



**DROOLING TREATMENT IN
CHILDREN WITH CEREBRAL PALSY:
a multicenter, controlled,
randomized clinical trial**

END OF TERM PROJECT

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1. ABSTRACT

BACKGROUND: Drooling is clinically defined as an excess of saliva that drops beyond the lip margin. It is present in approximately the 40% of the children that suffer Cerebral Palsy (which is defined as a motor dysfunction due to a non-progressive brain lesion during the period of development of the brain). Drooling causes a huge impact on the daily lives of these patients and can also imply health problems. There are a lot of treatments available for drooling, most of them have proved their effectiveness reducing the amount of drooling, but none of them have proved to be capable of stopping it. In addition, there is a lack of comparative studies between the different options.

These days, the main treatment for drooling is based in anticholinergic drugs (such as glycopyrrolate or trihexyphenidyl) despite the amount of side effects that they normally cause. An alternative to these treatments is the injection of botulinum toxine into the salivary glands. This treatment has proved to be effective and safe for the treatment of drooling and also causes fewer side effects than other options. Because of the lack of comparative studies between the different options, it is unknown which is the best treatment option.

OBJECTIVE: Compare the effectiveness and the side effects of three treatment options for drooling (glycopyrrolate, trihexyphenidyl and botulinum toxine injections) in order to prove that botulinum toxine injections are a better treatment option than the other two providing a better life quality to the patients.

DESIGN: multicentre, controlled, randomized clinical trial between the years 2016-2020.

PARTICIPANTS: children patients (between 4 and 18 years old) with cerebral palsy and drooling with a score ≥ 30 points in the Drooling Impact Scale, treated in Hospital Universitari Josep Trueta de Girona, Hospital Universitari Vall d'Hebron, Hospital Clínic de Barcelona, Hospital Sant Joan de Déu Barcelona, Hospital Universitario La Paz, Hospital Universitario 12 de octubre, Hospital Universitario Ramón y Cajal and Hospital Infantil Universitario Niño Jesús.

KEYWORDS: Drooling, Cerebral Palsy, Children, Glycopyrrolate, Trihexyphenidyl, Botulinum Toxine injections, Drooling Impact Scale.

2. ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
AEMPS	Asociación Española de Medicamentos y Productos Sanitarios
BoTA	Botulinum Toxin A
CEIC	Clinical Research Ethical Committee
CP	Cerebral Palsy
DIS	Drooling Impact Scale
DQ	Drooling Quotient
DSFS	Drooling Severity and Frequency Scale
EEG	Electroencephalogram
EMLA	Eutectic mixture of local anaesthetics
GMFCS	Gross Motor Function Classification System
IQ	Intellectual Quotient
MRI	Magnetic resonance imaging
TDS	Teacher drooling scale

3. INTRODUCTION

3.1.CEREBRAL PALSY

1. DEFINITION

Cerebral palsy (CP) is a heterogeneous syndrome resulted from a non-progressive brain lesion during the period of brain's development which consequences are a motor dysfunction and others associated impairments (1).

During the years, there has been different definitions for CP, but recently, the International Executive Committee for the Definition of Cerebral palsy has proposed a new definition, more according with the new reality of this disease: *"CP describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy, and by secondary musculoskeletal problems"* (2).

Despite the fact that the brain lesion is permanent and does not change, the motor manifestations can vary due to the brain development during childhood. Because of this fact, CP is a dynamic condition more than a static one (3,4).

Normally, the brain damage causing CP affects parts of the brain that are in charge of the control of muscles and movement(3). The motor dysfunction is characterised by an abnormal tone, posture or movements (5). The associated impairments can be visual or hearing problems, intellectual disability, epilepsy or communications issues (6).

Progressive disorders and non-cerebral diseases must not been diagnosed as CP (7).

2. PREVALENCE

The prevalence of CP is 2.11 per 1000 live births (8). This prevalence has maintained stable for the last few decades (5). Recent studies have shown that probably there has been a decrease in this prevalence to 1.77 per 1000 live births (7).

Each year 8.000 infants and 1.200-1.500 preschoolers are diagnosed with CP (3).

There has been an improvement of medical procedures to prevent CP, such as the use of antenatal corticosteroids, cooling for term-born asphyxiated infants or the use of magnesium sulphate. There has also been other factors that have contributed to the increase of the CP incidence, such as improved survival in preterm infants and higher numbers of multiple births (7,8).

The improvement of medical procedures has contributed to decrease the prevalence in children with a birth weight between 1000-2500 g (moderately low birth weight and very low birth weight). On the other hand, the increase in the survival of preterm infants with a extremely low birth weight (<1000 g) has contributed to the maintenance of the prevalence of CP this group, despite the improvement of the medical procedures (7).

The prevalence of CP is not the same according to the birth weight or the gestational age:

- Prevalence in children weighing 1000 to 1499 g is 35.9 per 1000 live birth in contrast with children weighing over 2500 g, in which group the prevalence is 0.89 per 1000 (7).
- Prevalence in children born before the 28 gestational week is 111.80 per 1000 live birth; in contrast with children born after the 36 gestational week, in which the prevalence is 1.35 per 1000 (8).

As it is represented in the relation between the birth weight and the gestational age with the prevalence of CP, these two facts are the main risk factors to develop CP (9).

The prevalence is also different according to the number of fetus during the pregnancy: for twins the prevalence increases to 12.6 per 1000 births and for triplets, its increases to 44.8 per 1000 births (10).

There are some differences in the prevalence of CP depending on the incomes: while the prevalence in the most affluent areas is 2.08 per 1000 births, in the most deprived ones is 3.33 per 1000 births (10).

3. CLASSIFICATION

There are multiple systems to classify CP, depending on the main characteristic we take into account: according to the anatomical site of the brain lesion (cerebral cortex, pyramidal tract, extrapyramidal system, cerebellum); according to the predominant motor abnormality (spasticity, dyskinesia, ataxia); according to the topographical involvement of extremities (diplegia, quadriplegia, hemiplegia); according to the timing of presumed insult (prepartum, intrapartum, postneonatal) or according to the degree of muscle tone (isotonic, hypotonic, hypertonic) (1).

Although there are all these methods to classify, CP normally is classified according to the predominant motor abnormality and the distribution of these abnormalities (5,10):

- **Spastic CP:** is the most common type (72-91%).

The main characteristic of this type is the spasticity of the muscle (the muscle is rigid and resists to be stretched or bent). This condition is maintained both awake and asleep periods. These patients can have a hemiplegic condition (a half of the body is affected); a diplegic condition (the lower limbs or the upper limbs are affected, being the lower limbs more affected than the upper limbs in general); or a tetraplegic condition (the four limbs are affected).

- **Dyskinetic CP:** less common than spastic CP (12-14%).

The principal feature of this type is the involuntary movements of different parts of the body (face, trunk or limbs). This condition gets worse in periods of emotional stress and is dormant during sleep.

There are 3 different subtypes of dyskinesia: chorea (rapid and spasmodic movements); athetosis (writhing); or dystonia (remain in an abnormal position).

- **Ataxic CP:** is the less common type (4-13%).

The principal characteristics are the wobbling of the trunk, abnormal eye movements and have difficulties keeping limbs stable.

- **Mixed:** is a combination of signs and symptoms of the previous types.

The intellectual quotient (IQ), the Gross Motor Function Classification System (GMFCS) and the walking ability are used to classify the severity of disability experienced by these children (7):

- IQ \geq 50 or GMFCS I-II or be able to walk without assistive devices → Mild severity.
- IQ <50 or GMFCS III-V or not be able to walk without assistive devices → Moderate to severe severity.

The GMFCS has been used widely for the past few years in clinical practise (11). In research and clinical fields, GMFCS has been incorporated as the principal method to describes and classify the severity of the motor disability of CP (12).

The GMFCS can be used to describe, classify, predict the future condition and evaluate changes in the state of the child (13). This system classifies the children in 5 levels, in which the first level (level I) is the best functional level and the last one (level V) is the one in which the child is completely dependent ([Annex 1](#)) (11,14).

The classification is based on the motor abilities of these children (such as lying, walking, running, etc). Because of the fact that the GMFCS can change over the years, it is necessary to re-evaluate the patient several times (15).

There is not the same proportion of children in each level. The most frequent level is level I (34.2%), followed by level II (25.6%), level V (15.6%), level IV(13.7%) and the less common is the level III (11.5%) (12).

4. ETHIOLOGY

There are multiple causes that can result in CP. It is thought it is a multifactorial disease (16).

The most important risk factors are (10):

- A low birth weight and low gestational age: children born with a weight under the percentile 10 are 4 to 6 times more likely to have CP.
- Multiple gestation: in twins pregnancies, children are 5 times more likely to develop CP; and in triplet pregnancies, 19 times.
- Intrauterine infections: chorioamnionitis represent an increase of 5 times the probabilities of CP in term infants and an increased of 2 in pre-term infants.

There are a lot of risk factors that can contribute to the appearance of CP. We can divide them according to the moment that they occur: prenatal, perinatal or postnatal:

Table 1: Risk factors of CP. Adapted from (6,9,10).

RISK FACTORS		
PRENATAL (75% of the cases)	<ul style="list-style-type: none"> - Chorioamnionitis - Multiple gestation - Intrauterine growth retardation - Prothrombotic abnormalities - Congenital infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, HIV) 	<ul style="list-style-type: none"> - Death of a co-twin - Placental abruption and others placental abnormalities - Toxins - Metabolic conditions - Cerebral ischemia
PERINATAL (10-15% of the cases)	<ul style="list-style-type: none"> - Low birth weight - Prematurity - Hypoxia-ischemia (neonatal encephalopathy) - Arterial and venous stroke - Neonatal seizures - Meconium aspiration - Respiratory distress syndrome 	<ul style="list-style-type: none"> - Trauma - Intracranial bleed - Kernicterus - Hypoglycaemia - Neonatal infection - Instrumental assisted delivery or emergency caesarean section
POSTNATAL (10% of the cases)	<ul style="list-style-type: none"> - CNS infections (group B Streptococcus, herpes, pneumococcus, meningococcus) 	<ul style="list-style-type: none"> - Trauma

5. SINGS AND SYMPTOMS

The clinical presentation varies a lot depending on the characteristics of the child. The most frequent clinical findings are: difficulties in feeding, delay in the normal neuropsychological development, floppiness or stiffness and coordination problems (depending on the type of CP). It is usual that these patients had associated problems, like seizures, cognitive impairment or vision and hearing problems (3).

