Developing a patient-reported outcome measure of eczema control

Draft 1.1 / Final Version 1.1
4th July 2018

Short title:	Developing an Index for the Control of Eczema (ICE)
Acronym:	ICE
Funding Source:	The British Skin Foundation

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SYNOPSIS

Title	Developing a patient reported outcome measure of eczema control
Acronym	ICE
Short title	Developing an Index for Control of Eczema (ICE)
Chief Investigator	Prof. Kim S Thomas
Aims and Objectives	AIM: To develop a patient reported outcome measure that capture's a patient's experience of eczema control. OBJECTIVES: 1. To generate items for an eczema control index (stage 1). 2. To refine items for an eczema control index (stage 2). 3. To reduce the number of items in the eczema control index to produce a final scale and assess for initial validation (stage 3). **Secondary aim:** To understand what individuals think when they are filling out the Patient Oriented Eczema Measure (POEM).
Study Configuration	This study comprises three stages; Stage 1: Item generation designed with input from an expert panel of patients, parents, clinicians and methodologists Stage 2: Item refinement using cognitive debriefing interviews Stage 3: Field testing: item reduction and producing an index using an online survey
Setting	Community based sample of people with eczema / parents of children with eczema living in the UK.
Number of participants	Stage 1: n/a – no participants involved Stage 2: minimum of 10 participants Stage 3 and 4: N = 500
Eligibility criteria	*Inclusion criteria* Live in the UK Be 16 years or older OR have parental consent to take part and have a parent present whilst they take part Self- report that either they or their child has been diagnosed with eczema by a doctor *Exclusion criteria* Not able to speak or understand English
Duration of study	Study duration: May 2018 – June 2019. Participation duration: Interviews will last approximately 30-60 minutes. The online survey will take approximately 10-15 minutes to complete.
Methods of analysis	Interviews: content analysis Survey: impact analysis, regression analysis, correlation analysis.

ABBREVIATIONS

CI	Chief Investigator overall
CRF	Case Report Form
GCP	Good Clinical Practice
NHS	National Health Service
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
UoN	University of Nottingham

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STUDY BACKGROUND INFORMATION AND RATIONALE

Eczema (syn. atopic eczema, atopic dermatitis) is a chronic, inflammatory skin condition characterised by periods of remission and relapse (1). The fluctuating nature of the disease should be considered when designing randomised controlled trials assessing the effectiveness of eczema treatments. The Harmonising Outcome Measures in Eczema (HOME) initiative is an international collaboration of patients, healthcare professionals, journal editors, regulatory authorities and the pharmaceutical industry working together to agree a core set of outcomes to be included in all eczema clinical trials. Recommendations from HOME on core outcomes are made at evidence-based consensus meetings (2-5). Long-term control was recommended as one of four key domains that should be measured in all future eczema trials, but the challenge remains over how best to define the construct of long-term control and how to measure long-term control in clinical trials (2, 4).

To resolve the lack of consensus on this definition, a substantial body of work has focused on this area in recent years. There has been a systematic review to assess how flares have been defined in randomised controlled trials and a systematic review of how long-term control has been measured in randomised controlled trials (6, 7). International qualitative studies have been conducted to establish and to elicit what concepts relating to long-term control are important to patients, carers and healthcare professionals. These qualitative studies suggested patients, carers and clinicians across multiple countries view long-term control of eczema as a multi-dimensional concept. The findings of the qualitative studies and other previously published literature have allowed us to develop a conceptual model of what is perceived by patients, carers and clinicians to be relevant to long-term control of eczema (8, 9).

These data informed discussions at the HOME V meeting, where consensus-decisions were reached on measuring long-term control in clinical trials as a combination of atopic eczema signs, symptoms, health-related quality of life and a patient global assessment (10). However, the instruments that would best capture all the various domains of long-term control is yet to be determined. There is currently no published validated outcome measure of eczema control that captures the aspects of the conceptual model that has been developed based on qualitative studies, systematic reviews and survey research. An outcome measure that captures a range of concepts related to eczema control could inform consensus decisions over preferred instruments for measuring long-term control of eczema at the HOME VII meeting in 2019.

STUDY OBJECTIVES AND PURPOSE

AIM

To develop an index to measure eczema control.

OBJECTIVES

1. To generate items for an eczema control index (stage 1).
2. To refine items for an eczema control index (stage 2).
3. To reduce the number of items in the eczema control index to produce a final scale and assess for initial validation (stage 3).

