Clinical trial results:
A randomised, double blind, double-dummy, placebo controlled trial of inhaled treatment to establish the mechanisms of prematurity-associated airway obstruction and inflammation.

Summary

EudraCT number	2015-003712-20
Trial protocol	GB
Global end of trial date	30 November 2019

Results information

Result version number	v1 (current)
This version publication date	27 January 2022
First version publication date	27 January 2022
Summary attachment (see zip file)	Inhaled Corticosteroids Alone and in Combination With Long-Acting β2 Receptor Agonists to Treat Reduced Lung Function in Preterm-Born Children A Randomized Clinical Trial (jamapediatrics_goulden_2021_oi_210075_1637630272.60457.pdf)

Trial information

Trial identification

Sponsor protocol code	SPON1451-15

Additional study identifiers

ISRCTN number	ISRCTN14767962
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	30-36 Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Research Governance Office, Cardiff University, +44(0)29 20 879 131, resgov@cardiff.ac.uk
Scientific contact	Research Governance Office, Cardiff University, +44(0)29 20 879 131, resgov@cardiff.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2019
Global end of trial reached?	Yes
Global end of trial date	30 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall aim of the research is to establish the reasons why children who were born prematurely have ongoing respiratory symptoms, potentially caused by narrowing of the airways (obstruction), inflammation and structural differences in the lung. The principle objective is to assess if 12 weeks of inhaler treatment can reduce this obstruction and inflammation.
To obtain updated information on the prevalence of respiratory symptoms (such as wheeze) in children who were born prematurely and investigate how these change over time.
To understand, in detail, the reasons (mechanisms) why inhaler treatment works in some participants, but not in others, by investigating the differences in laboratory markers of disease between responders and non-responders.
To understand more about the structure of the lungs and how this effects their function by comparing results from MRI scans.
To establish a cohort of children born prematurely in Wales for future studies.

Protection of trial subjects:

Trial has three parts
PART 1
Research nurse contacts those expressing interest following return of the questionnaire.
Home visit- Full study explained ,consent obtained, medical history, current medications, repeat respiratory and neurological questionnaire (parent/care giver), blood pressure, heart rate, oxygen saturations, height, weight, body composition, assess pubertal status, collect saliva sample (optional); urine sample. exhaled nitric oxide. lung spirometry, administer salbutamol inhaler, reassess lung spirometry.
Participants with FEV1 <=85% invited to part 2 provided with information - contacted at later date to book a visit if agreeable. Preterm born participant identified and willing to participate, noted to be taking inhaled corticosteroids, referred to consultant respiratory paediatrician to assess if washout from steroids appropriate before booking part 2
PART 2
Families invited to clinic visit- consent and assent taken, medical history, current medications, respiratory and quality of life questionnaire (parent/care giver), blood pressure, heart rate, oxygen saturation, height, weight, body composition, collect saliva sample (optional,) urine sample, perform skin-prick allergy test, exhaled nitric oxide test, lung spirometry, carbon monoxide transfer test, plethysmography, collect exhaled breath condensate,, exercise challenge test, reversibility test after exercise challenge, administer salbutamol inhaler, reassessing lung spirometry to test reversibility airway obstruction.
PART 3
60 Preterm born children with decreases in lung function, 20 Preterm born controls and 20 term born controls (both normal lung function) invited to participate at the Royal Hallamshire Hospital to undertake a hyperpolarised helium MRI scan. Asked to inhale small amount of specially produced helium prior to the scan, Informed consent and assent taken, checklist completed to ensure the participant meets the criteria to undergo the scan. The scan is radiation free

Background therapy:

On completion of the Part 1 visit 1 schedule of assessments, eligibility will be confirmed by the attending study clinician and recorded on the Case Report Form (CRF); the participant will be randomised to receive either monotherapy (fluticasone), combination therapy (fluticasone/salmeterol) or placebo. Inhaler technique will be demonstrated by the attending members of the clinical and nursing team. These children will be invited to attend 2 clinic visits for extensive lung function testing; the two visits will be separated by a 12- week treatment trial of inhaled medicines commonly used to treat asthma. We compared the results of tests before and after the treatment trial to establish if the medicines work

(Part 2). In order to generalise our results we will invite 50 children born at term (37 weeks gestation and over) with normal lung function, and 50 children born prematurely with normal lung function, to participate in each part of the trial as comparison groups .

