

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Effectiveness and safety of early intramuscular botulinum toxin injections to prevent shoulder deformity in babies with brachial plexus birth injury (POPB-TOX), a randomized controlled trial: study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032901
Article Type:	Protocol
Date Submitted by the Author:	12-Jul-2019
Complete List of Authors:	<p>Pons, Christelle; Fondation ILDYS; Laboratory of Medical Information Processing, INSERM UMR 1101 Eddi, Dauphou; CHRU de Brest Le Gal, G.; Centre Hospitalier Universitaire de Brest, Centre for Clinical Investigation INSERM CIC 1412 Garetier, Marc; Hopital d'Instruction des Armees Clermont-Tonnerre, Radiology; Laboratory of Medical Information Processing, INSERM UMR 1101 Ben Salem, Douraied; CHRU de Brest, Radiology; Laboratory of Medical Information Processing, INSERM UMR 1101 Houx, Laetitia; Centre Hospitalier Universitaire de Brest, Physical Medicine and Rehabilitation Department, Brest, France Fitoussi, Franck; Hopital Armand-Trousseau Quintero, Nathaly; Hopitaux de Saint-Maurice, Physical Medicine and Rehabilitation Brochard, Sylvain; Centre Hospitalier Universitaire de Brest, Physical Medicine and Rehabilitation Department, Brest, France; Laboratory of Medical Information Processing, INSERM UMR 1101 POPBtox group, POPBtox group</p>
Keywords:	brachial plexus birth injury, Shoulder < ORTHOPAEDIC & TRAUMA SURGERY, botulinum toxin, bone deformity

SCHOLARONE™
Manuscripts

1
2
3 **Effectiveness and safety of early intramuscular botulinum toxin injections**
4 **to prevent shoulder deformity in babies with brachial plexus birth injury**
5 **(POPB-TOX), a randomized controlled trial: study protocol**
6
7
8
9

10
11 Christelle Pons MD, PhD^{1,2,3} ; Dauphou Eddi PhD⁴ ; Grégoire le Gal MD, PhD⁵ ; Marc
12 Garetier MD^{2,6} ; Douraied Ben Salem MD, PhD^{2,7,8} ; Laetitia Houx MD^{1,2,3} ; Franck Fitoussi
13 MD, PhD⁹ ; Nathaly Quintero MD¹⁰ ; Sylvain Brochard MD, PhD^{1,2,3,8} ; and the POPB-TOX
14 Group (Marianne Alison, Madeleine Aslan, Jennifer Bastien, Gilles Dautel, Floriane Colin, Marion
15 Delpont, Bruno Dohin, Marie Agnes Galloy, Vincent Gautheron Salem Hassan Al Khoury, Pascal
16 Jehanno , Mélanie Kaas, Olivier Prodhomme, Mélanie Porte, Anne Gaelle Py, Helène
17 Rauscent, Emilie Rumilly, Katherine Sanchez Barr , Catherine Tréguier, and Philippe Violas)
18
19

- 20
21
22 1 Pediatric rehabilitation, Fondation ILDYS, Brest, France
23 2 Laboratory of Medical Information Processing, INSERM 1101, Brest, France
24 3 PMR department, Brest CHRU, Brest, France
25 4 DRCI, Brest CHRU, Brest, France
26 5 Centre for Clinical Investigation INSERM CIC 1412, Brest CHRU, Brest, France
27 6 Radiology department, hôpital d'Instruction des Armées Clermont-Tonnerre, Brest,
28 France
29 7 Radiology department, Brest CHRU, Brest, France
30 8 Université de Bretagne Occidentale, Brest, France
31 9 CHU Paris Est - Hôpital d'Enfants Armand-Trousseau; Paris, France
32 10 Hôpitaux de St Maurice, St Maurice, France
33
34
35

36 Corresponding author

37 Christelle Pons

38 SSR pédiatrique brestois, Fondation ILDYS, rue Alain Colas, 29200 Brest

39 Tel : 0256310145

40 christelle.ponsbecmeur@ildys.org
41
42

43 Word count : 5396
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Introduction

In children with Brachial Plexus Birth Injury (BPBI), denervation of the shoulder muscles leads to bony deformity in the first months of life, reducing active and passive range of motion (ROM), and causing activity limitation. The aim of this multicentre randomised controlled trial is to evaluate the effectiveness of botulinum toxin injections (BTI) in the shoulder internal rotator muscles of 12 month-old babies in limiting the progression of posterior subluxation of the glenohumeral joint, compared with a sham procedure mimicking BTI. The secondary aims are to evaluate the effectiveness of BTI in (I) limiting the progression of glenoid retroversion and 3D deformity and (II) improving shoulder range of motion and upper limb function, as well as to confirm the tolerance of BTI.

Methods and analysis

Sixty-two babies with unilateral BPBI and a risk of posterior humeral head subluxation will be included. Only those with at least 7% posterior subluxation of the humeral head compared with the contralateral shoulder on the MRI will be randomized to one of two groups: “BTI” and “Sham”. The BTI group will receive BOTOX injections at the age of 12 months in the internal shoulder rotator muscles (8UI/kg). The sham group will undergo a sham BTI procedure. Both groups will undergo repeated shoulder MRI at 18 months of age to quantify changes in the percentage of posterior migration of the humeral head (primary outcome), glenoid version and 3D bone deformity. Clinical evaluations (passive shoulder range of motion, Active Movement Scale) will be carried out at baseline and 15 and 18 months of age. The mini Assisting Hand Assessment will be rated between 10 and 11 months, and at 18 months of age. Adverse events will be recorded at least monthly for each child.

Ethics and dissemination

Full ethical approval for this study has been obtained.

Trial registration number

EudraCT: 2015-001402-34 in European Clinical Trial database; NCT03198702 in Clinical Trial database.

Keywords: Brachial Plexus Birth Injury, shoulder, botulinum toxin, bone deformity

Strengths and limitations of this study

We expect botulinum toxin injections to limit shoulder deformity and improve shoulder range of motion in children with brachial plexus birth injury.

35 This randomized controlled study will evaluate the safety and effectiveness of early botulinum
36 toxin injections in the shoulder internal rotator muscles.

37 The effect on bony deformities (glenohumeral subluxation and glenoid version), active and
38 passive range of motion and upper limb function will be evaluated.

39

40

41 INTRODUCTION

42

43

44 Brachial Plexus Birth Injury (BPBI) refers to injury to one or more cervical nerve roots
45 (C5-C8) and/or the first thoracic nerve root (T1), usually caused by traction during a difficult
46 birth. The incidence is around 1.5 per 1000 births[1]. In one third of cases, nerve recovery is
47 incomplete or absent[1,2], resulting in permanent impairment which in turn may lead to activity
48 limitation and participation as defined by the International Classification of Functioning[3,4].

49 BPBI greatly affects the musculoskeletal development of the shoulder complex[3,5,6].
50 Deformities occur very early, within the months following birth[6–8], and gradually worsen
51 with the child's growth[7,9]. Bony and joint deformities are caused by the partial denervation
52 of the shoulder muscles, which results in an imbalance of the forces acting on the glenohumeral
53 joint [6,10]. In particular, there is often a dominance of the internal rotator muscles [11,12].
54 Excess glenoid retroversion is typical, along with deformation of the glenoid fossa. This allows
55 posterior migration of the humeral head to occur, eventually progressing to complete
56 subluxation[6–8,13]. These deformities increase the risk of early degenerative joint changes
57 and pain during childhood and adulthood[14,15]. Active and passive shoulder range of motion
58 (ROM) are also reduced, causing a vicious circle in which the muscles cannot contract
59 effectively because of the bony deformities and altered lever arms [9]. These changes reduce
60 the functional capacity and quality of life of children with BPBI[16,17].

61 Botulinum toxin injections (BTI) are a common treatment to reduce muscle activity. This
62 treatment is mostly used to treat spasticity in children, particularly in the case of cerebral
63 palsy[18], however it may also be useful in children with BPBI[19,20], combined with other
64 treatments such as physiotherapy, occupational therapy, orthoses and, in some cases, surgery.
65 The dominant internal shoulder rotator muscles are often targeted in order reduce the strength
66 imbalance between agonist and antagonist muscles [21]. One study suggested that BTI might
67 be useful to reduce posterior subluxation or dislocation of the shoulder in babies with BPBI[22].
68 BTI could also improve passive and active shoulder ROM and functional capacity[20,23,24].
69 BTI is a minimally invasive treatment that is well tolerated in young children [25]. When used

1
2
3 70 prior to surgery, it could avert or reduce the complexity of surgical secondary orthopaedic
4
5 71 procedures (e. g. subscapularis release, latissimus dorsi and teres major transfers) [22,23].
6
7 72 Although the results of studies of early BTI for BPBI are encouraging, most studies are
8
9 73 retrospective, include small samples and do not have a control group. The current level of
10
11 74 evidence is thus insufficient to make robust conclusions regarding the effectiveness of
12
13 75 botulinum toxin injections in children with brachial plexus birth injury.

14 76 Randomized controlled trials to evaluate the efficacy of early BTI and to confirm its
15
16 77 tolerance in children with BPBI are therefore now warranted. With regard to the control
17
18 78 treatment, a sham procedure mimicking BTI without injection is ethically more appropriate
19
20 79 than an invasive placebo procedure because of the young age of the children involved.
21
22 80

22 81 **AIMS and HYPOTHESES**

23 82 24 83 **Aims**

25
26 84 The main aim of this study is to evaluate the effectiveness of BTI in the internal shoulder
27
28 85 rotator muscles of 12 month-old babies in limiting the progression of posterior subluxation of
29
30 86 the glenohumeral joint.

31
32 87 The secondary aims are (I) to compare the effectiveness of BTI with a sham treatment
33
34 88 in limiting the progression of glenoid retroversion and three-dimensional glenoid deformity;
35
36 89 (II) to compare the effectiveness of BTI with a sham treatment in improving active and passive
37
38 90 joint range of motion and upper limb function; (III) to assess the tolerance of BTI in babies with
39
40 91 BPBI; (IV) to evaluate the effects of BTI on muscle growth and fatty infiltration of the injected
41
42 92 muscles, as well as muscle volume balance around the shoulder, and (V) to determine the long-
43
44 93 term effect of BTI on frequency and type of surgical interventions.
45
46 94

46 95 **Hypotheses**

47
48 96 Our primary hypothesis is that BTI will limit posterior subluxation of the glenohumeral
49
50 97 joint in the BTI group compared with the Sham group.

51
52 98 We further hypothesize that the progression of glenoid retroversion and three-
53
54 99 dimensional deformities will be reduced, that active and passive range of motion will be
55
56 100 increased, and that number of secondary surgical interventions will be reduced in the BTI group
57
58 101 compared with the Sham group. The robust design of this study will confirm the results of
59
60 102 previous un-controlled studies, providing a strong level of evidence for BTI treatment. We also
103
104 103 hypothesize that BTI will be well tolerated by the babies [25]. With regards to morphological

1
2
3 104 changes following BTI, we expect slight atrophy to occur in the injected muscles, with some
4 105 fatty infiltration [26] but no change in non-injected muscles, leading to an improvement in the
5 106 volume balance of agonist and antagonist muscles [27].
6
7
8
9

10 108 **METHODS/DESIGN**

11 109 12 110 **Design**

13 111 A randomised, multicentre, double-blind, controlled, parallel group, superiority trial
14 112 will be performed (version 3, 17.01.2018). One group will receive BTI and the other will
15 113 undergo a Sham procedure.
16
17
18
19
20
21

22 115 **Ethics**

23 116 Full ethical approval for this study has been obtained by the ethical committee Ouest 1
24 117 of Tours and Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM).
25 118 The trial has been registered in the European Clinical Trial database (EudraCT: 2015-001402-
26 119 34) and Clinical Trial database (NCT03198702). All families will be given a written
27 120 information letter detailing the study and parents or guardians will sign informed consent prior
28 121 to the child's inclusion. Any modification or amendment to the protocol will be submitted to
29 122 the ethical committees and ANSM for approval. After approval, investigators and trial
30 123 participants will be informed of the changes by letter or email. All trial databases will also be
31 124 updated.
32
33
34
35
36
37
38
39
40

41 126 **Recruitment**

42 127 The sponsor is CHRU Brest. Babies will be recruited from six French hospitals (CHRU
43 128 Brest, Centre de Réadaptation pour enfant Flavigny-sur-Moselle, Hôpital National de Saint
44 129 Maurice, CHU Saint-Etienne, CHU Nîmes, CHU Rennes), all of which are specialized in the
45 130 management of children with brachial plexus palsy and have access to MRI. All doctors
46 131 involved are skilled in BTI. Hospitals were selected by the study coordinator and sponsor based
47 132 on their responses to a feasibility questionnaire. It is predicted that during the 29 months of
48 133 inclusion, around 2590 children will be born with BPBI in France [1], of whom 466 will left
49 134 with sequelae[1]. This study will recruit 13.5% of these babies (62 patients over 29 months).
50 135 The investigator in each of the specialist participating centres will inform clinicians in local
51 136 maternity units about the study, and flyers and posters will be displayed in the reception areas
52 137 of clinics and maternity units. Clinicians will be asked to refer babies with OBBP to their nearest
53
54
55
56
57
58
59
60

1
2
3 138 participating specialist centre and they will be provided with information leaflets to give to the
4
5 139 parents. External advertising will also include a webpage on the Brest CHRU website. If
6
7 140 inclusion goals are not achieved, more centers will be asked to participate.

8 141 A rehabilitation physician and/or a surgeon in each participating specialist centre will
9
10 142 identify potentially eligible babies for the study during routine consultations. The protocol will
11
12 143 be explained and proposed to parents of babies between 10 and 11 months of age who have a
13
14 144 high risk of bony deformity. An information letter will be given to the parents (supplementary
15
16 145 file). If the parents agree to their baby's participation, and the baby fulfils the inclusion criteria,
17
18 146 he or she will be enrolled in the study for 7 months.

19 147 The inclusion criteria are: male or female babies aged between 10 and 11 months with
20
21 148 unilateral BPBI; at least one of the following risk factors for posterior subluxation of the
22
23 149 humeral head: 10° less passive external ROM of the affected shoulder compared with the
24
25 150 contralateral shoulder and/ or a score below 6 on the Active Movement Scale (AMS) for
26
27 151 shoulder external rotation and abduction, elbow flexion or supination; whose parents or
28
29 152 guardians have signed the consent form. Babies with bilateral BPBI, microsurgery or shoulder
30
31 153 muscle surgery planned between 12 and 18 months of age, contraindications to the use of
32
33 154 botulinum toxin (hypersensitivity to botulinum toxin or the excipients used, or myasthenia),
34
35 155 contraindications to MRI (pace maker, metal implants, foreign metal body in the eye, etc.), MRI
36
37 156 not possible in the Paediatric Day Hospital setting because of contraindications to the
38
39 157 premedication protocol or organizational constraints, parents inapt to provide consent for the
40
41 158 participation of their child, or parents under the age of 18 years, will be excluded.

42

43 160 **Study procedure** (Figure 1 and Table 1)

44 161 At visit 1 (between 10 and 11 months of age), the parents or guardians will sign the
45
46 162 informed consent form and the baby will be included. The physician or surgeon will carry out
47
48 163 a physical examination and will collect socio-demographic data including history of BPBI in a
49
50 164 brother or sister, overweight or obesity of the mother, any medical conditions during the
51
52 165 pregnancy (e.g. gestational diabetes), the birth procedure (caesarean section, vaginal delivery
53
54 166 with epidural, induction of labour, instrumental delivery, shoulder dystocia, term and duration),
55
56 167 birth weight and length, and APGAR score.

