Protocol

Supporting self-care for eczema: two randomised controlled trials of online interventions

Eczema Care Online
Self-help toolkit

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Protocol Information

This protocol describes the ECO study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non- study participants; every care was taken in its drafting, but corrections or amendments may be necessary.

Compliance

This study will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, in accordance with current Data Protection Regulations and all other regulatory requirements, as appropriate.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

CEAC	Cost Effectiveness Acceptability Curves
CHU-9D	Child Health Utility Nine Dimensions
CONSORT	Consolidated Standards of Reporting Trials
DMEC	Data Monitoring and Ethics Committee
ECO	Eczema Care Online
EQ-5D-5L	EuroQol Five Dimensions Five levels
GCP	Good Clinical Practice
GP	General Practice or General Practitioner
ICER	Incremental Cost-Effectiveness Ratio
MCID	Minimum Clinically Important Difference
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	NHS Institute for Health Research
REC	Research Ethics Committee
PEI	Patient Enablement Instrument
PETS	Problematic Experiences of Therapy Scale
PMG	Programme Management Group
POEM	Patient-Oriented Eczema Measure
PSC	Programme Steering Committee
QALY	Quality Adjusted Life Years
RECAP	Recap for atopic eczema patients
RCT	Randomised Controlled Trial
PC	Parent / Carer
TSC	Trial Steering Committee
UoS	University of Southampton
YP	Young People

KEYWORDS
Eczema, atopic dermatitis, behavioural intervention, randomised controlled trial

1 TRIAL SYNOPSIS

Short title/Acronym:	Eczema Care Online (ECO) self-help toolkits
Full title:	Supporting self-care for eczema: two randomised controlled trials of online interventions

Populations:	RCT 1. Young people (YP) with eczema (aged 13-25 years) RCT 2. Parents/carers (PC) of children with eczema (aged up to 12 years)
Objective:	To determine the clinical and cost-effectiveness of two online interventions for eczema: one for young people with eczema (intervention-YP) and one for parents/carers of children with eczema (intervention-PC)
Study Designs:	Two multi-centre randomised controlled trials with internal pilots and nested health economic evaluations and mixed-methods process evaluation studies. One trial is for young people with eczema (trial-YP) and one for parents/carers of children with eczema (trial-PC)
Sample sizes :	Trial-YP (Young People): Minimum of 200 participants with 40 included in the internal pilot Trial-PC (Parent / Carer): Minimum of 200 participants with 40 included in the internal pilot
Interventions:	1. Online intervention to support eczema self-care for YP + usual care 2. Online Intervention to support eczema self-care for PC + usual care
Control group:	Usual eczema care with access to the intervention after 52 weeks follow-up
Follow up duration:	52 weeks
Recruitment sites	Both YP and PC participants will be recruited from approximately 70-80 GP surgeries across four sites (Southampton, Nottingham, Bristol, Thames Valley & South Midlands)
URL for randomisation:	www.lifeguideonline.org
Outcome measures	**Primary Outcome for trial YP and PC:** We will measure the difference in participant reported eczema severity between groups by administering POEM (Patient-Oriented Eczema Measure) 4-weekly for 24 weeks (weeks 0-24). **Secondary Outcomes for trial YP and PC:** 1. Eczema severity will be measured using the POEM (Patient-Oriented Eczema Measure) 4-weekly for 52 weeks. 2. Quality of Life will be measured at baseline, 24 week, and 52 week follow-up. In trial-YP (young people aged 13-25) this will be measured using the EQ-5D-5L. In trial-PC (parents / carers of children aged 0-12) child Quality of Life will be measured using the Child Health Utility (CHU-9D) for children aged 2-12 years.

	3. Long-term control will be measured by RECAP (Recap for atopic eczema patients. In both Trial-PC and Trial-YP at baseline, 24 weeks and 52 week follow-up. 4. Itch intensity measure (worst itch in last 24 hours). Itch intensity single item (only validated for adults). In Trial-YP but not for Trial-PC will be measured at baseline, 24 week and 52 week follow-up. 5. Self-perceived ability to understand and cope with health issues (enablement) will be measured using the Patient Enablement Instrument (PEI) at baseline, 24 week, and 52 week follow-up. 6. Service use and medication use will be measured through medical notes review of primary care records to capture baseline and trial period resource use. 7. Cost-effectiveness combining 2 and 6 above. **Other outcomes:** 8. Prior belief about the effectiveness of the intervention will be assessed at baseline. 9. Use of other websites for eczema will be measured at baseline. **Process measures:** 10. Self-reported barriers to adherence will be measured using the Problematic Experiences of Therapy Scale (PETS) at baseline, 24 week, and 52 week follow-up. 11. Frequency of treatment use (emollients, topical steroids, and topical calcineurin inhibitors) over the past week will be measured by self-report at baseline, 24 week, and 52 week follow-up. 12. Intervention usage (e.g. number of visits, time spent on the website, pages visited) will automatically be recorded by LifeGuide software for each participant.
Statistical methods	Sample sizes: The sample size for trial-YP and trial-PC is based on 4-weekly POEM scores using repeated measures over the first 24 weeks of the trial, seeking to detect a minimum clinically important difference (MCID) of 3 points between groups (s.d.

