Study Protocol: Exploring how patient characteristics influence the minimum important change (MIC) of the Patient Oriented Eczema Measure (POEM)

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STUDY PERSONNEL AND CONTACT DETAILS

Chief investigator:
Prof. Kim Thomas
Professor and Deputy Director (CI for CLOTHES trial)
Centre of Evidence Based Dermatology
University of Nottingham
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR
Phone: 0115 8468630
Email: kim.thomas@nottingham.ac.uk

Co-investigators:
Miss Laura Howells
PhD student
Centre of Evidence Based Dermatology
University of Nottingham
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Dr Joanne Chalmers
Senior Research Fellow
Centre of Evidence Based Dermatology
University of Nottingham
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Dr Sonia Ratib
Assistant Professor
Centre of Evidence Based Dermatology
University of Nottingham
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Lucy Bradshaw
Research Fellow (statistician for CLOTHES trial)
Nottingham Clinical Trials Unit
Room D2151 South Block
Queen's Medical Centre
Nottingham
NG7 2UH
UK

Dr Miriam Santer
Associate Professor in Primary Care Research (CI for BATHE trial)

Medicine
University of Southampton

Dr Beth Stuart
Senior Research Fellow (statistician for BATHE trial)
Medicine
University of Southampton

Dr Matthew Ridd
Consultant Senior Lecturer (CI for COMET trial)
School of Social and Community Medicine
University of Bristol

Miss Daisy Gaunt
Research Associate (statistician for COMET trial)
School of Social and Community Medicine
University of Bristol

Dr Nick Francis
Reader (CI for CREAM trial)
Cochrane Institute of Primary Care & Public Health
Cardiff University School of Medicine
Neuadd Meirionnydd
Heath Park
Cardiff CF14 4YS

Dr Chao Huang
Statistician (Statistician for the CREAM trial)
Cardiff University School of Medicine
Neuadd Meirionnydd
Heath Park
Cardiff CF14 4YS

Prof. Phyllis Spuls
Professor of Dermatology (CI for the randomized trial of methotrexate versus azathioprine)
Department of Dermatology
University of Amsterdam

Study Coordinating Centre:
Centre of Evidence Based Dermatology
University of Nottingham
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

SYNOPSIS

Title	Exploring how patient characteristics influence the minimum important change (MIC) of the Patient Oriented Eczema Measure (POEM)
Short Title	MIC of POEM: the effect of patient characteristics
Chief Investigator	Prof. Kim Thomas
Objectives	To assess if MIC estimates for the POEM differ by age, eczema severity, sex and ethnicity.
Study Configuration	Secondary analysis of six completed randomised controlled trials (RCT) in children and adults with eczema.
Setting	Existing datasets for RCTs with eczema patients as the sample population will be used. Recruitment varied in trials: community settings, primary care, secondary care
Eligibility criteria	Randomised controlled trials with eczema patients of any age or severity as the sample population. Eczema will be diagnosed by a doctor, ideally using a diagnostic criteria such as the UK Working Party diagnostic criteria. Must have POEM scores collected at baseline.
Duration of study	February 2017 – February 2018
Methods of analysis	Combine data from six RCTs for eczema treatment and divide into sub-groups based on age, eczema severity, sex and ethnicity. Distribution based methods for calculating the MIC will be carried out in each sub-group. These MIC estimates will be descriptively compared.

ABBREVIATIONS

BATHE	Bath additives for the treatment of childhood eczema (trial)
CI	Chief Investigator overall
CLOTHES	Clothes for the relief of Eczema (trial)
COMET	Choice of Moisturiser for Eczema Treatment (trial)
COS	Core Outcome Set
COSMIN	COnsensus-based Standards for the selection of health Measurement Instruments
CREAM	ChildRen with Eczema Antibiotic Management (trial)
HOME	Harmonising Outcome Measures in Eczema initiative
MAcAD	A randomized trial of methotrexate versus azathioprine
MCID	Minimum clinically important difference
MIC	Minimally important change
MID	Minimally important difference
POEM	Patient Oriented Eczema Measure
SWET	Softened Water Eczema Trial
UoN	University of Nottingham

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STUDY BACKGROUND INFORMATION AND RATIONALE

The Harmonising Outcome Measures in Eczema (HOME) initiative aims to develop a core outcome set (COS) for eczema clinical trials (1). HOME has agreed by consensus that clinician-reported signs, patient-reported symptoms, quality of life and long-term control are the core outcome domains to be included in all eczema clinical trials (1). Regarding the core outcome domain of patient–reported symptoms, consensus was reached that the Patient Oriented Eczema Measure (POEM) should be the recommended instrument to use. Since the POEM is recommended for use in eczema clinical trials, it is important that users of the scale understand how it can be used in conducting and interpreting clinical trials. The **CO**nsensus-based **S**tandards for the selection of health **M**easurement **In**struments (COSMIN) initiative is an international multidisciplinary team of researchers with the aim to improve the selection of health measurement instruments. The minimally important change (MIC), as defined by COSMIN, is "the smallest change in score in the construct to be measured which patients perceive as important" (2).