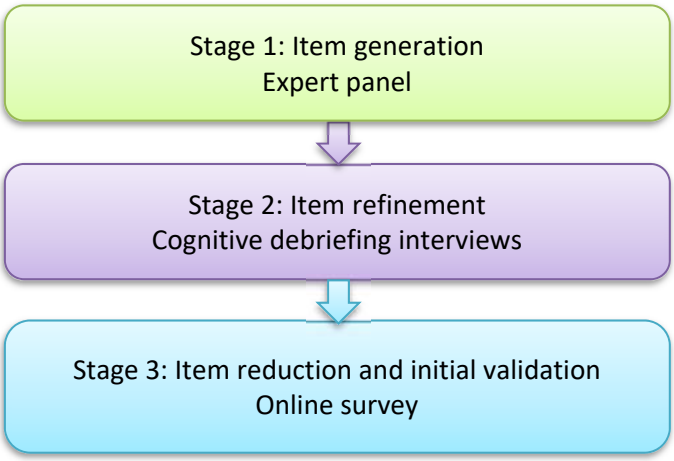
Secondary aim: To understand what individuals think when they are filling out the Patient Oriented Eczema Measure (POEM). This will be addressed in stage 2. This is a good opportunity to conduct this much needed work to further our understanding of the validity of the POEM.

STUDY DESIGN

STUDY REGIMEN

The study consists of three stages that inform each subsequent stage (Figure 1). This process has been informed by current guidelines on developing a patient reported outcome measure (11-14).

Figure 1. The 3 stages of the study



Stage 1: Item generation

An expert panel will be convened to agree an initial list for inclusion in the item selection survey. The expert panel will include healthcare professionals (HCPs) who treat individuals with eczema, people with eczema or who care for children with eczema and researchers with methodological expertise. Approximately 10 people will be included in the panel and it is aimed that there will be roughly equal number of HCPs/researchers to patients/parents. The members of the panel are considered to be involved in the design of the study (i.e. co-authors not participants). This panel will aim to include international members due to the fact that this study is intended to be useful for HOME initiative decisions about outcome measures at an international level and will form the basis of subsequent stages of validation to be conducted in other countries. A face to face meeting will be conducted to make key decisions. However, given the international involvement in this panel, a variety of methods will be used to gain input from individuals including teleconferencing, videoconferencing, and email. The tasks of the expert panel include (i) reviewing the conceptual framework previously developed, (ii) input on the wording of items to be included in the measure, (iii) input on designing the response categories to be included in the measure, (iv) determining the recall period to be considered. The expert panel will be provided with information required to make these decisions. This includes information on what to consider when developing questionnaire items and information on the concept of "long-term control" generated from systematic reviews, qualitative studies and discussions and consensus votes at the HOME V meeting (6-10). Face to face focus groups with patients / parents will be conducted to confirm the conceptual framework (this work has received ethical approval: FMHS Ethics ref F1406201).