There are some suggestive symptoms of the CP condition (9):

- During the first year the persistence of the neonatal reflexes or an early hand preference.
- Is suggestive of spastic CP an increase or decrease in the muscle tone, brisk tendon reflexes, sings of upper motor neuron (hyperreflexia, clonus, Babinski's sign or Rossolimo's sign¹) or abnormalities in gait (scissoring gait or toe-walking).
- The presence of microcephaly is suggestive of a severe CP.

6. DIAGNOSIS

The diagnosis of CP is clinical: a history of perinatal problems (such as prematurity, infections, neonatal encephalopathy, etc) added to a clinical of delayed motor milestones or abnormal movement patterns (6,16).

In spite of the fact that there is a clinical diagnosis, there are different tests that can be done in order to give more information about the characteristics of the injuries in each patient (6,9,10,16):

- A **Magnetic resonance imaging (MRI)** can be made, if it necessary, in order to identify the cause of the CP. This technique provides information about the timing of the brain injury and if there are some genetic implications in the development of the disease (6).

Some specific lesions are predictive of CP, like periventricular leukomalacia or intraventricular hemorrhage.

¹ Hyperreflexia: increase of the reflex.

Clonus: rapid succession of an alternation of muscle contraction and relaxation.

Babinski's sign: extension of the first finger toe during the flexor cutaneous plantar reflex.

Rossolimo's sign: flexion of the toe's fingers during the percussion of the plantar side.

According to the results in the MRI, we can distinguish 4 lesion groups: brain malformations; cortical/sub-cortical lesions; abnormalities of the periventricular white matter; postnatal brain injury (10).

10% of the cases, the MRI is normal. When this happens, metabolic and genetic causes should be considered as the main cause of the disturbance (6).

- A **cranial ultrasound** can be performed. Normally, the hemiplegic conditions have a normal ultrasound and the diplegic condition an abnormal one (10).

- **Neuroimaging:** abnormalities in the perfusion of the thalamus and the cerebellar hemispheres are suggestive of bilateral spastic condition. The grade in the decrease of this perfusion is predictive of the delay in the motor development of the child (10).

➤ It is also important the early detection of the impairments associated with CP. For this reason, it is necessary to make the following tests (16):

- **Electroencephalogram:** in all the children with seizures or with a high risk of develop epilepsy.

- **Ophthalmological study:** in all the CP patients.

- **Auditory tests:** in all the CP patients.

- **Radiographies:** is necessary take a hip X-ray at the starting of the standing position. Then, depending on the orthopaedic deformities, it would be necessary to take specific X-ray.

7. IMPAIRMENTS

Associated with CP there are a large number of impairments that must be taken into consideration (10):

Table 2: Impairments associated to CP (10)

IMPAIRMENTS	
Motor impairment	100% of the cases
Cognitive impairment	23-44% of the cases
Sensibility impairment	44-51% of the cases
Speech impairments	42-81%
Visual impairment	62-71%
Hearing impairment	25% of the cases
Epilepsy	22-40% of the cases
Feeding impairments	- Choking 56% of the cases - Long feeding time 28% of the cases - No orally 80% of the cases
Gastrointestinal impairments	- Constipation 59% of the cases - Vomiting 22% of the cases
Growth impairments	23% of the cases
Weight impairments	52% of the cases
Urinary incontinence	23.5% of the cases

- **Motor impairments:** a part from the main characteristics that we have seen before, there are other motor problems: drooling, hip luxations, contractures, scoliosis, lower physical fitness, gait abnormalities, etc.

- **Cognitive impairments:** defined as an IQ <70. It is more frequent in those children who also have epilepsy. A severe cognitive deficit (IQ<50) can happen in tetraplegic children.

In these children is frequent some non-verbal learning impairment (such as weak visual-spatial abilities) or some behaviour problems (like Attention deficit hyperactivity disorder (ADHD), dependency, hyperactivity or to be headstrong).

- **Sensibility impairments:** are more frequent in hemiplegic CP and normally are bilateral. The most usual problems are stereognosis and two-point discrimination of the hand.

In the adult life, almost a 30% of the patients suffer from chronic pain (the most frequent location is on the back).

- **Speech impairments:** the most common is dysarthria and dyskinetic CP is the most frequent type of CP with speech problems.

Patients with tetraplegic CP and an important mental retard normally have aphasia.

- **Visual impairment:** the most common conditions are strabismus and hemianopsia. It is thought that there is a cerebral visual disturbance added to the low visual acuity. This association could explain the visual problems in CP patients.

- **Hearing impairments:** are less common than visual impairments.

- **Epilepsy:** generalized epilepsy is more common in tetraplegic patients while partial epilepsy is more common in hemiplegic patients.

These seizures are characterised to have an early onset and to decrease over the years (normally at 16 years old).

- **Feeding impairments:** are frequent sucking and swallowing problems, as well as silent aspirations (that often produce pulmonary infections) and an increase of the number of dental caries. A lot of these children do not feed orally, and those that do it have choking problems or takes long feeding time.

- **Gastrointestinal impairments:** such as constipation or vomiting.

- **Growth impairments:** 25% of these children have a stunted growth with a decreased linear growth.

- **Weight impairments:** most of these children are undernourished, but they can be overweight or obese.

- **Urinary impairments:** frequently there is a primary urinary incontinence.

8. TREATMENT

The most important factor about the management of CP is to make a multi-disciplinary approach. The implication of several medical professionals is needed (such as a General Practitioner, Neurologists, Physiologists, Occupational Therapists, Speech Pathologists, Orthotists, Dieticians, Social Workers, Psychologists and Nurses), with special educational teachers and the input from the family (3,6).

This multidisciplinary approach is important in order to help to improve the movement skills, to reduce discomfort and pain and to prevent the development of long-term complications (3).

A part from the need for a special medical attention, a follow up during the years is also necessary.

It is also important to make a personalised treatment depending on the type of CP, the age, the impairments and the social and family background (16).

The treatment has 4 important bases (16):

- **PHARMACOLOGICAL TREATMENT:** depending on the type of CP there are some drugs available for the treatment. For spastic CP Botulinum Toxin A (BoTA), baclofen or diazepam can be used to reduce the spasticity. For dyskinetic CP anticholinergic drugs are used (like trihexiphenidyl). In some cases of these two types, an intrathecally treatment with baclofen can be used (5).

A part from the treatment of the motor conditions, treatment of the impairments associated with CP is vital: the use of antiepileptic drugs can be necessary, also some laxatives for constipation or vitamin D supplements if there is a deficiency or osteoporosis, etc (5).

- **PHYSIOTHERAPY:** there are multiple techniques available. It is important to coordinate these interventions with the other professionals.

- **ORTHOSES:** different devices can be used in order to help the walking of these children.

- **SURGICAL TREATMENT:** in some cases an orthopaedic surgery is necessary (such as an osteotomy, a tenotomy, a arthrodesis, etc) or a neurological surgery (such as a selective dorsal rhizotomy or the insertion of the intrathecal biclofen).

3.2.DROOLING

1. DEFINITION

Drooling or sialorrhea is defined as a hyper-secretion of saliva clinically diagnosed by quantitative sialometry (17). In the clinical practise, it is defined as an excess of saliva that drops beyond the lip margin (18).

While the terms drooling and sialorrhea are often used together, there is a slight difference: drooling is not necessarily explained by an increase of salivary flow (which is the main characteristic of sialorrhea); generally this flow is normal or even reduced, but there is a disturbance in the handling of saliva (17).

Drooling in infants or children beyond 4 years old is normal (the drooling condition decreases by 18 months old). When drooling is still present at the age of 4 years old, it is considered pathological and may need some kind of treatment (19).

2. EPIDEMIOLOGY

It is estimated that the prevalence of drooling in patients with CP is about 40% (17,20–23).

Regarding the type of CP or the GMFCS level the prevalence of drooling may change (21):

Table 3: Main difference according to the CP classification (21).

TYPE OF CP	% OF DROOLING	GMFCS	% OF DROOLING
Spastic bilateral CP	>40%	Level I	13%
Spastic unilateral CP	20-30%	Level II	36%
Dyskinetic CP	90%	Level III	20%
Ataxic CP	40-50%	Level IV	61%
Other types of CP	10%	Level V	95%

According to some studies, the distribution of the drooling severity is 10% mild drooling, 75% moderate drooling and 15% severe drooling (20).

3. CAUSES

There are many causes that can lead to an excess of saliva: some medication (such as muscarinic agonists, some antidopaminergic drugs, benzodiazepines or antipsychotic drugs), some systemic diseases, oral pathologies, psychiatric disorders, some toxic substances and neurological diseases (17).

In patients with CP a possible explanation for the drooling condition is the disruption of the oral-facial functions due to the motor disorders characteristics of CP. This leads to problems controlling saliva, talking and eating (21). These motor disorders are responsible for the poor coordination of oral-facial and palate-lingual musculature, that are in charge of the process of remove the saliva from the oral cavity (18).

There are some characteristics of CP that are more likely to be associated with drooling (20):

Table 4: CP characteristics and drooling (20).