Due to the rapid pace of development in the literature on the MIC, there is a variety of terminology used to explain this concept, the most common alternatives used being the minimal clinically important difference (MCID) and minimally important difference (MID). It has been proposed that MIC be used for longitudinal within-person changes in scores and MID used for cross-sectional between-person differences (3). Therefore, this protocol will refer to all methods used in this study as MIC estimates from this point forward.

The POEM has previously been cited as having an MIC of 3.4 points in an MIC study by Schram and colleagues (4). This MIC study used datasets from two trials: the MAcAD trial comparing methotrexate with azathioprine in adults with severe eczema and the PROVE trial comparing prednisolone with cyclosporine in adult patients with severe eczema (4). Subsequently, an MIC study by Gaunt and colleagues used data from the COMET trial , a feasibility trial of comparing Choice of Moisturiser in Eczema Treatment (COMET) in children aged 1 month to under 5 years from general practice settings (5). They used a combination of methods to calculate the MIC and found the results broadly concurred with an MIC of 3 points (5).

One issue within the literature is that MIC estimates are often reported as fixed values, when in fact they have been shown to be a variable concept that can be influenced by different factors (6). A number of studies have found that the MIC result found is dependent on baseline scores on the measurement instrument of interest. Regression towards the mean is a statistical phenomenon that if a variable is extreme on first measurement, it will be closer to the average on second measurement and vice versa (7). However, the variations in MIC estimates may also be a clinical phenomenon that a level of change will have differences in meaning for patients with different scores on the scale at baseline (8).

There may also be other patient characteristics that influence the MIC. Looking at pain and physical functioning subscales of the Western Ontario and McMaster University Osteoarthrtis Index questionnaire in five studies in patients with hip or knee problems, it was found that there was large variation in MIC values by both method used to calculate the MIC and patient characteristics (9). The authors provided three possible explanations for these variations. This variation may be a true difference of variation of MIC depending on population characteristics such as age, disease group, severity, treatment and period of follow up (9). However, other explanations were that the estimates are unreliable due to wide confidence intervals or that outcomes are method dependent (9). The literature points to the need for MIC studies to examine the role of both MIC methods and patient characteristics on variation in MIC estimates (9, 10). A complementary study to this study has examined the role of methods on MIC variation (Follow this link to access the protocol: www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/protocol-mic-clothes-laurahowells-final.pdf).

Despite previous studies reporting MIC estimates for the POEM use diverse populations that varied in age and severity, the variation in MIC by population requires further, more robust examination.

STUDY PURPOSE

This study will attempt to determine if there are important patient characteristics that may play a role in variation in MIC values whilst keeping the method consistent. Age, baseline severity, sex and ethnicity are all key characteristics that may potentially influence the MIC of the POEM. If there are variations, it may be useful for those deciding what MIC value to use to consider these characteristics in their population of interest.

STUDY DESIGN

STUDY CONFIGURATION

This study will utilise the datasets available from a variety of completed randomised controlled trials (RCTs) in eczema patients. Table 1 provides an overview of these RCTs and the characteristics of the sample population for each RCT. Table 2 provides information on how and when the POEM was collected in each RCT.

Note. If additional datasets become available to us that fit the eligibility criteria (outlined in this document) then these may be added into the study.

Secondary analysis of these existing dataset will be conducted.

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 practitioner practices in England and Wales
Choice of Moisturiser for Eczema Treatment	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

(COMET) trial					
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.
A randomized trial of methotrexate versus azathioprine (MAcAD)	Dutch Trial Register: NTR1916	42	adults aged 18-75 years	Severe eczema	inpatient and outpatient clinics of the Academic Medical Center of Amsterdam (referral centre for severe atopic eczema) or were referred by regional dermatologists

Table 2. POEM data collection by trial

	Baseline	weekly	2 weeks	4 weeks	8 weeks (2 months)	12 weeks (3 months)	16 weeks (4 months)	20 weeks	24 weeks	26 weeks (6 months)	28 weeks	32 weeks	34 weeks (8 months)	1 year
CLOTHES	P	P (for 6 months)	P	P	P	P	P	P	P	P			P	
SWET	V			V		V	V							
BATHE	V	P (For 15 weeks)	P	P	P	P	P	P	P		P	P		P
COMET	V	P (For 3 months)	P	P	P	P								
CREAM	V		V	V		P								
MAcAD	V		V	V	V	V			V				V at 36 weeks	V

V = face to face visit, P = patient completes by self

STUDY MANAGEMENT

The study will be managed from the central coordinating centre at the Centre of Evidence Based Dermatology, University of Nottingham (UoN)

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

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 February 2016 and be complete by February 2017.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Eligibility criteria

Inclusion criteria

- Study including eczema patients of any age
- Eczema will be diagnosed by a doctor, ideally using a diagnostic criteria such as the UK Working Party diagnostic criteria (11)
- Measure of POEM at baseline

Exclusion criteria

n/a

Participant Withdrawal

Since we will only be using data pre-collected for the original RCT, there will be no participant withdrawal necessary.

