ADAPT Trial

The Atopic Dermatitis Anti-IgE Paediatric Trial (ADAPT): The role of anti-IgE (omalizumab/Xolair) in the management of severe recalcitrant paediatric atopic eczema

Statistical Analysis Plan

Version 3.0

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Document version history log

Date	Version	Changes made
04/03/2015	1.0	
21/10/2016	2.0	1) Reduce the number of models required in the analysis by replacing primary ANCOVA model with a longitudinal model for primary outcome. 2) Include more specific details on primary analysis 3) Include more specific details on analyses. 4) Include a distinction between the Objective and Subjective SCORAD outcomes. In version 1 only 'SCORAD' was referred to. 5) Define Safety Set (SS) for Adverse events analysis 6) Include more details on how rescue medication and missing outcome data will be explored in sensitivity analysis
01/03/2017	3.0	Following a recommendation from the ADAPT DMC (received on 20/01/2017 at the 5th meeting of the DMC), specification of the MCID for the objective SCORAD has been added (see Section 3.6).

Contents

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1. Description of the trial

See protocol [ref version 8.0] for full details.
A study to determine clinical efficacy of Omalizumab (Xolair®, Novartis) for severe atopic eczema compared in children by means of a randomised double-blind placebo-controlled trial.

Participants will be recruited from the Paediatric Allergy and dermatology clinics at St Thomas' Hospital and will be self-referred or referred from colleagues at other tertiary, primary or secondary centres.

Inclusion: Children between the ages of 4-19 yrs with severe eczema (as defined in the protocol), raised specific immunoglobin E (SpIgE) (>0.35 IU/ml) or skin prick test (SPT) (>3mm) to at least 1 food allergen or 1 aeroallergen, AND/OR clinical impression that allergic exposures cause worsening eczema, Total immunoglobin E (IgE) level ≥300 kU/l, clinically proven IgE-mediated allergic disease

1.1 Principal research objectives to be addressed

Anti-IgE will reduce the levels of IgE in children with severe eczema, thereby alleviating their symptoms.

Primary objective: To establish the role of anti-IgE (omalizumab/Xolair) therapy in the management of children with severe recalcitrant paediatric atopic eczema.

Primary outcome measure:

- Objective SCORing Atopic Dermatitis (SCORAD) at 24 weeks of treatment

Secondary outcome measures:

- Treatment failure
- Alternative systemic therapy
- Patient-oriented Eczema Measure (POEM)
- (Children's) Dermatology Life Quality Index ((C)DLQI).
- Subjective SCORAD and Eczema Area and Severity Index (EASI)
- Effect on co-existing allergic disease assessed by PADQLQ
- Number of eczema exacerbations
- Number of infective episodes of eczema
- Allergen specific IgE
- Reactivity to food and aeroallergens
- Adverse events

1.2 Trial design including blinding

This will be a randomised double-blind placebo-controlled trial of Omalizumab (Xolair®, Novartis) therapy in children with severe eczema who have failed to respond adequately to, or tolerate, systemic therapy (including azathioprine, oral corticosteroid, oral or subcutaneous methotrexate, cyclosporine, mycophenolate mofetil or phototherapy). The aim is to recruit 62 children to the trial who have severe eczema defined as an objective SCORAD (a validated eczema severity score) of >40-83 (SCORAD range: 0-83, >40 indicates severe disease) at assessment.