Characteristic	% of drooling	Characteristic	% of drooling
Epilepsy	61.4%	Intellectual disability	54.8%
Special education	65.9%	Non-spastic motor type	Ataxic type: 68.7% Dyskinetic type: 83.3%
Quadriplegic impairment	69.8%	Inhability to control head posture	Never controls: 95.6% Sometimes controls: 68.2%
GMFCS level IV-V	IV: 58.1% V: 80.9%	Limited or no useful speech	Limited: 64% No: 82.8%
Poor lip closure	78.7% (leakage occurs) 74.3% (always open)	Anterior open bite	65.8%
Eating difficulties	66.7-97.6% depending on the kind of difficulty		

4. CONSEQUENCES

Drooling, more than just an aesthetic problem, is a health problem that can cause difficulty in the daily lives of the patients and their families and can cause problems in the child's development (24).

Drooling can have some medical complications, like skin maceration, bad odor, body fluid loss, infection, recurrent pneumonia for aspiration, speech disturbance or eating problems (18,24,25).

Some of the effects that a drooling condition can have in the daily life of children are: damage of books, furniture or school materials; need for a frequent change of clothes, interference in social relationships, low self-esteem and isolation; negative consequences on their education and independence; and an important reduction of their quality of life (20,24–26).

It has been observed that those children that drool have a lower language development status and a lower cognitive status than those who do not drool (24).

5. ASSESSMENT

Excess of saliva can be measured with different methods. There are objective measures (like the Drooling Quotient (DQ) or the Salivary flow rate) and others subjective ones (such as the Teacher Drooling Scale (TDS), the Drooling Severity and Frequency Scale (DSFS), the Drooling Impact Scale (DIS) ([Annex 2](#)) etc).

The problem is that there is not a standardized method to assess the saliva, and consequently to assess or compare the effectiveness of a treatment (27).

6. TREATMENT

For the drooling treatment there are multiple options that have different efficacy rates but there is not any that have shown to be totally effective (28).

There are different options of treatment (17,18):

- **Physiotherapy and re-education techniques:** these techniques include oral motor therapy, behaviour modification through biofeedback or oral-facial regulation therapy (17).

- **Pharmacological therapy:** muscarinic receptor antagonists or anticholinergic drugs are used (like atropine, scopolamine, glycopyrrolate or trihexyphenidil). The mechanism of action of these drugs is to decrease the release of acetylcholine. This leads to a blockage in the stimulation of the parasympathetic system (which acts increasing the secretion of saliva in the salivary glands). The main result is a decrease of the saliva secretion (17,22,29).

The main problem of these drugs are the side effects that they may cause: excessive dry mouth, constipation, urinary retention, blurred vision, irritability, confusion and toxic psychosis (30).

There are also some contraindications for the use of these drugs: cardiac problems, prostatic hypertrophy, paralytic ileus and pyloric obstruction (17).

Regarding to the two anticholinergic drugs used in our study, we can define some specific side effects (17,26,31):

Table 5: Side effects of glycopyrrolate and trihexyphenidyl (17,26,31)

SIDE EFFECTS OF GLYCOPYRROLATE	SIDE EFFECTS OF TRIHEXYPHENIDYL
- GI disturbance: constipation, vomiting, diarrhoea, intestinal pseudo-obstruction.	- GI disturbance: constipation.
- Urinary retention, urinary infections.	- Urinary retention.
- Dry mouth, thick mucoid secretions.	- Excessive dry mouth.
- Blurred vision.	- Blurred vision.
- CNS disturbance: somnolence.	- CNS disturbance: increased involuntary movements, decreased seizure control, delusions or hallucinations, drowsiness.
- Flushing.	- Flushing.
- Respiratory disturbance: nasal congestion, respiratory infections.	- Behavioural changes: irritability, hyperactivity, restlessness.
- Fever, heat prostration.	

· Contraindications for the administration of glycopyrrolate or trihexyphenidyl (29):

Table 6: Contraindications for glycopyrrolate or tryhexiphenidyl (29):

Glaucoma.	Use of solid oral potassium chloride.
Paralytic ileus.	Renal impairment.
Unstable cardiovascular status in acute hemorrhage.	Constipation or intestinal pseudo-obstruction.
Severe ulcerative colitis.	Hypersensitivity.
Myasthenia gravis.	

- **Minimally invasive therapies:** there are two different techniques that can be used:

Photocoagulation of the salivary gland ducts: this technique is used only in cases in which the other techniques have not been successful. The objective is to cause a partial destruction of the gland and to make an occlusion of the duct.

There are some complications that are originated by this technique: infections, cystic formations, hematomas and a postoperatively transient facial swelling (17).

Botulinum toxin injections: the toxin acts making an inhibition of the neuromuscular transmission by blocking the release of acetylcholine (17,18,25,26,31).

The injections can be made in the parotid gland or in the parotid and submandibular glands. An ultrasound-guided technique is necessary for the injection of the toxin. The use of some kind of anaesthesia is generally necessary during the procedure (23,32,33).

This procedure is not permanent (is necessary repeat it every 6 months approximately) (33,34).

There are some side effects related to the use of BoTA injections (33,35):

- Related to the injection site: pain, hematoma, swelling, intraoral blood, swallowing difficulty, infection, trauma to the facial nerve, rash for the ultrasound gel.
- Excessive dry mouth.
- Eating and swallowing problems, dysphagia.
- Facial weakness, recurrent mandibular dislocation.
- Transient fever.

There are also some contraindications to the use of this procedure (34):

- Dysphagia.
- Myastenia gravis.
- Important weakness or atrophy.
- Hypersensitivity.
- Serious side effects in a previous administration.

- Surgical methods and Radiotherapy (17,18,25,26,31):

Surgical methods: is the last option after the more conservative treatments have been tried. There are different procedures: a neurectomy or procedures to alter the anatomy of the gland. These procedures are recommended in some cases: moderate and persistent drooling in which the conservative treatments have not worked; severe cases with antecedents of failure using conservative treatments or have accomplished limited results; and moderate cases in which the patient has retarded cognitive development or shows a lack of co-operation for conservative treatments (17).

Radiotherapy: it should be avoided due to the risk of induce malignancy, delayed growth, xerostomia, mucositis, dental decay or osteonecrosis.

3.3.JUSTIFICATION

As we have seen, drooling condition is a problem that affects a large number of CP patients. Although drooling is not a life-threatening condition, it causes a huge impact in the daily-life of patients and parents or carers (18,20,24). Drooling has shown to be responsible for both physical (such as skin irritation, aspiration and pneumonia, tooth decays, dehydration, etc) and psychological (like isolation, embarrassment, social integration, bad odor, etc.) impairments (22,23,29,35–37).

In spite of the fact that it is an important problem for these families, there is not a standardized treatment for drooling. These days, the medical professionals use their clinical experience to decide which treatment option is better for each patient (38).

Nowadays, the use of anticholinergic drugs is often the first option treatment (after the use of oral-motor therapies in some cases). However, this option is restricted because of the side effects they can cause (like constipation, urinary retention or dry mouth) (30).

During the last few years, the use of BoTA injections for drooling reduction has been increased due to their effectiveness and the fact that they cause less side effects than anticholinergic drugs (32,33,35,39).

In our area, and according to the protocol of the Hospital Universitari Josep Trueta de Girona, the three option treatments that are used more frequently are two anticholinergic drugs (glycopyrrolate and trihexyphenidyl) and BoTA injections (40).

There are a number of studies that prove the effectiveness of the different treatment options, but there are not many of them that compare the effectiveness between two or three options:

- In some studies, the BoTA injections have proved their effectiveness by reducing drooling in more than 60% of the cases (33,34).
- The effectiveness of glycopyrrolate has also been proven in different studies, showing an effective action in a range of 50-70% (29,41).
- Finally, the effectiveness of trihexyphenidyl has been proven too, with a range of effectiveness of 60-80% (37,42).

Recently, one clinical trial has compared the effectiveness of trihexyphenidyl, scopolamine and BoTA for the reduction of drooling in CP children patients. The results of this study showed similar effectiveness between the trihexyphenidyl option (60.68%) and the BoTA injections option (64%) and a better one than with the scopolamine option (36.36%). They recommend this sequence of use: first trihexyphenidyl, second scopolamine and third BoTA injections. In this clinical trial, all the patients received the 3 treatments in a sequence (first trihexyphenidyl, second scopolamine and third BoTA injections). Furthermore, the washout period applied was not explained (34).

In addition, the quantification of drooling is difficult and there is not a standardized way to quantify it. As a result of this situation, comparisons between the different options are difficult. This situation also implies that the results in different studies can show a really different effect, depending on the scale or instrument used for the quantification of drooling (35,43).

As we have seen, a treatment protocol at the Hospital Universitari Josep Trueta de Girona establishing the order of utilization of each treatment has been introduced. They recommend starting with the use of trihexyphenidyl; if this option does not work or the patient experiment a lot of side effects, it is recommended to use glycopyrrolate; and, as the same as before, if this option does not work or causes a lot of side effects, it is indicated to use the BoTA injections (40).

Because of the lack of studies comparing the effectiveness of the treatment option, all the recommendations are done following the clinical expertise and the results of studies of a single option (38).

For all these reasons, it is necessary to carry out a clinical trial with the most used treatment options in order to identify the measure that has a better effectiveness with the fewest side effects possible.

4. HYPOTHESIS

4.1.MAIN HYPOTHESIS

The botulinum toxin injections are more effective than trihexyphenidyl or glycopyrrolate medication for the treatment of drooling in paediatric patients with cerebral palsy, implying a better quality of life.

4.2.SECONDARY HYPOTHESES

- The botulinum toxin injections have fewer side effects in both short-term and long-term than trihexyphenidyl or glycopyrrolate medication for the treatment of drooling in paediatric patients with cerebral palsy.
- Patient's family prefers the botulinum toxin injections treatment rather than the trihexyphenidyl or glycopyrrolate treatments.

5. OBJECTIVES

5.1.MAIN OBJECTIVE

To compare the effectiveness of trihexyphenidyl, glycopyrrolate and botulinum toxin injections in the treatment of drooling in paediatric patients with cerebral palsy in order to determinate the best treatment option.