57 168 Visit 2 (at 11 months of age) will involve MRI to confirm the diagnosis of bony
58
59 169 deformity (the humeral head on the involved side must be at least 7% more posterior than the
60
170 humeral head on the contralateral side). Once confirmed, randomisation will be carried out.
171
This will ensure that only babies with verified glenohumeral deformity are included, since

1
2
3 172 clinical tests are not sufficiently sensitive to confirm this. Babies who do not fulfil this
4
5 173 randomisation criterion will be withdrawn from the study and will pursue the usual medical
6
7 174 follow-up. The parents will be informed of the results of the MRI within 10 days by means of
8
9 175 a telephone call from the research investigators. The randomisation will allocate the babies to
10
11 176 one of two treatment groups (each with the same number of babies): BTI group and sham group.

12 177 Visit 3 (12 months +/-15 days of age) will include treatment (BTI or sham procedure).

13 178 Both groups will then attend seven follow up visits: visit 4 will be carried out ten days
14
15 179 after treatment administration, and visits 6-10 will be carried out each month until 18 months
16
17 180 of age. Visits 1, 7 and 10 will involve a standardized clinical examination by occupational
18
19 181 therapists or physiotherapists and visits 5, 6, 8 and 9 will involve a telephone call from a
20
21 182 member of the study team.

22 183 Un-blinding will be performed at visit 10 (18-months of age). Following un-blinding,
23
24 184 the baby will attend a follow-up visit at 24 months then yearly follow-up visits, as is usual
25
26 185 practice. The aim of this is to determine the safety of the use of botulinum toxin before the age
27
28 186 of two years (after which there is a marketing authorization for children with cerebral palsy),
29
30 187 and to compare the frequency and complexity of surgical interventions between groups until
31
32 188 the age of 10 years.

33 189

34 190 **MRI**

35
36 191 The babies included in this study will undergo MRI of both shoulders at visits 2 and 10
37
38 192 (at 11 and 18 months of age). A three-dimensional, T1-weighted gradient-echo sequence will
39
40 193 be used. This anatomical sequence highlights bones and muscles, including denervated
41
42 194 muscles[28]. The child will lie supine with his/her arms in neutral and hands pronated. The T1
43
44 195 protocol[27] will be adapted in each centre depending on the type of MRI scan they have.
45
46 196 Acquisition time will be less than 5 minutes per shoulder. No contrast injection will be required.
47
48 197 Images will have to include sternum and spine medially, the whole deltoid laterally and the
49
50 198 spine of the scapula at the back down. Premedication (sedation or general anaesthetic) will be
51
52 199 necessary for both MRI exams, at 11 and 18 months of age. The premedication will be adapted
53
54 200 to the clinical status of each child and the customs of each centre. After premedication, the child
55
56 201 will be monitored by a paediatrician in the day hospital of each centre using a validated protocol.

57 202

58 203 **Randomisation process and blinding**

59 204 Randomisation will be carried out using centralised computer randomisation by Internet,
60 205 according to the usual procedures in effect at Brest Regional University Hospital. After MRI

1
2
3 206 confirmation that the baby fulfils the randomisation criterion (visit 2), randomisation will be
4
5 207 performed by the study investigator on the day of the injection visit (visit 3, 12 months of age).
6
7 208 Randomization will be carried out via a specific dedicated website ([https://chu-brest.hugo-](https://chu-brest.hugo-online.fr/CSOnline/)
8
9 209 [online.fr/CSOnline/](https://chu-brest.hugo-online.fr/CSOnline/)). This website is available 24 hours a day.
10
11 210 Stratification will be carried out by centre and by microsurgery prior to inclusion, since early
12
13 211 surgery could influence the progression of bony deformity. Only the physician who will
14
15 212 perform the BTI and the pharmacist will receive the email specifying the randomization arm of
16
17 213 each baby. Neither the parents or guardians, nor the clinical and radiological evaluators will be
18
19 214 aware of the treatment administered. The doctors carrying out the BTI will not take part in
20
21 215 subsequent visits, to ensure the blinding of the examiner. A central analysis of MRI data will
22
23 216 be carried out in order to ensure blinding of the evaluator to the primary outcome measure.

24 218 **Study Treatments**

25 219 BTI procedure

26
27 220 The botulinum toxin that will be used in the study is BOTOX (Allergan, Dublin,
28
29 221 Ireland). Doses will be injected into the pectoralis major, subscapularis and teres
30
31 222 major/latissimus dorsi muscles in a single site for each muscle on one occasion (visit 3:
32
33 223 12months +/- 15 days of age). These muscles have been the target of BTI treatment to prevent
34
35 224 the progression of humeral head subluxation and to improve active and passive shoulder ROM
36
37 225 in previous studies of children with BPBI[22]. Following reconstitution, the toxin will be
38
39 226 injected intramuscularly using a transcutaneous approach with a 27 gauge, 25mm long sterile
40
41 227 needle. Ultrasound guidance will be used to identify the muscles. A detailed protocol has been
42
43 228 written to ensure standardization of the procedure (supplementary material 1). The chosen doses
44
45 229 are based on data in the literature in children and babies with BPBI[20,22,23]: a total of 8U/kg
46
47 230 will be injected (2U/kg in subscapularis, 3U/kg in pectoralis major and 3U/kg in teres
48
49 231 major/latissimus dorsi). Because there is no marketing authorisation for the use of botulinum
50
51 232 toxin in children under the age of two years, the chosen doses are smaller than the maximal
52
53 233 doses authorized for the treatment of spasticity in older children with cerebral palsy. Moreover,
54
55 234 the doses chosen correspond with doses used in previous studies. A standardized protocol for
56
57 235 the prevention and treatment of induced pain and post-injection pain will be systematically
58
59 236 used. This will involve the administration of topical anaesthesia (such as EMLA) and
60
237 paracetamol (dose according to the baby's weight) one hour prior to the injection. Distraction
238 techniques will be used during the injection. The parents will be instructed to bring reassuring,
239 familiar objects belonging to the baby (e.g. soft toy, pacifier, nursery rhyme, music). In order

1
2
3 240 to standardize practices and to ensure maximum safety and efficacy, staff from the different
4
5 241 centres will all be trained in BTI of the shoulder muscles using ultrasound guidance in babies
6
7 242 prior to participating in the study. Only physicians with at least five years of experience in BTI
8
9 243 will be authorized to perform the injections.

10 244

11 245 Sham procedure

12 246 The aim of the Sham procedure is to mimic the BTI and to maintain the blinding of the
13
14 247 research team and the parents or guardians. The same anesthetic procedure will be carried out
15
16 248 as for BTI. The physician performing the injection will prepare a syringe containing
17
18 249 physiological saline solution 10 minutes prior to the Sham procedure. The procedure will be
19
20 250 simulated with ultrasound and use of a blunt needle (that will not penetrate the skin) on the sites
21
22 251 selected for injection. All sites will be covered with adhesive dressings and tincture of betadine,
23
24 252 as for the BTI. With regard to the control treatment, a sham procedure mimicking BTI without
25
26 253 injection is ethically more appropriate than an invasive placebo procedure because of the young
27
28 254 age of the children involved.

29 255

30 256 Rehabilitation and medical follow up

31 257 To ensure comparability, the babies in both groups will receive 2 sessions of physiotherapy per
32
33 258 week. Physiotherapy will be standardized and based on evidence from studies of early
34
35 259 physiotherapy management [29,30]. It will involve: (I) maintaining passive range of motion of
36
37 260 all the upper limb joints, in particular shoulder external rotation, elbow extension and forearm
38
39 261 pronation; (II) active-assisted and active movements of the involved shoulder; (III) bimanual
40
41 262 functional training; (IV) training to integrate the involved upper limb in functional activities
42
43 263 and (V) parent education: child positioning, stimulation of active movement and function at
44
45 264 home. A standardized medical prescription will be given. An information and advice letter will
46
47 265 be given to the physiotherapists via the parents to standardize and optimise physiotherapy
48
49 266 treatment. Advice will be given to parents regarding exercises to carry out at home, they will
50
51 267 be taught to encourage use of the upper limb at home. All other medical treatment and
52
53 268 rehabilitation will be carried out according to usual procedures.

54 269

55 270 Adverse events

56 271 Adverse events relating to the use of botulinum toxin

57 272 The secondary effects of BTI are mostly mild, temporary and related to the dose and the
58
59 273 injection site. Local reactions such as contusions or pain at the injection site may occur, or

1
2
3 274 excessive, localised muscle weakness. Systemic effects are rare and include generalised allergic
4
5 275 reactions and effects related to product diffusion (rash, erythema, pruritus, anaphylactic
6
7 276 reaction, flu-like syndrome, headaches, dizziness, fever, shivering, hypertension, and
8
9 277 abdominal pain and dry mouth). Exceptionally, serious effects have been observed, a type of
10
11 278 excessive muscle weakness, dysphagia and aspiration pneumonia, however these occurred
12
13 279 principally when the recommended doses were not respected[25,31–33]. The safety of BTI in
14
15 280 infants under two years of age was shown to be good in a recent systematic review[25] and the
16
17 281 tolerance of this treatment also seems good in this population[22,33,34]. The specific effects
18
19 282 on muscle structure and the contractile properties of muscles are, however, poorly understood.
20
21 283 Moderate muscle atrophy and fatty infiltration may occur following injections[26,35,36].

22 284 According to the usual procedure used for the injection of botulinum toxin in each
23
24 285 hospital, an information sheet will be provided to each patient explaining the action to be taken
25
26 286 in the case of an adverse effect. According to this procedure, parents will be instructed to
27
28 287 urgently consult their general practitioner or the pediatric emergency department in the case of
29
30 288 the occurrence of a serious adverse effect such as generalized weakness or cardio-respiratory
31
32 289 insufficiency. There is no antidote to botulinum toxin therefore symptomatic treatment will be
33
34 290 administered, if required.

35 291 In the case of a serious adverse event, unblinding will be carried out. If an investigator
36
37 292 wishes to treat the child with aminoglycosides, which are contraindicated in the case of
38
39 293 treatment by botulinum toxin, unblinding will be carried out.

40 294 Parents will be questioned regarding adverse events at 10 days and then monthly
41
42 295 between 12 and 18 months of age using standardized questionnaires that include all possible
43
44 296 side effects.

45 297 46 298 Adverse events related to MRI premedication

47 299 The risks related to the premedication are the standard risks for the sedation or
48
49 300 anaesthesia of children (gastritis, anticholinergic effects, oxygen desaturation, excessive
50
51 301 sedation). The child will be examined for potential risks during a routine paediatric or
52
53 302 anaesthetic consultation.

54 303 55 304 Independent Data Monitoring Committee and un-blinding procedure

56 305 An independent data safety monitoring Committee (DSMC) comprised of five
57
58 306 independent members will be set up. The purpose of the DSMC will be to provide an
59
60

1
2
3 307 independent evaluation of any adverse events that occur during the research, as well as to
4
5 308 monitor the benefit / risk ratio.

6 309 Should an adverse event that requires different care than that planned in the study occur,
7
8 310 unblinding will be carried out. Unblinding will not be carried out in any other condition.

9
10 311

11 312 **Patient and Public involvement statement**

12 313 Patients were not involved in the development of the research, and will not be involved
13
14 314 in the recruitment and conduct of the study. Results of the study will be given to the parents
15
16 315 after the study during a medical consultation in their participating center.

17
18 316

19 317 **OUTCOME MEASURES**

20
21 318

22 319 **Primary Outcome (table 1)**

23
24 320 The primary outcome measure is the change in the percentage of posterior migration of
25
26 321 the humeral head measured on an axial MRI image between 11 months (before the BTI at 12
27
28 322 months) and 18 months of age (6 months post BTI) at visits 2 and 10. Posterior subluxation will
29
30 323 be evaluated using the method described by Waters, on an axial MRI slice taken just below the
31
32 324 coracoid process [37–39]. Percentage posterior subluxation will be calculated in the following
33
34 325 manner: a line will be traced from the medial border of the scapula to the middle of the glenoid
35
36 326 fossa. A segment will then be drawn perpendicularly to the line, from the widest part of the
37
38 327 humeral head (AC). The length of the anterior part of this segment (AB) divided by the (AC)
39
40 328 segment will be multiplied by 100 to obtain the percentage migration of the humeral head. A
41
42 329 percentage below 50% indicates posterior migration of the humeral head. This measurement is
43
44 330 quick to carry out and is used in both research and routine clinical practice in children and
45
46 331 babies with BPBI to help preoperative decision making for the type of intervention and post-
47
48 332 operative follow up[6,8,39]. Intra- and inter-rater reliability have been shown to be excellent,
49
50 333 with a 7% estimated measurement error [38]. MRI data will be analysed centrally (at Brest
51
52 334 CHRU) by two trained investigators using the same guidelines in order to minimise inter-rater
53
54 335 variability and to ensure the blinding of the evaluator.

55
56 336

57 337 **Secondary Outcome Measures (table 1)**

58 338 Glenoid retroversion and three-dimensional deformity

1
2
3 339 The following MRI measurements will be compared at visits 2 and 10 (11 and 18 months
4 of age) to determine the effectiveness of BTI relative to the sham treatment in limiting the
5 340 progression of glenoid retroversion and three-dimensional deformity:
6 341

- 7
8 342 1) 2D glenoid version will be measured on an axial image using Friedman's
9 technique[40]. This measurement has been validated and is used in clinical practice
10 343 and research[10,38].
11 344
12 345 2) 3D glenoid version and 3D migration of the humeral will be measured on MRIs
13 following 3D reconstruction. These original measurements were recently used for
14 346 the first time[41] and will provide an evaluation of 3D shoulder deformity and the
15 347 effect of BTI on the deformity.
16 348
17 349

22 350 Passive and active movement and upper limb function

23
24 351 Three standardized evaluations will be carried out by occupational therapists or
25 352 physiotherapists to compare the effect of BTI and the sham treatment on active and passive
26 joint range of motion and upper limb function. All therapists will undergo training prior to their
27 353 involvement in the study in order to ensure the reliability of measures.
28 354

- 29 355 1) Passive shoulder ROM will be measured at the baseline (before the MRI at visit 1,
30 between 10 and 11 months of age), at visits 7 and 10 (15-months and 18-months of
31 356 age visits).
32 357
33 358 2) The AMS (Active Movement Scale) will be rated at baseline (before the MRI at visit
34 1, between 10 and 11 months of age), and at visits 7 and 10 (15-months and 18-
35 359 months of age visits). This test evaluates upper limb strength in babies with BPBI
36 360 during active movements. Each movement is rated on an 8-point scale from 0 (no
37 361 movement) to 7 (complete movement against gravity). It has satisfactory
38 362 psychometric properties[42,43] in trained therapists.
39 363
40 364 3) The Mini-AHA (Mini-assistive Hand Assessment) will be rated at visit 1 and 10
41 365 (baseline and the 18-months of age visits). This functional evaluation measures
42 366 bimanual performance during games and tasks. It was designed for children aged
43 367 from 8 to 18 months[44].
44 368
45 369

54 369 Tolerance

55 370 The parents of the babies in both groups will be questioned at 10 days and each month
56 371 between 12 and 18 months of age using a standardized questionnaire that includes a list of all
57 372 possible side effects of BTI.

