# Effect of BTX-A treatment in hand and forearm muscles and tendons

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MAIN SPONSOR: Imperial College London
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IRAS Project ID: 296396
REC reference: N/A

**Protocol authorised by:**

| Name & Role | Date | Signature |
|---|---|---|

## Study Management Group

Chief Investigator: Dr Angela Kedgley

Co-investigators: Dr Maxim Horwitz, Dr Emmanouil Astrinakis, Miss Taiwo Kelani

Statistician: N/A

Study Management: N/A

## Clinical Queries

Clinical queries should be directed to Taiwo Kelani who will direct the query to the appropriate person

## Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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*This protocol describes the study entitled 'Effect of BTX-A treatment in hand and*
and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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# 1. Introduction

Cerebral palsy (CP) occurs in 2 to 3.5 of 1000 live births, with spastic CP, accounting for the majority of cases (1,2). This is a specific form of hypertonia that leads to an imbalance of muscle forces, which presents in the abnormal position of the limb. These abnormal positions can interfere with various motions of the upper limb, such as grasp-to-release function and the tasks involved in activities of daily living (ADLs) (3).

Tendon transfer is a popular surgical option to correct these deformities, whilst botulinum toxin type A (BTX-A) is a common non-surgical option and can be used to delay surgery and reduce spasticity. Repeat injections are considered where the clinical effects have diminished, and new goals have been established.

BTX-A has been reported as a safe and effective treatment with the ability to enhance performance in school activities, ADLs (4) and functional movement (5), particularly in children with mild movement impairments (6). There was an observation of increased muscle volume in the non-injected muscle and decreased volume in the injected muscle following BTX-A treatment in a population of children with spastic CP (7). Additionally, it has been found that BTX-A can induce muscle weakness in the target and non-target muscles (8,9), but there is little knowledge of how the mechanical properties of muscles contribute to this induced muscle weakness. Where a patient may require a tendon transfer surgery, following BTX-A treatment, the properties of the involved tendons may affect the outcome of surgery, due to the contribution of tendon mechanical properties to force generation of the muscle-tendon unit (10). This raises the questions of how BTX-A induced adaptations affect the functional ability of the upper extremity and how these adaptations may affect length of treatment. Addressing these questions will give us an indication of when decisions should be made to continue BTX-A treatment or to begin to consider surgery. Moreover, it is important to know if the continuous use of BTX-A affects the performance of the associated tendon in future surgical intervention. Currently, no objective evaluation is done to assess muscle and tendon mechanical properties prior to surgical intervention.

In order to build on the knowledge of the effects BTX-A has on the upper extremity, clinical hand assessments will be used in conjunction with biomechanical tools to investigate the mechanical and anthropometric adaptations. A novel technology, shear-wave elastography (SWE) will be used to evaluate the properties of muscles and tendons before and after BTX-A injections. The comparison of data collected before and after BTX-A treatment will inform the BTX-A induced adaptations. The data obtained from this study will be used to contribute to computational models in order to identify limits of suitability for a muscle or tendon to aid in surgical treatment.

This study will provide insight of the biomechanical adaptations of muscles and tendons after BTX-A treatment and how they contribute to joint function among a population of children with spastic CP. This will bring more understanding of the general behaviour of the musculoskeletal system following treatment which will benefit muscle and tendon selection for monitoring purposes or prospective surgical interventions and allow for a more objective guideline to be implemented.

## 2. Study Objectives

### 2.1 Primary Objective:

The primary objective of this study is to investigate the effect of BTX-A on the anthropometric and mechanical characteristics of muscles and tendons at various time points after BTX-A injections in children with spastic upper extremity CP.

### 2.2 Secondary Objective:

The secondary objectives are to use of shear wave elastography in upper limb musculature to better understand if this tool can be used to estimate tendon stiffness and to use the results of this study and computational models to identify limits of suitability for muscles and tendons to aid in surgical treatment following BTX-A injections.

## 3. Participant Entry

Children with spastic cerebral palsy between the ages of 4 and 18 years that are due to start BTX-A treatment in their upper limb will be recruited for this study. If the child and parent/carer are happy to take part, the parent/carer will be consented prior to enrolment and will sign the parent-carer consent form. With regards to those over 16 years, they will also be assented prior to enrolment.

### 3.1 Inclusion Criteria

1. Participants must be aged between 4 and 18 years.
2. Participants must be diagnosed with spastic cerebral palsy in at least one of their upper limbs.
3. Participants must be due to start BTX-A treatment for their affected upper limb.
4. Participants must have minimum ability to hold an object and stabilise it for use by the other hand.
5. Participants must be able to comprehend and complete the test protocol.
6. Participant or the participants parent/carer must be able to speak, read and understand English, in order to be involved in this study.

### 3.2 Exclusion Criteria

1. Any surgical intervention on the upper extremity in the last 6 months.
2. Any known allergy to adhesives.

3. Any known skin allergies.
4. Unable to obtain informed consent from participant's parent/carer.
5. The participant and the participants parent/carer are not able to speak, read and understand English.

### 3.3 Withdrawal Criteria

Participants will be informed, both verbally and in writing, of their right to withdraw from the study at any time without the withdrawal affecting the standard of care they receive or any future interactions they may have with Imperial College London or the NHS Trust. If any participant wishes to be withdrawn from the study then the information collected with consent up until that point would be retained and used in the study; however, no further data will be collected regarding the participant.

### 3.4 Sample size

Sample size: 8 healthy participants between the ages of 4 and 18.

### 3.5 Recruitment

For this study, potential participants due to start BTX-A treatment are invited to take part in the study and their parent/carer will be invited to take part in this research study by their hand surgeon when they are due to start BTX-A treatment. If interested, the potential participant's parent/carer contact details will be passed on to the co-investigator, (Miss Taiwo Kelani) and they will be provided the participant information sheet and any further information.

## 4. Study Design

### 4.1 Methodology

Participants will be asked to take part in all the tests listed below. This will take approximately 1 hour in total. The participants will attend three sessions at the 1st Floor, Paediatric Outpatients, Chelsea and Westminster Hospital (London, SW10 9NH). The first session being before they start BTX-A treatment, the second session will be between 3 weeks and 6 months after treatment and the third session will be at least 6 months after treatment. All the sessions will consist of the procedures described in sections 4.1.1, 4.1.2 and 4.1.3.

Upon arrival at the 1st Floor, Paediatric Outpatients Department, participants' carers will be asked to review the participant information sheet and sign the consent form, if they have not already done so. If the participant is over the age of 16 years of age, they will be asked to sign a consent form. For participants under the age of 16, they will sign an assent form. Demographic information regarding the participant's age (current year and month), diagnosis and any significant birth history or previous surgery will be documented. Participants must consent to the clinical care team

reviewing the ultrasound scan reports to ensure any incidental findings can be appropriately investigated and acted upon.

A camera with a tripod, will be used to video record future data processing. The participant will be seated at a table and the camera will be focused on the participant's upper extremity and the tabletop. For the best observation of participant's extremity, long hair will be restrained, if possible, and their sleeves will be rolled up above the elbow. The participant will be positioned sideways to the camera with uninvolved side closest to the camera and the involved side furthest from the camera. This position allows best visibility of the involved hand and thumb for the video.

Participants will be asked to take part in a series of three main activities: Shriners hospital upper extremity evaluation, ultrasound measurements and EMG measurements. Following each task, a 3-minute rest period will be designated in order to avoid the effects of fatigue.

### 4.1.1 Shriners Hospital Upper Extremity Evaluation (SHUEE)

The SHUEE is designed to evaluate both functional and spontaneous abilities, as well as to document dynamic segmental alignment when performing tasks (11). During this session, nine different activities will be performed. Each activity will be verbally explained, and participants will be allowed to trial the required motion prior to the start of the recording. For each task, all items must be placed on table, presented at midline, without reference to which hand should be used unless otherwise noted.

Money from wallet task: (1 minute)

For this task the participant is presented with a closed billfold style wallet and is asked to remove the paper bills from inside the wallet. If the participant doesn't use their involved extremity, the participant will be asked to do the task again letting the other hand help. The evaluator will replace the money in the wallet and the participant will repeat the task.

Fold piece of paper task: (1 minute)

For this task the participant is handed a plain sheet of paper and is asked to fold the paper in half in any fashion. If the participant doesn't use the involved extremity, the participant will be asked to do the task again letting the other hand help. The evaluator will flatten out the piece of paper and the participant will repeat the task.

Tear piece of paper task: (1 minute)

For this task the folded piece of paper is handed to the participant and is asked to tear the paper in two. The evaluator may initiate three tears and the paper does not have to be torn on the fold.

Unscrew bottle cap task: (1 minute)

For this task the participant is handed a screw cap bottle and is asked to remove the cap. The evaluator may loosen the cap and the cap does not have to be replaced by the participant. After participant completes the task, they will be asked to repeat it.

Pull Play-Doh® apart task: (1 minute)
For this task the evaluator will mould the Play-Doh® into a cylindrical shape and the participant will be asked to pull the Play-Doh® apart at least three times.

Accept coins/change task: (1 minute)
For this task the evaluator will give the participant three coins, placing them into the participants open palm. The participant should not use the table to facilitate supination so the participant can move away from the table for this task. If the participant doesn't use the involved extremity, the participant will be asked to do the task again using the other hand.

Touch opposite ear task: (1 minute)
For this task the participant is asked to touch their contralateral ear with their palm. If the participant doesn't use the involved extremity, the participant will be asked to do the task again using the other hand.

Place sticker on ball task: (1 minute)
For this task the participant is presented with a sticker and a ball and is asked to place the sticker on the ball. The ball is placed at arm's length from the participant to demonstrate elbow extension.

Put sock on task: (1 minute)
For this task the participant should have one sock and one shoe removed. The participant will be asked to put their sock back on. If the participant doesn't use involved extremity, the participant will be asked to do the task again letting the other hand help.

### 4.1.2 Shear-wave elastography ultrasound measurements

(20 minutes)
Shear-wave elastography (SWE) is a novel ultrasound technology for characterising mechanical properties of soft tissues through dynamic measurement of tissue displacement as a result of mechanical excitation. A LOGIQ E10 Ultrasound R2 system (GE Healthcare, Chicago, IL, USA) with a ML6-15-D probe (GE Healthcare, Chicago, IL, USA) will be used to collect SWE measurements including the shear-wave velocity during the relaxed and stretched states of the origin and insertion tendons of the muscles to be injected with BTX-A. As the shear modulus is equal to the shear-wave velocity multiplied by the density of the tissue, this will provide information regarding the elasticity of the tissue. In addition to this, the ultrasound measurements can provide tissue anthropometrics such as tissue length and cross-

sectional area. This will provide insight of the biomechanical adaptations after BTX-A treatment and how they contribute to joint function.

For this task the investigator will apply ultrasound gel between the probe and the participant's skin at the region of interest to limit tissue deformation caused by the operator. As the shear-wave velocity is dependent on the probe orientation relative to the muscle fibres, all the SWE acquisitions will be performed parallel to the direction of the muscle fibres and perpendicular to the participant's skin. When the ultrasound probe is correctly aligned, the shear-wave velocity and a sequence of 10 continuous images will be recorded. This will be repeated for the each of the muscles involved in the participant's BTX-A treatment.

### 4.1.3 EMG Measurements

(20 minutes)

The Modified Ashworth Scale (MAS) (11) evaluates the resistance to passive movement about a joint with varying degrees of velocity. The MAS is designed to evaluate spasticity. For this task the investigator will extend the participant's hand first from a position of maximal possible flexion to maximal possible extension. Afterwards, the investigator will flex the participant's hand first from a position of maximal possible extension to maximal possible flexion. Both of these motions will be repeated twice for each of the affected upper limbs.

Activity of the muscles due to be involved in BTX-A treatment and surrounding muscles will be observed during these motions using a Trigno wireless surface EMG system (Delsys, Natick, MA, USA).Wireless sensors will be placed on the skin of the participants using adhesive stickers. The participants will be instructed to inform the researcher prior to signing the consent form if they have any allergies or skin conditions. They have also been instructed that if they notice any drying irritation from the sensor adhesive during or immediately following the study, that they should inform the researcher and a clinician assist them. Ultrasound will be used to identify the muscles involved in the participant's BTX-A treatment and surface EMG sensors will be placed on said muscles to record muscle activity.

## 4.2 Data processing

The SHUEE uses a numerical scoring system. The participants performance is analysed and scored using the Spontaneous Functional Analysis (SFA), the Dynamic Positional Analysis (DPA), and the Grasp/Release Analysis (GRA).

<u>Spontaneous Functional Analysis (SFA):</u>

In order to assess the participant's actual function of the affected extremity, a spontaneous use score is recorded. For this portion of the scoring, a modified House

scale is used. The scale is shown in the table below. The SFA is recorded each of the 9 tasks.

| Modified House Scale | | |
|---|---|---|
| Class | Designation | Activity level |
| 0 | Does not use | Extremity not utilised in any capacity for completion of task. |
| 1 | Poor passive assist | Uses as stabilising weight only. |
| 2 | Passive assist | Can hold onto object paced in hand; may stabilise the object for use by other hand. |
| 3 | Poor active assist | Can actively grasp object and stabilise object for use by other hand. |
| 4 | Active assist | Can actively grasp and stabilise object for use by other hand; may manipulate object with affect hand. |
| 5 | Spontaneous use, partial to complete | Performs bimanual activities easily; may use the hands spontaneously or without reference to the other hand. |

Dynamic Positional Analysis (DPA):

The dynamic positional analysis score for each of the tasks is related to joint and limb segment movement. The DPA documents the dynamic, segmental alignment of the extremity when performing the task. The DPA assesses the following five functional/anatomical segments:

Thumb segment alignment:

- Thumb in palm – Any combination of metacarpophalangeal joint (MCP) flexion or interphalangeal joint (IP) flexion resulting in the thumb being placed beneath the fingers, in the palm. No visible web space is seen, from any angle at the first web space.
- Thumb Web Space Closed – No visible space at the first web space. Thumb is adducted and may have a hyperextended IP joint, but does not cross index metacarpal into palm. No visible web space is seen, from any angle at the first web space.
- Thumb Web Space Open – Thumb MCP in abduction. Any visible web space constitutes an “open” score. Participant able to extend or abduct thumb to grasp object. Participant does not have to maintain abducted posture to be given this score.

Finger Segment Alignment

Fingers are graded as a group because they frequently move in composite flexion or extension. The tasks used for thumb evaluation are used for finger evaluation.

- Flexion - MCP maintained in greater than 45° flexion. Fingers are held in palm, in variable flexion pattern at DIP joints.
- Neutral – Fingers are held in midrange with adequate alignment for task. Fingers easily fluctuate between flexion and extension patterns with no joint aberrations.
- Extension – Fingers are held in hyperextension at MCP or IP joints. Associated swan neck deformities or extensor splaying may also be present.

Wrist Segment Alignment

- Flexion – Wrist is held in flexed position throughout task; with or without ulnar deviation; any measurement between 0° - 80° of flexion.
- Anatomical neutral – Wrist in anatomical neutral position of 0º for all or portion of task; with or without ulnar deviation.
- Extension – Wrist extends past anatomical neutral position for all or portion of the task; any measurement between 0° - 70° of extension.
- Ulnar deviation – Wrist is held in an ulnarly deviated position throughout task; any measurement between 0° - 30°.
- Neutral – Wrist is in the neutral plane; within 5° of neutral.
- Radial deviation – Wrist is held in a radial deviated position throughout task; any measurement between 0° - 20°

Forearm Segment Alignment

- Extreme pronation – Excessive pronation, no active supination, resulting in palm away from body; any measurement 91° or greater.
- Pronation – Pronated at rest with no active supination during task, resulting in palm to floor; any measurement 0° - 90°.
- Neutral – Active movement from pronated position to neutral, resulting in 0° palm towards body.
- Supination – Active movement beyond neutral to supination with palm open to face. Anything 0° - 90°.

Elbow Segment Alignment

- Extreme flexion – Participant is unable to actively extend past 90º.
- Flexion – Participant is unable to extend past 30º.
- Extension – Participant is able to extend between 30º and 0º.

<u>Grasp and Release Analysis (GRA):</u>

The GRA documents if the participant can or cannot grasp and release the object with the wrist in the three different positions. A yes (Y) or no (N) for grasp and release is provided contingent on the participants ability to close and open fingers with the wrist

maintained in each position. Video examples of optimal grasp and release for each position are available online.

The SWE images obtained will be processed using a custom software developed in MATLAB (The MathWorks, Natick, MA, USA) to process the images semi-automatically.

The EMG signals obtained will be processed using a custom software developed in MATLAB that will ensure the signal is low-pass filtered for noise, full wave rectified and smoothed.

### 4.3 Equipment

A camera will be used to video record for future data processing.

For the SHUEE activity, the following will be used to obtain the corresponding SHUEE scores:

- Billfold style wallet to hold paper money
- 8 x 10 sheet of standard weight paper
- Three American dollar sized bills made of standard weight paper
- Four plastic coins of any size
- One wide-mouth clear 2-2 ½" diameter bottle with 2-2 ½" screw cap
- One Play-Doh® can
- Stickers of any size or type One 30" ball

For the ultrasound measurements, the following devices will be used:

- LOGIQ E10 Ultrasound R2 system (GE Healthcare, Chicago, IL, USA)
- A ML6-15-D probe (GE Healthcare, Chicago, IL, USA)
- Ultrasound gel

The equipment required for the tremor tests includes two triaxial accelerometer sensors (Delsys Trigno).