5.2.SECONDARY OBJECTIVES

- To determinate the side effects of each of these three treatments in both short and long-term.
- To define which treatment is more satisfactory to the patient's family.

6. METHODOLOGY

6.1. STUDY DESIGN

This project will be a controlled, randomized and multicentre clinical trial. The patients will be randomly divided in three different groups. The first group will receive trihexyphenidyl. The second group will receive glycopyrrolate. The third group will receive botulinum toxin injections.

This will be a simple blind trial: patients (and their families) will be aware of the type of treatment they will be receiving and the medical professional that will perform the procedure will also know it. In order to reduce the bias of the simple blind trial, the doctor who will make the monitoring of the patients and the statistical consultant will not have access to this information.

This study will be conducted in the hospitals of Catalunya (Hospital Universitari Josep Trueta de Girona, Hospital Universitari Vall d'Hebron, Hospital Clínic de Barcelola and Hospital Sant Joan de Déu Barcelona) and Madrid (Hospital Universitario La Paz, Hospital Universitario 12 de octubre, Hospital Universitario Ramón y Cajal and Hospital Infantil Universitario Niño Jesús). The Hospital Universitari Josep Trueta de Girona will be the centre of reference. With the purpose of form a Steering Trial Committee and favour the communications between the hospitals, a principal investigator will be assigned in each centre.

6.2. STUDY POPULATION

The patients will be children above 4 years old with cerebral palsy that also present a drooling condition that meet the criteria for the drooling treatment.

All the centres will inform about the number of patients with CP and drooling witch meet the inclusion criteria for this trial in order to evaluate the viability of this study.

Others hospitals of the area will be asked if they treat patients with the characteristics of our sample. If it is the case, these patients will be informed about the study and asked to join it.

- **INCLUSION CRITERIA**

- Children between 4 and 18 years old.
- To be diagnosed of cerebral palsy.
- To be diagnosed with drooling and have a DIS score \geq 30 points.
- Not being in treatment with some drooling measure.

- **EXCLUSION CRITERIA**

- Progressive neurological damage.
- Contraindications to some of one of the three drugs.
- Have been treat with some drooling treatment before.
- Impossibility for the patient's follows.

6.3.SAMPLE SIZE AND SAMPLING

- **SAMPLE SIZE**

Sample size calculations were realized using GRANMO application. In our study, accepting an alpha risk of 0.05 and a beta risk of 0.2, in a three-sided test, we will need a sample of 309 patients.

Using the DIS, we can considerate an improvement of the drooling condition if the score decrease at least 28 points (27). For our study we will considered as clinically significant a difference between our treatment options of 20% of effectiveness.

It is necessary to have 103 patients in the first group, 103 in the second and 103 in the third one in order to recognize as statistically significant difference at least of a 20%. The ratio between each group will be 1 and it has been predicted a drop-out rate of 10%.

- **SAMPLING**

A non probabilistic and consecutive sample method will be used in children patients with cerebral palsy and drooling that meet criteria for treatment.

The patients will be recruited to the study from the specific neuropaediatric consultation of the different hospitals participants on the clinical trial. The recruitment will begin in March 2016 and will finish in October 2018.

According to the statistics, the birth rate in Catalunya in 2014 was 71.589 and in Madrid was 65.505. The prevalence of CP in our media is 2.11 per 1000 births and the prevalence of drooling in these children is 40%. With this data, we can estimate that in one year, in these two autonomous regions, the number of children with CP and drooling will be 116. Because we need 309 patients for our study, it is presumed that we need 2.6 years to asses our sample.

All the patients that meet inclusion criteria and do not meet exclusion criteria will be asked to enroller in the study. The patients and their parents or carers will be informed about our study, the different treatments used and the possible side effects of each procedure. All this information will be explained in the information sheet ([Annex 5](#)). After the information have been provided, if the patients and their families agree to participate in the study, the informed consent will be provided ([Annex 6](#)). Once the parents or legal tutors will have signed it, the patients will be included to the study.

We randomly select the patients and they will be distributed in one of the three possible treatments (trihexyphenidyl, glycopyrrolate or botulinum toxin injections) in relation to the order of arrival to the surgeon consultation.

6.4.VARIABLES and INSTRUMENTATION

- **INDEPENDENT VARIABLE**

The independent variable will be the administration of one of the three different treatments for the reduction of the drooling rate and the improvement of the life quality of the patients. It will be measured as a nominal qualitative non dichotomous variable. The three treatment options will be:

- ✓ **Trihexyphenidyl:** oral administration, as pills.
- ✓ **Glycopyrrolate:** oral administration, as oral suspension.
- ✓ **Botulinum toxine injections:** intra-glandular injections in both submandibular gland and parotid gland.

- **DEPENDENT VARIABLE**

The dependent variable will be the improvement of the drooling condition. For measure this variable, we will use the “Drooling Impact Scale” ([Annex 2](#)). This method is a subjective assessment of the impact of drooling in the children’s life. It will be measured as a dichotomous nominal qualitative variable.

The scale will be administrated to all the parents or carers before the start of the procedures (baseline measure) and then it will be administrated again in each control visit: 1st month, 2nd month, 4th month, 6th month and 12th month.

This scale is composed by 10 questions, ranged 1 (minimum) to 10 (maximum). The parents or carers will be asked to respond the questionnaire according to their experience over the last week.

The patients will be classified into two groups depending of the outcome of this scale: improvement or unchanged/deterioration.

For be classified in the improvement group, the score of the DIS has to decrease at least 28 points regarding the baseline measure. If the score decrease less than 28 points or increase regarding the baseline measure, the patient will be classified in the unchanged/deterioration group.

- **SECONDARY DEPENDENT VARIABLE**

- ✓ *Side effects of each drug in short term (<12 months):* for measure this variable, in each visit, parents will be asked about the side effects that their child has suffered. Each side effect will be measured as a qualitative nominal dichotomous variable (presence or absence of the side effect) using a self-produced questionnaire with the most frequent side effects caused by these drugs ([Annex 3](#)).
- ✓ *Side effects of each drug in long term (>12 months):* in order to measure this variable, during the last control visit, parents will be asked if their children have suffered some symptom (from the short-term side effects list) during all the period treatment time. Each side effect will be measured as a qualitative nominal dichotomous variable (presence or absence of the side effect)².
- ✓ *Satisfaction of the children's parents:* at the end of the study (12th month), the parents will be asked about their satisfaction regarding the treatment administrated to their children with a self-produced questionnaire. It will be measured as an ordinal qualitative variable ([Annex 4](#)).

- **COVARIABLES**

To avoid confusion in the study results, we will collect some variables from the patient's clinical history, which can act as confusion factors and modify the interpretation of the results:

- Age: is a discrete quantitative variable, expressed in years.
- Sex: is a dichotomous nominal qualitative variable: male or female.
- Intellectual impairment: is a discrete quantitative variable, expressed in scores.
- GMFCS level: is an ordinal qualitative variable: level I, II, III, IV or V.
- Type of CP: is an ordinal qualitative variable.
- Presence/absence of epilepsy: is a dichotomous nominal qualitative variable.
- Oral-motor problems (such as poor lip closure, eating problems, speech problems, etc): is a dichotomous nominal qualitative variable: presence or absence.

² We will use the same side effects list for the short-term side effects and the long-term side effects variables because there are not studies regarding side effects for 1 year length.

6.5.INTERVENTIONS

Following the treatment's protocol used in the Hospital Universitari Josep Trueta de Girona (40), the interventions will be:

GROUP A: This group will receive trihexyphenidyl. This drug will be administrated orally 3 times per day. The pill's dose is 2mg. The initial dose will be 0.15 mg/Kg/day in 3 times. Each week, there will be an increase of the dose 0.05-0.2 mg/Kg/day, until a maximum 0.75 mg/Kg/day.

GROUP B: This group will receive glycopyrrolate. The drug is prepared as an oral suspension 1mg/1 ml. This drug will be administrated orally 3 times per day with a syringe. The initial dose will be 0.02 mg/Kg/dose. Each week, there will be an increase of the dose 0.02/Kg/dose mg until a maximum of 0.1mg/Kg/dose (maintenance dose). The maximum dose will be 3mg/dose.

GROUP C: This group will receive botulinum toxine injections. This treatment will be administrated by intramuscular injections each 6 months. This procedure will be accomplished with ultrasound-guide. There will also be necessary the use of an analgesic technique (general anaesthesia, nitrous oxide, Eutectic mixture of local anaesthetics (EMLA), etc). We will choose which anaesthetic technique fits better with each patient.

The botulinum toxine dose will depend of the weight of the patient: if the patient weigh is less than 25kg, the dose will be a maximum 4 U/Kg. If the patient weigh is more than 25kg, the dose will be a maximum of 100 U.

In both cases, the dose will be divided into the 4 glands (2 submandibular and 2 parothides).

6.6. DATA COLLECTION

Before the start of the trial, each one of the participating hospitals will be trained in the procedure method in order to guarantee the homogeneity of the procedures.

All the patients will receive an identification number in order to protect their anonymity and for maintain the blind to the statistician. The hospital will receive an identification number too.

The interventions and the corresponding follow-up will take place during a year. Patients will be call to a medical appointment for the follow-up 5 times: the first month of treatment, the second one, the fourth, the sixth one and, finally, after a year of treatment for a final appointment. Patients in the third group will also be call to and extra appointment 6 months after the first injection session for received the second one.

With the porpoise of guarantee the study adherence, all the parents or carers of the patients will received a letter or a phone call (depending on which one the family prefers) 1 week before the appointment.

All the visits will be performed by the same professional and all the questionnaires required will be taken in each visit.

After each visit, the professionals will complete the data collection sheet ([Annex 7](#)) in order to store all the patient's data.

