Rapid Eczema Trials MASTER Protocol

Rapid Eczema Trials

Rapid & Efficient Eczema Trials – a citizen science approach to conducting eczema clinical trials

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CI and Sponsor Approval Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

This protocol has been approved by:	
Trial Name:	Rapid Eczema Trials
CI Name:	Prof Kim Thomas
Trial Role:	Chief Investigator
Signature and date:	KS Thomas KS Thomas (Nov 14, 2023 19:13 GMT)
Date:	Nov 14, 2023

Sponsor statement:

Where Nottingham University Hospitals NHS Trust takes on the Sponsor role for oversight of protocol development, signing of the IRAS form by the Sponsor will serve as confirmation of approval of this protocol.

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Amendment number	Protocol version number	Type of amendment	Summary of amendment
SA001	2.0	Substantial	• Addition of Ms Firoza Davies as a protocol contributor • Clarification of criteria for identifying participants by GP practices. • Addition of Appendix B detailing the Eczema Bathing Study

Abbreviations

Abbreviation	Term
AE	Adverse Event
AI	Artificial Intelligence
AR	Adverse Reaction
CDLQI	Children's Dermatology Life Quality Index
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CS	Citizen Science
DAP	Data Analysis Plan
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EASI	Eczema Area and Severity Index
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HOME	Harmonising Outcome Measures for Eczema
ICF	Informed Consent Form
IDQoL	Infant's Dermatitis Quality of Life Index
ISRCTN	International Standard Randomised Controlled Trials Number
NCTU	Nottingham Clinical Trials Unit. NCTU is a UKCRC fully-registered CTU with expertise in the design, conduct, analysis and reporting of randomised trials.
NHS	National Health Service
NIHR	National Institute for Health Research
NRS	Numerical Rating Scale
MCID	Minimal Clinically Important Difference
PI	Principal Investigator
PPI	Patient and Public Involvement
PPIE	Patient and Public Involvement and Engagement
PIS	Participant Information Sheet
POEM	Patient Oriented Eczema Measure
PO-SCORAD	Patient Oriented Scoring Atopic Dermatitis
PSG	Programme Steering Group
PSC	Programme Steering Committee
PSP	Priority Setting Partnership
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RECAP	Recap of Atopic Eczema
REDCap	Research Electronic Data Capture
ROC	Receiver Operating Characteristics
TIDieR	Template for Intervention Description and Replication
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

Trial Summary

Trial Title	Rapid & Efficient Eczema Trials Programme
Trial Design	Master protocol for a series of prospective, pragmatic, randomised online eczema trials that have been prioritised and designed in partnership with members of the public. Details for each specific trial will be submitted for approval as a protocol amendment to this master protocol (see Appendix A). This novel programme of work has been designed to streamline the approach to conducting online clinical trials and improve efficiencies. The trials may be two-arm, parallel group trials or multi-arm trials depending on the topics prioritised for research by people living with eczema and the co-production groups designing the trials (members of the eczema research community with experience of living with eczema, researchers and healthcare professionals). All trials will be low risk behavioural interventions or advice trials . This could include trials that test self-management interventions (e.g. frequency of bathing), psychological interventions (e.g. stress management or mindfulness activities), advice on use of existing eczema treatments (e.g. how often to apply emollients), or testing of simple dietary intervention (e.g. low sugar diet).
Objectives	Aim: To improve the lives of people living with eczema by partnering with members of the public to co-produce and deliver multiple, efficient online randomised controlled trials (RCTs) and to share new knowledge with those who need it. Objective: To answer multiple research questions that members of the public and healthcare professionals have about the self-management of eczema.
Participants and eligibility criteria	People with lived experience of eczema (specific eligibility for each trial will be decided by the co-production groups).
Intervention and control	To be determined by the co-production groups and through consultation with the wider eczema citizen-science community.
Outcome measures	This project will include the core outcome set measurement instruments for patient-reported outcomes, as developed by Harmonising Outcome Measures for Eczema (HOME: www.homeforeczema.org). Since all trials will be completed online, it will not be possible to conduct face-to-face assessment of clinical signs (one of the HOME core outcome domains). Primary outcome: Choice of primary outcome to be determined by the co-production groups.

	Secondary outcomes: self-reported eczema symptoms (Patient Oriented Eczema Measure (POEM)); itch intensity (Peak Pruritus Numerical Rating Scale (NRS 24-hour peak itch)); eczema control (Recap of atopic eczema (RECAP)); skin-specific quality of life (Infants' Dermatitis Quality of Life (IDQoL), Children's Dermatology Life Quality Index (CDLQI), Dermatology Life Quality Index (DLQI) depending on age). Additional outcomes: other secondary outcomes may include i) use of interventions, ii) acceptability of interventions, iii) use of eczema treatments (e.g. number of days topical corticosteroids/emollients have been used); iv) adverse reactions, plus up to two additional outcomes that are felt to be relevant to a particular intervention under investigation.
Sample size	Sample sizes will be calculated for each of the individual trials, as they are dependent upon the research question. The justification for the sample size for each trial will be included in the protocol amendment as new research questions are added.

Trial Flow Chart

A flow chart will be added for each trial as it is developed and submitted as a protocol amendment.

1. Background and Rationale

1.1. Background

Eczema is an itchy, chronic skin condition. The main treatments are topical treatments such as moisturisers (emollients) and flare-control creams (e.g. topical corticosteroids and calcineurin inhibitors), but how best to use them is still uncertain. Inconsistent messages and confusion leads to poor treatment adherence[1]. Questions about skincare, washing and how to use eczema treatments are a high priority for patients[2], but are rarely the focus of large, high-quality randomised controlled trials (RCTs)[3].

Efficient methodologies are required to address these patient priorities in a timely and resource efficient manner, whilst providing robust evidence to inform management choices.

Citizen science (CS) has been variably defined[4], but here we mean the scientific method of working with members of the public to define, address and share answers to questions that are important to them. Citizen science democratises research[5], makes it more relevant, accessible and inclusive[5], and can improve uptake of study findings[6].

The Covid-19 pandemic has dramatically increased awareness of RCTs and the relevance of research to our daily lives, making this research both timely and achievable.

This research programme aligns with the Government's recent strategy document on the Future of UK Clinical Research Delivery[7], which calls for patient-centred research that is "streamlined, efficient and innovative", and supports the Government's agenda for reducing health inequalities in healthcare and research.

1.2. Overview of the whole Rapid Eczema Trials Programme

Aim of the Rapid programme: To improve the lives of people living with eczema by working with citizen scientists to deliver multiple, efficient online clinical trials and share new knowledge with those who need it.

Objectives:

- To establish an "Eczema Citizen Science Community" of people with lived experience of eczema who are willing to co-produce and help disseminate results of the RCTs.
- To embed strategies for engaging with people from diverse communities throughout the programme.
- To answer multiple prioritised research questions via online RCTs.
- To ensure new knowledge is shared rapidly and effectively with patients, health professionals and other stakeholders.
- To identify transferable learning for conducting trials co-produced with citizen scientists in other long-term conditions.

This work is configured across three distinct workstreams.

WORKSTREAM 1 (WS1): Prioritisation and development of citizen science trials

I. Establish cohort of people willing to contribute to citizen science eczema trials.
II. Prioritise research questions.
III. Co-design the research.
IV. Characterise and develop interventions.
V. Co-produce trials.

WORKSTREAM 2 (WS2): Online eczema trials

I. Conduct multiple, online trials.
II. Validate objective eczema severity assessment from digital images.

WORKSTREAM 3 (WS3)– Getting new knowledge to where it is needed.

I. Accelerate meaningful uptake of new knowledge.
II. Identify transferable learning for conducting citizen science trials in other health settings.
III. Identify factors in the implementation of interventions shown to be effective.

This master protocol pertains to delivery of the online trials (workstream 2) and process evaluation (workstream 3). Requests for ethical approval for the specific trials to be conducted as part of the Rapid Eczema Trials project will be submitted as protocol amendments once key trial design decisions have been made by the co-production groups. See Appendix A for a summary of the aspects to be defined through subsequent protocol amendments.

In addition to the trials and process evaluation, various aspects of the Rapid Eczema Trials programme will employ different engagement/communication methods relevant to the specific activity being undertaken. Most of these activities constitute patient and public involvement, co-design and engagement activities, thus not meeting the definition of research and therefore not requiring specific-ethics approval. NOTE: Whilst these activities do not require specific ethics approval and consent for participation, we have briefly outlined the whole programme in this protocol to ensure appropriate governance of this innovative programme of work.