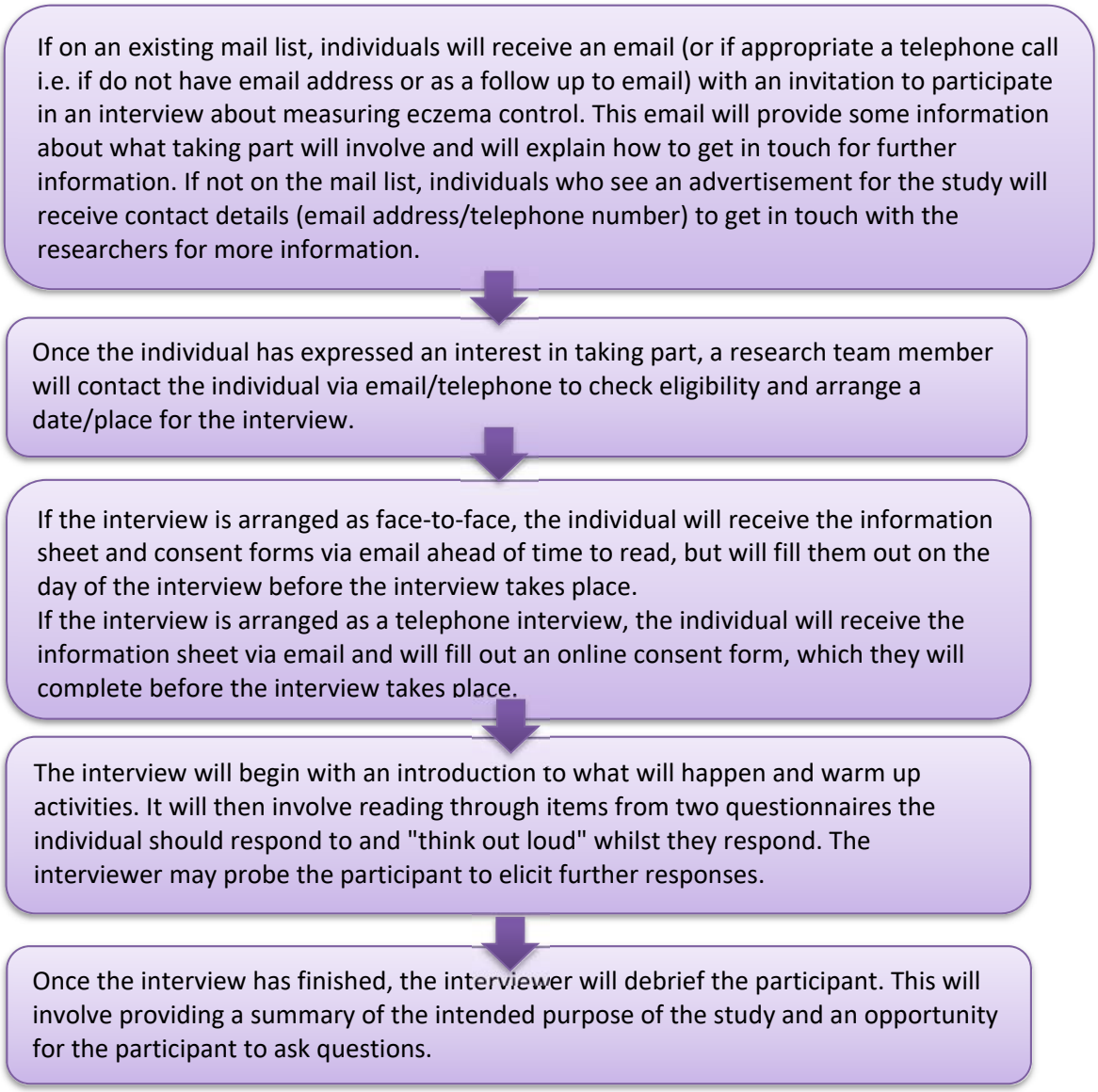
Output of stage 1: A preliminary list of items to be considered for inclusion in the index.

Stage 2: Item refinement

Cognitive debriefing interviews with approximately 5-10 adults with eczema and 5-10 parents of children with eczema (and their child may participate alongside their parent/guardian) will be conducted. The interviews will use a combination of "think aloud" methods and probing questions to gain insight into what individuals are thinking when they fill out two questionnaires, one about eczema control, which this study aims to develop into an index (the exact questions included in stage 2 will be developed in stage 1) and one about eczema symptoms (the Patient Oriented Eczema Measure, POEM), as this is an opportunity to reduce research waste by collecting much needed information about what users of the POEM are thinking when they use this scale. This is particularly relevant for the HOME initiative as POEM is a recommended core outcome measurement instrument. This approach can help ensure that the items included are comprehensible and relevant. A semi-structured interview guide will be followed. Interviews will be audio recorded and transcribed. Members of the research team have training and experience in conducting qualitative research. Figure 3 illustrates the process that each individual taking part in the study will experience. Further cognitive debriefing interviews may be conducted by our international collaborators at later stages to assess the comprehension and acceptability of the index in different cultures and/or languages.

Output of stage 2: A refined version of the items will be produced that will have been amended to produce items that are more comprehensive, relevant and acceptable to participants. Some items may be removed at this stage. We will also have collected information about the POEM, which will inform our understanding of how this scale is understood by users too.

Figure 3. Flowchart of procedure for participants in stage 2.
Note. The individual may withdraw from the study at any point of this flow chart.