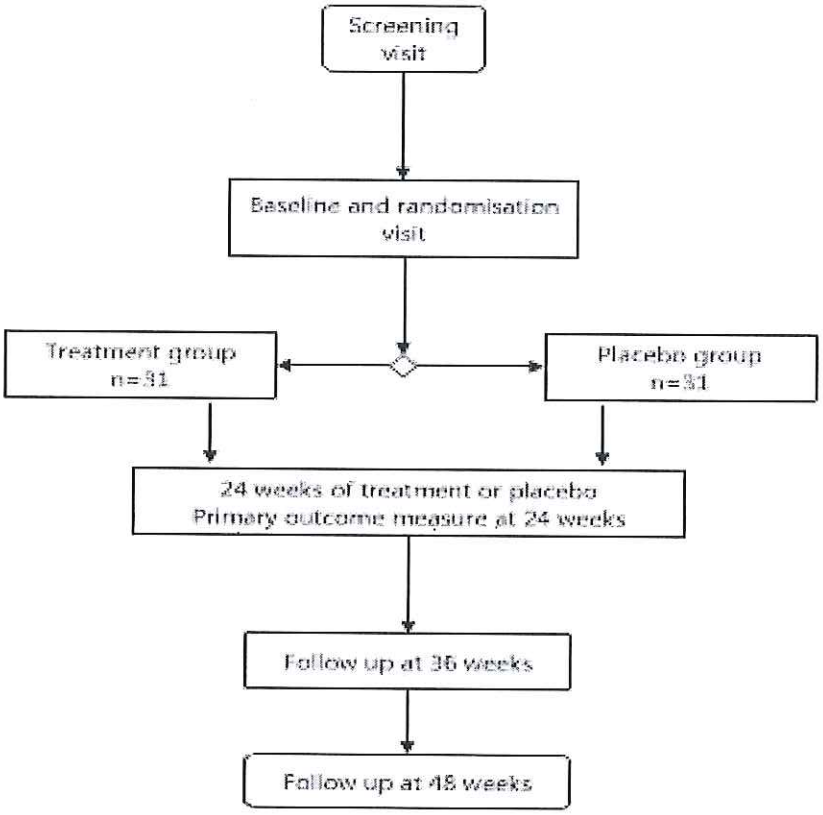

Figure 1: Trial Flowchart

Week (All visits ± 5 days unless stated)		0	2*	4	6*	8	10*	12	14*	16	18*	20	22*	24		36 (±2 wks)	48 (±2 wks)	Ongoing
Visit	Screening Visit	Baseline& randomisation																
Patient information and informed consent	X																	
Eczema history	X																	
Family history	X																	
Eczema impact	X													X			X	
Medical History and examination	X																	
Record of concomitant drugs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Adverse event			X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Questionnaire - (C)DLQI	X	X		X		X		X		X		X		X		X	X	
Questionnaire-POEM	X	X		X		X		X		X		X		X		X	X	
Questionnaire-PADQLQ	X	X		X		X		X		X		X		X		X	X	
SCORAD	X	X		X		X		X		X		X		X		X	X	
EASI	X	X		X		X		X		X		X		X		X	X	
Height/weight	X	(X)												X		X	X	
BP/routine observations	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Skin prick tests	X													X				
Bloods (FBC, eosinophils, U&E, LFT, Vitamin D, iron, bone profile, IgE)	X													X				X
Blood collection & storage for immunological studies	X													X				
Blood for genetics studies	X																	
Urinanalysis (glucose, protein, blood)		X												X		X	X	
Pregnancy test (βhCG)		X																
Skin swabs	X																	
Skin biopsy (optional)		X												X				X
Skin biopsy (genetics studies)		X																
Medical photography		X												X				
Eligibility criteria	X																	
Randomisation		X																
Anti-IgE or placebo injections (2 or 4 weekly)		X	X	X	X	X	X	X	X	X	X	X	X					
PO SCORAD																		X
Exacerbation/Infection																		X
Withdrawal																		X

Table 1

Note: Trial medication or placebo will be administered 2 or 4 weekly based on the latest manufacturer's dosing tables. The dose will be determined by the patient's weight and total IgE level. Thus some patients will not need to attend alternate injection visits (weeks 2, 6, 10, 14, 18, 22 marked*).

1.3 Method of allocation of groups

Participants will be allocated to treatment arm via an online randomisation system hosted by the UKCRC registered King's College London CTU (KCTU). The use of the online system will ensure concealment of treatment allocation for clinicians who are recruiting participants.

Allocation to treatment groups undertaken using minimisation including variables:

- IgE (≤1500, >1500)
- Age (<10 or ≥10 years)

1.4 Duration of the treatment period

Patients will undergo treatment for 24 weeks and continue to take their conventional treatments for eczema during this period and the follow up period.

1.5 Frequency and duration of follow-up

Each patient will be followed up for 48 weeks.

1.6 Visit windows

See **Error! Reference source not found.** 1 above or the protocol for more details.

1.7 Data collection

Data is collected by means of paper Case Report Forms during study visits. This information is then entered onto an online data and management system (MACRO by InferMed (www.infermed.com)). The database has been programmed by the KCTU.

1.8 Sample size estimation

Sample size power calculation for primary outcome: SCORAD at 24 weeks of treatment:
In order to determine the sample size, the following assumptions were made:
A 40% reduction in SCORAD in the treatment group (from 45 to 27), and a 10% reduction in the placebo group (45 to 40.5), equates to an absolute change in SCORAD of 13.5 points between the 2 groups (the assumed standard deviation (SD) is 15, based upon a study by Hindley[1]. With 62 patients (31 in each arm) we will be able to detect a clinically meaningful difference of 33% relative reduction in SCORAD, using a significance level of 5% with 90% power, and including a 15% drop out rate.

1.9 Brief description of proposed analyses

Analyses will be carried out by the trial statistician and the primary analysis will be validated by a second statistician. The principle of intention-to-treat (ITT) will be the main strategy of the analysis adopted for the primary outcome and all secondary outcomes. That is, all randomised patients will be analysed in the group randomised regardless of whether the correct study treatments were received, or other interventions received and regardless of any protocol deviations or violations. A safety set (SS) population will also be defined for describing adverse events in patients receiving the assigned intervention.

All regression analyses will include the minimisation variables IgE (≤1500, >1500) and age (<10 or ≥10 years) as covariates. This is because adjustment for these stratification factors in the randomisation process will maintain correct type I error rates. Additionally, for continuous outcomes, the outcomes measured at baseline will be

included in regression analysis to increase power. All p values will be two sided, and the significance level is set at 5%, unless otherwise stated.

2. Data analysis plan – Data description

2.1 Recruitment and representativeness of recruited patients

A Consolidated Standards of Reporting Trials (CONSORT) flow chart will be constructed[2] – see Figure 2. This will include the number of eligible patients, number of patients agreeing to enter the trial, number of patients withdrawing and lost to follow up, the number continuing through the trial, and the number included in the analyses.

