Eczema Bathing Study – how often should we bathe? (Short title: Eczema Bathing Study)

Statistical Analysis Plan

Version 1.0
(29 Aug 2024)

Based on Protocol version Final v2.0 31Oct2023 (Appendix B)

Trial registration: ISRCTN12016473

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents

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Abbreviations

Abbreviation	Description
CACE	Complier average causal effect
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
HOME	Harmonizing Outcomes for Eczema
IDQoL	Infant's Dermatitis Quality of Life Index
MAR	Missing at Random
NIHR	National Institute for Health Research
NRS	Numerical Rating Scale
PMG	Programme Management Group
POEM	Patient Oriented Eczema Measure
PSC	Programme Steering Committee
RCT	Randomised Controlled Trial
RD	Risk difference
RECAP	Recap of Atopic Eczema
RR	Relative risk
SAP	Statistical Analysis Plan
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
Not applicable – no changes to planned analysis				

Amendments to versions

Version	Date	Change/comment	Statistician

Additional contributors to the SAP (non-signatory)

Name	Trial role	Job Title	Affiliation
RAPID Bathing Study Trials Management Group (TMG)			The draft SAP has been circulated and discussed among all TMG members

1. INTRODUCTION & 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 eczema bathing trial.

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 made available if required by journal editors or referees when the main papers 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.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial and where appropriate in publications arising from the analysis.

Qualitative analysis plans are beyond the scope of this document.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

Title	Eczema Bathing Study – how often should we bathe?
Short title	Eczema Bathing Study
Chief Investigator	Prof Kim Thomas (Chief investigator) and Ms Amanda Roberts (PPI lead)
Objectives	AIM: To explore the impact of bathing frequency on eczema symptoms, quality of life and disease control in children and adults with eczema. OBJECTIVES: 1. To assess the impact of weekly bathing (1 or 2 times per week) compared to daily bathing (6 or more times per week) in people with atopic eczema over 4 weeks (syn. Atopic dermatitis, eczema). 2. To explore barriers and facilitators to changing bathing practices and to understand the impact of trial processes on trial participation.
Research question	Is weekly bathing better than daily bathing for people with eczema in terms of participant reported symptoms over 4 weeks?
Trial duration	Each participant will be enrolled for 4 weeks
Participants and eligibility criteria	People with eczema aged 1 year and older
Intervention and control	**Weekly bathing group**: no more than 1 or 2 times per week **Daily bathing group**: 6 or more times per week
Setting	Two-arm, parallel group, superiority randomised controlled trial, with internal pilot The internal pilot will assess: recruitment, adherence with intervention, completeness of data and any issues around online randomisation and consent. This trial has been co-designed by members of the Rapid Eczema Trials Research Community (www.RapidEczemaTrials.org).
Number of participants	390 (195 per arm)
Outcome measures	**Primary outcome:** • Eczema symptoms measured by Patient Oriented Eczema Measure (POEM). Includes 7 items, scored 0 to 28. Assessed weekly over 4 weeks. **Secondary outcomes:** • Itch intensity (Peak Pruritis Numerical Rating Scale (NRS) 24-hour peak itch) - one item, scored 0 to 10. Assessed at baseline and 4 weeks. • Eczema control (Recap of atopic eczema, RECAP) – 7 items, scored 0 to 28. Assessed at baseline and 4 weeks. • Skin-specific quality of life depending on age (Infants' Dermatitis Quality of Life Index (IDQoL - under 4 years), Children's Dermatology Life Quality Index (CDLQI - from 4 years to 15 years) or Dermatology Life Quality

	Index (DLQI - 16 years and over) – 10 items, scored 0 to 30. Assessed at baseline and 4 weeks.
	• Use of usual eczema treatments assessed weekly over 4 weeks:
	  ○ number of days in the last week flare control creams (topical corticosteroids or calcineurin inhibitors) used – this outcome will be used as an indication of days with eczema flares.
	  ○ number of days in the last week moisturisers (emollients) used.
	• Proportion of participants who achieve an improvement in POEM at week 4 of ≥3 points compared to baseline.
	• Global change in eczema compared to baseline. Assessed at week 4.
	• Adverse events: we do not anticipate adverse events related to changing bathing practices but will collect whether participants changed their eczema treatments or sought advice from a health care provider as a result of a worsening of the eczema.