1
2
3 373
4
5 374 Changes in muscle structure (BTI group only)
6
7 375 3D MRI reconstruction[27] and the validated technique described by Hogendoorn et
8
9 376 al.[45] will be used to respectively evaluate the direct effects of BTI injections on muscle
10
11 377 volume and fatty infiltration of the shoulder muscles. This evaluation will only be carried out
12
13 378 in the BTI group.

13 379

15 380 Future surgical interventions

17 381 To determine if BTI reduces the frequency and complexity of surgical interventions in
18
19 382 the long term, surgical procedures undergone by the children in both groups (recorded during
20
21 383 routine medical follow-up) will be compared up to the age of 10 years.

22 384

24 385 **Locations and data management**

25 386 Each centre will manage their own recruitment of babies and organization of MRIs,
26
27 387 clinical evaluations and treatment. Electronic data will be secured and analyzed in a central
28
29 388 database managed by the Brest CHRU. Data will be the property of CHRU Brest.

30 389 In accordance with Good Clinical Practice (GCP) guidelines, the sponsor is in charge of
31
32 390 obtaining agreement from all centers involved in the clinical research, in order to guarantee
33
34 391 direct access to all the clinical research sites, to all the source data, source documents and all
35
36 392 the reports for the purpose of Quality Control and audit by the sponsor.

37 393 All information required for the study will be entered in the paper case report forms
38
39 394 during evaluations, then transferred to the electronic case report form (Clinsigth). Items of
40
41 395 missing data will be coded. Each centre will be responsible for completing the CRFs for the
42
43 396 babies enrolled in their centre. Each investigator will receive an instruction document regarding
44
45 397 the use of this tool. The investigator will be responsible for the accuracy, quality and relevance
46
47 398 of all the data entered. In addition, the data will be immediately verified as they are entered,
48
49 399 using consistency checks. The investigator must validate any changes to the values in the CRF.
50
51 400 These modifications will be subject to an audit trail. A justification can be added when
52
53 401 applicable, as a comment. Data management and query processing will be carried out by a data
54
55 402 manager.

55 403

56 404 A Clinical Research Assistant (CRA) appointed by the sponsor will ensure the good
57
58 405 running of the study, data collection on the paper CRF, data recording in the electronic CRF,
59
60

1
2
3 406 data saving and reporting in accordance with the sponsor's Standardized Operating Procedures
4
5 407 as well as the GCP guidelines and current legislation and laws in force.

6 408 The investigator and the members of his/her team will agree to be available during all the
7
8 409 routine and planned Quality Control visits by the CRA. During these visits, the following will
9
10 410 be audited: signed informed consent, compliance with the study protocol and procedures, data
11
12 411 recorded in the CRF: accuracy, missing data, consistency between these data and their "source"
13
14 412 (medical files, original laboratory results, etc.), product management and investigator file. The
15
16 413 investigators agree to accept the quality assurance audits carried out by the sponsor as well as
17
18 414 the inspections carried out by the competent authorities. All data, documents and reports may
19
20 415 be subject to regulatory audits and inspections. Medical confidentiality cannot be invoked in
21
22 416 opposition to these audits and inspections.

23 417 Any data sent to the sponsor by the investigators (or any other specialised parties) during or
24
25 418 after the biomedical research will be anonymised. These data should not reveal any visibly
26
27 419 accurate names and addresses of enrolled (involved) individuals. Only the first letter of the
28
29 420 subject's name and first name will be saved along with a coded number indicating the order of
30
31 421 inclusion of the subjects. The sponsor will ensure that the parent of each research subject has
32
33 422 given permission in writing for access to personal information about the baby which is strictly
34
35 423 necessary for the quality control of the research.

36 424

425 **Sample size and statistical analysis**

37 426 No longitudinal data regarding the progression of bony deformities in children with
38
39 427 BPBI are available in the literature. Only transversal studies have been carried out, indicating
40
41 428 that posterior subluxation is significantly greater on the affected side compared with the healthy
42
43 429 side at the age of 4.8 months (affected side: 32.1% - SD=19.7% vs. healthy side: 49.8% -
44
45 430 SD=7.3%)[6]. The calculation of the number of subjects necessary for this study was based on
46
47 431 a difference of one standard deviation at 12 months, for a standard deviation of 5%.

48 432 In order to guarantee a power of 90%, a sample of 22 babies per group is required, thus a total
49
50 433 of 44. In order to account for babies lost to follow-up (10%) and babies who will not be treated
51
52 434 because of a lack of true subluxation on MRI, 62 babies will be recruited.

53 435 The characteristics of the babies in both groups will be described using means, standard
54
55 436 deviations, medians, quartiles or frequencies. Mean changes in 2D percentage humeral
56
57 437 subluxation, 3D humeral subluxation, 2D and 3D glenoid version, the AMS score and passive
58
59 438 shoulder ROM will be compared using analysis of covariance (ANCOVA) adjusted on the
60
439 initial values. If the hypotheses underlying the analysis of covariance model are not respected,

1
2
3 440 a non-parametric Wilcoxon test will be used. Shoulder muscle volumes and the mini-AHA
4
5 441 scores will be compared between the groups using a Student test or a non-parametric Mann-
6
7 442 Whitney test, depending on the distribution of the variable of interest. Lastly, the number of
8
9 443 serious and non-serious adverse events, and the degree of fibrosis and fatty infiltration will be
10
11 444 compared between the two groups using a Chi2 test or Fisher's exact test, so as the number of
12
13 445 secondary surgeries. $p < 0.05$ will be considered as statistically significant.

14 446 Data analysis will be carried out on an intention to treat basis by a biostatistician after
15
16 447 blind review and database freezing at the end of the study. No intermediate analysis is planned
17
18 448 during this trial.

19 449

20 450 **DISCUSSION**

21
22 451 This paper presents the background and design for a multicentre double-blind
23
24 452 randomised controlled trial to evaluate the effectiveness of BTI in the shoulder internal rotator
25
26 453 muscles of 12 months old babies in limiting the progression of posterior subluxation of the
27
28 454 glenohumeral joint, compared with a sham procedure. To our knowledge, this is the first study
29
30 455 with a sufficiently robust methodology to allow conclusions to be based on a high level of
31
32 456 evidence. The study has been approved by national French agencies: the Ministry of Research,
33
34 457 the National Ethical Committee and the National Drug Administration.

35 458 The babies included in the study will all receive 2 sessions of physiotherapy per week.
36
37 459 This choice was made because it is usual practice for babies with BPBI in France. In addition,
38
39 460 studies in other pathologies have shown that physiotherapy potentiates the effectiveness of BTI
40
41 461 [46]. Casting will not be used because it is invasive, has a low level of evidence and comports
42
43 462 a risk of interference with motor development in children who already have central nervous
44
45 463 system abnormalities [47].

46 464 The primary end-point, change in the percentage posterior migration of the humeral
47
48 465 head measured on an axial MRI image between 11 months (before BTI) and 18 months of age
49
50 466 (6 months post BTI), was chosen for its clinical relevance and its strong psychometric properties
51
52 467 compared with clinical or functional assessments in this population. Because the aim of this
53
54 468 study is to evaluate both bone deformity and muscle morphology in order to document the
55
56 469 consequences of BTI in non-spastic muscles and on shoulder muscle balance, we preferred
57
58 470 MRI over ultrasound since MRI can accurately measure both elements while ultrasound cannot.

59 471 Clinical evaluations carried out before and after BTI will determine the effects of the
60
472 treatment on shoulder ROM and functional capacity. Evaluations will be carried out monthly,
473
with alternate phone contacts and direct consultations in order to limit traveling, promote

1
2
3 474 adherence and limit losses to follow-up. Because there is currently no marketing authorisation
4
5 475 for BTI in infants under the age of two years, special attention was paid to the safety assessment.
6
7 476 The use of a systematic and detailed questionnaire will yield detailed and specific data,
8
9 477 confirming or not the safety of BTI before the age of two years.

10 478 Glenohumeral dysplasia can occur as early as 3 months of age. If this trial has positive
11
12 479 results and if the safety of BTI performed at 12 months of age in children with BPBI is proven,
13
14 480 studies evaluating the effect of BTI in the limitation of gleno-humeral deformity in younger
15
16 481 babies could be warranted.

17 482 The results of the study could lead to a request for an evaluation by the French National
18
19 483 Agency for Medicines and Health Products Safety (ANSM) for Temporary Recommendation
20
21 484 for Use (TRUs) of botulinum toxin in children with BPBI. It is expected that the results of this
22
23 485 trial will be published in peer-reviewed scholarly journals and international academic
24
25 486 conferences. If positive results

26 487 Conclusion

27 488 The POPBTOX trial is a nationwide, multicentre, randomised, controlled study that will
28
29 489 evaluate the effectiveness of BTI in the internal shoulder rotator muscles of 12 month-old babies
30
31 490 with BPBI in limiting shoulder deformity. Tolerance of the treatment will also be determined.
32
33 491 Existing results from uncontrolled studies suggest this treatment may be effective, however the
34
35 492 present study will allow robust conclusions to be drawn, potentially leading to a change in the
36
37 493 care of these children.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1 : Visits and study procedure

Action	Visit 1 : 10 months of age (Inclusion, medical and therapists)	Visit 2: 11 months of age (MRI)	Visit 3: 12 months of age (injection, medical follow-up)	Visit 4: D10 post-injection (medical follow-up)	Visit 5: 13 months of age (Phone call)	Visit 6: 14 months of age (Phone call)	Visit 7 : 15 months of age (medical and therapists)	Visit 8 : 16 months of age (Phone call)	Visit 9 : 17 months of age (Phone call)	Visit 10: 18 months of age (MRI, therapists medical)
<i>Informed consent</i>	X									
<i>Incl./excl. criteria</i>	X									
<i>Medical history</i>	X									
<i>Notification of existing and planned BPBI care</i>	X* →									
<i>Active and passive shoulder range of motion (ROM)</i>	X* →						X			X
<i>Active Movement Scale (AMS)</i>	X* →						X			X
<i>MRI of both shoulders</i>		X								X
<i>mini-AHA Scale</i>	X* →									X
<i>Ramdomisati on criterion</i>		X								
<i>Randomisatio n</i>			X							
<i>BTI Injections or Sham procedure</i>			X							
<i>Notification of care (surgery or other)</i>			X							
<i>Establishment of standardized physiotherapy follw-up</i>			X							
<i>Follow-up of physiotherapy</i>				X	X	X	X	X	X	X

<i>Adverse Events</i>		X	X	X	X	X	X	X	X	X
<i>Unblinding</i>										X

X* → : Will be carried out before MRI

Figure 1 : Flow chart

Supplementary material 1: Botulinum toxin injections procedure

The Botox will be injected intramuscularly by transcutaneous approach using a 27 gauge, 25mm long sterile needle. This information can be added in the main text.

In the study protocol, we specifically described the procedure to ensure standardization (provided below). We propose to add this as supplementary material in the article.

“One hour before the injections, preliminary ultrasound identification will be carried out so that anaesthetic cream can be applied to the skin over the future injection sites.

For all injections, the child will be held in the arms of one of his/her parents.

Teres Major:

The parent will recline on the examination table, with the baby in his/her arms facing him/her (“belly to belly”). The sleep mask will be positioned on the parent at this time to ensure the blinding. The paediatric auxiliary can help to hold the child if necessary. The teres major muscle will be located by ultrasound, and the skin disinfected. Injection and/or simulation of the injection of the muscle (sham procedure) will be performed using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.

Subscapularis:

The baby will remain in the arms of the parent, “belly to belly”. The arm on the injected side will be placed in maximum abduction by the paediatric auxiliary. The subscapularis muscle will be identified by ultrasound. The skin will be disinfected. Injection and/or simulation of the injection of the muscle will be performed (sham procedure) using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.

Pectoralis Major:

The face mask will be removed so that the parent can change position and the position of the baby can be changed. The parent will sit in a chair with the child on his/her lap in a sitting position. The face mask will be repositioned. The pectoralis major muscle will be identified by ultrasound. The skin will be disinfected. Injection and/or simulation of the injection of the muscle (sham procedure) will be performed using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.

Acknowledgements

The authors acknowledge Chloe Bureau, Bhushan Borotikar, Céline Dolou, Valentine Guiton, Mélanie Pelouin, Emmanuel Novak for their help in building this project and Johanna Robertson for her help in revising English.

Author contribution

CP and SB conceived the study and defined the original study protocol. NQP, FF, CP and SB developed the intervention parameters. MG and DBS defined the radiological parameters and developed radiological protocols. ED is responsible for the ethics applications and the ethical reporting of the study. FF, NQP, CP, LH, are responsible for recruitment, data collection and implementation of the study. GG is responsible for the study methodology. POPBtox group involves physicians who are only implicated for recruitment and data collection.

All authors have read and approved the final manuscript. CP, ED and SB drafted the final version of this manuscript

Funding

This work was supported by a French national PHRC 15 -282

Disclaimer

The funding body is not involved in the study design, data collection, management, analysis, and interpretation of data. The authors have the ultimate authority over these activities.

Competing interests Dr Pons reports non-financial support from Biogen, outside the submitted work. Dr. Brochard reports non-financial support from Allergan, outside the submitted work. Dr. Le Gal reports other from Portola Pharmaceuticals, other from Boehringer-Ingelheim, other from Pfizer, other from Bristol-Myers Squibb, other from LEO Pharma, other from Daiichi Sankyo, other from Bayer, other from Bayer, other from Pfizer, other from LEO Pharma, other from Sanofi, other from bioMérieux, outside the submitted work.

Sponsor

Brest CHRU, 2 avenue Foch, 29200 Brest, France

Ethics approval

The Ouest 1 Research Ethics Committee (n° 2015-R22) and ANSM (151357A-31) approved the protocol.

Data sharing statement

In accordance with the protocol, the study data will be published.

