1. **The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy.**


2. **Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement**


3. **Botulinum toxin assessment, intervention and follow-up for pediatric upper limb hypertonicity: international consensus statement**

Part I | tabulated evidence report

(1) cerebral palsy
(2) integrated therapy
(3) medico-legal and medico-economical aspects of BoNT
(4) common indications
(5) dosage and dose modifiers
(6) safety
(7) therapy and procedures
(8) assessment and evaluation
(9) therapy adherence
(10) research challenge

Part 2 | CP\textsuperscript{Graph} Treatment Modalities Gross Motor Function
2: Integrated therapy - evidence based

1. Range of conservative and surgical strategies considering all dimensions of ICF
   (PT, OT, Speech, Robotics, CIMT, HABIT, orthosis, casting, splints, baclofen, other pharmacotherapy, surgery, etc….Botulinum toxin)

2. Insufficient evidence to either support or refute the use of these interventions before or after BoNT injections

3. Robotic assisted therapy can serve as an intervention model where activity parameters can be measured during therapy intervention
<table>
<thead>
<tr>
<th>Functional Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP: Integrated / Multidisciplinary Therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Orthoses/aids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment indication: Concomitant treatment by a qualified therapist.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment indication: Frequent, comprehensive treatment option for higher levels of severity starting with G inscription IV/IV (grey III).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Botulinum Toxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment indication: Established for each level of severity.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intrathecal baclofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment indication: Long-term, continuous administration of intrathecal baclofen is indicated. Charlton et al. (2003) recommend using an intrathecal infusion pump. In adults, start with 100 μg/hr of infusion, slowly titrate to reach 300 μg/hr.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Orthopaedic surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment indication: Established for each level of severity. Surgical intervention: The higher the G inscription, the earlier it should be considered.</td>
</tr>
</tbody>
</table>
TREATMENT MODALITIES - GROSS MOTOR FUNCTION

Percentage of children with BSCP, for whom the respective form of treatment is suitable:

- A 0-25%
- B 25-50%
- C 50-75%
- D 75-100%

Check for surgical intervention

GMFCS Level I
GMFCS Level II
GMFCS Level III
GMFCS Level IV
GMFCS Level V

Orthopaedic surgery
Intrathecal baclofen
Botulinum Toxin
Oral medication
Orthoses/aids
Functional therapies

Freitag, 23. November 2012
Botulinum neurotoxin (BoNT)

1. Anaerob gram + bacteria
2. 7 Serotypes (A-G)
3. Light chain / heavy chain
4. Injection into the targeted tissue
5. Does not cross blood-brain-barrier
6. Not cytotoxic
7. New Terminology
   - Botox: onabotulinumtoxinA
   - Xeomin: incobotulinumtoxinA
   - Dysport: abobotulinumtoxinA
   - Neurobloc: rimabotulinumtoxinB
BoNT - Mechanism of action

1. Local / Focal inhibition
   - Neuro-muscular junction
   - Muscle spindle - down regulation of spinal circuit
   - Neuro-glandular junction

2. Heavy chain: binding & internalisation

3. Light chain: inhibition of cholinergic transmission

4. Cleavage of membrane-fusion proteins

5. Dose-dependent effect

Freitag, 23. November 2012
3: Medico-legal & Medico-economical aspects

1. Licenses for BoNT treatment show a great variety between countries, and are restricted to specific preparations
   => be familiar

2. Licensing does not reflect the clinical needs, especially for children with CP (multi-centre studies of different preparations on the way)
   => documentation

3. Strong level of pharmaco-vigilance is required:
   => severely affected children with bilateral CP, GMFCS Levels (III–) IV-V suffering from multiple additional impairments
   => careful decision-making on dosage, dilution, procedure and injection
   => control rests in the hands of the treating physician and has to be adapted
4: Common indications

1. Spastic movement > dystonic movement disorders
   => therapy goal defined according ICF dimensions

2. Increasing number of “focal” indications > multi-muscle, multi-level treatment approach
   => reversibility of BoNT during motor development

