Nebulised HS in children and young people with NMD or CP

A Chart Review assessing the effect of Nebulised Hypertonic Saline on Respiratory-related complications in children and young people with Neuromuscular Disease or Cerebral Palsy

Version 2, 04/04/2018

FUNDERS: This section does not apply

IRAS Project ID: 243535
REC reference: 18/YH/0103

Protocol authorised by:

Name & Role	Date	Signature

Study Management Group

Chief Investigator: Hui-Leng Tan

Co-investigators: Natalia Galaz Souza

Statistician: Mark Rosenthal

Study Management:

Clinical Queries

Clinical queries should be directed to Dr. Hui-Leng Tan who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
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Funder

[This section does not apply]

This protocol describes the Nebulised Hypertonic Saline in children with Neuromuscular disease or Cerebral Palsy study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DOB	Date of Birth
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ID	Identification number
ISF	Investigator Site File
NHANES	National Health and Nutrition Examination Survey
PI	Principal Investigator
PIS	Participant Information Sheet
RB&HFT	Royal Brompton and Harefield NHS Foundation
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SP	Subject Patient
VAS	Visual Analogue Scale

KEYWORDS

[Nebulised Hypertonic Saline, Neuromuscular disease, Cerebral Palsy, Children, Respiratory complications, Polygraphy]

STUDY SUMMARY

TITLE A Chart Review assesing the effects of Nebulised Hypertonic Saline on Respiratory-related complications in children and young people with Neuromuscular Disease or Cerebral Palsy

DESIGN Chart Review and Questionnaire application

AIMS 1)To explore whether treatment with 7% or 3% nebulised Hypertonic Saline in children and young people with Neuromuscular Disease or Cerebral Palsy decreases respiratory-related complications.

2) Assess whether the use of 3% or 7% nebulised Hypertonic Saline improves ease of airway clearance in children and young people with Neuromuscular Disease or Cerebral Palsy

OUTCOME MEASURES 1) Number of respiratory exacerbations requiring antibiotic treatment.

2) Number of hospitalisations due to respiratory exacerbations, using NHANES 2011 questionnaire for Hospitalisation and access to care HUQ.010.

3) Nocturnal oximetry and polygraphy outcomes: BasalSpO2 (%), Minimum SpO2 (%),Maximum SpO2 (%), Average SpO2, Oxygen desaturation index (ODI), Snoring and End tidal CO2 (EtCO2).

4) Rate of decline of pulmonary function.

5) Score on the ease of airway clearance pictorial analogue scale from participants.

6) Participants' perception of treatment.

POPULATION Children and young people with Neuromuscular disease or Cerebral Palsy who are treated at Royal Brompton Hospital and their parents or legal guardians.

ELIGIBILITY Inclusion cirteria: Children and young people with Neuromuscular disease or Cerebral Palsy who have their care at the Royal Brompton Hospital and are on treatment with nebulised Hypertonic Saline for at least 12 months.

Exclusion criteria: Children or young people also diagnosed with Cystic Fibrosis.

DURATION 6 months

REFERENCE DIAGRAM

[if appropriate]

1. INTRODUCTION

1.1 BACKGROUND

In the UK, Neuromuscular diseases have a prevalence of 118 per 100,000 people amongst adults and children. About 70% are inherited, and 13% are muscular dystrophies (1). Worldwide, the prevalence of Cerebral Palsy is 2.11 per 1000 live births (2).

The pathophysiology of neuromuscular diseases and cerebral palsy leads to restrictive pathology of the respiratory system. Children with neuromuscular diseases have several characteristics that may impair their respiratory function, such as weak bulbar and respiratory musculature, increased upper airway collapsibility and low lung compliance (3,4). Cerebral Palsy is defined as a group of disorders of the motor function, caused by a disturbance to the developing brain (5). Although pulmonary disease is not the primary diagnosis, some clinical characteristics may lead to respiratory failure. These include scoliosis, gastroesophageal reflux, and impaired swallowing, which leads to chronic aspiration, upper airway obstruction, recurrent infections, and possible bronchiectasis, developing lung disease (6). Bulbar musculature weakness impairs swallowing, which leads to chronic aspiration. Respiratory muscle weakness compromises the pump function and the effectiveness of cough. Upper airway collapsibility increases work of breathing and respiratory muscle fatigue. Low pulmonary compliance hinders the ability to expand the lung, which is exacerbated by respiratory muscle weakness, increasing the WOB. Low peak flow and decreased Vital Capacity (VC), which further decreases with progression of the disease (7), characterizes the pulmonary function of these patients. Consequently, cough may be impaired by low inspiration volumes, ineffective glottis closure and/or low expiratory force (4,8,9). Low Vital Capacity and ineffective cough in Neuromuscular disease has been associated with chronic airway inflammation and infection (9). Furthermore, children with Neuromuscular disease often have gastroesophageal reflux (GER) (10), which may cause airway inflammation (11). Chronic airway infection and colonisation of Pseudomonas aeruginosa and Gram-negative microorganisms have shown to increase morbidity of children with CP (12). GER, impaired swallowing and ineffective cough leads to chronic aspiration and contributes to recurrent pneumonias. Therefore, bronchiectasis and pulmonary fibrosis are commonly developed.

