

Keep Control of Eczema Study (Short title: Keep Control Study)

Statistical Analysis Plan

Final Version 1.0
(04 Sep 2026)

Based on Protocol (Appendix D) version 6.0 (dated 11 Aug 2026)

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Approval

The following people have reviewed the Statistical Analysis Plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas.

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Table of Contents

Approval	1
List of contributors and reviewers	2
1. INTRODUCTION AND PURPOSE	7
2. STUDY SYNOPSIS	8
2.1. Study background and rationale	8
2.2. Sample size and justification	11
2.3. Randomisation	11
2.4. Masking and breaking of masking	11
2.5. Outcome measures	12
2.6. Trial committees	16
3. GENERAL ANALYSIS CONSIDERATIONS	17
3.1. Primary estimand	17
3.2. Analysis sets	18
3.3. Interim analysis	18
3.4. Timing of final analysis	18
3.5. Statistical software	18
3.6. Derived variables	19
3.7. Procedures for missing data	20
3.7.1. Missing outcome data	20
3.7.2. Missing baseline data	20
3.7.3. Missing questionnaire data	21
4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS	22
4.1. Participant flow	22
4.2. Baseline characteristics	22
5. ASSESSMENT OF STUDY QUALITY	23
5.1. Integrity of randomisation method	23
5.2. Flare-ups and adherence with TCS advice	23
5.3. Follow-up and discontinuation	23
5.4. Protocol deviations	24
6. ANALYSIS OF EFFECTIVENESS	25
6.1. Primary analysis	25
6.2. Sensitivity analysis of primary outcome	27
6.3. Supplementary analysis of primary outcome	27

6.4.	Subgroup analysis of primary outcome	28
6.5.	Secondary outcomes.....	29
7.	ANALYSIS OF SAFETY	31
8.	EXPLORATORY ANALYSIS.....	31
9.	FINAL REPORT TABLES, FIGURES AND LISTINGS	32
10.	REFERENCES.....	33
11.	APPENDIX.....	34
11.1.	Derivation of atopic eczema according to UK Diagnostic Criteria	34

Abbreviations

Abbreviation	Description
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
HCP	Health Care Provider
HOME	Harmonizing Outcomes for Eczema
HTA	Health Technology Assessment
IDQoL	Infants' Dermatitis Quality of Life Index
ITT	Intention To Treat
MAR	Missing At Random
MHRA	Medicines and Healthcare products Regulatory Agency
MNAR	Missing Not At Random
NCTU	Nottingham Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PMG	Programme Management Group
PMM	Predictive Mean Matching
POEM	Patient Oriented Eczema Measure
PSC	Programme Steering Committee
RCT	Randomised Controlled Trial
RECAP	Recap of Atopic Eczema
SAP	Statistical Analysis Plan
TCS	Topical Corticosteroids
TMG	Trial Management Group
TSC	Trial Steering Committee
UKWP	UK Working Party

Changes from protocol

The table below details changes to the planned analyses in the SAP compared to the protocol, which after discussion with the TMG, are not considered to require a protocol amendment.

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification
Version 6.0, Appendix D, Analysis section of Details of Keep Control of Eczema Study	Does not include adjusting for use of systemic treatments	Section 6.1 Primary analysis	Amended to include adjusting for use of systemic treatments in model specification.	Recommended following feedback from protocol peer-review.
Version 6.0, Appendix D, Analysis section of Details of Keep Control of Eczema Study	States that if there is evidence of a differential effect over time, the difference in mean Recap score each week will be reported.	Section 6.1 Primary analysis	Sentence removed. New paragraph added to state that evidence of a differential effect over time will be explored by inclusion of treatment by time interaction in the model.	Following discussions from the blind review meeting. Analysis will proceed under assumption of no interaction to avoid a data driven model selection approach.
Version 6.0, Appendix D, Analysis section of Details of Keep Control of Eczema Study	Does not include additional subgroups	Section 6.4 Subgroup analysis of primary outcome	Amended to include subgroup analyses for route of recruitment, timing of steroid cream use during an eczema flare-up, participant views on using steroid creams for eczema flare-ups and gender.	Following discussions from the blind review meeting.

Amendments to versions

Updated					Timing in relation to unmasking of Trial	
Protocol Version	SAP Version	Date	Change/comment	Statistician	Timing in relation to unmasked interim monitoring	Statistician

1. INTRODUCTION AND PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the NIHR funded RAPID Keep Control of Eczema Study. The results reported will follow the strategy set out here, which adheres to the guidelines for the content of a statistical analysis plan (1).

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.
2. Explain in detail how the data will be handled and analysed to enable others to perform or replicate these analyses.

Additional exploratory or auxiliary analyses of data not specified in the protocol may be included in this analysis plan.

This analysis plan will be published on the study website, hence will be available publicly. It will be uploaded with the main papers, if required, when they are submitted for publication. Additional analyses suggested by reviewers or editors will be performed if considered appropriate. This should be documented in a file note.

Any amendments to the statistical analysis plan (SAP) after the first version of the SAP is agreed and signed off will be made by the unmasked statisticians and will be described and justified.

Health economic and qualitative analysis plans are beyond the scope of this document.

2. STUDY SYNOPSIS

2.1. Study background and rationale

Eczema is a chronic-relapsing itchy skin condition, that is characterised by periods of flare-up and remission. People with eczema are usually able to self-manage their condition with a combination of topical treatments. These include topical corticosteroids (TCS) to get control of flares, and emollients to manage dry skin and to help prevent future flare-ups.

NICE and MHRA guidance recommends that people with eczema are given advice by healthcare professionals about how long to use their TCS treatments for, (2) (3) but clinical guidelines vary in their recommendations and people are often given vague or unhelpful instructions, such as “use sparingly” or “use as required” (4).

This lack of clarity is partially driven by the lack of evidence to inform clinical practice. A recent Cochrane review of strategies for the use of TCS in eczema found no RCTs that addressed how long to apply TCS for an eczema flare-up (5).

“How best to use topical corticosteroids?” was identified as the top priority for future research in the eczema James Lind Alliance Priority Setting Partnership, and the Rapid Eczema Trials project was established to answer patient-driven questions such as this.

Table 1: Synopsis of study design and procedures

Title	Keep Control of Eczema Study
Short title	Keep Control Study
Chief Investigator	Prof Kim Thomas
Trial Design	Pragmatic, two-arm, parallel group, superiority randomised controlled trial
Objectives	AIM: To compare different strategies for using TCSs for the self-management of eczema over a period of 4 months in children and adults with eczema. OBJECTIVES: 1. To assess the impact of providing specific advice on how long to apply TCSs for during an eczema flare-up compared with no specific advice. 2. To explore barriers and facilitators in using the different strategies for controlling eczema flare-ups and to understand the impact of trial processes on trial participation.

	3. To explore feasibility of using photos to assess eczema severity in online clinical trials.
Research question	Does providing specific advice on “how long to apply TCSs for during an eczema flare-up” improve eczema control compared to “no specific advice”, over 4 months?
Trial duration	Each participant will be enrolled for 16 weeks. Recruitment will take place for up to 12 months.
Participants and eligibility criteria	People with eczema aged 1 year and older who currently use topical corticosteroids (TCS) to manage their eczema. Inclusion criteria • Aged ≥ 1 year with self-report of eczema (syn. atopic dermatitis, atopic eczema) • Used topical corticosteroid on a total of at least 3 days to manage eczema flare up in the last 8 weeks. • Willing to change how currently using TCS treatments whilst in the trial. • Usual residence in the UK. • Able and willing to give informed consent (or parent/legal guardian able and willing to give informed consent for children under 16 years). Exclusion criteria • Using a TCS preparation that includes antibiotics or antifungal (and have no other TCS available), as these products are not intended for long-term use. • Diagnosis unlikely to be atopic eczema: only present on hands (likely to be hand eczema or contact dermatitis); limited to locations where skin exposed to nickel e.g. jewellery (likely to be contact dermatitis); eczema only around varicose veins (likely to be varicose eczema). • Taking part in another eczema intervention trial. • Member of household already participating in this trial. • Eczema only present on the scalp (as this requires different topical steroid formulations) and/or only at sensitive body sites (e.g. groin, armpits or face (as the advice being tested is not applicable to treatment at sensitive sites, which may require a different potency and duration of treatment)). • Using clobetasol propionate 0.05% (trade name dermivate), a very strong TCS - to ensure participant safety. Potential participants invited through GP practices will be identified using search criteria as per protocol section 4.

Intervention and control	The study is an “advice trial”. Whilst both treatment strategies align with current practice, advice varies, and people are often given conflicting or vague advice. For the purposes of this trial, two advice strategies will be tested: Specific advice on duration of applying TCSs (treat flare-ups for longer): - Use TCSs during a flare-up and for 2 days after the skin is eczema free. No specific advice on duration of applying TCSs (treat flare-ups as usual): - Use TCSs during a flare-up as you normally would. Participants will be advised to use their usual prescribed TCS and will remain under the care of their usual healthcare professional.
Outcome measures	Primary outcome: - Eczema control measured by Recap of atopic eczema (RECAP) (6). Includes 7 items, scored 0 to 28. Assessed weekly over 16 weeks. Secondary outcomes: - Eczema symptoms (Patient Oriented Eczema Measure, POEM) (7). Includes 7 items, scored 0 to 28. Assessed monthly. - Total days of TCS used (days of TCS use each week 0 to 7 days) - collected weekly - Skin-specific quality of life (Infants' Dermatitis Quality of Life Index (IDQoL) (8) (under 4 years), Children's Dermatology Life Quality Index (CDLQI) (9) (from 4 years to 15 years) or Dermatology Life Quality Index (DLQI) (10) (16 years and over) depending on age) – 10 items, scored 0 to 30. Assessed at baseline and week 16. - Number of weeks when TCS not used (based on the use of TCS questions - assessed weekly). - Number of well controlled weeks (defined as number of weeks with Recap score <6). - Global change in eczema compared to baseline. Assessed at week 16. - Adverse events: - Contact with healthcare professional (HCP) because of a worsening of the eczema. - Contact with HCP due to concerns about side-effects.
Sample size / Number of participants	450 (225 per arm)

2.2. Sample size and justification

The sample size for the trial is based on RECAP scores assessed weekly for 16 weeks and is designed to detect a difference of 2.2 in RECAP scores between the two groups. A small difference of 2.2 has been chosen as this trial is evaluating a simple advice strategy. In this context, even a small improvement could be important to people living with eczema and could help them to self-manage their eczema more effectively. Although 2.2 is a small change, it is likely to be beyond measurement error (11).

Assuming a standard deviation in weekly RECAP scores of 6.5 and a correlation between repeated measurements of 0.8 (based on data from previous eczema RCTs), a sample size of 150 per group is required to detect this difference with 90% power and 5% two-sided significance level. Randomised participants will follow their allocated treatment strategy when they have a flare-up during the trial, however some participants may join the trial and not have an eczema flare-up. Based on previous online trials, we assume 80% of participants randomised will have at least one flare up and need to use TCS over the 16-week follow-up period. Inflating for this and allowing for 15% loss to follow-up, a total sample size of 450 is required.