3. Development of distinctive motor patterns
   (Rodda & Graham, Winters, Gage & Hicks)
   => adaptive approach to changing clinical patterns
5: Dosage and dose modifiers

1. Different preparations => different biological activity
   => dose conversion factors are NOT applicable

2. Individual dosages must be calculated independently „check & balance“
   - units per muscle, per injection site, per kg body weight per muscle (U/kg/muscle)
   - total units per kg body weight per session,
   - total units per treatment session

3. Dose modifiers
   - severity of CP
   - accompanying diagnoses
   - predominance of movement disorder (spasticity, dystonia)
   - activity and size of the injected muscle
   - dynamic versus fibrotic muscle
   - distribution of motor endplates
   - experience from previous BoNT injections
Dosage & Dilution

1. **ona**: Powder 50 & 100 Units / Vial
2. **abo**: Powder 500 Units / Vial
3. **inco**: Powder 50 & 100 Units / Vial
4. **rima**: Solution 0.5 & 1 ml / Vial = 2500 & 5000 Units / Vial

=> Dilute in 1 / 2 / 4 / 5 ml / Vial = different concentrations

=> small muscles 1-2 ml / Vial

=> large muscles 2-5 ml / Vial
There are no dose-ranging studies that address the optimum dose of BOTOX®/C210. Recommendations in previous studies, consensus statements and this document are expert opinion; that is to say, no RCTs have been published. Given recent concerns about adverse events, the authors have chosen total doses in units per Kg body weight for BOTOX®/C210, which are intermediate between the figures proposed in two previous consensus statements, and which err on the side of caution (Table 3). It is the responsibility of the treating physician to carefully choose the dose they consider appropriate for the individual case concerned.

In addition to the RCTs reviewed in detail by the authors, review of non-RCT literature confirms marked escalation in recommended doses of BOTOX®/C210, both in relation to specific indications such as spastic equinus as well as in multilevel protocols. For example, in 2000, Graham [78] made the following recommendations: maximum dose at any one site 50 Units, maximum dose in any one injection session 300 Units or 12 Units per Kg. In 2006, Heinen [79] in a European consensus statement reported a published total dose range up to 20–24 Units per Kg for this preparation (Table 3). It should be noted that both of these suggested upper dose limits were determined by expert opinion, not supported by clinical trial.

One Class I study exists for the use of Dysport®/C210, and this is only for the indication of spastic equinus [52].

Although the incidence of adverse events following injection of BoNT-A in the RCTs reviewed in this paper and in other literature remains relatively low, systemic adverse events can include generalized weakness, diplopia, dysphagia, aspiration, pneumonia and death. This serves as a warning that systemic spread of BoNT-A may occur in children with CP and much further work is required before high-dose protocols can be accepted as safe. Given that the major risks of serious systemic adverse events reside in the child, it seems prudent to make recommendations based on Table 3.

### Table 3 Products and doses

<table>
<thead>
<tr>
<th>Product</th>
<th>Dose U/kg body weight</th>
<th>Recommendation</th>
<th>Maximum Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX®</td>
<td>6–24 U/Kg</td>
<td>GMFCS I–IV without risk factors: 16–20 U/Kg</td>
<td>&lt; 300 U [53,57]</td>
</tr>
<tr>
<td></td>
<td>(up to 30 U/Kg used in occasional multilevel injections)</td>
<td>GMFCS V with risk factors: 12–16 U/Kg*</td>
<td>&lt; 400–600 U [79]</td>
</tr>
<tr>
<td>Dysport®</td>
<td>10–30 U/Kg</td>
<td>20 U/Kg [52]</td>
<td>200–500 U [54] (level U Recommendation)</td>
</tr>
<tr>
<td></td>
<td>(level B recommendation)</td>
<td></td>
<td>&lt; 900 U [79]</td>
</tr>
</tbody>
</table>

Risk factors include symptoms and signs of pseudobulbar palsy, swallowing difficulties, history of aspiration and respiratory disease. When risk factors are present, evaluate the level of risk and either further reduce the total dose or avoid using BoNT-A.