Children with Neuromuscular disease show a decline of Forced Vital Capacity (FVC), which is steeper at younger ages (13). This is especially important because the age at which FVC reaches 1 Lt and the rate of decline of FVC are variables that can predict mortality (14).

Pneumonia, respiratory exacerbations and failure are one of the most important causes of emergency admissions, hospitalisations and death in children with neuromuscular diseases and cerebral palsy (15-18). Physical health and the number of days spent outside home or hospitalised are important domains of life and predictor of Health-Related Quality of Life in children with Neuromuscular disease and children with Cerebral Palsy (19,20). In this context, it is of importance to research how to therapeutically aid airway clearance, decrease respiratory exacerbations and reduce the pulmonary function rate of decline.

Hypertonic Saline is a solution of salt water used as a nebulized medication in many conditions. Its clinical benefits include mucus clearance, microbiological diagnosis, improvement of lung function, decrease in respiratory exacerbations, cough triggering and improvement of quality of life (21). It has mucolytic and expectorant effect, reduces biofilm formation by Pseudomonas Aeruginosa and increases antioxidative thiols in the airway liquid (22).

Retrospective studies and clinical trials have shown that inhaled Hypertonic Saline is well tolerated, reduces pulmonary exacerbations, improves lung function and Lung Clearance Index, reduces absenteeism, improves Health Related Quality of Life in patients with Cystic Fibrosis independent of rhDNase treatment (23-26), and has anti-inflammatory effect in sputum decreasing

IL-8 (27). In asthmatic and healthy subjects, inhaled Hypertonic Saline have shown to enhance mucociliary clearance (28). To date, studies investigating Hypertonic Saline in bronchiectasis have produced conflicting results (29).

This study aims to assess the effectiveness of the use of nebulised Hypertonic Saline in respiratory outcomes in children and young people with Neuromuscular disease or with Cerebral Palsy.

1.2 RATIONALE FOR CURRENT STUDY

[To our knowledge, there is currently no available data concerning the use of nebulised Hypertonic Saline in the management of children and young people with Neuromuscular Disease or with Cerebral Palsy. This study aims to assess whether the use of nebulised Hypertonic Saline in children and young people with Neuromuscular disease or Cerebral Palsy is effective in the management and prevention of respiratory-related complications.

Hypothesis: Nebulised Hypertonic Saline in children and young people with Neuromuscular disease or Cerebral Palsy decreases respiratory-related complications.]

2. STUDY OBJECTIVES

[Primary Objective: To explore whether treatment with 3% and 7% Nebulised Hypertonic Saline in children and young people with Neuromuscular Disease or Cerebral Palsy decreases respiratory-related complications.

Secondary Objectives:
- Assess the effect of the treatment with nebulised hypertonic saline in children and young people with Neuromuscular disease or Cerebral Palsy on the number of courses of antibiotic prescribed compared to year before starting treatment.
- Determine whether the use of nebulised Hypertonic Saline in children and young people with Neuromuscular Disease or Cerebral Palsy reduces the frequency of hospitalisations due to respiratory exacerbations compared to year before commencing treatment.
- Explore the impact of the treatment with hypertonic saline on nocturnal oxygenation and ventilation in children and young people with Neuromuscular disease or with Cerebral Palsy.
- Evaluate whether the treatment with nebulised hypertonic saline in children and young people with neuromuscular disease or cerebral palsy improves the ease of airway clearance.
- In the subgroup of participants with neuromuscular disease who can perform spirometry, assess whether the use of Hypertonic Saline decreases rate of decline of pulmonary function compared to year before commencing treatment.
- Explore how parents of children and young people with Neuromuscular disease or with Cerebral Palsy perceive the treatment with nebulised hypertonic saline compared to previous management.
]

3. STUDY DESIGN

[Chart review of children and young people with Neuromuscular disease or with Cerebral Palsy who are cared for in the Royal Brompton Hospital and that have been treated with nebulised hypertonic saline for at least 12 months. Children and young people who are also diagnosed with Cystic Fibrosis will be excluded.

