Study Protocol

Exploring the optimum number of repeated measures of disease severity in eczema clinical trials.

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Short title: Repeated Measures of POEM in clinical trials

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SYNOPSIS

Title	Exploring the optimum number of repeated measures of disease severity in eczema clinical trials.
Short Title	Repeated measures of POEM in clinical trials
Chief Investigator	Prof. Kim Thomas
Aims and Objectives	AIM To inform HOME initiative consensus discussions about the minimum requirements for repeated measurements of core outcome measurement instruments. OBJECTIVES 1. To examine the variability of POEM scores over time and to assess the marginal benefit of additional POEM measures on the statistical power of a trial. 2. To demonstrate how the number of measures in repeated measures analysis of actual eczema clinical trials influences the outcome.
Study Configuration	A descriptive, exploratory study using secondary analysis eczema severity scores (POEM) from completed eczema trial datasets.
Setting	Participants were recruited for different trials via primary care, secondary care and community settings.
Eligibility criteria	**Inclusion criteria** • Randomised controlled trial of eczema treatment including participants of any age with eczema • Eczema will be diagnosed by a doctor or suitably qualified health care professional, or using recognised diagnostic criteria e.g UK Working Party diagnostic criteria (1). **Exclusion criteria** • Study includes fewer than 3 time points of eczema severity measurements.
Duration of study	August 2018 – June 2019
Methods of analysis	Correlation analyses and multilevel modelling (repeated measures analysis).

ABBREVIATIONS

BATHE	Bath additives for the treatment of childhood eczema (trial)
CI	Chief Investigator overall
CLOTHES	Clothing for the relief of eczema symptoms trial
COMET	Choice of Moisturiser for Eczema Treatment (trial)
CREAM	Children with eczema antibiotic management study (trial)
HOME	Harmonising Outcome Measures in Eczema initiative
PO-SCORAD	Patient-Oriented Scoring of Atopic Dermatitis
POEM	Patient Oriented Eczema Measure
RCTs	Randomised Controlled Trials
UoN	University of Nottingham

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STUDY BACKGROUND INFORMATION AND RATIONALE

Eczema (also known as atopic dermatitis or atopic eczema) is a chronic, inflammatory skin condition. The Patient Oriented Eczema Measure (POEM) is a measure of patient/parent-reported eczema symptoms recommended for use in eczema randomised controlled trials (RCTs) by the Harmonising Outcome Measures in Eczema (HOME) initiative (2). The measure asks how frequently a symptom has occurred over the last week on a 5 point Likert scale from "No days" to "Every day" and there are versions available for self-completion and parent completion (3). The symptoms measured in the POEM are itch, sleep, bleeding, weeping/oozing, cracking, flaking, and dryness (3). Eczema is a chronic relapsing disease, and measuring long-term control has been agreed as a core domain to be measured in all eczema clinical trials by the HOME initiative (4). Barbarot *et al.* found that the most common strategy for measuring long-term control in published RCTs was to use repeated measurement of outcomes such as clinical signs, quality of life and itch (5). Repeated measurement of POEM has been voted at a HOME consensus meeting as one method that should be used for measuring long term control of eczema (6).

Researchers conducting clinical studies may choose to measure the POEM at baseline and a pre-specified endpoint, or they may choose to measure the POEM more frequently throughout the study. There are clinical, practical and statistical implications for using an inappropriate number of repeated measures. There are some clinical trials where the investigators may choose to measure the outcomes at particular time points as they are interest in the changing treatment effects over time. This is not something where there can be general recommendations made as the timing and number of repeated measures should be made by the individual researchers depending on their specific research question and clinical expectations. However, in most clinical trials it is the average score over time that is the outcome of interest, but there are still benefits of repeated measures in this situation. If a measure of POEM was taken only once, they may be having an unusually high or low score on that day, whereas if multiple measures of POEM were taken throughout the time period, this is likely to be a better reflection of how their eczema symptoms have been overall during the study time period. Using repeated measurement of the outcome reduces intra-patient variability. This increases the study power and means that a smaller sample size can be used, thus improving the efficiency of trials (Vickers, 2003).

Whilst there are benefits of using repeated measures techniques, such as efficiency of trial design, there are limitations too. Firstly, the analysis can be more complex and sometimes difficult to interpret. The systematic review of long-term control of eczema RCTs found that even though most RCTs collected data for outcome measures at multiple time points, the analysis methods used often did not make best use of the data at all time points (5). If data is collected but not appropriately used in analysis, this means the participant burden and resources used to collect the data will cause research waste. Another problem with repeated measures is that the act of monitoring symptoms regularly by filling out the POEM may act as an intervention and influence outcomes. The feasibility of collecting outcomes repeatedly in RCTs also needs to be considered. Therefore, it is clear that the benefits to be gained from measuring frequently needs to be weighed against the costs and that there is a balance to be struck when deciding how frequently to measure the POEM.

We have chosen to address the issue of the number of repeated measures of disease severity required in eczema trials using POEM data as it is a patient-reported outcome that can be measured weekly and we have data available in numerous clinical trial datasets. Collecting the POEM weekly is the maximum amount of data that can be collected as the questionnaire asks about eczema symptoms over the last week. However, it remains unclear if weekly POEM scores are necessary to collect. This descriptive, exploratory study aims to provide a better understanding of the variability of POEM scores over time and the relative gains of repeated measurement of the POEM.

STUDY OBJECTIVES AND PURPOSE

AIM

To inform HOME initiative consensus discussions about the minimum requirements for repeated measurements of core outcome measurement instruments.

OBJECTIVES

1. To examine the variability of POEM scores over time and to assess the marginal benefit of additional POEM measures on the statistical power of a trial.
2. To demonstrate how the number of measures in repeated measures analysis of actual eczema clinical trials influences the outcome.