*Expert opinion.
„BOTOX doses used in controlled trials have a range of 1–9 U/kg body weight per treatment session and 0.3–2 (forearm) up to 4 (upper arm) U/kg body weight per muscle. Neurobloc is not included in the table, as there is limited experience with BoNT-B in children with PULH.“

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Dose range (U/kg BOTOX®)</th>
<th>Max. Dose per muscle (U BOTOX®)</th>
<th>Dose range (U/kg Dysport®)</th>
<th>Max. Dose per muscle (U Dysport®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pectoralis major</td>
<td>2</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Teres major</td>
<td>2</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Triceps brachii</td>
<td>2–4</td>
<td>100</td>
<td>10–15</td>
<td>250</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>2–3</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Brachialis</td>
<td>2–3</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Brachioradialis</td>
<td>0.5–2</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>0.5–2</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>0.5–2</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Pronator teres</td>
<td>1–2</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Pronator quadratus</td>
<td>0.5–1</td>
<td>25</td>
<td>5</td>
<td>150</td>
</tr>
<tr>
<td>Flexor digitorum profun-</td>
<td>0.5–2</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Flexor digitorum superfi-</td>
<td>0.5–2</td>
<td>50</td>
<td>5–10</td>
<td>150</td>
</tr>
<tr>
<td>Extensor digitorum communis</td>
<td>0.5–2</td>
<td>25</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Flexor pollicis longus</td>
<td>1</td>
<td>25</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>Flexor pollicis brevis/Opponens pollicis*</td>
<td>0.5–1</td>
<td>25</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>0.5–1</td>
<td>25</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Lumbricales</td>
<td>0.5–1</td>
<td>25</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Total dose per treatment session</td>
<td>16 U/kg</td>
<td>400</td>
<td>30 U/kg</td>
<td>1000</td>
</tr>
</tbody>
</table>

Please be aware that the recommendations for BOTOX® and Dysport® are not based on a fixed conversion ratio between the two preparations (please refer to ‘Preparations, conversion factors’ within the text). *Due to the proximity of the two muscles they are not listed separately.
### European Consensus: Heinen et al. 2010

Dose ranges [U = Units; kg bw = kilogram body weight] \(^{a}\)

**BoNT Serotype A**

- Preparation BOTOX®
  - range [U/kg bw] 1–20 (–25)
  - max total dose [U] 400 (–600)
  - range max dose/site [U] 10–50

- Preparation Dysport®
  - range [U/kg bw] 1–20 (–25)
  - max total dose [U] 500–1000
  - range max dose/site [U] 50–250

- Preparation Xeomin® (adult studies suggest dosage equivalence with Botox\(^{160, 161}\), but for children this needs to be confirmed)
  - range [U/kg bw] not established yet
  - max total dose [U] not established yet
  - max dose/site [U] not established yet

**BoNT Serotype B**

- Preparation Neurobloc® (mainly used as second line preparation in adult neurology in case of secondary non-response to BoNT/A)
  - range [U/kg bw] not established
  - max total dose [U] not established
  - max dose/site [U] not established

---

<table>
<thead>
<tr>
<th>bo(^{a})</th>
<th>abo</th>
<th>inco</th>
<th>rima</th>
</tr>
</thead>
<tbody>
<tr>
<td>onA (=)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>incoA</td>
<td></td>
<td>large muscles</td>
<td>small muscles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-6 U/kgBW</td>
<td>0.5-2 U/kgBW</td>
</tr>
<tr>
<td>boA</td>
<td></td>
<td>10-20 U/kgBW</td>
<td>5-10 U/kgBW</td>
</tr>
</tbody>
</table>

**Dose / kg bodyweight up to 24 kg - then adult dosages**

Freitag, 23. November 2012
BoNT - Cerebral Palsy: how to decide if BoNT could work

- Elevated muscle tone?
  - +
  - -

- Spasticity? (MTS, MAS)
  Define personal, ADL-relevant goals
  Does spasticity interfere with these goals?
  - +
  - -

