' in tables 3.4.1 and 3.4.2.

Those included in the sub-group analysis (i.e. had a poor potential to recover) were significantly older and had suffered significantly more severe strokes based on the NIHSS and had lower baseline Barthel Index and ARAT as indicated in Table 3.4.1.

Table 3.4.1 – Mean differences between those identified least likely to recover and those with a high potential in a range of variables

	Potential to recover	N	Mean	Std. Dev	Sig. (2-tailed)	Mean difference	95%CI lower to upper
Age (years)	Good	55	62	16.4	<0.0001	-11.6	-17.4 to -5.8
	Poor	38	74	11.5			
NIHSS	Good	55	13.0	5.4	<0.0001	-8.0	-9.9 to -6.0
	Poor	38	21.0	3.5			
NIHSS Arm	Good	55	3.4	0.7	<0.0001	-0.5	-0.7 to -0.2
	Poor	38	3.9	0.3			
NIHSS Leg	Good	55	2.5	1.0	<0.0001	-0.9	-1.3to -0.6
	Poor	38	3.4	0.6			
NIHSS Sensory	Good	55	0.9	0.7	<0.0001	-0.6	-0.9 to -0.4
	Poor	38	1.6	0.55			
NIHSS Inattention	Good	55	0.7	0.7	<0.0001	-0.8	-1.2 to -0.6
	Poor	38	1.5	0.65			
Barth Pre-Admission	Good	55	19.8	0.9	0.097	0.8	-0.2 to 1.8
	Poor	38	19.0	2.9			
Barthel Baseline	Good	55	5.2	4.9	<0.0001	4.9	3.5 to6.3
	Poor	38	0.3	1.3			
ARAT Baseline	Good	55	1.2	2.8	0.002	1.2	0.5 to2.0
	Poor	38	0.0	0			

Having identified that there were significant differences at baseline between these groups, analyses of outcomes at the six month assessment were also made. These analyses identified that the sub-group members had significantly worse measures in grip strength, ARAT, Barthel and Modified Rankin Scale at six months as presented in table 3.4.2.

Despite there being significant differences in function between the groups there were no significant differences between the two groups in stiffness or spasticity at six months. There were however, significant differences in the passive range of movement lost at both the wrist and elbow.

Table 3.4.2 – Measures of change from baseline to six months post stroke for those identified as least likely to recover versus the rest of the group

	Potential to recover	N	Mean	Std. Dev	Sig.	Mean Diff.	95%CI lower to upper
Wrist Ext 24minusBL	Good	55	-13.3	19.8	0.005	22.0	7.0 to37.0
	Poor	38	-35.3	42.9			
Elbow Ext 24minusBL	Good	55	-4.2	8.2	0.009	9.3	2.5 to16.2
	Poor	38	-13.5	19.8			
Wrist Stiff 24minusBL	Good	55	4.7	10.7	0.178	-3.6	-8.7 to1.7
	Poor	37	8.2	14.2			
Elbow Stiff 24minusBL	Good	55	2.1	15.0	0.135	-5.2	-12.1 to1.7
	Poor	37	7.4	18.0			
Wrist EMG 24minusBL	Good	55	5.5	8.9	0.66	0.8	-2.9 to4.5
	Poor	38	4.6	8.7			
Elbow EMG 24minusBL	Good	55	0.7	9.3	0.404	-3.1	-10.6 to4.4
	Poor	38	3.8	21.6			
Maximum Grip Strength	Good	55	6.2	6.7	<0.001	4.91	2.9 to 6.9
	Poor	38	1.3	2.9			
ARAT 24minusBL	Good	55	21.6	22.8	<0.001	20.2	13.9 to26.6
	Poor	38	1.4	4.7			
Barthel 24minusBL	Good	55	8.7	5.2	<0.001	4.2	1.9 to 6.5
	Poor	38	4.4	5.6			
Length of Stay	Good	55	52.6	30.4	0.004	-18.4	-30.9 to -5.9
	Poor	38	71.1	28.7			
Modified Rankin Scale	Good	55	3.1	1.1	<0.001	-1.4	-1.9 to -0.9
	Poor	38	4.5	1.0			

Ext measured in degrees, Stiff measured in Nm/deg, EMG measured in μ V

3.4.2. Sub-group analysis between the treatment and placebo groups

Of the 38 participants included in the sub-group analysis, 17 were in the treatment group and 21 were in the placebo group. There were no significant differences between groups at baseline (See table 3.4.3).

Table 3.4.3 – Demographics at baseline for the sub-group who were identified least likely to recover function

INTENTION TO TREAT		Treatment Group	Placebo Group	P-value
	Numbers	17	21	
	Age (years)	72.5 (13.2)	75.2 (10.2)	0.48
	Sex female (%)	8 (47%)	8 (38%)	
Type of Stroke	Infarct (Thrombolysed)	13 (1)	10 (5)	
	Haemorrhage	3	6	
	NIHSS	20.6 (3.6)	21.2 (3.5)	0.64
NIHSS Sub-Group	Arm	3.9 (0.3)	3.9 (0.4)	0.82
	Leg	3.3 (0.7)	3.5 (0.6)	0.28
	Sensation	1.6 (0.5)	1.6 (0.6)	0.93
	Inattention	1.6 (0.5)	1.5 (0.7)	0.56
Barthel	Pre stroke	18.9 (4.1)	19.0 (1.6)	0.86
	Admission	0.9 (2.3)	0 (0)	0.14
	Stroke to Injection (days)	17.0 (9.2)	21.4 (9.8)	0.16

3.4.2.1. Spasticity between the treatment and placebo groups in the sub-group analysis

Spasticity in the elbow behaved the same way in the sub-group analysis as it had done so in the full ITT analysis described in section 3.2.1. Spasticity significantly decreased in the treatment group following injection and remained lower than that observed at baseline until six-month follow up. Over the same time period spasticity continued to increase from baseline in the placebo group, with a slight decrease at six months (Table 3.4.4). There was a significant difference between the groups from week two to week six but this was lost by week 12.

Table 3.4.4 – Development of spasticity at the elbow for each time point in the placebo and treatment groups

ELBOW		Raw results						Calculated mean difference from baseline				
		Base line	Week 2	Week 4	Week 6	Month 3	Month 6 post stroke	Week 2 minus BL	Week 4 minus BL	Week 6 minus BL	Month 3 minus BL	Month 6 minus BL post stroke
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
EMG at slow stretch (µV)	Placebo	7 (10)	8.3 (8.6)	10.8 (13.4)	14.6 (19.0)	20.8 (41.2)	15.3 (23.8)	1.3 (6.4)	3.2 (17.6)	7.3 (22.6)	13.6 (43.9)	8.1 (27.3)
	Treatment	9 (7)	4.2 (3.5)	3.9 (2.6)	3.9 (2.8)	5.1 (4.2)	8.2 (10.8)	-5.5 (6.4)	-5.8 (6.2)	-5.8 (6.6)	-4.6 (10)	-1.5 (9.6)
	Mean Diff.	2	-4.1	-7	-10.7	-15.7	-7.1	-6.8	-9	-13.1	-18.2	-9.6
	P - Value	0.4	0.07	0.044	0.02	0.09	0.26	0.003	0.054	0.02	0.074	0.14
	(95% CI)	-3 to 8	-8.5 to 0.4	-13.7 to -0.2	-19.6 to -1.7	-34.6 to 3.1	-19.7 to 5.5	-11.1 to -2.4	-18.2 to 0.2	-24.1 to -2.1	-38.3 to 1.9	-22.7 to 3.6

Spasticity at the forearm muscles was also similar to the full ITT analysis with much more variable presentations in EMG activity. A significant difference between the two groups was only observed at week 6 (Table 3.4.5).

Table 3.4.5 – Development of spasticity at the wrist for each time point in the placebo and treatment groups

WRIST		Raw results						Calculated mean difference from baseline				
		Base line	Week 2	Week 4	Week 6	Month 3	Month 6 post stroke	Week 2 minus BL	Week 4 minus BL	Week 6 minus BL	Month 3 minus BL	Month 6 minus BL post stroke
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
EMG at slow stretch (µV)	Placebo	6 (8)	9.7 (7.1)	7.0 (5.5)	13.6 (13.6)	8 (7)	12 (7)	3.5 (7.2)	0.6 (8.9)	7.6 (13.5)	1.0 (7.5)	4.0 (8.9)
	Treatment	4 (3)	4.4 (4.8)	4.3 (4.1)	3.7 (2.5)	6 (5)	10 (9)	0.1 (5.6)	0 (9.0)	-0.6 (3.4)	1.8 (6.0)	5.4 (8.6)
	Mean Diff.	2	-5.3	-2.7	-9.9	2	2	-3.4	-0.6	-8.2	0.8	1.4
	P-value	0.28	0.015	0.11	0.004	0.42	0.56	0.12	0.82	0.016	0.71	0.63
	(95% CI)	-6 to 8	-9.4 to 1.1	-6.1 to 0.6	-16.4 to -3.5	-6 to 3	-8 to 4	-7.8 to 1.0	-5.9 to 4.7	-14.6 to -1.7	-3.7 to 5.4	-4.4 to 7.2

3.4.2.2. Development of contracture at the elbow

The development of stiffness at the elbow continued in the placebo group from baseline, whereas stiffness was reversed in the treatment group and remained less than baseline for the first 12 weeks following the injections (Table 3.4.6). Loss of range was 4.5 times faster in the placebo group than the treatment group. This resulted in a 13 degree significant difference ($p=0.04$) between the two groups at week 12.

Table 3.4.6 – Development of contractures at the elbow each time point in the placebo and treatment groups

ELBOW		Baseline	Week 2 minus BL	Week 4 minus BL	Week 6 minus BL	Month 3 minus BL	Month 6 minus BL post stroke
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Stiffness at slow stretch (mN/deg)	Placebo	12.9 (10.7)	0.1 (15.8)	3 (15.4)	4.1 (16.1)	7.0 (19.8)	12.1 (21.0)
	Treatment	15.3 (8.0)	-5.5 (10.6)	-6.9 (7.8)	-3.2 (9.5)	-0.3 (8.9)	1.7 (12.1)
	Mean Diff.	2.3	-5.6	-9.9	-7.3	-7.3	-10.4
	P - Value	0.46	0.23	0.025	0.11	0.15	0.079
	95% CI	-4.1 to 8.8	-14.9 to 3.7	-18.4 to - 1.3	-16.4 to 1.8	-17.4 to 2.9	-22.1 to 1.3
Range of extension at slow stretch (Degrees)	Placebo	0.9 (2.6)	-4.3 (14.0)	-7.8 (16.3)	-9.0 (16.3)	-17.7 (25.1)	-17.6 (23.1)
	Treatment	0.9 (2.7)	0.4 (3.0)	-2.6 (7.0)	-3.6 (8.4)	-4.8 (9.7)	-8.4 (13.9)
	Mean Diff.	0.1	3.9	5.2	5.4	12.9	9.2
	P - Value	0.99	0.25	0.23	0.22	0.04	0.14
	95% CI	-1.7 to 1.8	-3.0 to 10.7	-3.5 to 13.9	-3.5 to 14.3	0.7 to 25.2	-3.1 to 21.5

3.4.2.3. Development of contracture at the wrist

The development of stiffness at the wrist continued in the placebo group from baseline, whereas stiffness was initially reversed in the treatment group.

Stiffness in the treatment group gradually increased from week two but slower than in the placebo group, and a significant difference between groups was observed at all time points (with the exception of week six) (Table 3.4.7).