Methods used during the design of the Rapid Eczema Trials may include, but are not restricted to:

- Online surveys
- Discussion groups
- Workshops
- Engagement activities
- Piloting and testing of trial materials and methods
- Development of podcasts, blogs, infographics, animations and training materials
- Q&A sessions with experts

1.3. Trial Rationale

Why this research is important

Globally, eczema is the most common skin condition[8]. Eczema affects a quarter of infants[9], 1 in 5 children of school age, and often continues into adulthood[10]. It has high cost to both the healthcare provider and patients[11], and results in itch, sleep loss and psychological distress[12]. Eczema affects people of all ethnicities[13] and socio-economic groups[14], although diverse ethnic groups are under-represented in dermatology research[15].

This programme will provide robust answers to multiple questions about the management of eczema. Our programme will answer **multiple important questions** that can be addressed through randomised controlled trials conducted at scale and at pace, and we will rapidly mobilise new knowledge to people who need it.

We will engage with diverse communities, with health benefits to patients and the NHS within the timescale of the award.

Existing research

Our 2013 James Lind Alliance Priority Setting Partnership (PSP)[2], involved 399 people with eczema, and prioritised 14 topics. Of these, seven are suitable for inclusion in this project and remain unanswered[16]. A crowdsourcing prioritisation exercise by the Global Parents of Eczema Research initiative, using natural language processing of online social media posts[17], confirmed ongoing debate in these topics.

The specific focus for the first round of prioritisation will be determined by the Prioritisation Co-production team, but we anticipate that the programme will initially focus on **how best to use existing treatments for eczema** (topical corticosteroids (flare-control creams) and emollients/over-the-counter products) and **best ways of bathing/washing**. These topics cover four of the PSP priority areas for research and systematic reviews have confirmed evidence-gaps.

A systematic review of international eczema guidelines[18] highlights variability in the recommendations for using topical corticosteroids, emollients and bathing practices, and this variation is driven by lack of robust evidence to inform practice.

Our Cochrane systematic review on the best and safest ways of using topical corticosteroids in eczema[19], confirms large gaps in our understanding of how to best use these common treatments, including questions like: how long to treat an eczema flare for; and whether topical corticosteroids and emollients can be applied concurrently.

Addressing these uncertainties will inform future updates of national and international eczema clinical guidelines and help ensure clear, consistent messages to patients and clinicians and improve the lives of people living with eczema.

1.3.1. Justification for participant population

Patient and public partner feedback has recommended that the trials be as inclusive as possible and so we will initially aim to include all people with eczema, regardless of age or eczema severity. However, the nature of interventions prioritised for testing, by patients and researchers, in the Rapid Eczema Trials may sometimes be more suitable to specific groups of people with eczema, in which case eligibility will be limited to those of most relevance for the question being addressed. This decision will be made by members of the co-production groups, with advice and support from the Trial Management Group (TMG) and Programme Steering Group (PSG).

1.3.2. Justification for design

This programme will combine the strengths of collaborative citizen science with robust trial design to rapidly and efficiently answer research questions through a series of pragmatic, parallel group online RCTs conducted according to this master protocol. Trial integrity and quality will be ensured by working in collaboration with the Nottingham Clinical Trials Unit (NCTU).

Our innovative approach ensures that trials can be conducted, and results implemented, more quickly (Table 1).

Table 1: Summary of efficiencies in Rapid Eczema Trial design and conduct

Stage of research	Traditional approach to eczema trials	Rapid Eczema Trials
Prioritisation of questions	• Usually prioritised by researchers	• Prioritised by people living with eczema
Funding	• Funding secured individually	• Funding agreed for whole programme from outset
Trial design	• Individual trials • Designed from scratch each time	• Multiple online trials based on a standardised master protocol
Trial set-up	• Bespoke per trial • Separate ethics approvals • Bespoke database • Typically, at least 6 months	• Standardised protocol, outcomes and analysis plan • Ethics approval for standardised template protocol with review of new research questions as amendments to the master protocol • Shared infrastructure for data collection and database

		• New research questions added as prioritisation and intervention development is complete • Trials may be conducted in parallel
Recruitment	• Through GP surgeries or hospitals, with individual sites set up and trained • Face-to-face clinic visits for informed consent, randomisation and data collection • Usually takes 1 to 2 years	• Cohort of citizen scientists established and ready to advertise trials amongst a broad community of people with eczema • Online consent, randomisation and data collection allowing recruitment without geographical or socio-economic boundaries • Aim to recruit in 4 to 6 months per research question
Data cleaning	• Monitoring undertaken by trial team and data queries raised to recruiting sites	• Online data collection with patient-reported outcomes only
Analysis	• Bespoke per trial • Typically allow 6 months between completing follow up of all participants and submission of report	• Standardised statistical analysis plan • Aim to complete analysis within 2 months of final follow-up
Dissemination of results	• Delayed until academic publications completed and peer reviewed • Often takes 12+ months from last visit to publication	• Rapid sharing of results using accessible formats through Eczema Citizen Science Community • Aim to share results within 3 months of database lock
Knowledge Mobilisation / impact on practice	• Usually limited due to time and resource constraints at end of trial	• Knowledge mobilisation planned from outset and co-designed to facilitate rapid uptake of new knowledge
Time required per trial	• 4+ years	• 12 to 18 months

We aim to answer multiple research questions as efficiently as possible, with new research questions being added during the programme as they become available from workstream 1.

All trials will share this master protocol to address the questions prioritised and developed by the co-production groups, ensuring consistent data collection to facilitate speedy set-up and rapid analysis of results. Comparator interventions may vary according to the specific question being addressed (see table 2). Similarly, a standardised statistical analysis plan will be used across all trials.

Areas pre-specified in this standardised master protocol include: overall trial design; setting (online); trial conduct; details of the core outcomes; approach to randomisation, blinding and allocation concealment; broad approach to statistical analysis; PPIE involvement; and governance and oversight arrangements.

Other aspects will be agreed by the co-production groups and will be submitted for ethics approval for each new research question as an appendix to the protocol. These aspects will include clarification of: i) the specific research question; ii) eligibility criteria (e.g. children/adults, severity of eczema); iii) recruitment strategies (ensuring inclusivity), iv) choice and definition of intervention and comparator; v) choice of outcomes, including likely adverse reactions, and vi) duration of follow-up.

Co-production groups will be supported by a multi-disciplinary TMG to ensure that the trial design is appropriate for the research question.

The co-production groups will decide the most appropriate duration of follow-up for specific research questions (up to a maximum 6 months) using the following general principles:

- **Proof of principle trials with 4-6 weeks follow-up** – little or no existing trial evidence, and rapid onset of intervention response is likely.
- **Definitive trials with 4 to 6 months follow-up** – some evidence exists, but a more robust evidence base demonstrating benefits for people with eczema over several months is required to change practice.

If a trial of longer duration is felt to be warranted (e.g. up to 12 months), this will be discussed with the TMG and approval sought from the independent PSG.

Examples of possible trials that would be suitable for delivery as Rapid Online Eczema Trials are shown in Table 2.

Please note, these are examples only. Actual research questions and interventions are to be developed by the Eczema Citizen Science community.

Table 2: Examples of trials that would be feasible to conduct as Rapid Eczema Trials

Research question	Is it better for people with eczema to bathe frequently or less often?	How long should topical corticosteroids be applied for to control an eczema flare?	How often should moisturisers be applied to keep control of eczema?	Q1: Is avoidance of soap effective for the management of eczema? (Intervention A versus Comparator) Q2: Is avoidance of shampoo effective for the management of eczema? (Intervention B versus comparator)
Type of trial	Proof of principle	Definitive trial	Proof of principle	Proof of principle
Participant	Children with eczema, all eczema severities	People with eczema, all ages, all eczema severities (planned sub-group analysis based on eczema severity)	People with eczema, all ages, all eczema severities	People with eczema, all ages, all eczema severities
Intervention	Bathe weekly (plus usual eczema care)	Usual prescribed topical corticosteroid applied until symptoms resolve, plus additional 3 days (max of 14 days)	**Intervention A:** Emollients applied 2-3 times per day **Intervention B:** Emollients applied 4+ times per day	**Intervention A:** Usual prescribed leave-on emollient used as soap substitute when bathing **Intervention B:** avoid shampoo on the body when bathing (use mild soap/wash products during bathing)
Comparator	Bathe daily (plus usual eczema care)	Usual care - topical corticosteroid applied as required	Emollient applied once per day	Use mild soap/wash product during bathing and shampoo hair as normal
Outcome	Eczema symptoms (POEM)	Eczema control (RECAP)	Eczema Symptoms (POEM)	Eczema Symptoms (POEM)
Duration of follow-up	4 weeks	6 months	4 weeks	6 weeks

1.3.3. Choice of treatment

Interventions will be defined and characterised by co-production groups consisting of people with lived experience of eczema, healthcare professionals and researchers with experience of intervention development.

Intervention materials and instructions will be designed to be accessible (including pictures and simple language) and inclusive (available in different languages and formats). Where relevant, the intervention will be described using the TIDieR checklist to allow replication of the intervention[20].

Comparator Interventions: Comparator groups will be defined as appropriate to the trial in questions. A control group using standard eczema care is defined as using treatments for eczema (e.g. emollients and flare-control creams) as advised by their treating clinician(s). This is likely to be the control intervention for most of the comparisons, but the co-production group will advise on choice and specification of the comparator intervention for specific research questions. For example, for a trial looking at frequency of bathing, the comparator group may be defined as daily bathing (plus usual eczema care) and the intervention group as weekly bathing (plus usual eczema care).

Details of the interventions to be compared will be provided as a protocol amendment for each new trial developed.

1.3.4. Sub-studies

Process evaluation: Nested process evaluation studies may be incorporated into individual trials depending on the nature of the interventions being tested and the perceived value of process evaluation insight.
These process evaluations will use a variety of methods including interviews, surveys and focus groups.

2. Aims, Objectives and Outcome Measures

2.1. Aims and Objectives

Aim: To improve the lives of people living with eczema by partnering with citizen scientists to deliver collaborative research and to share new knowledge with those who need it.

Objective: To answer multiple questions that members of the public and healthcare professionals have about the self-management of eczema through multiple, efficient online RCTs.

2.2. Outcome Measures

2.2.1. Primary outcome

The primary outcome will be chosen by the co-production groups and is most likely to be one of the HOME-approved core outcome instruments.

2.2.2. Secondary outcomes

We will include the agreed patient-reported outcomes in the Eczema Core Outcome Set (www.homeforeczema.org). These include:

- eczema symptoms (Patient-oriented Eczema Measure (POEM)[21]) - 7 items, scored 0 to 28;
- itch intensity (Peak Pruritis Numerical Rating Scale (NRS)[22] 24-hour peak itch) - one item, scored 0 to 10;
- eczema control (RECAP)[23] – 7 items, scored 0 to 28;
- skin-specific quality of life (Infants' Dermatitis Quality of Life Index (IDQoL)[24], Children's Dermatology Life Quality Index (CDLQI)[25] or Dermatology Life Quality Index (DLQI)[26]depending on age) – 10 items, scored 0 to 30

Since these will be online trials, it will not be possible to assess clinician-rated signs of eczema (one of the HOME core domains).

Other secondary outcomes, in additional to the core outcome set, will include i) reported use of intervention and control, ii) acceptability of intervention and control, iii) use of eczema treatments, e.g. number of days topical corticosteroids/emollients have been used; iv) adverse reactions (relevant adverse reactions to be defined by co-production groups).

In addition, up to two 'trial-specific' outcomes may be specified by the co-production working group if required (e.g. process outcomes for a behavioural intervention). Responder burden will be considered carefully when deciding on additional outcomes and baseline characteristics to include.

Participant prior beliefs about the effectiveness of the chosen interventions will be collected and used to inform sensitivity analysis.

Further details of the analysis metric, method of aggregation, and time point for each outcome will be provided as a protocol amendment once the trial design has been agreed with the co-production groups.

3. Trial Design and Setting

3.1. Trial Design

The programme will consist of a series of pragmatic, online, parallel group, randomised controlled trials.

3.2. Trial Setting

All participants will be recruited, provide consent and be randomised online, with digital follow-up data collection via a dedicated app/weblink or text messaging service (i.e. self-referral with no in person visits).

4. Eligibility

Full eligibility criteria will be defined by the co-production groups relevant to each intervention. Participants identified through GP practices will have a recorded diagnosis of eczema on their medical records and will have been issued a prescription for emollients or topical corticosteroids in the last 2 years. We will exclude people who are aged less than 1 year, report eczema only on the hands, eczema limited to locations where exposed to nickel (e.g. from jewellery) and people with eczema around varicose veins, as these characteristics most likely represent alternative or unclear diagnoses.

Exclusions will be kept to a minimum to ensure generalisable results, but participants will only be able to take part in one eczema intervention trial at any one time (this will be monitored centrally based on data provided at baseline). Recruitment will also be limited to one person per household per trial. Participants outside of the UK will not be able to take part.

4.1. Inclusion Criteria

To be determined by the co-production groups and included in protocol amendment.

4.2. Exclusion Criteria

To be determined by the co-production groups and included in protocol amendment.

4.3. Participant identification

Participants will volunteer to take part in the Rapid Eczema Trials via the trial website www.RapidEczemaTrials.org. Signposting to the website will be through different methods, platforms and organisations (including, but not limited to):

- **Database search and mailout or text messages from GP practices**: may advertise Rapid Eczema Trials project or individual trials specifically
- **Eczema Citizen Science Community:** newsletters sent to people on the existing Rapid Eczema Trials mailing list with encouragement to promote the trial via their personal networks using snowballing recruitment.
- **Through existing mailing lists of people with eczema: e.g.** previous trial participants who provided consent to be re-contacted.
- **Social media:** Facebook, Instagram, Twitter, Reddit, Snapchat, TikTok, Youtube.
- **Eczema charities:** e.g. National Eczema Society (http://www.eczema.org/), Eczema Outreach Support (https://www.eos.org.uk/), Nottingham Support Group for Carers of Children with Eczema (http://www.nottinghameczema.org.uk/index.aspx).
- **Outreach and engagement events:** Throughout the Rapid Eczema Trials programme we will attend events to help mobilise knowledge about eczema and engage individuals who might be interested in joining our Eczema Research Community. If we have ongoing advertisements for an RCT during this time, we will take our advertisement flyers to these events.
- **Internal communication channels of partner organisations** (e.g. social media accounts, website, existing consented mailing lists and newsletters).
- **Call for Participants website** (https://www.callforparticipants.com). An open platform that brings together researchers to promote their trials and potential participants interested in taking part in trials.
- **NIHR People in Research website** (https://www.peopleinresearch.org/)
- **NIHR Be Part of Research website (**Be Part of Research.nihr.ac.uk)
- **Posters and flyers:** displayed in e.g**.** schools, clinical settings, community centres, grocery stores (with permissions from relevant staff members).
- **Other organisations/online platforms/ individuals** e.g. resharing via social media.

Advertising of the trials will be limited to the UK.

We are keen to minimise the risk of digital exclusion by engaging people offline as well as online: recruitment to all trials will include offline approaches such as working with community groups/leaders, snowballing techniques to enrol friends and family of our Eczema Research Community, targeted mail-out from GP surgeries and advertising materials in clinical settings.

To minimise social and culture exclusion, we will use inclusive images and language and recognise that eczema presents differently in people with darker skin tones. We will produce content in a variety of languages and formats to encourage uptake amongst different groups, with use of video content and infographics to avoid difficulties with written English.

Our citizen scientists (members of the Eczema Research Community) will be encouraged to lead on raising awareness of the project and encouraging others in their own networks and interest groups to join, thus continually renewing the membership of the Eczema Research Community over the duration of the programme. We will use a combination of paid social media advertisements to target diverse communities, in addition to unpaid methods (i.e. snowballing, tagging on social media platforms): including people of different ages, from diverse ethnic backgrounds and lower social-economic groups.

4.4. Screening

Eligibility screening will be conducted online prior to randomisation into the trial and will be based on self-report. The outcome of the eligibility screening will be displayed on screen to the potential participant, and if they are eligible the participant will be directed to complete the consent should they wish to take part.

Details of reasons for exclusion from the trial will be retained for reporting of the CONSORT flow diagram in trial reports.

We will instigate several strategies to address misrepresentation of eligibility during screening[27]. These include, but may not be limited to:

- sharing videos and information that explains the reasons for randomisation and why it is important in clinical trials to discourage people from trying to join multiple times in order to get the intervention of their choice;
- registration details will be monitored centrally for duplicate registrations.