REFERENCES

- 1 Chauhan SP, Blackwell SB, Ananth CV. Neonatal brachial plexus palsy: incidence, prevalence, and temporal trends. *Semin Perinatol* 2014;**38**:210–8. doi:10.1053/j.semperi.2014.04.007
- 2 Hoeksma AF, ter Steeg AM, Nelissen RGHH, *et al.* Neurological recovery in obstetric brachial plexus injuries: an historical cohort study. *Dev Med Child Neurol* 2004;**46**:76–83.
- 3 Julka A, Vander Have KL. Shoulder sequelae of neonatal brachial plexus injuries: orthopedic assessment and management. *J Pediatr Rehabil Med* 2011;**4**:131–40. doi:10.3233/PRM-2011-0165
- 4 Zafeiriou DI, Psychogiou K. Obstetrical brachial plexus palsy. *Pediatr Neurol* 2008;**38**:235–42. doi:10.1016/j.pediatrneurol.2007.09.013
- 5 Pearl ML. Shoulder problems in children with brachial plexus birth palsy: evaluation and management. *J Am Acad Orthop Surg* 2009;**17**:242–54.
- 6 Van Gelein Vtringa VM, Jaspers R, Mullender M, *et al.* Early effects of muscle atrophy on shoulder joint development in infants with unilateral birth brachial plexus injury. *Dev Med Child Neurol* 2011;**53**:173–8. doi:10.1111/j.1469-8749.2010.03783.x
- 7 van der Sluijs JA, van Ouwerkerk WJ, de Gast A, *et al.* Deformities of the shoulder in infants younger than 12 months with an obstetric lesion of the brachial plexus. *J Bone Joint Surg Br* 2001;**83**:551–5.
- 8 van der Sluijs JA, van Ouwerkerk WJR, Manoliu RA, *et al.* Secondary deformities of the shoulder in infants with an obstetrical brachial plexus lesions considered for neurosurgical treatment. *Neurosurg Focus* 2004;**16**:E9.
- 9 Waters PM. Update on management of pediatric brachial plexus palsy. *J Pediatr Orthop B* 2005;**14**:233–44.
- 10 Pöyhiä TH, Nietosvaara YA, Remes VM, *et al.* MRI of rotator cuff muscle atrophy in relation to glenohumeral joint incongruence in brachial plexus birth injury. *Pediatr Radiol* 2005;**35**:402–9. doi:10.1007/s00247-004-1377-3
- 11 Crouch DL, Plate JF, Li Z, *et al.* Computational sensitivity analysis to identify muscles that can mechanically contribute to shoulder deformity following brachial plexus birth palsy. *J Hand Surg Am* 2014;**39**:303–11. doi:10.1016/j.jhsa.2013.10.027
- 12 Kleiber T, Popovic N, Bahm J, *et al.* A modeling approach to compute modification of net joint forces caused by coping movements in obstetric brachial plexus palsy. *J Brachial Plex Peripher Nerve Inj* 2013;**8**:10. doi:10.1186/1749-7221-8-10
- 13 Moukoko D, Ezaki M, Wilkes D, *et al.* Posterior shoulder dislocation in infants with neonatal brachial plexus palsy. *J Bone Joint Surg Am* 2004;**86-A**:787–93.
- 14 Partridge C, Edwards S. Obstetric brachial plexus palsy: increasing disability and exacerbation of symptoms with age. *Physiother Res Int* 2004;**9**:157–63.
- 15 Kirkos JM, Kyrkos MJ, Kapetanios GA, *et al.* Brachial plexus palsy secondary to birth injuries. *J Bone Joint Surg Br* 2005;**87**:231–5.
- 16 Hulleberg G, Elvrum A-KG, Brandal M, *et al.* Outcome in adolescence of brachial plexus birth palsy. 69 individuals re-examined after 10–20 years. *Acta Orthop* 2014;**85**:633–40. doi:10.3109/17453674.2014.964614
- 17 Squitieri L, Larson BP, Chang KWC, *et al.* Understanding quality of life and patient expectations among adolescents with neonatal brachial plexus palsy: a qualitative and quantitative pilot study. *J Hand Surg Am* 2013;**38**:2387–2397.e2.
- 18 Novak I, McIntyre S, Morgan C, *et al.* A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013;**55**:885–910.

doi:10.1111/dmcn.12246

19 Ruchelsman DE, Pettrone S, Price AE, *et al.* Brachial plexus birth palsy: an overview of early treatment considerations. *Bull NYU Hosp Jt Dis* 2009;**67**:83–9.

20 Gobets D, Beckerman H, de Groot V, *et al.* Indications and effects of botulinum toxin A for obstetric brachial plexus injury: a systematic literature review. *Dev Med Child Neurol* 2010;**52**:517–28. doi:10.1111/j.1469-8749.2009.03607.x

21 Brochard S, Alter K, Damiano D. Shoulder strength profiles in children with and without brachial PLEXUS PALSY. *Muscle Nerve* 2014;**50**:60–6. doi:10.1002/mus.24099

22 Ezaki M, Malungpaishrope K, Harrison RJ, *et al.* Onabotulinum toxinA injection as an adjunct in the treatment of posterior shoulder subluxation in neonatal brachial plexus palsy. *J Bone Joint Surg Am* 2010;**92**:2171–7. doi:10.2106/JBJS.I.00499

23 Michaud LJ, Louden EJ, Lippert WC, *et al.* Use of botulinum toxin type A in the management of neonatal brachial plexus palsy. *PM R* 2014;**6**:1107–19. doi:10.1016/j.pmrj.2014.05.002

24 Shin YB, Shin MJ, Chang JH, *et al.* Effects of Botulinum Toxin on Reducing the Co-contraction of Antagonists in Birth Brachial Plexus Palsy. *Ann Rehabil Med* 2014;**38**:127–31. doi:10.5535/arm.2014.38.1.127

25 Bourseul J-S, Molina A, Lintanf M, *et al.* Early Botulinum Toxin Injections in Infants With Musculoskeletal Disorders: A Systematic Review of Safety and Effectiveness. *Arch Phys Med Rehabil* Published Online First: 27 December 2017. doi:10.1016/j.apmr.2017.11.013

26 Williams SA, Reid S, Elliott C, *et al.* Muscle volume alterations in spastic muscles immediately following botulinum toxin type-A treatment in children with cerebral palsy. *Dev Med Child Neurol* 2013;**55**:813–20. doi:10.1111/dmcn.12200

27 Pons C, Sheehan FT, Im HS, *et al.* Shoulder muscle atrophy and its relation to strength loss in obstetrical brachial plexus palsy. *Clin Biomech (Bristol, Avon)* 2017;**48**:80–7. doi:10.1016/j.clinbiomech.2017.07.010

28 Kamath S, Venkatanarasimha N, Walsh MA, *et al.* MRI appearance of muscle denervation. *Skeletal Radiology* 2008;**37**:397–404. doi:10.1007/s00256-007-0409-0

29 Bialocerkowski A, Kurlowicz K, Vladusic S, *et al.* Effectiveness of primary conservative management for infants with obstetric brachial plexus palsy. *Int J Evid Based Healthc* 2005;**3**:27–44. doi:10.1111/j.1479-6988.2005.00020.x

30 Justice D, Rasmussen L, Di Pietro M, *et al.* Prevalence of Posterior Shoulder Subluxation in Children With Neonatal Brachial Plexus Palsy After Early Full Passive Range of Motion Exercises. *PM R* 2015;**7**:1235–42. doi:10.1016/j.pmrj.2015.05.013

31 Papavasiliou AS, Nikaina I, Foska K, *et al.* Safety of Botulinum Toxin A in Children and Adolescents with Cerebral Palsy in a Pragmatic Setting. *Toxins (Basel)* 2013;**5**:524–36. doi:10.3390/toxins5030524

32 Albavera-Hernández C, Rodríguez JM, Idrovo AJ. Safety of botulinum toxin type A among children with spasticity secondary to cerebral palsy: a systematic review of randomized clinical trials. *Clin Rehabil* 2009;**23**:394–407. doi:10.1177/0269215508099860

33 Dahan-Oliel N, Kasaai B, Montpetit K, *et al.* Effectiveness and safety of botulinum toxin type a in children with musculoskeletal conditions: what is the current state of evidence? *Int J Pediatr* 2012;**2012**:898924. doi:10.1155/2012/898924

34 Desiato MT, Risina B. The role of botulinum toxin in the neuro-rehabilitation of young patients with brachial plexus birth palsy. *Pediatr Rehabil* 2001;**4**:29–36.

35 Fortuna R, Vaz MA, Youssef AR, *et al.* Changes in contractile properties of muscles receiving repeat injections of botulinum toxin (Botox). *J Biomech* 2011;**44**:39–44. doi:10.1016/j.jbiomech.2010.08.020

36 Schroeder AS, Ertl-Wagner B, Britsch S, *et al.* Muscle biopsy substantiates long-term

- 1
2
3 MRI alterations one year after a single dose of botulinum toxin injected into the lateral
4 gastrocnemius muscle of healthy volunteers. *Mov Disord* 2009;**24**:1494–503.
5 doi:10.1002/mds.22661
6
7 37 H Kozin S. Correlation Between External Rotation of the Glenohumeral Joint and
8 Deformity after Brachial Plexus Birth Palsy. *Journal of pediatric orthopedics* 2004;**24**:189–
9 93. doi:10.1097/01241398-200403000-00011
10 38 Lippert WC, Mehlman CT, Cornwall R, *et al.* The intrarater and interrater reliability
11 of glenoid version and glenohumeral subluxation measurements in neonatal brachial plexus
12 palsy. *J Pediatr Orthop* 2012;**32**:378–84. doi:10.1097/BPO.0b013e31825611bd
13 39 Waters PM, Smith GR, Jaramillo D. Glenohumeral deformity secondary to brachial
14 plexus birth palsy. *J Bone Joint Surg Am* 1998;**80**:668–77.
15 40 Friedman RJ, Hawthorne KB, Genez BM. The use of computerized tomography in the
16 measurement of glenoid version. *J Bone Joint Surg Am* 1992;**74**:1032–7.
17 41 Brochard S, Mozingo JD, Alter KE, *et al.* Three dimensionality of gleno-humeral
18 deformities in obstetrical brachial plexus palsy. *J Orthop Res* 2016;**34**:675–82.
19 doi:10.1002/jor.23049
20 42 Curtis C, Stephens D, Clarke HM, *et al.* The active movement scale: an evaluative tool
21 for infants with obstetrical brachial plexus palsy. *J Hand Surg Am* 2002;**27**:470–8.
22 43 Bialocerowski A, O'shea K, Pin TW. Psychometric properties of outcome measures
23 for children and adolescents with brachial plexus birth palsy: a systematic review. *Dev Med*
24 *Child Neurol* 2013;**55**:1075–88. doi:10.1111/dmcn.12194
25 44 Greaves S, Imms C, Dodd K, *et al.* Development of the Mini-Assisting Hand
26 Assessment: evidence for content and internal scale validity. *Dev Med Child Neurol*
27 2013;**55**:1030–7. doi:10.1111/dmcn.12212
28 45 Hogendoorn S, van Overvest KLJ, Watt I, *et al.* Structural changes in muscle and
29 glenohumeral joint deformity in neonatal brachial plexus palsy. *J Bone Joint Surg Am*
30 2010;**92**:935–42. doi:10.2106/JBJS.I.00193
31 46 Fehlings D, Novak I, Berweck S, *et al.* Botulinum toxin assessment, intervention and
32 follow-up for paediatric upper limb hypertonicity: international consensus statement. *Eur J*
33 *Neurol* 2010;**17 Suppl 2**:38–56. doi:10.1111/j.1468-1331.2010.03127.x
34 47 Anguelova GV, de Vlugt E, Vardy AN, *et al.* Cocontraction measured with short-
35 range stiffness was higher in obstetric brachial plexus lesions patients compared to healthy
36 subjects. *Journal of Biomechanics* 2017;**63**:192–6. doi:10.1016/j.jbiomech.2017.08.015
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

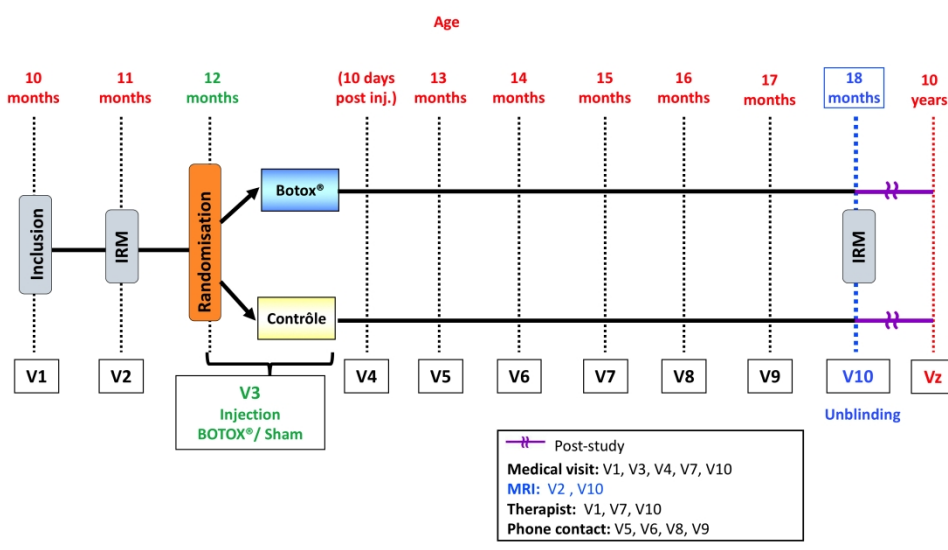


Figure 1 : Flow chart

1360x789mm (72 x 72 DPI)

Supplementary file 1: Botulinum toxin injections procedure

The Botox will be injected intramuscularly by transcutaneous approach using a 27 gauge, 25mm long sterile needle. This information can be added in the main text.

In the study protocol, we specifically described the procedure to ensure standardization (provided below). We propose to add this as supplementary material in the article.

“One hour before the injections, preliminary ultrasound identification will be carried out so that anaesthetic cream can be applied to the skin over the future injection sites.

For all injections, the child will be held in the arms of one of his/her parents.

Teres Major:

The parent will recline on the examination table, with the baby in his/her arms facing him/her (“belly to belly”). The sleep mask will be positioned on the parent at this time to ensure the blinding. The paediatric auxiliary can help to hold the child if necessary. The teres major muscle will be located by ultrasound, and the skin disinfected. Injection and/or simulation of the injection of the muscle (sham procedure) will be performed using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.

Subscapularis:

The baby will remain in the arms of the parent, “belly to belly”. The arm on the injected side will be placed in maximum abduction by the paediatric auxiliary. The subscapularis muscle will be identified by ultrasound. The skin will be disinfected. Injection and/or simulation of the injection of the muscle will be performed (sham procedure) using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.

Pectoralis Major:

The face mask will be removed so that the parent can change position and the position of the baby can be changed. The parent will sit in a chair with the child on his/her lap in a sitting position. The face mask will be repositioned. The pectoralis major muscle will be identified by ultrasound. The skin will be disinfected. Injection and/or simulation of the injection of the muscle (sham procedure) will be performed using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.”



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P5
	2b	All items from the World Health Organization Trial Registration Data Set	P5
Protocol version	3	Date and version identifier	P5
Funding	4	Sources and types of financial, material, and other support	P19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1 and 19
	5b	Name and contact information for the trial sponsor	P5 and 19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P11 and 13-14

Introduction

1	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P3-4
2				
3				
4		6b	Explanation for choice of comparators	P4
5				
6	Objectives	7	Specific objectives or hypotheses	P4-5
7				
8	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P5
9				
10				
11				
12	Methods: Participants, interventions, and outcomes			
13				
14	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P5
15				
16				
17	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P6
18				
19				
20	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P8-9
21				
22				
23		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA_
24				
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P14
27				
28				
29		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P9
30				
31	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P11-13
32				
33				
34				
35				
36				
37	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P6-7 fig1, table1
38				
39				
40				
41				
42				
43				
44				
45				
46				

1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including P14-15
 2 clinical and statistical assumptions supporting any sample size calculations
 3

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size P5
 5
 6

7 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:
 9

10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any P7-8
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 13 or assign interventions
 14
 15

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, P8
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 18 mechanism
 19

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to P8
 21 interventions
 22
 23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome P8
 25 assessors, data analysts), and how
 26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's P10
 28 allocated intervention during the trial
 29
 30

31 **Methods: Data collection, management, and analysis**

32
 33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related P8, P11-13
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 36 Reference to where data collection forms can be found, if not in the protocol
 37
 38

39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be P15
 40 collected for participants who discontinue or deviate from intervention protocols
 41
 42

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P13-14
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P14-15
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P14-15
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P15
11				
12				
13				
14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P11
17				
18				
19				
20				
21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P7, P10, P13
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P13-14
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P5
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P5
38				
39				
40				
41				
42				
43				
44				
45				
46				

1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P6
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P13
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P19
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P13-14
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P19
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	SM for editor
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA
35				
36				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.