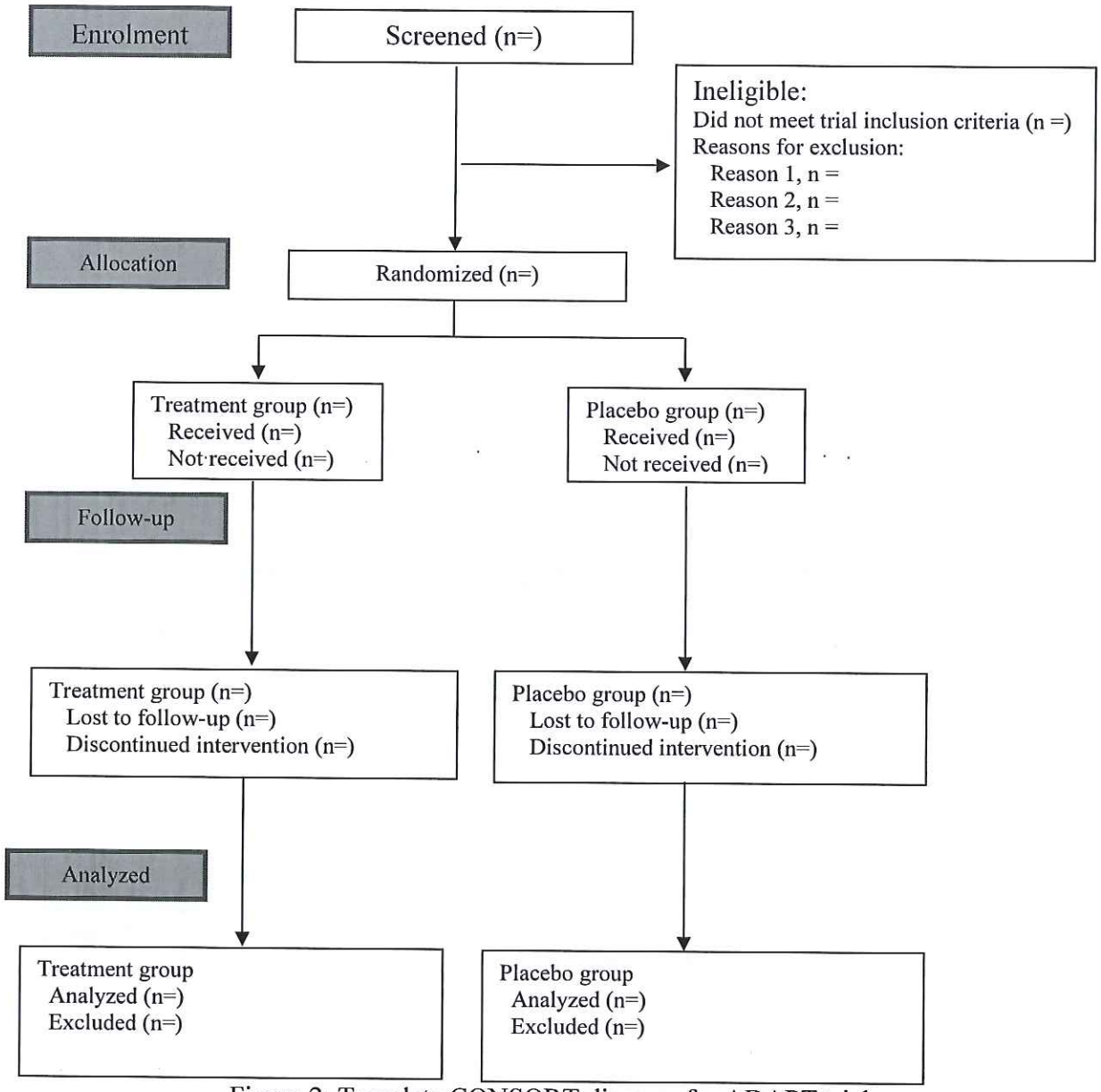

Figure 2: Template CONSORT diagram for ADAPT trial

2.2 Baseline comparability of randomised groups

All baseline descriptive variables of participants (including systemic therapies in use at start and other concomitant medications) will be summarised by treatment arm and overall using suitable measures of central tendencies for continuous data (means and medians), variability (SD and interquartile range(IQR)), and frequencies and proportions for categorical data. No significance testing will be undertaken.

2.3 Adherence to allocated treatment

The number withdrawing from the treatment schedule will be reported by treatment arm. Also the number receiving the injection outside the planned visit window of 5 days or more (based on date since baseline date) will be reported by visit number and treatment arm. The mean cumulative dose by planned dose will be plotted by treatment arm and separately for those receiving monthly and fortnightly injections.

2.4 Loss to follow-up and other missing data

The number lost to follow up will be tabulated by treatment arm and visit.
The proportions of participants missing objective SCORAD values will be summarised in each arm and at each time point. The baseline characteristics (age, gender, objective and subjective SCORAD, BMI, asthma (Y/N), food allergy (Y/N), rhinoconjunctivitis (Y/N) and referral source (self-referred/tertiary) of those missing follow up will be compared to those with complete follow up.
The recorded reasons for withdrawal from the trial will be summarised.