2.3. Randomisation

Randomisation will be carried out by the participant using an online system managed by NCTU, as described in protocol section 6.2. Participants will be randomised 1:1 to either the intervention group (treat flare-ups for longer) or control group (treat flare-ups as usual) using a minimisation algorithm with a probabilistic element balancing on the following factors:

- Symptom severity POEM score (0-7 mild, 8-16 moderate, 17-28 severe)
- Age (<4 years, 4-11 years, 12-15 years, 16-25 years, 26-55 years, >55 years)
- Potency of TCS (mild, moderate, potent)

The randomised allocated group will not be released to participants until after baseline variables have been entered and stored on the trial database.

2.4. Masking and breaking of masking

As this is an advice trial, it is not possible to mask trial participants to their randomised allocation. To mitigate the potential bias caused by lack of masking, we will collect prior belief in the impact of intervention strategy at baseline and explore this in a sensitivity analysis.

The trial statisticians, trial team at NCTU and members of the Trial Management Group will be masked to treatment allocation until the database has been hard-locked.

2.5. Outcome measures

Table 2: Summary of the outcome measures

Outcome measures	Description, source and derivation of scores	Type of variable	Analysis timepoint	Method of analysis	Population level summary measure ¹
Primary outcome					
Eczema control measured by RECAP of atopic eczema (RECAP) assessed weekly over 16 weeks <i>(HOME core outcome)</i>	RECAP is a 7-item questionnaire to assess experience of eczema control and can either be self-completed or caregiver completed for younger children (6). Each of the seven questions in RECAP carries equal weight and are scored from 0 to 4. Scores from the seven questions are summed to create a total score ranging from 0 to 28, higher scores indicating less well-controlled eczema (https://www.nottingham.ac.uk/research/groups/cabd/resources/recap.aspx).	Continuous	Weekly over 16 weeks	Mixed effects linear regression to compare average RECAP score as a continuous repeated measures variable over the 16 weeks.	Difference in means (95% confidence interval (CI), p-value)
Secondary outcomes					
Patient-reported symptoms assessed monthly, using POEM <i>(HOME core outcome)</i>	POEM comprises seven questions relating to eczema symptoms over the past week. Each question carries equal weight and the responses to each question are scored from 0 to 4 (7). The overall POEM score is calculated as the sum across all seven questions, ranging from 0 to 28, higher scores indicating greater severity of eczema	Continuous	Week 4, 8, 12 and 16	Mixed effects linear regression to compare average POEM score as a continuous repeated measures variable over the 16 weeks.	Difference in means (95% CI)

Outcome measures	Description, source and derivation of scores	Type of variable	Analysis timepoint	Method of analysis	Population level summary measure ¹
	symptoms (https://www.nottingham.ac.uk/research/groups/ceb/ebd/resources/poem.aspx).				
Number of days TCS used	Collected weekly using question “How many days [have you/has your child] used steroid creams or ointments for [your/their] eczema in the last week?” Response options 0 to 7 days. The overall proportion of days TCS used will be calculated for each participant by dividing the total number of days TCS were reportedly used over the 16 weeks by the total possible number of days of TCS use (defined as the number of completed questionnaires multiplied by 7).	Continuous	Week 16	Linear regression model to compare the mean proportion of days TCS used.	Difference in mean proportions (95% CI)
Skin specific quality of life (QoL) at week 16 (HOME core outcome)	Derived from Adult QoL (DLQI), Children’s QoL (CDLQI), Infants’ QoL (IDQOL) questionnaire forms, respectively (8-10). Assessment method depends on age at randomisation: - Age < 4 years – Infants Quality of Life Index (IDQoL). A 10 item questionnaire completed by caregiver - Age 4 to 15 years - Children’s Dermatology Life Quality Index (CDLQI). A 10 item	Continuous	Week 16	Linear regression to compare average QoL score for each age-specific questionnaire.	Difference in means (95% CI) for each questionnaire

Outcome measures	Description, source and derivation of scores	Type of variable	Analysis timepoint	Method of analysis	Population level summary measure ¹
	questionnaire which can be completed by the child with help of caregiver if needed Age ≥ 16 years - Dermatology Life Quality Index (DLQI). A 10 item questionnaire completed by the patient. For all of the questionnaires, the responses to the ten items are summed to create a total score ranging from 0 to 30, with higher scores indicating greater impairment on quality of life. Scores will be presented separately for each questionnaire and will not be combined.				
Number of weeks when TCS not used	Derived from the question asked weekly on number of days used TCS in the last week, with the number of weeks when TCS not used defined as 0 days. The proportion of weeks when TCS not used will then be calculated as the number of weeks TCS not used divided by the total number of weeks participant responded to the question.	Continuous	Week 16	Linear regression model to compare the mean proportion of weeks with TCS not used.	Difference in mean proportions (95% CI)
Number of well-controlled weeks	Derived from weekly RECAP questionnaire with a well-controlled week defined as score < 6. The proportion of well-controlled weeks will then be calculated as the number of weeks with a	Continuous	Week 16	Linear regression model to compare the mean proportion of weeks with a well-	Difference in mean proportions (95% CI)

Outcome measures	Description, source and derivation of scores	Type of variable	Analysis timepoint	Method of analysis	Population level summary measure ¹
	RECAP score < 6 divided by the total number of weeks with an available RECAP score, excluding weeks with missing RECAP scores.			controlled RCEAP score.	
Global change in eczema compared to baseline	Assessed at week 16 using the question "Over the last 4 months, how has [your/your child's] eczema been?" with response options of: a lot better than normal, better than normal, about the same, worse than normal and a lot worse than normal.	Categorical	Week 16	Descriptive	N/A
Contact with health care provider (HCP) because of a worsening of the eczema	Assessed each month. Participants will be derived as having a contact with a HCP due to worsening of eczema if they respond as 'yes' to speaking to a HCP about eczema and select "eczema got worse" as reason.	Binary	Week 4, 8, 12 and 16	Descriptive at each timepoint	N/A
Contact with HCP due to concerns about side-effects of TCS	Assessed each month. Participants will be derived as having a contact with a HCP due to concerns about side effects of TCS if they respond as 'yes' to speaking to a HCP about eczema and select "Concerns about side-effects of steroid creams" as reason.	Binary	Week 4, 8, 12 and 16	Descriptive at each timepoint	N/A

1 – Analyses with a between-group effect estimate will be adjusted by minimisation variables (age, baseline POEM score, and potency of TCS), baseline score (if collected) and other baseline variables as specified in the protocol (UK Diagnostic criteria, number of days TCS used to treat last flare-up, attitudes towards use of TCS, use of TCS to prevent flares, use of steroids (for any condition)), and use of systemic treatments.

2.6. Trial committees

A Trial Management Group (TMG) was assembled to oversee the trial. The Trial Management Group (TMG) included individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, Statistician, Trial Manager, Data Manager, plus members of the co-production groups and other co-applicants as appropriate. The role of the group was to ensure high-quality trial conduct, to time and within budget, to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

A Programme Management Group (PMG) and Programme Steering Committee (PSC) also met regularly over the course of the study. Their role and membership are outlined in the PMG and PSC Charter.

Since the programme includes only low-risk trials it was agreed with the sponsor and funder that a Data Monitoring Committee (DMC) was not required.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1. Primary estimand

Attribute	Definition
Target population	Children and adults (aged ≥ 1 year) with eczema who currently use steroid cream to manage their eczema.
Endpoint	Eczema control over 4 months assessed weekly using the RECAP questionnaire.
Treatment conditions	Comparator: No specific advice on duration of applying TCSs (treat flare-ups as usual - use TCS during a flare-up as you normally would). Intervention: Specific advice on duration of applying TCSs (treat flare-ups for longer - use TCS during a flare-up, and for 2 days after the skin is eczema free). In both groups, participants will continue with usual self-management strategies to manage eczema (e.g. emollients to moisturise, emollient wash products etc).
Population level summary measure	Difference in mean RECAP control score over 4-month trial period between the two treatment conditions.
Intercurrent events	
Non-adherence to allocated group i.e. participants in control group 'treat for longer' or participants in intervention group do not use steroids for 2 additional days	Treatment policy – all participant data included in analysis regardless of adherence with the allocated strategy.
Change to usual eczema treatments (including starting a new treatment) during the trial	Treatment policy – all participant data included in analysis regardless of whether there is a change in usual eczema treatment.

3.2. Analysis sets

Outcome	Analysis set ¹	Definition
Primary outcome	Full analysis set	All randomised participants who complete at least one RECAP questionnaire during the follow-up period. Participants are analysed according to randomised allocation regardless of adherence to allocated TCS strategy during a flare-up.
	Sensitivity analysis*	Multiple imputation for missing primary outcome data including all randomised participants.
	Supplementary analysis*	Subset of participants in the full analysis set who reported at least one flare-up.
Secondary outcomes	Full analysis set	As defined above for primary outcome.
Safety outcomes	Safety analysis set	All randomised participants who completed at least one safety questionnaire. Participants are analysed according to randomised group (as randomised) regardless of adherence with the allocated group.
	Exploratory analysis	All randomised participants.
Exploratory outcome (from Photo Assessment Feasibility Study)	Exploratory analysis	All randomised participants.

1 – Applies to all analyses: For participants who enter the study twice through randomisation, only their first entry will be included in the analysis.

3.3. Interim analysis

There are no formal interim analyses planned for this study due to the short-anticipated recruitment period.

3.4. Timing of final analysis

All final analyses will be performed once the target sample size for the trial has been reached, follow-up completed, and the database locked.

3.5. Statistical software

All analyses will be performed using Stata version 19.5 or above.

3.6. Derived variables

Derived variables and the algorithms for their calculation are listed below:

Derived variable	Algorithm for the calculation
Days from randomisation to discontinuation	Date of discontinuation minus date of randomisation
Diagnosis of eczema according to UK Diagnostic Criteria	Derived from 'About Your Eczema' questionnaire form. See Appendix 11.1 for details of derivation.
Reported contact with healthcare provider due to worsening of eczema	For those who have completed the question about speaking to a healthcare professional about eczema derived as: • 'Yes' if selected "Eczema got worse" from the reasons for healthcare contact. • 'No' if selected any other reason from the reasons for healthcare contact or no to the question about speaking with a HCP.
Reported contact with healthcare provider due to concerns over side effects of TCS	For those who have completed the question about speaking to a healthcare professional about eczema derived as: • 'Yes' if selected "Concerns about side-effects of steroid creams" from the reasons for healthcare contact. • 'No' if selected any other reason from the reasons for healthcare contact or no to the question about speaking with a HCP.
Missing questionnaire items: RECAP, POEM & QoL	Fully complete (no questions missing) Partially completed & scoreable (one question missing) Partially completed & not scoreable (more than one question missing but not all) Not completed (all questions missing)

3.7. Procedures for missing data

3.7.1. Missing outcome data

Missing primary and secondary outcome data will be assumed to be missing at random (MAR). The primary analyses for the outcomes will be conducted on participants who have available data for at least one follow-up questionnaire.

Key characteristics will be summarised at baseline by group according to inclusion in the primary analysis to help assess potential attrition bias in the primary analyses.

A sensitivity analysis for the primary outcome will assess the robustness of the study results to missing data using multiple imputation, as described in Section 6.2. There will be no imputation for any of the secondary outcomes.

3.7.2. Missing baseline data

For baseline RECAP and all other outcome variables measured at baseline (i.e. all secondary outcomes), we will monitor missing baseline data and where missing impute using the mean of the observed baseline values in order to adjust for the baseline score in the analysis (12).

For other baseline covariates specified to adjust for in the analysis (UK diagnostic criteria, number of days TCS used to treat last flare-up, attitudes towards use of TCS, use of TCS to prevent flares, use of steroids (for any condition), and use of systemic treatments), we will monitor missing data and use simple imputation in order to adjust for the baseline score in the analysis.

3.7.3. Missing questionnaire data

Questionnaire	Derivation of outcome scores with missing items
Eczema control (RECAP)	For missing items on the RECAP questionnaire, the total score will be calculated according to guidance on the Centre for Evidence Based Dermatology website: (https://www.nottingham.ac.uk/research/groups/cebd/resources/recap.aspx) • If one question is left unanswered this is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28. • If two or more questions are left unanswered the questionnaire is not scored.
Symptom severity (POEM)	For missing items on the POEM questionnaire, the total score will be calculated according to guidance on the Centre for Evidence Based Dermatology website: (http://www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx) • If one question is left unanswered this is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28. • If two or more questions are left unanswered the questionnaire is not scored.
Skin specific quality of life including IDQoL (infant), CDLQI (children), DLQI (adult)	For missing items in IDQoL, CDLQI, DLQI, the total score will be calculated according to guidance for each questionnaire on the Cardiff University website: (https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires) • If one question is unanswered, this is allocated a score of 0 and the scores are summed in the usual way, out of 30. • If two or more questions are unanswered, the questionnaire is not scored.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1. Participant flow

A CONSORT flow diagram will summarise the flow of participants through the study. This will present:

- The number of potentially eligible participants who expressed interest in the trial through commencing pre-screening
- The number of participants not eligible at screening
- The number of participants who did not consent
- The number of participants excluded prior to randomisation due to incomplete baseline data
- The number of participants randomised to the allocated group
- The number of participants included in the primary analysis by allocated group

4.2. Baseline characteristics

Baseline data will be summarised overall and by allocated group. Variables will be summarised in terms of:

- Demographic information (e.g. age at randomisation, gender, and ethnicity)
- Baseline eczema characteristics (e.g. UK Diagnostic Criteria for eczema, symptom severity based on POEM score)
- Baseline skin specific quality of life
- Summary of use of topical steroid creams/ointments at baseline (e.g. TCS used for eczema in the previous week, highest potency of TCS used to treat eczema flare-up)

Continuous data will be summarised in terms of the mean, standard deviation, median, lower and upper quartiles, minimum, maximum, and number of observations. Categorical data will be summarised in terms of frequency counts and percentages.

5. ASSESSMENT OF STUDY QUALITY

5.1. Integrity of randomisation method

Integrity of randomisation will be assessed by the distribution of randomised participants in the two groups across minimisation variables, reported in the baseline characteristics table. Descriptive statistics will also be presented according to baseline RECAP score, and other baseline variables, as specified in Section 4.2 and the protocol to assess balance between the groups at baseline.

5.2. Flare-ups and adherence with TCS advice

Participants are asked about flare-ups and use of steroid creams/ointments to treat flare-ups at weeks 4, 8, 12 and 16. At each time point the following will be summarised by group:

- Whether a participant has experienced an eczema flare-up in the previous month, and, if yes, the number of flare-ups within the month
- The number of days steroid creams were used to treat a specific flare-up within the last month (mean, standard deviation, median, lower and upper quartiles, minimum, maximum, and number of observations)

For participants allocated to the specific advice group reporting flare ups, whether the participant used steroid creams/ointments for 2 days after the skin looked and felt eczema free will be summarised (response options of yes/no/still treating ongoing flare).

Acceptability of the randomised allocation to participants, collected at week 16, will be assessed in terms of participants' self-reported:

- Ease of using steroid creams as asked
- Any change to the duration of treatment of flare-ups
- Intention to continue using steroid creams as had been during the study.

Acceptability outcomes will be summarised by group and reported descriptively in terms of frequency counts and percentages.

The number and percentage of participants who have reported a change in their eczema treatments during the study, and the type of change, will be summarised.

5.3. Follow-up and discontinuation

Completeness of follow-up will be reported weekly up to week 16 by allocated group. Weekly follow-up will be summarised by the total number of weekly questionnaires completed (mean, standard deviation, median, lower and upper quartiles, minimum, and maximum), the number and percentage of participants who completed at least one questionnaire, the weeks during which questionnaires were completed (1-4, 5-8, 9-12, 13-16), and the timepoint-specific questionnaire completion.

Participant withdrawals will be summarised by the number and percentage of participants who requested to withdraw from receiving study questionnaires, and the number of days

from randomisation to withdrawal (mean, standard deviation, median, lower and upper quartiles, minimum, and maximum).

Baseline characteristics according to inclusion in primary analysis will be presented descriptively to check for attrition bias. This will compare those who are followed up (with at least one follow-up questionnaire completed), to those with no data beyond baseline.