	6.5). Assuming a correlation between repeated measures of 0.70, with 90% power and 5% significance, this requires a total sample size of 77 per group in each of the two trials. Allowing for 20% loss to follow up gives a total sample size of 200 in each of the two trials. Analysis: Independent analyses will be carried out for trial-YP and Trial-PC. The primary analysis will be a generalised linear mixed model. All analyses will control for key covariates, such as age, gender, and baseline severity. For secondary outcome measures, linear models will be used for continuous outcomes or an appropriate distribution or non-parametric approach if the assumptions required for linear models are not met. Logistic regression will be used for binary outcome measures. All analyses will be on an intention to treat basis.

2 DRAFT SCHEDULE OF OBSERVATIONS AND PROCEDURES

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Outcomes collected	Baseline	4-Weekly for 52 weeks	24 weeks	52 Weeks (end of study)
Participant completed				
POEM	**X**	**X**		
Essential Demographics	**X**			
CHU-9D (for parents / carers of children aged 2-12 only)	**X**		**X**	**X**
EQ-5D-5L (Trial-YP only)	**X**		**X**	**X**
PEI	**X**		**X**	**X**
PETS	**X**		**X**	**X**
Treatment use self-report	**X**		**X**	**X**
Prior belief about effectiveness	**X**			
Online resource use	**X**			
Non-essential Demographics	**X**			
Long-term control (Recap for atopic eczema patients. In both Trial-PC and Trial-YP	**X**		**X**	**X**
Itch intensity measure (worst itch in last 24 hours). Itch intensity single item (only validated for adults). In	**X**		**X**	**X**

Trial-YP but not for Trial-PC				
Research team completed				
Medical notes review for medication use, service use, and referrals				**X** (including 3 month pre-baseline period)

Data collection during intervention period is kept to a minimum to reduce participant burden and reduce chance of regular monitoring over-shadowing any treatment effects.

3 LAY SUMMARY

Eczema (also known as atopic eczema or atopic dermatitis) is an inflammatory skin disorder characterised by red itchy skin and dryness. Eczema can affect any part of the body but typically settles in the skin creases in children and young people. Eczema is very common, affecting around one in five children and one in ten adults. Eczema leads to poor quality of life because of sore or bleeding skin, itching and poor sleep. Most people with eczema benefit from two treatments: (1) moisturisers (emollients) for dry skin, which need to be applied daily; and (2) topical corticosteroids for inflamed skin and eczema flares. Commonly, if eczema is not well-controlled it is because treatments are not used regularly or in large enough quantities. There are many reasons why people may find it difficult to use eczema treatments: they can be time-consuming to apply; treatments may sting when first applied to inflamed skin; there are concerns about the safety of some treatments; and because patients often receive conflicting advice about how and when to use treatments [1].

We have developed online toolkits to help parents/carers of children with eczema (aged 0-12 years) and young people with eczema (aged 13-25 years) manage eczema more effectively. Topics covered by the toolkits include information about eczema treatments, infections, talking to your healthcare professional, diet and allergy, sleep and itch, physical activity, managing eczema at school or work, coping with stress, and transitioning to self-management. We aim to test the effectiveness and cost-effectiveness of these online toolkits in two studies: one for parents / carers of children with eczema and one for young people with eczema. Parents/carers and young people with eczema will be invited to take part in the studies through their GP surgeries. Participants will be asked to register online and complete an online consent form and baseline questionnaire before being allocated by chance (randomly) to either the study website, or to the control group. All participants will continue with their normal eczema treatments during the study. Participants will be asked to fill in a very short 4-weekly questionnaire about their eczema and a longer questionnaire after 24 weeks and 52 weeks. Participants in the control group will get access to the intervention after 52 week follow-up. If the study websites are effective, health professionals will be encouraged to prescribe them as part of standard care.

4 BACKGROUND AND RATIONALE

Eczema can cause substantial impact on quality of life because of constant itching that can result in sleep loss and difficulty in concentrating [2]. The visible nature of eczema may also result in loss of confidence and bullying by others. Families of children with eczema express frustration that they do not receive enough information about how to manage the condition,[3] as do adults with eczema.[4] NICE guidance on eczema [5] highlights that the main cause of treatment failure is non-adherence and there is a need for new techniques to support adherence.[6, 7] Reasons for non-adherence include:

- Therapy being time-intensive [8, 9]
- Poor understanding of treatments and how to use them [8]
- Under-use of topical corticosteroids related to fear of side-effects [10]
- Conflicting advice from different health professionals regarding how to use topical corticosteroids [11]
- Child refusal [9]

Self-care includes all the health behaviours that people undertake to look after their condition, including treatment adherence. Non-adherence is related to people's understanding of their condition and its treatment, as well as perceived need for treatments and concerns about adverse consequences of treatments.[12]

Self-care is particularly complex in eczema as it involves regular application of topical treatments (mainly emollients for maintenance and topical corticosteroids for flares) and avoidance of triggers (e.g. soap or dust). Currently, many patients or parents/carers receive little or conflicting advice on how to manage their condition, or obtain advice of variable quality from the internet.[13] There is a need for high quality evidence-based interventions accessible for all, as well as evidence of whether such interventions work.