FIRST VISIT: when the patient come to the neuropaediatric surgery for his/her CP follow-up, the professional will establish if the patient meet the inclusion criteria and does not meet the exclusion one for our study. Once have been confirmed that the patient can be part of the study, the parents or carers will be asked if they want to participate and the information sheet will be provided ([Annex 5](#)). The patient and their family will be assured that there are not any consequence if they decided reject participate in the study. If they decide to participate it, they have to sign the informed consent in order to be involved in the project ([Annex 6](#)).

PRE-TREATMENT: before the start of one of the three treatment options, all the patients will be called to the surgery in order to re-explain the specific treatment they are going to take. Also, the professionals will show the different questionnaires that they will have to fulfil during the follow-up and will answer any question they have.

INTERVENTION: each patient will start to receive their treatment according to the group they have been assigned.

The parents or carers of the patients in the A group (trihexyphenidyl) and in the B group (glycopyrrolate) will be provide with their medication in the pharmacy of their hospital.

Depending on the clinical response and the tolerability of the treatment, the dose would be increase weekly, as it is specified in the intervention section.

The patients in the C group (botulinum toxine injections) will receive it each 6 months in the neuro-paediatric surgery.

FOLLOW-UP: it will be 5 follow-up visits during the study: 1st month, 2nd month, 4th month, 6th month and 12th month.

In all the visits, the parents/carers will be asked to answer the following questionnaires:

- Drooling Impact Scale.
- Side effects in short-time.

During the last visit (12th month of treatment) they will be asked to answer the following questionnaires:

- Drooling Impact Scale.
- Side effects in long-term.
- Satisfaction regarding the treatment.

7. STADISTICAL ANALYSIS

- **UNIVARIATE ANALYSIS**

The results will be expressed as percentages for categorical variables and as mean +/- SD for continuous variables, assuming a normal distribution. If is not possible to assume a normal distribution, median (using quartiles or percentiles) will be estimated.

- **BIVARIATE ANALYSIS**

The relationship between our qualitative variables will be expressed using contingency tables.

Both independent (type of treatment) and dependent (response or not response to the treatment) variables are qualitative variables. For this reason, comparison between these variables will be done with the χ^2 test.

Results were considered statistically significant at $p < 0.05$.

- **MULTIVARIATE ANALYSIS**

A multivariate analysis will be done with the purpose of adjust co-variables in order to detect possible confusion caused by them that can explain the relationship found between our dependent and independent variables.

Considering our dependent variable, we need to do a Logistic Regression Model, because is a qualitative variable with two categories.

8. ETHICAL CONSIDERATIONS

This protocol will be sent to the Clinical Research Ethical Committee (CEIC) of Hospital Universitari Josep Trueta de Girona in order to be evaluated. Modifications of the protocol will be done it in case the CEIC consider it necessary. After the local approval of the protocol, it will be sent to the CEIC of all the involved hospitals to be evaluated.

The centres authorities of all the participating hospitals will be asked to approve the study before the start of the trial.

Before the approval of the clinical trial, the study must be approved by the Asociación Española de Medicamentos y Productos Sanitarios (AEMPS).

Following the actual recommendations, our clinical trial will be submitted to ClinicalTrials.gov and will be registered with an International Standard Randomized Controlled Trial Number.

The principles of the Helsinki Declaration will be followed during all the trial process.

In addition, we will take into consideration the Spanish Legislative Royal Decree 1/2015, *del 24 de Julio, de Investigación Biomédica*, that regulates the use of medication and sanitary products. It will be also take into consideration the Spanish Organic Law 14/2007, *3 de Julio, de Investigación Biomédica*, that regulates biomedical investigation involving humans and the invasive procedures (as intraglandular injections).

Concerning about the patients, all of them and their parents or carers will be given the patients information sheet ([Annex 5](#)) with all the information about the clinical trials. Once the information has been delivered and understudied, the parents will be asked to sign the informed consent ([Annex 6](#)) in order to be enrolled in our trial. The principle of autonomy will be respect in all the process.

According to the Spanish Legislative Royal Decree 223/2004, *del 6 de febrero, para la regulación de los ensayos clínicos con medicamentos*, an insurance policy will be contracted.

According to the Spanish Organic Law 15/1999, *de 13 de diciembre, de Protección de Datos de Carácter Personal* and the later Spanish Legislative Royal Decree 1720/2007, *del 21 de Diciembre*, all the information of the patients (name, surnames, clinical history, etc) will be confidential and the anonymity will be guaranteed in all the trial process. The participants will have the right to consult, modify and delete their personal data from their personal life.

9. STUDY LIMITATIONS

Making a revision of our protocol, there are some limitations that should be taking into consideration because can interfere in our research. The most important limitations are explained below:

- Because we use a non-probabilistic and consecutive recruitment process, we can have a selection bias (called “Healthy worker bias”). The patients that are more concern about their condition will be the one that comes more to the surgery. As a result, these patients will have more chances to be involved in our study.
- During the follow-up, there can be patients that abandon the study because a lack of response with the treatment used. This can be as a result of the treatment but also because of the personal conditions of the patients, letting us without some important information about the effectiveness of the treatment in some specific group of patients.
- As a result of the administration conditions of the different treatments, it is impossible to make a double-blind trial because both patients/parents and the professionals will be aware about the treatment group in which the patient is. To minimize this bias, the health professional that will perform the follow-up and also the statistician will not be aware of which participant belongs to each group.
- Our principal outcome, the decrease of drooling, will be measured with a quality of life scale. This measure is considered a soft endpoint. Consequently, it could be some limitations in the results interpretation.
- As a result of being the parents or carers those who respond the questionnaire used as a principal outcome and the impossibility to blind them can lead to an observer bias. The knowledge of the medication that their child is receiving can influence in their perception of the effectiveness of the treatment.
- Regarding the questionnaire used (DIS), is a validated questionnaire to have proved to be useful for assess the effect of drooling interventions. Because it is not validated in our language (and it is necessary to have a good English comprehension for both administrate and fill the questionnaire), it is need a validation in our language before the start of our clinical trial. The validation will be carried out by an independent group before the beginning of our study.

10. WORK PLAN

INVESTIGATORS: the neuropaediatrics of the paediatric department of the participating hospitals. From each of the 8 participating hospitals, a principal investigator will be chosen in order to create a Trial Steering Committee for coordinate the trial.

COLLABORATORS: nursing staff, a statistician and a pharmacist.

The study will take an overall of 4 years. The organization of the study will be divided in 5 phases, explained bellow:

A. PHASE 1: Coordination phase: (4 months). It will involve the investigators and collaborators.

This phase will be divided in several steps:

- ✓ **Step 1:** Protocol elaboration: formulation of objectives and study variables will be defined to answer a formulated hypothesis. A large literature search will be done. The methodology of the study will be established.
- ✓ **Step 2:** Organizational meeting: to coordinate all the participating hospitals, several meetings will be performed.
- ✓ **Step 3:** Elaboration of a chronogram: after mutual agreement, a chronogram will be designed.
- ✓ **Step 4:** Evaluation of the protocol and authorizations: before the start of the trial, the study will get all the ethical and administrative authorizations after the evaluation of the proper committees.

B. PAHSE 2: Recruitment of patients, intervention and data collection: (3.6 years). It will involve the investigators and collaborators.

This phase will be divided in several steps:

- ✓ **Step 1:** Recruitment of the sample and group assignment: the recruitment of the patients will take place in the neuropaediatric surgery of all the participating hospitals by the investigators.

The investigator will evaluate if the patients meet the inclusion criteria and does not meet the exclusion ones.

After that, all the patients and their parents or carers will be informed about the clinical trial and asked if they want to participate. If they agree, they will be asked to sign the informed consent.

Right after, the patients will be randomized in one of the three groups.

- ✓ **Step 2:** Intervention: each group will receive their treatment according to the medical instructions given. The duration of the treatment will be of a year.
- ✓ **Step 3:** Data collection: in each control visit, all the parameters of our study variables will be collected by our staff. Before the start of the data collection, this staff will be trained in order to do it properly.

All the information recollected, will be updated to our database and will be reviewed periodically so as to assure that the process is being done correctly.

- C. PHASE 3: Processing data base and statistical analysis: (2 months). It will involve the statistician and the investigators.

Because of the long period needed to collect our sample (2.6 years) and the period of follow-up required (1 year), we will do 2 data analysis: one in the middle of the study and one at the end. With this information, in the middle of the process we will know if it is ethical to continue with our study.

The mild-term analysis will be carried out by an independent committee.

- D. PHASE 4: Interpretation of the results: (2 months). It will include the investigators.

After the statistical analysis will be done, the investigators will draw their conclusions about the results.

- E. PHASE 5: Publication of the results: (2 months). It will be done by the investigators.

With all the results, the investigators will write the corresponding papers and will be sent to different medical journals for their publication.

A dissemination strategy will be carried out, apart from the journal publications, presenting the results in a Conference during the Congress of the “Sociedad Española de Neurología Pediátrica in 2020”.

• **CHRONOGRAM:**

	2015		2016			2017	2018		2019			2020	
	N	D	J	F	M-D		J-O	N-D	J-O	N	D	J	F
PHASE 1: Coordination phase(investigators and coordinators)													
Protocol elaboration													
Organizational meeting and elaboration of a chronogram													
Evaluation and authorizations													
PHASE 2: Recruitment of patients, intervention and data collection (investigators and coordinators)													
Recruitment and group assignment													
Intervention													
Data collection													
PHASE 3: Processing data base and statistical analysis (statistician and investigators)													
Statistical analysis													
Mild-term analysis													
PHASE 4: Interpretation of the results (investigators)													
Results interpretation													
PHASE 5: Publication of the results (investigators)													
Final report elaboration													
Publication and dissemination													

11. FEASIBILITY

This clinical trial will take place in 8 hospitals: 4 in Catalunya (Hospital Universitari Josep Trueta de Girona, Hospital Universitari Vall d'Hebron, Hospital Clínic de Barcelola and Hospital Sant Joan de Déu Barcelona) and 4 in Madrid (Hospital Universitario La Paz, Hospital Universitario 12 de octubre, Hospital Universitario Ramón y Cajal and Hospital Infantil Universitario Niño Jesús).