2.1. Sample size and justification

The sample size for the trial is based on POEM scores assessed weekly for 4 weeks and is designed to detect a difference of 2.2 in POEM scores between the two groups. A small difference of 2.2 has been chosen as it is not anticipated that there will be large effects from a change in bathing frequency, but even small differences could be important for people looking for self-management options to try at home. This difference represents a small change that is likely to be beyond measurement error (Howells, Ratib et al. 2018).

Assuming a standard deviation in weekly POEM scores of 6.5 and a correlation between repeated measurements of 0.8 (based on data from previous eczema RCTs), a sample size of 156 per group is required to detect this difference with 90% power and 5% two-sided significance level. Allowing for 20% loss to follow-up, gives a total sample size of 390 participants.

2.2. Blinding

The blinding to allocation of individuals involved in this trial is described below:

Participants (including parents/carers of children aged less than 16 years)	Not blinded
Chief investigator	Blinded
Trial team at NCTU	Not blinded
Trial statistician, senior statistician	Blinded prior to the final analysis
Trial Management Group (TMG) members	Blinded
Programme Management Group (PMG) members	Blinded
Programme Steering Committee (PSC) members	Blinded

2.3. Trial committees

The study will be managed by a Trial Management Group (TMG) which will meet approximately monthly to monitor recruitment and data collection. The TMG consist of 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 is 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) will also meet regularly over the course of the study. Their role and membership is 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.

2.4. Outcome measures

Outcomes for the trial are specified in Table 1 and include the agreed patient-reported outcomes from the Harmonizing Outcomes for Eczema (HOME) initiative's recommended core outcome set (http://www.homeforeczema.org/):

- Eczema symptoms using the Patient Orientated Eczema Measure (POEM)
- Itch intensity using the Peak Pruritis Numerical Rating Scale (NRS)
- Eczema control using the Recap of atopic eczema tool (RECAP) and
- Skin specific quality of life using the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI) or Infants' Dermatitis Quality of Life Index (IDQOL) depending on age.

Table 1: Summary of the outcome measures

Outcome measures	Source	Derivation	Analysis metric
Primary outcome			
Eczema symptoms measured by the Patient-oriented Eczema Measure (POEM) –assessed weekly over 4 weeks (Charman, Venn et al. 2004) *(HOME core outcome)*	Derived from POEM questionnaire form.	POEM is measured weekly and 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 as detailed below: • 0 = no days • 1 = 1-2 days • 2 = 3-4 days • 3 = 5-6 days • 4 = Every day 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. (https://www.nottingham.ac.uk/research/groups/cebd/resources/poem.aspx)	Difference in means (95% CI), p-value
Secondary outcomes (assessed weekly over the 4 weeks)			
Number of days in the last week flare control creams (topical corticosteroids or calcineurin inhibitors) used assessed weekly over 4 weeks	'About Your Usual Eczema Treatments' form. Assessed using the question "How many days have [you/your child] used flare control creams (such as hydrocortisone, Betnovate, Elocon, Protopic, Elidel) for [your /your child's] eczema in the last week?"	This outcome will be used as an indication of days with eczema flares (Thomas, Stuart et al. 2015)	Difference in means (95% CI)

Outcome measures	Source	Derivation	Analysis metric
Number of days in the last week moisturisers (emollients) used assessed weekly over 4 weeks	'About Your Usual Eczema Treatments' form. Assessed using the question "How many days have [you/your child] used moisturisers (such as Diprobase, Doublebase, Epaderm, E45, Aveeno) for [your /your child's] eczema in the last week?"	N/A	Difference in means (95% CI)
Secondary outcomes (assessed at week 4)			
Proportion of participants who achieve an improvement in POEM at week 4 of ≥ 3 points	Derived from POEM questionnaire form.	Change in POEM score is POEM score at baseline minus POEM score at week 4. Binary indicator on presence of a change in POEM score ≥ 3 points (Y/N).	Relative risk (RR) (95% CI) Risk difference (RD) (95% CI)
Eczema control at week 4 *(HOME core outcome)*	Derived from Eczema control (RECAP) questionnaire form (Howells, Chalmers et al. 2020)	Assessed using the Recap of Atopic Eczema (RECAP) measure which has 7 items to assess experience of eczema control and can either be self-completed or caregiver completed for younger children. The responses to the seven items are summed to create a total score ranging from 0 to 28, higher scores indicating less well controlled eczema.	Difference in means (95% CI)
Itch intensity at week 4 *(HOME core outcome)*	Itch Intensity questionnaire form. Assessed using the Peak Pruritus Numerical Rating Scale (NRS) which asks "On a scale of 0 to 10, with 0 being 'no	N/A	Difference in means (95% CI)