Table 3.4.7 – Development of contractures at the elbow each time point in the placebo and treatment groups

WRIST		Baseline	Week 2 minus BL	Week 4 minus BL	Week 6 minus BL	Month 3 minus BL	Month 6 minus BL post stroke
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Stiffness at slow stretch (mN/deg)	Placebo	11.5 (6.2)	2.4 (4.0)	3.8 (6.7)	2.5 (9.6)	5.6 (10.2)	12.9 (16.8)
	Treatment	14.3 (6.6)	-3.0 (12.2)	-1.4 (5.4)	-1.2 (5.7)	0.4 (7.1)	2.7 (7.5)
	Mean Diff.	2.8	-5.4	-5.2	-3.7	-5.2	-10.2
	P - Value	0.18	0.08	0.02	0.17	0.08	0.02
	95% CI	-1.3 to 6.9	-11.6 to 0.8	-9.5 to - 0.9	-9.1 to 1.7	-11.2 to 0.7	-18.8 to -1.7
Range of extension at slow stretch (Degrees)	Placebo	85.9 (10.0)	-10.7 (11.9)	-16.1 (16.0)	-25.9 (23.2)	-36.6 (37.8)	-48.0 (46.8)
	Treatment	80.9 (11.3)	-7.2 (11.7)	-6.8 (13.7)	-11.8 (17.1)	-18.0 (29.1)	-19.6 (32.2)
	Mean Diff.	-5	3.5	9.3	14.2	18.6	28.4
	P - Value	0.39	0.38	0.08	0.04	0.1	0.03
	95% CI	-16.5 to 6.7	-4.5 to 11.5	-1.2 to 19.7	0.4 to 28.0	-4 to 41.3	2.3 to 54.5

Both groups gradually lost range of movement at the wrist over time, with the loss of range in the placebo group being 2.1 times faster over the first three months. The loss of range was significantly different ($p=0.03$) between groups by six months with a mean difference between the groups of 28.4° (2.3° to 54.5°).

3.4.2.4. Function

Table 3.4.8 indicates the six outcome measures that were used at six months, and which might indicate a functional benefit between groups. The most likely measure to indicate benefit to arm function would be the ARAT. Just two patients in the treatment group and one patient in the placebo group recovered function (based on scoring greater than 2 on the grasp sub-section of the ARAT). Given this lack of change in function an odds ratio was not calculated. This lack of functional arm recovery was reflected in the mean ARAT scores at six months of 1.8 and 1.0 out of a possible 57 points.

The only measure that did reach significance was the modified Rankin scale. The mean difference of 0.8 was statistically significant ($p < 0.01$, 95%CI= 1.5 to 0.2). It is also clinically significant as it meant that the placebo group (mean 4.9, SD=0.8) scored five “Severe disability (bedridden, incontinent and requiring constant nursing care and attention)” compared to the treatment group (mean 4.1, SD=1.0) scored four “Moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance).”

The only other measure that tended towards significance was the Caregiver strain index ($p = 0.058$). A score of greater than seven indicates high stress and that further referral should be made. The treatment group scored a mean 4.3 (SD=3.6) compared to the placebo group who scored a mean 7.8 (SD=3.7).

Table 3.4.8 – Between group differences in functional outcomes at six months

in the sub-group identified as least likely to recover

	Group	N	Mean	Std. Dev.	Sig.	Mean Diff.	95%CI lower to upper
ARAT 24minusBL	Treatment	17	1.8	4.9	0.595	0.8	-2.3 to3.9
	Placebo	21	1.0	4.6			
Barthel 24minusBL	Treatment	17	5.9	5.9	0.161	2.6	-1.1 to6.3
	Placebo	21	3.3	5.3			
EQ5D5L Index	Treatment	14	-0.09127	0.27168	0.537	0.06469	-0.14767 to0.27706
	Placebo	14	-0.15597	0.27499			
Modified Rankin Scale	Treatment	17	4.1	1.0	0.008	-0.8	-1.5 to-0.2
	Placebo	21	4.9	0.8			
Functional Ambulatory Scale	Treatment	15	2.5	1.6	0.174	0.7	-0.3 to1.8
	Placebo	16	1.8	1.2			
Caregiver Strain Index	Treatment	11	4.3	3.6	0.058	-3.5	-7.1 to0.1
	Placebo	8	7.8	3.7			

4. Discussion

This study showed that spasticity can be identified and measured much earlier than has previously been reported by using EMG assessment. It also suggested that spasticity could be divided into two particular patterns of abnormal muscle activity. The randomised control study showed that treatment with botulinum toxin and electrical stimulation could decrease spasticity and significantly slow contracture development in the short term when compared to electrical stimulation alone. There was no significant difference in contracture formation at the six-month follow up between the treatment and placebo groups, and functional recovery was not affected. In a sub-group analysis of patients who had been identified as the least likely to recover function (using pre-randomisation clinical measures) the treatment effect and the clinical significance between the treatment and placebo groups was much greater than the whole group intention to treat analysis.

The following chapter will review the results of the current study in the context of previous research. Limitations of the current study will be recognised as each of three broad themes are discussed. The first theme will focus on spasticity (onset, patterns, measurement and the treatment of spasticity). The main theme of contracture development and whether it can be slowed will then be discussed. The final theme will deliberate on current practice and future issues (focus on functional recovery, general limitations of the study clinical practice implications).

4.1. Spasticity onset and development

In this study spasticity occurred within the first two weeks post stroke, and was identified as early as the second day after stroke. Spasticity occurred before any stiffness was identified and any range of movement was lost (i.e. contracture formation). The prevalence of patients who develop spasticity following severe strokes was much greater than has previously been reported.

The finding that spasticity occurs early following stroke is not surprising given the current understanding of pathophysiology. An increase in Ia afferent activity is the most likely cause of the majority of abnormal stretch reflex activity following stroke (Nielsen et al 2007). There is no reason to assume that this increased activity would be delayed following a stroke. This is in contrast to spinal cord injuries where the mechanism of spinal shock might cause a period of loss of reflexes.

Previous prospective studies investigating the onset and prevalence of spasticity have not used EMG to identify spasticity, and this is the main reason why direct comparison between the present study and other prospective studies is not possible (a second difference is that the current study only recruited patients who had no arm function and were expected to have spasticity rather than all stroke survivors). Previous studies did not directly measure abnormal muscle activity, but instead assessed muscle stiffness (using the Modified Ashworth scale) to assess spasticity. The use of these scales, both clinically and in research, continues despite being repeatedly recognised as an invalid measure of spasticity (Nielsen and Sinkjaer 1996, Pandyan et al 1999, Patrick and Ada 2006, and Fleuren et al 2010). Waiting for a secondary consequence

(muscle stiffness) will delay the identification of spasticity, and also prevents the identification of spasticity that does not go on to result in stiffness.

Studies using the (modified) Ashworth scale have been used as evidence in spasticity consensus statements and clinical guidelines. One example is a consensus statement by 26 European physicians, that suggested spasticity gets worse over time “some have suggested that 19% of patients after stroke have spasticity at 3 months and 38% at 12 months after the original trauma” Wissel et al (2009, p18). Wissel et al (2009) used evidence from one prevalence study and one short longitudinal study to form this statement. The prevalence study was carried out at twelve months but no longitudinal methodology was involved (Watkins et al 2002). Sommerfeld et al (2004) carried out the longitudinal assessment of prevalence which slightly contradicts the consensus statement, as they reported a prevalence of 21% within a week post stroke which had decreased to 19% at three months.

The findings by Sommerfeld et al (2004) are very different when compared to a more recent study by Urban et al (2010). Urban et al (2010) identified no spasticity within five days post stroke (n=211) and 42.6% (n=90) at six-month follow-up in a prospective longitudinal study. Opheim et al (2015) assessed spasticity at six time-points over the first year post stroke. In a group of 117 patients, this study reported that 25% of participants had a modified Ashworth Scale of at least one by day three, and that 46% of participants scored at least one on the MAS at one year post stroke.

While prevalence is clearly highly variable in these studies - something described by Wissel et al (2013) when they attempted to investigate prevalence

in studies that only used the modified Ashworth Scale – there is uniformity that ‘severity’ of spasticity appears to increase over time (Sommerfeld et al 2004, Urban et al 2010, Welmer et al 2006 and Opheim et al 2015), but this was not the case in the current study.

The perceived increase in the severity of spasticity, when measured using the (modified Ashworth scale), is most probably due to an increase in contracture formation within the muscle and not related to spasticity. This interpretation is strengthened by the observations from the present study, which showed that spasticity (abnormal muscle activity on EMG) decreased after twelve weeks while stiffness substantially increased between the twelve and six month assessment points.

This finding of a decrease in spasticity by six months as observed in the placebo group (see tables 3.2.2 and 3.2.3 p92) was unexpected. Having not predicted this outcome, the literature was reviewed and it became clear that this finding has been reported in previous studies. Thilmann (1991), in a cross-sectional study found, that the magnitude of spasticity decreased after the first six months which is in line with Malhotra et al (2012). Cousins et al (2010) also described a decrease in spasticity within the placebo group of a randomised controlled trial after 8 weeks. Ada et al (2006) also present a graph which indicates the same finding but does not discuss the finding. The commonality between the four papers listed in this paragraph and the current study is that all used EMG to measure spasticity.

4.1.1. Spasticity Measurement

Using an objective neurophysiological measure to assess a neurophysiological impairment (i.e. spasticity) should be best practice, although in clinical practice this may be difficult to achieve. Clinicians have depended on substitute measures of assessment, and it was felt important that the present study compare the best clinical measure of 'clinical spasticity' (the Tardieu scale) against the EMG identified spasticity. The present study found that specificity of the Tardieu scale is 1.0 but that sensitivity was respectively 0.53 and 0.49 at the elbow and wrist. The study used a score of ≥ 1 on the Tardieu scale. A score of one on the Tardieu scale indicates "slight resistance throughout the course of the passive movement, with no clear catch at a precise angle" Boyd and Graham (1999) pS25 and this is not consistent with what might be considered "clinical spasticity" (i.e. a catch is perceived). When a more clinically relevant score is used (i.e. ≥ 2 on the Tardieu), spasticity was only identified in 20% (elbow) and 13% (wrist) of patients at onset of abnormal muscle activity. This data is consistent with the Sommerfeld et al (2004) study discussed previously that reported a spasticity prevalence of 21% one week post stroke.

Two previous studies have assessed the Tardieu scale against a neurophysiological scale. Patrick and Ada (2006) provided evidence that, relative to the Ashworth scale, the Tardieu scale was a more valid measure of spasticity when both were compared against a neurophysiological measure. This 2006 study measured elbow and ankle flexors/plantarflexors in patients a mean three years post stroke ($SD=1.3$), and considered spasticity on the Tardieu scale as ≥ 2 . Naghdi et al (2014) considered spasticity on the Tardieu scale as ≥ 1 and found that the Modified Tardieu scale was not a valid measure

of spasticity in a group of 20 patients with a diagnosis of stroke (mean 33 months SD=31) when compared to neurophysiological measures in the wrist flexors. There are two differences between the Patrick and Ada (2006) and the Naghdi et al (2014) studies that may explain the divergent results – the neurophysiological measure used to assess spasticity and the joint being measured. While Patrick and Ada (2006) used a similar method to assess spasticity as the present study methodology described in chapter 2 (correlation coefficient between Tardieu and the peak EMG activity was $r=0.86$, $p=0.001$), Naghdi et al (2014) used Hmax/Mmax ratio (correlation coefficient between Tardieu and Hmax/Mmax ratio was $r=0.26$, $p=0.27$). Aymard et al (2000) identified variations in the Hmax/Mmax ratio between the soleus muscle of the leg and flexor carpi radialis muscle of the arm which may explain this variation to a point. The more likely cause for the different results between Patrick and Ada (2006) and Naghdi et al (2014) is the variation in the muscle or joints being assessed. Naghdi et al (2014) assessed the wrist flexors which are more prone to stiffness and are, anecdotally, less likely to develop clonus when compared to the ankle which was assessed by Patrick and Ada (2006). The fact stiffness is more likely to be increased at the wrist is compounded by the decision to use a Tardieu scale of ≥ 1 rather than two and above as used by Patrick and Ada (2006).