- (Multi-) focal spasticity?
  - +
  - -

- Good range of motion?
  - +
  - -

Therapy goal BoNT:
- Function & Activity & Participation (Locomotion)

Structure: BoNT & casting or hygiene, pain, positioning versus surgery

Injection protocol

Love et al. 2010 EJ of Neurology Vol. 17, Supplement 2
DOSING-LOOP BOTULINUM TOXIN

REPEAT THE LOOP UNTIL EVERY STEP IS WITHIN THE ACCEPTED DOSE RANGE, THEN PROCEED TO THE INJECTION PROCEDURE

1 CLINICAL EXAMINATION WHICH MUSCLES SHOULD BE TREATED?

7 INJECTION PROTOCOL DOSE | MUSCLE

Reduce number of muscles if necessary

2 UNITS | KG BW | MUSCLE

3 MAXIMUM UNITS | MUSCLE

4 MAXIMUM UNITS | SITE

5 TOTAL DOSE | SESSION TOTAL DOSE | KG BW* | SESSION

*kg bw – kilogram bodyweight


Freitag, 23. November 2012
<table>
<thead>
<tr>
<th>Datum</th>
<th>Gewicht</th>
<th>NaCl 0,9% / Vial</th>
<th>Präparat (B, N, X, D)</th>
<th>M. iliopsoas re</th>
<th>M. iliopsoas li</th>
<th>M. Rec fem re</th>
<th>M. Rec fem li</th>
<th>Gesamtdosis</th>
<th>Units / kg KG</th>
<th>Chargennummer / Unterschrift des Arztes</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.06.12</td>
<td>25</td>
<td>4</td>
<td>Botox 2x50 2x50 3x25 3x25 ...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>350</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Used for over 20 years

2. AE: focal (local, distant), generalized and procedural

3. Safety discussion (Germany, USA, etc.)
   => Germany 06/2007 – 09/2008: No evidence showing a causal connection between the fatal outcome of five reported patients and their prior treatment with BoNT.
   => USA, FDA 01/2008 – 08/2009: boxed warnings on their labels: spread from the area of injection to other areas of the body with potentially life-threatening swallowing and breathing difficulties and even death.

4. Cave: more severe GMFCS and/or accompanied impairments
Safety

180 Patients - 616 sessions - 54 AE - 8.8%

AE rating: light: 5.0%, moderate: 3.1%, severe: 0.2%

Predictive Risk of occurrence of AE in correlation to dose / kg bodyweight

Retrospectiv versus prospective assessment of AE differs
1. Repeated multiple, painful, but elective procedure

2. The right for a pain free therapy (ethical necessity)

3. Optimal regimen will vary between individuals & institutions:
   - influenced by the age of the child
   - the GMFCS
   - the number of muscles to be treated

4. Accurate localization technique
1. Purpose-built classification tools and standardized clinical assessments => same language => using consistent and valid instruments, matched to the dimensions of the ICF

2. SCPE, GMFCS, MACS, HIP-SURVEILLANCE

3. Clinical Examination:
   - Modified Ashworth Scale (MAS)
   - Modified Tardieu Scale (MTS)
   - Active / passive Range of Motion
   - (3-D / observational) Gait analysis (PRS)
   - Goal Attainment Scaling (GAS)

Spasticity versus Contracture

Evaluation vor Injektion, Ultraschall-gesteuerte Botulinumtoxin, Evaluation 4-6 Wochen nach BoNT

Freitag, 23. November 2012
<table>
<thead>
<tr>
<th>Tool</th>
<th>ICF domain</th>
<th>Domain of measurement</th>
<th>Properties</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Body</td>
<td>Spasticity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structures</td>
<td></td>
<td>Valid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Activities</td>
<td></td>
<td>Reliable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Participation</td>
<td></td>
<td>Responsive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Function</td>
<td>Clinical</td>
<td>Research</td>
</tr>
<tr>
<td>Australian Spasticity Assessment Scale (ASAS) [36]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Tardieu Scale (MTS) [18]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle length as measured by range of joint motion (ROM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goal Attainment Scaling (GAS) [45]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Video Gait Analysis (VGA or 2DGA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3DGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician Rating Scale (PRS) [38]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional Independence Measure for Children (WeeFIM®) [43]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric Evaluation of Disability Inventory (PEDI) [41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross Motor Function Measure (GMFM-66) [44]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Addresses this domain/possesses this property/fulfills this purpose; ?: may possess this property.
Example patients - select assessment tools