Stage 3: Item reduction and index development

A UK based online survey will be conducted. We will be recruiting adults with eczema and parents of children with eczema (and their child may participate alongside their parent/guardian). Participants who are interested in the study will be provided with a link where they can find out some more information about the study before they follow a link to the survey if they are still interested in taking part. It will be made clear that they are providing consent if they complete any part of the survey. The participants will then fill out the rest of the survey which is summarised here:

- Demographics – age, sex, ethnicity, duration of eczema, who diagnosed the eczema, region of UK, where found the study
- UK Working Party atopic eczema diagnostic criteria questions (15). This is to allow us to assess how many respondents fulfil the diagnostic criteria. Sensitivity analyses can be conducted based on this information if this is deemed necessary.
- Single item global assessment of eczema today (6 point Likert scale from clear to very severe). This is to gain an overall sense of current eczema severity.
- Single item global assessment of eczema control over the same recall period as the items developed in stage 1. This is to be used as the dependent variable in a regression analysis to decide which combination of items predict eczema control.
- Patient-Oriented Eczema Measure (16). This is a well-validated measure of patient-reported eczema symptoms. This will be used to enable initial construct validation of the newly developed measure of eczema control.
- Questions developed for the measure of eczema control (max. 25).
- Beneath each question developed for the measure of eczema control, participants will be asked whether they (or their child) have experienced this item in the recall period of the item (response options yes/no) and whether the concept covered in this item is something that is important to them (response options 5 point Likert scale from not important to extremely important).

Output of stage 3: A list of items assessed for relevance and impact to inform the development of the model.

STUDY MANAGEMENT

The study will be managed from the Centre of Evidence Based Dermatology, University of Nottingham.

Laura Howells (PhD student) will be responsible for participant recruitment, data collection, data storage, and data analysis alongside other colleagues.

The Chief Investigator (KT) has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Study Duration:

April 2018 – June 2019

Participant Duration:

Stage 1: N/a

Stage 2: Participants will take part in one interview that will last 30 minutes – 1 hour. Recruitment will begin in May 2018 and interviews are anticipated to end by July 2018.

Stage 3: Participants will take part in an online survey that will take 10-15 minutes to complete. Recruitment aims to begin in July 2018 and the survey is anticipated to close by October 2018.

End of the Study

The end of the study will be the last online survey completed by the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Stage 1: N/a

Stage 2: We will recruit a convenience sample of participants using a variety of different means including mailing lists and social media. We will use purposive sampling principles to aim to recruit a sample that reflects diversity of ages, eczema severities, ethnicities and gender. Participants will be recruited from a mailing list (n=79) of individuals who expressed interest for a previous related study in 2016 and provided consent to be contacted about future studies and contact details (email address and/or telephone number). We may also use social media, the National Eczema Society, and Centre of Evidence Based Dermatology mailing lists of individuals interested in taking part in future studies. A member of the study team will make the initial approach and will inform the participant of all aspects pertaining to participation in the study.

Stage 3: Participants will be recruited via social media, existing databases of email addresses of people interested in taking part in research at the Centre of Evidence Based Dermatology (CEBD) that fit with current data protection regulations, patient charities e.g. National Eczema Society Website/Facebook page, community settings e.g. schools, community centres, grocery stores. We aim to recruit people from across the UK.

Due to the qualitative nature of this study, and the limited resources available, we are not able to include interpreters and translator services in this study. Participants will therefore be required to understand and speak English. This is necessary as we are developing an English language questionnaire in the UK. Further cognitive debriefing interviews may be conducted by our international collaborators at later stages to assess the comprehension and acceptability of the index in different cultures and/or languages.

It will be explained to potential participants that entry into the study is entirely voluntary. It will also be explained that they can withdraw at any time. The Participant Information Sheet (PIS) and consent procedures will clearly state that In the event of their withdrawal their data collected so far cannot be erased.

Eligibility criteria

Stage 1: n/a

Stage 2 and stage 3:
Inclusion criteria
Live in the UK
Be 16 years or older OR have parental consent to take part and have a parent present whilst they take part
Self- report that either they or their child has been diagnosed with eczema by a doctor
Exclusion criteria
Not able to speak or understand English

Note. There is no age limit on the children taking part, as they will always have a parent/guardian present, and it will be up to the parent/guardian's discretion as to whether they feel it is appropriate for the child to participate in the interview / survey. Level of involvement may vary between age groups.

ANALYSES AND SAMPLE SIZE

Stage 1: n/a

Stage 2: Content analysis will be used. An a priori coding framework will be developed and applied to the data in a top-down approach. The coding framework will cover cognitive and question based problems we are interested in (e.g. comprehension, ability to recall etc.) NVivo (qualitative data analysis software) may be used to help organise the data. The items will be adjusted if problems with the items are identified and these refined items will be included in stage 3. The interviews will take place in "rounds" so that based on the initial findings, the scale can be subsequently amended and tested in subsequent interviews.

