Clinical trial results:
The role of anti-IgE (omalizumab) in the management of severe recalcitrant paediatric atopic eczema

Summary

EudraCT number	2010-020841-29
Trial protocol	GB
Global end of trial date	31 August 2017

Results information

Result version number	v1 (current)
This version publication date	02 May 2019
First version publication date	02 May 2019
Summary attachment (see zip file)	FINAL STUDY REPORT (ADAPT REC Final study report 2018 08 31.pdf)

Trial information

Trial identification

Sponsor protocol code	ADAPT

Additional study identifiers

ISRCTN number	ISRCTN15090567
ClinicalTrials.gov id (NCT number)	NCT02300701
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
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Scientific contact	Susan Chan, King's College London, +44 02071889730, susan.chan@kcl.ac.uk
Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
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Public contact	Dr Susan Chan, Guy`s & St Thomas` NHS Foundation Trust, +44 02071889730, susan.chan@kcl.ac.uk
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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	31 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2017
Global end of trial reached?	Yes
Global end of trial date	31 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Our hypothesis is that anti-IgE will reduce the levels of IgE in children with severe eczema, thereby alleviating their symptoms.

Protection of trial subjects:

Management of exacerbations and any additional therapy (eg.oral steroids or antibiotics) will be recorded.
All adverse events and side effects will be recorded in the CRF as per the Trial assessments, with the exception of abnormal blood results that are considered not clinically significant by the Investigator and will be managed as below.
Adverse events linked to the existing condition (atopic dermatitis) will be collected separately to help distinguish between expected events related to condition or side effects of concomitant medications.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2014
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: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	36

Adolescents (12-17 years)	25
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from a single clinical site in London between 2016 and 2017.

Pre-assignment

Screening details:

Inclusion Criteria
1. Children aged 4-19yrs with:-
2. Severe eczema an objective SCORAD (a validated eczema severity score) of over 40
ii. in a patient unresponsive to optimal topical therapy (potent topical steroids and topical calcineurin inhibitors) or systemic therapy1
iii. in whom there is no impression of lack of compliance
iv. with a (C

Period 1

Period 1 title	Whole Group (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Participants will be allocated to treatment arm via an online dynamic algorithm which will be developed and hosted by the UKCRC registered King's College London CTU. The use of the online system will ensure concealment of treatment allocation for clinicians who are recruiting participants.

Arms

Are arms mutually exclusive?	Yes
Arm title	Omalizumab

Arm description:

Children will receive omalizumab treatment for 24 week.

Arm type	Experimental
Investigational medicinal product name	Xolair
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/skin-prick test
Routes of administration	Subcutaneous use

Dosage and administration details:

The appropriate dose and dosing frequency of Xolair (omalizumab) is determined by baseline total IgE (range: 30 to 1 500 IU/ml), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients will have their IgE level determined by serum total IgE assay for their dose assignment. Based on these measurements, the dose of Xolair (omalizumab) will be calculated using the formula: 0.016 x weight (kg) x total IgE level (kU/l) or using the latest manufacturers dosing tables (according to the current Summary of Product Characteristics). 75 600 mg of Xolair (omalizumab) in 1 to 4 injections may be needed for each administration as shown in the tables. The dose of Xolair (omalizumab) stated on the table, closest to that child's weight and IgE levels, will be administered. Thus, if the total IgE level is above the upper limit stated on the dosing table, the highest dose of Xolair. They will remain on this dose throughout the 24 weeks of treatment

Arm title	Placebo

Arm description:

Children on placebo for 24 weeks

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The appropriate dose and dosing frequency of placebo is determined in the same way as for Xolair by baseline total IgE (range: 30 to 1 500 IU/ml), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients will have their IgE level determined by serum total IgE assay for their dose assignment. Based on these measurements, the dose of placebo will be calculated using the formula: 0.016 x weight (kg) x total IgE level (kU/l) or using the latest manufacturers dosing tables (according to the current Summary of Product Characteristics for Xolair). They will remain on this dose throughout the 24 weeks of treatment.