All trials will be of simple advice to use existing treatments in specific ways, or different ways of managing eczema at home. As such, we do not anticipate misrepresentation of eligibility to be a major concern for the internal validity of the trials as the incentive to 'cheat' will be low.

5. e-Consent

These are low risk trials of interventions to support self-management of eczema at home. As such, our approach to gaining informed consent will be proportionate to the low level of risk and will be provided as e-Consent.

Potential participants will be guided to the trial website (www.RapidEczemaTrials.org), where they will be provided with online information about the trial. Information will be provided in a variety of engaging and formats appropriate for all ages (may include videos, infographics and/or printable materials).

Contact details will be provided for the trial team, should potential participants have questions that they would like to ask prior to signing the informed consent form for the trial or if they have any questions throughout the trial.

Following an initial self-reported eligibility screen completed by the participant online, electronic consent will be gained prior to completion of trial procedures and questionnaires. A completed online consent form from each participant will always be obtained prior to participating in the trial.

Throughout the trial the participant will have the opportunity to ask questions about the trial via the trial e-mail. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. The participant's right to withdraw from the trial will remain.

For children aged less than 16 years, e-consent will be provided by the parent/carer. In addition to providing e-consent, parents/carers will be asked to confirm that they have discussed participation in the trial with their child (if appropriate) and that their child is willing to take part. Children under 16 years will be provided with the opportunity to give optional assent on the e-consent form.

6. Enrolment and Randomisation

6.1. Enrolment/Registration

Enrolment will take place online via a dedicated website (www.RapidEczemaTrials.org) linked to a secure, bespoke online database hosted by NCTU. There will be no trial recruiting sites.

6.2. Randomisation

We will use a web-based randomisation service using restricted allocation methods (such as stratification and/or minimisation) to balance key variables likely to be associated with the primary outcome between groups.

Potential participants will be randomised online once consent has been provided, they have submitted their baseline information, including the outcomes specified above, and eligibility confirmed.

Randomisation will be provided by a secure online randomisation system at NCTU. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

Following randomisation, an email and/or text will be sent to the research team and to the participant confirming enrolment into the trial. Participants will be provided with details of their allocated treatment/intervention (if appropriate). The research team will not be aware of intervention allocation unless needed for distribution of interventions.

Participants will be randomised at the level of the individual in a 1:1 ratio to relevant trial arms. If a different ratio is deemed necessary for a specific trial, this will be clarified in a protocol amendment for that trial.

Groups will be balanced (using stratification and/or minimisation) for the following variables:

- Eczema severity POEM scores: 0-7 (mild), 8-16 (moderate), 17-28 (severe)
- Age (age bands to be defined per trial)
- Other variables specific to individual trials maybe agreed by the co-production group

Full details of the randomisation specification for each trial will be stored confidentially at NCTU.

6.3. Blinding and concealment

Due to the nature of the interventions being considered, participants will usually be aware of their treatment allocation, but the trial statisticians and majority of the research team, will be blinded to treatment allocation.

Participant prior beliefs about the effectiveness of the chosen interventions will be collected and used to inform sensitivity analysis.

7. Trial treatment / intervention

To be determined by the co-production groups and included in protocol amendment.

8. Trial procedures and assessments

8.1. Summary of assessments

A summary of the trial schedule will be included in the trial amendment once details of individual trials are known.

8.2. Schedule of Assessments

All screening and assessments will take place online.

T0: Screening, randomisation and baseline assessment visit

Participants will complete a brief eligibility screen prior to completing the online consent form. The outcome of the eligibility assessment will be displayed on screen.

If eligible for the trial and consent is provided, participants will be asked to complete the following:

- Demographic information, randomisation variables, UK Diagnostic criteria[28], characteristics of eczema, use of eczema medications, prior belief about the interventions, previous involvement in the trial development, additional baseline information relevant to the specific trial interventions
- Core outcome instruments (POEM (7 items), NRS 24-hour itch (1 item), RECAP (7 items), quality of life instruments (10 items))
- Other outcome instruments: additional outcomes specific to the intervention, use of eczema treatments

For children who are unable to complete patient reported outcomes themselves, proxy reporting by a parent or carer will be accepted, but participants will be encouraged to complete patient reported outcomes in discussion with their child.

Follow-up data collection timepoints

The schedule of follow-up visits will vary depending on the duration of the trial.

For a 6-week proof of principle trial, this is likely to be at baseline, week 1, week 2 and week 6 (but maybe be more, or less, frequent depending on the views of the co-production group).

For a 6-month trial, this is likely to be at baseline, month 2, month 4 and month 6 (but maybe be more, or less, frequent depending on the views of the co-production group).

In addition to outcomes listed above, data will be collected on adherence to intervention and safety.

8.3. Trial Procedures

Face-to-face trial visits are not required for the eczema trials in this programme.

All trial procedures will be completed online with data collection through secure, bespoke links sent via email, text or other appropriate methods. Participants will be sent email and text reminders to complete their questionnaires (or notifications from within an app if used). Participants will be offered the opportunity to take part in an optional prize draw to encourage completion of trial outcomes. The need for additional payments to compensate for additional expense incurred by taking part in the trial will be decided on a trial-by-trial basis.

All data will be collected using the REDCap (Research Electronic Data Capture) platform. Data collection tools will be usable on a range of digital devices, including smartphones.

Validated questionnaires will be used as recommended by the HOME core outcome set for eczema[29] as these have all been assessed as being feasible to use in a trial setting and having sufficient validity, reliability and responsiveness.

Other secondary outcomes and baseline characteristics will be assessed using bespoke questions if a validated instrument is not available. Details of exact questions for these will be included in protocol amendments for specific trials.

8.4. Collection, Storage and Analysis of Clinical Samples

We do not anticipate collecting any clinical samples as all assessments are made online with no face-to-face contact with the research team.

If a particular research question warrants collection of samples details of these arrangements will be included as a protocol amendment for the specific trial.

8.5. Sub studies

8.5.1.1. Process evaluation

Trials, even those delivered in partnership with citizen scientists, should generate new knowledge which might have a positive societal impact; any limitation or bias that might undermine this should be identified and addressed[30]. To this end (and when deemed appropriate by the co-production groups) we will undertake nested process evaluation within/alongside the trials.

For each Rapid Eczema Trial, we will work with the co-production groups to establish nested process evaluations. These will generate contextualised understanding of each intervention to support interpretation of trial outcomes and recommendations for implementation, specifically considering questions of acceptability, feasibility, and adherence with intervention. The co-production groups will define the scope and method of these evaluations. Trained research staff will undertake qualitative data collection and analysis; if citizen scientists wish to take part in these activities they will be appropriately trained and supported.

We will advocate a range of simple methods - online surveys, participant diaries, participant interviews, participant focus groups. The co-production groups will identify and refine appropriate evaluation methods for each intervention evaluation. We will provide training for the co-production groups where this is felt to be necessary.

The complexity of each intervention will shape the design of the bespoke evaluations. Online surveys may adequately assess the acceptability and feasibility of relatively simple interventions. Other methods (interviews, research diaries) may be required to explore the benefits and difficulties of more complex interventions.

The size of each Rapid Eczema Trial and the methods used in the intervention evaluations will inform the number of trial participants included in each process evaluation. Analysis will be shaped by the scale and scope of each evaluation, but we would expect descriptive statistics and/or qualitative thematic analysis as a minimum. We will ensure that the process evaluation findings are generalisable to the broader clinical population. We will ensure that the process evaluations are inclusive of all socio-demographic groups.

In addition, at the completion of each Rapid Eczema Trial, we will review recruitment, retention and data quality; specifically considering the diversity and appropriateness of the trial population for the intervention being tested. We will ask NCTU staff to maintain a log of issues or difficulties with trial delivery; we will reflect upon these in focus groups or structured interviews with NCTU staff.

At the conclusion of each Rapid Eczema Trial, members of the research team will review findings with external experts/stakeholders (i.e. clinicians, researchers, members of the public not involved in the Rapid Eczema Trials programme delivery). These workshops will address the acceptability of trial findings, contribution to eczema care knowledge, and implementation of findings. They will directly feed into the Knowledge Mobilisation activities for the project and will conclude with recommendations for how best to operationalise learning for greatest effect.

8.6. Withdrawal and discontinuation procedures

8.5.1 Withdrawal prior to randomisation

Any participant who does not provide consent during the recruitment process, **prior to randomisation**, will not be randomised, and no further data will be collected.

8.5.2 Discontinuation and withdrawal post randomisation

Participants may withdraw their consent for follow-up and/or other trial-related activities or receiving trial-related communications. To withdraw, participants will be asked to contact the research team so that appropriate action can be taken to ensure that the participant's wishes are followed.

Participants may withdraw from different activities.

Withdrawal type	Withdrawal procedure	Use of data
Discontinue follow-up questionnaires	Any participant that requests to discontinue from trial questionnaires will be marked as withdrawn from questionnaire collection on the trial database and no further contact will be made with the participant for the purpose of obtaining questionnaire follow-up data.	Any data collected prior to participant withdrawal will be retained and used.
Discontinue allocated intervention but continue with follow-up	Any participant that requests to discontinue their allocated intervention but is willing to continue questionnaire follow-up will be marked as withdrawn from allocated intervention on the trial database but contact will continue to be made with the participant for the purpose of obtaining questionnaire follow-up data.	Any data collected will be used

As these trials are being conducted online with minimal contact with the research team, participants wishing to stop completing the questionnaires or stop their allocated intervention, will probably simply stop. In these cases, participants will continue to receive links to the trial questionnaires through until the end of their planned follow-up and adherence data will be used to capture adherence with allocated interventions.

8.7. Post Trial Care

Once their participation in the trial is over, participants will be advised to revert to their usual self-management practice and use of eczema treatments as directed by their routine clinical care team.

9. Adverse Event Reporting

9.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service (NRES).

We do not anticipate AEs for the types of lifestyle and advice trials that the Rapid Eczema Trials programme will deliver, but our approach to reporting adverse events and identification of related adverse effects that could be attributed to the individual trials will be outlined in the protocol amendment for each trial (e.g slips in the bath or shower for a trial on frequency of bathing).

10. Data Handling and Record Keeping

10.1. Source Data

All data for the Rapid Eczema Trials will be via participant-report through electronic questionnaires and stored directly into the trial database, thus this is the source data. Participants' medical records will not be accessed.

10.2. CRF Completion

All data collection will be via online questionnaires completed by participants. There will be no Case Report Forms completed by sites. This section is therefore not applicable.

10.3. Data Management

Central data management for the Rapid Eczema Trials will be minimal as there will be no recruiting sites or source documentation. As such, data queries will not be raised for missing questionnaire responses.

All data will be handled according to the Rapid Eczema Trials Data Management Plan.

10.4. Archiving

It is the responsibility of the Chief Investigator to ensure all essential trial documentation are securely retained for at least 5 years.

The Trial Master File and trial documents held by NCTU on behalf of the sponsor shall be archived using secure archive facilities at Nottingham University Hospitals NHS Trust. This archive shall include all trial databases and associated meta-data encryption codes.

10.5. Data Sharing

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Participants' contact details, including name, telephone/mobile number and email may be shared between NCTU and third parties (where required) for the sole purpose of issuing questionnaires and electronic reminders (text/email) for the trial.

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the research team will have access to these data.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in computer files.

Data generated as a result of this trial will be available for inspection on request by Nottingham University Hospitals NHS Trust, the REC, local R&D departments and the regulatory authorities.

Anonymised participant datasets may be shared with researchers external to the trial research team on request.

Since one of the aims of the Rapid Eczema Trials programme is to share resources to allow others to run high-quality and efficient eczema trials for themselves, we will openly share this master protocol, master analysis plans, database coding, data dictionaries, analysis code and other relevant trial materials via an appropriate platform.

11. Quality control and quality assurance

11.1. Site Set-up and Initiation

N/A – no research sites are involved in this research programme

11.2. Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan.

11.3. Audit and Inspection

The Trial Master File and evidence of audits will be made available upon request for regulatory inspections.

11.4. Notification of Serious Breaches

The Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to this project.

11.5. End of Trial Definition

The end of each trial will be the final database lock. NCTU will notify the REC once the final trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of the final trial.

12. Statistical Considerations

12.1.1. Power Calculations / sample size calculation

The total number of participants for each trial required will depend on the questions prioritised and the chosen primary outcome. The justification for the sample size for each trial will be included in the protocol as new research questions are added. The principles of sample size calculation for each research question will be based on 90% power, 5% significance and also consider the family wise error rate if multi-arm trials with a shared control group are used. Target sample sizes will also account for potential loss to follow-up.

For some research questions, the co-production groups may feel that it is important to be able to detect an effect within different groups (e.g. adults/children), in which case the overall sample size will be determined to ensure sufficient power within each participant group.

12.2. Analysis of Outcome Measures

Analysis and reporting of each trial will be in accordance with CONSORT guidelines. A standardised statistical analysis plan will be developed and agreed with the independent programme steering committee. The analysis plan for each trial will be finalised prior to database lock and release of the treatment allocations.

Primary comparative analyses for each trial will be conducted according to randomised allocation regardless of adherence (e.g. intention to treat principle) with due emphasis on confidence intervals for between-arm comparisons. Primary and secondary outcomes will be analysed using appropriate regression models with adjustment for the randomisation variables and baseline score (if applicable)[31]. Where possible, regression models will also adjust for other baseline prognostic covariates (based on evidence considered by co-production groups).

Sensitivity analyses will be considered on a case-by-case basis for each trial including:

- Using multiple imputation for missing data
- Using the information on prior belief in the effectiveness of the proposed interventions.
- According to diagnosis of eczema based on the UK Diagnostic Criteria for eczema

The effect of adherence with the allocated intervention may also be investigated if appropriate.

12.2.1. Planned Interim Analysis

There are no planned interim statistical analyses for any of the trials in view of the short-anticipated recruitment period.

12.2.2. Planned Final Analyses

Data analysis for each trial will be performed when the target sample size for the trial has been reached, follow-up completed, and database locked.

12.2.3. Planned Subgroup Analyses

For some research questions, the co-production groups may feel that it is important to be able to detect an effect within different groups (e.g. adults/children), in which case the overall sample size will be determined to ensure sufficient power within each participant group and the intervention effect will be estimated for each participant group.

In addition, the need for subgroup analysis to explore whether the intervention effect varies according to baseline characteristics will be considered on a case-by-case basis for each trial by the co-production groups. Where specified, these subgroup analyses will be performed by including appropriate interaction terms in the regression model for the primary outcome. Trials will not be powered to detect any interactions hence any subgroup analyses will be treated as exploratory.

13. Qualitative Process Evaluation Analysis

Data will be analysed thematically using a framework approach.

A standard Rapid Eczema Trials framework will be developed to incorporate three broad thematic areas which can be applied in all trial process evaluations. Thematic areas will be (i) acceptability of the intervention; (ii) benefits (or difficulties) experienced; (iii) improvements for the future.

Quantitative process evaluation may be conducted depending on the nature of the trial and process evaluation planned.

14. Trial Organisational Structure

The roles and responsibilities for each organisation are documented in the Contractual Agreement and the responsibilities of the Sponsor/CI/NCTU specifically are detailed in the Delegation of Responsibilities.

14.1. Sponsor

Nottingham University Hospitals NHS Trust

14.2. Trials Unit

The trials will be co-ordinated by NCTU.

14.3. Trial Management Group

The Trial Management Group (TMG) will include those 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.

14.4. Programme Steering Committee

The role of the Programme Steering Committee (PSC) and its membership is outlined in the PSC Charter.

14.5. Data Monitoring Committee

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

14.6. Finance

This project is funded by National Institute for Health & Care Research Programme Grants for Applied Research (NIHR203279).

14.7. Participant gratitude and stipends

Participants will be offered the opportunity to enter a prize draw, but we do not anticipate making payments to individuals for participation. If a particular trial might result in costs to the individual, then the need to provide reimbursement for costs will be considered on a trial-by-trial basis.
No travel will be required as interventions and data collection are to be completed at home.

15. Ethical Considerations

The trials will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964.

The trials will be conducted in accordance with the Research Governance Framework for Health and Social Care, and subsequent amendments and the Data Protection Act 2018 and Guidelines for Good Clinical Practice (GCP). The protocol will be submitted to and approved by the REC prior to use.

16. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 and the UK General Data Protection Regulation (GDPR).

All participants will be assigned a unique trial number on randomisation into the trial. First names will be stored to allow personalised messages to individual participants when sending questionnaires and reminders. Details of ethnicity and other protected characteristics will be stored to enable monitoring of inclusivity.

Text messages and emails will be used to send participants reminders about trial procedures and to provide links to the required questionnaires using a unique personalised link. Participants who do not complete follow-up questionnaires will be sent text/email/phone reminders by the trial team as appropriate.

NCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party (except where this is required for trial purposes e.g. to send interventions or text reminders to participants) or organisations for which the participant has given explicit consent for data transfer (e.g. Laboratory staff, competent authority, Sponsor).

Participants wishing to receive update newsletters will be added to the trial mailing list. All participants will be sent a summary of the results that will not include personal identifiers.

Reports of qualitative data findings may include direct quotes from participants, but these will not be identifiable to individuals.

17. Insurance and Indemnity

Nottingham University Hospitals NHS Trust will act as sponsor for the trial. Delegated responsibilities will be assigned to the NCTU and University of Nottingham. Insurance and indemnity for trial participants and NHS trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96) 48. There are no special compensation arrangements, but trial participants may have recourse to the NHS complaints procedure.

The University of Nottingham has appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

Nottingham University Hospitals NHS Trust is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

18. Publication Policy

Results of these trials will be submitted for publication in a peer-reviewed journals, but it is anticipated that results will be released back to the Eczema Research Community as quickly as possible on completion of the trials, using lay-friendly formats. Prior to release, results will be quality checked according to the NCTU statistics standard operating procedure, and interpretation of the

trial results will be discussed with members of the co-design groups, the Trial Management Group and the Trial Steering Group.

Since this is a citizen-science project, copies of the trial materials including the trial protocol, analysis plan, database code and analysis code will be made freely available for others to use.

Academic journal manuscript will be prepared by the research team and members of the co-production groups and authorship will be determined by mutual agreement. Copies of published manuscripts should be submitted to NIHR Programme Manager for information.

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The following disclaimers should be included:

> "This study/project is funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (NIHR203279). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care."
>
> "This study/project was supported by the UK Dermatology Clinical Trials Network. The UK DCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network."

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Appendices

Appendix A
Aspects to be confirmed in subsequent trial amendments for specific Rapid Eczema trials.

Aspect of protocol	Points to be clarified
Trial title	• Title of trial
Principal Investigators	• Each trial will have a research lead and a PPI lead who will be responsible for delivery of the trial
Contributors	• Any additional contributors
ISRCTN registration number	• Each trial will be registered on the ISRCTN clinical trial registry before recruitment commences
Trial flowchart	• Details to be confirmed specific to trial
Research question and hypotheses	• Limited to non-drug and advice trials that can be implemented at participants' home without medical supervision
Participants / eligibility criteria	• Eligibility criteria for specific trials
Trial design	• Minimum two-arm trials, but may include multiple trial arms • Details of any pilot phase and progression criteria
Trial duration	• Either short-term proof of principle trial (4 to 6 weeks) or definitive trial (6 months) • Timing of assessments
Recruitment strategies	• Details of how participants will be identified. • Clarification of payments for participants if applicable. • Details of any incentives or prize draws
Intervention and control	• Interventions developed to be pragmatic to reflect normal practice • Inclusive and accessible to as many people as possible • Consider whether participants are given access to alternative intervention at end of trial
Outcomes	• Summary of assessment timepoints and data collected • Clarification of primary outcome • Additional secondary outcomes relevant to the specific trial • Clarification of approach to adverse event reporting (including verification of ARs if necessary) • Wording of non-validated questionnaires and baseline variables
Trial procedures	• Consent process/requirements including assent for children • Details of assessments • Monitoring arrangements
Blinding	• Ability to blind (or not) the trial interventions clarified

	• Clarify who will be blinded
Sample size	• Justification of sample size
Randomisation	• Randomisation method clarified • Stratification/minimisation variables confirmed (including age bandings) • Allocation ratio confirmed
Analysis	• Analysis metric, method of aggregation and timepoint for each outcome • Clarification of analysis method based on above • Baseline prognostic factors to adjust for in analysis • Sensitivity analysis and sub-group analyses • Definition of adherence to intervention
Process evaluation	• Details of evaluation to be included will be outlined if appropriate
Data sharing	• Details of data sharing arrangements if different to master protocol.
Study-specific documents	Checklist of any study-specific documents that have been developed to be included in amendment e.g. • Participant Information Sheet (PIS) • Participant video scripts • Participant questionnaires • Intervention information for participants • Wording for participant communication/reminders • GP invite letter • GP text message wording • Posters/advertising materials (if relevant) • Process Evaluation Interview PIS • Process Evaluation Interview ICF • Process Evaluation Interview invite letter Checklist of any master documents to be used without additions/amends e.g. • Informed Consent Form (ICF)

Summary of Assessments

Example of possible assessment timepoints (to be confirmed once trial design known)

	TRIAL PERIOD							
	Enrolment	**Randomisation**	**Post-randomisation**					**Follow-up**
TIMEPOINT**	**$-t_1$**	**0**	**t_1**	**t_2**	**t_3**	**t_4**		**t_x**
ENROLMENT:								NA

Eligibility screen (including self-report of eczema diagnosis)	X							NA
Informed consent	X							NA
Minimisation variables	X							NA
Randomisation		X						NA
INTERVENTIONS:								NA
[Intervention A]								NA
[Intervention B]								NA
[Additional trial arms as agreed by co-production groups]								NA
ASSESSMENTS:								NA
Demographics and baseline characteristics		X						NA
UK Diagnostic criteria		X						
Prior belief in intervention		X						NA
POEM		X	X	X	X	X		NA
NRS 24-hour itch		X	X	X	X	X		NA
RECAP		X	X	X	X	X		NA
Quality of life (DLQI, CDLQI, IDQI as appropriate)		X				X		NA
EQ5D / CHU-9D if appropriate		X				X		NA
Use of eczema medications		X	X	X	X	X		NA
Acceptability of intervention						X		NA
Adherence to intervention			X	X	X	X		NA
Safety outcomes (reactions)			X	X	X	X		NA

Additional outcomes specific to chosen intervention		X	X	X	X	X		NA

Contacts

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Appendix B

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

Trial summary

Trial Title	Eczema Bathing Study – how often should we bathe? (Short title: Eczema Bathing Study)
Trial Design	Two-arm, parallel group, superiority randomised controlled trial, with internal pilot.
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
Outcome measures	**Primary outcome:** • Eczema symptoms measured by Patient Oriented Eczema Measure (POEM).[21] Includes 7 items, scored 0 to 28. Assessed weekly over 4 weeks. **Secondary outcomes:** • Itch intensity (Peak Pruritis Numerical Rating Scale (NRS)[22] 24-hour peak itch) - one item, scored 0 to 10. Assessed at baseline and 4 weeks. • Eczema control (Recap of atopic eczema, RECAP)[23] – 7 items, scored 0 to 28. Assessed at baseline and 4 weeks.

	• Skin-specific quality of life (Infants' Dermatitis Quality of Life Index (IDQoL)[24] (under 4 years), Children's Dermatology Life Quality Index (CDLQI)[25](from 4 years to 15 years) or Dermatology Life Quality Index (DLQI)[26](16 years and over) depending on age) – 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.[32]
	  ○ 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.[33]
	• 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.

Sample size / Number of participants	390 (195 per arm)

Lay Summary

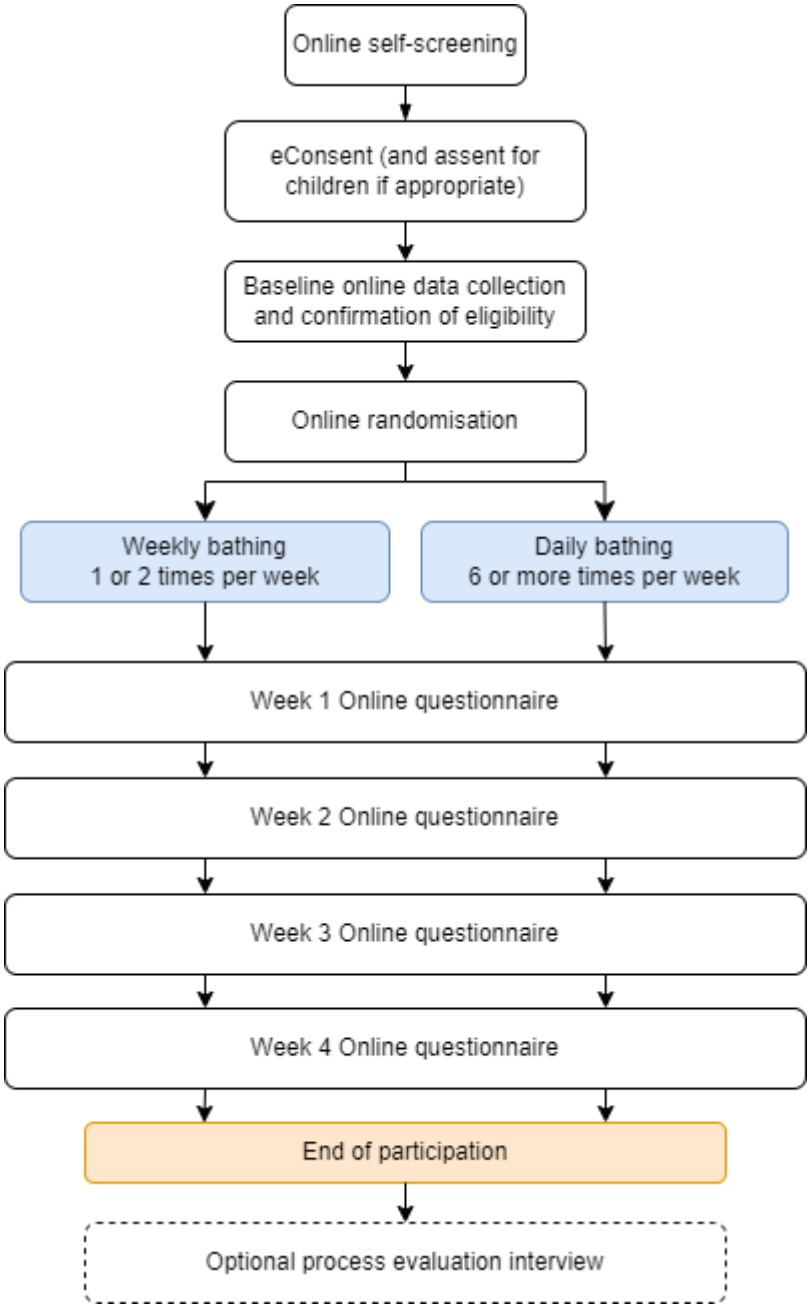
This study is part of the Rapid Eczema Trials project. We hope to answer many questions about how to manage eczema through this project. People with eczema are helping to design and run these studies. This means that the project will answer important questions for people with eczema.

In this Eczema Bathing Study, we will test how often people with eczema should have a bath or a shower to best manage their eczema. People will join the study by signing up on the study's website. They will give information about their eczema and how they usually bathe. For this study, bathing means taking a bath or a shower. They will then be put into one of two groups by a computer. One group will be asked to have a bath or shower no more than 1 or 2 times a week. The other group will be asked to have a bath or shower 6 or more times a week. People will be asked to follow this advice for four weeks. They will be asked to complete some questions, sent to them by email/text message each week. People can take part from home and do not need to travel.

People aged 1 year or older, who have eczema, can join the study. We are encouraging people from all different backgrounds to take part.

As soon as the study results are known, we will share the results as quickly as possible on the study's website (www.RapidEczemaTrials.org).

Trial flowchart



Details of Eczema Bathing Study

Aspect of protocol	
Trial title	Eczema Bathing study – how often should we bathe? (Short title: Eczema Bathing Study)
Principal Investigators	Prof Kim Thomas (Chief investigator) and Ms Amanda Roberts (PPI lead)
Contributors	Co-applicants and contributors as outlined in Master Protocol PPI co-design team members: Tressa Davey, Tracy Owen, Joanne Harwood, Mars Eddis-Finbow, Fiona McOwen, Aaron Foulds, Devin Patel, Goldie Putrym, Kelly Hang, Tim Burton, Shakeela Riaz Other contributors: Nicholas Hilken, University of Nottingham; Eleanor Harrison, University of Nottingham; Leila Thuma, University of Nottingham
ISRCTN registration number	[To be added once registration completed]
Research question and hypotheses	Is weekly bathing better than daily bathing for people with eczema in terms of participant reported symptoms over 4 weeks?
Trial aim and 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.
Participants / eligibility criteria	People with eczema aged 1 year and older. **Inclusion criteria** • Aged ≥1 year with self-report of eczema (syn. Atopic dermatitis, atopic eczema) • 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:** • None or very mild eczema symptoms (POEM score ≤2) • 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); or eczema only around varicose veins (likely to be varicose eczema) • Started a new eczema treatment (including antibiotics for eczema) other than emollients in the last 4 weeks • Taking part in another eczema intervention trial • Unable or unwilling to change bathing practices for 4 weeks • Planning to swim more than twice a week in the next 4 weeks (including surfing, scuba diving etc.) • Member of household already participating in this trial As per protocol section 4, participants identified through GP practices will have a recorded diagnosis of eczema on their medical records and have been issued a prescription for emollients or topical corticosteroids in the last 2 years.
Trial design	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 member of the Rapid Eczema Trials Research Community (www.RapidEczemaTrials.org).
Trial duration	Each participant will be in the trial for 4 weeks with weekly outcome assessment. Recruitment will take place for up to 12 months. The pilot phase will end once 20% of the target sample size has been recruited or after 4 months, whichever is the sooner. The end of trial is defined in protocol section 11.5.

Internal pilot progression criteria	The following criteria will be considered at the end of the pilot phase.
	
	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.
	
	• 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)
Recruitment strategies	Participants will be identified through online and offline methods, including the use of GP practices as Participant Identification Centres (PICs), as described in protocol section 4.3. Information about the trial will be available on the website (www.RapidEczemaTrials.org) in a variety of engaging formats appropriate for all ages. Payments will be made available for people financially disadvantaged by taking part in the trial (£20 per participant paid at the outset of the trial after randomisation). Participants wishing to access this fund will be asked to complete a short online form providing their contact details and preferred method of payment (bank transfer or vouchers). If participants choose to receive the payment by bank transfer, appropriate bank details will be requested. All data relating to payments will be stored securely, in a separate place to the main trial database. Access will be restricted to only those members of the team who will be managing the payments. Participants who complete questionnaires at week 4 will be offered the opportunity to enter a free prize draw to win £25, a child-friendly book about eczema, or both, according to their preference. Potential participants will be encouraged to contact the trial team if they have any questions prior to registering for the trial online.
Intervention and control	• **Weekly bathing group** = 1 or 2 times per week • **Daily bathing group** = 6 or more times per week Following randomisation, participants will be provided with intervention instructions detailing how often they should bathe according to their allocation. Participants should follow this for 4 weeks. Intervention materials have been designed to be accessible (including pictures and simple language) and inclusive (available in different formats). Participants will be asked not to change any of their other bathing practices e.g. method of bathing, use of wash products etc. Participants can wash their face and body using a flannel/sponge in the sink in between showers or baths, and can wash their hair in between showers or baths. Participants may use their usual eczema treatments (e.g. emollients and flare control creams) whenever they need to as per usual practice. They

	will be asked not to change their usual eczema treatments (or start a new treatment) during the trial, if medically possible. Withdrawal procedures are as described in protocol section 8.6. Post-trial care is described in protocol section 8.7.

Outcomes	Outcomes include the Harmonizing Outcomes for Eczema (HOME) initiative's recommended core outcome set.
	
	Primary outcome:
	• Eczema symptoms measured by Patient Oriented Eczema Measure (POEM)[21]. Includes 7 items, scored 0 to 28. Assessed weekly over 4 weeks.
	
	Secondary outcomes:
	• Itch intensity (Peak Pruritis Numerical Rating Scale (NRS)[22] 24-hour peak itch) - one item, scored 0 to 10. Assessed at baseline and 4 weeks.
	• Eczema control (Recap of atopic eczema, RECAP)[23] – 7 items, scored 0 to 28. Assessed at baseline and 4 weeks.
	• Skin-specific quality of life (Infants' Dermatitis Quality of Life Index (IDQoL)[24](under 4 years), Children's Dermatology Life Quality Index (CDLQI)[25](from 4 years to 15 years) or Dermatology Life Quality Index (DLQI)[26](16 years and over) depending on age) – 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.[32]
	  ○ 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.[33]
	• 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.
	
	Additional variables will be collected to inform analysis and interpretation of the trial. These include:
	
	• Minimisation variables, prior belief on the frequency of bathing and eczema symptoms, demographics, UK Diagnostic Criteria for Eczema and usual bathing practices (e.g. usual temperature of the water, use of shampoo, use of emollient wash products, and application of emollients/flare control creams after bathing). Assessed at baseline only.

	• Number of times had bath or shower in the previous week, assessed weekly over 4 weeks to evaluate adherence to allocated frequency of bathing routine. • Ease of bathing as allocated, willingness to continue, things that helped or made it difficult to bathe as allocated, experience of being in the trial (for process evaluation). Assessed at 4 weeks. For children under 16 years, proxy reporting by a parent or carer will be accepted as per protocol section 8.2.
Trial procedures	Informed e-consent will be obtained as per protocol section 5. For children under 16, consent will be obtained from the parent/carer but there will be an optional assent section for the child to complete if they wish. All assessments will be carried out online as per protocol section 8.3. For children who are unable to complete patient reported outcomes themselves, proxy reporting by a parent or carer will be accepted as per protocol section 8.2. Parents/carers will be advised that this should be the same adult throughout the trial if possible. Parents and children will be encouraged to complete the questionnaires together wherever possible. An email/text message with a unique link to the questionnaires will be sent each week to the participant/parent/carer. For weeks 1, 2 and 3 participants will receive a maximum of 2 reminders by email/text message for each questionnaire if it has not been completed. At the final 4-week timepoint, participants will receive text message, email or phone call reminders to complete the final follow-up questionnaires (for up to 2 weeks after the questionnaire is due). A summary of assessments diagram is provided below. We will regularly monitor attempts to re-randomise the same individual or enrol multiple people per household on an ongoing basis. Electronic forms collecting data for screening, consent and eligibility will be recorded and processed with automatic and/or manual checks. These checks will include ensuring identifiers and contact details are unique for participants, so no duplicate entries for the same participant may be made. Eligibility checks will ensure only those who meet all the prescribed inclusion and exclusion criteria can join the trial.
Blinding	Due to the nature of the intervention, it is not possible to blind trial participants to their randomised allocation. To mitigate the potential bias caused by lack of blinding, we will collect prior belief in the impact of bathing on eczema symptoms 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 blinded to treatment allocation.
Sample size	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.[33] 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.
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 randomised allocated group will not be released to participants until after baseline variables have been entered and stored on the trial database.
Analysis	The analysis and reporting of the trial will be in accordance with CONSORT guidelines, with the primary comparative analyses being conducted according to randomised allocation regardless of actual frequency of bathing. A statistical analysis plan will be finalised prior to database lock and release of the treatment allocations. The primary analysis will use all available longitudinal outcome data and will use a linear mixed effects model to estimate the difference in mean POEM score over the 4-week trial period with 95% confidence interval. The model will include fixed effects for the minimisation variables (age, baseline POEM score and usual method of bathing) as well as 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 and whether participants are currently using systemic treatments. It will allow for observations nested within participants over time using random effects. If there is evidence of a differential effect over time, the difference in mean POEM score each week will be reported. Sensitivity analyses for the primary outcome will use multiple imputation for missing outcome data. Further supplementary analysis will investigate potential effects of compliance with allocated frequency of bathing to estimate the complier average causal effect (CACE). Participants will be considered as adherent if the number of times they report bathing/showering in the previous week is as per the allocated frequency of bathing strategy each week over the 4-week trial period. Subgroup analyses for the primary outcome will be performed according to age at randomisation, usual method of bathing (bath/shower/other), diagnosis of eczema according to UK Diagnostic Criteria and prior belief on the frequency of bathing and eczema symptoms by including an appropriate interaction term in the mixed effect model. The trial is not powered to detect any interactions hence the subgroup analyses will be treated as exploratory. Between-group comparison of secondary outcomes will use an appropriate regression model for the outcome (linear for continuous outcomes, logistic for binary) with adjustment as described above for the primary outcome and baseline outcome measure for continuous variables if available. For secondary outcomes assessed weekly, mixed effects models will be used to allow for observations nested within participants over time using random effects.
Process evaluation	A nested, qualitative interview study will consider questions of acceptability, feasibility, and adherence with regards to changed bathing practices. Interviews will also consider trial procedures. A purposive sample of those willing to take part in a research interview will be constructed to include a range of age, gender, ethnicity, prior belief in the impact of bathing on eczema symptoms and acceptability of the interventions after 4 weeks. Equal numbers will be recruited from each arm of the trial (n = 15 to 20 per arm). Only adults (aged 16+) will be included in this process evaluation. Additional consent will be taken from those that participate in a research interview. Online informed consent will be taken prior to the interview, and consent confirmed verbally at the start of the interview. Interviews will be undertaken online or by telephone, at a time convenient to the participant. Data will be digitally recorded if participants consent to this. Interviews will be timed to take place after an individual has completed their final follow-up assessment at four weeks.

	Interviews will explore the participants (i) experience of changing bathing patterns; (ii) any difficulties or challenges that they experienced in this; (iii) any difference that this made to their eczema; (iv) their willingness to continue with their allocated bathing pattern; (v) their assessment of the effectiveness of the intervention and vi) their experience of taking part in the trial. Digital recordings will be transcribed (either internally or using an approved transcription service) and anonymised. Transcripts will be stored as per our Data Management Plan. Recordings will be destroyed once transcripts have been approved as an accurate record. An inductive, thematic approach will be taken in analysing the data. This will develop a more detailed and contextualised understanding of the bathing intervention. A trained researcher will lead the analysis, with the support of Dr Paul Leighton.
Data sharing	Data from the trial may be shared as per protocol section 10.5.
Trial-specific documents	The following documents have been developed for the Eczema Bathing Study and included in an amendment: • Eczema Bathing Study Participant Information Sheet (website text) • Eczema Bathing Study video script (suitable for older children, adults and people with low literacy) • Eczema Bathing Study child video script (suitable for young children) • Eczema Bathing Study intervention guidance - Weekly Bathing • Eczema Bathing Study intervention guidance - Weekly Bathing - Parent • Eczema Bathing Study intervention guidance - Daily Bathing • Eczema Bathing Study intervention guidance - Daily Bathing - Parent • Eczema Bathing Study participant communication wording • Eczema Bathing Study questionnaires • Eczema Bathing Study GP invite letter Adult • Eczema Bathing Study GP invite letter Parent • Eczema Bathing Study GP invite text message wording • Eczema Bathing Study Poster (for GP surgeries/pharmacies/schools etc) • Eczema Bathing Study Process Evaluation Interview PIS • Eczema Bathing Study Process Evaluation Interview Invitation letter • Eczema Bathing Study Process Evaluation Interview Topic Guide • Rapid Master Process Evaluation Interview ICF The Eczema Bathing Study will use the current version of the following approved Rapid Master documents with no additions/amendments:

	• Rapid Master Adult Informed Consent Form • Rapid Master Parent Informed Consent Form (with child assent if appropriate) Additional advertising materials may be used e.g. social media posts, and these will adhere to the Rapid Principles for advertising materials document.

Summary of Assessments

	TRIAL PERIOD					
	Enrolment	Baseline	Follow-up			
TIMEPOINT	**0**	**0**	**Week 1**	**Week 2**	**Week 3**	**Week 4**
ENROLMENT:						
Eligibility screen (including self-report of eczema diagnosis)	X					
Informed e-consent (and child assent if appropriate)	X					
Eczema Symptoms (POEM) – exclude if POEM ≤2		X	X	X	X	X
Minimisation variables		X				
Randomisation		X				
INTERVENTIONS:						
Weekly bathing (1 or 2 times per week)			◆—	—	—	—◆
Daily bathing (6 or more times per week)			◆—	—	—	—◆
ASSESSMENTS:						
Demographics and baseline characteristics		X				
UK Diagnostic criteria		X				
Usual bathing practices		X				
Prior belief in intervention		X				
Peak Pruritis NRS		X				X
Eczema Control (RECAP)		X				X

Quality of Life (DLQI, CDLQI, IDQI as appropriate)		X				X
Use of eczema medications		X	X	X	X	X
Global change in eczema compared to baseline						X
Acceptability of intervention						X
Adherence to intervention			X	X	X	X
Adverse events – changes in eczema treatments and healthcare professional contact due to worsening of eczema						X

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