BMJ Open

Effectiveness and safety of early intramuscular botulinum toxin injections to prevent shoulder deformity in babies with brachial plexus birth injury (POPB-TOX), a randomized controlled trial: study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032901.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Aug-2019
Complete List of Authors:	Pons, Christelle; Fondation ILDYS; Laboratory of Medical Information Processing, INSERM UMR 1101 Eddi, Dauphou; CHRU de Brest Le Gal, G.; Centre Hospitalier Universitaire de Brest, Centre for Clinical Investigation INSERM CIC 1412 Garetier, Marc; Hopital d'Instruction des Armees Clermont-Tonnerre, Radiology; Laboratory of Medical Information Processing, INSERM UMR 1101 Ben Salem, Douraied; CHRU de Brest, Radiology; Laboratory of Medical Information Processing, INSERM UMR 1101 Houx, Laetitia; Centre Hospitalier Universitaire de Brest, Physical Medicine and Rehabilitation Department, Brest, France Fitoussi, Franck; Hopital Armand-Trousseau Quintero, Nathaly; Hopitaux de Saint-Maurice, Physical Medicine and Rehabilitation Brochard, Sylvain; Centre Hospitalier Universitaire de Brest, Physical Medicine and Rehabilitation Department, Brest, France; Laboratory of Medical Information Processing, INSERM UMR 1101 POPBtox group, POPBtox group
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Paediatrics
Keywords:	brachial plexus birth injury, Shoulder < ORTHOPAEDIC & TRAUMA SURGERY, botulinum toxin, bone deformity

SCHOLARONE™
Manuscripts

1
2
3 **Effectiveness and safety of early intramuscular botulinum toxin injections**
4 **to prevent shoulder deformity in babies with brachial plexus birth injury**
5 **(POPB-TOX), a randomized controlled trial: study protocol**
6
7
8
9

10
11 Christelle Pons MD, PhD^{1,2,3} ; Dauphou Eddi PhD⁴ ; Grégoire le Gal MD, PhD⁵ ; Marc
12 Garetier MD^{2,6} ; Douraied Ben Salem MD, PhD^{2,7,8} ; Laetitia Houx MD^{1,2,3} ; Franck Fitoussi
13 MD, PhD⁹ ; Nathaly Quintero MD¹⁰ ; Sylvain Brochard MD, PhD^{1,2,3,8} ; and the POPB-TOX
14 Group
15

- 16
17
18
19 1 Pediatric rehabilitation, Fondation ILDYS, Brest, France
20 2 Laboratory of Medical Information Processing, INSERM 1101, Brest, France
21 3 PMR department, Brest CHRU, Brest, France
22 4 DRCI, Brest CHRU, Brest, France
23 5 Centre for Clinical Investigation INSERM CIC 1412, Brest CHRU, Brest, France
24 6 Radiology department, hôpital d'Instruction des Armées Clermont-Tonnerre, Brest,
25 France
26 7 Radiology department, Brest CHRU, Brest, France
27 8 Université de Bretagne Occidentale, Brest, France
28 9 CHU Paris Est - Hôpital d'Enfants Armand-Trousseau; Paris, France
29 10 Hôpitaux de St Maurice, St Maurice, France
30
31

32
33 Corresponding author

34 Christelle Pons

35 SSR pédiatrique brestois, Fondation ILDYS, rue Alain Colas, 29200 Brest

36 Tel : 0256310145

37 christelle.ponsbecmeur@ildys.org
38
39

40 Word count : 5441
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ABSTRACT

Introduction

In children with Brachial Plexus Birth Injury (BPBI), denervation of the shoulder muscles leads to bony deformity in the first months of life, reducing active and passive range of motion (ROM), and causing activity limitation. The aim of this multicentre randomised controlled trial is to evaluate the effectiveness of botulinum toxin injections (BTI) in the shoulder internal rotator muscles of 12 month-old babies in limiting the progression of posterior subluxation of the glenohumeral joint, compared with a sham procedure mimicking BTI. The secondary aims are to evaluate the effectiveness of BTI in (I) limiting the progression of glenoid retroversion and 3D deformity and (II) improving shoulder range of motion and upper limb function, as well as to confirm the tolerance of BTI.

Methods and analysis

Sixty-two babies with unilateral BPBI and a risk of posterior humeral head subluxation will be included. Only those with at least 7% posterior subluxation of the humeral head compared with the contralateral shoulder on the MRI will be randomized to one of two groups: "BTI" and "Sham". The BTI group will receive BOTOX injections at the age of 12 months in the internal shoulder rotator muscles (8UI/kg). The sham group will undergo a sham BTI procedure. Both groups will undergo repeated shoulder MRI at 18 months of age to quantify changes in the percentage of posterior migration of the humeral head (primary outcome), glenoid version and 3D bone deformity. Clinical evaluations (passive shoulder range of motion, Active Movement Scale) will be carried out at baseline and 15 and 18 months of age. The mini Assisting Hand Assessment will be rated between 10 and 11 months, and at 18 months of age. Adverse events will be recorded at least monthly for each child.

Ethics and dissemination

Full ethical approval for this study has been obtained. The findings will be disseminated in peer-reviewed publications.

Trial registration number

EudraCT: 2015-001402-34 in European Clinical Trial database; NCT03198702 in Clinical Trial database.

Keywords: Brachial Plexus Birth Injury, shoulder, botulinum toxin, bone deformity

Strengths and limitations of this study

1
2
3 34 We expect botulinum toxin injections to limit shoulder deformity and improve shoulder range
4
5 35 of motion in children with brachial plexus birth injury.
6
7 36 This randomized controlled study will evaluate the safety and effectiveness of early botulinum
8
9 37 toxin injections in the shoulder internal rotator muscles.
10
11 38 The effect on bony deformities (glenohumeral subluxation and glenoid version), active and
12
13 39 passive range of motion and upper limb function will be evaluated.
14
15 40
16 41

42 INTRODUCTION

43
44
45 Brachial Plexus Birth Injury (BPBI) refers to injury to one or more cervical nerve roots
46
47 (C5-C8) and/or the first thoracic nerve root (T1), usually caused by traction during a difficult
48
49 birth. The incidence is around 1.5 per 1000 births[1]. In one third of cases, nerve recovery is
50
51 incomplete or absent[1,2], resulting in permanent impairment which in turn may lead to activity
52
53 limitation and participation as defined by the International Classification of Functioning[3,4].

54
55 BPBI greatly affects the musculoskeletal development of the shoulder complex[3,5,6].
56
57 Deformities occur very early, within the months following birth[6–8], and gradually worsen
58
59 with the child's growth[7,9]. Bony and joint deformities are caused by the partial denervation
60
61 of the shoulder muscles, which results in an imbalance of the forces acting on the glenohumeral
62
63 joint [6,10]. In particular, there is often a dominance of the internal rotator muscles [11,12].
64
65 Excess glenoid retroversion is typical, along with deformation of the glenoid fossa. This allows
66
67 posterior migration of the humeral head to occur, eventually progressing to complete
68
69 subluxation[6–8,13]. These deformities increase the risk of early degenerative joint changes
70
71 and pain during childhood and adulthood[14,15]. Active and passive shoulder range of motion
72
73 (ROM) are also reduced, causing a vicious circle in which the muscles cannot contract
74
75 effectively because of the bony deformities and altered lever arms [9]. These changes reduce
76
77 the functional capacity and quality of life of children with BPBI[16,17].

78
79 Botulinum toxin injections (BTI) are a common treatment to reduce muscle activity. This
80
81 treatment is mostly used to treat spasticity in children, particularly in the case of cerebral
82
83 palsy[18], however it may also be useful in children with BPBI[19,20], combined with other
84
85 treatments such as physiotherapy, occupational therapy, orthoses and, in some cases, surgery.
86
87 The dominant internal shoulder rotator muscles are often targeted in order reduce the strength
88
89 imbalance between agonist and antagonist muscles [21]. One study suggested that BTI might
90
91 be useful to reduce posterior subluxation or dislocation of the shoulder in babies with BPBI[22].

1
2
3 69 BTI could also improve passive and active shoulder ROM and functional capacity[20,23,24].
4
5 70 BTI is a minimally invasive treatment that is well tolerated in young children [25]. When used
6
7 71 prior to surgery, it could avert or reduce the complexity of surgical secondary orthopaedic
8
9 72 procedures (e. g. subscapularis release, latissimus dorsi and teres major transfers) [22,23].
10
11 73 Although the results of studies of early BTI for BPBI are encouraging, most studies are
12
13 74 retrospective, include small samples and do not have a control group. The current level of
14
15 75 evidence is thus insufficient to make robust conclusions regarding the effectiveness of
16
17 76 botulinum toxin injections in children with brachial plexus birth injury.

17 77 Randomized controlled trials to evaluate the efficacy of early BTI and to confirm its
18
19 78 tolerance in children with BPBI are therefore now warranted. With regard to the control
20
21 79 treatment, a sham procedure mimicking BTI without injection is ethically more appropriate
22
23 80 than an invasive placebo procedure because of the young age of the children involved.

24 81

25 82 **AIMS and HYPOTHESES**

26 83

27 84 **Aims**

28
29 85 The main aim of this study is to evaluate the effectiveness of BTI in the internal shoulder
30
31 86 rotator muscles of 12 month-old babies in limiting the progression of posterior subluxation of
32
33 87 the glenohumeral joint.

34
35 88 The secondary aims are (I) to compare the effectiveness of BTI with a sham treatment
36
37 89 in limiting the progression of glenoid retroversion and three-dimensional glenoid deformity;
38
39 90 (II) to compare the effectiveness of BTI with a sham treatment in improving active and passive
40
41 91 joint range of motion and upper limb function; (III) to assess the tolerance of BTI in babies with
42
43 92 BPBI; (IV) to evaluate the effects of BTI on muscle growth and fatty infiltration of the injected
44
45 93 muscles, as well as muscle volume balance around the shoulder, and (V) to determine the long-
46
47 94 term effect of BTI on frequency and type of surgical interventions.

48 95

49 96 **Hypotheses**

50
51 97 Our primary hypothesis is that BTI will limit posterior subluxation of the glenohumeral
52
53 98 joint in the BTI group compared with the Sham group.

54
55 99 We further hypothesize that the progression of glenoid retroversion and three-
56
57 100 dimensional deformities will be reduced, that active and passive range of motion will be
58
59 101 increased, and that number of secondary surgical interventions will be reduced in the BTI group
60
102 compared with the Sham group. The robust design of this study will confirm the results of

1
2
3 103 previous un-controlled studies, providing a strong level of evidence for BTI treatment. We also
4 104 hypothesize that BTI will be well tolerated by the babies [25]. With regards to morphological
5 105 changes following BTI, we expect slight atrophy to occur in the injected muscles, with some
6 106 fatty infiltration [26] but no change in non-injected muscles, leading to an improvement in the
7 107 volume balance of agonist and antagonist muscles [27].
8
9
10
11
12

13 109 **METHODS/DESIGN**

14 110 15 111 16 112 17 113 **Design**

18 114 A randomised, multicentre, double-blind, controlled, parallel group, superiority trial
19 115 will be performed (version 3, 17.01.2018). One group will receive BTI and the other will
20 116 undergo a Sham procedure.
21
22
23
24

25 117 26 118 **Ethics**

27 119 Full ethical approval for this study has been obtained by the ethical committee Ouest 1
28 120 of Tours and Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM).
29 121 The trial has been registered in the European Clinical Trial database (EudraCT: 2015-001402-
30 122 34) and Clinical Trial database (NCT03198702). All families will be given a written
31 123 information letter detailing the study and parents or guardians will sign informed consent prior
32 124 to the child's inclusion. Any modification or amendment to the protocol will be submitted to
33 125 the ethical committees and ANSM for approval. After approval, investigators and trial
34 126 participants will be informed of the changes by letter or email. All trial databases will also be
35 127 updated.
36
37
38
39
40
41
42
43
44

45 128 46 129 **Recruitment**

47 130 The sponsor is CHRU Brest. Babies will be recruited from six French hospitals (CHRU
48 131 Brest, Centre de Réadaptation pour enfant Flavigny-sur-Moselle, Hôpital National de Saint
49 132 Maurice, CHU Saint-Etienne, CHU Nîmes, CHU Rennes), all of which are specialized in the
50 133 management of children with brachial plexus palsy and have access to MRI. All doctors
51 134 involved are skilled in BTI. Hospitals were selected by the study coordinator and sponsor based
52 135 on their responses to a feasibility questionnaire. It is predicted that during the 29 months of
53 136 inclusion, around 2590 children will be born with BPBI in France [1], of whom 466 will left
54 137 with sequelae[1]. This study will recruit 13.5% of these babies (62 patients over 29 months).
55
56
57
58
59
60

1
2
3 137 maternity units about the study, and flyers and posters will be displayed in the reception areas
4
5 138 of clinics and maternity units. Clinicians will be asked to refer babies with OBBP to their nearest
6
7 139 participating specialist centre and they will be provided with information leaflets to give to the
8
9 140 parents. External advertising will also include a webpage on the Brest CHRU website. If
10
11 141 inclusion goals are not achieved, more centers will be asked to participate.

12 142 A rehabilitation physician and/or a surgeon in each participating specialist centre will
13
14 143 identify potentially eligible babies for the study during routine consultations. The protocol will
15
16 144 be explained and proposed to parents of babies between 10 and 11 months of age who have a
17
18 145 high risk of bony deformity. An information letter will be given to the parents. If the parents
19
20 146 agree to their baby's participation, and the baby fulfils the inclusion criteria, he or she will be
21
22 147 enrolled in the study for 7 months.

23 148 The inclusion criteria are: male or female babies aged between 10 and 11 months with
24
25 149 unilateral BPBI; at least one of the following risk factors for posterior subluxation of the
26
27 150 humeral head: 10° less passive external ROM of the affected shoulder compared with the
28
29 151 contralateral shoulder and/ or a score below 6 on the Active Movement Scale (AMS) for
30
31 152 shoulder external rotation and abduction, elbow flexion or supination; whose parents or
32
33 153 guardians have signed the consent form. Babies with bilateral BPBI, microsurgery or shoulder
34
35 154 muscle surgery planned between 12 and 18 months of age, contraindications to the use of
36
37 155 botulinum toxin (hypersensitivity to botulinum toxin or the excipients used, or myasthenia),
38
39 156 contraindications to MRI (pace maker, metal implants, foreign metal body in the eye, etc.), MRI
40
41 157 not possible in the Paediatric Day Hospital setting because of contraindications to the
42
43 158 premedication protocol or organizational constraints, parents inapt to provide consent for the
44
45 159 participation of their child, or parents under the age of 18 years, will be excluded.

46 160

47 161 **Study procedure**

48 162 The study procedure is described in figure 1 and table 1.