5.4. Protocol deviations

Non-adherence with the allocated group will be reported as described in Section 5.2 (Flare ups and adherence with TCS advice).

All protocol deviations that the NCTU become aware of will be recorded on a protocol deviation log. Protocol deviations will be summarised individually including the participant number, allocated group, number of days from randomisation to deviation, deviation (protocol/eligibility/other), and any further details on deviation.

6. ANALYSIS OF EFFECTIVENESS

All analyses and reporting will be in accordance with CONSORT guidelines. No formal adjustment for multiple significance testing will be applied: secondary outcomes will be considered supportive to the primary analysis.

6.1. Primary analysis

The primary analysis will be in accordance with the intention to treat (ITT) principle, where participants will be analysed regardless of adherence to their allocated treatment. The primary analysis will investigate the between-group comparison of mean RECAP scores using a mixed effects linear regression model, with observations over time (level 1) nested within participants (level 2). The model will adjust for minimisation variables (age at randomisation, baseline POEM score, and potency of TCS), along with baseline RECAP score and other baseline variables as specified in the protocol (UK Diagnostic criteria, number of days TCS used to treat last flare-up, attitudes towards the use of TCS, the use of TCS to prevent flare-ups, the use of steroids (for any condition)), and the use of systemic treatments. The model will include minimisation factors and baseline covariates as fixed effects, with a participant-level random intercept and slope. The model will also include an unstructured covariance matrix to account for multiple nested repeated measures over time. The between-group effect estimate will be presented as the adjusted difference in mean RECAP score over the 16 weeks, with the corresponding 95% confidence interval (CI) and p-value.

Baseline variables age at randomisation, baseline POEM score, and baseline RECAP score, will be included as continuous variables assuming a linear association with the outcome (13). Other baseline model covariates will be included as categorical, see table below.

Baseline variable	Categories
Potency of TCS	Mild/Moderate/Potent
Diagnosis of eczema according to the UK Diagnostic Criteria	No/Yes
Attitudes towards the use of TCS (<i>"Which of the following statements do you most agree with?"</i>)	Happy to use steroid creams in short bursts to control eczema flare-ups/ Have some concerns about using steroid creams, but understand that they are sometimes needed/ Have strong concerns about using steroids creams and try to limit their use
Use of TCS to prevent flare-ups (<i>"When do you/does your child use steroid cream? (tick all that apply)", Yes if selected "To prevent eczema flare-ups (this is sometimes called maintenance therapy or weekend therapy)", No if otherwise</i>)	No/Yes
The use of steroids (for any condition) (<i>"Do you/Does your child use any of the following for any medical condition (not eczema)? Select all that apply." Yes if selected "Steroid nasal sprays", "Steroid creams", or "Steroid tablets". No if selected "None of the above"</i>)	No/Yes
Number of days TCS used to treat last eczema flare-up	0/1-2/3-4/5-6/7-10/≥ 10
Use of systemic treatments (<i>"(Do you/Does your child use any of the following for eczema? (Select all that apply)", Yes if select "Steroid tablets", "Other prescribed tablet medications (not including antihistamines)", "UV light treatment", or "Injections (for example methotrexate or dupilumab)". No if selected "None of the above".</i>)	No/Yes

Note that the above categories may be collapsed if there are not enough participants in certain categories, as appropriate.

The model assumptions will be assessed to ensure normality of residuals of the fixed effects and random effect components are met. If there is strong evidence that assumptions are violated, an appropriate transformation will be considered.

If the model fails to converge, a simpler model will be used. The model will include, at a minimum, fixed effects for allocated group, time and minimisation variables, and a random effect for the participant.

To explore if there is evidence of a differential effect over time and to aid interpretation of the results from the analysis above, an additional analysis will include an interaction term between allocated group and time in the model.

6.2. Sensitivity analysis of primary outcome

Sensitivity analysis using multiple imputation

A sensitivity analysis for the primary outcome will investigate the impact of missing outcome data on the primary analysis by using multiple imputation for missing outcome data, under the assumption data are missing at random (MAR). Multiple imputation using a Predictive Mean Matching (PMM) approach will impute outcome data for missing weekly RECAP scores. The model will follow the primary analysis model specification described in Section 6.1, adjusting for the same baseline covariates. Other variables identified as predictive of missingness will also be included in the imputation model following examination. If possible, missing data will be imputed separately by allocated group. The number of datasets imputed will be based on the proportion of participants with missing RECAP scores, with a minimum of five imputed datasets generated.

The analysis specified in Section 6.1 will be repeated on the imputed datasets and results of the analyses will be combined using Rubins rules for multiply imputed data. This analysis will assume that unobserved outcomes are MAR and depend on observed characteristics but not the unobserved outcomes.

A further sensitivity analysis may be conducted to investigate the robustness of the results if the MAR assumption does not hold. This analysis will follow the assumption that data are missing not at random (MNAR), using the controlled multiple imputation method (14). If conducted, delta (d) based multiple imputation will be used to modify the value imputed under a MAR assumption by a fixed amount to explore how the results change if participants with missing outcomes had better/worse outcomes than predicted (based on the MAR assumption). A range of d values will be used in the sensitivity analyses.

Sensitivity analysis using a different analysis set

If there is evidence of a low retention rate for the primary outcome, a sensitivity analysis may be conducted by repeating the primary analysis described in Section 6.1, including only participants with at least one weekly follow-up per month (weeks 1-4, 5-8, 9-12, and 13-16). This analysis will explore the robustness of the primary analysis to missing outcome data.