Parents or legal guardians will be asked to complete two questionnaires to further complement data from hospital records.

Participants between 10 and 18 years old will be asked to complete one questionnaire to complement hospital records.]

[Duration: 6 months.]

[We aim to review all charts of participants recruited that meet criteria between December 2011 and May 2018. We aim to recruit 40 participants from each group, including children, young people, and parents or legal guardians, as this will be a pilot study. Only participants recruited will have their charts reviewed]

3.1 STUDY OUTCOME MEASURES

Primary Endpoints:
- Number of respiratory exacerbations requiring antibiotic treatment.
- Number of hospitalsiations due to respiratory exacerbations, using NHANES 2011 questionnaire for Hospitalisation and access to care HUQ.010.
- Nocturnal oximetry and polygraphy outcomes: Basal SpO2 (%), Minimum SpO2 (%), Maximum SpO2 (%), Average SpO2 (%), Oxygen desaturation index (ODI), Snoring and End tidal CO2 (EtCO2).
- Rate of decline of pulmonary function.

Secondary Endpoints:
- Score on the ease of airway clearance pictorial analogue scale from all participants.
- Participants' perception of treatment.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

[This section does not apply]

4.2 INCLUSION CRITERIA

[Children and young people under 18 years old with Neuromuscular disease or with Cerebral Palsy treated with nebulised Hypertonic Saline for at least 12 months and their parents or legal guardians.]

4.3 EXCLUSION CRITERIA

[Children or young people who are also diagnosed with Cystic Fibrosis, as the effectiveness of nebulised Hypertonic Saline have already been studied extensively in this group.]

4.4 WITHDRAWAL CRITERIA

[This section does not apply.]

5. ASSESSMENT AND FOLLOW-UP

[This section does not apply]

6. STATISTICS AND DATA ANALYSIS

[Sample Size:

We aim to recruit 40 participants for each group, including children and young people and their parents or legal guardians, as this is a pilot study.

Statistical Analysis Plan:

Primary endpoint analysis:
- Univariate X^2 analysis for categorical variables to investigate ***Courses of antibiotic treatment.***
- Univariate X^2 analysis for categorical variables to investigate ***Number of hospitalisations***.

- Student t testing will be used to analyse ***nocturnal oxygenation and ventilation outcomes*** comparing one year before and after starting treatment with Hypertonic Saline.

- Independent t testing and Mann-Whitney U test to analyse ***Rate of decline in pulmonary function***.

- Cox proportional hazard model to test differences in primary endpoints ***for different baseline FVC***.

Secondary enpoint analysis:
- Univarate analysis to analyse ***Ease of airway clearance.***

- Univariate analysis on ***perception of treatment***.]

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

7. REGULATORY ISSUES

7.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Yorkshire & The Humber - Leeds West Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

7.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

7.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

7.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

7.5 SPONSOR
Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

7.6 FUNDING
This section does not apply.

7.7 AUDITS
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Hui-Leng Tan.

9. PUBLICATION POLICY

[Data ownership rights will lie with the institution. Findings of this study will be presented as a Dissertation and will be available through Open Access. We aim to publish findings in peer-review journals. Dr. Hui-Leng Tan will take the lead in the publication and dissemination.]

10. REFERENCES

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APPENDICES

- **Appendix 1** Questionnaire on Hypertonic Saline treatment for parents and legal guardians.
- **Appendix 2** Questionnaire on Hypertonic Saline treatment for participants 16 – 18 years.
- **Appendix 3** Questionnaire on Hypertonic Saline treatment for participants 10 – 15 years.
- **Appendix 4** Consent form
- **Appendix 5** Consent form
- **Appendix 6** Assent form

Hypertonic saline treatment questionnaire
PARENTS/LEGAL GUARDIAN

Participant ID: | | | | | | | Date: ____/_____/____

1)Overall, do you feel that nebulised hypertonic saline your child / young person has had has been