The study will be carried out by the staff of each hospital (neuropaediatrics, nurses and a pharmacist). We will also hire a statistical for the statistical analysis.

The medication will be bought by each hospital and prepared by the nurses or the pharmacological department if it is necessary.

The hospitals will provide the needed informatics equipment for the data collection. In our reference hospital (Hospital Universitari Josep Trueta de Girona), an informatics room will be transferred to our statistical for the analysis of the data.

Interventions will be performed by the same team in each hospital. All of them have a large experience administrating the three treatment options.

It is estimated that we will need 2.6 years to asses our sample. Because there are not a drooling register, this is just an approximation based on the birth rate of the two autonomous regions involved. We cannot predict exactly the number of patients that will come to our surgeries and it is possible that not every patient meet the inclusion criteria. For these reasons, is possible that the recruitment period will have to be prolonged.

12. BUDGET

EXPENSES	COSTS
STAFF COSTS	0€
MATERIALS AND SERVICES	
1) Medication:	
Trihexyphenidyl*	300€/patient/year (103 patients, 1 year)= 30.900€
Glycopyrrolate*	2710€/patient/year (103 patients, 1 year)= 279.130€
Botulinum Toxin A*	430€/patient/year (103 patients, 1 year)= 44.290€
2) Medical devices:	
Needles, syringes and gauzes	30€
3) Insurance:	
Insurance policy	10.000€
4) Statistical expert	35€/h (100h of work)= 3.500€
5) Scientific publications	1.500€
6) AEMPS authorisation application	1.500€
TRAVELS AND ALLOWANCES	
1) Coordination meetings:	
Travels, accommodation and allowances	500€
2) Paediatric Congress:	
Congress registration	500€
Travel, accommodation and allowance	300€
TOTAL	372.150€

* In the three treatment groups, the cost of the medication has been calculated based on the maximum dose possible.

13. IMPACT ON THE NATIONAL HEALTH SYSTEM

Drooling is a really common problem in children with CP (over a 40% of them). In these children, this condition has a huge impact in their daily life in terms of social inclusion (they tend to be rejected by others and isolated), self-esteem (it can lead to a lower self-esteem) and also can have a negative repercussion in their health (like skin problems or respiratory infections due to aspiration of the saliva).

Despite all the problems that drool implies there is not a standardized treatment for managed it. There are a lot of treatment options, like oral-motor therapies, drugs, surgery, etc. There are several studies that prove the effectiveness of all these different treatments, but there are not so many that compares the different options between them.

Because this reason, the clinical practise is based on the professional expertise of the doctor who treats the patient. Normally, the treatment starts with an anticholinergic drug and, when this fails, professionals choose between changing to another anticholinergic drug and proving another technique like BoTA injections or even surgery. The main problem is that there is not enough scientific evidence about the benefits of one option over another.

With this study we want to compare the three most used treatment options in our area in order to decide which one is the best and in which order we have to act. Our aim is to prove that the new treatment option, the BoTA injections, is the best treatment option and the one with fewer side effects. In addition, the administration of the medication (despite the fact that is an invasive procedure) it is needed just each 4-6 months and usually is performed under anaesthesia. For all these reasons, it seems beneficial for this kind of patients that normally have more impairments and need several treatments.

Even though BoTA injections treatment is not the cheapest treatment (it is the trihexyphenidyl treatment), the fewer side effects expected can lead to a decrease of medical consultation and also hospital stays, which means a decrease of hospital costs.

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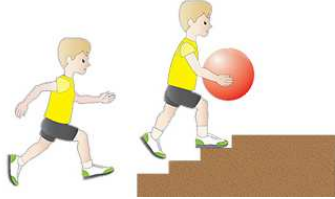

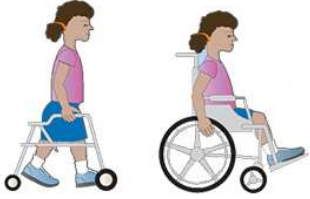


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15. ANNEXES

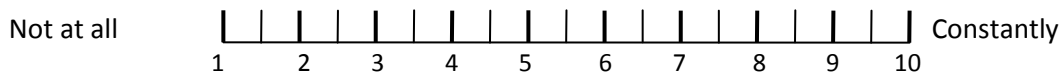
ANNEX 1: GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM³

LEVEL	DESCRIPTION	EXAMPLE
I	<p>ABILITIES:</p> <ul style="list-style-type: none"> - Perform usual activities (like running or jumping). - Walk indoors and outdoors and climb stairs without the need of the hands for support. <p>LIMITATIONS:</p> <ul style="list-style-type: none"> - Decrease of speed, balance and coordination. 	
II	<p>ABILITIES:</p> <ul style="list-style-type: none"> - Walk indoors and outdoors and climb stairs with a railing. <p>LIMITATIONS:</p> <ul style="list-style-type: none"> - Difficulties with uneven surfaces, inclines or in crowds. - Minimal ability to run or jump. 	
III	<p>ABILITIES:</p> <ul style="list-style-type: none"> - Walk with assistive mobility devices indoors and outdoors on level surfaces. - May be climb stairs using a railing. <p>LIMITATIONS:</p> <ul style="list-style-type: none"> - May be needs a wheelchair (the child can propel manually for a short distances and may require assistance for long ones or uneven surfaces). 	
IV	<p>LIMITATIONS:</p> <ul style="list-style-type: none"> - The walking ability is severely limited even with assistive devices. - The child needs the use of wheelchairs most of the time (they may propel a power wheelchair). <p>ABILITIES:</p> <ul style="list-style-type: none"> - The child may participate in standing transfers. 	
V	<p>LIMITATIONS:</p> <ul style="list-style-type: none"> - Impairment in all the motor function areas. - Important restriction of voluntary control of movements and the ability to maintain head and neck position against gravity. - Impossibility to sit or stand independently (even with adaptive equipment). - Impossibility to walk independently (may be able to use powered mobility). 	

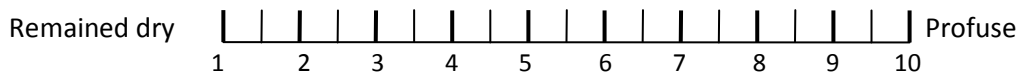
³ Table adapted from: <https://www.cerebralpalsy.org.au/what-is-cerebral-palsy/severity-of-cerebral-palsy/gross-motor-function-classification-system/>

ANNEX 2: DROOLING IMPACT SCALE⁴

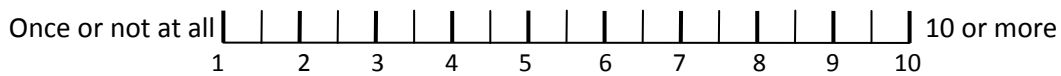
1. How frequently did your child dribble?



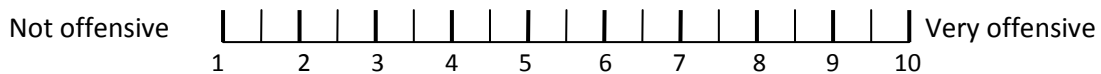
2. How severe was the drooling?



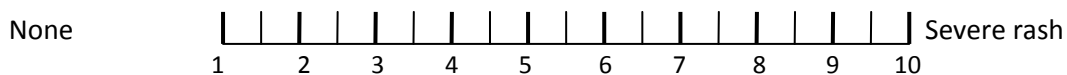
3. How many times a day you have to change bibs or clothing due to drooling?



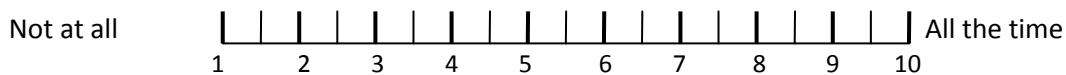
4. How offensive was the smell of the saliva on your child?



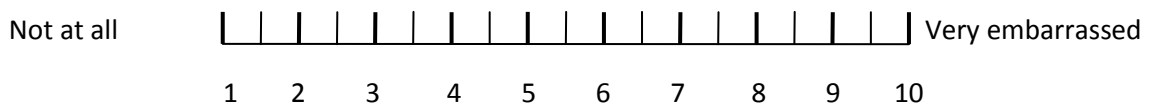
5. How much skin irritation has your child had due to drooling?



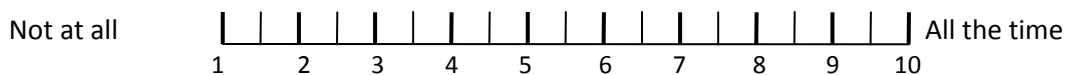
6. How frequently did your child's mouth need wiping?



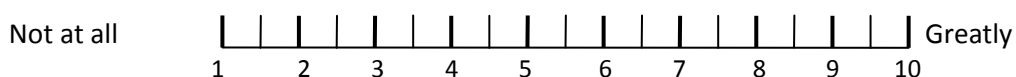
7. How embarrassed did your child seem to be about his/her dribbling?



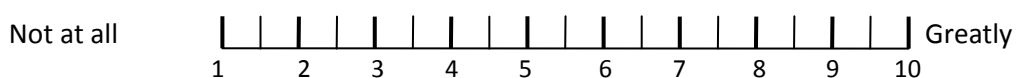
8. How much do you have to wipe or clean saliva from household items, e.g. toys, furniture, computers?



9. To what extend did your child's drooling affect his or her life?



10. To what extend did your child's dribbling affect you and your family's life?



⁴ Image from: Reid S, Johnson H, Reddihough D. The Drooling Impact Scale: a measure of the impact of drooling in children with developmental disabilities. Dev Med Child Neurol. 2010;52(2):e23-8

ANNEX 3: SIDE EFFECTS

Have your child experimented any of these following symptoms?