Evidence for comparator:

The trial was a randomised, double blind, double-dummy placebo-controlled. Eligible participants were randomised to receive blinded study medication, stratified by inhaled steroid status: not currently taking inhaled steroids (non-ICS) or weaned from inhaled steroids. Non-ICS participants, expected to comprise approximately 87% of the eligible children, were randomised to:
a) Combination therapy- Inhaled long acting β2 agonist (25µg salmeterol xinafoate, total daily dose of 100µg) and corticosteroid (50µg fluticasone propionate, total daily dose of 200µg);
b) Monotherapy- Inhaled steroid only (50µg fluticasone propionate, total daily dose of 200µg);
c) Placebo.
Participants who were successfully weaned off steroids prior to visit 1 of part 2, expected to comprise approximately 15% of children, were randomised to:
a) Combination therapy- Inhaled long acting β2 agonist (25µg salmeterol xinafoate, total daily dose of 100µg) and corticosteroid (50µg fluticasone propionate, total daily dose of 200µg);
b) Monotherapy- Inhaled steroid only (50µg fluticasone propionate, total daily dose of 200µg)
The children were monitored for any adverse events during the 12-week treatment period and were reassessed after this period undergoing repeat spirometry and exercise testing. The trial was overseen by an independent trial and safety monitoring committee.

Actual start date of recruitment	21 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 53
Worldwide total number of subjects	53
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	43
Adolescents (12-17 years)	10
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We used our research patient database to identify potentially eligible participants, which contained liked-anonymised participant data only. We requested updated contact details from the NHS Wales Informatics Service for participants who gave consent to be contacted regarding further research.
We initially sent a postal questionnaire .

Pre-assignment

Screening details:

Potential participants were approached if they agreed to future contact when completing the original study. Study information was mailed inviting them to take part in completing the questionnaire and inviting them to a screening visit.
A research nurse made telephone or email contact (as preferred by the family) to establish baseline eligibility.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Serevent® (25µg salmeterol xinafoate), and Flixotide® (50µg fluticasone propionate) metered-dose inhalers used for the active arms of the trial. Matching placebo canister, containing no active substances, was sourced.
For blinding purposes, all canisters removed from their original actuators and placed in plain-coloured actuators provided to the IMP manufacturer who provided evidence of the equivalency of Serevent and Flixotide actuators. The active inhalers and placebo were identical .

Arms

Are arms mutually exclusive?	Yes
Arm title	Monotherapy

Arm description:

Preterm born children with decreases in lung function (FEV1 <=85%) randomised to receive 1 of 3 different inhalers to be taken for 12 weeks:
Monotherapy treatment consisted of the following:-
i) Fluticasone, two sucks to be taken twice a day (100 micrograms total per dose) - also Placebo added
ii) Placebo (dummy) inhaler containing no active drug, two sucks to be taken twice a day

Arm type	Active comparator
Investigational medicinal product name	Fluticasone Proprionate
Investigational medicinal product code	R03BA05
Other name	Flixotide
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

200µg microgram(s per day

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Placebo (dummy) inhaler containing no active drug, two sucks to be taken twice a day

Arm title	Combination Therapy

Arm description:

Preterm born children with decreases in lung function (FEV1 <=85%) randomised to receive 1 of 3 different inhalers to be taken for 12 weeks:
The combination treatment consisted of :-
ii) Fluticasone and salmeterol together, two sucks to be taken twice a day (100 micrograms fluticasone, 50 micrograms salmeterol per dose)

Arm type	Active comparator
Investigational medicinal product name	Salmetrol Xinfoate
Investigational medicinal product code	R03AC12
Other name	Serevent
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

100µg microgram(s)

Investigational medicinal product name	Fluticasone Proprionate
Investigational medicinal product code	R03BA05
Other name	Flixotide
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

200µg micrograms

Arm title	Placebo

Arm description:

Pretermborn children with decreases in lung function (FEV1 <=85%) randomised to receive 1 of 3 different inhalers to be taken for 12 weeks:
The placebo treatment consisted of :-
iii) Placebo (dummy) inhaler containing no active drug, two sucks to be taken twice a day

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

2 sucks to be taken twice per day
For blinding purposes, all canisters removed from their original actuators and placed in plain-coloured actuators incorporating an atomising mouthpiece and fitted with dustcaps. One pressurised container delivers 120 actuations. The matching placebo canister, contains no active substances.. The remaining excipients (hydrofluroalkane as propellant) are identical between active and placebo canisters.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

2 sucks to be taken twice per day
For blinding purposes, all canisters removed from their original actuators and placed in plain-coloured actuators incorporating an atomising mouthpiece and fitted with dustcaps. One pressurised container delivers 120 actuations. The matching placebo canister, contains no active substances.. The remaining excipients (hydrofluroalkane as propellant) are identical between active and placebo canisters.