The clear difference between the current study and these two previous studies are the mean time post stroke. Since these previous studies were assessing patients at least six months post stroke it is likely that stiffness would have been present. While the Tardieu scale differs in many ways from the Ashworth Scale they are both dependent on the assessor identifying an increase in stiffness.

The catch associated with clinical spasticity is thought to be the muscle contracting - strongly enough to slow or halt the passive movement occurring - as a result of a high velocity stretch. It is possible that this catch may only become strong enough to be perceived after a latent period from stroke onset during which time two possible changes may occur. The first is that initial changes related to contracture formation may have developed increasing the opportunity of a catch being perceived and the second is that an increase in the output from the abnormal muscle activity has occurred. While either of these hypotheses would explain the poor specificity of the Tardieu identified at this early stage further exploration is required to investigate.

4.1.2. Spasticity Patterns

This study detected two patterns of abnormal muscle activity which are described as velocity dependent and, position and velocity dependent. A previous study described three patterns of EMG activity but the pure position dependent spasticity described by Malhotra et al (2008) was not seen in this study. It is possible that this form of position dependent spasticity was an erroneous classification. While a similar phenomenon was observed in the present study, it was not reproducible. In patients presenting with position and velocity dependent spasticity in this study, the velocity dependent element occurred at varying time-points but always before the position dependent activity. In some cases, the activity appeared to begin around the same time and might well have been classed as purely positional. It was possible to review a second set of measurement recordings, as the slow and fast passive movements were repeated immediately. They invariably showed a clearer variation between the onset of activity during high and low velocity movements.

Ashby and Burke (1971), Powers et al (1989) and more recently Levin et al (2013), have reported similar findings of a static stretch response in the elbow which corresponds with the position dependent spasticity observed in the current study. Indeed, such a position dependent response seems to have been described by Liddell and Sherrington (1924), and was more clearly described by Denny-Brown and Liddell (1927). In the study by Ashby and Burke (1971), seven out of 15 participants had sustained prolonged muscle activity when the stretch was maintained at the end of range using a manual technique. The other eight participants' muscle activity ceased when movement stopped. The participants in the Ashby and Burke (1971) study ranged from three weeks to two years post event, and chronicity may account for this variability in presentation. In a cross-sectional study of time course of spasticity investigating one month, three months and twelve months post stroke, Thilmann (1991) did not identify any participants who had ongoing activity on cessation of movement. This study used a mechanical device to move the arm but importantly did not go through the full range of motion to end range. Many studies have used this methodology of moving a joint through a mid-range at varying velocities in order to measure the velocity-dependent nature of spasticity, as defined by Lance (1980).

Those studies that have reported an ongoing stretch response at cessation of movement have always done so when the joint was at the end of range. The muscle being assessed will therefore have been in a position of maximum length and therefore the muscle spindles will have been at a maximal stretch position. This implies that there might be a length dependency element to spasticity in some participants.

The neurophysiological mechanism governing the dynamic component of the stretch reflex is well reported and is due to stretching of the primary muscle spindles which result in Ia afferent activity. It is hypothesised that the static component results from the secondary muscle spindles, which activates group II afferents, which continue to fire for the duration that a muscle is stretched (Matthews et al 1984). Stretch reflexes are known to be length dependent with the stretch reflex being more sensitive in the arm at longer lengths (Burke et al 1971a).

Once varying patterns of abnormal muscle activity are identified then the potential to distinguish any clinical variations is possible. The abnormal muscle activity that only occurs when a joint is moved at more than 150 degrees per second (the Lance definition) is unlikely to interfere with function and may not require treatment at all. Conversely, a muscle that continues to fire even when the movement has ceased is at much greater risk of developing stiffness (as observed in the position and velocity dependent spasticity presentation). This would mean that people presenting with the second pattern of activity are at more risk of developing contracture and are likely to benefit from botulinum toxin. This is because the muscles are in an almost continuously active state and as observed in animal studies such muscle will lose range much faster than less active muscle when held in a shortened position (De La Tour et al (1979), Tabary et al (1981) and Williams et al (1988).

4.1.3. Spasticity treatment

The present study showed that spasticity was treated by botulinum toxin in both the elbow flexors and wrist flexors but that the treatment effect was not

maintained beyond the 12-week assessment. The pharmacokinetics of the drug indicates that the effects last between four to six weeks (de Paiva et al 1999). Many studies have suggested that efficacy may last up to twelve weeks, but these studies have generally used the Ashworth scale, which might explain the variation as decreased stiffness may be perceived for longer than the effect of the drug. This was observed in the present study when the Tardieu Scale was used for assessment.

There are two further possible explanations as to why the effect of the treatment did not last as long as expected. The first is that the dose of botulinum toxin used was too low to sustain an effect for twelve weeks. The doses provided in this study were half the dosage recommended in the Royal College of Physicians guidelines 2009 (Turner -Stokes et al 2009). This half dose was felt appropriate as there was concern that injecting larger doses might negatively impact normal recovery.

A second reason why the treatment effect on spasticity did not appear to last specifically in the wrist was that the surface EMG placement may not have been kept uniform. This issue will be discussed in more depth in section 4.4.4.

By identifying that spasticity had been effectively treated it was appropriate to then investigate whether decreasing spasticity could stop or slow the development of contractures.

4.2. Contractures

The whole study ITT analysis found that the treatment group had lost less range of motion than the control group (mean difference=14°, 95%CI=6.1 to 21.6) in the wrist at six weeks. While this is statistically significant it is perhaps more importantly clinically significant. Similarly, stiffness was found to be significantly less in the treatment group (mean difference=4.2mN/deg, 95%CI=-7.7 to -0.7) at the six week assessment. No long-term benefit was observed at six-month follow up at the wrist.

The results of the wrist contrasted to the elbow where spasticity was significantly improved until the twelve-week assessment but with less of a treatment effect in range or stiffness. The one point when a significant benefit at the elbow, in the treatment group, occurred was at the twelve-week assessment in the elbow range of movement. At this point a significant difference between the two groups was observed however it was of minimal clinical significance.

One could argue from the results at the elbow that since spasticity was clearly treated at the elbow but no significant difference between groups in stiffness or range was observed, spasticity is not causative of joint stiffness or loss of range. This view does not appear to be supported as treatment of spasticity using botulinum toxin decreased the stiffness in the elbow from baseline to six weeks whereas in the placebo group stiffness had continued to increase after baseline. The fact there was no significance between groups may be because stiffness takes longer to occur at the elbow compared to the wrist. While there is no evidence to support this hypothesis, the extra connective tissue that is

present in the forearm flexors compared to the elbow flexors makes this a theoretical possibility. According to the work of Williams and Goldspink (1984) the fact that there is greater perimysium in the forearm relative to the upper arm means collagen deposition is likely to be greater with a resultant increase in stiffness. Further investigation as to whether this could provide an explanation for the current results is warranted.

One further difference between the development of stiffness at the elbow and wrist joint was that the wrist extensors were electrically stimulated ensuring a passive movement was provided to the joint. Both groups received cyclical electrical stimulation to the forearm extensors. This treatment has shown some benefit in slowing the loss of range at a joint without improving measures of spasticity or stiffness (Malhotra et al 2012). The current study employed similar treatment parameters to the Malhotra study so that both groups benefitted from this treatment equally and the actual loss of range might have been greater had the electrical stimulation not been used.

The combination of botulinum toxin to treat the flexors and electrical stimulation to treat the extensors might be greater than either of the two treatments acting independently. It is likely that this is the case given what is known about contracture development and stiffness. Further academic discussion on how the treatment protocol could have been changed to investigate this issue will be presented in section 4.4.2.

4.2.1. Contracture development in the sub-group analysis

The a-priori sub-group analysis of those patients identified as being least likely to recover function from the presentation at clinical onset comprised of 38

participants, 17 in the treatment group, and 21 in the placebo group. The results of this sub-group analysis are highly important, both to the understanding of contracture development, and in highlighting that further investigations of spasticity and contracture development must focus on this sub-group. Analysis revealed that the sub-group developed contractures more rapidly than the whole group. Further, the placebo group of the sub-group lost range at the elbow 1.6 times faster and the wrist 1.5 times faster than the ITT placebo group over the first six months. Despite the increased rate of contracture development in this sub-group the mean differences between treatment and placebo groups were similar to the six week time point of the mean differences between groups in the ITT analysis. (i.e. Sub group mean difference was 14.2° 95%CI=0.4 to 28.0 whereas the ITT mean difference between groups at the same time point was 14° , 95%CI=6.1 to 21.6).

In the sub-group, there was a continued treatment effect that resulted in a significant difference between the treatment and placebo groups at the six-month assessment. At six months the treatment group had maintained much more range of movement than the placebo group (mean difference= 28.4° 95%CI=2.3 to 54.5) and developed less stiffness (mean difference= 10.2mN/deg , 95%CI=18.8 to 1.7). These differences were statistically significant and clinically meaningful for the wrist. At the elbow the results of the sub-group analysis were similar to the ITT analysis. The only statistically significant difference in the sub-group analysis between the placebo and treatment groups was found at the same time point of six weeks post stroke when a mean difference of 12.9° (95%CI=0.7 to 25.2) between the groups was identified.

The scientific literature clearly suggested that this group, who were less likely to recover, would benefit greatest from early preventative treatment and this has been borne out. Two previous randomised controlled trials investigating early treatment with botulinum toxin, albeit with the Ashworth scale as their primary outcome measure, appear to have used much less severely impaired participants. Hesse et al (2012) used an inclusion criteria of “partly independent in the basic activities of daily living (>25/100 on the Barthel Index)”. Similarly, Rosales et al (2012) had two groups with NIHSS scores at baseline [mean (SD)] of 4.9 (3.0) and 4.5 (2.7). Despite these less severely affected participants, both studies reported similar benefits to the current study in reducing contracture formation.

The results of the sub-group analysis will assist in developing the understanding of how contractures develop by identifying which stroke survivors are most at risk of developing them. There were two other groups within the study who also contribute to this area of understanding and are now presented.

4.2.2. Possible causation of contractures

There are two groups of outliers - neither of which were included in the randomised controlled trial phase of the study - who are of great importance in trying to further clarify the causes of contracture progression.

Both of these outlier groups consist of just three people each. The first group were the group of three who did not develop any abnormal muscle activity in the first six weeks, and never recovered any function throughout the six months.

One of these three subsequently died but at six-month follow up the other two were independently walking and wore an arm sling to ‘de-weight’ the arm while

walking. This meant that their arm was kept in pro-longed flexion at the elbow. By six months neither of these participants had developed evidence of spasticity, stiffness or loss of range. This group, who had no arm function, provides further evidence that spasticity appears to be required for contractures to develop within the first six months.