2.5 Adverse event reporting

Information on adverse events will be collected by means of spontaneous reports from patients and carers, clinical observation and clinical examinations and blood tests. A safety set (SS) population will be defined for describing adverse events. This will include all patients who receive at least one injection of the treatment.

Adverse events (AEs) will be tabulated separately by type (adverse events, adverse reaction, unexpected adverse reaction, serious adverse event, serious adverse reaction or unexpected serious adverse reactions), and by treatment arm. The numerator will indicate the number of affected participants at each time point by randomised intervention. The denominators will show how many participants were in the trial at its corresponding time point. If appropriate, the difference in proportion (95% confidence interval) will be estimated and time to event curves by treatment arm will be plotted. All adverse events will be listed individually. In addition to AEs recorded during the trial we will tabulate the following by treatment arm
Blood tests:

a) Kidney function:
    i. Urea (normal/abnormal)
    ii. Creatinine (normal/abnormal)

b) Full blood count - FBC (normal/abnormal)
c) Eosinophils (normal/abnormal)
d) Urea and electrolytes - U&E (normal/abnormal)
e) Liver function test - LFT (normal/abnormal)
f) IgE level (normal/abnormal)
g) Vitamin D (normal/abnormal)
h) Iron level (normal/abnormal)
i) Bone profile (normal/abnormal)

Normal and abnormal ranges will be defined using the ranges specified by the laboratory processing the samples.

Coding adverse events : Events will be coded using terms of the clinical investigators choosing with reference to Medical Dictionary for Regulatory Activities (MedDRA) at the 'Preferred Terms' level.

2.6 Assessment of outcome measures (unblinding)

Not applicable

2.7 Descriptive statistics for outcome measures

The distributions of all efficacy outcomes (in Section 3) will be assessed using histograms (continuous/count) or bar charts (ordinal/binary) both overall and by group at each assessment point. A single table will be outputted with summary statistics for all outcomes by group and visit point. Furthermore, summary statistics will be plotted by line graphs for each outcome across time by intervention (e.g., the dose and frequency of rescue medicine). Only participants with a completely recorded outcome will be used to calculate the summary measure.

2.8 Description of therapists/therapies

Not applicable

3. Data analysis plan – Inferential analysis

3.1. Analysis of primary outcome

Outcome Definition: Eczema severity measured using objective SCORAD at 24 weeks of treatment.

3.1.1 Primary Analysis

A linear mixed model will be used to obtain an estimate for the mean difference in objective SCORAD between the two treatment groups. Participant will be included as a random intercept (investigating adding a random slope on time), time (investigating the possibility of linearizing this effect across 8, 12, 16, 20 and 24 weeks), time-by-group interaction, baseline objective SCORAD, IgE (≤1500, >1500), age (<10 or ≥10 years) as fixed effects. The estimated treatment effect at 24 weeks will be reported with 95% confidence intervals and corresponding p value. The main conclusion of the trial will be based on this analysis time point.

The response is y_{ij} the objective SCORAD measurement for patient i at time t_j. Both random intercept model (a), and random intercept and slope model (b) will be fitted as specified below,

a)

$$Y_{ij} = \beta_0 + \beta_1 TRT_i + \beta_2 SCORAD_i^0 + \beta_3 IgE_i + \beta_4 Age_i + \beta_5 t_{12} + \beta_6 t_{16} + \beta_7 t_{20} + \beta_8 t_{24} + \beta_9 t_{12} * TRT_i + \beta_{10} t_{16} * TRT_i + \beta_{11} t_{20} * TRT_i + \beta_{12} t_{24} * TRT_i + b_i + e_{ij}$$

And

b)

$$Y_{ij} = \beta_0 + \beta_1 TRT_i + \beta_2 SCORAD_i^0 + \beta_3 IgE_i + \beta_4 Age_i + \beta_5 t_{12} + \beta_6 t_{16} + \beta_7 t_{20} + \beta_8 t_{24} + \beta_9 t_{12} * TRT_i + \beta_{10} t_{16} * TRT_i + \beta_{11} t_{20} * TRT_i + \beta_{12} t_{24} * TRT_i + b_{1i} + b_{2i} t_j + e_{ij}$$

j = 1 to 5 time points (8, 12, 16, 20 and 24 weeks), i = 1 to 62 participants,
TRT_i: dummy variable ($TRT_i = 0$ or 1) of patient i
IgE_i: dummy variable for IgE (= 0 or 1) of patient i
$SCORAD_i^0$: baseline SCORAD of patient i
Age_i: Age of patient i
t_{xx}: dummy variable for time (= 0 or 1) at time point xx weeks

where b_i and b_{1i} are random intercepts, b_{2i} is random slopes, both e_{ij} and b_{1i}, following normal distributions. An unstructured covariance matrix will be used[3]. Models will be fitted using REML. The treatment effect at 24 weeks, $\beta_1 + \beta_{12}$, will be reported.

Model (a) will be the primary analysis model unless there is strong evidence for misspecification of the model. The random slope model is less restrictive and possibly more realistic in its assumptions, i.e., the objective SCORAD trajectories for each individual starting from different level and following different trend with different slope. The primary interest is in determining whether $\beta_1 + \beta_{12}$ is significant and whether this varies between the two models (a and b).