Number of subjects in period 1	Monotherapy	Combination Therapy	Placebo
Started	20	19	14
Completed	18	17	13
Not completed	2	2	1
Consent withdrawn by subject	-	1	1
Adverse event, non-fatal	1	-	-
child worried about treatment	1	-	-
Poor Compliance	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description:

1) Children aged 7-12 at the time of screening
2) Born at a gestational age ≤34 weeks
3) Resident in the south Wales area whom, in the opinion of the Investigator, are possible to follow up
4) Fully informed proxy consent from parents/guardians and assent from child where possible
5) Preterm-born children found during screening to have FEV1 ≤85% predicted

Reporting group values	Overall Trial	Total	
Number of subjects	53	53	
Age categorical			
1) Children aged 7-12 at the time of screening 2) Born at a gestational age ≤34 weeks 3) Resident in the south Wales area whom, in the opinion of the Investigator, are possible to follow up 4) Fully informed proxy consent from parents/guardians and assent from child where possible			
Units: Subjects			
7-12 years	53	53	
Age continuous			
- Children aged 7-12 at the time of screening - Born at a gestational age ≤34 weeks - Resident in the south Wales area whom, in the opinion of the Investigator, are possible to follow up - Fully informed proxy consent from parents/guardians and assent from child where possible			
Units: years			
arithmetic mean	10.8		
standard deviation	± 1.2	-	
Gender categorical			
1) Children aged 7-12 at the time of screening 2) Born at a gestational age ≤34 weeks 3) Resident in the south Wales area whom, in the opinion of the Investigator, are possible to follow up 4) Fully informed proxy consent from parents/guardians and assent from child where possible			
Units: Subjects			
Female	29	29	
Male	24	24	

Subject analysis sets

Subject analysis set title	Overall Trial
Subject analysis set type	Full analysis

Subject analysis set description:

To test why children who were born prematurely have ongoing respiratory symptoms, potentially caused by narrowing of the airways (obstruction), inflammation and structural differences in the lung and to assess if 12 weeks of inhaler treatment can reduce this obstruction and inflammation

Reporting group values	Overall Trial		
Number of subjects	53		
Age categorical			
1) Children aged 7-12 at the time of screening 2) Born at a gestational age ≤34 weeks 3) Resident in the south Wales area whom, in the opinion of the Investigator, are possible to follow up 4) Fully informed proxy consent from parents/guardians and assent from child where possible			
Units: Subjects			
7-12 years	53		
Age continuous			
- Children aged 7-12 at the time of screening - Born at a gestational age ≤34 weeks - Resident in the south Wales area whom, in the opinion of the Investigator, are possible to follow up - Fully informed proxy consent from parents/guardians and assent from child where possible			
Units: years			
arithmetic mean	10.8		
standard deviation	± 1.2		
Gender categorical			
1) Children aged 7-12 at the time of screening 2) Born at a gestational age ≤34 weeks 3) Resident in the south Wales area whom, in the opinion of the Investigator, are possible to follow up 4) Fully informed proxy consent from parents/guardians and assent from child where possible			
Units: Subjects			
Female	29		
Male	24		

End points

End points reporting groups

Reporting group title	Monotherapy

Reporting group description:

Preterm born children with decreases in lung function (FEV1 <=85%) randomised to receive 1 of 3 different inhalers to be taken for 12 weeks:
Monotherapy treatment consisted of the following:-
i) Fluticasone, two sucks to be taken twice a day (100 micrograms total per dose) - also Placebo added
ii) Placebo (dummy) inhaler containing no active drug, two sucks to be taken twice a day

Reporting group title	Combination Therapy

Reporting group description:

Preterm born children with decreases in lung function (FEV1 <=85%) randomised to receive 1 of 3 different inhalers to be taken for 12 weeks:
The combination treatment consisted of :-
ii) Fluticasone and salmeterol together, two sucks to be taken twice a day (100 micrograms fluticasone, 50 micrograms salmeterol per dose)