Sensitivity analysis with additional baseline adjustments

A sensitivity analysis may be conducted by repeating the primary analysis with additional adjustment for baseline variables with an observed imbalance between groups.

6.3. Supplementary analysis of primary outcome

A supplementary analysis for the primary outcome will investigate the between-group comparison of mean RECAP scores for participants who reported at least one flare-up between baseline and week 16. The model will follow the same model specification as the primary analysis model, described in Section 6.1.

6.4. Subgroup analysis of primary outcome

Pre-specified subgroup analyses will explore whether the intervention effect varies according to the following characteristics measured at randomisation:

Subgroup	Category
Age at randomisation	1-11 years/12-55 years/≥56 years
Potency of TCS	Mild/Moderate/Potent
POEM score	Mild (0-7)/Moderate (8-16)/Severe (17-28)
Diagnosis of eczema according to UK Diagnostic Criteria	No/Yes
Prior belief on the impact of using steroid creams for longer on eczema control	Thinks using steroid creams for slightly longer during a flare-up doesn't help keep control of eczema/Thinks using steroid creams for slightly longer during a flare-up does help keep control of eczema /Does not know if using steroid creams for slightly longer during a flare-up keeps control of eczema
Route of recruitment	From GP or Doctor/Other
Timing of steroid cream use during an eczema flare-up	As soon as flare-up starts/ Prefer to wait a few days, to see if flare-up if getting worse
Participant views on using steroid creams for eczema flare-ups	Happy to use or have some concerns about using steroid creams/ Have strong concerns about using steroids creams and try to limit their use
Gender	Male/Female

Note that the subgroup analyses depend on the distribution of participants among categories. These may be collapsed depending on data sparsity.

Subgroup analyses will present the RECAP score by group and by category at key timepoints, and an extended summary of all weeks may be included in the Appendix. The outcome will be summarised descriptively as the mean and standard deviation of RECAP score. Analysis models for each subgroup will include an interaction term between allocated group and subgroup. The model will estimate the adjusted difference in mean RECAP score over the 16 weeks, and the adjusted interaction effect. Note that the trial is not powered to detect interactions between allocated group and subgroup, therefore all subgroup analyses will be treated as exploratory.

6.5. Secondary outcomes

Secondary outcomes will be analysed using an appropriate regression model in accordance with the type of outcome measure. The model will adjust for minimisation factors and baseline covariates as fixed effects, and participant as a random effect. The between group effect estimates will be summarised with the specific summary measure, as stated in Table 2. Between group effect estimates will be reported with the corresponding confidence interval (CI).

The analyses of secondary outcomes will be considered supportive to the primary outcome and estimates and confidence intervals, where presented, should be interpreted in this light.

Patient-reported symptoms assessed monthly using POEM

This continuous outcome will be analysed using a mixed effects linear regression model as specified in Section 6.1, with POEM scores collected at weeks 4, 8, 12, and 16, included as repeated measures. The between-group effect will be reported using a difference in mean POEM scores over 16 weeks, along with the corresponding 95% CI.

Skin specific quality of life at week 16 (IDQoL, CDLQI, and DLQI)

This continuous outcome collected at week 16 will be analysed using a linear regression model, and adjustments will follow the secondary outcome model specification outlined above including baseline score. The between-group effect will be reported separately for each age-specific questionnaire (IDQoL, CDLQI, and DLQI) using the adjusted difference in mean score at week 16, along with the corresponding 95% CI (15).

Proportion of days TCS used

For the continuous outcome ‘number of days TCS used’, the participant-level total for the number of days TCS were used over the 16 weeks will be summarised by group in terms of the mean and standard deviation. For each participant, the proportion of days TCS used will be calculated, using the total number of possible days TCS could be used as the denominator. This denominator will be derived from calculating the number of weeks that the questionnaire was completed, multiplied by 7.

Proportion of weeks when TCS not used & Proportion of well-controlled weeks

For the continuous outcome ‘number of well-controlled weeks’, this will be summarised for each week by group in terms of frequency counts and percentages. For each participant, the corresponding proportion of weeks will be calculated, using the total number of weeks with non-missing outcome data as the denominator.

Analysis of proportion outcomes

Each outcome will be analysed using a linear regression model, weighted according to the number of questionnaires completed, and adjusting for the prespecified fixed effects described in Section 6.1 (16). The model will report the adjusted difference in mean proportion of days or weeks, as appropriate, along with the corresponding 95% CI. As outcomes are not measured repeatedly over time, a mixed-effects model is not required. Participants will be included in the analysis if they have outcome data for at least one of the 16 weeks, and will be excluded if all outcome data between weeks 1 and 16 are missing.

Note that outcomes presented as proportions assume that the outcome (use of TCS or well-controlled weeks) was the same at times when the questionnaire was not completed as when the questionnaires were completed.

Depending on the extent of missing outcome data, a sensitivity analysis may be conducted for each outcome to assess the robustness of results. The models will treat missing weeks as weeks with a poor outcome i.e. when TCS was used or as weeks that were not well-controlled, and the results will be compared with corresponding secondary analyses above.

Other secondary outcomes

All other secondary outcomes (including safety outcomes) will be reported descriptively in each group without formal statistical comparisons. Continuous outcomes will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical outcomes will be summarised in terms of frequency counts and percentages.

7. ANALYSIS OF SAFETY

Safety data will be collected monthly through self-reported questionnaires during the study, and the outcomes will be considered as secondary outcomes:

- Contact with health care provider (HCP) because of a worsening of the eczema
- Contact with HCP due to concerns about side-effects of TCS

Analysis of safety data will be reported at each timepoint descriptively in terms of frequency counts and percentages, see Table 1. Free-text responses on reasons for healthcare contact will be summarised in a footnote separately for each outcome, due to worsening of the eczema, and due to concerns about side effects. The number and percentage of participants who have reported contact with a healthcare provider at least once during the study for each safety outcome above, will also be reported.