3.1.2 Planned Sensitivity analyses

To investigate the robustness of the results of the primary analysis we will undertake a number of sensitivity analyses to include:

1. **Adjusting for participants initiated on alternative systemic therapy**
   To assess the robustness of the primary analysis, this analysis will be performed to estimate underlying treatment effect which would have been observed in the absence of patients receiving systemic therapy

   Outcome Definition: objective SCORAD values at 8, 12, 16, 20, 24 weeks
   Covariate definition of alternative systemic therapy: S_{ij} is participant i who is initiated on azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, prolonged systemic oral steroids (oral prednisolone > 30 days) or ultraviolet therapy after start of omalizumab/placebo prior to week j (Yes or No).

   Analysis: A sensitivity analysis using a model based approach to adjustment for alternative systemic therapy will be undertaken based on methods suggested in White et al[4]. The effect of systemic therapy is adjusted by adding an additional term S_{ij} as a covariate in model (a). The updated model is below,

$$Y_{ij} = \beta_0 + \beta_1 TRT_i + \beta_2 SCORAD_i^0 + \beta_3 IgE_i + \beta_4 Age_i + \beta_5 t_{12} + \beta_6 t_{16} + \beta_7 t_{20} + \beta_8 t_{24} + \beta_9 t_{12} * TRT_i + \beta_{10} t_{16} * TRT_i + \beta_{11} t_{20} * TRT_i + \beta_{12} t_{24} * TRT_i + \beta_{13} S_{ij} + b_i + e_{ij}$$

   $\beta_1 + \beta_{12}$ will provide an adjusted estimate of the treatment effect at week 24 by addressing the possible presence of the alternative systemic therapy.

2. **Adjusting for participants initiated on alternative systemic therapy and receiving 'rescue medication' by 6 months**

   Outcome Definition: objective SCORAD values at 8, 12, 16, 20, 24 weeks
   Covariate definition of alternative systemic therapy: S_{ij} is participant i who is initiated on azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, prolonged systemic oral steroids (oral prednisolone > 30 days) or ultraviolet therapy after start of omalizumab/placebo prior to week j (Yes or No).
   Covariate definition of 'on' rescue medication: R_{ij} participant i who receives a short dose ($\leq$ 30 days) of oral prednisolone at a dose of up to 40mg/day, prior to week j (Yes or No). The participant will be deemed to be 'on rescue medication' from start of first dose to 3 weeks after last dose.

   Analysis: The same as for sensitivity analysis no.1. The effect of rescue medication is adjusted by adding an additional term R_{ij} as a covariate in the model which is defined as whether or not the patient i was on rescue medication prior to week j. The updated model is as below,

$$Y_{ij} = \beta_0 + \beta_1 TRT_i + \beta_2 SCORAD_i^0 + \beta_3 IgE_i + \beta_4 Age_i + \beta_5 t_{12} + \beta_6 t_{16} + \beta_7 t_{20} + \beta_8 t_{24} + \beta_9 t_{12} * TRT_i + \beta_{10} t_{16} * TRT_i + \beta_{11} t_{20} * TRT_i + \beta_{12} t_{24} * TRT_i + \beta_{13} S_{ij} + \beta_{14} R_{ij} + b_i + e_{ij}$$

   $\beta_1 + \beta_{12}$ will provide an adjusted estimate of the treatment effect at week 24 by taking into account of the alternative systemic therapy and rescue medication.

3. Adjusting for participants initiated on alternative systemic therapy, receiving 'rescue medication' by 6 months and topical steroids use

Outcome Definition: objective SCORAD values at 8, 12, 16, 20, 24 weeks
Covariate definition of alternative systemic therapy: S_{ij} is participant i who is initiated on azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, prolonged systemic oral steroids (> 30 days) or ultraviolet therapy after start of omalizumab/placebo prior to week j (Yes or No).
Covariate definition of 'on' rescue medication: R_{ij} participant i who receives a short dose ($\leq$ 30 days) of oral prednisolone at a dose of up to 40mg/day, prior to week j (Yes or No). The participant will be deemed to be 'on rescue medication' from start of first dose to 3 weeks after last dose.
Covariate definition of topical steroids: cumulative use of topical steroids (number of days used) by 24 weeks.

Analysis: The same as for sensitivity analysis no.2. The effect of topical steroids use is adjusted by adding an additional term T_{ij} as a covariate in the model which is defined as the cumulative days of topical steroid for patient i prior to week j. The updated model is as below,

$$Y_{ij} = \beta_0 + \beta_1 TRT_i + \beta_2 SCORAD_i^0 + \beta_3 IgE_i + \beta_4 Age_i + \beta_5 t_{12} + \beta_6 t_{16} + \beta_7 t_{20} + \beta_8 t_{24} + \beta_9 t_{12} * TRT_i + \beta_{10} t_{16} * TRT_i + \beta_{11} t_{20} * TRT_i + \beta_{12} t_{24} * TRT_i + \beta_{13} S_{ij} + \beta_{14} R_{ij} + \beta_{15} T_{ij} + b_i + e_{ij}$$

$\beta_1 + \beta_{12}$ will provide an adjusted estimate of the treatment effect by taking into account of the alternative systemic therapy, rescue medication and topical steroids use.