Outcome measures	Source	Derivation	Analysis metric
	itch‘ and 10 being ’worst itch imaginable‘, how would you rate your/your child’s itch at the worst moment during the previous 24 hours?” (Yosipovitch, Reaney et al. 2019)		
Skin specific quality of life at week 4 *(HOME core outcome)*	Derived from Adult QoL (DLQI), Children’s QoL (CDLQI), Infants’ QoL (IDQOL) questionnaire forms, respectively. (Finlay and Khan 1994, Lewis-Jones and Finlay 1995, Lewis-Jones, Finlay et al. 2001)	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 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, higher scores indicating greater impairment on quality of life.	Difference in means (95% CI) for each questionnaire
Global change in eczema compared to baseline, assessed at week 4	‘Adherence & Acceptability’ form.	N/A	Descriptive

Outcome measures	Source	Derivation	Analysis metric
	Assessed using the question "Over the last 4 weeks, how has [your/your child's] eczema been?"		
Secondary outcomes (safety outcomes)			
Change in eczema treatments	'Changes in treatment & healthcare contact' form at 4 weeks Assessed using the question "Have [you/your child] started a new eczema treatment or changed how you use your eczema treatments in the last 4 weeks (since [date of randomisation])?"	N/A	Descriptive
Sought advice from a health care provider as a result of a worsening of the eczema.	'Changes in treatment & healthcare contact' form at 4 weeks Assessed using the question "In the last 4 weeks (since [date of randomisation]), have [you/your child] contacted a healthcare professional (e.g. doctor, nurse, pharmacist) because the eczema got worse?"	N/A	Descriptive

3. INTERIM ANALYSIS

There are no formal interim analyses of clinical outcomes planned during the trial. However, there will be an internal pilot, and the following progression criteria will be considered as cause for concern at the end of the pilot phase (once 20% of the target sample size has been recruited or after 4 months):

Recruitment: < 20% of total sample size at 4 months

Adherence:

- Daily bathing group: > 25% of participants reported to have bathed/showered < 6 times per week for two or more of the follow-up weeks
- Weekly bathing group: > 25% of participants reported to have bathed/showered >2 times per week for two or more of the follow-up weeks

Data completeness:

- <85% of participants with POEM scores at week 1 and <70% of participants with POEM scores at 4 weeks (for those who have reached this timepoint)

Aspects that do not meet these milestones will be flagged as cause for concern. Remedial actions will be discussed and implemented with input from the wider programme team and Independent Programme Steering Committee (PSC).

4. GENERAL ANALYSIS CONSIDERATIONS

4.1. Analysis sets

The full analysis set will include all randomised participants. For participants who enter the study twice, only their first entry will be included in the analysis.

Comparative analyses will be conducted according to randomised allocation regardless of actual frequency of bathing (e.g. intention to treat principle). The primary analysis of the primary outcome will be conducted on participants with at least one weekly follow-up POEM score.

4.2. Estimand

The following primary estimand strategy will be considered for assessment of effectiveness:

Estimand component	Definition
Population	People with eczema aged 1 year and older
Endpoint	Eczema symptoms using the POEM assessed weekly assessed over 4 weeks
Treatment conditions	• Weekly bathing: no more than 1 or 2 times per week over a 4-week period • Daily bathing: 6 or more times per week over a 4-week period

Estimand component	Definition
	In both groups, participants will continue with usual medications and care to manage eczema (e.g. emollients, topical steroids etc)
Population level summary estimate	Difference in mean POEM score over 4 weeks between the two treatment conditions (weekly vs daily bathing)
Intercurrent events	
Non-adherence to allocated group i.e. bathing frequency not as allocated	Treatment policy – *all participant data included in analysis regardless of adherence with the allocated frequency of bathing.*
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.*

4.3. Timing of final analysis

Final analysis of the primary outcome will be conducted after the last participant has reached the 4-week follow-up point and the database has been locked.

4.4. Statistical software

Analyses will be performed using Stata version 18.0 or above.