Reporting group title	Placebo

Reporting group description:

Pretermborn children with decreases in lung function (FEV1 <=85%) randomised to receive 1 of 3 different inhalers to be taken for 12 weeks:
The placebo treatment consisted of :-
iii) Placebo (dummy) inhaler containing no active drug, two sucks to be taken twice a day

Subject analysis set title	Overall Trial
Subject analysis set type	Full analysis

Subject analysis set description:

To test why children who were born prematurely have ongoing respiratory symptoms, potentially caused by narrowing of the airways (obstruction), inflammation and structural differences in the lung and to assess if 12 weeks of inhaler treatment can reduce this obstruction and inflammation

Primary: Analysis of Covariance of percentage predicted FEV1

End point title	Analysis of Covariance of percentage predicted FEV1

End point description:

Analysis of Covariance was performed on outcomes, the post-treatment value was adjusted for sex, gestation, bronchopulmonary dysplasia, intrauterine growth restriction, pre-treatment corticosteroid status, group and pre-treatment value. Adjusted post-treatment values were compared between groups, with the null hypothesis of no difference, and using the Games Howell adjustment for multiple comparisons. The sample size required was 53, multiple imputation was employed to impute missing data

End point type	Primary

End point timeframe:

12 weeks

End point values	Monotherapy	Combination Therapy	Placebo	Overall Trial
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	20[1]	19[2]	14[3]	53[4]
Units: % predicted FEV1				
arithmetic mean (standard deviation)	81.6 (± 12.0)	88.0 (± 7.1)	73.9 (± 11.5)	80.2 (± 11.9)

Notes:

[1] - 18 completed and results imputed for 2 participants

[2] - data for 17 and imputed data for 2 participants

[3] - data for 13 and imputed data for 1 participant

[4] - 48 completed analysis and 5 participants data imputed, total 53 participants.

Statistical analyses

Statistical analysis title	Analysis of Covariance of percentage predicted FEV

Statistical analysis description:

Analysis of Covariance was performed on outcomes, the post-treatment value was adjusted for sex, gestation, bronchopulmonary dysplasia, intrauterine growth restriction, pre-treatment corticosteroid status, group and pre-treatment value. Adjusted post-treatment values were compared between groups, with the null hypothesis of no difference, and using the Games Howell adjustment for multiple comparisons. The sample size required was 53, multiple imputation was employed to impute missing data.

Comparison groups	Placebo v Monotherapy
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.05 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	15.7
Variability estimate	Standard error of the mean
Dispersion value	4.1

Notes:

[5] - This was the analysis as defined in the statistical analysis plan

[6] - P-values for group comparisons were adjusted for multiple comparisons using the Games Howell method.

Statistical analysis title	Analysis of Covariance of percentage pr...

Statistical analysis description:

Analysis of Covariance was performed on outcomes, the post-treatment value was adjusted for sex, gestation, bronchopulmonary dysplasia, intrauterine growth restriction, pre-treatment corticosteroid status, group and pre-treatment value. Adjusted post-treatment values were compared between groups, with the null hypothesis of no difference, and using the Games Howell adjustment for multiple comparisons. The sample size required was 53, multiple imputation was employed to impute missing data.

Comparison groups	Combination Therapy v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.05 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	14.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.3
upper limit	21
Variability estimate	Standard error of the mean
Dispersion value	3.5

Notes:

[7] - This was the analysis as defined in the statistical analysis plan

[8] - P-values for group comparisons were adjusted for multiple comparisons using the Games Howell method.

Statistical analysis title	Analysis of Covariance of perce...

Statistical analysis description:

Analysis of Covariance was performed on outcomes, the post-treatment value was adjusted for sex, gestation, bronchopulmonary dysplasia, intrauterine growth restriction, pre-treatment corticosteroid status, group and pre-treatment value. Adjusted post-treatment values were compared between groups, with the null hypothesis of no difference, and using the Games Howell adjustment for multiple comparisons. The sample size required was 53, multiple imputation was employed to impute missing data.