The other important group of three people came from the group who had recovered function so that they were not included in the randomised controlled trial. These three people were the only participants in the group of sixteen to recover function who did not achieve either 56 or 57 on the ARAT at six-month follow up. These three patients all had a prior diagnosis of dementia. The dementia was severe enough to limit activities of daily living and all three did not use the arm functionally during the day. All three at six-month follow up had developed contractures.

This suggests that it is the regular use of the arm functionally throughout the day that is important in prevention of contracture rather than just the presence of motor activity. Previous studies have highlighted that strength is a predictor of contracture development (Kwah et al 2012) but these three people suggest function is even more important.

This information is of importance in clinical treatment. There are two specific impairments following stroke where a patient may recover motor activity and potentially even arm function but not use the arm functionally (without prompting) - those patients who have a hemi-neglect, and those with cognitive impairments. These groups are therefore at risk of developing contractures even though they may appear to be unlikely to do so on testing of function. This

data is only based on a very small group but could be vitally important to include if a treatment algorithm was being developed in the future to identify patients at risk of contracture development.

4.2.3. Assessments of contractures

One particular issue with the current study methodology was the measurements of contracture. It can be argued that, to measure range of movement, a standardised torque should be employed during the stretch (Magnusson et al 1996). For instance, if an assessor only used a maximum of 10nM of pressure before deciding that the end point of a joint had been reached on one assessment but then used 50nM the next time, one could expect that the range would appear to have increased.

If a standardised torque is not employed then other variables might theoretically be the cause of a change in range of motion such as tolerance of the patient to stretch (Magnusson et al 1996). Folpp et al (2006) found that such an improvement in tolerance to stretch produced a mean 8° (95%CI 5° to 12°) treatment effect. The current trial showed that range of movement decreased, so increased stretch tolerance is unlikely to have been an issue in the current study.

Using a standardised torque in the current study would have necessitated the use of a large rigging system, such as that used described by Harvey et al (2006). It was important that the present study used simple methods that could

be carried out in people's homes or residential care homes. It should also be acknowledged that maintaining a standardised torque throughout the whole range of movement of a joint (particularly the wrist that moves through almost 180°) is very difficult to achieve. It is unlikely that even the rigging system, designed to maintain a constant torque, actually achieves this aim throughout the whole muscle and joint range.

It was always the aim of this study to allow the whole methodology to begin being used in practice if the evidence identified a useful outcome. Range of movement is the easiest outcome measure for clinicians to use, and in this study the placebo group lost range 2.9 (4.5) times faster in the elbow and 1.7 (2.1) times faster in the wrist over the first twelve weeks in the intention to treat (sub-group) analysis.

4.3. Functional recovery

This study treated patients who had not recovered any arm function by the time that spasticity was identified. Based on other studies, this lack of initial functional recovery over the early days post stroke suggested that full functional recovery was unlikely (Prabhakaran et al 2008 Nijland et al 2010). Therefore, the expectation for this study was that there would be minimal recovery of function in either treatment or placebo group in the ITT cohort.

In fact, seven individuals in each group (around 15% of the population) recovered almost full function (ARAT score between 53 and 57). Analysis of these 14 patients did not detect any differences in demographic or initial stroke severity to the whole group. Additionally, the results from the sub-group indicated that those with severe strokes (NIHSS>15) derived greater benefit from treatment than those with less severe strokes. When these results are considered together, it suggests that a better predictor of functional recovery is required than was used in this study.

Since this study was initiated, better methods at attempting to prognosticate arm recovery post stroke have been described. The use of shoulder abduction and finger extension muscle strength (SAFE assessment) described by Nijland et al (2010), and the SAFE assessment combined with motor evoked potential and magnetic resonance imaging (Stinear et al 2012), are two methods that appear to allow better identification of people who are unlikely to recover function. Using a better method to establish who is least likely to recover function will allow stratification of patients into groups at greatest risk of developing contractures versus those at lower risk.

4.3.1. The influence of treatment on functional recovery

The aim of spasticity treatment is to decrease an overactive muscle. With this in mind, the treatment of spasticity on its own is unlikely to specifically improve function except in a small proportion of patients (with dystonic features on EMG). While in this study there was no significant difference between groups, there was a tendency towards the treatment group improving more than the placebo group. Any functional improvement observed in this study is possibly due to the treatment choices made by the physiotherapists. The treating therapist only has a short period of time to provide treatment on a daily basis and, depending on the assessment, may focus this treatment on passive therapies with the aim of preventing contracture, or more active and functionally orientated therapeutic activities. If the therapist perceived less stiffness in one patient then much more functional task specific treatments may have been provided. This would have increased that patient's likelihood of achieving function in the medium term. A second possibility is that if arm spasticity is not treated in a timely manner, then the resulting stiffness and pain will make any recovery of arm movement that does occur more difficult. If arm movement becomes associated with pain then it is not as likely to be moved. This will make the less affected arm become more active in order to compensate and lead to the development of learned non-use of the affected arm. By maintaining the soft-tissue integrity of the arm for a longer period of time there may be an extended window for natural recovery to occur. This hypothesis is more likely to be seen over a longer follow up period than was possible in this six-month study. Any further study would ideally follow up participants for two years following stroke, and may include more than one cycle of injections.

4.3.2. Previous studies relating to functional improvement

The phase II study by Cousins et al (2010), which acted as a point of reference for the present study, found a significant statistical and clinical difference in the group of patients who had no recovery of activity at injection. In looking at the differences between the studies, the improvement in the placebo group in the present study appears to have been greater than in the Cousins et al (2010) study. The current study used electrical stimulation as a standardised physiotherapy procedure. It is also possible that the lack of significance in the present study was the result of variations in standard physiotherapy care between the two studies.

Rosewilliam et al (2012) described a possible functional benefit in a randomised controlled trial involving a similar electrical stimulation protocol to the present study. The difference between the two studies was that Rosewilliam et al (2012) used a six-week treatment period whereas the present study used a twelve-week treatment period. The increased electrical stimulation treatment period provided in the present study may have resulted in the greater functional recovery of this placebo group compared to the Cousins et al (2010) botulinum toxin study. This potential issue exemplifies the importance of expanding studies to multi-centre investigations in order to ensure the generalisability of the results and show external validity (Bellomo et al 2009). This is one limitation of the current study and the next section will review other potential limitations to the study.

4.4. Limitations of the current study

The current study was a single site study. Two meta-epidemiological studies have investigated the size of intervention effects between single centre and multi centre randomised trials when either a dichotomous outcome (Dechartres et al 2011) or continuous outcome (Bafeta et al 2012) is used. Both studies found that single centre studies provided larger intervention effects (Dechartres et al 2011, Bafeta et al 2012). Two issues could interfere with generalisability in a single centre study. One is that the group being investigated are not diverse (Bellomo et al 2009). In this current study, this did not appear to be the case. 31% of the participants were not from the UK, and people from at least eleven different countries were included. Participants also showed large differences in terms of socio-economic and cultural backgrounds.

The second factor is a potential confounding factor specific to the trial site such as “highly atypical expertise and commitment” (Bellomo et al, p3116, 2009). This factor is very relevant to the current study and might limit the generalisability of the results to the rest of the NHS and beyond. The physiotherapists who work at the Trust involved in the study are almost unique in their keen commitment to advancing practice and experience in stroke recovery. This is indicated by the fact that 89% of the injections in the trial were carried out by a physiotherapist and that electrical stimulation is normal practice in the hospital for patients who have no arm recovery.

4.4.1. Prevalence of spasticity

This study identified a much higher prevalence of spasticity than previous studies. Although the main reasons for this have already been discussed, a limitation of the present study is the sampling technique used. In order to calculate prevalence, the whole population needs to be assessed. This study only targeted patients who had suffered the most severe strokes so it is only possible to state that the prevalence is high in this specific group. While other studies appear to have assessed the whole population, they have excluded patients who were not able to consent for themselves. The current study was careful to include these stroke survivors as they were more likely to develop spasticity given their more severe stroke. A further study needs to be completed to investigate the true prevalence of spasticity by recruiting sequential stroke admissions. Using the same technique but including less severely affected patients may assist in the understanding of how patients motor recovery occurs, and whether they are indeed less likely to develop spasticity. Some of the abnormal muscle activity observed in the acute stage could be a normal process of recovery that becomes inhibited as a person regains function.

4.4.2. Trial methodology

This study used a double blind randomised controlled trial methodology which has been credited as providing the strongest evidence for a clinical effect and is generally considered the gold standard for clinical trials (Bland 2015). Through randomisation, patients will be placed in either the placebo or treatment group entirely through chance. Within neurological rehabilitation the use of this

randomised controlled trial has been questioned (Ottenbacher 1995, DeJong et al 2005, Horn et al 2012) and in some cases even condemned (Kersten et al 2010). The common problem reported by all these papers is that there are so many variables to be considered in neurological rehabilitation that it is very difficult to account for all of them (DeJong et al 2005, Horn et al 2012). Such a problem is not exclusive to neurological rehabilitation and, by ensuring a large enough sample size to carry out expected sub-group analyses, such a problem could be negated (Bland 2015). Other concerns with the RCT as a methodology include difficulty in the stroke population to consent, ethical problems with randomisation, and difficulty with blinding patients (Horn et al 2012). These problems are not however confined to stroke rehabilitation and can be overcome with planning. All such issues have been overcome in the present study.

In some randomised controlled trials, there is a cross-over component to the intervention. This means that everyone would receive the treatment followed by a wash-out period and placebo followed by a wash-out period (Harris et al 2006). The present study wanted to treat people in the acute stage where natural recovery will have an effect on outcomes. The long treatment effect of Botulinum toxin was also a consideration and would have meant at least three months were required between each injection. The result was that a simple two arm parallel study was employed in this case.

The trial also ensured that both the patient and anyone involved in providing care and normal treatment were blinded to the study (in addition to the blinded assessor). Through blinding of all interested parties the risk of intentional or unintentional bias was greatly reduced (Day and Altman 2000).

4.4.3. Treatment groups

The basic objective of the current study was to try and prevent contracture by using both botulinum toxin and electrical stimulation. This study employed two groups– a treatment group (where the participant received an injection of botulinum toxin), and a placebo group (where the participant received an injection of saline solution), and both groups received electrical stimulation. Because there were two treatments (botulinum toxin and electrical stimulation) aiming to achieve the same objective, other methodologies could potentially have been used (Craig et al 2008).

One method would have been to use a four-armed trial, sometimes termed a 2x2 factorial, design where the subject was randomised to treatment A or placebo and then to treatment B or placebo (Stampfer et al 1985).

The current trial would thus have looked like this;

BTX-A injections with E-stim	BTX-A injections with placebo E-stim
Placebo injections with E-stim	Placebo injections with placebo E-stim

A second possible study is a three-armed study which would have looked like this;

BTX-A with E-stim	Placebo with E-stim	Placebo with placebo E-stim
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These designs would have provided information on the interaction between the two treatments (Stampfer et al 1985). The main drawback to increasing the arms of a study is that a much larger sample size is needed to gain significance.

Given the difficulty with recruitment, and time limitations of the current study, it was providential that a larger sample size was not required.

A further reason that the above two suggested methods were not employed was the use of placebo electrical stimulation. As explained above, only in cases of clinical equipoise should a placebo be used (Hellman and Hellman 1991), and there is evidence for a clinical effect with electrical stimulation. Pooled analysis of eleven trials indicates that the use of electrical stimulation in such a group of patients results in muscle strengthening, and leads to improvements at an activity level (Nascimento et al 2014). It could be argued that there is less clear evidence of a treatment effect for electrical stimulation in slowing contracture development, though there is some (Pandyan et al 1997).

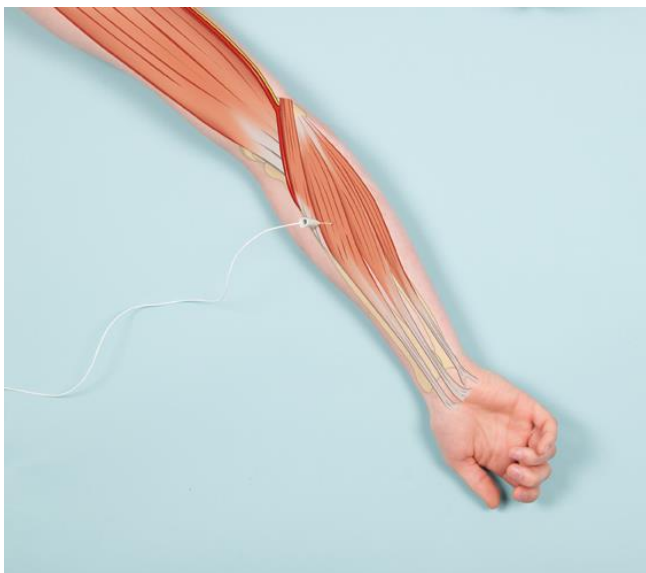
Another factor was that the team at the recruiting hospital already routinely provided electrical stimulation to patients with no arm function. Withdrawing treatment for inclusion in a trial may be deemed unethical by some (and would have caused difficulty for therapists inviting patients to become involved) and so use of placebo electrical stimulation was not considered (National Institute for Health Research 2010).

4.4.4. EMG placement

In order to assess spasticity using surface EMG it is imperative that uniformity of electrode placement is ensured. Placement to the forearm is notoriously difficult and this may have caused errors in measurement that could have confounded the statistical testing. The European consensus (SENIAM) on electrode placement includes all leg and upper arm muscles with the exception of the forearm muscles, presumably as there are so many in close proximity

(Hermans et al 1999). While the current study protocol used a standardised approach of palpation, it is conceivable that the surface EMG position varied slightly. Despite ensuring precise placement through the use of skilled handling and palpation, evidence of which muscle the surface electrode was placed on was not possible (unless Ultrasound had been used). This means that the surface electrode in some cases could have been placed over palmaris longus which is a muscle that was not injected. This may have produced an increase in the measured EMG activity in the treatment group.

Figure 5.9 - Muscles of the forearm



This figure shows some of the muscle of the forearm with brachioradialis removed. The muscles include – pronator teres, flexor carpi radialis (with needle), flexor digitorum superficialis and flexor carpi ulnaris. (with permission from Harding et al (2013))

4.5. Implications of the research

This study was instigated with the aim of providing information that would change clinical practice and rationale. While the size of the study and results will not result in changes to clinical guidelines, there are several important implications for clinicians and researchers. This section has been divided into clinical implications and research implications although some of the implications are equally relevant to both areas.

4.5.1. Clinical implications

Botulinum toxin is safe to use at this early stage following stroke. Clinicians have tended to use a wait and see approach when spasticity is identified clinically and then been cautious with treatment. Even within the research team involved in this study, there was concern that treatment with botulinum toxin at such an early stage would be detrimental to recovery. This study has indicated that recovery is not impacted at a functional level (or at an impairment level (Lindsay et al 2015)). This evidence, combined with the Cochrane review 'Pharmacological interventions other than botulinum toxin for spasticity after stroke' (carried out as part of this PhD), strengthens the argument against the traditional approach to spasticity management whereby anti-spasmodics are employed initially. This study has shown by inference that delaying the treatment of spasticity will allow contractures to develop.

Patients who develop contractures following stroke appear to have abnormal muscle activity and a lack of function. Muscle strength may not be a good

indicator for contracture development, especially in patients who have dementia, and who are unlikely to use the arm for functional activities. Problems with validity of clinical scales of spasticity have been highlighted in this thesis. The use of EMG to assess spasticity in this study was simple to deliver in both the clinical and home environment. The additional information gained from using EMG to assess spasticity makes its use in clinical practice worthwhile – particularly in an out-patient spasticity clinic setting. Since the EMG machine would be set up already it would take an additional 3 minutes to carry out assessments using EMG measurement. These types of clinics are spending over £8,000 to purchase an ultrasound machine whereas the cost of the EMG equipment used in this study was less than £3,000. Using an EMG machine to assess spasticity in chronic stroke is likely to allow better identification of contractures, and thus decrease the amount of people having unnecessary treatment.

4.5.2. Theoretical and research implications

While the use of EMG within the clinical setting would be useful, the use of EMG to further investigate spasticity within the research context is extremely important. While EMG has been used to assess spasticity, this study has highlighted that such investigations need to move a muscle through full range and hold at the end of range rather than move through a muscle's mid-range at varying velocities. The hypothesis that secondary muscle spindles, which activate group II afferents, may be the most important mechanism in causing contracture development (p117) needs further investigation, and could even identify novel therapeutic avenues to contracture prevention.

Another implication from the current study is the need to investigate dosage and frequency of injections of botulinum toxin. While spasticity was treated in both the elbow flexors and wrist flexors the effect of the treatment did not continue for 12 weeks which has been observed in previous results. The dose of botulinum toxin is recognised to contribute to the duration of efficacy, with higher doses leading to longer benefit. The dosage used in this study was half the recommended dose described in the RCP guidelines (Turner-Stokes et al 2009). This dosage was felt appropriate as the concern that injecting larger doses might impact negatively on normal recovery was a strong influence on informing the whole process. It is possible that these doses were too low to achieve the sustained 12-week effect.

There are two options to improve the treatment effect which need further study. The first is to simply increase the dose, but this might overly weaken the muscles and thus prevent potential functional recovery occurring. The alternative option would be to increase the frequency of injections. If a patient had recovered function in the intervening time then re-injections would not be necessary. In individuals where no recovery had been observed, re-injecting the muscles at an interval of between six and ten weeks at a similar dose may be beneficial. It would be hoped that using a shortened interval between injections would help continue to prevent stiffness and loss of range, but this would need to be investigated in further studies.

The summary of product characteristics state that re-injections should occur no sooner than 12 weeks following injection (Allergan SMPC (2015)). This 12 week delay is to prevent theoretical antibody formation, but this has not been reported as a problem in spasticity patients (Turner-Stokes et al 2009). Current clinical

practice has taken a pragmatic approach to this issue, and re-injections might be done more frequently when necessary. Three recent studies using botulinum toxin at shorter intervals have been conducted, but these were in the treatment of blepharospasm and cervical dystonia, and used Xeomin (incobotulinumtoxinA) (Evidente et al 2013, Truong et al 2013 and Evidente et al 2014). Patients were injected as necessary at as short as 6-week intervals, and Truong et al (2013) and Evidente et al (2014) carried out antibody assays on all participants periodically, and found that no participant developed neutralising antibodies over a one year period. Further investigation of botulinum toxin dosing and treatment effect would be valuable to inform better clinical decision making and patient outcomes.

The final implication from this study is that, given the positive results, it is important to carry out a further multi-centre randomised control trial. This trial would differ from the current trial in that it would need to use a better prognostic method to identify patients who are considered to have no functional recovery potential at all. The study will need to use contracture development as the primary outcome measure, but ideally would have a long follow-up period (of perhaps two years) to assess whether prevention of the contracture initially can lead to functional benefits later on. Such a study would also require some form of cost-effectiveness analysis to be included to investigate whether the treatment's clinical effectiveness is worth the cost to the Health Service.

5. Conclusion

This study set out to answer four questions and has provided six potentially important findings. The first finding came from a systematic review of the literature investigating the use of pharmacological methods to treat spasticity post stroke. This review found that there was insufficient evidence to determine if systemic antispasmodics were effective at reducing spasticity or improving function following stroke but did detect some very low-quality evidence that suggests there is an increased risk of adverse effects in people who take antispasmodics when compared with placebo.

The initial screening phase of the study showed that use of electromyography is an effective method of identifying and categorising spasticity. Moreover, the study results established that spasticity occurred much sooner after stroke than had previously been predicated.

Through the double blind randomised control trial, injections of botulinum toxin to the arm in the treatment group resulted in a significant slowing in the development of contracture formation including: stiffness being reversed; a slowing in the loss of range at both elbow and wrist joints.

During the study, and against predictions, a significant number of patients recovered function in their arm. This suggests that a better predictor must be found and employed in order to assess who is likely to recover function after a stroke in further studies.

In the sub-group – considered to have suffered the most severe strokes – there were significant differences, and much more clinically significant differences,

between treatment and placebo patients in the development of wrist contractures. Further studies should concentrate on this sub-group.

Finally, three people (in the group of sixteen assessed as having recovered function during the prospective stage) did not achieve either 56 or 57 on the ARAT at six-month follow up. These three patients all had a prior diagnosis of dementia that was severe enough to limit activities of daily living. None of the three used their arm functionally during the day and had all developed contractures at six-month follow-up.

A further multi-centre study would be useful in proving the generalisability of these results in order that the early use of botulinum toxin to reduce contracture development could be included in to clinical guidelines.

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Appendix 1

Proposed mechanisms involved in spasticity and potential involvement in post stroke spasticity

As described in the main text on page nine, Burke et al (2013) identified three major mechanisms by which spasticity may develop.

- Changes in the properties of the spinal motoneuron
- Changes in the afferent input to the spinal motoneuron
- Changes in reflex circuits that affect the motoneuron

This appendix will present the evidence for these mechanisms in further detail and describe reasons why some of the mechanisms do not fit into current understanding of post stroke spasticity.

Changes in the properties of the spinal motoneuron

The changes in the properties of the spinal motoneuron primarily relate to calcium dependent 'persistent inward currents' (Gorassini et al 2004). These currents amplify the input by between three and five times and cause sustained motoneuron firing through sustained excitatory drive following minimal synaptic excitation (Gorassini et al 2004). While there is good evidence for this in spinal cord injury Mottram et al (2010), Mottram et al (2009) found that persistent inward currents played only a minor role in spasticity following stroke. Dietz and Sinkjaer (2007) suggest this is the primary mechanism involved in spasms.

Changes in the afferent input to the spinal motoneuron

Burke et al (2013) reviewed three mechanisms by which afferent feedback from the muscle might change following an upper motor neuron lesion (enhanced

fusimotor drive via γ motor neuron activation, decreased pre-synaptic inhibition and homosynaptic depression). Of the three mechanisms only the third has good evidence in the stroke population (Lamy et al 2009 and Burke et al 2013). Enhanced fusimotor drive has been disproven by Wilson et al (1999) and Nielsen et al (1993). Faist et al (1994) identified that decreased pre-synaptic inhibition only occurred in spinal spasticity and not that arising from stroke. A study by Lamy et al (2009) identified a small decrease in pre-synaptic inhibition in a group of stroke patients when compared to 42 healthy controls. This study identified two concerns with their results. The first was that the less affected stroke side produced the same results as the affected side. They were also concerned at the lack of correlation Ashworth scale which is less of an issue.

The one established and generally accepted mechanism is post activation depression (also termed homosynaptic depression) between the Ia afferent and the motoneuron. This presentation is described in the main text of the thesis and was initially described in the cat by Curtis and Eccles (1960) who identified variations in the size of Ia excitatory postsynaptic potentials (EPSPs) varied with frequency of stimulation. The depression of the Ia EPSPs with longer intervals occurred as a result of previous transmitter release (Grey et al 2008) however once again the aetiology of this is not understood (Grey et al 2008). Aymard et al (2000) found that post activation depression correlated with the amount of spasticity in a population post stroke measured using the H-reflex.

Changes in reflex circuits that affect the motoneuron

A number of circuits have been identified as potentially playing a role in spasticity. Many of the changes in reflex circuits that have been observed

during testing of stroke patients have identified the same two issues highlighted by Lamy et al (2009) study (discussed above). Changes observed do not correlate with the degree of spasticity (when measured using a clinical assessment technique) and may also be observed in the less affected stroke side (Burke et al 2013).

Identified circuits include; recurrent inhibition (via Renshaw cells (Burke et al 2013)) and motor axon collaterals (Nielsen et al 2007)); Reciprocal Ia inhibition (from the antagonist muscle) (Nielsen et al 2007); non-reciprocal group I inhibition (previously termed Ib inhibition) (Burke et al 2013) from the Golgi tendon organs; Ib facilitation (Burke et al 2013); and Group II facilitation (Burke et al 2013) and inhibition (Nielsen et al 2007).

While the circuitry of these spinal reflexes is generally well studied, the importance of some mechanisms remains unclear (Lamy 2009). It has been suggested that different individuals might have varying circuit involvement (Burke et al 2013).

Discussion

The main difficulties in investigating these mechanisms further are highlighted in the main thesis already. It is possible that the importance of a single reflex circuit, or particular mechanism, may vary over time following a stroke. Without longitudinal studies that begin within the first two to three days following stroke this will remain a hypothesis.



National Research Ethics Service

NRES Committee North West - Greater Manchester South

3rd Floor - Barlow House
4 Minshull Street
Manchester
M1 3DZ

21 April 2011

Private & Confidential

Dr S Sturman, Consultant Neurologist
City Hospital
Dudley Road
Birmingham
B18 7QH

Dear Dr Sturman

Study Title:	Is it clinically effective to treat arm flexor spasticity, with Botulinum toxin – type A (BoNTA) and physiotherapy, as soon as signs of abnormal muscle activity are observed? (A phase II study)
REC reference number:	10/H1003/111
Protocol number:	PB-PG-0808-16319
EudraCT number:	2010-021257-39

Thank you for your response to the Committee's request for further information on the above research and submitting revised documentation. This has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Investigator CV – Dr Steve Sturman		18 March 2010
Investigator CV - Mr Cameron Lindsay		
Investigator CV - Dr Anand Pandyan		
Protocol	2	11 January 2011
REC application	3.0	01 November 2010
Covering Letter		29 October 2010
Summary/Synopsis	1	10 September 2010
Sample Diary/Patient Card	1	10 September 2010
GP/Consultant Information Sheets	2	04 January 2011
Participant Information Sheet	3	03 March 2011
Participant Consent Form	4	30 March 2011
Participant Consent Form – patient unable to physically sign	4	30 March 2011
Legal representative information sheet	4	30 March 2011
Participant Consent Form: Legal representative	4	30 March 2011
Questionnaire: The caregiver strain index		
Questionnaire: EQ-5D		
Covering letter for Caregiver Strain Index	1	19 January 2011
Caregiver Strain Index	1	19 January 2011
Summary of products characteristics		14 October 2010
Referee's or other scientific critique report		10 January 2011
Evidence of insurance or indemnity		
Response to request for further information		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

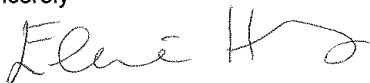
We would also inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H1003/111

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely



 **Dr Ann Wakefield**
Chair

Email: elaine.hutchings@northwest.nhs.uk

Enclosure: "After ethical review – guidance for researchers"

Copy to: Nicola Leighton
Keele University
Office of Research and Enterprise
Dorothy Hodgkin Building
Staffordshire
ST5 5BG

Dr Jocelyn Bell
Sandwell and West Birmingham Hospital NHS Trust
City Hospital
Dudley Road
Birmingham
B18 7QH

Safeguarding public health



Dr S Sturman
SANDWELL AND WEST BIRMINGHAM HOSPITALS NHS TRUST
DEPARTMENT OF NEUROLOGY
CITY HOSPITAL, DUDLEY ROAD
BIRMINGHAM
B18 7QH
UNITED KINGDOM

26/07/2011

Dear Dr S Sturman

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our reference: 21457/0202/001-0001
Eudract Number: 2010-021257-39
Product: Botox
Protocol number: PB-PG-0808-16319

NOTICE OF ACCEPTANCE

I am writing to inform you that the Licensing Authority accepts your request for a clinical trial authorisation (CTA), received on 27/06/2011.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed.

Yours sincerely,

**Clinical Trials Unit
MHRA**



Medicines and Healthcare products Regulatory Agency
151 Buckingham Palace Road London SW1W 9SZ
T 0203 080 6000 www.mhra.gov.uk

An executive agency of the Department of Health

**Sandwell & West Birmingham Hospitals
NHS Trust**



RESEARCH AND DEVELOPMENT

C E Clarke, BSc, MD, FRCP
J Bell, BSc, MSc, PhD
S Baxter, BSc
B Baines BA (Hons)

R&D Director
Head of R&D
RM&G Manager
R&D Administrator

(0121) 507 4811
(0121) 507 4092
(0121) 507 4091
Fax (0121) 507 4945

Arden House
City Hospital
Dudley Road
Birmingham
B18 7QH

CEC/SB/R&D Ref: 10STRO04

25 October 2011

Dr Steve Sturman
Consultant Neurologist
Department of Neurology
City Hospital

Dear Dr Sturman

Study Title: Is it clinically effective to treat arm flexor spasticity, with Botulinum toxin - type A (BoNTA) and physiotherapy, as soon as signs of abnormal muscle activity are observed? (A phase II study)

REC Ref: 10/H1003/111

CSP Number: 36398

Thank you for submitting your request to conduct this research in the Trust.

Conditions of Approval

I am pleased to inform you that the request is approved for the project you describe, and that your research can proceed subject to the following conditions:

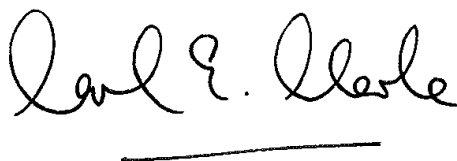
1. That you keep an up to date and accurate record of your research in a study file, and that you make this file and other records available for audit by the Research and Development Office when requested.
2. That you inform the R&D office of any changes to the study, related documentation or study personnel.
3. That you notify the R&D office of any adverse events arising from this research in accordance with Trust Procedure for safety reporting in research.
4. That where the research continues for more than 1 year, you provide the R&D office with an annual report of your research progress, when approval will be reviewed.

Documents approved by Research & Development Department

Documents	Version	Date
Protocol	3	04 July 2011
Summary/Synopsis	1	10 September 2010
Participant Information Sheet	3	03 March 2011
Legal Representative Information Sheet	4	30 March 2011
Participant Consent Form	4	30 March 2011
Participant Consent Form – patient unable to physically sign	4	30 March 2011
Participant Consent Form – legal representative	4	30 March 2011
GP/Consultant information Sheets	2	04 January 2011
Covering letter for Caregiver Strain Index	1	19 January 2011
Questionnaire: The Caregiver Strain Index		
Questionnaire: EQ-5D		
Caregiver Strain Index	1	19 January 2011
Summary of Product Characteristics		14 October 2010
MHRA		
REC Favourable Opinion Letter and subsequent amendments		21 April 2011

With best wishes for the success of this project.

Yours sincerely,



Carl E. Clarke

Professor C. E. Clarke, BSc, MD, FRCP
R&D Director

Copy: Cameron Lindsay – camlin3@hotmail.com
BBC CLRN – espbbeclrn@uhb.nhs.uk
Dr Anand Pandyan – a.d.pandyan@keele.ac.uk

K E E L E
UNIVERSITY**Appendix 5****Departments of Physiotherapy and Rehabilitation Medicine**

Information Sheet (V4) for:

(Name of patient)

Is it clinically effective to treat arm flexor spasticity, with botulinum toxin – type A (BoNTA) and physiotherapy, as soon as signs of abnormal muscle activity are observed? – A phase II study

You are invited to take part in the above study which is looking at the effects of early treatment with Botulinum Toxin on recovery of arm function following a stroke. If you are interested in participating in this study, it is important that you understand why the research is being done and what it will involve before you make a decision. Please take time to read the following information carefully, and discuss it with others if you wish, prior to confirming your willingness to participate in this study. If any information is unclear or if you would just like more information please contact **Mr Lindsay [Cameron], Dr Sturman, or Dr Pandyan (contact details can be found at the end of this form)**.

If you do not want to take part in this study, we would like to assure you that your current medical care will not be compromised in anyway and we would like to thank you for giving us a bit of your time.

The purpose for this study and the details of how the study will be carried out

The results from this study will contribute to an educational training programme leading to a PhD being undertaken by Cameron Lindsay at Keele University under the supervision of Dr Anand Pandyan (Contact details for both are at the end of this form). It is a study being funded by the NHS. Many people do not recover arm function following a stroke. People who do not recover arm function are at a risk of developing spasticity, pain and limb deformities. Botulinum toxin is already being used successfully for the treatment of established spasticity after stroke. In a previous pilot trial it was found that early use of Botulinum Toxin could lead to some improvement in function compared to those who were not injected with Botulinum toxin. In this research project we would like to confirm whether this is the case.

Who is eligible to participate in this study

Adult patients admitted to Sandwell or the City Hospital Birmingham with a stroke who have not recovered arm function will be eligible to participate in this clinical trial. Only patients who show evidence of spasticity will go in to the treatment phase of the study.

Do I have to take part?

It is up to you to decide to join the study. Participation in this clinical trial is **entirely voluntary** and you are **not obliged** to support this clinical trial. If you do decide to take part you will be given this information sheet to keep and be asked

to **sign a consent form**. If you decide to take part you are still **free to withdraw at any time** without giving a reason. A decision to withdraw at any time, **will not** affect the standard of care you receive. Also, if you decide not to take part in this study the standard of care you receive **will not** be affected in any way.

What will happen, if I decide to take part in this trial?

If you are recruited to the trial we will initially need to check your health status and the extent of your disabilities. For this we will need access to your medical records and carry out an appropriate medical examination. In addition, we will need to measure the extent of your arm weakness, the range through which your arm can be moved, stiffness and the levels of spasticity. The time taken for these measurements will not exceed 40-minutes. If you show signs of spasticity you will automatically progress to the treatment phase of the study.

Screening phase

- If you do not show signs of spasticity on initial assessment, we will monitor your levels of spasticity either daily or every alternate day, as clinically indicated, for a period of up to six weeks.
- If you were to develop spasticity at any point during the screening phase you will be automatically progressed to the treatment phase.
- If you do not develop spasticity or if you were to have a full recovery of arm function a final measurement will be taken and you will have completed the study.

Treatment phase

- You will be randomly allocated to one of two groups. A computer does this allocation and we will not be able to influence this process.
- If you are allocated to the treatment group you will receive an injection of Botulinum toxin Type A (Botox®) to the muscles that are at a risk of developing spasticity.
- If you are allocated to the control group you will receive an injection of the “placebo” or “sham” or “dummy” treatment to the relevant muscles. As the drug is colourless and has no externally distinct characteristics, it will not be possible for you to identify which group you have been allocated to.
- We plan to recruit 150 patients to this trial. This means that 75 patients will be randomly allocated to each group and people in the control group will not get the active treatment. It will not be possible to identify or influence the allocation process.