Informed consent

Parents/legal guardians provided written informed consent prior to the original trials.

Criteria for terminating the study

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

ANALYSES

Preparation of Datasets

The datasets for each trial outlined in Table 1 will be combined into one STATA data file. The datasets will be categorised into sub-groups according to the characteristics of age, sex, ethnicity and baseline POEM severity. Table 2 proposes what sub-groups we will examine. Further sub-groups may be analysed if there is deemed an adequate sample size.

Table 2. Proposed sub-groups to examine:

Characteristic	Sub-groups		
Age (adult or child)	Adult	Child	
Age *(*children categorised)	0-2 years	3-7 years	8-17 years
Sex	Male	Female	
Ethnicity	White	Non-white	

Eczema severity* (POEM score at baseline)	Clear to mild *(score of 0-7)*	Moderate (score of 8-16)	Severe to very severe *(score of 17-28)*

*Based on established bandings of the POEM (12)

Methods

We will use a standardised method for all MIC estimates in this study.

The preferred method for MIC estimates are anchor-based methods (7, 10, 13). However, this is not feasible in this study that combines multiple RCTs which do not all contain a comparable anchor.

An effect size is measured by the difference between the score at baseline and follow-up divided by the standard deviation of the baseline score. It has been proposed that there is remarkable universality of an effect size of 0.5 corresponding with a difference between the score at baseline and follow-up that is similar to the MIC:

$0.5 = (MIC/SD_{(baseline)})$

Therefore $0.5 \times SD_{(baseline)}$ has been suggested as an estimate of the MIC (14, 15).

Using the above methods to calculate the MIC, we will:

1) Calculate the MIC estimate of the POEM for each individual dataset

2) Combine the individual patient data for all trials and calculate the MIC

3) Calculate the mean, standard deviation and the MIC for the POEM scores for each sub-group based on the characteristics in Table 2.

The results will be presented descriptively in a coherent table and a graphical format to allow researchers and clinicians to examine the variation according to each patient characteristic and make informed decisions about what MIC estimate is likely to be most applicable to their population of interest in future research and practice. Where appropriate, we will also use Levene's equality of variance tests to examine the statistical differences in variances between sub-groups. This will inform whether the MIC estimates differ statistically significantly, or not, between sub-groups.

Sensitivity Analysis

Since the COMET trial includes participants who do not meet the UK Working Party's Diagnostic Criteria we will conduct sensitivity analyses where we exclude these participants to assess how this alters the results.

Sample size and justification

The sample size is pre-determined by the datasets available to us. As far as we are aware there are no guidelines for sample size required for MIC studies (9). COSMIN recommend a minimum of 100 participants for other validation studies such as construct and criterion validity (6).

ETHICAL AND REGULATORY ASPECTS

The study team will all sign a collaboration agreement before the study commences. As is outlined in this document, participant anonymity will be maintained as the datasets will be shared with the study team in an anonymised format.

ETHICS COMMITTEE AND REGULATORY APPROVALS

This study does not need to seek ethical approval. Since this research is secondary analysis for methodological purposes, the study falls under the remit of the ethics approval granted for the CLOTHES trial.

INFORMED CONSENT AND PARTICIPANT INFORMATION

Patient informed consent was obtained for each RCT when the team recruited into the RCT. As this is a collaborative project using existing datasets in RCTs conducted by members of our study team no further consent is required.

RECORDS

DATA PROTECTION

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 Data Protection Act, 1998. Access to the information will be limited to the study staff and investigators. Computer held data including the study database will be held in a secure file.

Any medical information provided will be kept confidential.

QUALITY ASSURANCE & AUDIT

RECORD RETENTION AND ARCHIVING

In accordance with the UoN 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.

The study documents held by the Chief Investigator shall be finally archived at secure archive facilities at the UoN or off-site as appropriate.

STATEMENT OF CONFIDENTIALITY

Data generated as a result of this study will be available for inspection on request by the UoN.

PUBLICATION AND DISSEMINATION POLICY

We intend to submit the research as a journal paper for a relevant academic journal. We intend to present the results at the HOME V meeting in June 2017. 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 and will use this study alongside other MIC studies for the POEM to form part of the guidance on using the POEM.

USER AND PUBLIC INVOLVEMENT

N/a

STUDY FINANCES

Funding source

This study is funded by the British Skin Foundation.

Participant stipends and payments

N/a

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator and principal supervisor of PhD: Prof. Kim Thomas

Signature: _____

Date: _____

PhD student: Miss Laura Howells

Signature: _____

Date: _____

Lead Statistician: Dr Sonia Ratib

Signature: _____

Date: _____

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