Comparison groups	Monotherapy v Combination Therapy
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.05 [10]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	12.6
Variability estimate	Standard error of the mean
Dispersion value	3.2

Notes:

[9] - This was the analysis as defined in the statistical analysis plan

[10] - P-values for group comparisons were adjusted for multiple comparisons using the Games Howell method.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events, including non-serious adverse events, were recorded in the participant's medical records and on their case report form. All adverse events were reported from consent of participant up to the final study visit

Adverse event reporting additional description:

13 adverse events in total throughout the trial - 7 adverse events seen in 4 children randomised to placebo, 2 adverse events seen in 2 children randomised to combination therapy and 4 adverse event seen in 4 children randomised to montherapy.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 53 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 2.65 %

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 53 (24.53%)		
General disorders and administration site conditions			
General symptom			
subjects affected / exposed	13 / 53 (24.53%)		
occurrences (all)	13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2016	• Flow chart updated to include QofL and Health Economic questionnaires • Information on accelerometry removed • Information on completion of CHU-9D questionnaire added • Detail on completion of health economic questionnaire and CHU-9D added • Detail added regarding collection of peak flow data • Amended to include detail on placebo formulation • Table 1 scheduled of procedures updated
21 September 2016	• Version control modified to reflect NWORTH procedures • Addition of ISRCRN • Description of intervention' updated with details of new IMP treatment groups • Flowchart updated to include: Cardiovascular assessment, Helium dilution test and FOT test. Removal of CO2 transfer test • Clarification of restrictions prior to part 1 home visit • Reversibility test: Removal of the specific use of Ventolin brand salbutamol • Clarification of restrictions prior to part 2 lab visit 1 • Clarification that the respiratory questionnaire will be repeated if part 1 visit 1 is >3 months after the initial questionnaire is completed • Addition of detail regarding cardiovascular assessment • Removal of CO transfer test • Addition of the FOT test • Addition of the inert gas washout test • Exercise challenge: Small clarifications to the procedure • Exercise challenge: Removal of the specific use of Ventolin brand salbutamol • Sputum induction: Addition of safety precaution- FEV1 to be within 90% of baseline before starting test • Change of treatment allocation to double-dummy design. Inclusion of Serevent in the combination therapy group and removal of Seretide • Clarification that participants must take each inhaler, twice daily (AM and PM) • Clarification of temperature storage requirements • Clarification that local pharmacy will dispose of returns • Change of process from on-line system to envelopes for emergency unblinding procedure • Removal of the specific use of Ventolin brand salbutamol • Removal of the specific use of Ventolin brand salbutamol • Derivation of sample size calculations have been described in more detail • Table 1 in the protocol Updated to reflect addition/removal of lung function tests
06 December 2016	• Clarification of source of placebo canister • Addition of section "treatment withdrawal criteria". • Discussion of potential inclusion of females of reproductive potential as requested by the MHRA • Addition of section "Nature and frequency of safety assessments" as requested by the MHRA

14 March 2017	• Addition of multiple breath washout (lung clearance index) to part 3 of study (LCI aspect removed from part 2) • Clarification of source of reference safety information • New source of placebo canister- Pharmaserve North West Ltd. • Removal of detail regarding use of masking device. • Change of manufacturer from Catalent to St Marys Pharmaceutical Unit
27 July 2017	• Additional recruitment strategy added- contact of participants outside of current RHiNO database • Typographical error: change to $p<0.05$ • Clarification of data required for internal pilot of sample size assumptions
07 December 2017	• Change to number of research sites • Addition of Statistician's signature • Additional research sites added • Clarification of IMP packaging and labelling procedure • Change of text in relation to nomenclature for consistency with IMP manufacture and randomisation
13 March 2018	• Additional recruitment of potential participants • Addition of Adverse event to schedule of procedures for Part 3 MRI • Reference to data management plan • Change to the inhaler procurement • Change to the number of inhalers provided to participants • Revision of temperature storage requirements • Change to the inhaler procurement • Revision of temperature storage requirements • Corrected spelling errors
16 October 2018	• Typographical errors corrected • Clarification of number of weeks between visit 1 and 2, to ensure convenience for children and parents • Change to xenon as the hyperpolarised gas used in MRI • Addition of an MRI performed before and after a bronchodilator • Clarification of placebo canister supplier- GSK • Clarification that GSK placebo inhalers are CE marked • Clarification that a third batch of inhalers will be procured in late 2018 • Clarification of FEV1 % required for pre-term born and term born control children. • Derivation of sample size calculations have been described in more detail

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported