The efficacy of repeat botulinum toxin injections in the management of spasticity in children and young adults with cerebral palsy: A systematic review

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List of Abbreviations

BT = Botulinum Toxin

COPM = Canadian Occupational Performance Measure

CP = Cerebral Palsy

DF = dorsiflexion

GMFCS = Gross Motor Function Classification System

HRQL = Health Related Quality of Life

NZ = New Zealand

NICE = National Institute for Health and Care Excellence

PF = plantarflexion

PT = physiotherapy

OT = occupational therapy

RCT = randomised controlled trial

ROB 2 = Version 2 of The Cochrane Risk-Of-Bias Tool for Randomized Controlled Trials

ROM = range of motion

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ABSTRACT

Background: Botulinum toxin (BT) is a common treatment intervention for the management of spasticity in children with Cerebral Palsy (CP). There are no national or internationally recognised clinical guidelines that provide clear information about the recommended frequency of repeat doses of BT and there are inconsistencies in clinical practice. The primary aim of this review was to determine the efficacy of repeat BT injections in the management of clinical outcomes in children with CP. The secondary aim was to compare the efficacy findings with the current National Institute for Health and Care Excellence (NICE) clinical guidelines to determine if the guidelines incorporate evidence-based recommendations concerning the timing and frequency of botulinum toxin injections.

Method: A systematic literature search was conducted across five databases to identify relevant articles. Eligibility criteria included participants aged between birth to 21 years old at time of enrolment, clinical diagnosis of CP, presence of spasticity, treatment intervention of two or more BT treatments, and a comparison intervention of either a different frequency of BT, other interventions, or no BT treatment. Three independent reviewers identified eligible studies. Nineteen randomised controlled trials (RCTs) and 17 observational studies met the inclusion criteria, and the 19 RCTs were analysed in this project. Study characteristics and findings were extracted, and methodological quality was assessed using Version 2 of the Cochrane risk-of-bias tool for randomised controlled trials (RoB 2). A descriptive analysis was performed to assess outcomes and determine the efficacy of i) different frequencies of repeat BT injections, ii) repeated BT versus no BT, and iii) repeated BT versus other interventions.

Results: A higher frequency of BT (4-monthly versus 12-monthly) resulted in significant short-term improvements in gait and adverse events were found to be twice as frequent. Reduced frequency of BT was found to improve outcomes in occupational performance when compared to OT only. Repeated BT compared with placebo injection resulted in improvements in gait and active ROM. Repeated BT compared

with other interventions such as BT only, OT only or surgical intervention resulted in significant improvements in ROM and spasticity.

Implications: The findings of this review provide evidence to support repeated BT improves spasticity, ROM and gait in the short-term only when compared to physiotherapy (PT) only, OT only or placebo injection. The recommended treatment frequency of BT is 12-monthly when the goal is to improve ROM and spasticity and 4-monthly when goal is to improve gait in the short-term only. Seven future recommendations suggest additional guidelines and changes to current NICE guidelines for translation to clinical practice. Future studies to investigate the long-term effectiveness of repeated BT in children with CP is required ensuring findings capture health related quality of life (HRQL) as a measure of participation.

1 INTRODUCTION

1.1 Cerebral palsy and neuromuscular impairments

Cerebral Palsy (CP) is a group of movement and postural abnormalities that are caused by non-progressive injury to the central nervous system that arises in utero, during birth, or up two years of old (García Salazar et al., 2015; Kruse et al., 2018; Qin et al., 2018; Ward et al., 2017). Cerebral Palsy is reported to be the most common cause of physical disability in children and depending on the magnitude and area of the brain lesion, can cause sensorimotor impairments, motor dysfunction and postural abnormalities (Falisse et al., 2018; Honkavaara & Rintala, 2018; Love et al., 2010; Qin et al., 2018; Ward et al., 2017). The neuromuscular impairments of CP include muscle weakness, hypertonia, disproportionate muscle co-contraction, decreased muscle-tendon length, and reduced selective muscle control (Brandenburg et al., 2019; García Salazar et al., 2015; Kruse et al., 2018; Schless et al., 2019).

Hypertonia is commonly observed in children with CP (Shamsoddini et al., 2014), and is defined as resistance to passive movement (Evans et al., 2017). Hypertonia may result from non-neural mechanical and structural changes to the musculotendinous unit, such as joint contracture, or from neural impairment such as

spasticity (Matsukiyo et al., 2017; Willerslev-Olsen et al., 2013). Spasticity is defined as a velocity-dependent abnormal increase in resistance to passive stretch (Boyaci et al., 2014; Brandenburg et al., 2019; Fairhurst, 2012; Honkavaara & Rintala, 2010; Pierce et al., 2010; Tisha et al., 2019). Hypertonicity and spasticity can result from any illness that causes an upper motor neuron lesion (Evans et al., 2017). Spasticity is present in up to 90% of children with CP and CP is the most common cause of spasticity in children (Lapeyre et al., 2010; Shamsoddini et al., 2014). If spasticity is not addressed and treated, harmful consequences can ensue including joint contracture, deformity, pain, bony lesions, fractures, joint subluxation, dislocation, diminished independence and decreased functional ability (Pavone et al., 2016; Shamsoddini et al., 2014).

1.2 Botulinum Toxin

Botulinum Toxin (BT) injections are acknowledged as a standard treatment intervention for the management of spasticity in children with CP (Shamsoddini et al., 2014; Zeuner & Deuschl, 2016). Botulinum toxin is injected into the target muscle group and causes muscle weakness by temporarily inhibiting the release of acetylcholine from the presynaptic terminal of the neuromuscular junction (Kaushik et al., 2018). Botulinum toxin has been evaluated and described in the literature as effective in inducing muscle relaxation, minimising spasticity, and improving joint ROM by two weeks post injection, with some research reporting improvements up to four months post injection (García Salazar et al., 2015; Love et al., 2010; Löwing et al., 2017; Zeuner & Deuschl, 2016).

1.3 Efficacy of repeated botulinum toxin injections

The physiological impacts of BT on nerve terminals persists for 12 to 16 weeks (Friedman et al., 2000). These impacts can continue for up to 18 months depending on physiological features of the muscle prior to BT, including power, endurance, spasticity, connective tissue extensibility, and joint ROM (Boyd & Graham, 1997). Thus, the effect of BT is temporary and repeated injections are routinely administered (Kahraman et al., 2016).

The evidence around the recommended frequency of repeat BT injections is not clear. In observational research, some studies have indicated benefits of repeated BT on ROM and function (Valentine et al., 2020, Choi et al., 2019, Mirska et al., 2019) and others have indicated no effect (Tedroff et al. 2009). A 2016 systematic review of 13 experimental and observational studies reported most studies found repeated BT resulted in short term improvements in ROM but changes in motor function were variable across the studies (Kahraman et al., 2016). Two randomised controlled trials (RCTs) compared 4-monthly versus 12-monthly BT and found no significant between-group differences in passive joint ROM and function (Hastings-Ison et al., 2016 & Kanovsky et al., 2009), raising questions about the benefit of more frequent injections. In addition, a narrative review by Multani et al. (2019a) questioned the ongoing clinical use of BT due to decreasing effects as children aged, and the possibility that repeated BT may actually increase the risk of contracture due to a loss of contractile elements and an increase in fibrosis.

1.4 Clinical Guidelines for Botulinum Toxin Management

There is a lack of specificity in the literature with regard to the recommended frequency and timing of BT for the treatment of spasticity in children with CP, with no clear internationally-recognised guidelines available (Shamsoddini et al., 2014; Ward et al., 2017). Recommendations in peer-reviewed literature between 1999 and 2008 have suggested that treatment frequency should range between 3-12 months (Eames et al., 1999; Graham et al., 2000; Simpson et al., 2008). These recommendations were based on influences for instance clinical intuition, avoidance of anticipated antibodies to BT, accessibility, and cost (Eames et al., 1999; Graham et al., 2000; Simpson et al., 2008).

In New Zealand (NZ) and according to Starship Hospital (2019), the Cerebral Palsy Society of NZ (2018), and The Paediatric Society of New Zealand and Starship Foundation (2018), there are currently no NZ-based clinical guidelines for the management and treatment of spasticity in children with CP. In the United Kingdom, NICE have a set of guidelines for clinicians to refer to regarding BT use in children with CP (National Institute for Health and Care Excellence, 2016). Their guidelines advise

that the frequency and dose of BT intervention should be individualised to the patient and dependent on the treating specialist and multi-disciplinary team. These guidelines align with NZ clinical practice, but they do not incorporate the latest recommendation that BT treatment intervention less than 12 months is not indicated for spastic equinus (National Institute for Health and Care Excellence, 2016). An Australian-based systematic review by Williams et al. (2020), examined clinical practice guidelines, consensus statements and Cochrane systematic reviews in the management of spasticity in adults and children. Twenty-five papers were included in the review, with only six including child participants with CP. The review recommended BT should only be provided to treat focal spasticity as part of a combined approach involving a specialised multidisciplinary team. Short-term and long-term use was advised although the recommended time frame for review and repeat injection was variable across different guidelines. Thus, the current guidelines do not provide specific recommendations related to repeated BT treatment frequency for children with CP and spasticity.

1.5 Objective

In response to i) inconsistent findings related to the efficacy of BT in children with CP, ii) no recent systematic review in this field, and iii) the lack of specificity and evidence-base in current clinical guidelines, this systematic review aimed to determine the efficacy of repeat BT injections in the management of clinical outcomes in children with CP. The secondary aim was to compare the efficacy findings with the current National Institute for Health and Care Excellence (NICE) clinical guidelines to determine if the guidelines incorporate evidence-based recommendations concerning the timing and frequency of botulinum toxin injections.

2. METHOD

A systematic review of the literature was performed using methodology described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (Moher et al., 2015). The review was registered on Prospero on 28th April 2021.

2.1 Search Strategy

A literature search was carried out independently by first reviewer (BM) using the following electronic databases: EBSCO (CINAHL, MEDLINE, SPORTdiscus), Scopus, and Web of Science. The search terms are included in Table 1. Article title and abstract, and full text as necessary, were screened independently by two pairs of reviewers (BM and SO, BM and GA) according to the eligibility criteria in Table 2. The participants were children aged from birth to 21 years old with a formal diagnosis of CP, and any other cause of spasticity was excluded. The interventions included intramuscular injections of a derivative of BT delivered at two or more treatment sessions into the same muscle group. To capture the breadth of relevant literature that might inform clinical recommendations, the comparison interventions could be either a different frequency of injection, other therapy, placebo, or no intervention. The outcomes were also broad to include any clinical measures of impairment, activity, or participation that might be clinically relevant. Given the volume of RCTs in this field was anticipated to be low (Kahraman et al., 2016, Multani et al., 2019a), both experimental and observational research was included. Any disagreements about inclusion were resolved through discussion or through consultation with a third reviewer. The methodological quality of RCTs was assessed by first reviewer (BM) according to Version 2 of the Cochrane Risk-of-bias Tool for Randomised Trials (RoB 2) (Higgins et al., 2011); this tool is recommended to evaluate the risk of bias in RCTs to ensure appropriate conclusions are made (Flemyng et al., 2020).

2.2 Data extraction

For the included studies, data was extracted by first reviewer (BM) using a data extraction table constructed on Microsoft Excel. In instances where there was one

study with more than one publication, reports were discussed between first (BM) reviewer and second (SO) reviewer and the publication with the most complete data was used. The following details were extracted for each article: study design, sample size, participant characteristics, target muscle, frequency, dose of BT, outcome measures and study findings. In addition, outcomes were grouped into categories of different frequencies of repeated BT, repeated BT vs other interventions, and repeated BT vs placebo injection.

2.3 Data Analysis

Studies were divided into three categories based on the comparison interventions: repeated BT versus placebo BT, comparison of different frequencies of BT, and repeated BT versus other interventions. Study findings were evaluated descriptively. Outcomes were also evaluated using the ICF outcome domains of body function and structure, activity and participation and potential harms. These findings were compared to the current National Institute for Health Care Excellence (NICE) guidelines.

Table 1
Search Terms

	Keywords	Subject headings incorporated with keywords*
	#1 Paediatric* OR Pediatric* OR child* OR infan* OR adolescen* OR "young adult*"	#4 Pediatrics, Children, Infant, Child, Adolescent
	#2 "Cerebral Palsy" OR Spastic* OR equinus OR diplegi*	#5 Cerebral Palsy
	#3 "botulinum toxin" OR dysport OR "abobotulinum toxin" OR botox OR "onabotulinum toxin" OR Vistabel OR Allergan OR Clostridium OR "neuromuscular agent*"	#6 Botulinum Toxin, Botulinum Toxins, Type A
#7	#1 OR #4	
#8	#2 OR #5	
#9	#3 OR #6	
#10	#7 and #8 and #9	
#11	#10 and 'English only' articles	

*Subject headings refined as appropriate within each database.

Table 2
Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Participants	Participants with spasticity and a formal diagnosis of CP. Aged between birth to 21 years old at initial BT treatment intervention	Spasticity caused by anything other than CP. In vitro or non-human trials.
Intervention	Delivery of BT via injection intramuscularly directly into the target muscle group (alone or in combination with additional therapy). Delivery of two or more BT injection treatment sessions into the same muscle group.	Delivery of any toxin other than a derivative of BT. Treatment of sialorrhea where BT is injected into the salivary glands.
Comparison	Comparison group of either a different frequency of injection, other therapy, placebo, or no intervention.	
Outcome	Study measures the effect of repeat BT injection using any quantitative clinical outcome measures of spasticity, range of motion, impairment, activity, or participation.	
Trial Design	Primary research using experimental or observational study design	Case reports, systematic reviews.
Type of publications	Studies published in English with full text available	Abstract-only articles, conference

3 RESULTS

3.1 Identification and Selection of Studies

After the removal of duplicates the electronic database literature search generated 1,326 citations. After exclusion based on title and abstract, 167 articles were attained for full-text review. Following full-text review 131 articles were excluded. The remaining 36 articles were reviewed according to study design and categorised as observational or experimental (RCT's). A total of 17 observational articles were put aside for later analysis (outside of this thesis). The remaining 19 experimental RCT's that met the selection criteria were included in the review. Figure 1 shows the PRISMA flow chart that summarizes the study selection process.

3.2 Description of Included Studies

Participants

The demographic characteristics of the included studies are shown in Table 3. A total of 1,092 children with CP and 20 typically developing children were included across the 19 articles. The number of participants varied throughout the different studies ranging from 20-214 participants (mean 58.5). The studies demonstrated large variability in the age of participants at enrolment ranging from 11 months to 18 years (mean age of 6 years 8 months). There were more male than female participants across 18 studies (males n = 615, females n = 437), with one study not reporting participants sex (Ibrahim et al., 2007). Geographical classification of CP was recorded in 16 studies with over half diplegic CP (n = 535), almost one third hemiplegic (n = 308) and approximately one sixth quadriplegic (n = 161). Gross Motor Function Classification System (GMFCS) was recorded in less than half of the included studies and representation varied with GMFCS level 1 most prevalent in 40% of articles (Table 3). All studies were conducted on children with physiological classification of spastic CP with one study comparing children with spastic CP to typically-developing children (Barber et al., 2013).

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Chart

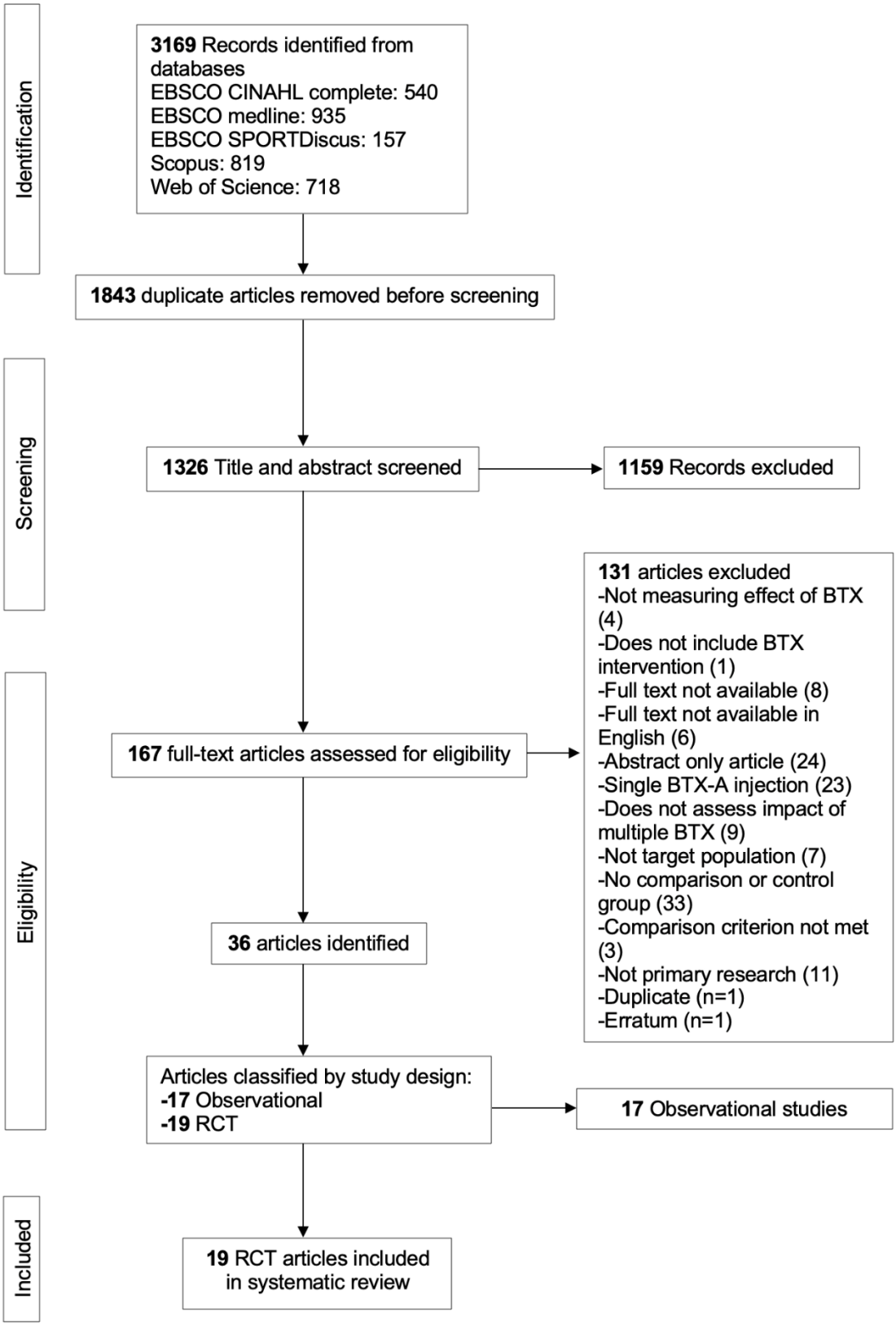

Table 3
Patient Characteristics

Author	Number of participants	Age range	Mean Age	Sex	Cerebral Palsy Classification	GMFCS level
Ackman., et al. 2005	39	3-9y	Mean: 5.8y	19M 20F	H: 26 D: 13	I: 37 II: 2
Barber et al., 2013	35	2–5y	INT: 3y 9m (SD 1y 3m), CTRL: 4y (SD 1y 2m)	22M 13F	H: 5 D: 10 TD: 20	I: 10 II: 5
Boyd, et al. 2001	39	1-4y	3y 2m (range 1y 7m to 4y 10m)	24M 15F	Not reported	II: 1 III: 11 IV: 13 V: 14
Edwards et al., 2015	41	2-8y	4y	27M 14F	Not reported	IV: 3 V: 38
Graham et al., 2008	91	1-5y	INT: 3y 2m; CTRL: 2y 11m	59M 32F	D: 29 Q: 62	II: 5 III: 18 IV: 34 V: 34
Hastings-Ison et al., 2015	42	2-5y	3y 6m (SD 13m)	23M 19 F	H: 21 D: 21	I: 20 II: 19 III: 3
Hawamdeh et al.,2007	60	3-15y	INT: 6y +/- 2y 9m, CTRL 5y +/- 2y 5m	35M 25F	D: 60	Not reported
Ibrahim et al., 2007	60	3-7y	INT 1: 4y 4m+/-1y 5m, INT 2: 4y 3m+/-11m, INT 3: 4y 6m+/-1y 3m, CTRL: 4y 5m+/-9m	Not reported	H: 60	Not reported
Kanovsky et al., 2009	214	1-8y	3y 8m (SD 1y 6m)	86M 128F	D: 214	Not reported
Koman et al., 2000	114	2-16y	INT: 3y 2m, CTRL: 3y 3m	68M 46F	H: 32 D: 82	Not reported
Koman et al., 2013	73	3–18y	Not reported	47M 26F	H: 39 D: 8 Q: 26	Not reported

Lidman et al., 2015	20	1y6m -10y	3y 1m	14M 6F	Not reported	Not reported
Lowe et al., 2007	42	2–8y	4y (SD 1y 7m)	31M 11F	H: 42	I: 42
Moore et al., 2008	58	2-8y	INT: 5.3y, CTRL: 4.82y	36M 22F	H: 9 D: 39 Q: 10	Not reported
Olesh et al., 2010	24	1y10m- 4y 10m	3y 8m (SD 9m)	19M 5F	H: 24	Not reported
Sutherland et al., 1999	20	2y5m – 12y6m	6.1y	16M 4F	H: 10 D: 9 Q:1	Not reported
Tedroff et al., 2010	15	11m – 1y10m	1y 4m	7M 8F	H: 6 D: 9	I: 8 II: 6 III: 1
Van Heest et al., 2015	34	4-17y	INT1: 9y 4m, INT2 9y, CTRL: 10y 2m	23M 11F	H: 34	Not reported
Willoghby et al., 2012	91	1-5y	3y 2m	59M 32F	D: 29 Q: 62	Not reported
Total	1112	11m-18y	3y1m – 10y2m (mean 6y8m)	615M 437F	H: 308 D: 523 Q: 161	I: 117 II: 38 III: 33 IV: 50 V: 48

Note. CTRL = Control group. D = Diplegia. F = Female. H = Hemiplegia. INT = Intervention group. M = Male. m = month. Q = Quadriplegia. SD = Standard Deviation. y = year. GMFCS = Gross Motor Function Classification System, with Level 1 being least impaired and Level 5 being most impaired.

Study Designs

All articles included in this systematic review were randomised control trials as outlined in Figure 1.

Botulinum Toxin Dose and Frequency

Brands of BT used included Dysport (Kanovsky et al., 2009; Moore et al., 2008), Botox (Barber et al., 2013; Boyd et al., 2001; Edwards et al., 2015; Graham et al., 2008; Hastings-Ison et al., 2015; Koman et al., 2013; Koman et al., 2000; Lidman et al., 2015; Olesh et al., 2010; Sutherland et al., 1999; Tedroff et al., 2010), both Botox and Dysport (Hawamdeh et al., 2007; Ibrahim et al., 2007) and 21% of studies did not report the brand (Ackman et al., 2005; Lowe et al., 2007; Van Heest et al., 2015; Willoughby et al., 2012). The dose of BT ranged from 0.5 to 30U/kg according to size of the target muscle, participant's body weight, and severity of spasticity. Muscles of the lower limb were injected in 68% of studies including ankle plantar flexors (medial and lateral gastrocnemius and soleus muscles), hip adductors and knee flexors. Upper limb muscles were injected in 26% studies, including thumb adductors, opposers and flexors, elbow flexors, forearm pronators, wrist flexors and extensors, and finger flexors. One study injected both upper and lower limb muscles but specific muscle groups were not identified (Edward et al., 2015). The interval between BT doses varied across studies from 1 to 12 months. Total repeated injections sessions ranged from 2 to 8 doses.

Outcome measures

There were a variety of outcome measures incorporated throughout the studies listed in Appendix A. These included measures of ROM, spasticity, strength, hip displacement, muscle morphology, gait, adverse events, motor responsiveness, functional mobility, quality of life, upper limb function, occupational performance, self-care and functional skills, function and participation, cognitive abilities, and gross motor function.

Of the 19 included studies, all studies included measures under the body structures and function domain of the ICF. Just over half (53%) included measures

classified under the activity domain and 27% includes measures under the participation domain of the ICF. Five studies included measures from all domains of the ICF (Hastings-Ison et al., 2015; Lidman et al., 2015; Lowe et al., 2007; Olesh et al., 2010; Van Heest et al., 2015).

Classification of Studies

Studies were allocated to one of three groups: i) comparing repeated BT to no BT (Table 4), ii) comparing different frequencies of BT injections (Table 5) and iii) comparing repeated BT treatment to other interventions (Table 6). Tables 4, 5 and 6 present the characteristics of the studies including BT dose, muscles injected, interval between repetitions of BT, and number of repetitions of BT.

3.3 Methodological quality

Overall, most of the studies exhibited either some concerns or high risk of bias (74%) with high risk in over one third of included articles (3**7**%). The ROB 2 ratings can be found in Tables 4, 5, and 6 alongside each study. Further details about quality ratings can be found in Appendix B. In domain 1, risk of bias arising from the randomisation process, most articles were low risk (low n = 12; some risk n = 7; high risk n = 0). In domain 2, risk of bias due to deviations from the intended interventions, all articles demonstrated low risk of bias (low n = 19; some risk n = 0; high risk n = 0). In domain 3, missing outcome data, most articles presented with low risk of bias and 32% presenting as high risk of bias (low n = 12; some risk n = 1; high risk n = 6). In domain 4, risk of bias in selection, almost all articles presented low risk of bias (low n = 18; some risk n = 0; high risk n = 1). In domain 5, overall risk of bias, high risk of bias and some risk of bias scored higher than low risk of bias indicating most articles presented with some form of bias (low n = 5; some risk n = 7; high risk n = 7).

3.4 Efficacy of repeated Botulinum Toxin injections

Studies comparing repeated Botulinum Toxin intervention to placebo injection

Five articles compared repeated BT to placebo injection (Ackman et al., 2005; Koman et al., 2013; Koman et al., 2000; Moore et al., 2008; Sutherland et al., 1999). A summary of these articles can be found in Table 4.

Koman et al. (2013), appraised the safety and efficacy of three doses of BT compared to placebo injection in the upper extremity of children with CP and upper limb spasticity. Upper limb function revealed a significant increase in the BT group compared to placebo injection at the final 26 week follow-up. Active wrist extension was significantly improved in the BT group when compared to placebo injection at 26 weeks with improvement in wrist extension observed without loss of flexion in the BT group only. They found improved active ROM and function at 26 weeks.

A similar study by Koman et al. (2000), compared two doses of BT to placebo injection in the lower limb. They found significantly greater active ankle DF ROM with knee flexed in the BT group when compared to placebo injection at 4 and 12 weeks. However no significant between-group differences in passive ankle DF were seen. Active ankle ROM and gait improved at 12 weeks. No significant between-group differences in hoffmann's reflex and antibody production to BT from baseline to 12 weeks was found.

Sutherland et al. (1999), also compared two doses of BT to placebo injection of the lower limb. Significant improvements in gait pattern were identified including peak DF in swing and peak DF in stance in the BT group when compared to placebo injection. No significant between-group differences in ankle alignment at foot contact and time and distance parameters was found. They did not include findings of between-group analysis for ROM or muscle strength.

Moore et al. (2008), examined the effects of up to eight lower limb BT doses compared to placebo injection over 2 year follow up. There were no significant between-group changes in gross motor function, ROM, spasticity, adverse events or self-care and functional skills discovered. Repeated BT did not appear to influence the need for additional interventions, as participants in both groups (43% BT group; 46% placebo injection) required at least one additional intervention or underwent relevant orthopaedic surgery during follow-up. Details of surgery or additional interventions were not reported.

Ackman et al. (2005), compared three doses of BT, three doses of BT with casting, and three placebo injections with casting. They failed to report planned between-group comparisons for any outcome measure.

In summary, studies did not find a significant effect of repeated BT on passive ROM when compared to placebo injection. Two high-quality studies show repeated BT improves gait at 8 weeks (Sutherland et al., 1999) and 12 weeks (Koman et al., 2000) when compared to placebo injection. Two high-quality studies reveal improvements in active ROM at 12 weeks (Koman et al., 2000) and 26 weeks (Koman et al., 2013) when compared to placebo injection. In studies assessing antibody production to BT (Koman et al., 2000) and adverse events (Moore et al., 2008), no between-group results supported the effects of repeated BT when compared to placebo injection. In studies assessing function including gross motor function (Moore et al., 2008), self-care and functional skills (Moore et al., 2008), or motor response (Koman et al., 2000) no between-group results supported the effects of repeated BT (without casting) when compared to placebo injection.

Table 4
Studies comparing repeated Botulinum Toxin intervention to placebo injection

Author and Quality rating	Study Aim	Sample size	Intervention	Control	Outcome timepoints	Findings/outcomes
Koman et al., 2013 	To evaluate the safety and efficacy of upper extremity intramuscular inj of BT in a cross-section of children with varying levels of function	Total: 73 INT: 38 CTRL: 35	INT: x 3 BT at 0, 8w and 20w (if clinically indicated) **Dose**: Not reported **Ms inj:** Not specified presume UL **Brand BT:** Botox	CTRL: Placebo inj at 0, 8w and 20w. **Ms inj:** Not specified presume UL	0, 4, 8, 14, 20, and 26w	**Active ROM:** Mean wrist ROM sig ↑ INT vs CTRL at 20w (p=0.022) and 26w (p=0.003). Wrist extn sig ↑ INT vs CTRL at 26w (p=0.014). **Melbourne 0-26w:** Sig ↑ INT vs CTRL at 26w. **HRQL:** No sig dif btwn-groups **UERS:** No sig dif btwn-groups in domains including shoulder, elbow, forearm, or hand. **HC scale and modified HC:** No sig within-group change **Summary: Significant finding (ROM and function)**
Koman et al., 2000 	To document the efficacy and safety of neuromuscular blockade using IM inj of BT	Total: 114 INT1: 56 CTRL1: 58	INT: x 2 BT at 0 and 4w **Dose:** 4U/kg **Ms inj:** MG and LG of each involved leg **Brand BT:** Botox	CRTL: x 2 Placebo inj at 0 and 4w	0, 2, 4, 8 and 12w after first inj	**Active ROM:** Ankle DF KF: Sig ↑ INT vs CTRL at 4w and 12w (p<0.05). **Passive ROM:** No sig dif btwn-groups in passive ankle DF KE. CTRL: No sig change from baseline. **PRS:** Sig ↑ INT vs CTRL at all FU visits (p<0.05). **Motor response:** INT was sig dif from CTRL at 4w (p<0.05). Sig ↓ INT at all FU (p<0.05) **Hoffmann's reflex and AB to BT:** No sig dif 0-12w

						Summary: Significant finding (AROM and gait)
Sutherland et al., 1999 	The purpose of this study was to quantify the gait of subjects receiving two inj of either BT or saline into the GM	Total: 20 INT: 10 CTRL: 10	x2 BT at 0 and 4w **Dose:** 4.0 U/kg Hemi and asymmetric di received total dose in affected GM. Bilateral same dose divided into both GM. **Ms inj:** MG and LG **Brand BT**: Botox	X2 Placebo inj at 0 and 4w	Gait analysis 3D five camera: before 0w and 8w DF and dymanic EMG tib ant, GM and SM: baseline and 8w post inj	**Peak DF swing:** Sig ↑ in INT (p=0.006), mean ↑ INT +6.2° (range +17 to 0°) and the mean ↓ CTRL −3.8° (range +7 to −18°). **Peak DF stance:** sig ↑ in INT (p= 0.006), mean ↑ INT 12.5° (range + 45 to − 6°) and mean ↓ CTRL -3.6° (range +10 to −17°). **Dynamic DF at 10% of the gait cycle:** INT sig ↑ in INT(p=0.02) mean change +5.4° (range + 28 to − 4°). **Video recording (Gait):** Sig dif (p=0.054) btwn-groups. Changes were demonstrated in INT and not in CTRL. N=4 INT changed from a toe-toe gait pattern to a foot-flat gait pattern. **Passive ROM:** ankle DF No sig change with KE or KF. KF at 90°: INT mean ↑ 1.3° (range −15° to +15°) and CTRL mean ↓ of DF by −5.4° (range −20 to 0 change). With KE INT had mean ↓ of −0.56° (range + 8 to − 10°) and CTRL had a mean ↓ of −6.3° (range +5 to −20°). **Ankle alignment at foot contact (Gait):** no statistically sig change btwn-groups **Time/distance parameters (Gait):** No sig dif in step length (p=0.33), stride length (p=0.37), cadence (p=0.61), or walking velocity (p=0.40). **Dynamic EMG:** No sig dif btwn-groups **Summary: Significant finding (gait and PROM)**

Moore et al., 2008 	We examined the effects of multiple BT inj cycles for leg spasticity in CP, aiming to test the strategy of pragmatic long-term repeated use of BT	Total: 58 INT: 30 CTRL: 28	BT every 3m if clinically indicated over 2y (up to 8 doses) **Dose:** 15U/kg 1st dose, ↑ max 5U/kg through next 3 doses and then remained at 30U/kg. **Ms inj**: Not reported **Brand BT:** Dysport	Placebo inj	0, 1 and 2y	**Orthopaedic surgery or additional intervention:** n=13 in each group (43% INT, 46% CTRL) received at least one additional intervention or underwent relevant surgery during FU. **Mean change scores for GMFM, ROM, MAS, AE, or PEDI at 1 or 2y:** No sig dif btwn-groups dif **Summary: Insignificant finding**
Ackman., et al. 2005 	To compare cumulative efficacy (3 treatment sessions) of BT alone, casting alone and the combination of BT and casting in the management of dynamic equinus in ambulatory children with spastic CP	Total 39 INT 1: 12 INT 2: 13 CTRL: 14	INT 1: 3 x BT at 0, 3, and 6m **Dose**: 4U/kg per extremity. **MS inj:** bilateral MG and LG. **Brand BT**: Not specified	CTRL: Placebo inj + 3w casting, at 0, 3, and 6m	0, 3, 6, 7.5 and 12m	**Planned btwn-group comparisons not reported.** **Active ROM:** No sig dif in DF 0-12m in any group. **Passive ROM:** No sig dif in DF 0-12m in any group. INT2: Sig gains in passive DF with KF ($p \leq 0.01$) 0- 7.5m, DF with KE ($p \leq 0.04$) 0- 3, 6, and 7.5m. CTRL: Sig ↑ in passive DF with KF and KE 0 to 7.5m ($p \leq 0.03$). **Spasticity:** INT1: No sig change at any time; INT2: No sig change on AS at any time, but sig ↓ on TS ($p \leq 0.05$) 0 to 6, 7.5, and 12m. Sig ↑ on the TS scale ($p \leq 0.05$) 7.5-12m. CTRL: Sig ↓

	INT 2: 3 x BT + 3w casting at 0, 3, and 6m **Dose**: 4U/kg per extremity. **MS inj:** bilateral MG and LG. **Brand BT**: Not reported	in ankle spasticity ($p \leq 0.02$) 0 to all timepoints on TS not AS. From 6 to 7.5m a sig ↓ in spasticity was detected using the TS, but not the MAS. Sig ↑ on the TS scale ($p \leq 0.05$) and AS ($p \leq 0.05$), 7.5-12m. **Strength:** INT1: No sig change PF of DF strength. INT2: Sig ↓ DF strength (6 to 7.5m) then ↑ (7.5m to 12m). No change PF strength. CTRL: Sig gains in DF strength (0 to 6, 7.5, and 12m). No significant changes in ankle PF strength. **Gait Parameters:** INT 1: No sig change in velocity, stride length, ankle kinematics, peak power generation at the ankle during push-off; INT 2: Sig ↑ in stance phase variables (0 to 7.5m) and peak DF swing (0 to all timepoints). No change peak power push off, gait speed, stride length. CTRL: Sig ↑ in all ankle kinematic variables (0 to all timepoints) excluding PDFSw at 1y. Sig short term ↑ in ankle kinematics (6 to 7.5m). No sig change in peak power generation at the ankle during push-off, velocity or stride length and active ankle DF. **Summary: Insignificant finding for BT only**

Note. AB = Antibody. AE = Adverse Events. Btwn = between. BT = Botulinum toxin. CP = Cerebral Palsy. CI = Confidence Interval. CTRL = Control group. DF = Dorsiflexion. Di = Diplegia. dif = Differences. EMG = Electromyography. Extn = Extension. FU = follow up. GM: Gastrocnemius muscle. GMF = Gross Motor Function. HA = Hip adductors. HC = House classification. Hemi = Hemiplegic. HRQL: Health Related Quality of Life. Inj = Injected. INT = Intervention group. KE = Knee extension. KF = Knee Flexion. Kg = kilogram. LG = Lateral Gastrocnemius. MAS = Modified Ashworth Scale. Melbourne = Melbourne Assessment of Unilateral Upper Limb Function. m: month/s. MG: Medial gastrocnemius. ms = muscle. PDFSw = Peak Dorsiflexion During Swing. PEDI = Pediatric Evaluation of Disability Index. PRS = Composite Physician Rating Scale. PT = Physiotherapy. ROM =

Range of Motion. Sig = Significant. SM = Soleus muscle. Tib ant = Tibialis Anterior TS = Tardieu scale. U = Unit. UERS = Upper Extremity Rating Scale. vs = versus. w = week/s. y = year/s.

Studies comparing different frequencies of Botulinum Toxin injections

Six articles were recognised as comparing different frequencies of BT (Barber et al., 2013; Edwards et al., 2015; Hastings-Ison et al., 2015; Kanovsky et al., 2009; Lowe et al., 2007; Tedroff et al., 2010). A summary of these articles can be found in Table 5.

The study by Hastings-Ison et al. (2016), as mentioned in the introduction, compared 4-monthly BT to 12-monthly BT over 26 months. They found no significant between-group differences in ROM, peak DF in stance phase, or HRQL. No serious adverse events were reported, however the more frequent BT group had twice the occurrence of mild and moderate adverse events. A similar study by Kanovsky et al. (2009), also compared 4-monthly BT to 12-monthly BT. They found significant improvements in gait at 25 months in the 4-monthly BT group when compared to 12-monthly BT. No significant between-group differences in ROM, time to development of contracture, time to referral for surgery to correct contractures, neutralizing antibodies, adverse events or gross motor function were found.

Lowe et al. (2007), investigated repeat BT over 30 months. They compared three doses of BT at baseline, 6 and 18 months to two doses of BT at 6 and 18 months. They found no significant between-group differences in spasticity, self-care, occupational performance, function and participation. Tedroff et al. (2010), evaluated the effect of BT on spasticity, contracture development and gait pattern for up to 3.5 years. The intervention group received between three to eight doses of BT and the control group received between zero to five doses of BT. They found a significant between-group difference in knee joint ROM, but no significant between-group differences in ankle joint ROM. Significant between-group differences in knee flexor spasticity were identified with a larger reduction in the intervention group. No significant between-group differences were found in PF spasticity, gait, self-care or gross motor function. A complication of this study was the control group had no BT during the first year. Botulinum toxin was introduced at 1 year to just over half of the participants (n = 5

out of 9 participants). This study was a moderate-quality study that had the smallest sample size included in this review of just fifteen participants.

Edwards et al. (2015), assessed the safety of repeated BT injections by examining two doses of BT compared to one dose placebo injection and one dose BT. They found no significant between-groups differences for all moderate and serious adverse events. Barber et al. (2013), compared single BT and three doses of BT in children with CP. They also compared outcomes to typically developing children and was the only study that enrolled typically developing children as a control group in this review. There were no significant between-group differences among intervention groups for medial gastrocnemius muscle volume, fascicle length, or physiological cross sectional area. Range of motion was not compared between the two intervention groups involving children with CP.

In summary, gait significantly improved with increased frequency of BT in one high-quality study (Kanovsky et al., 2009) and one moderate-quality study showed no significant change (Tedroff et al., 2010). Adverse events were found to be twice as frequent with increased frequency of BT in one high-quality study (Hastings-Ison et al., 2015) with one high-quality (Kanovsky et al., 2009) and one low-quality study (Edwards et al., 2015) finding no significant differences. One moderate-quality study found repeated BT significantly improved knee joint ROM and did not significantly improve ankle ROM (Tedroff et al., 2010). No significant differences in spasticity were established between two and three repeated BT doses by a moderate-quality study (Lowe et al., 2007). When repeated BT frequency is increased (up to eight doses) knee joint spasticity was significantly improved in a moderate-quality study (Tedroff et al., 2010). No significant between-group differences were found when comparing increased frequency to reduced frequency in time to development of fixed contractures, time to referral for surgery to correct fixed contractures, gross motor function, self-care, occupational performance, function, participation, muscle volume, fascicle length, physiological cross sectional area, or antibody production to BT.

Table 5
Studies comparing different frequencies of Botulinum Toxin injections

Author	Study Aim	Sample size	Intervention	Control	Measurement Timepoints	Findings/outcomes
Hastings-Ison et al., 2015	To compare two BT injection frequencies: 12m vs 4m	Total: 42 INT: 21 CTRL: 21	4monthly BT over 26m (x6 doses) **Dose** Di: 6U/kg each side, total 12U/kg **Dose** Hemi: 6U/kg affected side **Ms inj** Di: GM both LL **Ms inj** Hemi GM and SM affected side **Brand BT** Botox	12monthly BT over 26m (x2 doses) **Dose** Di: 6U/kg each side, total 12U/kg **Dose** Hemi: 6U/kg affected side **Ms inj** Di: GM both LL **Ms inj** Hemi GM and SM affected side	Baseline, and after 26m. Except for 3DG, measured 2w pre and 4w post the final inj	**Passive ROM:** DF: No sig btwn-group dif 0-26m (mean dif 3.3°, 95% CI -4.7 to 11.2°). Sig dif btwn hemi and di (p=0.01; 95% CI 0.24–1.37). Hemi ↓ average 8.5deg, di ↑ average 1.6deg. **AE:** No serious AE in either group. INT twice the number of AE (INT: n=46; CTRL: n=26). **FMS, FAQ, QOL, peak ankle DF during stance** (mean dif 6.8°, 95% CI -3.4 to 17.0°), **HRQL or Motor responsiveness** (p=0.19): No sig btwn-group dif 0-26m. **Summary: Significant finding (non-serious AEs)**
Kanovsky et al., 2009	Compared the long-term efficacy and tolerability of two dosage regimens of BT in children with CP and lower-limb spasticity	Total: 214 INT: 110 CTRL: 104	4monthly BT over 2y (x6 doses) **Dose:** 30U/kg equal both limbs **Ms inj:** GM **Brand BT:** Dysport	12monthly BT over 2y (x2 doses) **Dose**: 30U/kg equal both limbs **Ms inj:** GM	0, 4, 8, 12, 16, 20, 24 and 28m	**AB:** At baseline n=1 present in each group. At 28m AB were detected in n=5 INT and n=2 CTRL. **AE:** n=89 (81%) in INT and n=88 (85%) in CTRL. Majority were mild or moderate in INT (71% and 45% respectively) and CTRL (72% and 56% respectively). **Passive ROM** DF: (p=0.055; CI: 0.00 INT, 3.41 CTRL), **Time to development of fixed contractures** (p=0.533; 95% CI 0.28, 1.94), **Time to referral for surgery to correct fixed contractures** (p=0.156; 95% CI 0.10,

						1.45) or **GMFM:** No sig btwn-group dif 0-28m **Subjective functional assessment of change in gait pattern:** At 25m INT sig more likely than CTRL to have better responses on the subjective functional assessment of change in gait pattern by blinded assessor (p=0.034; 95% CI 1.046, 3.167) or the parent or guardian (p=0.031; 95% CI 1.059, 3.197). **Summary: Significant finding**
Lowe et al., 2007 	To investigate whether there was a difference in clinical outcomes for young children with spastic hemiplegic CP receiving OT, if they had repeat episodes of BT over a 30m period. The study also investigated incidence of AE associated with repeated BT use in upper limbs	Total: 42 INT: 21 CTRL: 21	3 x BT at 0, 6 and 18m + OT for 30 m, with first 6m reported earlier (Lowe et al. 2006) **Dose:** 0.5–2.1 U/kg **MS inj:** EF, FA, WF, WE, FF, TA, TO and TF **Brand:** Not reported	2 x BT at 6 and 18m + OT **Dose:** 0.5–2.1 U/kg. **MS inj:** EF, FA, WF, WE, FF, TA, TO and TF	0, 1, 3, and 6m in original trial were again administered in the extension study at 7, 9, 12, 15, 18, 19, 21, 24, 27, and 30m	**Spasticity:** EF (p=0.629), pronators (p=0.153), WF (p=0.368), FF (p=0.572), TA (p=0.200), and TO (p=0.448), **QUEST**: (p=0.963), **Home programmes** (100% each group), **Splinting** (43% v 41%, p=4.86), **Contracture casting** (n=26 v n=23 serial casts, p=1.09), **PEDI** (functional scores (p=0.499) and caregiver assistance scores (p=0.352.), **COPM:** Performance scores (p=0.315); satisfaction scores (p=0.560); **parent-GAS** (p=0.237), **Therapist-GAS** (p=0.957): **All outcomes no sig btwn-groups dif 0-30m** **Summary: Insignificant finding**

	of children with spastic hemiplegic CP					
Tedroff et al., 2010 	To evaluate the effect of BT treatment on ms tone, contracture development and gait pattern in young children with CP	Total: 15 INT:6 CTRL: 9	INT: Baseline-1y: x 2 BT inj, 6m apart + stretching program 1-3.5y: n=6 Continued BT (median 3.5 additional inj range 1–6) **Dose** 6U/kg **Ms inj** GM affected limb **Brand** Botox	CTRL: Baseline-1y: No BT (stretching program only) 1-3.5y: n=5 commenced BT (median 4 inj range 3-5) **Dose and ms inj** not reported presume LL	0, 1, and 3.5y Gait pattern assessed at 5y INT: n=5 and CTRL: n=8 vs n=16 TD children previously used at gait laboratory	**Passive ROM Knee joint:** Sig dif btwn-groups in popliteal angle from 0, both at 1y (p=0.017) and 3.5y (p=0.016). Popliteal angle was sig ↓ in INT from 0-1y, mean -12° (95% CI -22° to -4°, p=0.009) which was reversed and approached baseline at 3.5y. CTRL: gradual ↓ KE ROM at 1 and 3.5y, sig dif from 0-3.5y with an 11° ↑ (95% CI 4° to 18°, p=0.003) **Passive ROM Ankle joint:** No sig dif btwn-groups at any time. INT: At 3.5y ROM returned to baseline. CTRL: Sig ↓ from 0-3.5y (95% CI: -16° to -2.0°, p=0.013) **Spasticity KF:** Sig dif btwn-groups 0-3.5y (p=0.05) with a larger ↓ in INT. No sig within-group changes for either group at 1 and 3.5y vs baseline. **Spasticity PF:** No sig btwn-group dif at any time. INT ↓ at 1 and 3.5y, sig dif from 0-3.5y (mean AS -1.0; 95% CI: -1.4 to -0.6, p=0.04). CTRL: No sig changes at 1 and 3.5y **GMFM:** No sig btwn-group dif found. GMFM-66 sig ↑ in both groups over time. INT: mean ↑ 13.6 points (p=<0.0001) during the first y, and 23.6 points (p=0.0002) from 0-3.5y. CTRL: mean ↑ of 10.1 points (p=0.0001) and 20.9 points (p<0.0001) respectively, during equivalent time periods

						PEDI: No sig btwn-group dif found. Sig ↑ in both groups at 1 and 3.5 years. **GGI:** No sig dif btwn-groups found at 5y when compared to TD (p=0.31). Mean at 5y INT and CTRL: 385 (SD=278) and TD: 700 (SD=619) **Summary: Significant finding (Knee PROM and spasticity)**
Edwards et al., 2015	To determine safety of BT injections to reduce spasticity and improve care and comfort of non-ambulatory children with CP	Total: 41 INT: 23 CTRL: 18	x2 BT did not specify time btwn inj **Dose:** 0.5U-4U/ms **Ms inj:** Not specified, presume UL **Brand BT:** Botox	1st dose: placebo inj 2nd dose: BT did not specify time btwn inj **Dose:** 0.5U-4U/ms **Ms inj:** Not specified, presume UL	0, 2, 4 and 16w after each procedure	**AE:** No sig dif for all moderate/serious AE btwn-groups in either dose 1 (95% CI= 0.43–4.00; p=0.64) or dose 2 (95% CI= 0.30–1.75; p=0.47) **Incidence of AE**: No sig between-group diff. INT: n=3 serious AE in 3 children (13%) and n=7 moderate AE in 5 children (22%). CTRL: n=2 serious AE in 1 child (1%) and n=4 moderate AE's 3 children (17%) **Summary: Insignificant finding**
Barber et al., 2013	12m prospective investigation of changes in MG morphology in who had received no previous BT and were randomised to receive either single or multiple (3) BT inj to MG. MG morphological	Total: 35 INT1: 7 INT2: 8 CTRL: 20	INT 1: 1 x BT at baseline **Dose:** 6U/kg. Di bilateral inj, hemi unilateral inj **Ms inj:** MG, LG and SM at baseline. INT 2: 3 x BT at 0, 4 and 8m **Dose:** 6U/kg. Di bilateral inj, hemi unilateral inj **Ms inj:** MG, LG and SM	TD children	0 and 12m	**Anthropometric measures (mass, height, leg length, fibula length), MG muscle volume, fascicle length and PCSA 0-12m**: Sig ↑ in all three groups (within-group). **Passive ROM (0-12m):** DF and PF No sig dif within-groups. Did not include btwn-group analysis of INT1 and INT2 (only against CTRL) **No sig btwn-group dif INT1 and INT2 0-12m:** MG ms volume, fascicle length or PCSA. **Summary: Insignificant finding**

	changes were compared to age-matched TD peers	**Brand BT:** Botox

Note. AB = Antibodies. AE = Adverse Events. AS = Ashworth scale. Btwn = between. BT = Botulinum toxin. CP = Cerebral Palsy. CI = Confidence Interval. COPM = Canadian Occupational Performance Measure. CTRL = Control group. DF = Dorsiflexion. Di = Diplegia. dif = Differences. EF = elbow flexors. FAQ = Gillette Functional Assessment Questionnaire. FF = finger flexors. FMS = Functional Mobility Scale. FP = forearm pronators. GAS = Goal Attainment Scale. GGI = Gillette Gait Index. GM = Gastrocnemius muscle. GMFM = Gross Motor Function Measure. HA = hip adductor. Hemi = Hemiplegia. HRQL = Health Related Quality of Life. HS = hamstring. Inj = Injection. INT = Intervention group. KE = Knee extension. KF = Knee Flexion. Kg = kilogram. LG = Lateral Gastrocnemius. m: month/s. ms = muscle. OT = Occupational Therapy. PCSA = Physiological Cross Sectional Area. PEDI = Pediatric Evaluation of Disability Inventory functional skills. PF = Plantarflexion. QOL = Child Health Questionnaire. QUEST = Quality of Upper Extremity Skills Test. ROM = Range of Motion. Sig = Significant. SD = Standard Deviation. SM = Soleus muscle. TA = thumb adductor. TD = Typically developing. TF = thumb flexor. TO = thumb opponens. U = Unit. UL = Upper Limb. w = week/s. WE = wrist extensors. WF = wrist flexors. y = year/s.

Studies comparing repeated Botulinum Toxin to other interventions

Eight articles were classified as comparing repeated BT to other interventions including PT only (Boyd, et al. 2001; Graham et al., 2008; Hawamdeh et al., 2007; Ibrahim et al., 2007), OT only (Lidman et al., 2015; Olesh et al., 2010; Van Heest et al., 2015), or usual care (Willoughby et al., 2012). A summary of these articles can be found on Table 6.

Three studies investigated BT combined with therapy versus therapy alone. Olesh et al. (2010), evaluated the effects of repeated BT (three doses) every 4 months combined with OT with OT alone. The BT group demonstrated a significant improvement in occupational performance, wrist flexor and pronator spasticity, and goal attainment scale when compared to OT only. No significant between-group differences were discovered for spasticity of elbow flexors, QUEST and fine motor and upper limb skills. Hawamdeh et al. (2007), compared three doses of BT at 3-4 month intervals with PT with PT only. Significant improvements in ROM and spasticity were found in the BT group compared to PT only. No significant improvement were found for gross motor function in the BT group at 30 months follow up. Lidman et al. (2015), examined the influence of repeat BT combined with OT compared to OT only. They found a superior effect in upper limb function of the BT group when compared to OT only. They did not include between-group findings for ROM or occupational performance. Active supination ROM and occupational performance improved within both groups. No adverse events were reported.

Three studies investigated BT combined with bracing versus therapy or usual care. Graham et al. (2008), compared 6-monthly BT over 3 years to the hip adductor and hamstring muscles with hip abduction bracing to PT only. No significant between-group difference in the annual rate of change of hip displacement was detected. Planned GMFCS follow up measures were not reported. Boyd et al. (2001), assessed the effectiveness of repeated BT combined with a variable hip abduction orthosis compared to PT only. No significant between-group differences in gross motor function was found. Planned spasticity assessments were not reported. Willoughby et al. (2012), compared the long-term impact over 3 years of repeated BT and hip abduction bracing compared

with usual care. No significant between-group differences in hip displacement, hip morphology, mean age at preventive surgery and mean age at reconstructive surgery were identified.

Ibrahim et al. (2007), compared three doses of BT to gastrocnemius only, hip adductors only, or both gastrocnemius and hip adductors to PT only. Significant between-group improvements in spasticity were found across all intervention groups when compared to PT only. They also found treatment of both gastrocnemius and hip adductors reduced spasticity significantly more than gastrocnemius only or hip adductors only. Van Heest et al. (2015), assessed surgery treatment compared to three repeated BT injections plus OT, and OT only. They found significant improvements of upper limb function in the surgical group compared to the BT group and OT only group. They found significantly increased mean pinch strength of the affected hand in the surgical group and OT only group when compared to BT group. Occupational performance significantly improved in the surgical group when compared to the BT group and control group. No significant differences were found among groups in HRQL.

In summary, one moderate-quality study found significant improvements in ROM with repeated BT compared to PT only (Hawamdeh et al., 2007). Two moderate-quality studies, and one low-quality study found significant improvements in spasticity with repeated BT compared to OT only (Olesh et al., 2010) or PT only (Hawamdeh et al., 2007; Ibrahim et al., 2007). One low-quality study discovered treatment of two muscle groups was more effective in reducing spasticity than a single muscle group (Ibrahim et al., 2007).

3.5 Evaluation of The *International Classification of Functioning*, Disability and Health domains

Body structure and function

Range of Motion

Although ROM was the most common outcome measure assessed in 58% of included studies, almost half did not include between-group analysis (Ackman et al., 2005; Barber et al., 2013; Lidman et al., 2015; Sutherland et al., 1999) with one study not reporting any planned ROM results (Van Heest et al., 2015). A high-quality study (Hastings-Ison et al., 2015) and moderate-

quality study (Kanovsky et al., 2009) compared different frequencies of BT (4-monthly versus 12-monthly) and found no significant difference in lower limb passive ROM up to 28 weeks post injection.

Tedroff et al. (2010), supplies moderate-quality evidence for a significant effect of increased frequency of BT on knee joint passive ROM but no effect on ankle joint passive ROM. When repeated BT was compared to placebo injection, two studies found significant between-group improvements in active ROM of the lower limb at 12 weeks (Koman et al., 2000) and active ROM of the upper limb at 26 week follow-up (Koman et al., 2013). These findings are only applicable to short-term improvements due follow up timeframe ranging from 12-26 weeks. In the studies that compared repeated BT to other interventions, a moderate-quality study by Hawamdeh et al. (2007), discovered significant improvements in lower limb passive ROM when comparing repeated BT and PT to PT only for up to 30 months. Range of motion results for the BT group were not reported in a moderate-quality study (Van Heest et al., 2015).

Table 6
Studies comparing repeated Botulinum Toxin to other interventions

Author	Study Aim	Sample	Intervention	Control	Measurement timepoints	Findings/outcomes
Graham et al., 2008 	Tests hypothesis that BT of HA and HS combined with abduction bracing will reduce the progression of hip displacement in children with spastic CP. Secondary study aims to examine safety, utility, and compliance issues associated with the use of the variable hip abduction orthosis in combination with BT	Total: 91 INT: 47 CTRL: 44	BT every 6m for 3y if clinically indicated (x6 doses) with hip abduction brace worn 6-8h p/d. **Dose:** 4-16 U/kg to each ms **Ms inj:** HA, HS **Brand BT:** Botox	PT only	0 and every 6m for 3y	**MP:** No sig dif in annual rate of change btwn-groups when analysed incorporating weighting of individual hips. INT: Unweighted mean summary change per y 2.6% and CTRL 5.7% and showed a dif of 3.1% (95% CI, 0.0% to 6.2%; p = 0.05). The weighted mean dif btwn-groups was 1.4% per y (95% CI, 20.6% to 3.4% per year; p = 0.16). **Progressive hip displacement:** Present in both groups. INT: Rate of hip displacement ↓ by 1.4% per y (95% CI, 20.6% to 3.4%; p = 0.16) when weighted for differing numbers of MP. **GMFCS:** baseline results reported, outcomes not reported in results **Summary: Insignificant finding**
Olesh et al., 2010 	To test the effectiveness of repeat BT inj in the affected arm of 22 children with hemi CP	Total: 24 INT: 12 CTRL: 12	3 x BT every 4m + OT **Dose:** 0.5U/kg: AP, FPL & FDS. 1U/kg: FDP, FCR, FCU & PrT. 2U/kg: BB **Ms inj:** AP (n=9), FPL	OT only	INT: 0 and 6w after inj, week before next inj (16w) and 1y CTRL: 0, 6w, 16w and 1y	**Spasticity:** Sig btwn-group dif. Modified TS lower in INT for forearm pronators (p=0.009) and wrist flexors (p=0.029). Not sig dif for elbow flexors (p=0.07). **COPM 0-12m:** sig btwn-group dif ↑ at 12m INT vs CTRL (p=0.047). No sig changes in COPM satisfaction scores (p=0.090). **QUEST:** summary scores no sig btwn-group dif (p=0.833). Motor performance grasp section ↑ successively over each cycle for both groups, no additional ↑ in

			(n=5), FDS (n=8), FDP (n=8), FCR (n=2), FCU (n=6), PrT (n=10), and BB (n=11). **Brand BT:** Botox			INT. Protective extn did not ↑ in either group. **GAS (0-12m):** Sig diff btwn-groups (p=0.047) **PDMS-FM:** No sig dif btwn-groups. **Summary: Significant finding (spasticity, function, goals)**
Van Heest et al., 2015 	To establish the comparative effectiveness of surgical and nonsurgical treatment options in upper limb CP management	Total: 34 INT1: 16 INT2: 14 CTRL1: 10	INT 1: surgical tendon transfer surgery and OT. Cast 4w. INT 2: 3 x BT baseline, 3m, 6m + OT **Dose**: 0.5-1.0 U/kg TA and 1-2 U/kg PrT and FCU **Ms inj:** PrT, FCU, and AP. **Brand BT:** Not reported	OT only	0, (4.5m INT2 6m CTRL and INT1), and 12m	**Mean pinch strength (affected hand) 0-12m:** Sig ↑ INT1 and CTRL relative to INT2 (p = 0.004) Mean ↑ INT1: 0.7 kg, INT2: 0.4 kg and CTRL: 0.6 kg. **SHUEE-DPA 0-12m:** Sig ↑ INT1 vs INT2 and CTRL (p < 0.001). Mean ↑ INT1 21.6% (66% at baseline to 88% at 12m) INT2 5.3%, (61% at baseline to 66% at the 12m) and CTRL 1.0%, (64% at baseline to 63% at 12m). **COPM:** Satisfaction: INT1 sig ↑ vs INT2 and CTRL (p=0.002). Mean ↑ INT1: 4.4, INT2: 2.0, and CTRL: 0.9. **PODCI-parent, PedsQL standard version and CP version, COPM performance, SHUEE-SFA, Box and Blocks test, and AHA:** No sig dif found among groups. **Summary: Significant finding (strength, function)**
Hawamdeh et al., 2007 	To determine the long-term effects of multiple inj of BT on ms tone and functional abilities in children with CP	Total: 60 INT: 40 CTRL: 20	INT: 3 x BT at 3-4m and PT **Dose:** 6-12 U/kg, max per visit: 200 U.	PT only	0, after 12-15m, and after 27-30m	**Passive ROM:** DF: Sig ↑ in INT vs CTRL following inj at 3m (p=0.04) and 18m (p=0.007). INT: Sig ↑ btwn 1st- 2nd evaluations after last inj (p=0.000). **Spasticity:** Sig ↓ in INT vs CTRL following inj at 3m (p=0.000) and 18m (p=0.005). INT: Sig ↑ btwn 1st -2nd

			Ms inj: LG and MG **Brand BT:** Botox or Dysport			evaluations after last inj (p=0.002). Sig + correlation btwn age and degree of ms tone at 18m after last inj in INT (p=0.004) not seen in CTRL (p=0.32). **GMF:** Sig ↑ btwn 1st-2nd evaluations after last inj in INT (p=0.000). No sig ↑ in INT at 3m after last inj (p=0.96). **Summary: Significant finding (ROM, spasticity, function)**
Boyd, et al. 2001 	The short-term aim was to determine the effectiveness of combined use of BT to the HS and HA and a variable hip abduction orthosis (SWASH), on gross motor function in children with moderate to severe spastic CP, compared to current standard of care. Long term aim will be to determine if this combined treatment alters the natural history of hip displacement or need for surgery in this patient group.	Total: 39 INT 1: 19 CTRL 1: 20	2 x BT every 6m plus SWASH brace 6-8h/d + night brace (where appropriate) for 12m **Dose:** 4.0-16.0U/kg every 6m **Ms inj:** HS and HA **Brand BT**: Botox	PT only	GMFM and subjective assessment of SWASH: 0 and 12m MAS, MTM and Standardized antero-posterior hip x-rays: 6 and 12m	**GMFM:** No sig dif btwn-groups 0-12m. INT: Mean ↑ 6.0%; 95% CI ± 6.7. Moderate correlation btwn change in total GMFM and GMFCS (P<0.001). CTRL Mean ↑ 6.1%; 95% CI ± 6.5. **Soft tissue surgery:** INT: first y n=2; CTRL first y: n=7. **Summary: Insignificant finding**
Ibrahim et al., 2007	Compared btwn the various effects of BT when inj at GM or HA or at	Total: 60 INT 1: 15 INT 2: 15 INT 3: 15	INT 1: 3 x BT at 3-4m + PT **Dose:** 6-12U/kg	PT only	0 and 6m after last inj	**Spasticity:** Sig ↑ following inj in all INT groups vs CTRL. Sig ↑ in all parameters btwn INT2 and INT3 in favour of INT3 (p=0). Sig ↑ in ms tone (p=0) btwn INT1

–	both sites in ambulant spastic hemi CP children	CTRL: 15	**Ms inj:** GM **Brand:** Botox or Dysport INT 2: 3 x BT at 3-4m + PT **Dose:** 6-12U/kg **Ms inj:** HA **Brand:** Botox or Dysport INT 3: 3 x BT at 3-4m + PT **Dose:** 6-12U/kg **Ms inj:** GM, HA **Brand:** Botox or Dysport			and INT3 in favor of INT3 (p=0). No sig dif btwn INT1 and INT2 (p=1). **Gait Parameters:** Sig ↑ of the unaffected step length and ↓ in step width and foot angle (P=0.04, P=0.003, P=0.002 respectively) in INT1 vs CTRL 1. Sig ↑ of the unaffected step length and ↓ in step width and foot angle (p=0.006, p=0.002, p=0.003 respectively) in INT3 vs CTRL. Sig ↑ in cadence and speed of walking in INT3 vs CTRL 1 (p=0.03, p=0.004 respectively). Sig ↑ in all gait parameters btwn INT2 an INT3 in favour of INT3. Sig ↑ in cadence (p=0.04) and speed of walking (p=0.01) btwn INT1 and INT3 in favour of INT3. Sig ↑ in affected step length in INT3 when comparing pre and post measures (p=0). No sig dif btwn step width (p=0.96) and foot angle (p=0.92) btwn INT1 and INT3. No sig dif btwn INT1 and INT3 in step width (p=0.96) and foot angle (p=0.92). No sig dif btwn INT1, INT2, INT3 vs CTRL for step length. **Summary: Significant finding (spasticity, gait)**
Lidman et al., 2015 –	To investigate the effects of repeated BT injections combined with OT, including a splint, compared with OT alone on hand function in children with unilateral spastic CP, in all International	Total: 20 INT1: 10 CTRL1: 10	x 2 BT doses + OT. Time btwn BT inj not reported **Doses per ms:** BB 15–30U/mL, Brac 10–15U/mL, m. BR 10–15U/mL, PT	OT only	0, 3, 6, 9, and 12m.	**Active ROM 0-12m:** No sig btwn-group differences supination ↑ in both groups (INT median dif of 22° and CTRL 15°). At 12m 100% INT and 60% CTRL ↑ >10°. Elbow extn: 16.67% INT and 75% CTRL ↑ by >10°. **Passive ROM 0-12m:** No sig btwn-group differences supination: 30% INT and 10% CTRL ↑ >10°. Elbow extn: 0% INT and 10% CTRL 1 ↑ >10°.

	Classification of Functioning, Disability and Health domains.		10–20U/mL, PQ 5–20U/mL, AP 5–10U/mL, and FPB 3U/mL. **Brand**: Botox			**COPM:** No btwn-group dif reported. Both groups ↑ after each treatment block at 3 and 9m. performance domain: both ↑. At 3m first goal ↑ 70% INT and 80% CTRL, second goal ↑ 100% INT and 80% CTRL. At 9m first goal ↑ 70% both group and second goal ↑ 80% INT and 70% CTRL. Satisfaction domain: both groups ↑. At 3m first goal ↑ 70% both groups and second goal 100% INT and 60% CTRL. At 9m first goal ↑ 70% INT and 60% CTRL and second goal ↑ 80% INT and 60% CTRL. **AE:** no AE's after BT reported at parent interviews 1 m after inj **AHA 0-12m:** Superior effect in INT vs CTRL ($p<0.03$). INT ↑ median 7.5 AHA units (95% CI 2.5–12.0) and CTRL ↑ median of 0 AHA units (95% CI -3.5 to 8.0). **Summary: Insignificant finding**
Willoughby et al., 2012 –	To study the long-term impact of 3y of BT injections and abduction bracing on hip development in children with bilateral spastic CP. We wanted to know if early treatment improved hip development and reduced the need for surgery.	Total: 91 INT: 47 CTRL: 44	BT + abduction brace over 3y, number of inj not specified **Dose:** Not reported **Ms inj:** Not reported-presume LL **Brand BT:** Not reported	Usual care (details not specified)	Does not report	**Mean MP:** No sig dif btwn-groups at most recent FU. 15.9% in INT and 15.2% in CTRL ($p=0.79$; 95% CI -4.58 to 5.976). **Mean age at preventive surgery:** No sig dif btwn-groups (INT 6y 7m; CTRL 5y 1m) **Mean age at reconstructive surgery:** No sig dif btwn-groups in (INT 8y 10m; CTRL 9y 2m ($p=0.698$)). **Hip morphology:** No sig dif btwn-groups (Mann–Whitney U test=867.50, $p=0.11$). **Summary: Insignificant finding**

Note. AP = adductor pollicis. BB = biceps brachii. AE = Adverse Events. AHA = Assisting Hand Assessment. AP = adductor pollicis. BB = biceps brachii. BT = Botulinum toxin. BR = brachioradialis. Brac = brachialis. Btwn = between. CP = Cerebral Palsy. CI = Confidence Interval. COPM = Canadian Occupational Performance Measure. CTRL = Control group. DF = Dorsiflexion. dif = Differences. Extn = Extension. FCR = flexor carpi radialis. FCU = flexor carpi ulnaris. FDP = flexor digitorum profundus. FDS = flexor digitorum superficialis. FPB = flexor pollicis brevis. FPL = flexor pollicis longus. FU = follow up. GAS = Goal attainment scale. GMFCS = Gross Motor Function Classification System. GMFM = Gross Motor Function Measure. Inj = Injection. INT = Intervention group. KE = Knee extension. KF = Knee Flexion. Kg = kilogram. LG = Lateral Gastrocnemius. HA = hip adductor. HS = hamstring. M = Male. MAS = Modified Ashworth Scale. m: month/s. MP = Migration Percentage. ms = muscle. MTM = Modified Tardieu method. OT = Occupational Therapy. PDMS-FM = Peabody Developmental Motor Scale- Fine motor. PedsQL = Pediatric Quality of Life Inventory. p = per. PF = Plantarflexion. PODCI = Pediatric outcomes data collection instrument. PQ = pronator quadratus. PrT = pronator teres. QUEST = Quality of Upper Extremity Skills Test. ROM = Range of Motion. SHUEE-DPA = Shriners Hospital Upper Extremity Evaluation Dynamic Positional Analysis. SHUEE-SFA = Shriners Hospital Upper Extremity Evaluation Spontaneous Functional Assessment. Sig = Significant. SWASH = Sitting Walking And Standing Hip orthosis. TA = thumb adductor. TS = Tardieu scale. U = Unit. w = week/s. y = year/s.

Spasticity

Spasticity was measured in 37% (n = 7) of included studies. When comparing different frequencies of BT, a moderate-quality study by Tedroff et al. (2010), assessed lower limb spasticity and found a significant between-group difference in knee flexor spasticity in the intervention group (three to eight doses of BT) when compared to the control group (three to five doses of BT) at 3.5 years follow-up. This was the longest follow-up period incorporated in this review. A moderate-quality study by Lowe et al. (2007), compared two doses of BT to three doses of BT and found no significant between-group difference in spasticity at 30 months. When comparing repeated BT to placebo injection, a moderate-quality study by Moore et al. (2008), found no significant between-group differences in ROM. When comparing repeated BT to other interventions, two moderate-quality studies found a significant between-group reduction of spasticity at 12 months when compared to OT only (Olesh et al., 2010) and up to 30 months when compared to PT only (Hawamdeh et al., 2007). A low-quality study by Ibrahim et al. (2007), reports significant between-group improvements in spasticity up to 18 months across all intervention groups when compared to PT only. Planned spasticity assessment results were not reported in one low-quality study (Boyd et al., 2001).

Gait pattern

Gait assessment was completed in 32% (n = 6) of studies. Two high-quality studies comparing two doses of BT at baseline and 4 weeks to placebo injection showed significant between-group improvements in the BT group in gait (Sutherland et al., 1999) and the Physician Rating Scale (Koman et al., 2000). These studies both assessed the short-term impact of repeated BT with final measures taken at 8 weeks (Sutherland et al., 1999) and 12 weeks (Koman et al., 2000). These studies show that repeated BT provides short-term improvements gait when compared to no BT. One moderate-quality study found a significant improvement in gait with 4-monthly BT compared to 12-monthly BT at 25 months (Kanovsky et al., 2009). A similar high-quality study comparing 4-monthly BT to 12-monthly BT only measured peak ankle DF

during stance, finding no significant between-group differences from baseline to 26 months (Hastings-Ison et al., 2015). A low-quality study by Ibrahim et al. (2007), found repeat BT to different sets of muscle groups, significantly improved gait measures when compared to PT only at 6 months follow-up. They also found significant improvements in gait in the group that injected two muscle groups when compared to a single muscle group at one injection session.

Hip Displacement

Three studies (16%) reported findings for hip displacement measured using migration percentage of anteroposterior hip radiographs (Boyd et al., 2001; Graham et al., 2008; Willoughby et al., 2012). All of the studies measuring hip displacement, compared repeated BT to other interventions. A high-quality study (Graham et al. 2008) and two low-quality studies (Boyd et al., 2001; Willoughby et al., 2012) all found no significant between-group differences in hip displacement when comparing repeated BT to PT only (Boyd et al., 2001; Graham et al. 2008) or usual care (Willoughby et al., 2012).

Muscle strength

Muscle strength was measured in 16% (n = 3) of studies and was not assessed in studies comparing different frequencies of BT. When repeated BT was compared with placebo injection, a high-quality study by Sutherland et al. (1999), did not include findings of the between-group analysis for muscle strength. When comparing repeated BT to other interventions, a moderate-quality study by Van Heest et al. (2015), found surgical intervention and OT only had significantly improved mean pinch strength when compared to repeated BT.

Progression to surgery

Repeated BT did not have a significant impact on progression to surgery. No significant between-group differences in progression to surgery were identified when repeated BT was compared to placebo injection (Moore et al., 2008), PT only (Boyd et al., 2001), usual care (Willougby et al., 2012), or different frequencies of BT (Kanovsky et al., 2009).

Activity Limitations

Motor function

Repeated BT did not significantly improve gross motor function when comparing different frequencies of BT (Kanovsky et al., 2009; Tedroff et al., 2010), when compared to PT only (Boyd et al., 2001; Hawamdeh et al., 2007), or when compared to placebo injection (Moore et al., 2008). Gross motor function was measured in 32% (n = 6) of studies and no significant between-group differences were found at 12 months (Boyd et al., 2001), 24 months (Moore et al., 2008), 28 months (Kanovsky et al., 2009), 30 months (Hawamdeh et al., 2007) or 42 month follow-up (Tedroff et al., 2010). Graham et al. (2008), recorded baseline GMFCS but did not report results at final 36 month follow-up.

Occupational performance

Occupational performance was assessed using the COPM and included in 21% of studies (n = 4). One moderate-quality study compared different frequencies of BT (three doses BT versus two doses BT) and found no significant between-group differences at 30 months (Lowe et al., 2007). Findings for studies comparing BT to other interventions varied. One moderate-quality study (Lidman et al., 2015) found no significant between-group differences at 12 month follow-up compared to OT only, and two moderate-quality studies found a significant between-group improvement when compared to OT (Olesh et al., 2010) or the surgical group (Van Heest et al., 2015) at 12 month follow-up. The frequency of repeated BT was similar across studies (Table 5 and 6).

Participation

Health Related Quality of Life

No significant improvements in HRQL were found with repeated BT when compared to different frequencies of BT (Hastings-Ison et al., 2015), placebo injection (Koman et al., 2013), surgical intervention or OT only (Van Heest et al., 2015). Health related quality of life was assessed in 16% (n = 3) of studies and there were no

significant between-group differences at 6.5 months (Koman et al., 2013), 12 months (Van Heest et al., 2015) or 26 months post-injection (Hastings-Ison et al., 2015).

Potential harms

Adverse Events

Repeated BT did not significantly alter the number of adverse events when compared to placebo injection (Moore et al., 2008) or different frequencies of BT (Edwards et al., 2015; Kanovsky et al., 2009). Adverse events were recorded in 21% (n = 4) of studies with no significant between-group differences found in incidence or severity of adverse events (Edwards et al., 2015; Hastings-Ison et al., 2015; Kanovsky et al., 2009; Moore et al., 2008).

Antibody production to Botulinum Toxin

Repeated BT did not significantly impact the presence of antibodies to BT when comparing different frequencies of repeated BT (Kanovsky et al., 2009) and when compared to placebo injection (Koman et al., 2000). Antibody production to BT was only recorded in 16% (n = 2) of studies with both high-quality studies finding no significant between-group differences at 3 months (Koman et al., 2000) or 28 months (Kanovsky et al., 2009).

4 DISCUSSION

The purpose of this systematic review was to determine the efficacy of repeat BT injections in the management of clinical outcomes in children with CP and compare the findings with the current NICE clinical guidelines to determine if the guidelines incorporate evidence-based recommendations concerning the timing and frequency of BT injections.

4.1 Evaluation of body function and structure

Range of Motion and Spasticity

Active ROM significantly improved in the short- to medium-term in the repeat BT group when compared to placebo injection at 12 weeks in the lower limb and 26 weeks in the upper limb (Koman et al., 2000; Koman et al., 2013). Passive ROM of the

lower limb significantly improved when comparing repeated BT to PT only or no BT up to 3.5 years (Tedroff et al., 2010). However, different treatment frequencies of BT did not have a significant impact on ROM (refs). This suggests that repeat BT may improve active and passive ROM, but increased frequency of BT treatments (4-monthly versus 12-monthly) is unlikely to provide further improvements in ROM in the treatment of spastic equinus. This finding may be muscle specific and further research is needed to determine if this is the same in other muscles. It could be argued that if a child is provided the correct dose of BT to the correct muscle group, optimal improvements in ROM should be achieved and therefore providing subsequent BT injections within a short timeframe would not be expected to significantly improve ROM further. Perhaps this is due to ROM being made up of neural and non-neural components, with BT only treating the neural aspect (ref). The child is left with muscle and joint contracture that is not influenced by BT, so other interventions are needed to stretch the muscle for example splinting and surgery (ref).

Repeated BT significantly improved spasticity when compared to PT only, OT only or decreased frequency of BT (refs). However, one moderate-quality study (Moore et al., 2008) showed repeated BT at 2 year follow-up found no significant between-group changes when compared to placebo injection, indicating no long-term significant improvements in spasticity. These results make sense given the known effects of BT only last four months post injection (García Salazar et al., 2015; Love et al., 2010; Löwing et al., 2017; Zeuner & Deuschl, 2016).

The findings of this review are supported by the wider literature that demonstrates that repeat BT provides short-term improvements in spasticity and ROM that are not significant in the long-term (Dabrowski et al., 2018; Dinu et al., 2013; Fattal et al., 2008). Observational literature shows significant improvements in spasticity with the first BT dose, that reduces with subsequent doses, indicating impact of BT may reduce over time (Dabrowski et al., 2018). More longitudinal studies assessing repeated BT may provide additional information about the long-term impact of repeat BT on spasticity and ROM. Importantly, higher frequencies of BT did not significantly

impact ROM or spasticity in spastic equinus suggesting 12-monthly BT is sufficient to maintain improvements in ROM and spasticity. These findings are essential when planning repeat BT treatment frequency.

Gait Pattern

The review findings demonstrated that repeat BT provides short-term improvements in gait when compared to placebo injection or PT only (Ibrahim et al., 2007; Koman et al., 2000; Sutherland et al., 1999). In the two studies comparing 4-monthly BT versus 12-monthly BT, changes in gait after 2 years of treatment contrasted between the studies. However, the study that showed improvements in gait with increased BT frequency measured gait on a subjective rating scale (Kanovsky et al., 2009), which may be prone to issues with reliability, whereas the study that found no changes in gait with increased BT frequency (Hastings-Ison et al., 2015) measured ankle DF objectively with 3-dimensional gait analysis (Hastings-Ison et al., 2015). As with the effects on spasticity noted above, the wider literature suggests that initial BT treatments may provide greater improvements in gait compared to subsequent BT treatments (Dabrowski et al., 2018; Fattal et al., 2008; Hong et al., 2017), which might explain that lack of additional benefit from more frequent injections. It was also found when two muscle groups were injected at one treatment session, this had a significant improvement in gait in the short term when compared to injection of a single muscle group (Ibrahim et al., 2007). These findings are expected as children with CP have spasticity of multiple muscle groups impacting their gait. Overall, the findings suggest that repeated BT can change gait in the short term, but that increased frequency may not have a significant long-term impact on gait. These short-term changes in gait are likely related to the short-term effects on ROM and spasticity.

In summary, 12-monthly BT treatment frequency is advised to two or more muscle groups at one treatment session when improving gait in the long-term.

Hip Displacement

Repeated BT was not found to reduce hip displacement when compared to PT only or usual care up to 3 years follow-up (ref). Therefore, the findings of this review do not support repeated BT as an effective treatment for prevention of hip displacement.

4.2 Evaluation of Effects on Activity and Participation

Gross Motor Function and Health Related Quality of life

No significant improvements in gross motor function or HRQL with repeated BT were ascertained from this review. Observational literature also suggests repeated BT does not change function children with CP (Fattal et al., 2008). Only a few studies (n = 3) measured HRQL; this is concerning as the wider literature distinctly outlines improvements in HRQL are more significant to a person's well-being than improvements of body impairments (Bjornson and McLaughlin, 2001; Ko et al., 2011; Park, 2017; World Health Organisation, 2012). The World Health Organisation (2012) describes measures of impairment, behaviour, disability and function offer an indication of the impact of disease, but do not assess HRQL precisely. They endorse HRQL as the primary aim in health care and advise a holistic approach, rather than focus on absence of disease or illness. However, Ko et al. (2011) found that most research focuses on improvements in function rather than HRQL, and that more severe GMFCS levels were associated with reduced HRQL, highlighting the importance of measuring both function and HRQL. Park (2017) claimed HRQL outcomes can be used to forecast the anticipated status of children with CP in the future, giving a better indication than functional assessments. Furthermore, Bjornson and McLaughlin (2001) found the relationship between clinical impairments and a patient's well-being were insignificant and contradictory, further supporting the measurement of HRQL as the most important outcome in CP management and research. Despite these recommendations to use HRQL assessment over functional assessment, this was not reflected in the results of this systematic review.

Occupational performance

All studies that measured occupational performance delivered BT injection to the upper limb. Moderate quality evidence showed that three doses of repeated BT at 3-monthly or 4-monthly intervals plus OT, compared to OT only or surgical intervention, significantly improved occupational performance (Van Heest et al., 2015, Olesh et al., 2010). However, the moderate-quality study by Lowe et al. (2007) found no significant differences in occupational performance when comparing 6-monthly versus 12-monthly BT over 18 months. While this suggests the frequency of BT may not provide further improvements, the difference between the intervals may not have been enough to warrant a significant change. This evidence suggests repeated BT plus OT is effective in improving occupational performance when compared to OT only and therefore repeated BT combined with OT is recommended when targeting upper limb occupational performance with treatment frequency of 3-4 monthly.

4.3 Evaluation of Potential Harms

Adverse Events

Adverse events were not found to be significantly different between-groups in this review (Edwards et al., 2015; Hastings-Ison et al., 2015; Kanovsky et al., 2009; Moore et al., 2008).

Observational literature conveyed adverse events were either mild or moderate and resolved within two days (Fattal et al., 2008). This finding opposes a recently published RCT by Dabrowski et al. (2021) that demonstrated that adverse events did not increase with increasing dose or repetition of BT injections in children with CP.

4.4 Limitations of this review

A limitation of this review is the results are transferable to a specific population and specific muscle group depending on what was used in each individual study. For example, it is possible that the effects of repeated BT are different when applied to spastic PF compared to wrist flexors.

Studies included in this review included short term follow-up periods, limiting ability to depict long-term outcomes (Table 3). The sample size of most studies was

small and the participant age range was large making it difficult to assess effect of repeated BT on a particular age group. We were therefore unable to conclude longitudinal differences throughout childhood.

Another limitation is the majority of studies presented with either moderate or high-risk of bias on the ROB2 (Appendix B). This lowered the quality of evidence and the certainty about the findings of this review.

4.5 The National Institute For Healthcare Guidelines

Refer to Appendix C for details of NICE guidelines. The NICE guidelines specify BT use to be considered for treatment of focal spasticity of the upper and lower limb caused by acquired non-progressive brain injury (National Institute for Health and Care Excellence, 2016). They recommend trial of BT for improving gross motor function and postural or functional difficulties in children and young people with spasticity. The guidelines includes specific recommendations related to assessment, injection site, injection frequency. Table 7 shows a summary of the studies included in this review and the NICE guidelines that were included in the study protocols.

Table 7
NICE guidelines

Author	Guideline 1.5.17: Assessment of muscle tone, ROM and motor function.			Guideline 1.5.13: Injection of BT into more than one muscle group.	Guideline 1.5.18: Decision for repeat BT injections is goal-centred
	Muscle tone	ROM	Motor Function		
Ackman et al., 2005	✓	✓	✓	✓	X
Barber et al., 2013	X	✓	X	✓	X
Boyd et al., 2001	✓	X	√	✓	✓
Edwards et al., 2015	X	X	X	X	X
Graham et al., 2008	X	X	X	✓	X
Hastings-Ison et al., 2015	X	✓	✓	✓	X
Hawamdeh et al., 2007	✓	✓	✓	✓	X
Ibrahim et al., 2007	✓	X	✓	✓	X
Kanovsky et al., 2009	X	✓	✓	X	✓
Koman et al., 2000	X	✓	✓	✓	X
Koman et al., 2013	X	✓	✓	X	X
Lidman et al., 2015	X	✓	✓	✓	✓
Lowe et al., 2007	✓	X	✓	✓	✓
Moore et al., 2008	✓	X	✓	X	X
Olesh et al., 2010	✓	X	✓	✓	✓
Sutherland et al., 1999	X	✓	✓	✓	X
Tedroff et al., 2010	✓	✓	✓	X	X
Van Heest et al., 2015	X	✓	✓	✓	✓
Willoughby et al., 2012	X	X	X	X	X

Note. ✓= included. X=not included.

Assessment domains

Guideline 1.5.17 recommends performing an assessment of muscle tone, range of movement, and motor function. Appendix A outlines the specific outcome measures used in the studies. Only two moderate-quality studies (Hawamdeh et al., 2015; Tedroff et al., 2010) and one low-quality study (Ackman et al., 2005) included assessment of ROM, spasticity and motor function. Most studies included at least one of these outcome measures, with one high-quality study (Graham et al., 2008) and two low-quality studies (Edwards et al., 2015; Willoughby et al., 2012) not recording a measure of ROM, spasticity or motor function. Motor function was the most prevalent assessment, recorded in 79% or articles and spasticity the least common, found in just 42% of articles. In summary most studies included in this systematic review include a measure of ROM, muscle tone or motor function (84%), but only 16% included all three assessments. This likely relates to the different aims across the studies. If all studies

included assessment of muscle tone, ROM and motor function, this would generate more specific information about the long-term impact of repeated BT.

Injection site

Guideline 1.5.13 recommends considering injection of BT to more than one muscle group. Most of the studies included consideration of BT injection to multiple muscle groups at a single treatment session (68%). This guideline is supported by a low-quality study by Ibrahim et al. (2007) that compared injection of two muscle groups to a single muscle group at one injection session, and found significant improvements in gait in the multiple-muscle group.

Injection Frequency

Guideline 1.5.18 recommends repeat BT injections are considered when response to treatment goal is satisfactory, the treatment effect has worn off and new goals are identified. When determining the response to treatment, there is no clear guideline on how to measure treatment effect, although measures of spasticity, ROM, and motor function suggested in guideline 1.5.17 could be used. An assessment of treatment effect wearing off was not documented in any of the studies, and the guidelines do not indicate how to determine if the treatment effect has worn off or the specific timeframes for reassessment. A non-controlled study by Esquenazi et al. (2020) compared retreatment criteria and retreatment intervals of four studies concerning participants treated with BT; they found benefits of BT persisted beyond 12 weeks for most participants and most did not require retreatment before 16 weeks. In this review, two moderate-quality studies (Hawamdeh et al., 2007; Lowe et al., 2007) and one low-quality study (Ibrahim et al., 2007) found effects of BT can still be noted up to 6 months, and that 12-monthly injection intervals are efficacious for spasticity and ROM in the ankle plantarflexors. In relation to goal setting, almost one third (32%) of studies included assessment of goals. Four studies (21%) integrated an outcome measure to assess participants goals (Lidman et al., 2015; Lowe et al., 2007; Olesh et

al., 2010; Van Heest et al., 2015). As the review findings suggest a BT frequency of 12-monthly when goal is to improve ROM and spasticity in both the upper and lower limb.

Commencement and monitoring

The NICE clinical guidelines do not provide recommendations for age of commencement to BT treatment. The studies included in this review show repeat BT was safe for use in children from 11 months to 18 years of age with no significant increase in serious adverse events (Edwards et al., 2015; Hastings-Ison et al., 2015; Kanovsky et al., 2009; Moore et al., 2008) or antibody production to BT found (Kanovsky et al., 2009; Koman et al., 2000). The studies included in this review had follow-up time frames ranging from just 2 months to 3.5 years with an average follow-up of 16 months.

The current NICE guidelines do not include recommendations for prevention of surgical interventions. This is supported by the findings of this review. The included studies identified repeated BT use was not found to be effective in reducing progression to surgery (Boyd et al., 2001; Kanovsky et al., 2009; Moore et al., 2008; Willougby et al., 2012), delaying development of contracture (Kanovsky et al., 2009) or change of age for reconstructive surgery (Willougby et al., 2012).

Summary of Recommendations

The findings of this systematic review suggest additional guidelines and changes to current guidelines.

1. Based on the review findings that repeat BT may improve ROM and spasticity in the medium to long term (12 to 30 months post injection) (Hawamdeh et al., 2007, Ibrahim et al., 2007), Koman et al., 2013, Koman et al., 2000, Olesh et al., 2010, Tedroff et al., 2010), repeated BT is recommended for treatment of focal spasticity in the upper or lower limbs of children with CP for the long-term management (up to 3.5 years) of spasticity and ROM.
2. Based on the review findings of no serious adverse events with repeated BT (Edwards et al., 2015, Hastings-Ison et al., 2015, Kanovsky et al., 2009, Moore

et al., 2008), it is suggested that repeated BT is safe to use in children from 11 months to 18 years of age.

3. Based on the findings and recommendations of Bjornson and McLaughlin (2001), Ko et al. (2011), Park (2017), and the World Health Organisation (2012), research and clinical use of repeated BT should include HRQL assessment.
4. Based on the review findings that 4-monthly BT does not improve ROM or spasticity more than 12-monthly BT in the treatment of spastic equinus (Hastings-Ison et al., 2015, Kanovsky et al., 2009), it is recommended that when treating spasticity and decreased ROM in the ankle plantarflexors, the optimal BT treatment frequency is 12-monthly intervals.
5. Based on the review findings of Kanovsky et al. (2009) the optimal repeated BT treatment frequency for improving gait is 12-monthly intervals.
6. Based on findings that multi-muscle injections improve gait (Ibrahim et al., 2007), injection of two muscle groups is more beneficial than single muscle group when goal is to improve gait.
7. Based on the review findings that repeated BT does not improve gross motor function or delay of development of contracture or progression to surgery (Boyd et al. (2001), Kanovsky et al. (2009). Moore et al. (2008), Tedroff et al. (2010) and Willougby et al. (2012), it is recommended that other interventions are considered to address these impairments and activity limitations.

5 CONCLUSION

The review presented low to moderate-quality evidence that repeated BT when compared to PT only, OT only or placebo injection improves spasticity and ROM in the short-term only. The recommended retreatment frequency of BT is 12-monthly when goal is to improve ROM and spasticity in the ankle in the short term only, based on high-quality evidence. There is a lack of inclusion of participation and quality of life outcome measures utilised by the studies included in this review. Current guidelines

lack specificity in relation to recommended frequency of repeated BT and this review has provided information to refine these recommendations. Further longitudinal research is required to determine recommendations for repeated BT treatment distribution throughout childhood.

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7 REFERENCES

Ackman, J. D., Russman, B. S., Thomas, S. S., Buckon, C. E., Sussman, M. D., Masso, P., ... & Aiona, M. D. (2005). Comparing botulinum toxin A with casting for treatment of dynamic equinus in children with cerebral palsy. *Developmental medicine and child neurology*, *47*(9), 620-627

Alhusaini, A. A., Crosbie, J., Shepherd, R. B., Dean, C. M., & Scheinberg, A. (2011). No change in calf muscle passive stiffness after botulinum toxin injection in children with cerebral palsy. *Developmental Medicine and Child Neurology.* 53, 553–558.

Auckland University of Technology (n.d.). *Research Ethics.* Retrieved from https://www.aut.ac.nz/research/researchethics

Barber, L., Hastings-Ison, T., Baker, R., Kerr Graham, H., Barrett, R., & Lichtwark, G. (2013). The effects of botulinum toxin injection frequency on calf muscle growth in young children with spastic cerebral palsy: a 12-month prospective study. *Journal of children's orthopaedics*, *7*(5), 425-433.

Berrin, S. J., Malcarne, V. L., Varni, J. W., Burwinkle, T. M., Sherman, S. A., Artavia, K. (2007). Pain, fatigue, and school functioning in children with cerebral palsy: a pathanalytic model. *Journal of Pediatric Psychology. 32*(3), 330–337.

Bjornson, K. F., & McLaughlin, J. F. (2001). The measurement of health-related quality of life (HRQL) in children with cerebral palsy. *European Journal of Neurology*, *8*, 183-193.

Boyd, R. N., Dobson, F., Parrott, J., Love, S., Oates, J., Larson, A., ... & Graham, H. K. (2001). The effect of botulinum toxin type A and a variable hip abduction orthosis on gross motor function: a randomized controlled trial. *European Journal of Neurology*, *8*, 109-119.

Boyd, R., & Graham, H. K. (1997). Botulinum toxin A in the management of children with cerebral palsy: indications and outcome. *European Journal of Neurology*, 4, 15– 21.

Brandenburg, J. E., Sieck, G. C., & Fogarty, M. J. (2019). A Critical Evaluation of Current Concepts in Cerebral Palsy. *Physiology (Bethesda, Md.)*, *34*(3), 216–229.

Breau, L. M., Camfield, C. S., McGrath, P. J., & Finley, G. A. (2003). The incidence of pain in children with severe cognitive impairments. *Arch Pediatric Adolescent Medicine*, *157*(12), 1219 –1226.

Cerebral Palsy Society of NZ. (2018). *Treatments.* https://cerebralpalsy.org.nz/cerebral-palsy/treatments/

Choi, J. Y., Kim, S. K., & Park, E. S. (2019). The Effect of Botulinum Toxin Injections on Gross Motor Function for Lower Limb Spasticity in Children with Cerebral Palsy. *Toxins*, *11*(11), 651.

Dabrowski, E., Bonikowski, M., Gormley, M., Volteau, M., Picaut, P., & Delgado, M. R. (2018). Abobotulinumtoxin a efficacy and safety in children with equinus foot previously treated with botulinum toxin. *Pediatric neurology*, *82*, 44-49.

Dabrowski, E., Chambers, H. G., Gaebler-Spira, D., Banach, M., Kaňovský, P., Dersch, H., ... & Heinen, F. (2021). Incobotulinumtoxin A efficacy/safety in upper-limb spasticity in pediatric cerebral palsy: randomized controlled trial. *Pediatric neurology*, *123*, 10-20.