SIDE EFFECTS		
Constipation	YES	NO
Vomiting	YES	NO
Diarrhoea	YES	NO
Urinary retention	YES	NO
Fever	YES	NO
Dry mouth	YES	NO
Respiratory infections: sinusitis, pneumonia, bronchitis, etc.	YES	NO
Eating or swallowing problems	YES	NO
Pain, hematoma or swelling in the injection site	YES	NO
Irritability, hyperactivity, restlessness, etc	YES	NO
Others (explain them)	YES	NO

• **CATALAN/ SPANISH VERSION:**

Ha experimentat algun dels següents símptomes?/¿Ha experimentado alguno de los siguientes síntomas?

EFECTES SECUNDARIS/EFECTOS SECUNDARIOS		
Estrenyiment/Estreñimiento	SÍ	NO
Vòmits/Vómitos	SÍ	NO
Diarrea/Diarrea	SÍ	NO
Retenció urinària/Retención urinaria	SÍ	NO
Febre/Fiebre	SÍ	NO
Boca seca/Boca seca	SÍ	NO
Infeccions respiratòries: sinusitis, pneumònia, bronquitis, etc./Infecciones respiratorias: sinusitis, neumonía, bronquitis, etc.	SÍ	NO
Problemes per menjar o deglutir/ Problemas para comer o tragar	SÍ	NO
Dolor, hematoma o inflor al lloc de la injecció/ Dolor, hematoma o hinchazón en el lugar de la inyección	SÍ	NO
Irritabilitat, hiperactivitat, agitació, etc./Irritabilidad, hiperactividad, agitación, etc.	SÍ	NO
Altres (expliqui'ls)/ Otros (explíquelos)	SÍ	NO

ANNEX 4: TREATMENT'S SATISFACTION

Are you satisfied with your child's treatment?	
Very dissatisfied.	
Dissatisfied.	
Neither.	
Satisfied.	
Very satisfied.	

- CATALAN/SPANISH VERSION:

Està satisfet amb el tractament del seu fill? / ¿Está satisfecho con el tratamiento de su hijo?	
Molt insatisfet/Muy insatisfecho	
Insatisfet/Insatisfecho	
Ni sí ni no/Ni sí ni no	
Satisfet/Satisfecho	
Molt satisfet/Muy satisfecho	

ANNEX 5: INFORMATION SHEET

- **CATALAN VERSION**

Hospital's information	FULL DE CONSENTIMENT	Drooling treatment in children with cerebral palsy: a multicenter, controlled, randomized, clinical trial.
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FULL D'INFORMACIÓ SOBRE L'ASSAIG CLÍNIC:

DROOLING TREATMENT IN CHILDREN WITH CEREBRAL PALSY: A MULTICENTER, CONTROLLED, RANDOMIZED CLINICAL TRIAL.

L'equip d'investigadors clínics del Servei de Pediatria de l'Hospital Universitari Josep de Girona, juntament amb els equips d'investigadors clínics de la resta d'hospitals participants en l'estudi, proposa la realització de l'estudi citat, basat en observacions pròpies i en treballs científics d'investigació mèdica.

INTRODUCCIÓ:

La sialorrea és un problema freqüent que afecta als nens que pateixen paràlisi cerebral. La prevalença de sialorrea en aquesta població ronda el 40%.

La sialorrea es caracteritza per la impossibilitat de gestionar la saliva i la seva eliminació i la conseqüent caiguda d'aquesta més enllà del marge del llavi. Tot i que no és un problema que amenaci la vida d'aquests pacients, el baveig excessiu pot comportar múltiples problemes a la vida d'aquests nens: des de rebuig per part de la societat, aïllament social o baixa autoestima, fins problemes mèdics com irritació de pell o infeccions respiratòries per aspiració de saliva. Hi ha múltiples tractaments per a la sialorrea, però cap ha demostrat acabar amb el problema i hi ha poca informació sobre quina és la millor tècnica a fer servir.

OBJETIU I REALIZACIÓ DE L'ESTUDI:

L'estudi actual pretén definir quin tractament, entre els més utilitzats en el nostre medi, és més efectiu en el tractament de la sialorrea i els hi reporta una millor qualitat de vida a aquests pacients. A més d'aquest objectiu principal, aquest estudi també pretén determinar quina opció terapèutica comporta menys efectes secundaris (a curt i llarg termini) i també amb quin tractament les famílies dels pacients estan més satisfetes.

PROCEDIMENTS:

Els tres medicament objecte d'aquest estudi son: trihexifenidil, glicopirrolat i toxina botulínica. Els tres han demostrat la seva eficàcia en la disminució de la sialorrea i la seva seguretat per al seu ús en nens amb paràlisi cerebral.

Un cop feta la primera visita i determinat si el pacient és candidat a ser inclòs en el nostre estudi, i prèvia informació del procediment de l'estudi als pares o tutors dels pacients i la firma del consentiment informat, es distribuirà als pacients en 3 grups de forma aleatòria. Cada grup rebrà un dels tres tractaments objecte de l'estudi. El tractament durarà UN ANY, durant el qual es faran 5 visites de control per valorar l'efectivitat i els efectes secundaris del tractament. Les visites es realitzaran el primer mes de tractament, el segon, el quart, el sisè i el dotzè. En cada visita es valorarà si la qualitat de vida dels pacients ha millorat i quins són els efectes secundaris experimentats. En la darrera visita, a més es valoraran els efectes secundaris a llarg termini i la satisfacció de la família amb el tractament.

En la següent taula s'indica el calendari de visites i les mesures a valorar:

Mesures clíniques	Inicial	1 mes	2 mesos	4 mesos	6 mesos	12 mesos
Droling Impact Scale (DIS)	X	X	X	X	X	X
Efectes secundaris a curt termini	X	X	X	X	X	
Efectes secundaris a llarg termini						X
Satisfacció de la família amb el tractament						X

POSSIBLES BENEFICIS:

La participació en aquest estudi implica que el seu fill prendrà un tractament de forma aleatòria que, si bé ha demostrat la seva eficàcia per disminuir la sialorrea, és possible que no sigui la millor opció terapèutica. Nosaltres preveiem que la millor opció serà l'ús d'injeccions de toxina botulínica intragladulars. Si es demostra la nostra hipòtesis, el tractament de la sialorrea podrà passar d'haver de seguir un tractament diari i amb bastants efectes secundaris a un tractament administrat dos cops a l'any i del que s'han reportat molts pocs efectes secundaris.

RISCS I INCONVENIENTS:

Els medicaments objecte de l'estudi, encara que generalment són ben tolerats, poden causar efectes secundaris digestius, urinaris, de visió, de sequedat bucal o alteracions del comportament. Tots els participants estaran estricament vigilats en quant a la seguretat del tractament.

Durant l'estudi es realitzaran controls clínics els mesos 1, 2, 4, 6 i 12 del tractament. Si en alguna de les visites de seguiment es detecta algun efecte secundari greu, es suspendrà immediatament la medicació i el prendran les mesures necessàries.

Tots els pacients de l'assaig tenen una assegurança clínica segons el Real Decreto 223/2004, *del 6 de febrero, para la regulaci3n de los ensayos clínicos con medicamentos*, per fer front a possibles eventualitats derivades de l'assaig. Tots els esdeveniments greus que es manifestin durant l'estudi, es considerin o no relacionats amb el mateix, s'hauran de comunicar a l'investigador principal (telèfon: 972809070).

PARTICIPACI3 VOLUNTÀRIA:

La participació del seu fill/a en aquest assaig clínic és voluntària, per la qual cosa, tot i que inicialment acceptés participar, vostè podrà sol·licitar als responsables de l'estudi, en qualsevol moment i sense necessitat d'especificar el motiu, la baixa de l'estudi així com l'eliminació de tota la informació recollida, sense que això repercuteixi en les seves cures mèdiques.

Pot comentar la informació recollida amb la seva família, amb el seu metge o amb qualsevol que consideri oportú per a sentir-se ben aconsellat. El metge de l'estudi li contestarà qualsevol pregunta o dubte que no hagi quedat clar.

COMPENSACIÓ:

Els investigadors no tenen benefici econòmic amb aquest estudi.

La seva participació no li suposarà cap despesa i els hi seran reintegrats les despeses extraordinàries (com menjars i trasllats) si vostè ho sol·licita. Vostè no haurà que pagar per els medicaments administrats durant l'estudi.

CONFIDENCIALITAT:

Totes les dades de caràcter personal i informació recollida o generada a l'estudi quedaran protegides d'acord amb la legislació vigent sobre protecció de dades de caràcter personal (Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal y el posterior Real Decreto 1720/2007, del 21 de Diciembre). Ningú, excepte el seu metge i el personal directament relacionat amb aquest estudi, podrà conèixer la seva identitat. Únicament les autoritats sanitàries podran tenir accés a les seccions rellevants de l'estudi, si així ho sol·liciten.

- **SPANISH VERSION**

Hospital's information	HOJA DE CONSENTIMIENTO	Drooling treatment in children with cerebral palsy: a multicenter, controlled, randomized clinical trial.
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HOJA DE INFORMACIÓN SOBRE EL ENSAYO CLÍNICO:

DROOLING TREATMENT IN CHILDREN WITH CEREBRAL PALSY: A MULTICENTER, CONTROLLED, RANDOMIZED CLINICAL TRIAL.

El equipo de investigadores clínicos del Servicio de Pediatría del Hospital Universitario Josep Trueta de Girona, junto con los equipos de investigadores clínicos del resto de los hospitales participantes en el estudio, propone la realización del estudio mencionado, basado en observaciones propias y en trabajos científicos de investigación médica.

INTRODUCCIÓN:

La sialorrea es un problema frecuente que afecta a los niños que padecen parálisis cerebral. La prevalencia de sialorrea en esta población ronda el 40%.

La sialorrea se caracteriza por la imposibilidad de manejar la saliva y su eliminación y la consecuente caída de esta más allá del margen del labio. Aunque no es un problema que amenace la vida de estos pacientes, el babeo excesivo puede acarrear múltiples problemas en la vida de estos niños: desde rechazo por parte de la sociedad, aislamiento social o baja autoestima, hasta problemas médicos como irritación de piel o infecciones respiratorias por aspiración de saliva.