4. Excluding data post initiation of alternative systemic therapy

In the first instance we will ignore all objective SCOARD scores following initiation of alternative systemic therapy i.e. azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, prolonged systemic oral steroids (> 30 days) or ultraviolet therapy. The primary analysis model will be fitted to data before the time of alternative systemic therapy for such patients along with all observed data for patients who do not initiate alternative systemic therapy. This analysis assumes the alternative systemic therapy patients would have had similar outcomes to those observed with the same history and profile.

Since the alternative systemic therapy patients would typically have had worse outcomes a pattern-mixture Multiple Imputation (MI) approach[3] will then be used to subsequently explore the impact of worse outcomes among patients initiating alternative systemic therapy. Imputation under MAR will initially be performed separately within each arm following the guidance suggested by White et al[5]. The variables in the imputation model will be the same as those in the analysis model without including more auxiliary variables after taking into account of the relative small sample size of this study[6]. We define δ_S as the postulated mean difference in the rate of change of the objective SCORAD score between the observed and alternative systemic therapy cases over 24 weeks. For each patient initiating alternative systemic therapy we will then modify the MAR imputed observations accordingly by δ_S. Imputed data sets will be analysed using the primary analysis model. Results will be combined across imputed data sets using Rubin's rules. We will repeat the analysis for a range of δ_S's corresponding to 25%, 50%, 75% and 100% increase in the objective SCORAD observed over 24 weeks in all patients.

5. Adherence-adjusted analysis

Outcome definition: objective SCORAD at 24 weeks

Analysis: An analysis of complier average causal effect (CACE) by a two-stage least squares instrumental variable regression would be performed for the primary endpoint. Here, we defined 'complier' as those who complete more than 50% of injections (that is injections received relative to injections planned for 24 week study period in groups). Randomisation will be used as an instrumental variable for treatment received with the same covariates in primary analysis models.

3.1.3 Missing data analyses

The number and proportion of participants missing objective SCORAD value by visit number will be tabulated. The primary analysis includes all observed data and assumes the probability of missing data is not dependent on the values of the unobserved data themselves, conditional on the observed values of the variables included in the analysis model (MAR assumption). Sensitivity analysis will explore departures from the main MAR analysis assumption for all patients on the primary outcome using a pattern-mixture MI approach[3].

Imputation under MAR will initially be performed separately within each arm following the guidance suggested by White et al[5]. The variables in the imputation model will be the same as those in the analysis model without including more auxiliary variables (e.g. predictors of missingness) after taking into account of the relative small sample size of this study[6]. Imputations will then be modified to reflect departures from the MAR assumption. We will investigate the impact of a better or poorer response than that predicted by MAR (lower/higher objective SCORAD scores) for patients with missing data.

We define δ as the postulated mean difference in the rate of change of the objective SCORAD score between the observed and unobserved cases over 24 weeks. For each patient in each intervention arm we then modify the MAR imputed observations accordingly by δ. Imputed data sets will be analysed using the primary analysis model. Results will be combined across imputed data sets using Rubin's rules. We will repeat the analysis for a range of δ's corresponding to +/- 10, 20, 30, 40 and 50% of the rate of change of the objective SCORAD observed over 24 weeks in all patients. We will also consider the possibility that data is missing informatively in one arm only. Only imputations for active arm patients will be modified for a range of δ's corresponding to +/- 10, 20, 30, 40 and 50% of the rate of change of the objective SCORAD observed over 24 weeks in the active arm and the primary analysis repeated. Subsequently only imputations for placebo patients will be modified for a range of δ's corresponding to +/- 10, 20, 30, 40 and 50% of the rate of change of the objective SCORAD observed over 24 weeks in the placebo arm and the primary analysis repeated.

We also plan to conduct further sensitivity analysis which combines the approach outlined here with that described in Section 3.1.2 where the data following initiation of alternative systemic therapy is additionally set missing and adherence is taken into account. We will vary the δ adjustment by rescue status and general missing status. Imputed data sets will be analysed using the primary analysis model to consider the impact of rescue medication and missing data together. Imputed data sets will also be analysed using the adherence-adjusted analysis model. This will enable us to consider the impact of rescue medication, missing data and adherence together.

3.2 Analysis of secondary outcomes

The endpoint for secondary analyses will be week 24. If there is substantial (>15%) missing outcome data at week 24 secondary outcomes analyses will be undertaken using all available data points over time from week 8 to week 24 using the appropriate generalised linear mixed model for the outcome type.

3.2.1 Subjective SCORAD

Outcome Definition: Subjective SCORAD values at 24 weeks.

Analysis: Analysis of covariance will be used with subjective SCORAD as the outcome variable and including treatment group, baseline subjective SCORAD and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) as covariates. The estimated treatment effect (mean difference) will be reported with 95% confidence intervals and corresponding p value.

3.2.2 Treatment failure within 24 weeks (Y/N)

Outcome definition: Treatment failure is defined as a patient in whom, after the 1st 12 weeks of treatment, have persistent severe eczema despite 2 courses of rescue therapy (short course of oral prednisolone (≤30 days) up to dose 40mg/day).