NB: Treatment, even if you are in the control group, can cause discomfort at the time of injection and this discomfort could last for a day or two.

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put 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. In this study there is an equal chance that you are allocated to the treatment or control group.

Details of the drug being used in this trial

Botulinum toxin is used to reduce the unwanted activity in your muscles. The drug is used extensively in the treatment of adults and children with established spasticity. Although no specific side effects have been associated with the drug used in this study, people have complained of mild flu like symptoms, pain and bruising following injections of botulinum toxin. Very rarely, transient swallowing difficulties lasting about two weeks have also been reported. All of the above symptoms are entirely reversible. This drug will need to be injected into the muscle by a doctor. Dr Sturman, the consultant on this project who has considerable experience on the use of Botulinum toxin in stroke, will be supervising treatment.

Electrical stimulation

You will be provided with an electrical stimulation device for the duration of the research. This device attaches to your forearm and provides an electrical stimulation to the forearm muscles that makes them tighten and move the wrist. Initially a therapist will put this on for you however we will either teach you or a carer to apply treatment so that you can continue to benefit from this treatment. Treatment with electrical stimulation will be given to all patients.

Measurements

In order to assess the effect of the injections we will take measurements of muscle activity at 2, 4 and 6 weeks following injection. We will also take measurements of arm weakness, range of movement, stiffness and muscle activity at 3 months and 6 months after the initial treatment. At these two points we will also request you fill in a questionnaire to measure quality of life. We will also request that your main carer fills in a questionnaire at this point. The time required for these measurements should not exceed 45-minutes. If you have already been discharged from hospital by the time of these assessments we will arrange transport for you to come to the clinic, if you wish.

Diary and Weekly telephone calls

On discharge from hospital we would like to phone you on a weekly basis to check how you are doing with the electrical stimulator. A diary will also be provided to help remind you to carry out the electrical stimulation; we would also like you to write in this diary how frequently you require NHS appointments on discharge.

Questionnaire

You will be asked to fill in a questionnaire regarding your thoughts on your quality of life and how your health status has changed. This questionnaire is a tick box sheet and takes less than 2 minutes to complete.

What will I have to do?

Once consent has been obtained you will need to do the following:

1. Be available for a baseline measurement
2. Be available for the injections

In addition we will need to take follow-up measurements, and, ask you to fill in a questionnaire and a diary. If you have been discharged from the hospital we will

need to contact you once a week, to check that all is going well, for the first three months within the study. The end of the Study is at 6 months following the Stroke.

Are there any alternatives to the treatment that is being used?

Physiotherapy is a recognised means of alleviating spasticity, but it does not work in all patients. You will be receiving physiotherapy as all the other patients after a stroke. So far there are no drug treatments for the prevention of spasticity. Three different companies currently market Botulinum toxin. Of the three products currently available in the market we are using Botox®. The two other products act in a similar way and are called Dysport® and Neurobloc®.

What are the possible disadvantages and advantages of taking part in the research?

The disadvantage of taking part in the research is that patients who go in to the treatment phase of the study will be given by an injection into one or several muscles. This may cause mild flu like symptoms, pain and bruising following treatment. As pointed out earlier, allergic reactions and swallowing difficulties can theoretically develop after treatment with Botulinum toxin, but these are very rare.

Injections of high doses of botulinum toxin into healthy muscles have been shown to cause temporary weakness in the muscles injected. However, research shows that using small doses of botulinum toxin in stroke patients (as used in this study) may improve strength instead of producing weakness.

The advantage of taking part in the trial is that Botulinum Toxin may prevent the development of spasticity and pain in the arm, and as shown in an earlier study may result in a more functionally active hand. People in the control group are likely to have no additional benefit, however, without a control group it will not be possible to confirm if treatment with botulinum toxin can be given to all stroke patients who develop spasticity.

What if new information becomes available?

It is possible that new information becomes available about the treatment/drug that is being studied during the course of this research project. If this happens we will tell you about it and discuss, with you, whether you want to continue in the study. If you decide to withdraw, your medical treatment and therapy will not be affected in any way. However, if you decide to continue in the study you will be asked to sign an updated consent form.

What happens when the research study stops?

At the end of the study we will analyse the data to check if additional treatment with botulinum toxin is clinically indicated. On completing the analysis if your doctors were of the view that you will benefit from treatment with Botulinum toxin the treatment will be provided to you via the normal NHS channels.

What if something goes wrong during this study?

Although the risks associated with treatment involving Botulinum toxin are low it is important to point out that if taking part in this research project harms you there are no special compensation arrangements. However, if you are harmed due to someone's negligence, then you may have grounds for a legal action but you

may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Will my taking part in this study be kept confidential?

If you consent to take part in the research we will need to inspect your medical records and notes. However, your name and contact details will not be divulged to any third party outside the research team. Also, all information which is collected about you during the course of the research will be treated anonymously, i.e. it will not be possible to identify you from the data collected and any data collected will be stored on a secure computer. Any information, about you, which leaves the hospital, will have your name and address removed so that you cannot be recognised from it. **We will, however, inform your GP about your participation in this study.**

What will happen to the results of the research study?

The results from this study will contribute to an educational training programme being undertaken by the researcher at Keele University. On completing this trial we will need to analyse the data to identify whether early treatment with Botulinum toxin prevents the development of spasticity and helps the recovery of arm function. The results of this study will be published in Conferences and Medical Journals. Copies of any such publications can be obtained by contacting Dr AD Pandyan. Once again we would like to stress that you will not be specifically be identified from the published data.

It is also possible that we will want to use the data collected in this study to support our other research projects. If you have no objections for us to use the data collected from you, during the course of this study, you will need to indicate this on the appropriate section in the consent form. If the data is used to support future research it will not be possible to specifically identify you from the data.

We would now like to thank you for having taken the time to enquire about our study. If you have any further questions please contact us and we will be happy to answer all your questions.

If we have answered all your questions and you want to support this study you will now need to sign the consent / assent form. If however, you have decided not to participate, we would like to thank you for taking the time to find out about this study.

We cannot promise the study will help you but the information we get from this study will help improve the treatment of people who have a Stroke in the future.

Thank you.

Mr Cameron Lindsay
Advanced Physiotherapist
City Hospital Birmingham
Dudley Road
Birmingham B18 7QH

Dr. S Sturman
Consultant Neurologist
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham B15 2W

Prof. A D Pandyan
School of Health and Rehabilitation
Keele University
Keele Staffs – ST5 5BG

Case Report Form**Appendix 6****Demographic Data**

Site

Subject Initials

Subject I.D.

Date

Gender: Male ☐ Female ☐

Age:

Ethnic Group:

First Language:

Previous stroke: No (If **NO** go to **Current Stroke**) Yes ☐ (If yes go to next question)Previous Stroke Type: TIA ☐ POCI ☐ LACI ☐
PACI ☐ TACI ☐**Current Stroke**:Type of Stroke: Haemorrhage ☐ Infarct ☐Thrombolysed: Yes ☐ No ☐Type: POCI ☐ LACI ☐ PACI ☐ TACI ☐

Area specified on CT

.....

Hemiplegic Side: R L Normal dominant side: R L

National Institute of Health Stroke Scale on admission

		<u>Score</u>
Level of Consciousness	0 = Alert 1 = Not alert but rousable to minor stimulation 2 = Not alert and requires repeated stimulation to attend 3 = Responds on with reflex motor effects	
LOC Questions	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly	
LOC Commands	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	
Best Gaze	0 = Normal gaze 1 = Partial gaze palsy 2 = Forced deviation	

Vision	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	
Facial Palsy	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	
Motor Arm	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm	
Motor Leg	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg	
Limb Ataxia	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain: _____	
Sensory	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	
Best Language	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	
Dysarthria	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain: _____	
Extinction and Inattention (formerly Neglect)	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize	



KEELE
UNIVERSITY

Appendix 7

Departments of Physiotherapy and Rehabilitation Medicine

CONSENT FORM V4

Study title: Is it clinically effective to treat arm flexor spasticity, with Botulinum toxin – type A (BoNTA) and physiotherapy, as soon as signs of abnormal muscle activity are observed?

Please initial against each point below

I confirm that I have read the information sheet (v3.0) about this study
 I confirm that I understand the above information sheet about this study
 I confirm that I have had the opportunity to ask questions about this study to Cameron Lindsay and that all my questions have been satisfactorily answered

.....
.....
.....

I understand that staff involved in the study may examine those sections of my medical notes that are relevant to my taking part in research.
 I give permission for these individuals to have access to my records.

.....
.....

I understand that **my participation is voluntary** and that I am **free to withdraw at any time, without giving any reason**, without my medical care or legal rights being affected or compromised in any way. I am under no obligation to partake in the study.

.....

I agree to take part in this study

.....

I permit the use of anonymous data from this trial to support other research projects

.....

I permit the study to advise my GP that I am participating in this research project

.....

.....
 (Patient name)

.....
 (Patient signature) (Date)

.....
 (Witness name)

.....
 (Witness Signature) (Date)

.....
 (Researcher name)

.....
 (Researcher signature) (Date)

1 copy for patient; 1 copy for researcher; 1 copy to be kept with hospital notes

Researchers: **Dr A D Pandyan**, School of Health and Rehabilitation Keele University, Keele 01782734252. Fax: 01782734255. **Dr. S Sturman**, Consultant Neurologist, City Hospital Birmingham, Dudley Road, B18 7QH. 0121 554 3801 **Cameron Lindsay**, Advanced Physiotherapist, City Hospital Birmingham, Dudley Road, B18 7QH. 07971 866 483

Appendix 8

Name	Role in Study	Start Date	Tasks Performed	Signature
C Lindsay*	Research Physiotherapist	May 2011	1,2,3,5,6,7,12,13,14,15,16,17,19,20,21,22,23	
S Sturman*	Principal Investigator	May 2011	1,2,3,6,7,8,9,12,13,14,15	
A Pandyan	Principal Investigator	May 2011	12,13,14	
D Hicklin*	Injector	May 2011	6,18,	
S Clegg*	Pharmacist	May 2011	4,6,10,11	
J Simpson*	Research Pharmacist	May 2011	4,6,10,11	
F Siddiqui*	Prescriber	May 2011	6,9	
K Sharobeem*	Prescriber	May 2011	6,9	
J Khaira*	Prescriber	May 2011	6,9	
C Simcox	Physiotherapist	May 2011	3,6,22	
C Finnemore	Physiotherapist	May 2011	6,22	
J Bearsmore	Physiotherapist	May 2011	6,22	
P Harding*	Consultant Physio	May 2011	3,17 (Needs GCP)	
S Kurdowar	Stroke research Nurse	July 2011	3	
	Stroke research Nurse			
Sarah	Pharmacy Tech	May 2011	6	

1. Finally determine eligibility	13. Ethics/R&D Submissions
2. Obtain informed consent	14. Bi-annual Ethics Report
3. Screen patients/give patients information as part of consent process	15. Maintain SOPS file
4. Randomisation and allocation of patients	16. Pre randomisation assessment
5. Complete CRF's	17. Baseline Measures
6. Sign CRF's	18. Injector
7. Report SAEs, AEs	19. Week 2,4,6 assessment
8. Report SUSARS	20. Midpoint assessment
9. Prescription of trial regimes	21. Endpoint assessment
10. Order, receive, store and dispense trial drugs	22. Teaching patient/carer to use E-Stim on D/C
11. Maintain pharmacy file	23. Maintain Main Trial Folder
12. Data Protection (Caldicott Guardian)	

*These people require Certificates of GCP to participate in the Trial due to the Tasks delegated to them.