4.5. Derived variables

The algorithms for the calculation of derived variables (except outcome measures in Table 1) in this study are described below:

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.

4.6. Procedures for missing data

Missing questionnaires data

Missing questionnaire items will be summarised and the following rules will be used to calculated scores:

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.
Eczema control (RECAP)	For missing items on 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.
Skin specific quality of life including IDQoL (infant), CDLQI (children), DLQI (adult)	For missing data 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.

Missing baseline data

POEM is a compulsory measure (post -consent confirmation of eligibility) at baseline so no scores should be missing. For other outcome variables measured at baseline (Eczema Control [RECAP], Quality of Life [DLQI, CDLQI, IDQI], Use of eczema medications), 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 (White and Thompson 2005).

For other baseline covariates specified to adjust for in analysis (usual frequency of bathing, whether participants usually wash their hair in the bath/shower, whether they use emollient wash products, use of moisturisers and flare control creams after bathing, diagnosis of eczema according to the UK Diagnostic Criteria, whether participants are currently using systemic treatments), we will monitor missing data and use simple imputation in order to adjust for the baseline score in the analysis.

Missing outcome data

A mixed effect model will be used to analyse the primary outcome and secondary outcomes assessed weekly. This is a principled maximum-likelihood based method which assumes that the

probability that a response is missing depends on the observed data, but not on the unobserved data i.e. the missing data is missing at random (MAR). The main analyses for these outcomes will include participants with the outcome collected at least one follow-up time point up to 4 weeks.

Key baseline characteristics according to allocated group and inclusion in the primary analysis will be summarised descriptively to explore if attrition has introduced any imbalances. Sensitivity analyses for the primary outcome will use multiple imputation for missing outcome data as described in Section 7.2.

There will be no imputation for any of the secondary outcomes.

5. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

5.1. Participant flow

A CONSORT diagram will summarise the number of people expressing interest in the trial, numbers eligible, reasons for exclusion (if known), numbers randomised to the two groups, adherence to the allocated frequency of bathing strategy, losses to follow-up and the numbers analysed.

5.2. Baseline characteristics

The baseline characteristics of the two groups will be summarised with respect to:

- Demographic information
- Baseline eczema characteristics including UK diagnostic criteria for eczema, POEM score, itch intensity and RECAP
- Baseline skin specific quality of life
- Usual bathing practices including prior belief of the effect of the frequency of bathing on eczema symptoms

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

6. ASSESSMENT OF STUDY QUALITY

6.1. 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 (weekly bathing) or control group (daily bathing) using a minimisation algorithm with a probabilistic element balancing on the following factors:

- Eczema severity POEM score (3-7 mild, 8-16 moderate, 17-28 severe).
- Age (<4 years, 4-11 years, 12-15 years, 16-25 years, 26-55 years, >55 years)
- Usual method of bathing (bath or not bath)

The number and percentages of participants randomised to the two groups in each category will be tabulated as part of the baseline characteristics (see Section 5.2).

6.2. Adherence

The number of times participants report that they had a bath or shower in the previous week at week 1, 2, 3 and 4 will be summarised in each group using the mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations. The number and percentage of participants adherent with the allocated frequency of bathing each week (as defined in the table below) will be tabulated (presented as `frequency of bathing as requested').

Variable	Definition
Weekly adherence	Participants are asked the number of times that they had a bath or shower in the previous week for 4 weeks. Adherence each week with allocation is defined as bathing/showering: • 6 or more times per week in the 'daily bathing group' and • 2 times or less in the 'weekly bathing group'
Overall adherence over 4 weeks	Participants are considered adherent with allocation if they are adherent in each of the 4 weeks i.e. • Report bathing 6 or more times per week for 4 weeks in the 'daily bathing group' • Report bathing 2 times or less per week for 4 weeks in the 'weekly bathing group'

The number and percentage of participants in each group who were adherent to the allocated frequency of bathing strategy over the 4-week trial period will be presented (as defined above) for the subset of participants with complete data on frequency of bathing (i.e. completed all weekly questionnaires) and for all participants using the assumptions for missing data described below.

1. Bathing/showering frequency per week will assumed to be as at baseline for participants with no reported data on frequency of bathing (i.e. no weekly questionnaires completed)
2. If participants miss a questionnaire(s) and go onto complete a subsequent questionnaire, frequency of bathing/showering will be based on the next subsequent observation carried backwards. For example if the week 2 questionnaire is missed and participants report that they bathed 6 times in week 3 then it will be assumed that they also bathed 6 times in week 2.
3. If participants complete questionnaires initially and miss later questionnaires (e.g. complete at week 1 and 2, did not complete 3 or 4) then it will be assumed that frequency of bathing/showering was as at baseline for the later missed questionnaires.
4. Overall adherence with the allocated frequency of bathing group will then proceed according the table above.

Responses to the questions at week 4 to the questions about how easy participants found it to bathe as asked, whether they will carry on bathing as they have been doing after the end of the study and their typical method of bathing in the 4-week trial period will be tabulated by allocated group.

6.3. Follow-up and discontinuations

Follow-up questionnaires are at week 1, week 2, week 3, week 4. The number and percentage of participants completing the questionnaires will be summarised by allocated group according to 'total number of questionnaires completed (0,1,2,3,4)', 'timepoint specific questionnaire completion', 'requested to discontinue receiving trial questionnaires' as well as the number of days between randomisation and discontinuation.

6.4. Protocol deviations

Non-adherence with the allocated frequency of bathing strategy will be reported as described in Section 6.2 (Adherence).

Protocol deviations that the NCTU become aware of during the trial, other than non-adherence with the intervention, will be recorded on a protocol deviation log. Details of the deviation will be listed.

7. ANALYSIS OF EFFECTIVENESS

The analysis and reporting of the trial 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 outcome. Between group analyses will be presented as weekly bathing compared to daily bathing.

Descriptive statistics appropriate for the outcome will also be presented for all outcomes by allocated group.

7.1. Primary analysis

The primary analysis for the total POEM score will be performed using mixed effects linear regression model, with observations over time (level 1) nested within participants (level 2). The model will adjust for minimisation variables (age, baseline POEM score, and usual method of bathing) and other baseline variables as specified in the protocol (usual frequency of bathing, whether participants usually wash their hair in the bath/shower, whether they use emollient wash products, use of moisturisers and flare control creams after bathing, diagnosis of eczema according to the UK Diagnostic Criteria, whether participants are currently using systemic treatments). The baseline covariates will be included as fixed effects with a random effect for participant (random intercept and slope on time) and an unstructured covariance matrix. Age, usual frequency of bathing, and baseline POEM score will be included as continuous variables assuming a linear association with the outcome (Kahan, Rushton et al. 2016). Categorical variables will be included as described in the table below.

Baseline variable	Categories
Usual method of bathing	Bath/No bath
Whether participants usually wash their hair in the bath/shower	No/Yes
Whether they use emollient wash products	No/Yes
Use of moisturisers and flare control creams after bathing	Moisturising creams/No moisturising creams
Diagnosis of eczema according to the UK Diagnostic Criteria	No/Yes
Whether participants are currently using systemic treatments	No/Yes

The between group effect will be presented as the adjusted difference in mean POEM score over the 4-week period with 95% confidence interval. If there is evidence of a differential effect over time, the difference in mean POEM score each week will be reported.

The assumptions of the normality of the residuals from the fixed part of the model and the normality of the random effects at the cluster level (level 2) will be checked. Appropriate transformations will be considered if there is strong evidence that the assumptions for linear mixed model may not be met.

If there are convergence problems with the model specified above, then a simpler model will be used including, as a minimum, fixed effects for allocated group, time and the minimisation variables with a random effect for the participant.

7.2. Sensitivity analysis of primary outcome

Sensitivity analyses for the primary outcome will use multiple imputation for missing outcome data. Missing weekly POEM scores will be imputed using a Predictive Mean Matching (PMM) approach with the imputation model including baseline POEM score, other covariates included in the primary analysis model and baseline variables identified as predictive of drop-out (by examination only). Imputations will be done separately for each allocated group if possible. The number of datasets imputed will be based on the proportion of participants with missing POEM scores and will be at least 5.

The analysis specified in Section 7.1 will be repeated on the imputed datasets and results of the analyses will be combined using Rubin rules for multiply imputed data. This analysis will assume that unobserved outcomes are missing at random and depend on observed characteristics but not the unobserved outcomes.

To explore the robustness of the results to the missing at random assumption, sensitivity analysis may be conducted under a missing not at random assumption using controlled multiple imputation Choose(Cro, Morris et al. 2020). If conducted, delta (d) based multiple imputation will be used to

modify the value imputed under a missing at random 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 missing at random assumption). A range of d values will be used in the sensitivity analysis.

7.3. Secondary analysis of primary outcome

To explore the effect of consistently following treatment allocation, we will perform a complier average causal effect (CACE) analysis using instrumental variable regression for repeated measures (with randomised group as the instrument) to obtain the intervention effect of weekly bathing for people with eczema who would bathe less than twice a week. This will be compared to the estimate from the as randomised analysis which is more useful for estimating the effect of a weekly bathing strategy.

We will perform CACE analyses based on the definition of compliance listed in Section 6.2 (i.e. frequency of bathing as allocated in each of the four weeks).

7.4. Subgroup analysis of primary outcome

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

Subgroup	Levels
Age at randomisation	1-11 years/ 12-55 years/ 56+ years
Usual method of bathing	Bath/no bath
Diagnosis of eczema according to UK Diagnostic Criteria	Yes/No
Prior belief on the impact of frequency of bathing on eczema	Thinks bathing everyday is helpful for people with eczema/ Thinks bathing less often is helpful for people with eczema/ Does not know if frequency of bathing makes a difference

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

POEM scores each week will be presented descriptively by allocated group and subgroup. The subgroup analyses will be performed by including an interaction term with allocated group in the regression model for the primary outcome. The subgroup specific adjusted difference in means (and 95% confidence interval), the adjusted interaction effect (and 95% confidence interval) and p-value for the interaction effect will be reported in a table. Note that the trial is not powered to detect any interactions hence the subgroup analyses will be treated as exploratory.

7.5. Secondary outcomes

The following secondary outcomes will be analysed using appropriate regression models depending on the type of outcome variable, adjusting for minimisation variables and other baseline variables as specified in the protocol. The between group effect will be reported using an appropriate adjusted effect estimate (see Table 1) along with a corresponding 95% 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.

Proportion of participants who achieve an improvement in POEM at week 4 of ≥ 3 points

This binary outcome will be analysed using a logistic regression model, adjusting for minimisation variables and other baseline variables as specified in the protocol. The between group effect will be reported using an adjusted relative risk (RR) and risk difference (RD), along with corresponding 95% confidence intervals for each, obtained using Stata's Margins command with standard errors computed using the delta method (Norton, Miller et al. 2013).

Continuous outcomes at 4 weeks

The following continuous outcomes:

- Itch intensity at week 4
- Eczema control at week 4
- Skin specific quality of life at week 4 (IDQoL, CDLQI and DLQI)

will be analysed using linear regression model, adjusting for minimisation variables, baseline score and other baseline variables as specified in the protocol. The between group effect will be reported using a difference in means, along with corresponding 95% confidence intervals.

Number of days in the last week moisturisers and flare control creams used assessed weekly over 4 weeks

This weekly assessed continuous outcome will be analysed using a mixed effects linear model as described for the primary outcome, plus adjusting for baseline 'number of days in the last week moisturisers used' and 'number of days in the last week flare control creams used' respectively. The assumptions for the multi-level linear model will be checked. If there is strong evidence that they are violated an appropriate transformation will be considered or quantile regression at each time point will be used to estimate the difference in medians between the two groups adjusting for the minimisation variables.

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.

8. ANALYSIS OF SAFETY

Safety outcomes in this trial (change in eczema treatments and sought healthcare advice due to worsening eczema) are included as secondary outcomes and will be reported descriptively (as per Section 7.5).

9. FINAL REPORT TABLES AND FIGURES

Rapid eczema bathing study dummy tables for final analysis_v1_29Aug2024

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 age 2 years*
    ii. History of flexural involvement
    iii. History of a 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 2 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 – Appendix 1 and 2 of https://www.nottingham.ac.uk/~mzzfaq/dermatology/eczema/contents.html).

Table 3 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 2: Components of UK diagnostic criteria and how collected in RAPID

Criteria	*Question*	*Derivation for meeting criteria*	*Derivation for 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 *(not used in children under 4 years)*	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 hayfever?"	Derived as "yes" if response of "yes" to either question (i.e. suffered from asthma or hayfever)	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 (ie 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 3: 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 *Note items that are not completed will be treated as unknown rather than not present.*
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 *Note items that are not completed will be treated as unknown rather than not present.*