In 2018, 9 out of 10 British households had access to the internet with 86% of adults using the internet every day.[14] Almost 60% of adults currently use the internet to access health information, a figure which continues to rise.[14] Although information about eczema is widely available on the internet, it is of variable quality, often promoting commercial products of unproven efficacy explicitly or surreptitiously. Patients and parents/carers find it difficult to know which information is reliable.[13]

We have developed two online interventions to support eczema management; one for parents and carers of children aged 0-12 with eczema (intervention-PC), and one for young people aged 13-25 with eczema (intervention-YP). The interventions build on a previous online intervention we developed and tested in a pilot trial for parents and carers of children with eczema aged 0-5 years, called Supporting Parents and Carers of Children with Eczema (SPaCE) [15]. The ECO interventions contain a series of eczema management and lifestyle modules that are important for eczema management and to people with eczema. Topics include information about eczema treatments, infections, talking to your healthcare professional, diet and allergy, sleep and itch, physical activity, managing eczema at school or work, coping with stress, and transitioning to self-management. The interventions include aspects that are tailored to the individual and

interactive and audio-visual features. The interventions were developed following the Person-Based Approach to intervention development [16, 17] to ensure they are meaningful, optimally engaging, and relevant to our target users. If these interventions are effective, health professionals would be encouraged to recommend their use as part of standard NHS care.

5 STUDY OBJECTIVES

	Objective	Time point used to evaluate
Primary objective for trial-YP and trial-PC:	To determine the clinical effectiveness of online interventions for eczema: one for young people with eczema (intervention-YP) and one for parents/carers of children with eczema (intervention-PC)	24 weeks
Secondary objective for trial-YP and trial-PC :	1. To determine the cost effectiveness of two online interventions for eczema (intervention-YP and intervention-PC) from a National Health Service and personal social service perspective. 2. To determine mechanisms of action and factors related to participant engagement and adherence to intervention-YP and intervention-PC.	52 weeks 52 weeks

6 STUDY DESIGN

This study comprises two independent randomised controlled trials (RCTs):

1. Trial-YP: to assess the effectiveness of an online intervention (intervention-YP) in young people with eczema aged 13-25 years
2. Trial-PC: to assess the effectiveness of an online intervention (intervention-PC) in parents and carers of children with eczema aged 0-12 years

Both RCTs will include an internal pilot phase and nested health economic and process evaluation studies. A minimum of 200 participants will be recruited to trial-YP and a minimum of 200 participants will be recruited to trial-PC. All participants will be recruited via GP surgeries.

Potential participants for trial-PC and potential participants for trial-YP aged 16-25 years will be sent an invitation pack containing information about the study, information about how to contact the study team and a link to go online if they would like to take part. If they follow the link, they will be asked to provide informed consent and complete initial screening and baseline measures.

Parents or carers of potential participants for trial-YP aged 13-15 years will be sent a different mail pack enclosing information about the study, information about how to contact the study team and a URL to complete consent online if they are happy for their child to take part. The child will then be sent an invitation pack containing information about the study and a link to go online if they would like to take part. If they follow the link, they will be asked to provide assent and complete initial screening and baseline measures.

Participants will then be randomised to one of two groups:

1. Usual care (with access to the online intervention after 52 weeks of follow-up)
2. Usual care plus immediate access to the online intervention

6.1 OUTCOME MEASURES

All participant reported outcome measures and intervention usage data will be collected online, via the LifeGuide software (www.lifeguideonline.org). LifeGuide is a unique set of open source software used to develop and trial complex online behavioural interventions. Outcome measures are very similar across trial-YP and trial-PC, where there are any differences these are highlighted.

6.1.1 Primary outcome

The primary outcome for both trials will be eczema severity over 24 weeks measured by 4-weekly POEM (Patient-Oriented Eczema Measure).[18, 19] 24 Weeks has been shown in previous NIHR-funded eczema trials to be a sufficient duration to capture the chronic-relapsing nature of eczema. Loss to follow-up is likely to be greater at 52 weeks – this is particularly important for a trial in which consent and follow-up assessments are all conducted online.

POEM includes 7 questions about the frequency of eczema symptoms over the previous week that are summed to give a score from 0 (no eczema) to 28 (worst possible eczema). POEM is a patient reported outcome that measures symptoms that are important to the patient and takes around 1 minute to complete. POEM can be completed by young people and children or by proxy (carer report), demonstrates good validity, repeatability and responsiveness to change [20]. POEM has been recommended as a core outcome measure for symptoms by the international Harmonising Outcome Measures for Eczema group [21].

6.1.2 Secondary outcomes

1. Eczema severity will be measured using the POEM (Patient-Oriented Eczema Measure) 4-weekly from week 0 to 52 week follow-up.