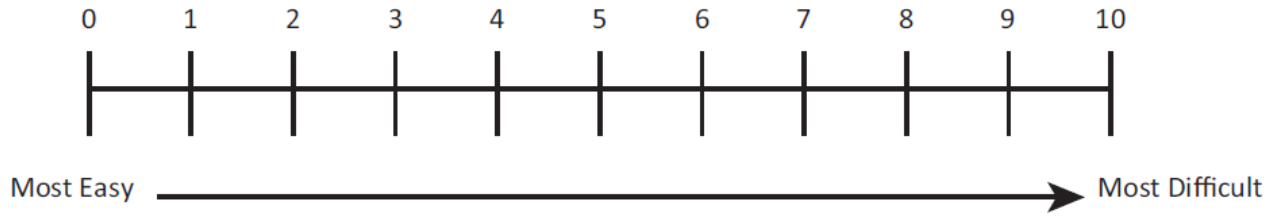
___Useful
___Not useful
___I don't know

What have you found most useful about it?

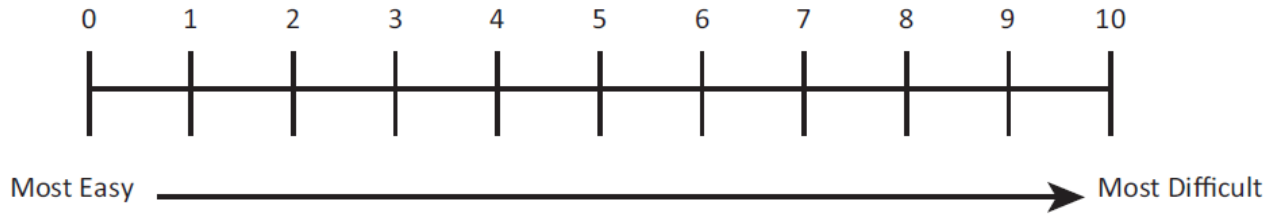
What have you found most difficult/ troublesome about it?

2)Please score how easy you think it has been to clear sputum from your child's airway

Before starting Hypertonic Saline



After starting Hypertonic Saline



Participant ID: | | | | | | | Date: ____/_____/____

In the 12 months <u>before</u> starting Hypertonic saline, how many courses of antibiotics did your child need? If you don't remember, please leave it blank.

Oral

IV

In the 12 months <u>after</u> starting Hypertonic saline, how many courses of antibiotics did your child need? If you don't remember, please leave it blank.

Oral

IV

In the 12 months <u>before</u> starting Hypertonic saline, how many times did you have to take your child to see a doctor because s/he was unwell with a chest infection? If you don't remember, please leave it blank.

In the 12 months <u>after</u> starting Hypertonic saline, how many times did you have to take your child to be seen by a doctor because s/he was unwell with a chest infection? If you don't remember, please leave it blank.

Hypertonic saline questionnaire

Ages 16 to 18 years

Participant ID: | | | | | | | Date: ____/_____/____

1)Overall, do you feel that nebulised hypertonic saline has been

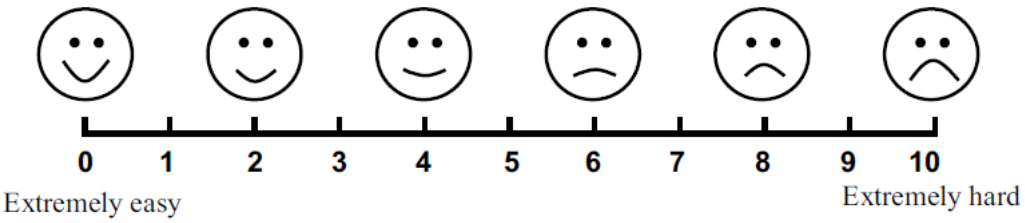
___Useful
___Not useful
___ I don't know

What have you found most useful about it?

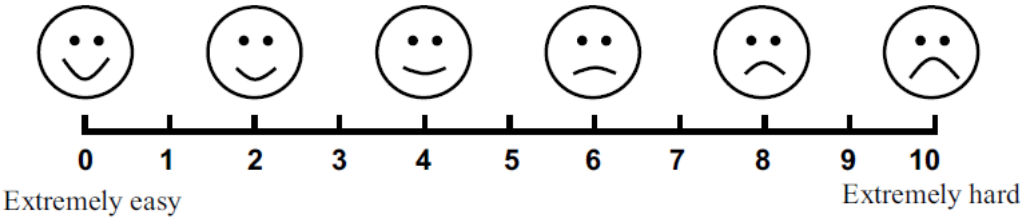
What have you found most difficult/ troublesome about it?