STUDY DESIGN

STUDY CONFIGURATION

This study will use the datasets available from RCTs including people with eczema. The datasets we have available to date are NIHR funded studies conducted in the UK and includes children with eczema. Table 1 provides an overview of these RCTs and the characteristics of the sample population for each.

Note. If additional datasets become available to us that fit the eligibility criteria required to include the dataset then these may be added into the study. Each trial included in the study is treated as an individual dataset.

Secondary analysis of these existing dataset will be conducted. We have focused on assessing disease severity using POEM as this is the recommended core outcome instrument for assessing patient-reported eczema symptoms in the HOME initiative and we have datasets available with weekly data collected.

Table 1. RCTs to be included in the study

Trial	Trial Registration No	N	Ages (based on eligibility criteria)	Severity (based on eligibility criteria)	Recruitment setting
Clothes for the relief of Eczema (CLOTHES) trial	ISRCTN: 77261365	300	children aged 1-15 years	Moderate – severe eczema	Secondary care settings and from the community in the UK
Softened Water Eczema Trial (SWET)	ISRCTN: 71423189	336	children aged 6 months to 16 years	Moderate – severe eczema	Secondary and primary care in the UK

Bath additives for the treatment of childhood eczema (BATHE) trial	ISRCTN: 84102309	481	children aged 1-11 years	Only excluding inactive or very mild eczema	General practices in England and Wales
Choice of Moisturiser for Eczema Treatment (COMET) trial	ISRCTN: 21828118	197	children aged 1 month to 4 years	All severities of eczema	Self-referral and in consultation at general practices in the UK
ChildRen with Eczema Antibiotic Management (CREAM) trial	ISRCTN: 96705420	113	children aged 3 months to 7 years	Clinically infected eczema	Secondary and primary care in the UK.

STUDY MANAGEMENT

This study is being conducted as part of the PhD of Laura Howells.

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

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

The data custodian will be the Chief Investigator.

DURATION OF THE STUDY

Study Duration: This study is expected to commence October 2018 and be complete by June 2019.

SELECTION AND WITHDRAWAL OF RCTS AND PARTICIPANTS

Eligibility criteria

Inclusion criteria

- Randomised controlled trial of eczema treatment including participants of any age with eczema

- Eczema will be diagnosed by a doctor or suitably qualified health care professional, or using recognised diagnostic criteria e.g UK Working Party diagnostic criteria (1).

Exclusion criteria

- Study includes fewer than 3 time points of POEM measurement, including baseline measures.

- **Criteria for terminating the study**

There are no foreseen reasons why the study may need to be terminated as all datasets are from completed RCTs and data collection is complete.

ANALYSES AND INTERPRETATION

Objective 1: To examine correlation structures between POEM scores over time and assess the marginal benefit of additional POEM measures on the statistical power of a trial.

- Produce correlation matrices between POEM scores across the time points for each RCT.
- Examine the correlation matrices to assess if the correlation structures follow any predictable patterns.
- Compare correlation structures across the datasets.
- Assuming a constant effect over the trial period, apply mathematical equations presented in Vickers (2003) to allow us to assess the marginal benefit of additional repeated measurements in terms of statistical power and efficiency in trial design.
- Looking at these results across all the trials, provide an interpretation of the number of repeated measurements that appear to be optimal for each trial.

Objective 2: To explore how the number of measures in repeated measures analysis of eczema clinical trials influences the inferences.

- Using the interpretation of the number of repeated measures that appear to be optimal, based on the analyses in objective 1, explore the impact of varying the number of repeated measures in trial analysis to allow a real-world demonstration of the effects. A repeated measures design will be used to assess for differences in mean POEM scores between treatment groups within the BATHE trial, the CLOTHES trial and potentially other trials that are available. Each trial will be analysed separately. We are focusing on these two trials as they were designed to compare treatment efficacy and collected weekly POEM data.
- For each analysis, the relevant assumptions will be tested.
- If covariates were specified in the original trial analysis, they will be included.
- Results will be presented narratively and graphically.

Sample size and justification

As this study is using secondary analysis, the sample size is pre-determined by the sample size of the datasets available to us. However, the analyses are primarily intended to be descriptive and exploratory, so the sample size can be considered sufficient.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

Since this research is secondary analysis for methodological purposes, the study falls under the remit of the ethics approval granted for each of the RCTs. The conduct of this study without further research ethics committee review has been approved by the University of Nottingham, Faculty of Medicine & Health Sciences Research Ethics Committee (258-1712).

INFORMED CONSENT AND PARTICIPANT INFORMATION

Anonymity will be maintained as the datasets we are given will be in an anonymised format. Informed consent was a requirement of each of the individual RCTs included in this study. Since this study is methodological research that will be based on secondary analysis, the informed consent process used for the original RCTs will suffice for this study.

PUBLICATION AND DISSEMINATION POLICY

We intend to submit the research as a journal paper for a relevant academic journal. We also intend to share this work at methodology and dermatology conferences. On the Centre of Evidence Based Dermatology website we will produce a lay version of the results. The results of this study will also inform discussions at the HOME VII consensus meeting.

USER AND PUBLIC INVOLVEMENT

Qualitative research including focus groups with people who have eczema or care for a child with eczema helped inform our understanding of what level of measurement individuals would find feasible within their daily life and the barriers they faced for frequent measurement. Patients, parents and patient representatives will be present at the HOME meetings and will be involved in the consensus decisions based on this evidence.

STUDY FUNDING

This study is funded by the British Skin Foundation as part of the PhD of Laura Howells.

SIGNATURE PAGES

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Date: 26/9/18.

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