Early Use of Botulinum Toxin in Spasticity post Stroke (EUBoSS)

Blinded Clinical Trial Prescription

Appendix 9

EUdraCT number: 2010-021257-39	Pharmacist (Sig)	
Version 1	Physiotherapist (Sig)	
SWBH NHS Trust	P. Investigator (Sig)	

Place Patient Label Here

Patient Trial/Study No:

Confirm patient name here

Date: _____

Please prepare a syringe containing:

	Units of Botulinum Toxin Type A / BOTOX or Placebo
	ml of 0.9% Sodium Chloride

and a further syringe containing:

	Units of Botulinum Toxin Type A / BOTOX or Placebo
	ml of 0.9% Sodium Chloride

Signature of Prescriber: _____

Date of Prescription: _____

For intra-muscular injection in to

Muscle	Maximum dose allowed (Units)	Dose to inject (Units)	Injectors signature when administered	Date
Biceps:	50			
Brachialis:	50			
Flexor Digitorum Profundus:	30			
Flexor Digitorum Superficialis:	30			
Flexor Carpi Radialis:	20			
Flexor Carpi Ulnaris:	20			
Remainder (to be disposed of)	--			

Maximum dose / person: 200 BOTOX® Units

Early Use of Botulinum Toxin in post Stroke Spasticity (EUBoSS)**Appendix 10****Unblinding Standard Operating Procedure**

EUdraCT number: 2010-021257-39	Pharmacist (Sig)	
Version 1	Physiotherapist (Sig)	
SWBH NHS Trust	Investigator (Sig)	

Background

This patient has agreed to be on the EUBoSS Trial. The patient will have been given either a placebo injection of 0.9% NaCl solution or active injection of Botulinum Toxin reconstituted in 0.9% NaCl solution. To ensure scientific rigour the patient and injector have been blinded to what type of injection they received.

It is not expected that any adverse reactions to either injection will occur however this standard operating procedure should be followed in the case of a possible adverse reaction.

Unblinding Criteria

Blinding will only be broken where it is uncertain whether an adverse event is associated with the study drug AND knowledge of the drug allocation will have a direct bearing on the course of treatment.

Unblinding Information

The Principal Investigator should be contacted in the first instance (or delegated Consultant to cover leave). The Principal Investigator is Dr Sturman (Contact through IVOR). Dr Sturman will then assess the situation and decide if it is necessary to unblind the patient from the Trial.

Unblinding Procedure

1. Dr Sturman will contact Pharmacy who hold the unblinding information. If within hours this will be the Clinical Trial Pharmacy Team. If out of hours this will be the On-Call Pharmacist through switchboard.
2. The pharmacist will ensure the correct identification of the patient by cross checking the details provided by Dr Sturman with the dispensing log:
 - a. Name
 - b. Date of Birth
 - c. RXK (Hospital Number)
3. The pharmacist will identify the correct number in the randomisation folder for the patient from the dispensing log.
4. The sealed envelope containing the unblinded information shall then be retrieved from the pharmacy file.
5. The envelope is then opened by the pharmacist who will inform Dr Sturman immediately of the group the patient was in.
6. The Pharmacist shall then complete an unblinding notification form with the following information.
 - a. Patients details: Treatment pack number, patient RXK number, Date of birth and Trial Number.
 - b. Reason for unblinding
 - c. Unblinding details: Name, Pharmacist Position, Signature of Pharmacist performing the unblinding and date and time of unblinding.
7. The unblinding notification information should be sent to: Cameron Lindsay

Appendix 11

[illegible]

Site

Subject Initials

Subject I.D.

Date

Range of movementPatient position: High Lying in bed ☐ Sitting in Chair ☐

	PROM	AROM	Power	Additional information
Sh Flex				
Sh Abd				
Sh L. Rot				

Does shoulder have: Pain

Tightness

Subluxation

Spasticity

Aims of these measures are to assess

Velocity (for emg angle and force angle – both for fast and slow)

EMG activity (EMG angle fast and slow)

Pattern of EMG (EMG angle fast and slow)

Stiffness (force angle fast and slow)

ROM (EMG angle slow)

Angle at which EMG occurs (EMG angle fast and slow)

Patient Position

With patients shoulder in 90° abduction and resting on table.

Spasticity/Contracture	Elbow Flexion	Elbow Extension
Slow angle EMG		
Fast angle EMG		
Slow Force angle		
Fast force angle		
Tardieu scale		R1 R3 ()

Patient Position

With patients shoulder in neutral and elbow in 90° flexion and in mid position (pronation/supination) resting on table.

Spasticity/Contracture	Wrist Flexion	Wrist Extension
Slow angle EMG		
Fast angle EMG		
Slow Force angle		
Fast force angle		
Tardieu Scale		R1 R3 ()

ATTACH PRINT OUT AT BACK OF FORM

Site

Subject Initials

Subject I.D.

Date

Muscle function

Aims of these measures are to assess

Maximum strength

Rate of force production

Fatigue

Duration

Patient Position

With shoulder in 45° flexion and resting on pillow.

Apply load cell to palmar aspect / dorsal aspect of forearm 3 finger breadths from wrist crease. With elbow in Supination.

Isometric strength	Elbow Flexion	Elbow Extension
Maximum strength		
Fatigue of strength		

Patient Position

With elbow at 90° flexion and in mid position (pronation/supination) resting on table.

Apply load cell to palmar aspect/dorsal aspect of hand in line with 5th MCP joint.

Isometric strength	Wrist Flexion	Wrist Extension
Isometric strength		
Fatigue of strength		

Patient Position

With elbow at 90° flexion and in mid position (pronation/supination). Maintain wrist in neutral.

Isometric strength	JAMAR (Grip Strength)
Isometric voluntary strength	
Fatigue of strength	

ATTACH PRINT OUT AT BACK OF FORM

Site

Subject Initials

Subject I.D.

Date

Action Research Arm Test Score

Scoring:

- 3 = Performs test normally
- 2 = Completes test, but takes abnormally long time or has great difficulty
- 1 = Performs test partially
- 0 = Can perform no part of test

a. Subtest grasp

		Score	Score
		Left	Right
1.	Block 10 cm (If score = 3, total = 18 and → GRIP)		
2.	Block 2.5 cm (If score = 0, total = 0 and → GRIP)		
3.	Block 5 cm		
4.	Block 7.5cm		
5.	Cricket ball		
6.	Stone		

b. Subtest Grip

		Score	Score
		Left	Right
1.	Pour water from glass to glass (pronation) (If score = 3, total = 12 and → PINCH)		
2.	Tube 2.25cm (If score = 0, total = 0 and → PINCH)		
3.	Tube 1cm		
4.	Washer over Bolt		

c. Subtest Pinch

		Score	Score
		Left	Right
1.	Ball bearing, 6mm, 3rd finger and thumb (If score = 3, total = 18 and → GROSS MOVT)		
2.	Marble, 1st finger and thumb (If score = 0, total = 0 and → GROSS MOVT)		
3.	Ball bearing, 2nd finger and thumb		
4.	Ball bearing, 1st finger and thumb		
5.	Marble, 3rd finger and thumb		
6.	Marble 2nd finger and thumb		

d. Subtest Gross Movement

		Score	Score
		Left	Right
1.	Place hand behind head (If score = 3, total = 9. If score = 0, total = 0)		
2.	Place hand on top of head		
3.	Hand to mouth		

Site

Subject Initials

Subject I.D.

Date

PainThe most pain
you can imagine**Do you have pain anywhere during the ARAT?**

Do you have pain ALL THE TIME

Yes []

No []

Do you have pain at:

REST

MOVEMENT

NIGHT

The scale to the right is a measure of pain.**The top red circle indicates pain as bad as it could be****The bottom clear circle indicates no pain at all****Which circle best describes the pain that you feel?**

Ability to use the SPIN screen

Could the patient understand the scale:

Yes

No

Not sure

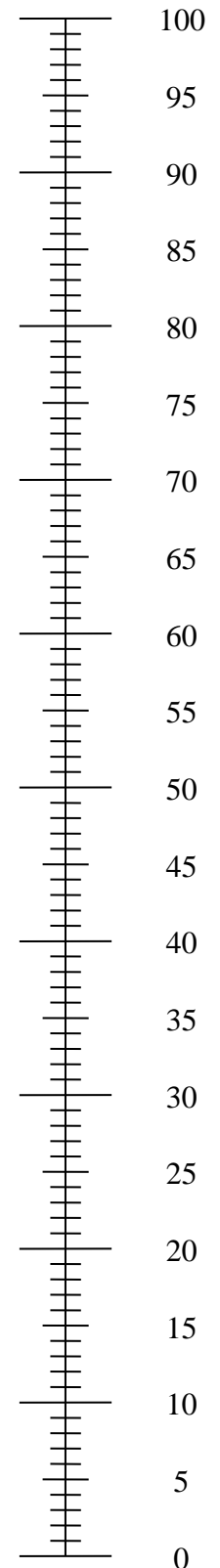
Cross-section area of Bicep:

Ultrasound Assessment of Biceps

Muscle thickness

With the patient in sitting resting forearm on pillow and elbow at 90 degrees. Measure the distance between acromion process and the medial epicondyle of the humerus. Divide this distance in to thirds and place the transducer at the distal third in a transverse plane. Ensure a good quantity of contact gel between the transducer and skin is used to minimise pressure required. Ensure the transducer is perpendicular to the skin before freezing image and saving.

Measure the distance between the medial epicondyle of the humerus to the ulnar styloid process and divide this distance in to fifths. Place the transducer at the proximal two fifths in a transverse plane on the anterior/flexor surface. Ensure a good quantity of contact gel between the transducer and skin is used to minimise pressure required. Ensure the transducer is perpendicular to the skin before freezing image and saving.



No pain at all

Site

Subject Initials

Subject I.D.

Date

Barthel Score:**FEEDING**

0 = unable

1 = needs help cutting, spreading butter, etc., or requires modified diet

2 = independent _____

BATHING

0 = dependent

1 = independent (or in shower) _____

GROOMING

0 = needs to help with personal care

1 = independent face/hair/teeth/shaving (implements provided) _____

DRESSING

0 = dependent

1 = needs help but can do about half unaided

2 = independent (including buttons, zips, laces, etc.) _____

BOWELS

0 = incontinent (or needs to be given enemas)

1 = occasional accident

2 = continent _____

BLADDER

0 = incontinent, or catheterized and unable to manage alone

1 = occasional accident

2 = continent _____

TOILET USE

0 = dependent

1 = needs some help, but can do something alone

2 = independent (on and off, dressing, wiping) _____

TRANSFERS (BED TO CHAIR AND BACK)

0 = unable, no sitting balance

1 = major help (one or two people, physical), can sit

2 = minor help (verbal or physical)

3 = independent _____

MOBILITY (ON LEVEL SURFACES)

0 = immobile or < 50 yards

1 = wheelchair independent, including corners, > 50 yards

2 = walks with help of one person (verbal or physical) > 50 yards

3 = independent (but may use any aid; for example, stick) > 50 yards _____

STAIRS

0 = unable

1 = needs help (verbal, physical, carrying aid)

2 = independent _____

TOTAL (0-20): _____**Specific rehabilitation of the arm should concentrate on**

Passive	[]
Active Assisted	[]
Muscle Strengthening/Active	[]
Functional	[]