Author's response to reviews

Title: Evaluation of the effects of Botulinum toxin A injections when used to improve ease of care and comfort in children with cerebral palsy whom are non-ambulant: A double blind randomized controlled trial.

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Author's response to reviews: see over
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Study Protocol
Title: Evaluation of the effects of Botulinum toxin A injections when used to improve ease of care and comfort in children with non-ambulant cerebral palsy: A double blind randomized controlled trial
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Response to reviewer’s comments.

Thankyou for reviewing our manuscript. We have responded to each point raised, with the reviewers comments highlighted in bold.

Reviewer 1

1. Please describe aim in abstract once, and indicate primary and secondary outcome measures, explain how they are related in the introduction, and make sure that this description is consistent throughout the paper. Further explanation of what is measured by the COPM would help. It is for example not clear whether ‘pain, and health status’ are part of ‘ease of care and comfort’?

Thankyou. Please see revised abstract (page 2, line 4) in which the aim is described once and the outcome measures are introduced (page 3, lines 1-7). Further detail regarding the outcome measures is included in the background (page 8-9). We have clarified what is measured by the COPM on page 8 (see below).
“Previous studies of BoNT-A with children with cerebral palsy have largely focused on children classified GMFCS I – III [13-15, 34-43]. In these studies, assessments of motor function have been used to test the ability of BoNT-A to bring about functional improvements. In this study with children who have non-ambulant CP and limited voluntary movement, improvements in motor function are not widely expected and are not the focus of investigation. Children with non-ambulant CP rely on their parents for performance of daily activities. Spasticity and contracture, with associated discomfort and pain, contribute to these tasks being difficult, time consuming and/or stressful for parents. In our clinical BoNT-A injecting program, parents of children with severe CP regularly set goals for intervention around improving ease of care (for example, parents may hope for it to be easier to get their child’s arm through a sleeve, quicker to apply lower limb orthotics, or easier to perform transfers), and improving their child’s comfort (for example, that their child will tolerate sitting in their wheelchair for longer periods, require less pain medication or have fewer night wakings due to discomfort). Efficacy will be determined through measurement of changes in parental perceptions of the ease of carrying out daily cares for their child, and their child’s comfort, pre and post treatment using the Canadian Occupational Performance Model.”

2. With respect to the overall design of the study there is some confusion about the two cycles of the study, especially the aim and additional value of the second cycle remains unclear to me. In the abstract it is stated that the aim is to describe the efficacy and safety of repeated BoNT-A injections, but no background was given in the introduction, and it is not described what kind of analysis will be applied to answer this question. So please clarify, by adding information to the introduction about why this research question concerning repeated injections is of interest, and describe the outcome measures and
analysis plan for the second phase.

Thankyou, this has been clarified. Please note that we have chosen to change ‘phases’ to ‘cycles’. Please see added detail to the background (justification of areas measured, page 8 (starting line 10) and page 9), description of tools (pages 20-23) and an analysis plan (page 23-4), outlined below:

**Analyses**

**Cycle I - efficacy of BoNT-A injections for improving ease of care and comfort**

Analysis will follow standard principles for RCTs, using two-group comparisons on all participants on an intention to treat basis. Data from each outcome measure will be summarised for each group and descriptive statistics (frequencies, means, medians, 95% confidence intervals) calculated dependent on data distribution. We anticipate that groups will be similar on baseline measures. The primary comparison for hypothesis one at 4 weeks will be the COPM performance and satisfaction scores. Generalised estimating equations (GEEs) will be used to compare treatment groups at follow-up, with time (0, 4 and 16 weeks) and study group, as well as a time by group interaction as covariables.[89] We will use the Gaussian family, identity link, and an unstructured correlation structure. Secondary analyses will compare the outcomes between groups for ease of care, quality of life, pain and health status using GEEs as outlined above (STATA 11).

**Cycle I: safety of BoNT-A injections compared with sham**

Two Chi-squared tests of independence will be conducted to assess the relationship between treatment and sham and all adverse events vs. moderate and serious events. The continuity correction chi-square will enable analysis by 2x2 tables using Fisher’s exact test.