49 163 At visit 1 (between 10 and 11 months of age), the parents or guardians will sign the
50
51 164 informed consent form and the baby will be included. The physician or surgeon will carry out
52
53 165 a physical examination and will collect socio-demographic data including history of BPBI in a
54
55 166 brother or sister, overweight or obesity of the mother, any medical conditions during the
56
57 167 pregnancy (e.g. gestational diabetes), the birth procedure (caesarean section, vaginal delivery
58
59 168 with epidural, induction of labour, instrumental delivery, shoulder dystocia, term and duration),
60
61 169 birth weight and length, and APGAR score.

1
2
3 170 Visit 2 (at 11 months of age) will involve MRI to confirm the diagnosis of bony
4
5 171 deformity (the humeral head on the involved side must be at least 7% more posterior than the
6
7 172 humeral head on the contralateral side). Once confirmed, randomisation will be carried out.
8
9 173 This will ensure that only babies with verified glenohumeral deformity are included, since
10
11 174 clinical tests are not sufficiently sensitive to confirm this. Babies who do not fulfil this
12
13 175 randomisation criterion will be withdrawn from the study and will pursue the usual medical
14
15 176 follow-up. The parents will be informed of the results of the MRI within 10 days by means of
16
17 177 a telephone call from the research investigators. The randomisation will allocate the babies to
18
19 178 one of two treatment groups (each with the same number of babies): BTI group and sham group.

18 179 Visit 3 (12 months +/-15 days of age) will include treatment (BTI or sham procedure).

20 180 Both groups will then attend seven follow up visits: visit 4 will be carried out ten days
21
22 181 after treatment administration, and visits 6-10 will be carried out each month until 18 months
23
24 182 of age. Visits 1, 7 and 10 will involve a standardized clinical examination by occupational
25
26 183 therapists or physiotherapists and visits 5, 6, 8 and 9 will involve a telephone call from a
27
28 184 member of the study team.

29 185 Un-blinding will be performed at visit 10 (18-months of age). Following un-blinding,
30
31 186 the baby will attend a follow-up visit at 24 months then yearly follow-up visits, as is usual
32
33 187 practice. The aim of this is to determine the safety of the use of botulinum toxin before the age
34
35 188 of two years (after which there is a marketing authorization for children with cerebral palsy),
36
37 189 and to compare the frequency and complexity of surgical interventions between groups until
38
39 190 the age of 10 years.

39 191

41 192 **MRI**

42
43 193 The babies included in this study will undergo MRI of both shoulders at visits 2 and 10
44
45 194 (at 11 and 18 months of age). A three-dimensional, T1-weighted gradient-echo sequence will
46
47 195 be used. This anatomical sequence highlights bones and muscles, including denervated
48
49 196 muscles[28]. The child will lie supine with his/her arms in neutral and hands pronated. The T1
50
51 197 protocol[27] will be adapted in each centre depending on the type of MRI scan they have.
52
53 198 Acquisition time will be less than 5 minutes per shoulder. No contrast injection will be required.
54
55 199 Images will have to include sternum and spine medially, the whole deltoid laterally and the
56
57 200 spine of the scapula at the back down. Premedication (sedation or general anaesthetic) will be
58
59 201 necessary for both MRI exams, at 11 and 18 months of age. The premedication will be adapted
60
202 to the clinical status of each child and the customs of each centre. After premedication, the child
203 will be monitored by a paediatrician in the day hospital of each centre using a validated protocol.

204

205 **Randomisation process and blinding**

206 Randomisation will be carried out using centralised computer randomisation by Internet,
207 according to the usual procedures in effect at Brest Regional University Hospital. After MRI
208 confirmation that the baby fulfils the randomisation criterion (visit 2), randomisation will be
209 performed by the study investigator on the day of the injection visit (visit 3, 12 months of age).
210 Randomization will be carried out via a specific dedicated website ([https://chu-brest.hugo-
211 online.fr/CSOnline/](https://chu-brest.hugo-online.fr/CSOnline/)). This website is available 24 hours a day.

212 Stratification will be carried out by centre and by microsurgery prior to inclusion, since early
213 surgery could influence the progression of bony deformity. Only the physician who will
214 perform the BTI and the pharmacist will receive the email specifying the randomization arm of
215 each baby. Neither the parents or guardians, nor the clinical and radiological evaluators will be
216 aware of the treatment administered. The doctors carrying out the BTI will not take part in
217 subsequent visits, to ensure the blinding of the examiner. A central analysis of MRI data will
218 be carried out in order to ensure blinding of the evaluator to the primary outcome measure.

219

220 **Study Treatments**

221 **BTI procedure**

222 The botulinum toxin that will be used in the study is BOTOX (Allergan, Dublin,
223 Ireland). Doses will be injected into the pectoralis major, subscapularis and teres
224 major/latissimus dorsi muscles in a single site for each muscle on one occasion (visit 3:
225 12months +/- 15 days of age). These muscles have been the target of BTI treatment to prevent
226 the progression of humeral head subluxation and to improve active and passive shoulder ROM
227 in previous studies of children with BPBI[22]. Following reconstitution, the toxin will be
228 injected intramuscularly using a transcutaneous approach with a 27 gauge, 25mm long sterile
229 needle. Ultrasound guidance will be used to identify the muscles. A detailed protocol has been
230 written to ensure standardization of the procedure (supplementary file 1). The chosen doses are
231 based on data in the literature in children and babies with BPBI[20,22,23]: a total of 8U/kg will
232 be injected (2U/kg in subscapularis, 3U/kg in pectoralis major and 3U/kg in teres
233 major/latissimus dorsi). Because there is no marketing authorisation for the use of botulinum
234 toxin in children under the age of two years, the chosen doses are smaller than the maximal
235 doses authorized for the treatment of spasticity in older children with cerebral palsy. Moreover,
236 the doses chosen correspond with doses used in previous studies. A standardized protocol for
237 the prevention and treatment of induced pain and post-injection pain will be systematically

1
2
3 238 used. This will involve the administration of topical anaesthesia (such as EMLA) and
4
5 239 paracetamol (dose according to the baby's weight) one hour prior to the injection. Distraction
6
7 240 techniques will be used during the injection. The parents will be instructed to bring reassuring,
8
9 241 familiar objects belonging to the baby (e.g. soft toy, pacifier, nursery rhyme, music). In order
10
11 242 to standardize practices and to ensure maximum safety and efficacy, staff from the different
12
13 243 centres will all be trained in BTI of the shoulder muscles using ultrasound guidance in babies
14
15 244 prior to participating in the study. Only physicians with at least five years of experience in BTI
16
17 245 will be authorized to perform the injections.

18 19 247 Sham procedure

20
21 248 The aim of the Sham procedure is to mimic the BTI and to maintain the blinding of the
22
23 249 research team and the parents or guardians. The same anesthetic procedure will be carried out
24
25 250 as for BTI. The physician performing the injection will prepare a syringe containing
26
27 251 physiological saline solution 10 minutes prior to the Sham procedure. The procedure will be
28
29 252 simulated with ultrasound and use of a blunt needle (that will not penetrate the skin) on the sites
30
31 253 selected for injection. All sites will be covered with adhesive dressings and tincture of betadine,
32
33 254 as for the BTI. With regard to the control treatment, a sham procedure mimicking BTI without
34
35 255 injection is ethically more appropriate than an invasive placebo procedure because of the young
36
37 256 age of the children involved.

38 258 Rehabilitation and medical follow up

39
40 259 To ensure comparability, the babies in both groups will receive 2 sessions of physiotherapy per
41
42 260 week. Physiotherapy will be standardized and based on evidence from studies of early
43
44 261 physiotherapy management [29,30]. It will involve: (I) maintaining passive range of motion of
45
46 262 all the upper limb joints, in particular shoulder external rotation, elbow extension and forearm
47
48 263 pronation; (II) active-assisted and active movements of the involved shoulder; (III) bimanual
49
50 264 functional training; (IV) training to integrate the involved upper limb in functional activities
51
52 265 and (V) parent education: child positioning, stimulation of active movement and function at
53
54 266 home. A standardized medical prescription will be given. An information and advice letter will
55
56 267 be given to the physiotherapists via the parents to standardize and optimise physiotherapy
57
58 268 treatment. Advice will be given to parents regarding exercises to carry out at home, they will
59
60 269 be taught to encourage use of the upper limb at home. All other medical treatment and
270
271 270 rehabilitation will be carried out according to usual procedures.

1
2
3 272 **Adverse events**

4
5 273 Adverse events relating to the use of botulinum toxin

6 274 The secondary effects of BTI are mostly mild, temporary and related to the dose and the
7
8 275 injection site. Local reactions such as contusions or pain at the injection site may occur, or
9
10 276 excessive, localised muscle weakness. Systemic effects are rare and include generalised allergic
11
12 277 reactions and effects related to product diffusion (rash, erythema, pruritus, anaphylactic
13
14 278 reaction, flu-like syndrome, headaches, dizziness, fever, shivering, hypertension, and
15
16 279 abdominal pain and dry mouth). Exceptionally, serious effects have been observed, a type of
17
18 280 excessive muscle weakness, dysphagia and aspiration pneumonia, however these occurred
19
20 281 principally when the recommended doses were not respected[25,31–33]. The safety of BTI in
21
22 282 infants under two years of age was shown to be good in a recent systematic review[25] and the
23
24 283 tolerance of this treatment also seems good in this population[22,33,34]. The specific effects
25
26 284 on muscle structure and the contractile properties of muscles are, however, poorly understood.
27
28 285 Moderate muscle atrophy and fatty infiltration may occur following injections[26,35,36].

27 286 According to the usual procedure used for the injection of botulinum toxin in each
28
29 287 hospital, an information sheet will be provided to each patient explaining the action to be taken
30
31 288 in the case of an adverse effect. According to this procedure, parents will be instructed to
32
33 289 urgently consult their general practitioner or the pediatric emergency department in the case of
34
35 290 the occurrence of a serious adverse effect such as generalized weakness or cardio-respiratory
36
37 291 insufficiency. There is no antidote to botulinum toxin therefore symptomatic treatment will be
38
39 292 administered, if required.

39 293 In the case of a serious adverse event, unblinding will be carried out. If an investigator
40
41 294 wishes to treat the child with aminoglycosides, which are contraindicated in the case of
42
43 295 treatment by botulinum toxin, unblinding will be carried out.

44 296 Parents will be questioned regarding adverse events at 10 days and then monthly
45
46 297 between 12 and 18 months of age using standardized questionnaires that include all possible
47
48 298 side effects.

49 299

50
51 300 Adverse events related to MRI premedication

52
53 301 The risks related to the premedication are the standard risks for the sedation or
54
55 302 anaesthesia of children (gastritis, anticholinergic effects, oxygen desaturation, excessive
56
57 303 sedation). The child will be examined for potential risks during a routine paediatric or
58
59 304 anaesthetic consultation.

60 305

1
2
3 306 Independent Data Monitoring Committee and un-blinding procedure

4
5 307 An independent data safety monitoring Committee (DSMC) comprised of five
6
7 308 independent members will be set up. The purpose of the DSMC will be to provide an
8
9 309 independent evaluation of any adverse events that occur during the research, as well as to
10
11 310 monitor the benefit / risk ratio.

12 311 Should an adverse event that requires different care than that planned in the study occur,
13
14 312 unblinding will be carried out. Unblinding will not be carried out in any other condition.

15 313

16
17 314 **Patient and Public involvement statement**

18
19 315 Patients were not involved in the development of the research, and will not be involved
20
21 316 in the recruitment and conduct of the study. Results of the study will be given to the parents
22
23 317 after the study during a medical consultation in their participating center.

24 318

25 319 **OUTCOME MEASURES**

26 320

27 321 **Primary Outcome**

28
29 322 The primary outcome measure is the change in the percentage of posterior migration of
30
31 323 the humeral head measured on an axial MRI image between 11 months (before the BTI at 12
32
33 324 months) and 18 months of age (6 months post BTI) at visits 2 and 10 (table 1). Posterior
34
35 325 subluxation will be evaluated using the method described by Waters, on an axial MRI slice
36
37 326 taken just below the coracoid process [37–39]. Percentage posterior subluxation will be
38
39 327 calculated in the following manner: a line will be traced from the medial border of the scapula
40
41 328 to the middle of the glenoid fossa. A segment will then be drawn perpendicularly to the line,
42
43 329 from the widest part of the humeral head (AC). The length of the anterior part of this segment
44
45 330 (AB) divided by the (AC) segment will be multiplied by 100 to obtain the percentage migration
46
47 331 of the humeral head. A percentage below 50% indicates posterior migration of the humeral
48
49 332 head. This measurement is quick to carry out and is used in both research and routine clinical
50
51 333 practice in children and babies with BPBI to help preoperative decision making for the type of
52
53 334 intervention and post-operative follow up[6,8,39]. Intra- and inter-rater reliability have been
54
55 335 shown to be excellent, with a 7% estimated measurement error [38]. MRI data will be analysed
56
57 336 centrally (at Brest CHRU) by two trained investigators using the same guidelines in order to
58
59 337 minimise inter-rater variability and to ensure the blinding of the evaluator.

58 338

59 339 **Secondary Outcome Measures**

1
2
3 340 Glenoid retroversion and three-dimensional deformity

4
5 341 The following MRI measurements will be compared at visits 2 and 10 (11 and 18 months
6
7 342 of age) (table 1) to determine the effectiveness of BTI relative to the sham treatment in limiting
8
9 343 the progression of glenoid retroversion and three-dimensional deformity:

10 344 1) 2D glenoid version will be measured on an axial image using Friedman's
11
12 345 technique[40]. This measurement has been validated and is used in clinical practice
13
14 346 and research[10,38].

15 347 2) 3D glenoid version and 3D migration of the humeral will be measured on MRIs
16
17 348 following 3D reconstruction. These original measurements were recently used for
18
19 349 the first time[41] and will provide an evaluation of 3D shoulder deformity and the
20
21 350 effect of BTI on the deformity.

22 351

23
24 352 Passive and active movement and upper limb function

25 353 Three standardized evaluations will be carried out by occupational therapists or
26
27 354 physiotherapists to compare the effect of BTI and the sham treatment on active and passive
28
29 355 joint range of motion and upper limb function. All therapists will undergo training prior to their
30
31 356 involvement in the study in order to ensure the reliability of measures.

32 357 1) Passive shoulder ROM will be measured at the baseline (before the MRI at visit 1,
33
34 358 between 10 and 11 months of age), at visits 7 and 10 (15-months and 18-months of
35
36 359 age visits).

37 360 2) The AMS (Active Movement Scale) will be rated at baseline (before the MRI at visit
38
39 361 1, between 10 and 11 months of age), and at visits 7 and 10 (15-months and 18-
40
41 362 months of age visits). This test evaluates upper limb strength in babies with BPBI
42
43 363 during active movements. Each movement is rated on an 8-point scale from 0 (no
44
45 364 movement) to 7 (complete movement against gravity). It has satisfactory
46
47 365 psychometric properties[42,43] in trained therapists.

48 366 3) The Mini-AHA (Mini-assistive Hand Assessment) will be rated at visit 1 and 10
49
50 367 (baseline and the 18-months of age visits). This functional evaluation measures
51
52 368 bimanual performance during games and tasks. It was designed for children aged
53
54 369 from 8 to 18 months[44].