Number of subjects in period 1	Omalizumab	Placebo
Started	30	32
Completed	28	31
Not completed	2	1
Withdrawn before starting IMP	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Whole Group

Reporting group description: -

Reporting group values	Whole Group	Total	
Number of subjects	62	62	
Age categorical Units: Subjects			
Children (2-11 years)	36	36	
Adolescents (12-17 years)	25	25	
Adults (18-64 years)	1	1	
Gender categorical Units: Subjects			
Female	30	30	
Male	32	32	

End points

End points reporting groups

Reporting group title	Omalizumab
Reporting group description:	
Children will receive omalizumab treatment for 24 week.	
Reporting group title	Placebo
Reporting group description:	
Children on placebo for 24 weeks	

Primary: Mean difference in oSCORAD between arms

End point title	Mean difference in oSCORAD between arms[1]
End point description:	
End point type	Primary
End point timeframe:	
Baseline to week 24	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see attached study report for results

End point values	Omalizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	32		
Units: Whole	32	32		

Attachments (see zip file)	Summary results/ADAPT REC Final study report 2018 08 31.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to week 48 post randomisation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Omalizumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Omalizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)	6 / 32 (18.75%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Eosinophilic oesophagitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Whiplash	Additional description: Admitted for observation following car accident. Whiplash injury including headache and abdominal pain and joint ache.		
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction	Additional description: Unknown cause		
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected anaphylaxis			

subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic	Additional description: Reaction to unknown food		
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Infected eczema			
subjects affected / exposed	1 / 30 (3.33%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema herpeticum			
subjects affected / exposed	2 / 30 (6.67%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exacerbation of eczema			
subjects affected / exposed	1 / 30 (3.33%)	3 / 32 (9.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Omalizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)	32 / 32 (100.00%)	
Vascular disorders			
Angiodema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Circumcision			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Injection site pain			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Chicken pox			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Breast lump			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Nightmare			
subjects affected / exposed	1 / 30 (3.33%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Secondary suture of wound			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Shaking			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Sore feet			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Thirsty			
subjects affected / exposed	1 / 30 (3.33%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Toothache			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Unwell			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	

Vitamin D deficiency			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Urticaria			
subjects affected / exposed	7 / 30 (23.33%)	1 / 32 (3.13%)	
occurrences (all)	7	1	
Allergy to animal			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Allergic reaction to excipient			
subjects affected / exposed	10 / 30 (33.33%)	10 / 32 (31.25%)	
occurrences (all)	10	10	
Allergic rhinitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Itchy eyes			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Asthma aggravated			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Asthma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	0	0	
Chest infection			
subjects affected / exposed	0 / 30 (0.00%)	5 / 32 (15.63%)	
occurrences (all)	0	5	
Cold			
subjects affected / exposed	1 / 30 (3.33%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Cold symptoms			
subjects affected / exposed	1 / 30 (3.33%)	6 / 32 (18.75%)	
occurrences (all)	1	6	
Congestion			

subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Coryzal symptoms			
subjects affected / exposed	6 / 30 (20.00%)	12 / 32 (37.50%)	
occurrences (all)	6	12	
Cough			
subjects affected / exposed	2 / 30 (6.67%)	10 / 32 (31.25%)	
occurrences (all)	2	10	
Difficulty breathing			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Exacerbation of asthma			
subjects affected / exposed	1 / 30 (3.33%)	7 / 32 (21.88%)	
occurrences (all)	1	7	
Pneumonia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Tightness in chest			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	4 / 30 (13.33%)	4 / 32 (12.50%)	
occurrences (all)	4	4	
Injury, poisoning and procedural complications			
Needle issue	Additional description: Accidental needle stick		
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headaches			
subjects affected / exposed	10 / 30 (33.33%)	4 / 32 (12.50%)	
occurrences (all)	10	4	
Dizziness			

subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Iron deficiency			
subjects affected / exposed	3 / 30 (10.00%)	3 / 32 (9.38%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 30 (13.33%)	1 / 32 (3.13%)	
occurrences (all)	6	1	
Acid reflux			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Loose stools			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	5 / 30 (16.67%)	1 / 32 (3.13%)	
occurrences (all)	5	1	
Stomach ache			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Stomach pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	1 / 30 (3.33%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Hepatobiliary disorders			
Eczema aggravated			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Blisters			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Burning sensation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
cold sore			
subjects affected / exposed	0 / 30 (0.00%)	6 / 32 (18.75%)	
occurrences (all)	0	6	
Eczema aggravated			
subjects affected / exposed	25 / 30 (83.33%)	29 / 32 (90.63%)	
occurrences (all)	25	29	
Exacerbated eczema			
subjects affected / exposed	7 / 30 (23.33%)	5 / 32 (15.63%)	
occurrences (all)	7	5	
Eczema weeping			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Eczema herpeticum			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Hives			
subjects affected / exposed	1 / 30 (3.33%)	1 / 32 (3.13%)	
occurrences (all)	1	1	
Infected eczema			
subjects affected / exposed	18 / 30 (60.00%)	27 / 32 (84.38%)	
occurrences (all)	18	27	
Paronychia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Pruritis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	

Pustules			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Infected skin			
subjects affected / exposed	3 / 30 (10.00%)	5 / 32 (15.63%)	
occurrences (all)	3	5	
Peeling skin			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Thinning skin			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Swelling	Additional description: swelling to ear		
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	6 / 30 (20.00%)	0 / 32 (0.00%)	
occurrences (all)	6	0	
Musculoskeletal and connective tissue disorders			
Aching limb			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Wrist fracture			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Pain in jaw			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Leg pain muscular			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Pain in arms and legs			

subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Swollen ankles			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 30 (30.00%)	13 / 32 (40.63%)	
occurrences (all)	9	13	
Infected penis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Head lice			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Runny nose			
subjects affected / exposed	0 / 30 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Infected nail bed			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Infection of gum			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Sore throat			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	7 / 30 (23.33%)	2 / 32 (6.25%)	
occurrences (all)	7	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2014	Protocol change: • Baseline systemic steroids omitted. • Addition of treatment failure and alternative systemic therapies as secondary outcome measures as it was thought important to address whether treatment/placebo was associated with more failure of treatment • EASI eczema scoring added as this is increasingly used in studies • Samples to be stored for genetics studies (subject to consent). Also administrative changes to the protocol.
26 September 2014	Changes to the secondary outcome measures and Secondary efficacy parameters. The age group between treatment group changed, Participants will be allocated to treatment group using minimisation. This is to ensure that there will be minimal imbalance of total IgE (≤1500, >1500) and age (<10 or ≥10 years) between treatment groups. In addition, there are various other administrative changes throughout the whole protocol and the labels
30 July 2015	The inclusion of the Transepidermal Water Loss test (TEWL), an additional optional test at Baseline, Week 24, 36 and 48.The exclusion criteria has been amended with pre-existing hepatic or renal impairment being removed, and the definition of 'Exacerbations of eczema' in section 6.2 of the protocol has been clarified. Additionally, the timepoint for urine testing has been changed from baseline to screening and the protocol has been revised to clarify the Xolair dosing for IgE levels at the limits of the dosing table. In addition, skin swabs will now not be taken from family members or at the end of treatment for any infections. There have been various other administrative changes and clarifications throughout the protocol and section 8.3 has been updated to bring it in line with the statistical analysis plan.
27 September 2016	Inclusion of a new secondary outcome measure as listed below and the statistics section has also been updated in line with the new version of the Statistical analysis plan. Below is a list of all changes made to the protocol: 1. Trial Flowchart TEWL timing updated from screening to baseline visit, in line with the rest of the protocol. 2. Clarification of primary outcome measures 3. Inclusion of a new secondary outcome measure - 'Change in use of potent topical steroids and calcineurin inhibitors: the weight, extent and frequency of use will be recorded at each visit.' 4. Clarification of inclusion criteria 5. Clarification on treatment of eczema exacerbations to include that treatment can follow that 'as decided by the supervising physician' as well as the regimen included in the protocol. 6. Statistics section updated in line with latest version of the Statistical Analysis Plan (SAP, version 2.0) 7. Addition of protocol version history 8. Staff update on the ADAPTrial study website and administrative corrections to the parent and child consent forms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28330497

http://www.ncbi.nlm.nih.gov/pubmed/28535776