**Cycle II: efficacy of repeated episodes of BoNT-A injections vs. single episode**

The primary outcome measure for cycle II will be the COPM administered at 4 weeks post injections. The secondary outcome measures will be the same as cycle I (CP CHILD, CPQOL, CCHQ and PPP. The primary comparison will be the COPM performance and satisfaction scores. Generalised estimating equations (GEEs) will be used to compare treatment groups at follow-up, with time (0, 16 weeks and 10 months) and study group, as well as a time by group interaction as covariables. We will use the Gaussian family, identity link, and an unstructured correlation structure. Secondary analyses will compare the outcomes between
groups for ease of care, quality of life, pain and health status using GEEs as outlined above (STATA 11).

Cycle II: safety of repeated BoNT-A injections compared with sham
Adverse events in cycle II will be collected as per cycle I. Rates of adverse events will compared between groups using Poisson regression.

Other comments (minor):
3. Title suggestion: in my opinion, ‘non-ambulant’ would be a better description of the population than ‘marked’ CP.
Thankyou, we have made this change accordingly throughout the paper.

4. Background: give a description of GMFCS level IV as well (p.3)
Thankyou, we have done this. Please see page 3, line 25:
“Children classified as GMFCS IV require supportive seating for trunk control and to maximise upper limb function, and assistance for transfers. Self-mobility is limited to possible use of a powered wheelchair.”

5. ‘spasms’ are not expected in this group, please delete (p.3)
With respect, in our combined experience, children in this group do experience muscle spasms. Children regularly present to our service for treatment of pain and discomfort associated with muscle spasms, particularly those with mixed patterns of spasticity and dystonia. Such children will most likely be recruited to our study as participants. Therefore we have chosen not to delete this. Please see Lundy 2009 for further description of spasms occurring in this population.


6. What is meant by ‘significant overall reduction in pain’? Did both groups improve? (so no effect of BoNT treatment? (p.4 last paragraph)
This referred to a report of current clinical practice, with no control group (i.e. treatment group only). The children in the study, who were all treated with BoNT-A, had significant (p<
0.001) improvement in their paediatric pain profile scores at 3 months post treatment. We have clarified in the manuscript that this was a report of clinical outcomes, not a comparison between groups. Please see page 5, line 12.

7. What was the diagnosis of the paediatric population? (p. 5, second paragraph)
This was a typo and has been corrected to adult population.

Method: In general well described, except for analysis of cycle 2.
9. Aims are repeated in the study design part. My suggestion is to transfer this part to the end of the introduction. (p. 7/8)
We have incorporated this paragraph into the first paragraph of the abstract, to correct the repetition. See page 2, starting at line 4.

10. Please give some more information about COPM, e.g. explain what is measured by ‘performance and satisfaction in areas of concern’ using the COPM (p.8, hypothesis 1). Same applies to hypothesis 5 in which the outcome is described as ‘individual family concerns’. (p.8)
Thankyou, we have done this. Please note that we have re-phrased the hypotheses to make clearer the aim of cycle 2 and the safety aspect of the study, and to reduce repetition. See below, from page 11:

“The specific hypotheses to be tested are:-

Cycle I

1. Intramuscular injections of BoNT-A combined with a regime of standard therapy will result in improved parental ratings of performance and satisfaction in areas of concern for their child’s comfort and ease of care, as measured by the COPM, compared to standard therapy alone.

2. Intramuscular injections of BoNT-A combined with a regime of standard therapy will result in greater reduction in pain compared to standard therapy alone.
3. Intramuscular injections of BoNT-A combined with a regime of standard therapy will result in greater improvements in quality of life compared to standard therapy alone.

4. Intramuscular injections of BoNT-A combined with a regime of standard therapy will not result in an increased likelihood of adverse events compared to standard therapy alone.

Cycle II

1. Repeated BoNT-A injections will result in greater overall improvements in pain, quality of life, burden of care and individual family concerns for ease of care and comfort, compared with a single episode of BoNT-A.

2. Repeated BoNT-A injections will not increase the likelihood of an adverse event in a population of children with non-ambulant CP, compared with a single episode of injections.”

11. Change 4 months to 16 weeks (or what is appropriate, but in line with abstract) (p.8)
Thankyou, we have clarified the end time point as 16 weeks throughout the paper.

12. Exclusion criterion 5: ‘Entry to study will be delayed.’ Please describe for how long?
Thankyou, this has been described on page 13, line 3: “Entry to the study will be delayed until anti-spasticity medication has been stable for two months.”

13. Sample size: calculation is based on pain scores (secondary outcome), but not on the primary outcome measure. I assume that there are COPM data available to perform a power analysis (p. 10)
Thankyou, we have added detail to our description of sample size development (see below, from page 13).

“Sample size calculations were primarily based on the findings from a placebo controlled trial of the analgesic effects of BoNT-A in a sample of 16 children with marked CP (Barwood et al. 2000). In this study, the response within each subject group was normally distributed with a standard deviation of 0.56. The mean difference in pain scores between the experimental and control groups at follow-up was 0.74. If the true difference in experimental and control means is 0.74, we will be able to reject the null hypothesis that the population means of both groups are equal with probability (power) .981. The type 1 error associated with this nest of this null hypothesis is 0.05. We also examined a study of upper limb botulinum toxin A and occupational therapy, with a heterogeneous sample of 72 subjects that included 28 (39%) children with quadriplegic cerebral palsy (Wallen et al, 2007). In this study, COPM outcomes at 3 months post injection resulted in a SD=1.6. A difference of 2 points on the performance and satisfaction scales of the COPM, 80% power and significance level of 0.05 gives a sample size of 24 (12 in each group). Based on these previous studies and Factoring in a buffer for drop-outs, we plan to recruit 20 participants to each group (total sample 40 subjects).

For the secondary hypothesis of safety in our double blind sham controlled trial with 20 subjects in each group we examined a recent SBRCT of BoNTA in children with bilateral CP (Graham et al. 2008). That study reported a 6 percent rate of serious adverse events in the BoNT-A group (failure rate in controls of 0.01). If the true failure rate in the experimental group is 0.333 then we will be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal in probability (power) 0.797 with a type I error 5 percent using an uncorrected chi-squared statistic.”

14. Randomization: the large age range (2-16) is a risk factor for unequal groups at baseline. Is stratification by age group considered to get comparable groups?
We are stratifying according to primary site of injections in order to have roughly equal numbers of upper and lower limb injections in each group. In the interests of carrying out a pragmatic trial, we chose not to stratify further according to age. We do not expect a difference in performance on the primary or secondary outcome measures according to age. BoNT-A doses are given according to body weight and goals for treatment will be individualised, using the COPM. One of the advantages of using a non-standardised, individualised assessment tool such as the COPM is that it allows for consistent measurement of a clinically heterogeneous group, reducing the need for stratification. In
order to clarify this for our readers, we have now expanded on this in the background (pages 8-9).

15. Explain ‘productivity’ p.16
This has been clarified, please see page 19, line 23: “...productivity (participation at school and in play)...”

16. The same care giver should be filling out the PPP. I think this applies to all questionnaires, especially COPM (p.18)
Thankyou. This was our plan and we have now clarified this in the manuscript (page 20, line 15)

17. Analysis: please add an analysis plan for adverse events? (p.18)
Please find this on page 23-4 (see point 2, above).

Reviewer 2
Major Compulsory Revisions
About Background:

Page 3: “When injected into target muscle, BoNT-A enters the presynaptic terminal, and binds to acetylcholine preventing its release and thus reducing spasticity.” is not correct. BoNT-A does not bind directly to acetylcholine but to one, in vesicles located receptor. After cleavage of the active portion of the BoNT leaves of these vesicles and inactivates SNAP 25, which leads to a prevention of the exocytosis of acetylcholine.
The basics must be represented correctly.
Thankyou, we have corrected this. Please see page 4, line 18: “When injected into a target muscle, BoNT-A enters the presynaptic terminal, and prevents the exocytosis of acetylcholine, thus reducing spasticity.”

Method / Design:
In children between 2 and 16 years the relationship between spasticity and contracture of the muscles are very heterogeneous.
Page 3 "Spasticity commonly leads to muscle contractures ...". For very young children are more likely to outweigh the spastic component, with the older
children more likely outweighs the structural component.

(1) The study group should be divided into age groups (eg 2-6, 6-10 and 10-16 years). Alternatively, it could also be a subdivision according to the weighting of spasticity (dynamic movement restriction) and contracture of muscles (structural restriction of movement). The relationship between pain and the relationship between contracture / spasticity is not known.

Thank you for this suggestion. We agree that this group of children is heterogeneous in presentation particularly with regards to the degree of spasticity vs. contracture, and that older children are more likely to experience contracture than younger children. We have chosen not to split the sample further into groups according to age or relative amount of spasticity vs. contracture for the following reasons:

- Splitting the sample into 3 groups as suggested, and then into treatment and sham groups, would decrease the available sample size in each group, significantly reducing statistical power to detect a meaningful change on the outcome measures.