Dinu, I. Ş., Seblany, H. T., Safer, M., & PLEŞCA, D. A. (2013). Effects of botulinum toxin-type a in the treatment of cerebral palsy in children. *FARMACIA*, *61*(4), 748-755.

Eames, N. W., Baker, R., Hill, N., Graham, H. K., Taylor, T., Cosgrove, A. (1999). The effect of botulinum toxin A on gastrocnemius length: magnitude and duration of response. *Developmental Medicine and Child Neurol*ogy. 41, 226– 32.

Edwards, P., Sakzewski, L., Copeland, L., Gascoigne-Pees, L., McLennan, K., Thorley, M., ... & Boyd, R. N. (2015). Safety of botulinum toxin type A for children with nonambulatory cerebral palsy. *Pediatrics*, *136*(5), 895-904.

Esquenazi, A., Delgado, M. R., Hauser, R. A., Picaut, P., Foster, K., Lysandropoulos, A., & Gracies, J. M. (2020). Duration of symptom relief between injections for AbobotulinumtoxinA (Dysport®) in spastic paresis and cervical dystonia: Comparison of evidence from clinical studies. *Frontiers in neurology*, *11*, 576117.

Evans, S. H., Cameron, M. W., & Burton, J. M. (2017). *Hypertonia.* Washington, DC: Elsevier Science.

Fattal-Valevski, A., Domenievitz, D., Giladi, N., Wientroub, S., & Hayek, S. (2008). Long-term effect of repeated injections of botulinum toxin in children with

cerebral palsy: a prospective study. *Journal of children's orthopaedics*, *2*(1), 29-35.

Falisse, A., Jonkers, I., De Groote, F., Bar-On, L., & Desloovere, K. (2018). A spasticity model based on feedback from muscle force explains muscle activity during passive stretches and gait in children with cerebral palsy. *Public Library of Science. 13*(12).

Farag, S. M., Mohammed, M. O., El-Sobky, T. A., ElKadery, N. A., & ElZohiery, A. K. (2020). Botulinum Toxin A Injection in Treatment of Upper Limb Spasticity in Children with Cerebral Palsy: A Systematic Review of Randomized Controlled Trials. *JBJS Reviews. 8*(3).

Flemyng, E., Dwan, K., Moore, T. H., Page, M. J., & Higgins, J. P. (2020). Risk of bias 2 in Cochrane reviews: a phased approach for the introduction of new methodology. *Cochrane Database of Systematic Reviews*, (10).

Fortuna, R., Vaz, M. A., Youssef, A. R., Longino, D., Herzog, W. (2011). Changes in contractile properties of muscles receiving repeat injections of botulinum toxin (Botox). *Journal of Biomechanics*, 44(1), 39-44.

Friedman, A., Diamond, M., Johnston, M. V., & Daffner, C. (2000). Effects of botulinum toxin A on upper limb spasticity in children with cerebral palsy. *American Journal of Physical Medicine and Rehabil*itation, 79, 53– 59.

García Salazar, L. F., Santos, G. L. dos, Pavão, S. L., Rocha, N. A. C. F., & Russo, T. L. de. (2015). Intrinsic properties and functional changes in spastic muscle after application of BTX-A in children with cerebral palsy: Systematic review. *Developmental Neurorehabilitation*, *18*(1), 1–14.

Graham, H. K., Boyd, R., Carlin, J. B., Dobson, F., Lowe, K., Nattrass, G., ... & Reddihough, D. (2008). Does botulinum toxin A combined with bracing prevent hip displacement in children with cerebral palsy and “hips at risk”?: A randomized, controlled trial. *JBJS*, *90*(1), 23-33.

Hastings-Ison, T., Blackburn, C., & Opie, N. (2014). Reproducibility of an instrumented measure for passive ankle dorsiflexion in conscious and anaesthetized children with cerebral palsy. *Developmental Medicine & Child Neurol*ogy, 56, 378–85.

Hastings-Ison, T., Blackburn, C., Rawicki, B., Fahey, M., Simpson, P., Baker, R. (2016). Injection frequency of botulinum toxin A for spastic equinus: a randomized clinical trial. *Developmental Medicine & Child Neurology*, 58(7), 750–7.

Hastings-Ison, T., Sangeux, M., Thomason, P., Rawicki, B., Fahey, M., & Graham, H. K. (2018). Onabotulinum toxin-A (Botox) for spastic equinus in cerebral palsy: a prospective kinematic study. *Journal of Children’s Orthopaedics*. 12(4), 390–397.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... & Sterne, J. A. (2011). The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *British Medical Journal*, *343*.

Hong, B. Y., Chang, H. J., Lee, S. J., Lee, S., Park, J. H., & Kwon, J. Y. (2017). Efficacy of repeated botulinum toxin type a injections for spastic equinus in children with cerebral palsy—a secondary analysis of the randomized clinical trial. *Toxins*, *9*(8), 253.

Honkavaara, M., & Rintala, P. (2010). The Influence of Short Term, Intensive Hippotherapy on Gait in Children with Cerebral Palsy. / Der Einfluss Von Kurzzeit-Intensiv-Hippotherapie Auf Den Gang Von Kindern Mit Cerbralparese. *European Journal of Adapted Physical Activity*, *3*(2), 29–36.

Kahraman, A., Seyhan, K., Değer, Ü., Kutlutürk, S., & Mutlu, A. (2016). Should botulinum toxin A injections be repeated in children with cerebral palsy? A systematic review. *Developmental medicine and Child Neurology*, 58(9), 910-917.

Kanovsky P, Bares M, Severa S, Richardson A, Dysport Paediatric Limb Spasticity Study G. Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-limb spasticity in children with cerebral palsy. (2009). Dev Med Child Neurol.;51(6):436–45.

Kaushik, P., Gowda, V., Shivappa, S., Mannapur, R., & Jaysheel, A. (2018). A randomized control trial of botulinum toxin A administration under ultrasound guidance against manual palpation in spastic cerebral palsy. Journal of Pediatric Neurosciences, 13(4), 443–447.

Ko, J., Lee, B. H., & Kim, M. (2011). Relationship between function and health-related quality of life of school-aged children with cerebral palsy. *Journal of Physical Therapy Science*, *23*(2), 189-195.

Koman, L. A., Brashear, A., Rosenfeld, S., et al. (2001). Botulinum toxin type a neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. *Pediatrics*, 108, 1062– 1071.

Kruse, A., Schranz, C., Tilp, M., & Svehlik, M. (2018). Muscle and tendon morphology alterations in children and adolescents with mild forms of spastic cerebral palsy. *BMC Pediatrics*, *18*(1), 1–9.

Garcia Salazar, L. F., Santos, G. L. D., Pavao, S. L., Rocha, N. A. C. F., & Russo, T. L. D. (2015). Intrinsic properties and functional changes in spastic muscle after application of BTX-A in children with cerebral palsy: systematic review. *Developmental Neurorehabilitation*, *18*(1), 1-14.

Hastings-Ison, T., Blackburn, C., Rawicki, B., Fahey, M., Simpson, P., Baker, R., & Graham, K. (2016). Injection frequency of botulinum toxin A for spastic equinus: a randomized clinical trial. *Developmental Medicine & Child Neurology*, *58*(7), 750-757.

Hawamdeh, Z. M., Ibrahim, A. I., & Al-Qudah, A. A. (2007). Long-term effect of botulinum toxin (A) in the management of calf spasticity in children with diplegic cerebral palsy. *Europa medicophysica*, *43*(3), 311-318.

Ibrahim, A. I., Hawamdeh, Z. M., & Al-Qudah, A. A. (2006). Functional outcome of botulinum toxin injection of gastrocnemius and adductors in spastic hemiplegic cerebral palsied children. *Europa Medicophysica*, *43*(1), 13-20.

Kaňovský, P., Bareš, M., Severa, S., Richardson, A., & Dysport Paediatric Limb Spasticity Study Group. (2009). Long-term efficacy and tolerability of 4-monthly versus yearly botulinum toxin type A treatment for lower-limb spasticity in children with cerebral palsy. *Developmental medicine & child neurology*, *51*(6), 436-445.

Koman, L. A., Mooney, J. F., Smith, B. P., Walker, F., & Leon, J. M. (2000). Botulinum toxin type a improved ankle function in children with cerebral palsy and dynamic equinus foot deformity. *JBJS*, *82*(6), 874.

Koman, L. A., Smith, B. P., Williams, R., Richardson, R., Naughton, M., Griffin, L., & Evans, P. (2013). Upper extremity spasticity in children with cerebral palsy: a randomized, double-blind, placebo-controlled study of the short-term outcomes of treatment with botulinum A toxin. *The Journal of hand surgery*, *38*(3), 435-446.

Leonard, J., & Graham, H. (2009). *Treatment of motor disorders in cerebral palsy with botulinum neurotoxin.* Elsevier INC.

Lidman, G., Nachemson. A., Peny-Dahlstrand, M., & Himmelmann, K. (2015). Botulinum toxin A injections and occupational therapy in children with unilateral spastic cerebral palsy: a randomized controlled trial. *Developmental Medicine & Child Neurology*, 57, 754–761.

Linder, M., Schindler, G., Michaelis, U., et al. (2001). Medium-term functional benefits in children with cerebral palsy treated with botulinum toxin type A: 1-year follow-up using gross motor function measure. *European Journal of Neurology*, *8*, 120– 126.

Love, S. C., Novak, I., Kentish, M., Desloovere, K., Heinen, F., Molenaers, G., O'Flaherty, S., & Graham, H. K. (2010). Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement. *European Journal of Neurology*, *17*, 9-37.

Lowe, K., Novak, I., & Cusick, A. (2007). Repeat injection of botulinum toxin A is safe and effective for upper limb movement and function in children with cerebral palsy. *Developmental Medicine & Child Neurology*, *49*, 823– 829.

Löwing, K., Thews, K., Haglund-Åkerlind, Y., & Gutierrez-Farewik, E. M. (2017). Effects of Botulinum Toxin-A and Goal-Directed Physiotherapy in Children with Cerebral Palsy GMFCS Levels I & II. *Physical & Occupational Therapy in Pediatrics*, *37*(3), 268–282.

Matsukiyo, A., Goh, A.-C., & Asagai, Y. (2017). Relationship between muscle-tendon length, range of motion, and resistance to passive movement in children with normal and increased tone. *Journal of Physical Therapy Science*, *29*(2), 349–355.

Minamoto, P.T,, Suzuki, K. P., Bremner, S. N., Lieber, R. L., & Ward, S. R. (2015). Dramatic changes in muscle contractile and structural properties after 2 botulinum toxin injections. Muscle & Nerve, *52*(4), 649-657.

Mirska, A., Kułak, W., Okurowska-Zawada, B., & Dmitruk, E. (2019). Effectiveness of multiple botulinum toxin sessions and the duration of effects in spasticity therapy in children with cerebral palsy. *Child's Nervous System*, *35*(1), 141.

Mitchell, L. E., Ziviani, J., & Boyd, R. N. (2015). Characteristics associated with physical activity among independently ambulant children and adolescents with unilateral cerebral palsy. Developmental Medicine & Child Neurology. *57*(2), 167–174.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L. A. (2015). Preferred Reporting Items for Systematic Review

and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Systematic reviews*, 4(1), 1.

Molenaers, G., Fagard, K., Van Campenhout, A., & Desloovere, K. (2013). Botulinum toxin A treatment of the lower extremities in children with cerebral palsy. *Journal of Children's Orthopaedics*, *7*(5), 383–387.

Moore, A., Ade-Hall, R., Smith, C. T., et al. (2008). Two-year placebo-controlled trial of botulinum toxin A for leg spasticity in cerebral palsy. *Neurology*, *71*, 122– 128.

Multani, I., Manji, J., Hastings-Ison, T., Khot, A., & Graham, K. (2019a). Botulinum Toxin in the Management of Children with Cerebral Palsy. *Pediatric Drugs,* 21**,** 261–281.

Multani, I., Manji, J., Tang, M. J., Herzog, W., Howard, J, & Graham, H. K, (2019b). Sarcopenia, Cerebral Palsy, and Botulinum Toxin Type A. *Journal of Bone and Joint Surgery*, 7(8).

National Institute for Health and Care Excellence. (2016). *Spasticity in under 19s: management.* https://www.nice.org.uk/guidance/cg145/chapter/1-Guidance#botulinum-toxin-type-a

Palisano, R. J., Cameron, D., Rosenbaum, P. L., Walter, S. D., & Russell, D. (2006). Stability of the gross motor function classification system. *Developmental medicine and child neurology*, *48*(6), 424-428.

Papavasiliou, A. S., Nikaina, I., Bouros, P., Rizou, I., & Filiopoulos, C. (2012). Botulinum toxin treatment in upper limb spasticity: treatment consistency. *European Journal of Paediatric Neurology*, *16*, 237– 242.

Papavasiliou, A. S., Rapidi, C-A., Filiopoulos, C., Rizou, C., & Skouteli, H. N. (2006). Evaluation of a multimodal management of prematurity-related spasticity. *Pediatric Neurol*ogy, 35, 400–407.

Park, E. Y. (2017). Relationship between activity limitation and health-related quality of life in school-aged children with cerebral palsy: a cross-sectional study. *Health and quality of life outcomes*, *15*(1), 1-7.

Parkinson, K. N., Dickinson, H. O., Arnaud, C., Lyons, A., & Colver, A. (2013). Pain in young people aged 13 to 17 years with cerebral palsy: cross-sectional, multicentre European study. *Arch Disability Child*. *98*(6), 434.

Pavone, V., Testa, G., Restivo, D. A., Cannavò, L., Condorelli, G., Portinaro, N. M., & Sessa, G. (2016). Botulinum toxin treatment for Limb Spasticity In Childhood Cerebral Palsy. *Frontiers In Pharmacology*, *7*.

Olesch, C. A., Greaves, S., Imms, C., Reid, S. M., & Graham, H. K. (2010). Repeat Botulinum Toxin-A Injections In The Upper Limb Of Children With Hemiplegia: A Randomized Controlled Trial. *Developmental Medicine and Child Neurology*, 49, 823-829.

Qin, Y., Li, Y., Sun, B., He, H., Peng, R., Zhang, T., Li, J., Luo, C., Sun, C., & Yao, D. (2018). Functional Connectivity Alterations in Children with Spastic and Dyskinetic Cerebral Palsy. *Neural Plasticity*, 1.

Read, F. A., Boyd, R. N & Barber, L. A. (2017). Longitudinal assessment of gait quality in children with bilateral cerebral palsy following repeated lower limb intramuscular botulinum toxin-A injections. *Research in Developmental Disabilities*, 68, 35–41.

Russo, R. N., Crotty, M., Miller, M. D., Murchland, S., Flett, P., & Haan, E. (2007). Upper-limb botulinum toxin A injection and occupational therapy in children with hemiplegic cerebral palsy identified from a population register: a single-blind, randomized, controlled trial. *Pediatrics*. *119*(5), 1149-1158.

Russo, R. N., Miller, M. D., Haan, E., Cameron, I. D., & Crotty, M. (2008). Pain characteristics and their association with quality of life and self-concept in children with hemiplegic cerebral palsy identified from a population register. Clinical Journal of Pain. *24*(4), 335 –342.

Schless, S., Cenni, F., Bar, O. L., Hanssen, B., Kalkman, B., O'brien, T., Aertbeliën, E., Van Campenhout, A., Molenaers, G., Desloovere, K., Schless, S.-H., & Bar-On, L. (2019). Medial gastrocnemius volume and echo-intensity after botulinum neurotoxin A interventions in children with spastic cerebral palsy. *Developmental Medicine & Child Neurology*, *61*(7), 783–790.

Shamsoddini, A., Amirsalari, S., Hollisaz, M.-T., & Rahimnia, A. (2014). Management of Spasticity in Children with Cerebral Palsy. *Iranian Journal of Pediatrics*, *24*(4), 345.

Simpson, D., Gracies, J., Graham, H, K. (2008). Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review). *Neurology*, 70, 1691–8.