The number of participants who have reported contact with a healthcare provider about eczema for reasons other than above will be reported separately for each of the additional reasons listed below:

- Regular review
- Repeat prescription
- Other reason

A summary for each reason will be reported descriptively in terms of frequency counts and percentages. Free text on details of the reason if selected "Other reason" will be categorised and summarised in terms of frequency counts and percentages.

8. EXPLORATORY ANALYSIS

An exploratory analysis will be performed to explore the feasibility of using photos to assess eczema severity. Analysis will be reported descriptively in terms of the proportion of participants who consented, consented and submitted at least one photo, the proportion of participants who submitted at least one photo at each timepoint, and the proportion of photos that were of sufficient quality to generate an EczemaNet EASI score.

Scores generated from the photos will be used to evaluate the feasibility, validity, and responsiveness of eczema severity assessments based on the EczemaNet assessment of clinical images. Depending on the data available and the distribution of participants across outcome categories, the association between EczemaNet severity scores and patient-reported outcomes from the trial will be assessed descriptively. Continuous outcomes will be summarised in terms of the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. Categorical outcomes will be summarised in terms of frequency counts and percentages. This analysis will be conducted among participants who uploaded at least one photograph of their eczema at week 4 or week 16.

9. FINAL REPORT TABLES, FIGURES AND LISTINGS

The final report of the tables, figures and listings is:

RAPID keep control of eczema dummy tables for final analysis v1.0 04Sep2026.

10. REFERENCES

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11. APPENDIX

11.1. Derivation of atopic eczema according to UK Diagnostic Criteria

The UK Working Party (UKWP) Diagnostic Criteria for Atopic Dermatitis are satisfied where there is:

- An itchy skin condition in the last 12 months
- Plus three or more of:
 - i. Onset below the age of 2 years*
 - ii. History of flexural involvement
 - iii. History of generally dry skin
 - iv. Personal history of other atopic disease**
 - v. Visible flexural dermatitis as per photographic protocol

*Not used in children under 4 years

**In children aged under 4 years, history of atopic disease in a first degree relative may be included.

Table 3 below describes how the information needed for the components of the UKWP Diagnostic Criteria are collected in RAPID (to match as closely as possible with UKWP criteria questionnaire – Word documents for the appropriate age groups found at https://xerte.nottingham.ac.uk/play_53210).

Table 4 shows how atopic eczema according to the UKWP diagnostic criteria is derived from the information collected in RAPID for children under 4 years and participants aged 4 years or more.

Table 3: Components of UK diagnostic criteria and how collected in RAPID

Criteria	Question	Derivation of meeting criteria	Derivation of not meeting criteria
An itchy skin condition in the last 12 months	"In the last year, has your child/have you had an itchy skin condition?"	Response of "yes"	Response of "no"
Onset below age 2 years (<i>not used in children under 4 years</i>)	How old was your child/were you when this skin condition began?	Response of "under 2"	Response of "2 to 5", "6 to 10", "over 10"
History of flexural involvement	Has this skin condition ever affected the skin creases in the past?	Response of "yes"	Response of "no"
History of a generally dry skin	"In the last year, has your child/have you suffered from dry skin in general?"	Response of "yes"	Response of "no"
Personal history of other atopic disease in participants aged 4 and above	"Has your child/have you ever suffered from asthma?" and "Has your child/have you ever suffered from hay fever?"	Derived as "yes" if response of "yes" to either question (i.e. suffered from asthma or hay fever)	Derived as "no" if response of "no" to both questions
History of atopic disease in a first degree relative in children aged under 4 years	"Does anyone in your child's immediate family (i.e. mother, father, brother or sister) suffer from eczema, hay fever or asthma?"	Response of "yes"	Response of "no"
Visible flexural dermatitis	Can you see any eczema in any of these body areas today? (For children under 4: around the eyes, on the cheeks, side and/or front of the neck, fronts of elbows, outer forearms, behind the knees, outer lower legs, fronts of ankles For participants aged 4 and above: around the eyes, side and/or front of the neck, fronts of elbows, behind the knees, fronts of ankles).	At least one response of "yes"	Response of "no" to all body areas asked about on questionnaire

Table 4: Derivation of atopic eczema in RAPID by age

Age group	Meets diagnostic criteria for atopic eczema	Does not meet diagnostic criteria for atopic eczema
Children under 4 years	An itchy skin condition in the last 12 months AND three or more of: - History of flexural involvement - History of a generally dry skin - History of atopic disease in a first degree relative - Visible flexural dermatitis	No itchy skin condition in the last 12 months OR An itchy skin in the last 12 months but the criteria are met for less than three of: - History of flexural involvement - History of a generally dry skin - History of atopic disease in a first degree relative - Visible flexural dermatitis <i>Note items that are not completed will be treated as unknown rather than not present.</i>
Participants aged 4 or more	An itchy skin condition in the last 12 months AND three or more of: - Onset below age 2 years - History of flexural involvement - History of a generally dry skin - Personal history of other atopic disease - Visible flexural dermatitis	No itchy skin condition in the last 12 months OR An itchy skin in the last 12 months but the criteria are met for less than three of: - Onset below age 2 years - History of flexural involvement - History of a generally dry skin - Personal history of other atopic disease - Visible flexural dermatitis <i>Note items that are not completed will be treated as unknown rather than not present.</i>