Analysis: Logistic regression model will be used with the treatment failure as outcome variable and including treatment group, and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) as covariates. The estimated treatment effect (Odds Ratio) will be reported with 95% confidence intervals and corresponding p value.

3.2.3 Alternative systemic therapy started within 24 weeks (Y/N)

Outcome definition of alternative systemic therapy: patients in whom a) alternative systemic therapy has been started as a result of treatment failure as defined in 3.2.2 OR b) where alternative systemic therapy is being considered at 24 weeks

Analysis: Logistic regression model will be used with alternative systemic therapy as the outcome variable and including treatment group, and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) as covariates. The estimated treatment effect (Odds Ratio) will be reported with 95% confidence intervals and corresponding p value.

3.2.4 Eczema Area and Severity Index (EASI) & Patient-oriented Eczema Measure (POEM)

Outcome definition EASI: Eczema Area and Severity Index (EASI) is a tool to determine the level of severity and extent of atopic eczema. Ranges from 0 to 72 (full or half scores) are allowed at 24 weeks.
Outcome definition POEM: Patient-oriented Eczema Measure (POEM) is a validated, patient-derived assessment measure for monitoring atopic eczema severity. Ranges from 0 to 28.

Analysis: Analysis of covariance will be used with EASI and POEM, respectively as the outcome variable and including treatment group, baseline EASI/POEM and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) as covariates. The estimated treatment effect (mean difference) will be reported with 95% confidence intervals and corresponding p value.

3.2.5 Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ)

Outcome definition: Paediatric Allergic Disease Quality of Life Questionnaire *(PADQLQ)* at 24 weeks. Ranges from 0 to 156.

Analysis: Analysis of covariance will be used with PADQLQ as the outcome variable and including treatment group, baseline PADQLQ and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) as

covariates. The estimated treatment effect (mean difference) will be reported with 95% confidence intervals and corresponding p value.

3.2.6 (Children's) Dermatology Life Quality Index ((C)DLQI)

Outcome definition: (C)DLQI questionnaire at 24 weeks. Ranges from 0 to 30.

Analysis: Analysis of covariance will be used to with (C)DLQI as the outcome variable and including treatment group, baseline (C)DLQI and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) as covariates. The estimated treatment effect (mean difference) will be reported with 95% confidence intervals and corresponding p value.

3.2.7 Skin prick test (SPT) reactivity

Outcome definition 1: The mean value per participant of the following skin prick tests (SPT): cow's milk, egg white, soy, wheat, peanut, Brazil nut, hazelnut, almond, walnut, cashew, pistachio, pecan, macadamia, sesame, pine nut, cod, alternaria, house dust mite, birch pollen, Timothy grass pollen, cat, dog, rabbit, horse and shrimp.

Analysis: The difference in the mean change (baseline and 24 weeks) will be calculated and presented with a 95% confidence interval. Only participants with completed baseline SPT performed will be analysed. All participants will contribute to the descriptive analysis. The number of participants with positive tests at baseline and 24 weeks will be tabulated by treatment arm. The analysis will then be repeated separately by respiratory allergens and food allergens.

Outcome definition 2: The number of positive SPT (>3mm) per participant at 24 weeks.

Analysis: Poisson regression will be used. The Pearson Chi-Square goodness-of-fit tests will be carried out to measure the distribution of the dependent variable to test identifies the distribution of the data and ensures the selection of the correct statistical model. Negative binomial regression model will be adopted if the Poisson regression is over dispersed. If there are a disproportional number of zero counts, the zero counts and number of SPT will be modelled as two separate processes using a zero inflated Poisson regression model. The model will include treatment group, and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) and baseline number of positive SPT as covariates.

3.2.8 *Infective episodes of eczema count*

Outcome definition: Infective exacerbation(s) recorded at study visits (on the case report form) over 24 week period

Analysis: Poisson regression will be used. The Pearson Chi-Square goodness-of-fit tests will be carried out to measure the distribution of the dependent variable to test identifies the distribution of the data and ensures the selection of the correct statistical model. Negative binomial regression model will be adopted if the Poisson regression is over dispersed. If there are a disproportional number of zero counts, the zero counts and number of infective episodes will be modelled as two separate processes using a zero inflated Poisson regression model. The model will include treatment group, and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) as covariates.

3.2.9 Eczema exacerbations count

Outcome definition: The number of eczema exacerbations by 24 weeks

Exacerbations of eczema are defined as follows:

- Increase in SCORAD by 15 points from last recorded SCORAD
  AND
- Patient perception of worsening eczema

An eczema exacerbation will be recorded as y/n on the case report form

Analysis: Poisson regression will be used. The Pearson Chi-Square goodness-of-fit tests will be carried out to measure the distribution of the dependent variable to test identifies the distribution of the data and ensures the selection of the correct statistical model. Negative binomial regression model will be adopted if the Poisson regression is over dispersed. If there are a disproportional number of zero counts, the zero counts and number of eczema exacerbations will be modelled as two separate processes using a zero inflated Poisson regression model. The model will include treatment group, and the minimisation variables (IgE (≤1500, >1500) and age (<10 or ≥10 years) as covariates.