1. BSCP
   GMFCS Level 2, 4 years of age
   - mod. Tardieu Scale
   - a/p ROM
   - Video Gait doc.
   - GAS
   - X-Ray hip

2. Dyskinetic CP
   GMFCS Level 5
   16 years of age
   - Positioning
   - Pain
   - CPCHILD
   - X-Ray hip & spine
   - autonomic function
   - GAS

3. USCP right side
   GMFCS Level 1
   6 years of age
   - MACS level
   - AHA-Test
   - a/p ROM
   - mod. Tardieu Scale (large joints)
   - GAS
World consensus: BoNT/A evaluation of effectiveness

- BoNT-A is established as effective in the management of spastic equinus to improve gait. (level A)
- BoNT-A is probably effective to improve goal attainment and function in the management of spastic equinus (level B)
- BoNT-A is similar to serial casting in the management of spastic equinus with current data being inadequate or conflicting (level U)
- BoNT-A injections to the adductor muscles is probably effective in some specific areas of goal attainment (level B)
- BoNT-A injections to the adductor muscles do not improve gross motor function (level A)
- BoNT-A injections to the adductor (and hamstring) muscles may delay hip displacement, but does not affect long-term outcome (level A)
- BoNT-A injections to multiple lower limb muscles have inadequate and conflicting data in respect of gait, goal attainment and function (level U)
It is recommended that BoNT treatment for spasticity is used as part of an integrated multidisciplinary rehabilitation programme to optimise the likelihood of treatment goals being achieved. BoNT should be used to address clearly identified problems resulting from muscle over-activity confined to one or a group of muscles that contribute to a specific functional deficit. BoNT will not necessarily recover lost function, but may improve functional outcomes by allowing range of motion to be regained, reducing pain and restoring more balanced muscle function, leading to improvement in movement control. BoNT treats muscle over-activity, while targeted therapy treats muscle under-activity; consequently, BoNT treatment is usually an adjunct to therapy rather than the other way round.

What is the effectiveness of BoNT treatment for children and adults with neurological impairments?

A summary of the scientific evidence for the effectiveness of BoNT treatment in children and adults with neurological impairments is provided (Table 2). Detailed appraisal of this evidence is contained within the seven specialty International Consensus Statements in this supplement.

### Table 2 Effectiveness of BoNT for children and adults with neurological impairments

<table>
<thead>
<tr>
<th>Treatment outcomes from intra-muscular injections</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limb hypertonicity</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Upper limb hypertonicity</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Neck region hypertonicity</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Reduced spastic muscle over-activity</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Reduced dystonic muscle over-activity</td>
<td>U&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A</td>
</tr>
<tr>
<td>Increased range of motion</td>
<td>U</td>
<td>B</td>
</tr>
<tr>
<td>Increased gross motor function</td>
<td>U</td>
<td>B</td>
</tr>
<tr>
<td>Increased goal achievement</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Reduced pain</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment outcomes from intra-glandular injections</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced saliva secretion</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

<sup>a</sup>Lack of sensitive outcome measures & difficulty in assembling homogenous groups for clinical trials affect this finding. A, established effective; B, probably effective; U, inconclusive; ●, not appropriate.
This systematic review found high level evidence supporting the use of BoNT-A as an adjunct to managing the upper limb in children with spastic CP.

BoNT-A should not be used in isolation but should be accompanied by planned occupational therapy.

Further research is essential to identify children most likely to respond to BoNT-A injections, monitor longitudinal outcomes, determine timing and effect of repeated injections and the most effective dosage, dilution and volume schedules.

The most effective adjunct therapies including frequency and intensity of delivery also requires investigation.
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