2 Quality of Life will be measured in both trials at baseline, 24 week, and 52 week follow-up. In trial-YP, Quality of Life will be measured using the EQ-5D-5L self-completed by the young person. In trial-PC, Quality of Life will be measured by proxy using the Child Health Utility - Nine Dimensions (CHU-9D) for those children aged 2 to 12 years.

3. Long-term control will be measured by RECAP (Recap for atopic eczema patients. In both Trial-PC and Trial-YP measured at baseline, 24 week, and 52 week follow-up.

4. Itch intensity measure (worst itch in last 24 hours). Itch intensity single item (only validated for adults). In Trial-YP but not for Trial-PC measured at baseline, 24 week, and 52 week follow-up.

5. Enablement, the self-perceived ability to understand and cope with health issues, will be measured using the Patient Enablement Instrument (PEI) at baseline, 24 week, and 52 week follow-up.

6. Health service use and medication use will be measured by medical notes review for the 3 month period prior to baseline and the whole 52 week trial period.

7. Cost-effectiveness combining 2 and 6 above.

6.1.3 Other outcomes

8. Prior belief about the effectiveness of the intervention will be measured at baseline.

9. Online resource use (websites or apps) for eczema will be measured at baseline.

6.1.4 Process measures

10. Self-reported barriers to adherence will be measured using the Problematic Experiences of Therapy Scale (PETS) at baseline, 24 week, and 52 week follow-up.

11. Frequency of treatment use (adherence) will be measured by self-report at baseline, 24 week, and 52 week follow-up.

12. Intervention usage data for each participant will be automatically recorded by LifeGuide Software for the duration of the 52 week trial period.

6.2 DEFINITION OF END OF STUDY

The two RCTs may have different end dates. Each RCT will end the date of the last follow-up of the last participant.

7 SELECTION AND ENROLMENT OF PARTICIPANTS

7.1 INVITATION TO PARTICIPATE

Participants in both trials will be invited to take part in this study through their GP surgery.

Database searches will be carried out by practice staff to identify lists of potential participants on the basis of age, eczema diagnosis and recent relevant prescription. Lists of potential participants will then be screened by GPs to assess suitability to receive a study invitation.

If the potential participant wishes to take part, they will log in to the website where they will consent to take part and answer the POEM questionnaire. This will determine whether they are eligible to take part in the study.

Eligible participants will then be directed to the next section of the website where they will be randomised. If they are not eligible, they will be informed on screen and shown the 'participant not eligible' information document.

Trial-YP: Study invitation packs containing a cover letter from GP practice and participant information about the study will be sent to the parent or legal representative of potential participants aged 13-15, and directly to potential participants aged 16-25, with a diagnosis of eczema recorded in their GP record and who has obtained a relevant prescription in the previous 12 months.

Trial-PC: Study invitation packs containing a cover letter from GP practice and participant information about the study will be sent to the parent or legal representatives of children aged 0-12 with a diagnosis of eczema recorded in their GP record and who has obtained a relevant prescription in the previous 12 months.

Invitation packs to potential participants will contain an invite letter from the GP practice, participant information sheet with contact details so that potential participants can ask questions of the research team, a 1 page summary sheet, and a URL to the intervention website with a unique ID to log in.

Invitation packs to the parents or legal representatives of potential participants aged 13-15 (trial-YP) will contain an invite letter from the GP practice, participant information sheet with contact details to ask questions of the research team, a 1 page summary sheet, and a URL with a unique ID to log in to complete parental consent.
Upon receipt of parental consent the research team will post a study invite pack directly to the potential participant aged 13-15.

7.2 INCLUSION CRITERIA

Participants will be eligible for inclusion in trial-YP if:

- They are a young person aged 13-25 years with eczema
- They were identified from GP records as having eczema and have obtained a prescription for eczema treatment in the past 12 months
- Have a POEM score greater than 5 to include mild to severe eczema, but exclude those with very mild eczema to avoid floor effects
- Have internet access

Participants will be eligible for inclusion in trial-PC if:

- They are a parent / carer of a child aged 0-12 years with eczema
- Their child was identified from GP records as having eczema and has obtained a relevant prescription in the past 12 months
- Their child has a POEM score greater than 5 to include mild to severe eczema, but exclude those with very mild eczema
- They have internet access

Only 1 person per household will be able to take part in each trial. If a parent / carer in trial-PC has more than one child who meets the inclusion criteria they will be asked to specify one child to participate in the trial.

7.3 EXCLUSION CRITERIA

Potential participants from trial-YP and trial-PC will be excluded if:

- They are unable to give informed consent
- They are unable to read and write English as the intervention content and outcome measures are in English.
- Potential participants will also be excluded if they have taken part in another eczema intervention in the past 3 months.
- Potential participants will be excluded if they took part in think aloud interviews as part of ECO intervention development. (Qualitative interviewees who did not view intervention materials will NOT be excluded).

7.4 CONSENT

Consent to enter the trial will be sought online from each participant only after full study details and study team contact information (telephone number and email address) have been given and time allowed for consideration and to ask questions. The right of the participant to refuse to participate without giving reasons will be respected. All participants are free to withdraw at any time from the trial without giving reasons and without prejudicing further treatment. All participants will give informed consent (including explicit consent to access relevant data from the intervention and their medical records) before they are randomised into an ECO trial.

Trial-YP: Online informed consent will be obtained from participants aged 16-25.
Parent/guardian consent for young people aged 13-15 will be obtained online and then the child will be sent an invitation pack inviting them to take part in the study if they wish. Assent will then be completed online when the child logs in.

Trial-PC: Online Informed consent will be obtained from all parents / guardians.

Participants in both trials will be invited to take part in a qualitative study (as part of the nested mixed-methods process evaluation), and will be asked at baseline if they consent to be contacted about the interviews. When the interviews are due, participants will then be contacted by phone / text message/email, given further information about the interview study and given the opportunity to ask questions. They will then be asked either to login to give their consent online or provide written consent prior to the interview. Where face-to-face interviews are carried out written informed consent will be sought in person. Participants will be free to withdraw at any time simply by contacting the research team.

7.5 CONFIDENTIALITY DATA PROTECTION

The confidentiality of all participants taking part in the study will be preserved. The study team will also ensure that participants' anonymity is maintained and that their identities are protected from unauthorised parties. They will not be identified by their names, but by an identification code.

Participant data will not be identified by their names, but by an identification code. Transcribers of the qualitative process evaluation interviews will sign a confidentiality agreement.

Participant data will be collected online via LifeGuide software and stored securely on servers hosted by the University of Southampton. GP notes review data will be collected by research study team or GP site personnel at the end of the study. At the end of the study, data will be exported, and stored securely on University premises. The participant data is pseudo anonymised by assigning each participant a participant identification number which will adapted for use in LifeGuide. Any follow-up data collected by telephone will be entered remotely at site. All data will be retained in accordance with current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

7.6 RANDOMISATION PROCEDURES

Participants will complete informed consent/assent and baseline questionnaires online within LifeGuide software. Eligible participants will then be randomised to the intervention group or control group by the software. Those who do not meet the eligibility criteria of a minimum POEM score greater than 5 will be presented with information explaining that they are not eligible for the study and signposted to NHS and National Eczema Society resources. The ECO study team will automatically be notified of all new participants that are randomised. It will not be possible to blind participants to their allocation group, but the trial statistician will remain blinded. Prior belief in the benefit of the intervention will be assessed. Randomisation will be carried out in blocks and stratified by age e.g. 13-17; 18-25 (trial-YP), and 0-5; 6-12 (trial-PC), baseline eczema severity (POEM scores 6-7; 8-16; 17-28) and recruitment site as these may influence how participants engage with the interventions.

8 SAFETY

No specific therapeutic intervention is proposed. This programme consists of online information to support eczema self-care. There is, therefore, no study-specific safety reporting procedures.

8.1 SAFEGUARDING

Steps have been taken to ensure safeguarding for both the participants and the researchers. A lone worker policy is in place for the interviewers to follow prior to fieldwork. A safeguarding policy is in place and researchers will have a copy in their interview pack to follow in case of concern arising during interviews with participants.

The participant information sheet advises potential participants that confidentiality may have to be breached if there is a disclosure relating to serious harm, abuse and/or other safeguarding concerns

9 INTERNAL PILOT

The procedure for the internal pilot trials will be conducted in accordance with the full trial protocol with patient recruited in the first three months. Trial-YP and trial-PC will be assessed

independently of each other, and one trial's performance will not affect the other. If the intervention and trial procedures are found to be acceptable and feasible during the initial 24 week period, participants will be able to continue using the intervention for a further six months until completion at a final 52 week follow-up.

We propose a total of 40 participants (20 per arm) will be recruited to trial-YP internal pilot, and 40 participants (20 per arm) will be recruited to trial-PC internal pilot. If changes to either of the interventions or trial procedures are needed we will stop the internal pilot phase and make adjustments as necessary, prior to starting the main trial. We will also consider increasing numbers in the pilot in order to evaluate effects of changes.

9.1 ASSESSING ACCEPTABILITY AND FEASIBILITY

During the internal pilot studies all aspects of the protocol will be assessed. This will include (but may not be limited to): study uptake, recruitment and follow-up procedures, randomisation, and participant engagement in accessing the intervention.

It is proposed that for trial-YP and trial-PC progression occurs based on recruitment criteria:

- If recruitment exceeds 70% of the recruitment predicted, the main trial goes ahead with plans for increased practice recruitment
- If recruitment is 50-70% of the recruitment predicted, then a discussion with our TSC is instituted and assuming a plan for increasing recruitment is credible, the trial proceeds with monthly recruitment updates, and discussions with the funder
- If recruitment is <50% of the recruitment predicted there should be a discussion with the TSC and funder and unless there is a very strong and credible plan to increase recruitment, progression to the main trial should be halted.

In terms of accessing the interventions:

- If at least 80% of participants in the intervention group access the online intervention at least once, the main trial will go ahead
- If 50-80% of participants in the intervention group access the online intervention, then take steps to increase engagement for the main trial
- If <50% of participants in the intervention group access the online intervention, there should be a discussion with our TSC and funder and unless there is a credible plan to increase engagement, progression to the main trial should be halted.

9.2 INTERNAL PILOT CONTINGENCY PLANNING

It is anticipated, due to the extensive developmental work undertaken with the ECO interventions that substantial difficulties are unlikely to occur. However, in the event that one or both of the interventions or aspects of the study protocol are found to pose major difficulties to undertaking the main RCT study, the internal pilot will end after participants have completed the 24 week follow-up. A period of up to 6 months will be scheduled in case any changes need to be made ahead of the main RCT.

10 STUDY PROCEDURES

10.1 STUDY PROCEDURES AND FOLLOW UP

The majority of study procedures will be carried out online through the online interventions (LifeGuide software). Participants wishing to take part in the study will provide consent and assent (where required) and complete an online baseline questionnaire as indicated in the schedule of observations before being randomised to either the intervention group or the control group. Participants in the intervention group will then have access to the intervention website (either intervention-YP or intervention-PC, depending on which trial they are in). Participants in the control group will be given access to the intervention website after 52 week follow-up.

All participants will be asked to complete a 4-weekly POEM measure online. Participants will also be asked to complete a 24 week and 52 week follow-up questionnaire online. Automated emails and text messages will be sent to notify participants when their follow-up questionnaires are available for completion.
Reminder emails and texts will be sent to non-responders after 5 days (and after 10 days for 24 and 52 week questionnaires), followed by reminder telephone calls approximately 4 days later from the research team, at which point participants will be invited to complete follow-up questions over the phone.

10.2 DEVIATIONS AND SERIOUS BREACHES

Any study protocol deviations, non-compliance, or breaches are departure from the approved protocol. These will be adequately documented in the deviation log and reported to the Chief Investigator and Sponsor immediately. The Sponsor will then advise of and/or undertake any corrective and preventative actions as required. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

All serious protocol deviations, non-compliance or serious breaches of Good Clinical Practice and /or the study protocol will immediately be reported to the relevant Research Ethics Committee (REC).

10.3 WITHDRAWAL

The participant or legal representative is free to withdraw consent from the study at any time without providing a reason. If a participant initially consents but subsequently withdraws from the trial, a clear distinction will be made where possible as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal from trial intervention
2. Withdrawal from further study follow-up
3. Withdrawal from entire study and does not want data to be used.

The study team will explain the value of remaining in study follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from the study will remain in follow-up as per the trial schedule. If participants additionally withdraw consent for further follow up, they will not be followed up further.

Details of study discontinuation (date, reason if known) will be recorded in the trial management database.

10.4 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

Blinding of randomisation and assessment procedures will be unnecessary as randomisation and follow-up will be automated and conducted by the LifeGuide software. Blinding of participants is not possible. Participants will be informed online as to which group they have been allocated to immediately and will be sent the notification via email. The trial statistician will remain blinded.

11 INTERVENTION AND GROUP DETAILS

Participants in both trials will be randomised to either 1) usual eczema care or 2) online intervention plus usual care. These groups are described below.

11.1 USUAL CARE GROUP

Participants randomised to usual care will continue to receive their usual medical advice and prescriptions provided by their GP surgery and other healthcare services. They will not be prevented from seeking additional online support but will not be supported in doing so by the study team and will not have access to the trial online interventions. Participants allocated to the usual care group will receive access to either intervention-YP or intervention-PC (depending on which trial they are in) after 52 week follow-up.

11.2 INTERVENTION-YP AND INTERVENTION-PC GROUP

Participants randomised to the intervention group will receive access to an online behavioural intervention to support eczema self-care in addition to usual eczema care, as above. The interventions were developed following the Person-Based Approach to intervention development [22], and drawing on a theoretical framework including the Extended-Common Sense Model [23], Social Cognitive Theory [24], the Behaviour Change Wheel and associated Theoretical Domains Framework [25]. All intervention content is evidence-based. The interventions were initially developed by the research team consisting of behavioural psychologists, patient representatives, clinicians (GPs, dermatology nurse consultant, dermatologists), and skin researchers before being optimised through extensive user feedback to ensure it is acceptable, feasible, and optimally engaging to our target users.

The online interventions target core behaviours linked to eczema treatment use (regular use of emollients and appropriate use of topical corticosteroids, eczema irritants and triggers, scratching, and emotional management. It uses behavioural techniques to support eczema self-care by building on aspects like knowledge, skills, self-efficacy, social support, and addressing

environmental factors such as social and physical opportunity. The intervention is designed to first tunnel participants through a core section before gaining access to the main menu with the choice of various topics of interest to people and families with eczema. Intervention content has been developed to be interactive and engaging, with tailoring to suggest topics that may be of relevance. The intervention also contains a series of animated videos focussing on the core target behaviours.

Intervention-YP has been developed for people aged 13 to 25 years with eczema. The intervention covers a wide range of topics that are important to people with eczema, as well as additional sections that are important particularly to this age group, such as information about finances, school / university /work, and cosmetics.

Intervention-PC has been developed for parents of children aged 0 to 12 years with eczema. This intervention covers the same wide range of topics relevant to eczema, as well as sections that are specifically relevant to parents and co-management of eczema, such as transitioning to co-management, dealing with child resistance, and managing your child's eczema at nursery and school.

12 STATISTICS AND DATA ANALYSES

12.1 METHOD OF RANDOMISATION

Participants will be randomised online through LifeGuide software. Randomisation will be carried out in blocks and stratified by age (e.g. 13-17; 18-25 (trial-YP), and 0-5; 6-12 (trial-PC), baseline eczema severity (POEM scores 6-7; 8-16; 17-28) and recruitment site as these may influence how participants engage with the interventions. Participants will not be blind to their allocation group, but the trial statistician will remain blinded.

12.2 SAMPLE SIZE

Trial-YP will include a minimum of 200 participants aged 13-25 years with eczema.
Trial-PC will include a minimum of 200 participants who are parents / carers of children with eczema aged 0-12 years.

12.3 STATISTICAL ANALYSIS PLAN (SAP)

Primary analysis will be a generalised linear mixed model. All analyses will control for key covariates, including age and baseline severity, and will be set out in full in the Statistical Analysis Plan. For secondary outcome measures, linear models will be used for continuous outcomes. Where the assumptions for linear models are not met, we will use other appropriate distributions or non-parametric methods if no suitable distribution can be found. Logistic regression will be used for binary outcome measures.

We will collect data on use of other websites at the start and end of the trial to check whether there is a difference between groups in accessing other eczema sites and plan sensitivity analyses to examine whether accessing other resources impacts on outcomes. All trials of online

interventions must assume that users in both groups may access other websites, and so trials provide a useful test of whether the intervention being evaluated is superior to the sites users can already access.

All analyses will be on an intention to treat basis, detailed in a Statistical Analysis Plan, and include participants from the internal pilot and full RCT. No interim analyses are planned. The study will be reported in accordance with the CONSORT statement.

13 NESTED HEALTH ECONOMIC EVALUATION

Two within trial economic evaluations will estimate whether intervention-YP and intervention-PC are cost-effective compared to usual care in trial conditions from an NHS and personal social services perspective. We will estimate the cost of the interventions and collect data on wider resource use, in particular eczema-related prescriptions and service use through medical notes review. A pre-defined proforma will be designed to guide resource use extraction to ensure all appropriate resource items are monitored and appropriate detail recorded (from 3 months pre-baseline to 52 weeks post-randomisation) to enable the valuation of those resources. Resource items will be valued using published unit costs for the most recent common price year to the time of analysis.

There is currently no agreed approach to valuing health outcomes in children in economic evaluations.[26] In the trial-PC for parents/carers of children aged 0-12 we will collect by proxy both the CHU-9D [20], a generic preference based instrument, in those 2 and over. Although the CHU-9D was developed for children aged 7 and over, its completion by proxy in younger age groups is currently being trialled [27] and the developer of the instrument has given us the additional guidance to use with parents/carers with children in this age group.

In the trial-YP (young people aged 13-25), all participants will be asked to self-complete the EQ-5D-5L in order to estimate their health related quality of life. To prevent any discontinuity, the EQ-5D-Y will not be used in those under the age of 16 as this is a different instrument to the EQ-5D-5L [28, 29]. All participants will be asked to complete the EQ-5D-5L at baseline, 24 weeks and 52 weeks and the scores from these will be converted to utility scores using UK preference weights in line with current recommendations at the time of the analysis [28, 30]. Following this, the utility values will be used to estimate Quality-Adjusted Life years (QALY) for the trial period using linear interpolation and area under the curve with and without baseline adjustment.[31]

Cost effectiveness (using change in POEM between baseline and 52 weeks) and cost utility analyses will be performed. Using information on costs and benefits, regression analysis will be conducted to estimate the incremental cost, incremental benefit and incremental cost utility of the online intervention compared to usual care (over the trial period). If one arm is clearly dominant (less costly and more effective) a recommendation can be made on this basis. If non-dominance occurs (that is if costs are greater and the interventions are more effective or if the intervention is cheaper and less effective), an incremental cost-effectiveness ratio (ICER) will be produced and a judgement about value for money will need to be made. ICERs will be calculated using accepted methodology.[32, 33]

Since costs and benefit data may be skewed, we will use non-parametric bootstrapping to estimate mean costs, mean QALY estimates, and net benefit. Estimates of cost and benefits will be graphically presented upon cost-effectiveness planes. Bootstrapping will also be used to

estimate cost-effectiveness acceptability curves (CEACs);[34, 35] these will show the probability of the intervention being the most cost-effective option at different monetary valuations of the outcome variable. A range of ceiling ratios (or willingness to pay per QALY threshold) values will be tested but this will include £20,000 and £30,000 per QALY given thresholds used by NICE in cost-utility analyses.[36]

14 NESTED PROCESS EVALUATION STUDY

A nested process evaluation study will be carried out to understand intervention processes and participants' experiences of using the intervention.

14.1 QUANTITATIVE PROCESS STUDY

We will use baseline data (such as age, gender, education, eczema severity) to examine the moderator effects of participant characteristics on intervention engagement (objectively recorded detailed website usage and self-reported treatment adherence) and outcome. We will also assess and analyse potential mediators of adherence and intervention outcomes; in particular changes in beliefs about treatment (Problematic Experiences of Therapy Scale), as well as intervention usage. Objective measures of intervention usage are automatically recorded (with informed participant consent), allowing evaluations of usage patterns, such as time spent on intervention, number of visits to the intervention website, pages visited and engagement with specific tools and features (such as audio-visual or interactive features).

14.2 QUALITATIVE PROCESS STUDY

Qualitative process interviews will be carried out with approximately 30-40 participants (15 to 20 from trial YP and 15-20 from trial-PC, or until saturation of the main themes are achieved). These interviews will provide in-depth understanding of patient and carers' experiences within the trial, and provide a better understanding of factors that may influence engagement with the intervention.

Interviews will be conducted by a member of the research team experienced in qualitative research methods (face-to-face, or by telephone, or skype if necessary) with participants who consented to be contacted about the study at baseline. We will purposively sample to ensure a range of age, gender, eczema severity, website usage, and research site. Potential participants will be contacted by a member of the research team to check whether they would like to take part in an interview or have any questions about the nested qualitative study.

If participants would like to take part, a mutually agreed time and place will be arranged. Face-to-face interviews may be carried out at participants' home, GP surgery, or University premises. They will then be asked either to login to give their consent online or provide written consent prior to the interview. Where face-to-face interviews are carried out written informed consent will be sought in person Consent will be obtained before commencing the interview. Interviewees from trial-PC may also be given the opportunity for their child to be interviewed about their experience of the ECO trial.

Interviews will initially use open-ended questions to allow participants to freely discuss their experiences and focus on topics that are important to them. The interviews will then probe key topics and areas of uncertainty about intervention processes. For example:

- Participants' experiences of engaging with the intervention, including facilitators and barriers to this and perceived value of interventions
- Participants' views of eczema, particularly whether they felt these had changed following using the interventions
- Participants' views of eczema treatments, particularly whether they felt these had changed following using the interventions
- Other potential mechanisms of action (e.g. barriers to treatment – child resistance)

Analysis: Qualitative data will first be analysed using inductive thematic analysis.[37] We will then explore how emerging themes may map onto our theoretical frameworks in order to relate our insights to generalisable theoretical constructs.

14.3 PROCESS EVALUATION ANALYSIS

We will triangulate findings from the quantitative and qualitative process analyses [38] to explore and test the causal mechanisms proposed, to help inform interpretation of trial results, and determine how implementation might be improved in future dissemination.

15 REGULATORY

15.1 CLINICAL TRIAL AUTHORISATION

The interventions being tested is purely an informational database and does not provide any personalised medical advice. This study is not a clinical trial of a medicinal product, so clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

16 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the study should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the study without giving reasons must be respected. Participants are free to withdraw from the study at any point without giving reasons and without prejudicing their usual treatment.

16.1 ETHICAL APPROVAL

The study protocol has received the favourable opinion of South Central – Oxford A Research Ethics Committee (19/SC/0351).

17 SPONSOR

The University of Southampton is acting as Sponsor for this trial.

17.1 INDEMNITY

The University of Southampton's public and professional indemnity insurance policy provides an indemnity to UoS employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS' Trust's responsibility for any clinical negligence on the part of its staff.

17.2 FUNDING

This study is funded by the National Institute for Health Research Programme Grants for Applied Research (PR-PG-0216-20007).

GP practices

GP practices will be reimbursed through service support payments from the NIHR CRN and research costs from the ECO study.

Participants

For each trial, participants will be entered into a prize draw to win one of 4 x £50 gift vouchers. Participants taking part in the nested qualitative study interviews will receive a £10 gift voucher for their time.

17.3 AUDITS AND INSPECTIONS

The study may be participant to inspection and audit by the University of Southampton (under their remit as Sponsor) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

18 STUDY OVERSIGHT GROUPS

The day-to-day management of the study will be co-ordinated through the trial management team in Southampton and Nottingham, and oversight will be maintained by the Programme Management Group and the Programme Steering Committee.

18.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The ECO Programme Management Group (PMG) will be the TMG for both RCTs. MS is the Chief Investigator of these trials and will chair the TMG.

The ECO PMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the PMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

18.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The ECO Programme Steering Committee (PSC) will be the TSC for both RCTs. The PSC/TSC will meet in person at least yearly. The ECO PSC/TCS consists of 4 independent members, including the Chair.

The ECO PSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the PSC, including the timing of meetings, frequency and format of meetings.

18.3 DATA MONITORING AND ETHICS

The aim of the DMEC is to safeguard the interests of study participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study. These duties will be carried out by the ECO Programme Steering Committee.

19 RECORD RETENTION AND ARCHIVING

Study documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure the PI will maintain all source documents and study related documents. All source documents will be retained for a period of 10 years following the end of the study.

20 PUBLICATION POLICY

For each RCT, data from all centres will be analysed together and published as soon as possible. All publications and presentations relating to the trial will be authorised by the NIHR and Programme Management Group. Participants and participating GP surgeries will be sent a summary of results once available.

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