- Trigno wireless EMG system (Delsys, Natick, MA, USA)
- LOGIQ E10 Ultrasound R2 system (GE Healthcare, Chicago, IL, USA)
- A ML6-15-D probe (GE Healthcare, Chicago, IL, USA)
- Ultrasound gel

### 4.4 Outcome measures

Primary outcome measure: The primary outcome measures are the elasticity of the tendons and the anthropometrics of the muscles before and after BTX-A injections.

Secondary outcome measure: The secondary outcome measure is the comparison of computational models for data collected before and after BTX-A injections.

# 5. Adverse Events

## 5.1 In the event of an irritation due to ultrasound gel or EMG sensor adhesive

Participants will be informed that if they notice any irritation due to the contact with the ultrasound gel or EMG sensor adhesive during or immediately following the study, they should inform the investigators. The area will be cleaned with soap and water. Participants will be informed that if the irritation persists for more than 24 hours, they should inform the investigators of this study so that we may advise them as to whether to consult their local medical clinic.

## 5.2 In the event of fatigue during the test procedure

As some physical tasks will be undertaken, the participant may suffer from fatigue. If this happens, the participant should inform the investigators and the tests will stop until the participant feels prepared to continue with the test procedure.

## 5.3 Reporting of non-serious adverse events and serious adverse events

If any injuries, illnesses, or accidents should occur, a clinician will be called and all accidents and near misses will be reported.

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

### 5.3.1 Non serious adverse events

All such events, whether expected or not, should be recorded- it should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

### 5.3.2 Serious adverse events

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to pre-existing condition, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the NHS REC where in the opinion of the Chief Investigator, the event was:

- ‘related’, ie resulted from the administration of any of the research procedures; and
- ‘unexpected’, ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office

**Contact details for reporting SAEs**
**RGIT@imperial.ac.uk**
**CI email (and contact details below)**
**a.kedgley@imperial.ac.uk**
**02075940747**
**Please send SAE forms to: RGIT@imperial.ac.uk**
**Tel: 0207 594 1862 (Mon to Fri 09.00 – 17.00)**

## 6 Assessment and follow up

All ultrasound scans will be reported to and reviewed by the clinical care team so that in the event of incidental findings these can be appropriately investigated and acted upon. There will be no routine follow up for participants. The end of study is defined as the end of the third data collection session or the final data collection session for that participant.

The end of study is defined as the end of the third data collection session or the final data collection session for that participant.

## 7. Statistics and data analysis

The sample size has been calculated using a power analysis calculation. The data will be analysed using Shapiro-Wilk test to test for normality. Depending on the results of the Shapiro-Wilk test, the data will be further analysed using t-tests and ANOVA tests for comparison of data.
Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

## 8 Regulatory Issues

### 8.1 Ethical Approval

The Study Coordination Centre has obtained approval from the NHS Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

### 8.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for

consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

The parent/carer will be required to complete and sign the consent form prior to their child's participation in the study. If the participant is over the age of 16 years of age, they will be asked to sign a consent form. For participants who are 15 and turn 16 whilst on the study, they will also be asked to sign a consent form. For participants under the age of 16, they will sign an assent form.

### 8.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Video data will be pseudonymised All study data will be pseudonymised from the first data collection session and the data will only be identified by a unique participant number which will be given to each participant. Confidentiality of participants will be maintained in video recordings as the camera will be focused and positioned to not show the participants face.

### 8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

### 8.5 Sponsor

Imperial College London will act as the main sponsor for this study.

### 8.6 Funding

The study is funded by the EPSRC.

### 8.7 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to Good Clinical Practice.

## 9 Study Management

The day to day management of the study will be coordinated by Miss Taiwo Kelani.

## 10 Publication Policy

Research participants will be provided with a summary report of the findings at the end of the study, at their request. Our findings will be shared with the wider academic and clinical community through presentation at scientific conferences and open events, and publication in peer reviewed archival periodical. It is Imperial College London policy that all scholarly work be made available to anyone, free of charge. The publication of results, reports and findings from this study will follow this same policy.

## 11 References


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