55 370

56 371 Tolerance

57
58
59
60

1
2
3 372 The parents of the babies in both groups will be questioned at 10 days and each month
4 373 between 12 and 18 months of age using a standardized questionnaire that includes a list of all
5 374 possible side effects of BTI.
6
7

8 375

9
10 376 Changes in muscle structure (BTI group only)

11 377 3D MRI reconstruction[27] and the validated technique described by Hogendoorn et
12 378 al.[45] will be used to respectively evaluate the direct effects of BTI injections on muscle
13 379 volume and fatty infiltration of the shoulder muscles. This evaluation will only be carried out
14 380 in the BTI group.
15
16
17

18 381

19 382 Future surgical interventions

20 383 To determine if BTI reduces the frequency and complexity of surgical interventions in
21 384 the long term, surgical procedures undergone by the children in both groups (recorded during
22 385 routine medical follow-up) will be compared up to the age of 10 years.
23
24
25
26
27

28 386

29 387 **Locations and data management**

30 388 Each centre will manage their own recruitment of babies and organization of MRIs,
31 389 clinical evaluations and treatment. Electronic data will be secured and analyzed in a central
32 390 database managed by the Brest CHRU. Data will be the property of CHRU Brest.
33
34
35

36 391 In accordance with Good Clinical Practice (GCP) guidelines, the sponsor is in charge of
37 392 obtaining agreement from all centers involved in the clinical research, in order to guarantee
38 393 direct access to all the clinical research sites, to all the source data, source documents and all
39 394 the reports for the purpose of Quality Control and audit by the sponsor.
40
41
42

43 395 All information required for the study will be entered in the paper case report forms
44 396 during evaluations, then transferred to the electronic case report form (Clinsigth). Items of
45 397 missing data will be coded. Each centre will be responsible for completing the CRFs for the
46 398 babies enrolled in their centre. Each investigator will receive an instruction document regarding
47 399 the use of this tool. The investigator will be responsible for the accuracy, quality and relevance
48 400 of all the data entered. In addition, the data will be immediately verified as they are entered,
49 401 using consistency checks. The investigator must validate any changes to the values in the CRF.
50 402 These modifications will be subject to an audit trail. A justification can be added when
51 403 applicable, as a comment. Data management and query processing will be carried out by a data
52 404 manager.
53
54
55
56
57
58
59
60

1
2
3 406 A Clinical Research Assistant (CRA) appointed by the sponsor will ensure the good
4
5 407 running of the study, data collection on the paper CRF, data recording in the electronic CRF,
6
7 408 data saving and reporting in accordance with the sponsor's Standardized Operating Procedures
8
9 409 as well as the GCP guidelines and current legislation and laws in force.

10 410 The investigator and the members of his/her team will agree to be available during all the
11
12 411 routine and planned Quality Control visits by the CRA. During these visits, the following will
13
14 412 be audited: signed informed consent, compliance with the study protocol and procedures, data
15
16 413 recorded in the CRF: accuracy, missing data, consistency between these data and their "source"
17
18 414 (medical files, original laboratory results, etc.), product management and investigator file. The
19
20 415 investigators agree to accept the quality assurance audits carried out by the sponsor as well as
21
22 416 the inspections carried out by the competent authorities. All data, documents and reports may
23
24 417 be subject to regulatory audits and inspections. Medical confidentiality cannot be invoked in
25
26 418 opposition to these audits and inspections.

27 419 Any data sent to the sponsor by the investigators (or any other specialised parties) during or
28
29 420 after the biomedical research will be anonymised. These data should not reveal any visibly
30
31 421 accurate names and addresses of enrolled (involved) individuals. Only the first letter of the
32
33 422 subject's name and first name will be saved along with a coded number indicating the order of
34
35 423 inclusion of the subjects. The sponsor will ensure that the parent of each research subject has
36
37 424 given permission in writing for access to personal information about the baby which is strictly
38
39 425 necessary for the quality control of the research.

40 426

41 427 **Sample size and statistical analysis**

42 428 No longitudinal data regarding the progression of bony deformities in children with
43
44 429 BPBI are available in the literature. Only transversal studies have been carried out, indicating
45
46 430 that posterior subluxation is significantly greater on the affected side compared with the healthy
47
48 431 side at the age of 4.8 months (affected side: 32.1% - SD=19.7% vs. healthy side: 49.8% -
49
50 432 SD=7.3%)[6]. The calculation of the number of subjects necessary for this study was based on
51
52 433 a difference of one standard deviation at 12 months, for a standard deviation of 5%.

53 434 In order to guarantee a power of 90%, a sample of 22 babies per group is required, thus a total
54
55 435 of 44. In order to account for babies lost to follow-up (10%) and babies who will not be treated
56
57 436 because of a lack of true subluxation on MRI, 62 babies will be recruited.

58 437 The characteristics of the babies in both groups will be described using means, standard
59
60 438 deviations, medians, quartiles or frequencies. Mean changes in 2D percentage humeral
439 subluxation, 3D humeral subluxation, 2D and 3D glenoid version, the AMS score and passive

1
2
3 440 shoulder ROM will be compared using analysis of covariance (ANCOVA) adjusted on the
4
5 441 initial values. If the hypotheses underlying the analysis of covariance model are not respected,
6
7 442 a non-parametric Wilcoxon test will be used. Shoulder muscle volumes and the mini-AHA
8
9 443 scores will be compared between the groups using a Student test or a non-parametric Mann-
10
11 444 Whitney test, depending on the distribution of the variable of interest. Lastly, the number of
12
13 445 serious and non-serious adverse events, and the degree of fibrosis and fatty infiltration will be
14
15 446 compared between the two groups using a Chi2 test or Fisher's exact test, so as the number of
16
17 447 secondary surgeries. $p < 0.05$ will be considered as statistically significant.

18 448 Data analysis will be carried out on an intention to treat basis by a biostatistician after
19
20 449 blind review and database freezing at the end of the study. No intermediate analysis is planned
21
22 450 during this trial.

23 451

24 452 **DISCUSSION**

25 453 This paper presents the background and design for a multicentre double-blind
26
27 454 randomised controlled trial to evaluate the effectiveness of BTI in the shoulder internal rotator
28
29 455 muscles of 12 months old babies in limiting the progression of posterior subluxation of the
30
31 456 glenohumeral joint, compared with a sham procedure. To our knowledge, this is the first study
32
33 457 with a sufficiently robust methodology to allow conclusions to be based on a high level of
34
35 458 evidence. The study has been approved by national French agencies: the Ministry of Research,
36
37 459 the National Ethical Committee and the National Drug Administration.

38 460 The babies included in the study will all receive 2 sessions of physiotherapy per week.
39
40 461 This choice was made because it is usual practice for babies with BPBI in France. In addition,
41
42 462 studies in other pathologies have shown that physiotherapy potentiates the effectiveness of BTI
43
44 463 [46]. Casting will not be used because it is invasive, has a low level of evidence and comports
45
46 464 a risk of interference with motor development in children who already have central nervous
47
48 465 system abnormalities [47].

49 466 The primary end-point, change in the percentage posterior migration of the humeral
50
51 467 head measured on an axial MRI image between 11 months (before BTI) and 18 months of age
52
53 468 (6 months post BTI), was chosen for its clinical relevance and its strong psychometric properties
54
55 469 compared with clinical or functional assessments in this population. Because the aim of this
56
57 470 study is to evaluate both bone deformity and muscle morphology in order to document the
58
59 471 consequences of BTI in non-spastic muscles and on shoulder muscle balance, we preferred
60
61 472 MRI over ultrasound since MRI can accurately measure both elements while ultrasound cannot.

1
2
3 473 Clinical evaluations carried out before and after BTI will determine the effects of the
4
5 474 treatment on shoulder ROM and functional capacity. Evaluations will be carried out monthly,
6
7 475 with alternate phone contacts and direct consultations in order to limit traveling, promote
8
9 476 adherence and limit losses to follow-up. Because there is currently no marketing authorisation
10
11 477 for BTI in infants under the age of two years, special attention was paid to the safety assessment.
12
13 478 The use of a systematic and detailed questionnaire will yield detailed and specific data,
14
15 479 confirming or not the safety of BTI before the age of two years.

16 480 Glenohumeral dysplasia can occur as early as 3 months of age. If this trial has positive
17
18 481 results and if the safety of BTI performed at 12 months of age in children with BPBI is proven,
19
20 482 studies evaluating the effect of BTI in the limitation of gleno-humeral deformity in younger
21
22 483 babies could be warranted.

23 484 The results of the study could lead to a request for an evaluation by the French National
24
25 485 Agency for Medicines and Health Products Safety (ANSM) for Temporary Recommendation
26
27 486 for Use (TRUs) of botulinum toxin in children with BPBI. It is expected that the results of this
28
29 487 trial will be published in peer-reviewed scholarly journals and international academic
30
31 488 conferences. After the trial, if positive results are highlighted in the children who had botulinum
32
33 489 toxin injections, the treatment will be proposed to the children in the sham group. These
34
35 490 children will however be older and the efficacy may be lower, especially for the bone deformity.

34 491 Conclusion

36 492 The POPBTOX trial is a nationwide, multicentre, randomised, controlled study that will
37
38 493 evaluate the effectiveness of BTI in the internal shoulder rotator muscles of 12 month-old babies
39
40 494 with BPBI in limiting shoulder deformity. Tolerance of the treatment will also be determined.
41
42 495 Existing results from uncontrolled studies suggest this treatment may be effective, however the
43
44 496 present study will allow robust conclusions to be drawn, potentially leading to a change in the
45
46 497 care of these children.

47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1 : Visits and study procedure

Action	Visit 1 : 10 months of age (Inclusion, medical and therapists)	Visit 2: 11 months of age (MRI)	Visit 3: 12 months of age (injection, medical follow-up)	Visit 4: D10 post-injection (medical follow-up)	Visit 5: 13 months of age (Phone call)	Visit 6: 14 months of age (Phone call)	Visit 7 : 15 months of age (medical and therapists)	Visit 8 : 16 months of age (Phone call)	Visit 9 : 17 months of age (Phone call)	Visit 10: 18 months of age (MRI, therapists medical)
<i>Informed consent</i>	X									
<i>Incl./excl. criteria</i>	X									
<i>Medical history</i>	X									
<i>Notification of existing and planned BPBI care</i>	X* →									
<i>Active and passive shoulder range of motion (ROM)</i>	X* →						X			X
<i>Active Movement Scale (AMS)</i>	X* →						X			X
<i>MRI of both shoulders</i>		X								X
<i>mini-AHA Scale</i>	X* →									X
<i>Ramdomisati on criterion</i>		X								
<i>Randomisatio n</i>			X							
<i>BTI Injections or Sham procedure</i>			X							
<i>Notification of care (surgery or other)</i>			X							
<i>Establishment of standardized physiotherapy follw-up</i>			X							
<i>Follow-up of physiotherapy</i>				X	X	X	X	X	X	X

<i>Adverse Events</i>		X	X	X	X	X	X	X	X	X
<i>Unblinding</i>										X

X* → : Will be carried out before MRI

Figure 1 : Flow chart

For peer review only

Acknowledgements

The authors acknowledge Chloe Bureau, Bhushan Borotikar, Céline Dolou, Valentine Guiton, Mélanie Pelouin, Emmanuel Novak for their help in building this project and Johanna Robertson for her help in revising English.

Author contribution

CP and SB conceived the study and defined the original study protocol. NQ, FF, CP and SB developed the intervention parameters. MG and DBS defined the radiological parameters and developed radiological protocols. ED is responsible for the ethics applications and the ethical reporting of the study. FF, NQ, CP, LH, are responsible for recruitment, data collection and implementation of the study. GG is responsible for the study methodology. POPBtox group involves physicians who are only implicated for recruitment and data collection.

All authors have read and approved the final manuscript. CP, ED and SB drafted the final version of this manuscript

Funding

This work was supported by a French national PHRC 15 -282

Disclaimer

The funding body is not involved in the study design, data collection, management, analysis, and interpretation of data. The authors have the ultimate authority over these activities.

Competing interests Dr Pons reports non-financial support from Biogen, outside the submitted work. Dr. Brochard reports non-financial support from Allergan, outside the submitted work. Dr. Le Gal reports other from Portola Pharmaceuticals, other from Boehringer-Ingelheim, other from Pfizer, other from Bristol-Myers Squibb, other from LEO Pharma, other from Daiichi Sankyo, other from Bayer, other from Bayer, other from Pfizer, other from LEO Pharma, other from Sanofi, other from bioMérieux, outside the submitted work.

Sponsor

Brest CHRU, 2 avenue Foch, 29200 Brest, France

Ethics approval

The Ouest 1 Research Ethics Committee (n° 2015-R22) and ANSM (151357A-31) approved the protocol.

Data sharing statement

In accordance with the protocol, the study data will be published.

The POPB-TOX Group included Marianne Alison, Madeleine Aslan, Jennifer Bastien, Gilles Dautel, Floriane Colin, Marion Delpont, Bruno Dohin, Marie Agnes Galloy, Vincent Gautheron Salem Hassan Al Khoury, Pascal Jehanno, Mélanie Kaas, Olivier Prodhomme, Mélanie Porte, Anne Gaele Py, Hélène Rauscent, Emilie Rumilly, Katherine Sanchez Barr, Catherine Tréguier, and Philippe Violas.

REFERENCES

- 1 Chauhan SP, Blackwell SB, Ananth CV. Neonatal brachial plexus palsy: incidence, prevalence, and temporal trends. *Semin Perinatol* 2014;**38**:210–8. doi:10.1053/j.semperi.2014.04.007
- 2 Hoeksma AF, ter Steeg AM, Nelissen RGHH, *et al.* Neurological recovery in obstetric brachial plexus injuries: an historical cohort study. *Dev Med Child Neurol* 2004;**46**:76–83.
- 3 Julka A, Vander Have KL. Shoulder sequelae of neonatal brachial plexus injuries: orthopedic assessment and management. *J Pediatr Rehabil Med* 2011;**4**:131–40. doi:10.3233/PRM-2011-0165
- 4 Zafeiriou DI, Psychogiou K. Obstetrical brachial plexus palsy. *Pediatr Neurol* 2008;**38**:235–42. doi:10.1016/j.pediatrneurol.2007.09.013
- 5 Pearl ML. Shoulder problems in children with brachial plexus birth palsy: evaluation and management. *J Am Acad Orthop Surg* 2009;**17**:242–54.
- 6 Van Gelein Vtringa VM, Jaspers R, Mullender M, *et al.* Early effects of muscle atrophy on shoulder joint development in infants with unilateral birth brachial plexus injury. *Dev Med Child Neurol* 2011;**53**:173–8. doi:10.1111/j.1469-8749.2010.03783.x
- 7 van der Sluijs JA, van Ouwerkerk WJ, de Gast A, *et al.* Deformities of the shoulder in infants younger than 12 months with an obstetric lesion of the brachial plexus. *J Bone Joint Surg Br* 2001;**83**:551–5.
- 8 van der Sluijs JA, van Ouwerkerk WJR, Manoliu RA, *et al.* Secondary deformities of the shoulder in infants with an obstetrical brachial plexus lesions considered for neurosurgical treatment. *Neurosurg Focus* 2004;**16**:E9.
- 9 Waters PM. Update on management of pediatric brachial plexus palsy. *J Pediatr Orthop B* 2005;**14**:233–44.
- 10 Pöyhiä TH, Nietosvaara YA, Remes VM, *et al.* MRI of rotator cuff muscle atrophy in relation to glenohumeral joint incongruence in brachial plexus birth injury. *Pediatr Radiol* 2005;**35**:402–9. doi:10.1007/s00247-004-1377-3
- 11 Crouch DL, Plate JF, Li Z, *et al.* Computational sensitivity analysis to identify muscles that can mechanically contribute to shoulder deformity following brachial plexus birth palsy. *J Hand Surg Am* 2014;**39**:303–11. doi:10.1016/j.jhsa.2013.10.027
- 12 Kleiber T, Popovic N, Bahm J, *et al.* A modeling approach to compute modification of net joint forces caused by coping movements in obstetric brachial plexus palsy. *J Brachial Plex Peripher Nerve Inj* 2013;**8**:10. doi:10.1186/1749-7221-8-10
- 13 Moukoko D, Ezaki M, Wilkes D, *et al.* Posterior shoulder dislocation in infants with neonatal brachial plexus palsy. *J Bone Joint Surg Am* 2004;**86-A**:787–93.
- 14 Partridge C, Edwards S. Obstetric brachial plexus palsy: increasing disability and exacerbation of symptoms with age. *Physiother Res Int* 2004;**9**:157–63.
- 15 Kirkos JM, Kyrkos MJ, Kapetanios GA, *et al.* Brachial plexus palsy secondary to birth injuries. *J Bone Joint Surg Br* 2005;**87**:231–5.
- 16 Hulleberg G, Elvrum A-KG, Brandal M, *et al.* Outcome in adolescence of brachial plexus birth palsy. 69 individuals re-examined after 10–20 years. *Acta Orthop* 2014;**85**:633–

1
2
3 40. doi:10.3109/17453674.2014.964614

4 17 Squitieri L, Larson BP, Chang KWC, *et al.* Understanding quality of life and patient
5 expectations among adolescents with neonatal brachial plexus palsy: a qualitative and
6 quantitative pilot study. *J Hand Surg Am* 2013;**38**:2387-2397.e2.