- We do not expect a difference in performance on the primary or secondary outcome measures according to age. BoNT-A doses are given according to body weight and goals for treatment will be individualised. One of the advantages of using a non-standardised, individualised assessment tool such as the COPM is that it allows for consistent measurement of a clinically heterogeneous group.

- We recognise that both spasticity and contracture impact on ease of care and comfort. Therefore we are adopting treatments that will address both spasticity (BoNT-A) and contracture (casting). The primary outcome measure (COPM) is an individualised measure of change in parental perception of performance and satisfaction of areas of concern for their child’s functioning. Division of the sample into groups according to relative spasticity/contracture is not necessary as we do not anticipate that performance on the COPM will be affected.

(2) The described “Assessment of spasticity and range of motion” (page 15) will hardly be sufficient.
We have a comprehensive clinical assessment protocol that measures spasticity before and after treatment, to assist with decision making about injection sites and doses. The efficacy of BoNT-A to reduce spasticity is widely recognised. The primary aim of this study is efficacy of Botulinum Toxin to address ease of care and comfort in children with non-ambulant cerebral palsy, thus we have focused on measures of individualised concerns for care and comfort, quality of life, pain and health status rather than those in the body structures and functions domain, such as spasticity. Further to this, we point out that the primary and secondary outcome measures that we have selected (COPM, CPQoL, CPCHILD, CCHQ) have strong psychometric properties, whereas accepted measures of spasticity and range of motion have relatively poor psychometrics.

Only two follow-up examinations after 4 weeks and 4 months seem inadequate. After 4 weeks the drug effect of the BoNT-A is safe there. Whether this is still present after 4 months, in an individual case is unclear.

We recommend that two additional follow-up that is after 8 weeks and 6 months (if not more BoNT effect is present). The proposed cycle 2 could be connected directly, so that would last for the duration of the study 12 months.

Our clinical program for children classified as GFMCS IV and V has been to re-inject BoNT 4-6 months after initial injection. We have designed a pragmatic study to reflect our current clinical practice, which includes review at 4 weeks (to assess peak effect and for safety screening) and 16 weeks (for assessment of completed treatment (BoNT-A + therapy) and for assessment prior to repeat injections). We do not believe that an additional 2 time-points are required and would be a hardship for families involved in the study, particularly those who have long distances to travel to the study site. We would also suggest that in terms of study design, there is no additional benefit of two extra review points in a randomised controlled trial where the primary outcome is the difference at endpoint.

Study treatment:
The planned maximum dose of 12 U / kg / body weight (or 400 units maximum), we consider a good choice.

Other recommended maximum doses, such as the "European consensus table 2006 on Botulinum toxin for children with cerebral palsy" and "The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy" by Heinen et al. however, should be mentioned and discussed.

Thankyou, please see page 14 line 24:
“The BoNT-A dosing regime was determined with reference to the European consensus table for the use of BoNT-A with children with CP [48], which suggests a safe range of 6-25 Units/kg/body weight with a total dose of 400-600 Units. These recommendations were modified slightly when reviewed in 2009 [49] to 1-20 Units/kg/body weight, suggested maximum dose 400 Units, with caution urged when planning doses for children with significant co-morbidities.”

Minor Essential Revisions

Title page:
The authors are provided with the numbers 1 and 2. The number 3 (Queensland Children’s Medical Research Institute, ...) cannot be find.

Thankyou, we have corrected this.

From a scientific point of view a sham injection seems to be much more complicated, particularly with regard to blinding, than a real placebo treatment.

From an ethical point of view it seems a workable compromise.

Thankyou, we agree.

Reference List:
From 70 references, the latest are from the year 2010 (4x). The list should be updated and current publications will be added.

Thankyou. We have updated the literature and have added new references: three from 2010, 2 from 2011 and two from 2012.

The reference number 24 (Delgado MR, et al.) is presented without a date (Neurology ??). The year should be added.

Thankyou, we have added the year (2010)

We thank the reviewers for their time and helpful suggestions. We hope that we have carried out the revisions to your satisfaction and that our paper will now be acceptable for publication in your journal.

Kind Regards
Megan Thorley
On behalf of the authorship team.