Starship. (2019). *Starship – Clinical Guidelines.* https://www.starship.org.nz/guidelines/browse?sp=starship-child-health

Schless, S., Cenni, F., Bar, O. L., Hanssen, B., Kalkman, B., O'brien, T., Aertbeliën, E., Van Campenhout, A., Molenaers, G., Desloovere, K., Schless, S.-H., & Bar-On, L. (2019). Medial gastrocnemius volume and echo-intensity after

botulinum neurotoxin A interventions in children with spastic cerebral palsy. *Developmental Medicine & Child Neurology*, *61*(7), 783–790.

Shamsoddini, A., Amirsalari, S., Hollisaz, M.-T., & Rahimnia, A. (2014). Management of Spasticity in Children with Cerebral Palsy. *Iranian Journal of Pediatrics*, *24*(4), 345.

Sutherland, D. H., Kaufman, K. R., Wyatt, M. P., Chambers, H. G., & Mubarak, S. J. (1999). Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. *Gait & posture*, *10*(1), 1-9.

Tedroff, K., Granath, F., Forssberg, H., & Haglund-Akerlind, Y. (2009). Long-term effects of botulinum toxin A in children with cerebral palsy. *Developmental Medicine & Child Neurology,* 51(2) 120-127.

Tedroff, K., Löwing, K., Haglund-Åkerlind, Y., Gutierrez-Farewik, E. M., & Forssberg, H. (2010). Botulinumtoxin A treatment in toddlers with cerebral palsy. *Acta paediatrica*, *99*(8), 1156-1162.

The Paediatric Society of New Zealand and Starship Foundation. (2018). *Cerebral Palsy*. https://www.kidshealth.org.nz/cerebral-palsy

Valentine, J., Forbes, D., Davidson, S., Paterson, L., Bear, N., Blair, E., Ward, R., & Elliott, C. (2020). A prospective study investigating gross motor function of children with cerebral palsy and GMFCS level II after long-term Botulinum toxin type A use. *BMC Pediatrics*, *20*(1).

Valevski, A., Domenievitz, D., Giladi, N., Wientroub, S., & Hayek, S. (2008). Long-term effect of repeated injections of botulinum toxin in children with cerebral palsy: a prospective study. *Journal of Child Orthopaedics, 2*, 29– 35.

Van Heest, A. E., Bagley, A., Molitor, F., & James, M. A. (2015). Tendon transfer surgery in upper-extremity cerebral palsy is more effective than botulinum toxin injections or regular, ongoing therapy. *JBJS*, *97*(7), 529-536.

Ward, R., Reynolds, J. E., Bear, N., Elliott, C., & Valentine, J. (2017). What is the evidence for managing tone in young children with, or at risk of developing, cerebral palsy: a systematic review. *Disability & Rehabilitation*, *39*(7), 619–630.

Willerslev-Olsen, M., Lorentzen, J., Sinkjær, T., & Nielsen, J. B. (2013). Passive muscle properties are altered in children with cerebral palsy before the age of 3 years and are difficult to distinguish clinically from spasticity. *Developmental Medicine & Child Neurology*, *55*(7), 617.

Williams, G., Singer, B. J., Ashford, S., Hoare, B., Hastings-Ison, T., Fheodoroff, K., ... & Hill, B. (2022). A synthesis and appraisal of clinical practice guidelines, consensus statements and Cochrane systematic reviews for the management of focal spasticity in adults and children. *Disability and Rehabilitation*, *44*(4), 509-519.

Willoughby, K., Ang, S. G., Thomason, P., & Graham, H. K. (2012). The impact of botulinum toxin A and abduction bracing on long-term hip development in children with cerebral palsy. *Developmental Medicine & Child Neurology*, *54*(8), 743-747.

Wong, A. M., Pei, Y-C., Lui, T-N., Chen, C-L., Wang, C-M., & Chung, C-Y (2005). Comparison between botulinum toxin type A injection and selective posterior rhizotomy in improving gait performance in children with cerebral palsy. *Journal Neurosurgery Pediatr*ics, 102, 385-89.

World Health Organisation. (2012). *WHOQOL User Manual.* World Health Organisation.

Zeuner, K. E., & Deuschl, G. (2016). Pharmacokinetics and pharmacodynamics of incobotulinumtoxinA influencing the clinical efficacy in post-stroke spasticity. *Expert Opinion on Drug Metabolism and Toxicology*, *12*(4), 457–466.

8 APPENDIX

Appendix A

Outcome measures

Author	Primary Outcome Measure	Secondary outcome measures
Ackman., et al. 2005	**Gait analysis** measured by Vicon motion system	**ROM:** DF measured by goniometer **Spasticity** measured by MAS and TA **Strength:** Ankle DF and PF strength Measured by MMT for DF and unilateral heel raises for PF
Barber et al., 2013	**Muscle morphology** measured by 2D and 3D ultrasound	**ROM:** DF and PF measured by goniometer
Boyd, et al. 2001	**Gross Motor Function** measured by GMFM total scores, goal scores and -66 score	**Spasticity** measured by MAS **Hip displacement** measured by anteroposterior hip radiographs **Soft tissue surgery** measured by MP >40%.
Edwards et al., 2015	**AE:** via questionnaire	
Graham et al., 2008	**Hip displacement** measured by anteroposterior hip radiographs	**Hip displacement leading to surgery** measured by anteroposterior hip radiographs
Hastings-Ison et al., 2015	**ROM:** DF measured using digital photograph and software	**Motor responsiveness** measured using three-dimensional gait analysis **Functional Mobility** measured by FMS completed by assessor blind to group allocation and completed by child's parent or usual carer **HRQL** measured by Child health Questionnaire completed by child's parent or usual carer **AE:** recorded by study coordinator at clinical review or by interview
Hawamdeh et al., 2007	**ROM:** DF measured by protractor goniometer with knee in max extension **Spasticity** measured by MAS **Gross Motor** measured according to GMF scale of Peacock and Staudt	
Ibrahim et al., 2007	**Spasticity** measured by MAS **Gait analysis** measured using footprint on chalk paper, tape	

	measure, protractor goniometer and electric stop watch.	
Kanovsky et al., 2009	**ROM** DF at 28m measured using goniometer	**ROM** DF at 4, 8, 12, 16, 20 and 24m measured using goniometer **Time to development of fixed contracture** defined by DF no better than -10deg either leg **Requirement for corrective surgery** **Time to referral for surgery to correct fixed contractures** measured by blinded physician **Gross Motor Function** measured by GMFM overall and goal total scores **Subjective Functional Assessment of change in gait**: judged by blinded assessor and parent or guardian **AB to BT** determined by laboratory **AE** coded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) 1995 dictionary
Koman et al., 2000	**ROM** DF measured using goniometer **Gait analysis** evaluated using a modification of the PRS	**Hoffmann's reflex and motor response** measured using surface electrodes **AB to BT** measured by blood samples
Koman et al., 2013	**Upper Limb Function** measured by the Melbourne	**ROM:** measured using UERS **Upper Limb Function** measured using HC and modified HC
Lidman et al., 2015	**Upper Limb Function** measured by AHA	**ROM** elbow extension and supination of forearm using goniometer **Occupational performance and goal setting** assessed using COPM
Lowe et al., 2007	**Motor performance** assessed by QUEST **Occupational performance and goal setting** assessed by COPM **Self-care and functional skills** assessed by guardian using PEDI **Function and participation** measured using GAS therapist and parent GAS. **Spasticity** measured using AS	Changes in primary outcome measures
Moore et al., 2008	**Gross Motor Function** measured using GMFM at 1y **Self-care and functional skills** measured by PEDI at 1y **Need for orthopaedic procedures during study** assessed by blinded PT	**Gross Motor Function** measured using GMFM at 2y **Self-care and functional skills** measured by PEDI at 2y **Weight change** over 2y measurement not reported **AE** assessed by blinded PT **Spasticity** using the MAS

Olesh et al., 2010	**Occupational performance and goal setting:** COPM **Function and participation** measured using GAS	**Spasticity** measured by MTS **Motor performance** assessed by QUEST **Fine motor and upper-limb skills** measured using PDMS-FM
Sutherland et al., 1999	**Gait analysis** using three-dimensional five-camera motion measurement system	**ROM** hip, knee and ankle measurement tool not reported **Strength** PF measured by single leg calf raises **Motor response** measured by EMG
Tedroff et al., 2010	**ROM** hip knee and ankle using goniometer **Spasticity** ankle PF, KF, and hip adductors using MAS **Gross Motor function** measured using GMFM-66 **Self-care and functional skills** assessed by guardian using PEDI	**Gait analysis** using three-dimensional six-camera motion analysis system
Van Heest et al., 2015	**Upper Limb Function** measured by SHUEE	**ROM** measurement not reported **Strength** pinch and grip measurement not reported **Upper Limb Function** measured using AHA **HRQL** measured using PODCI, PedsQL **Occupational performance and goal setting** assessed using COPM **Cognitive abilities** measured using CTONI
Willoughby et al., 2012	**Hip displacement** measured using most recent hip radiograph.	**Preventive and reconstructive operations** measured by hip surveillance and orthopaedic department records

Note. AB = Antibodies. AE = Adverse Events. AHA = Assisting Hand Assessment. AS = Ashworth Scale. BT = Botulinum Toxin. COPM = Canadian Occupational Performance Measure. CTONI = Comprehensive Test of Nonverbal Intelligence. DF = Dorsiflexion. EMG = Electromyograph. FAQ = Gillette Functional Assessment Questionnaire. FMS = Functional Mobility Scale. GMF = Gross Motor Function. GMFM = Gross Motor Function Measure. HC = House classification. HRQL = Health Related Quality of Life. MAS = Modified Ashworth Scale. Melbourne = Melbourne Assessment of Unilateral Upper Limb Function. MMT = Manual muscle test. MP = Migration Percentage. MTS = Modified Tardieu Scale. PDMS-FM = Peabody Developmental Motor Scale Fine Motor. PEDI: Pediatric Evaluation of Disability Inventory functional skills. PedsQL = Pediatric Quality of Life Inventory. PF = Plantarflexion. PODCI = Pediatric outcomes data collection instrument. PRS = Physician Rating Scale. PT = Physiotherapist. QUEST = Quality of Upper Extremity Skills Test. SHUEE = Shriners Hospital Upper Extremity Evaluation

Appendix B

Version 2 of the Cochrane risk-of-bias tool for randomized controlled trials - Results

Author	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions	Missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall Risk of Bias
Graham et al., 2008	+	+	+	+	+	+
Hastings-Ison et al., 2015	+	+	+	+	+	+
Koman et al., 2013	+	+	+	+	+	+
Koman et al., 2000	+	+	+	+	+	+
Sutherland et al., 1999	+	+	+	+	+	+
Kanovsky et al., 2009	?	+	+	+	+	?
Lowe et al., 2007	+	+	+	?	+	?
Moore et al., 2008	+	+	?	+	+	?
Olesh et al., 2010	+	+	+	?	+	?
Tedroff et al., 2010	+	+	+	?	+	?
Van Heest et al., 2015	?	+	+	+	+	?
Hawamdeh et al., 2007	?	+	+	?	+	?

Note. + = Low risk. ? = Some concerns. − = High risk.

Appendix C

National Institute for Health and Care Excellence Clinical Guideline: Spasticity in under 19s: Management*

1.5 Botulinum toxin type A*: General principles*

1.5.1 Consider botulinum toxin type A treatment in children and young people in whom focal spasticity of the upper limb is:

- impeding fine motor function
- compromising care and hygiene
- causing pain
- impeding tolerance of other treatments, such as orthoses
- causing cosmetic concerns to the child or young person.

1.5.2 Consider botulinum toxin type A treatment where focal spasticity of the lower limb is:

- impeding gross motor function
- compromising care and hygiene
- causing pain
- disturbing sleep
- impeding tolerance of other treatments, such as orthoses and use of equipment to support posture
- causing cosmetic concerns to the child or young person.

1.5.3 Consider botulinum toxin type A treatment after an acquired non-progressive brain injury if rapid-onset spasticity is causing postural or functional difficulties.

1.5.4 Consider a trial of botulinum toxin type A treatment in children and young people with spasticity in whom focal dystonia is causing serious problems, such as postural or functional difficulties or pain.

1.5.5 Do not offer botulinum toxin type A treatment if the child or young person:

- has severe muscle weakness
- had a previous adverse reaction or allergy to botulinum toxin type A
- is receiving aminoglycoside treatment.

1.5.6 Be cautious when considering botulinum toxin type A treatment if:

- the child or young person has any of the following:
    - a bleeding disorder, for example due to anti-coagulant therapy
    - generalised spasticity
    - fixed muscle contractures
    - marked bony deformity **or**
- there are concerns about the child or young person's likelihood of engaging with the post-treatment adapted physical therapy programme (see recommendation 1.2.15).

1.5.7 When considering botulinum toxin type A treatment, perform a careful assessment of muscle tone, range of movement and motor function to:

- inform the decision as to whether the treatment is appropriate
- provide a baseline against which the response to treatment can be measured.

A physiotherapist or an occupational therapist should be involved in the assessment.

1.5.8 When considering botulinum toxin type A treatment, give the child or young person and their parents or carers information about:

- the possible benefits and the likelihood of achieving the treatment goals
- what the treatment entails, including:
    - the need for assessments before and after the treatment
    - the need to inject the drug into the affected muscles
    - the possible need for repeat injections
    - the benefits, where necessary, of analgesia, sedation or general anaesthesia
    - the need to use serial casting or an orthosis after the treatment in some cases
- possible important adverse effects (see also recommendation 1.5.10).

1.5.9 Botulinum toxin type A treatment (including assessment and administration) should be provided by healthcare professionals within the

network team who have expertise in child neurology and musculoskeletal anatomy.

Delivering treatment

1.5.10 Before starting treatment with botulinum toxin type A, tell children and young people and their parents or carers:

- to be aware of the following rare but serious complications of botulinum toxin type A treatment:
    - swallowing difficulties
    - breathing difficulties
- how to recognise signs suggesting these complications are present
- that these complications may occur at any time during the first week after the treatment **and**
- that if these complications occur the child or young person should return to hospital immediately.

1.5.11 To avoid distress to the child or young person undergoing treatment with botulinum toxin type A, think about the need for:

- topical or systemic analgesia or anaesthesia
- sedation (see Sedation in children and young people, NICE clinical guideline 112).

1.5.12 Consider ultrasound or electrical muscle stimulation to guide the injection of botulinum toxin type A.

1.5.13 Consider injecting botulinum toxin type A into more than one muscle if this is appropriate to the treatment goal, but ensure that maximum dosages are not exceeded.

1.5.14 After treatment with botulinum toxin type A, consider an orthosis to:

- enhance stretching of the temporarily weakened muscle **and**
- enable the child or young person to practice functional skills.

1.5.15 If an orthosis is indicated after botulinum toxin type A, but limited passive range of movement would make this difficult, consider first using serial casting to stretch the muscle. To improve the child or young person's ability to tolerate the cast, and to improve muscle stretching, delay casting until 2–4 weeks after the botulinum toxin type A treatment.

1.5.16 Ensure that children and young people who receive treatment with botulinum toxin type A are offered timely access to orthotic services.

Continuing assessment

1.5.17 Perform an assessment of muscle tone, range of movement and motor function:

- 6–12 weeks after injections to assess the response
- 12–26 weeks after injections to inform decisions about further injections.

These assessments should preferably be performed by the same healthcare professionals who undertook the baseline assessment.

1.5.18 Consider repeat injections of botulinum toxin type A if:

- the response in relation to the child or young person's treatment goal was satisfactory, and the treatment effect has worn off
- new goals amenable to this treatment are identified.

**Guidelines sourced from:* National Institute for Health and Care Excellence. (2016).

Spasticity in under 19s: management.

https://www.nice.org.uk/guidance/cg145/chapter/1-Guidance#botulinum-toxin-type-a