3.3 Subgroup analysis

A sub-group analysis is planned for relevant secondary outcomes of interest to investigate whether intervention effects differ between those different adherence, defined as the injections received relative to injections planned for 24 week study period in groups(≤50%, >50%; ≤75%,>75%; ≤90%, >90%). All subgroup analyses will be analysed using the same method as for the primary outcome. The interaction between group and different adherence will be also tested. The results will be displayed by means of a forest plot.

3.4 Exploratory analysis

A longitudinal analysis will be undertaken using a linear mixed model to determine the difference in objective and subjective SCORAD at 48 weeks. The analysis procedures will be the same as in the primary analysis, but will include two more data at 36 weeks and 48 weeks. An overall treatment effect for objective/subjective SCORAD at different weeks will be estimated. The model will be checked for independence of residuals, distribution of residuals, equal variance of residuals, distribution of random effects (as appropriate), and extreme outliers and points with high leverage.
Note: it is anticipated that the treatment effect will be of interest predominately from 12 weeks as this is the minimum expected time to benefit.

3.5 Statistical considerations

3.5.1 Missing baseline data

It is unlikely that missing baseline data will be problematic for the primary analysis as it is anticipated that missing data for baseline SCORAD, IgE and age will be extremely low. However, if this happens, in case of loss of power using observed data, mean values will be calculated from the non-missing values for the baseline variable using pooled data from both treatment groups[7]. With reference to those categorical variables, the imputed mean will be rounded up to nearest category level. This is justifiable because randomisation ensures that baseline are independent of treatment group and keep the statistical efficiency in the estimation of treatment effect.

3.5.2 Missing outcome data

The primary analysis uses all observed outcome data and is conducted under the MAR assumption. As detailed in Section 3.1.3 we will conduct sensitivity analysis to assess the impact of departures from the MAR assumption on the results of the primary analysis.

3.5.3 Missing items in questionnaires

The number (%) with complete data will be reported. We will use the missing value guidance provided for questionnaires. If there are no guidance provided, we will impute for an individual if 20% or fewer items are missing. For example, in a scale with 10 items, prorating will be applied to individuals with 1 or 2 items missing. The average value for the 8 or 9 complete items will be calculated for that individual and used to replace the missing values. The scale score will be calculated based on the complete values and these replacements. If greater than 20% of items are missing in the questionnaire then the questionnaire score will be treated as missing and excluded from the analysis.

3.5.4 Interim analysis and data monitoring

No formal interim analysis will be undertaken prior to the final analysis; as a result no adjustment for interim analyses has been made. The data monitoring committee will review safety and efficacy data at time points of their choosing.

3.5.5 Multiple comparison

No multiplicity adjustments will be performed for the secondary analysis and results will be viewed as hypothesis generating.

3.6 Determining a clinically important difference

Through discussion and consultation with the funder and clinicians, a relative reduction of 33% in symptoms, which equates to an absolute difference of 13.5 in the 24 week change in objective SCOARD, was selected to be the minimum important treatment effect to detect. This takes into account the patient burden and high treatment cost.

The Minimum Clinically Important Difference (MCID) is the smallest difference in an outcome measure that represents a clinically relevant outcome to the patient, regardless of cost and burden. Published studies have recommended the use of both anchor- and distribution-based methods to determine the MCID[8].

A study by Schram et al.[9], which adopts an anchor-based approach, suggests a MCID for the objective SCORAD is 8.2. However, this is based on data from three RCT's on treatments for atopic eczema which include adults. The MCID reported by Schram et al. for children only, based on a subsample of n=25 with an average age of 9.4 years is 9.0.

Since the patients included in the study by Schram et al. also had a milder baseline severity a distribution-based method using data collected from the trial was also employed to calculate the MCID. Using the data from the first 47 ADAPT patients who completed week 24 assessments (75% of total sample size) adopting 0.7SD of the change in score from baseline gives a MCID of 8.5.

We will use these figures to guide interpretation of the results from the primary analysis.

4 Software

Data management: An online data collection system for clinical trials (MACRO; InferMed Ltd) will be used. This is hosted on a dedicated server at Kings College London (KCL) and managed by the Mental Health and Neurosciences Clinical Trials Unit (MH&N CTU). The MH&N CTU Data Manager will extract data periodically as needed and provide these in comma separated (.csv) format.

Statistical analysis: Stata will be used for data description and the main inferential analysis. R or SAS (Statistical software programmes) may be used for random effects models.

5 Amendments to version 1.0

AMENDMENTS TO THE SAP THAT WERE MADE AFTER THE SAP WAS SIGNED OFF BYTHE TSC:

1. Adherence-adjusted analysis was added to account for potential bias due to ITT analysis.
2. Move the Adherence analysis in planned sensitivity analysis to Subgroup analysis.
3. Exploratory analyses for objective and subjective SCORAD at 48 weeks were added.
4. The strategies for missing problem were defined in detail.
5. Define the Safety Set (SS) for Adverse events analysis
6. Included more specific details on primary analysis model.
7. Added more details on how missing outcome data will be explored in sensitivity analysis.
8. Added specification of the MCID for the objective SCORAD following advice received from the ADAPT DMC.

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