Stage 3: STATA (statistical data analysis software) will be used to analyse the data. Missing data will be reported. We will handle missing data using the appropriate methods for each analysis as advised by the study statistician and depending on the amount of missing data. Missing data of POEM will be handled as scale's developers recommend (16).

1. **Item level analysis**

   - We will look at the percentage of missing data for each item. If some items appear to be particularly problematic (e.g. over 15% of participants who have filled out this page have skipped the question), we will consider why this may be and if this item should still be included in further analyses.
   - We will assess the distribution of the scores for each individual item to assess if all response options are being used by the participants. We will consider if it would be beneficial to adapt the response options used.

2. **Item reduction and combining the items**

   Impact analysis:
   Aim: to exclude items of low relevance
   - Calculate "frequency" (% of participants who have experienced the item (responses yes/no) and "importance" (mean of response values for each item scored 1-5).
   - "Impact" = frequency x importance.
   - Pre-define items of low relevance as being those that score < 2 (maximum score of 5) as similar scale development process used (17).

   Regression analysis:
   Aim: to identify items with best ability to predict eczema control.
   - Potential items for the ICE are the independent variables, a single-item patient global assessment over the same period will be the dependent variable.
   - A stepwise approach to model building will be used

   Expert panel
   - The expert panel will confirm final items for the ICE guided by clinical judgements, experience, the conceptual model, and on the basis of results from the two analyses. E.g. whether to remove a concept if it is deemed to be covered by a similar item, whether removing an item will fail to capture an essential component of the eczema control conceptual model.

3. **Testing of the combined items**
    - The scores for the final scale will be described and shown graphically. We will assess the distribution of the total score of the set of items chosen for inclusion. Consider if floor or ceiling effects occur (defined as >15% of participants achieving highest or lowest possible score). If this occurs this may be improved by including more items that will help distinguish individuals.
    - Asses the known groups validity of the set of items. Specific hypotheses will be developed a priori to data analysis, but will depend on the final set of items chosen for inclusion in the scale.

Sample size and justification:

Stage 1: N/a

Stage 2: It is common practice to use between 10-30 participants in cognitive interviews (18). However, the items will be refined following a small number of interviews and it is aimed that they will be re-tested in new participants until no major issues with the items are identified. Therefore, recruitment aims to meet a minimum of 5 parents (and children if appropriate) and 5 adults, but this sample size may increase as necessary.

Stage 3: N=500 in total (50% adults with eczema and 50% parents of children with eczema). This is based on the rule of thumb of a minimum of 10 participants for every predictor variable considered for inclusion in the multivariate analysis (Harrell, 2015). Given we have set a limit of a maximum of 25 candidate items, we aim to recruit 250 parents and 250 adults with eczema so that we can do sub-group analyses (25 x 10 = 250). If less items are considered as candidate items in the analysis, we may be able to adjust sample size calculation.

ETHICAL ASPECTS

Informed consent

Stage 1: N/a

Stage 2: We will provide interview participants with a paper information sheet to read and a paper consent form to fill out before the interview takes place and they will have enough time to read this information. They will have the opportunity to ask the interviewer any questions they may have before they fill out the consent form. If a child and parent are participating together, the parent will be asked to provide consent on behalf of their child (required) and the child may also provide assent (optional as will depend on the ability of the child to do so). If there is disagreement between the parent and the child of if the child should participate, the child will not be interviewed. If the interview is taking place face-to-face, we will provide interview participants with a paper information sheet to read and a paper consent form to fill out at the venue just before the interview takes place. If the interview is taking place remotely (e.g. by telephone, Skype etc.), we will provide the information via email and the consent form will be filled out as an online version.

Stage 3: We will send participants a link to the online survey to give online informed consent. They will read information about the study (including eligibility criteria, a summary of the research aims, the voluntary nature of taking part in the survey, what will happen to their data and information on withdrawing from the study). If a parent and child are filling out the survey together, the parent will be asked to provide the consent. They will be informed that by proceeding to the survey they are agreeing that they have read the information provided, fulfil the eligibility criteria and are willing to take part voluntarily in this study.

Anonymity and confidentiality

Stage 1: N/a

Stage 2: Data provided by the individuals will be made anonymous by the research team before any aspects of the data are shared. Confidentiality will not be breached, unless the researcher feels it is necessary for the safety of the participants or others. This will be made clear to the individual via the participant information sheet and consent forms.