7 18 Novak I, McIntyre S, Morgan C, *et al.* A systematic review of interventions for
8 children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013;**55**:885–910.
9 doi:10.1111/dmcn.12246

10 19 Ruchelsman DE, Pettrone S, Price AE, *et al.* Brachial plexus birth palsy: an overview
11 of early treatment considerations. *Bull NYU Hosp Jt Dis* 2009;**67**:83–9.

12 20 Gobets D, Beckerman H, de Groot V, *et al.* Indications and effects of botulinum toxin
13 A for obstetric brachial plexus injury: a systematic literature review. *Dev Med Child Neurol*
14 2010;**52**:517–28. doi:10.1111/j.1469-8749.2009.03607.x

15 21 Brochard S, Alter K, Damiano D. Shoulder strength profiles in children with and
16 without brachial PLEXUS PALSY. *Muscle Nerve* 2014;**50**:60–6. doi:10.1002/mus.24099

17 22 Ezaki M, Malungpaishrope K, Harrison RJ, *et al.* Onabotulinum toxinA injection as an
18 adjunct in the treatment of posterior shoulder subluxation in neonatal brachial plexus palsy. *J*
19 *Bone Joint Surg Am* 2010;**92**:2171–7. doi:10.2106/JBJS.I.00499

20 23 Michaud LJ, Loudon EJ, Lippert WC, *et al.* Use of botulinum toxin type A in the
21 management of neonatal brachial plexus palsy. *PM R* 2014;**6**:1107–19.
22 doi:10.1016/j.pmrj.2014.05.002

23 24 Shin YB, Shin MJ, Chang JH, *et al.* Effects of Botulinum Toxin on Reducing the Co-
24 contraction of Antagonists in Birth Brachial Plexus Palsy. *Ann Rehabil Med* 2014;**38**:127–31.
25 doi:10.5535/arm.2014.38.1.127

26 25 Bourseul J-S, Molina A, Lintanf M, *et al.* Early Botulinum Toxin Injections in Infants
27 With Musculoskeletal Disorders: A Systematic Review of Safety and Effectiveness. *Arch*
28 *Phys Med Rehabil* Published Online First: 27 December 2017.
29 doi:10.1016/j.apmr.2017.11.013

30 26 Williams SA, Reid S, Elliott C, *et al.* Muscle volume alterations in spastic muscles
31 immediately following botulinum toxin type-A treatment in children with cerebral palsy. *Dev*
32 *Med Child Neurol* 2013;**55**:813–20. doi:10.1111/dmcn.12200

33 27 Pons C, Sheehan FT, Im HS, *et al.* Shoulder muscle atrophy and its relation to strength
34 loss in obstetrical brachial plexus palsy. *Clin Biomech (Bristol, Avon)* 2017;**48**:80–7.
35 doi:10.1016/j.clinbiomech.2017.07.010

36 28 Kamath S, Venkatanarasimha N, Walsh MA, *et al.* MRI appearance of muscle
37 denervation. *Skeletal Radiology* 2008;**37**:397–404. doi:10.1007/s00256-007-0409-0

38 29 Bialocerkowski A, Kurlowicz K, Vladusic S, *et al.* Effectiveness of primary
39 conservative management for infants with obstetric brachial plexus palsy. *Int J Evid Based*
40 *Healthc* 2005;**3**:27–44. doi:10.1111/j.1479-6988.2005.00020.x

41 30 Justice D, Rasmussen L, Di Pietro M, *et al.* Prevalence of Posterior Shoulder
42 Subluxation in Children With Neonatal Brachial Plexus Palsy After Early Full Passive Range
43 of Motion Exercises. *PM R* 2015;**7**:1235–42. doi:10.1016/j.pmrj.2015.05.013

44 31 Papavasiliou AS, Nikaina I, Foska K, *et al.* Safety of Botulinum Toxin A in Children
45 and Adolescents with Cerebral Palsy in a Pragmatic Setting. *Toxins (Basel)* 2013;**5**:524–36.
46 doi:10.3390/toxins5030524

47 32 Albavera-Hernández C, Rodríguez JM, Idrovo AJ. Safety of botulinum toxin type A
48 among children with spasticity secondary to cerebral palsy: a systematic review of
49 randomized clinical trials. *Clin Rehabil* 2009;**23**:394–407. doi:10.1177/0269215508099860

50 33 Dahan-Oliel N, Kasaai B, Montpetit K, *et al.* Effectiveness and safety of botulinum
51 toxin type a in children with musculoskeletal conditions: what is the current state of evidence?
52 *Int J Pediatr* 2012;**2012**:898924. doi:10.1155/2012/898924
53
54
55
56
57
58
59
60

- 1
2
3 34 Desiato MT, Risina B. The role of botulinum toxin in the neuro-rehabilitation of
4 young patients with brachial plexus birth palsy. *Pediatr Rehabil* 2001;**4**:29–36.
5
6 35 Fortuna R, Vaz MA, Youssef AR, *et al*. Changes in contractile properties of muscles
7 receiving repeat injections of botulinum toxin (Botox). *J Biomech* 2011;**44**:39–44.
8 doi:10.1016/j.jbiomech.2010.08.020
9
10 36 Schroeder AS, Ertl-Wagner B, Britsch S, *et al*. Muscle biopsy substantiates long-term
11 MRI alterations one year after a single dose of botulinum toxin injected into the lateral
12 gastrocnemius muscle of healthy volunteers. *Mov Disord* 2009;**24**:1494–503.
13 doi:10.1002/mds.22661
14
15 37 H Kozin S. Correlation Between External Rotation of the Glenohumeral Joint and
16 Deformity after Brachial Plexus Birth Palsy. *Journal of pediatric orthopedics* 2004;**24**:189–
17 93. doi:10.1097/01241398-200403000-00011
18
19 38 Lippert WC, Mehlman CT, Cornwall R, *et al*. The intrarater and interrater reliability
20 of glenoid version and glenohumeral subluxation measurements in neonatal brachial plexus
21 palsy. *J Pediatr Orthop* 2012;**32**:378–84. doi:10.1097/BPO.0b013e31825611bd
22
23 39 Waters PM, Smith GR, Jaramillo D. Glenohumeral deformity secondary to brachial
24 plexus birth palsy. *J Bone Joint Surg Am* 1998;**80**:668–77.
25
26 40 Friedman RJ, Hawthorne KB, Genez BM. The use of computerized tomography in the
27 measurement of glenoid version. *J Bone Joint Surg Am* 1992;**74**:1032–7.
28
29 41 Brochard S, Mazingo JD, Alter KE, *et al*. Three dimensionality of gleno-humeral
30 deformities in obstetrical brachial plexus palsy. *J Orthop Res* 2016;**34**:675–82.
31 doi:10.1002/jor.23049
32
33 42 Curtis C, Stephens D, Clarke HM, *et al*. The active movement scale: an evaluative tool
34 for infants with obstetrical brachial plexus palsy. *J Hand Surg Am* 2002;**27**:470–8.
35
36 43 Bialocerkowski A, O'shea K, Pin TW. Psychometric properties of outcome measures
37 for children and adolescents with brachial plexus birth palsy: a systematic review. *Dev Med*
38 *Child Neurol* 2013;**55**:1075–88. doi:10.1111/dmcn.12194
39
40 44 Greaves S, Imms C, Dodd K, *et al*. Development of the Mini-Assisting Hand
41 Assessment: evidence for content and internal scale validity. *Dev Med Child Neurol*
42 2013;**55**:1030–7. doi:10.1111/dmcn.12212
43
44 45 Hogendoorn S, van Overvest KLJ, Watt I, *et al*. Structural changes in muscle and
45 glenohumeral joint deformity in neonatal brachial plexus palsy. *J Bone Joint Surg Am*
46 2010;**92**:935–42. doi:10.2106/JBJS.I.00193
47
48 46 Fehlings D, Novak I, Berweck S, *et al*. Botulinum toxin assessment, intervention and
49 follow-up for paediatric upper limb hypertonicity: international consensus statement. *Eur J*
50 *Neurol* 2010;**17 Suppl 2**:38–56. doi:10.1111/j.1468-1331.2010.03127.x
51
52 47 Anguelova GV, de Vlught E, Vardy AN, *et al*. Cocontraction measured with short-
53 range stiffness was higher in obstetric brachial plexus lesions patients compared to healthy
54 subjects. *Journal of Biomechanics* 2017;**63**:192–6. doi:10.1016/j.jbiomech.2017.08.015
55
56
57
58
59
60

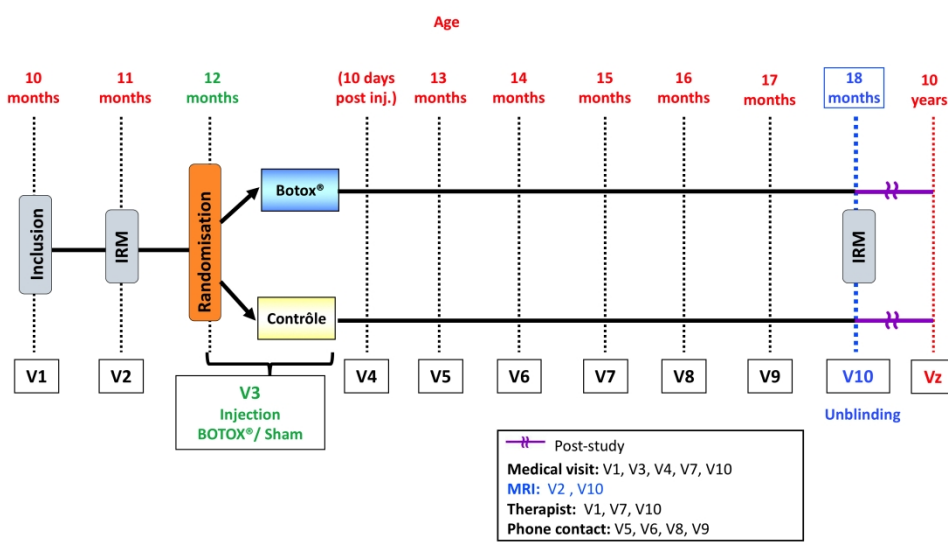


Figure 1 : Flow chart

1360x789mm (72 x 72 DPI)

Supplementary file 1: Botulinum toxin injections procedure

The Botox will be injected intramuscularly by transcutaneous approach using a 27 gauge, 25mm long sterile needle. This information can be added in the main text.

In the study protocol, we specifically described the procedure to ensure standardization (provided below). We propose to add this as supplementary material in the article.

“One hour before the injections, preliminary ultrasound identification will be carried out so that anaesthetic cream can be applied to the skin over the future injection sites.

For all injections, the child will be held in the arms of one of his/her parents.

Teres Major:

The parent will recline on the examination table, with the baby in his/her arms facing him/her (“belly to belly”). The sleep mask will be positioned on the parent at this time to ensure the blinding. The paediatric auxiliary can help to hold the child if necessary. The teres major muscle will be located by ultrasound, and the skin disinfected. Injection and/or simulation of the injection of the muscle (sham procedure) will be performed using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.

Subscapularis:

The baby will remain in the arms of the parent, “belly to belly”. The arm on the injected side will be placed in maximum abduction by the paediatric auxiliary. The subscapularis muscle will be identified by ultrasound. The skin will be disinfected. Injection and/or simulation of the injection of the muscle will be performed (sham procedure) using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.

Pectoralis Major:

The face mask will be removed so that the parent can change position and the position of the baby can be changed. The parent will sit in a chair with the child on his/her lap in a sitting position. The face mask will be repositioned. The pectoralis major muscle will be identified by ultrasound. The skin will be disinfected. Injection and/or simulation of the injection of the muscle (sham procedure) will be performed using a 27 gauge, 25mm long sterile needle. The ultrasound probe may be held by the nurse during the injection. After the injection, the skin will be cleansed with saline, and systematically covered with a dressing.”



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P5
	2b	All items from the World Health Organization Trial Registration Data Set	P5
Protocol version	3	Date and version identifier	P5
Funding	4	Sources and types of financial, material, and other support	P19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1 and 19
	5b	Name and contact information for the trial sponsor	P5 and 19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P11 and 13-14

Introduction

1	Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P3-4
2				
3				
4		6b	Explanation for choice of comparators	P4
5				
6	Objectives	7	Specific objectives or hypotheses	P4-5
7				
8	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P5
9				
10				
11				
12	Methods: Participants, interventions, and outcomes			
13				
14	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P5
15				
16				
17	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P6
18				
19				
20	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P8-9
21				
22				
23		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA_
24				
25				
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P14
27				
28				
29				
30		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P9
31				
32	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P11-13
33				
34				
35				
36				
37	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P6-7 fig1, table1
38				
39				
40				
41				
42				
43				
44				
45				
46				

1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P14-15
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P5
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	Sequence	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P7-8
11	generation			
12				
13				
14				
15				
16	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P8
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P8
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P10
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P8, P11-13
34	methods			
35				
36				
37				
38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P15
39				
40				
41				
42				

1	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P13-14
2				
3				
4				
5	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P14-15
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P14-15
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P15
11				
12				
13				
14	Methods: Monitoring			
15				
16	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P11
17				
18				
19				
20				
21				
22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
23				
24				
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P7, P10, P13
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P13-14
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P5
35				
36				
37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P5
38				
39				
40				
41				
42				
43				
44				
45				
46				

1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P6
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P13
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P19
11				
12				
13	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P13-14
14				
15				
16	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
17				
18				
19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P19
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	NA
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	SM for editor
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA
35				
36				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.