Hay múltiples tratamientos para la sialorrea, pero ninguno ha demostrado acabar con el problema y hay poca información sobre cuál es la mejor técnica a usar.

OBJETIVO Y REALIZACIÓN DEL ESTUDIO:

El estudio actual pretende definir qué tratamiento, de entre los más usados en nuestro medio, es más efectivo en el tratamiento de la sialorrea y les reposta una mejor calidad de vida a estos pacientes. Además de este objetivo principal, este estudio también pretende determinar qué opción terapéutica conlleva menos efectos secundarios (a corto y largo plazo) y también con qué tratamiento las familias de los pacientes están más satisfechos.

PROCEDIMIENTOS:

Los tres medicamentos objeto de este estudio son: trihexifenidilo, glicopirrolato y toxina botulínica. Los tres han demostrado su eficacia en la disminución de la sialorrea y su seguridad para su uso en niños con parálisis cerebral.

Una vez hecha la primera visita y determinado si el paciente es candidato a ser incluido en nuestro estudio, y previa información del procedimiento del estudio a los padres o tutores de los pacientes y la firma del consentimiento informado, se distribuirá a los pacientes en 3 grupos de forma aleatoria. Cada grupo recibirá uno de los tres tratamientos objeto del estudio. El tratamiento durará UN AÑO, durante el cual se harán 5 visitas de control para valorar la efectividad y los efectos secundarios del tratamiento. Las visitas se realizarán el primer mes de tratamiento, el segundo, el cuarto, el sexto y el doceavo. En cada visita se valorará si la calidad de vida de los pacientes ha mejorado y cuáles son los efectos secundarios experimentados. En la última visita, se valorará además, los efectos secundarios a largo plazo y la satisfacción de la familia con el tratamiento.

En la siguiente tabla se indica el calendario de visitas y las medidas a valorar:

Medidas clínicas	Inicial	1 mes	2 meses	4 meses	6 meses	12 meses
Droling Impact Scale (DIS)	X	X	X	X	X	X
Efectos secundarios a corto plazo	X	X	X	X	X	
Efectos secundarios a largo plazo						X
Satisfacción de la familia con el tratamiento						X

POSIBLES BENEFICIOS:

La participación en este estudio implica que su hijo tomará un tratamiento de forma aleatoria que, si bien se ha demostrado su eficacia para disminuir la sialorrea, es posible que no sea la mejor opción terapéutica. Nosotros prevemos que la mejor opción será el uso de inyecciones de toxina botulínica intraglandulares. Si se demuestra nuestra hipótesis, el tratamiento de la sialorrea podrá pasar de tener que seguir un tratamiento diario y con bastantes efectos secundarios a un tratamiento administrado dos veces al año y del que se han reportado muy pocos efectos secundarios.

RIESGOS E INCONVENIENTES:

Las medicaciones objeto de estudio, aunque son generalmente bien toleradas, pueden causar efectos secundarios digestivos, urinarios, de visión, de sequedad bucal o alteraciones del comportamiento. Todos los pacientes estarán estrictamente vigilados en cuanto a la seguridad del tratamiento.

Durante el estudio se realizarán controles clínicos en los meses 1, 2, 4, 6 y 12 del tratamiento. Si en alguna de las visitas de seguimiento se detecta algún efecto secundario grave, se suspenderá inmediatamente la medicación y se tomarán las medidas necesarias.

Todos los pacientes del ensayo tienen un seguro clínico según el Real Decreto 223/2004, *del 6 de febrero, para la regulación de los ensayos clínicos con medicamentos*, para hacer frente a posibles eventualidades derivadas del ensayo. Todos los acontecimientos graves que se manifiesten durante el estudio, se consideren o no relacionadas con el mismo, se deben comunicar al investigador principal (teléfono: 972809070).

PARTICIPACIÓN VOLUNTARIA:

La participación de su hijo/a en este ensayo clínico es voluntaria, por lo que, aunque inicialmente aceptara participar, usted podrá solicitar a los responsables del estudio, en cualquier momento y sin necesidad de especificar el motivo, la baja del estudio así como la eliminación de toda la información recogida, sin que esto repercuta en sus cuidados médicos.

Puede comentar la información recibida con su familia, con su médico o con quien considere oportuno para sentirse bien aconsejado. El médico del estudio le contestará a cualquier pregunta o duda que no haya quedado clara.

COMPENSACIÓN:

Los investigadores no tienen beneficio económico con este estudio.

Su participación en el estudio no le supondrá ningún gasto y les serán reintegrados los gastos extraordinarios (como comidas y traslados) si usted lo solicita. Usted no tendrá que pagar por los medicamentos administrados durante el estudio.

CONFIDENCIALIDAD:

Todos los datos de carácter personal e información recogida o generada en el estudio quedarán protegidos de acuerdo a la legislación vigente sobre protección de datos de carácter personal (Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal y el posterior Real Decreto 1720/2007, del 21 de Diciembre). Nadie, excepto su médico y el personal directamente relacionado con este estudio, podrá conocer su identidad. Únicamente las autoridades sanitarias podrán tener acceso a las secciones relevantes del estudio, si así lo solicitaran.

ANNEX 6: INFORMED CONSENT

• **CATALAN VERSION**

Hospital's information	FULL DE CONSENTIMENT	Drooling treatment in children with cerebral palsy: a multicenter, controlled, randomized clinical trial.
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CONSENTIMENT PER ESCRIT DELS PARES/TUTORS

TITOL DE L'ESTUDI: Drooling treatment in children with cerebral palsy: a multicenter, controlled, randomized clinical trial.

Jo.....

Com a pare, mare o tutor del nen/nena:

Confirmo que:

He llegit el full d'informació que se m'ha entregat.

He pogut fer preguntes sobre l'estudi.

S'han respost les meves preguntes de manera satisfactòria.

He rebut suficient informació sobre l'estudi.

He parlat amb (nom de l'investigador/pediatra/infermer):.....

Comprendc que la participació es voluntària, i que puc retirar-me de l'estudi quan vulgui, sense que això repercuteixi en les cures mèdiques i sense donar explicacions.

En conseqüència,

Dono la meva conformitat perquè el meu fill/filla participem en aquest estudi.

Sí No

Permeto que la informació que s'obtingui d'aquest estudi sigui utilitzada en investigacions futures relacionades amb nens amb malalties del neurodesenvolupament.

Sí No

Permeto que la informació sigui introduïda en la base de dades de l'hospital.

Sí No

Signatura del pare/mare/tutor del participant:

Signatura de l'investigador:

Data: ___ / ___ / ___

Data: ___ / ___ / ___

• **SPANISH VERSION**

Hospital's information	HOHA DE CONSENTIMIENTO	Drooling treatment in children with cerebral palsy: a multicenter, controlled, randomized clinical trial.
------------------------	------------------------	---

CONSENTIMIENTO POR ESCRITO DE LOS PADRES/TUTORES

TÍTULO DEL ESTUDIO: Drooling treatment in children with cerebral palsy: a multicenter, controlled, randomized clinical trial.

Yo.....

Como padre, madre o tutor del niño/niña:

Confirmando que:

He leído la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio.

Se han respondido mis preguntas de forma satisfactoria.

He recibido suficiente información sobre el estudio.

He hablado con (nombre del investigador/pediatra/enfermero):.....

Entiendo que la participación es voluntaria, y que puedo retirarme del estudio cuando quiera, sin que esto repercuta en los cuidados médicos y sin dar explicaciones.

En consecuencia,

Doy mi conformidad para que mi hijo/hija participe en este estudio.

Sí No

Permito que la información que se obtenga de este estudio sea utilizada en investigaciones futuras relacionadas con niños con enfermedades del neurodesarrollo.

Sí No

Permito que la información sea introducida en la base de datos del hospital.

Sí No

Firma del padre/madre/tutor del participante:

Firma del investigador:

Fecha: ___ / ___ / ___

Fecha: ___ / ___ / ___

ANNEX 7: DATA COLLECTION SHEET

CENTER NUMBER

--	--	--	--	--	--

PATIENT IDENTIFICATION NUMBER

--	--	--	--	--	--

AGE:

SEX:

MEDICAL INFORMATION:

Intellectual impairment:

GMFCS:

Type of CP:

Epilepsy:

Oral-motor problems:

BASELINE STATUS	
DROOLING IMPACT SCALE	<input style="width: 100px; height: 20px;" type="text"/>
<i>(Indicate the DIS score)</i>	

VISIT 1st MONTH	
- DROOLING IMPACT SCALE	<input style="width: 100px; height: 20px;" type="text"/>
<i>(Indicate the DIS score)</i>	
- SIDE EFFECTS	<div style="border: 1px solid black; height: 100px;"></div>
<i>(Write the side effects experimented by the patient)</i>	

VISIT 2nd MONTH	
- DROOLING IMPACT SCALE	<input style="width: 100px; height: 20px;" type="text"/>
<i>(Indicate the DIS score)</i>	
- SIDE EFFECTS	<div style="border: 1px solid black; height: 100px;"></div>
<i>(Write the side effects experimented by the patient)</i>	

VISIT 3rd MONTH

- DROOLING IMPACT SCALE

(Indicate the DIS score)

- SIDE EFFECTS

*(Write the side effects
 experimented by the patient)*

VISIT 4th MONTH

- DROOLING IMPACT SCALE

(Indicate the DIS score)

- SIDE EFFECTS

*(Write the side effects
 experimented by the patient)*

VISIT 5th MONTH

- DROOLING IMPACT SCALE

(Indicate the DIS score)

- SIDE EFFECTS

*(Write the side effects
 experimented by the patient)*

- TREATMENT SATISFACTION

*(Mark the parent's opinion
 regarding their satisfaction
 with the treatment)*

Very dissatisfied.	
Dissatisfied.	
Neither.	
Satisfied.	
Very satisfied.	