Stage 3: Participants answers will be completely anonymous and we will use all reasonable endeavours to keep them confidential. Participants will be provided with this information via written information before they proceed to the survey.

Participants giving up voluntary time

Stage 1: N/a

Stage 2: Participants will be made aware that their participation is voluntary and that they do not need to take part in this study. This will be made clear in the information sheet and in interactions with the researcher arranging the interview. Participants will receive reimbursement of any reasonable expenses (e.g. travel, childcare) and will receive a £20 Amazon voucher to thank them for giving up their time.

Stage 3: Participants will be made aware that their participation is voluntary and that they do not need to take part in this study. No reimbursements are required for this part of the study

as participants are able to take part in the study at a time and place that suits them. The online nature of this survey aims to minimize the impact taking part in this study will have on the individual's time.

Topic raises concerns for participant

Stage 1: N/a

Stages 2 and 3: The researchers will not be able to provide medical advice. Therefore, if any medical concerns arise the researchers will suggest participants visit their GP or healthcare professional to discuss their concerns. Similarly, if the topic raises any feelings of distress, researchers will suggest patients contact relevant support services. This information will be provided verbally at the end of the interview and using written information at the end of the survey.

Safeguarding of children who may participate

Stage 1: N/a

Stage 2: If a child is to take part in the interview, they will be required to have a parent/guardian present. The parent/guardian will provide informed consent on behalf of the child. The parent/guardian will be responsible for their child's safety. Laura Howells is anticipated to conduct these interviews and has an up to date enhanced CRB check.

Stage 3: If a child is to take part in the survey, they will be required to have a parent/guardian present. The parent/guardian will be asked to provide informed consent on behalf of the child. Although it is possible that a child will participate without the informed consent of their parent/guardian, this is beyond the control of the researchers and the same is true for any online research survey of this nature as the researcher relies on the participants to only take part if they meet the eligibility criteria clearly stated. It is within a parent/guardian's responsibility to monitor their child and ensure their child is safe when on-line.

Participant withdrawal from the study

Stage 1: N/a

Stages 2 and 3: Participants may withdraw from the study at any time. The participants will be made aware that this will not have any negative impact on them. Participants will be made aware (via the information sheet and consent form) that should they withdraw from the study, the data collected may still be used.

ETHICS COMMITTEE APPROVALS

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval from the University of Nottingham Faculty of Medicine and Health Sciences Ethics Committee. Substantial protocol amendments will be sent to the ethics committee before implemented. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the committee will be informed.

DATA PROTECTION

Interviews (stage 2): All data will be audio-recorded using a voice recording device and transcribed. All audio recordings of the interviews will be transcribed by a professional transcription service. Audio recordings and transcripts will be stored on a restricted access database at the university. This research data may be looked at by the team of researchers working on this project. Personal data will be stored separately from the results. All research data and records will be stored for a minimum of 7 years after publication. Anonymized data may be shared with other researchers and regulatory authorities including those working outside the University.

Survey (stage 3): All data will be collected and stored on Online Surveys (formerly BOS). The data will be downloaded and stored on a secure research drive at the University of Nottingham. All personal information will be password protected. Personal data will be stored separately from the results. All research data and records will be stored for a minimum of 7 years after publication. Anonymized data may be shared with other researchers and regulatory authorities including those working outside the University.

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the General Data Protection Regulations (GDPR), May 2018. Access to the information will be limited to the study staff and investigators. Computer held data including the study database will be held securely and password protected. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

RECORD RETENTION AND ARCHIVING

In accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by University of Nottingham representatives.

PUBLICATION AND DISSEMINATION POLICY

It is intended that this work will be submitted as a journal paper for a relevant academic journal. The work is also intended to inform future work and decisions made by the HOME membership regarding COS for eczema clinical trials and to be presented at the HOME VII meeting in Japan, 2019. The scale developed will be distributed to patients, the public and healthcare professionals via appropriate channels. Participants will not be identified in any publications.

USER AND PUBLIC INVOLVEMENT

As part of our expert panel individuals who have eczema themselves or care for a child with eczema are included as co-designers of this research. They have been involved in assessing the appropriateness and comprehensibility of patient facing information such as the patient information sheets, interview guide, questionnaire format and content and summary of findings for participants.

FUNDING SOURCE

This study is funded as part of a PhD studentship by the British Skin Foundation.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator and lead PhD supervisor: _____

Signature: _____

Date: _____

PhD student: _____

Signature: _____

Date: _____

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