2)Please score your perception of how easy it is to clear sputum.

Before starting Hypertonic Saline



After starting Hypertonic Saline



Hypertonic saline questionnaire

AGES 10 to 15 YEARS

Participant ID: | | | | | | |

Date: ____/_____/____

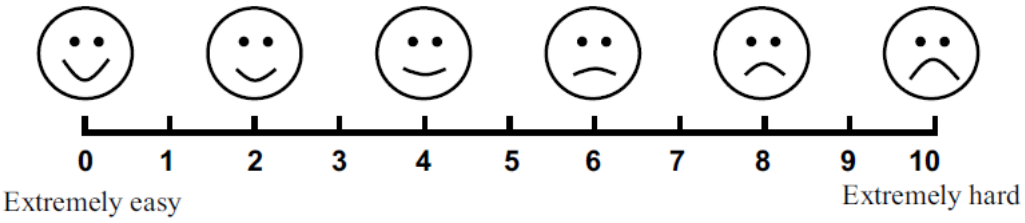
1) Do you feel that nebulised hypertonic saline has been

___Useful
___Not useful
___I don't know

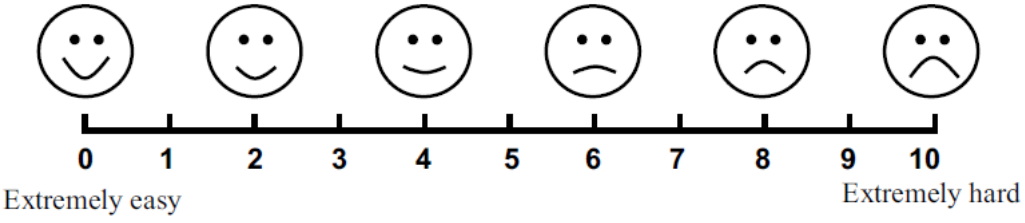
What do you like about it?	**What do you not like about it?**

2) Please point on the line below, between EXTREMELY EASY and EXTREMELY HARD, to show how easy it is to clear your sputum.

Before starting Hypertonic Saline



After starting Hypertonic Saline



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A Chart Review assessing the effect of Nebulised Hypertonic Saline on Respiratory-related complications in children and young people with Neuromuscular Disease or Cerebral Palsy

IRAS Project ID: 243535

CONSENT FORM

(16 - 18 years)

Participant Identification Number for this trial:
Name of Researcher:

Please initial box if you agree

1. I confirm that I have read and understood the information sheet version n°2 date 04/04/2018, for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐
2. I understand that participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the study research team will review relevant sections of my medical records and data. ☐
4. I understand that data collected during the study may be looked at by responsible individuals, from regulatory authorities, Imperial College London or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I agree to fill in the study questionnaires. ☐
6. I agree to my parents completing the study questionnaires. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed, 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

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Participant Identification Number for this trial:
Name of Researcher:

Please initial box if you agree

1. I confirm that I have read and understood the information sheet version n°2 date 04/04/2018, for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐
2. I understand that participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without affecting my child's medical care or legal rights being affected. ☐
3. I understand that the study research team will review relevant sections of my child's medical records and data. ☐
4. I understand that data collected during the study may be looked at by responsible individuals, from regulatory authorities, Imperial College London or from the NHS Trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's records. ☐
5. I agree to my child completing the study questionnaire. ☐

_____	_____	_____
Name of Parent	Date	Signature
_____	_____	_____
Name of Participant	Date	Signature (if appropriate)
_____	_____	_____
Name of Person taking consent	Date	Signature

When completed, 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes

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A Chart Review assessing the effect of Nebulised Hypertonic Saline on Respiratory-related complications in children and young people with Neuromuscular Disease or Cerebral Palsy

IRAS Project ID: 243535

INFORMED ASSENT FORM

Participant Identification Number for this trial:
Name of Researcher:

Please circle all that you agree

1. Do you understand what this study is about? **Yes/No**
2. Have you asked all the questions you want? **Yes/No**
3. Have you had your questions answered in a way you understand? **Yes/No**
4. Do you want to take part? **Yes/No**

If any answer is "No", don't sign your name.

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking assent	Date	Signature

When completed, 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes