



**Study Protocol: Exploring different methods to inform Minimally Important Change (MIC) estimates of the Patient Oriented Eczema Measure (POEM) using data from the CLOTHES trial**

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**Short title:** MIC of POEM using CLOTHES trial data  
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## STUDY PERSONNEL AND CONTACT DETAILS

**Chief investigator:** Prof. Kim Thomas  
Professor and Deputy Director  
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

Miss Lucy Bradshaw  
Research Fellow  
Nottingham Clinical Trials Unit  
Room D2151 South Block  
Queen's Medical Centre  
Nottingham  
NG7 2UH  
UK

**Study Coordinating Centre:**

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

## SYNOPSIS

Title	Exploring different methods to inform Minimally Important Change (MIC) estimates of the Patient Oriented Eczema Measure (POEM) using data from the CLOTHES trial
Short Title	MIC of POEM using CLOTHES trial data
Chief Investigator	Prof. Kim Thomas
Objectives	<ol style="list-style-type: none"> <li>1. To assess how the methods used (including both anchor- and distribution-based methods) influence the MIC estimates of the POEM.</li> <li>2. To assess whether using a patient or investigator assessment as an anchor measure produces a different MIC for the POEM (which is a patient-reported outcome measure).</li> </ol>
Study Configuration	Secondary analysis of completed CLOTHES trial datasets to calculate the MIC of the POEM scale, a patient reported outcome measure with a scale ranging from 0 to 28. Higher scores represent more severe disease.
Setting	CLOTHES trial Potential participants were identified through secondary care, primary care and through local advertising (self-referral). Recruitment took place in five recruiting centres in the United Kingdom: Queen's Medical Centre, Nottingham University Hospitals NHS Trust; Chase Farm Hospital, Royal Free London NHS Foundation Trust; Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust; Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust and St Mary's Hospital, Isle of Wight NHS Trust.
Eligibility criteria	All CLOTHES trial participants who had completed the necessary measures were included in this study. The measures in the CLOTHES trial were completed by children or parents/guardians of children aged 1-15 years who had moderate to severe eczema.
Duration of study	January 2016 – January 2017
Methods of analysis	Anchor based and distribution based methods for calculating the MIC. The change in scores on a patient global assessment of severity and an investigators global assessment of severity will be used for anchor methods. The MIC estimates provided from these methods will be descriptively compared.

## ABBREVIATIONS

CI	Chief Investigator overall
COS	Core Outcome Set
CLOTHES	Clothing for the relief of eczema symptoms trial
ES	Effect size
HOME	Harmonising Outcome Measures in Eczema initiative
IGA	Investigator Global Assessment
MCID	Minimal clinically important difference
MIC	Minimally important change
MID	Minimally important difference
NHS	National Health Service
PGA	Patient Global Assessment
R&D	Research and Development department
UoN	University of Nottingham
SD	Standard deviation
SDC	Smallest detectable change
SEM	Standard error of measurement

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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 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 this field, 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 previously acknowledged that the literature often interchanges the terms, but 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). A taxonomy describing the types of discrimination (change or differences) that could be encountered in studies of responsiveness devised by Beaton and colleagues in 2002 highlights that methods can differ in whether then are looking at changes within individuals, differences between individuals or looking at relative change (that controls for the difference between two groups when looking at change) (4). As each provides a unique type of information, it is important to consider which type is being used. Since methods that aim to look *only* at differences between individuals involve asking patients to rate whether they are better or worse than others in a group, this information is not available using the CLOTHES trial data (4). Therefore, the methods of this study will look at within individual changes only and relative change, so for ease will refer to all methods used in this study as MIC estimates from this point forward.

When researchers are planning a study, they calculate the sample size required on the basis of probability (powered) to detect a true clinically important change or difference in the chosen primary outcome. When interpreting the results of a trial, it is important to be able to ascertain if the improvement gained from an intervention is clinically meaningful. To calculate the sample size, depending on the study design, either an estimate of MIC or MID is therefore required (5). An MIC estimate can aid interpretation of the results of a trial (5). Beyond use in research, MIC estimates can be useful for clinical interpretability. For example, on an individual patient level a clinician can attach meaning to a patient’s change in the POEM score (5). Furthermore, an MIC score may be used to enable decisions regarding whether a treatment is worth continuing in a benefit-cost analysis (5).

One of the major challenges facing researchers who aim to determine a MIC for a patient-reported outcome measure, is that that the MIC is not a fixed attribute, but is a variable concept that can be influenced by a number of factors including methods used, demographics and baseline severity (5). Whilst a multitude of MIC estimates can detract from the usefulness of having a universal MIC threshold that can be used, it is important to acknowledge and explore how the MIC of the POEM can vary to increase confidence that MIC estimates used in research and clinical practice are appropriate (6).

The POEM has previously been cited as having an MIC of 3.4 points in an MIC study by Schram and colleagues (7). 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 (7). This study used the absolute mean change scores of patients with minimal change on an anchor determine the MIC, and assessed the cut-off point on Receiving Operator Characteristic (ROC) curves at which correct classification was optimised as a sensitivity analysis. 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 in children aged 1 month to under 5 years from general practice settings (8). They used a combination of anchor-based and distribution-based methods to calculate the MIC and found the results broadly concurred with an MIC of 3 points (8).

The Clothing for the relief of eczema symptoms (CLOTHES) trial includes children aged 1-15 years diagnosed with moderate-severe eczema, and therefore represents a sample from a different population to those in previous studies used for MIC calculations of the POEM (9). It has been recommended to cross-validate MIC estimates in multiple samples (10).

#### Variation in direction of change

It has been suggested that minimally important improvement and minimally important deterioration should be assessed separately as they might not be the same (11). Since minimally important improvement is the direction of change we are most interested in clinically, this study will focus on improvement when estimating the MIC. Therefore, the results should be interpreted with caution if users are interested in deterioration.

#### Variation in MIC methods

There are multiple approaches that can be used to calculate the MIC, and each may lead to a different result. Methods are often described as two broad categories: anchor-based methods and distribution-based methods (6). Anchor-based methods use an external criterion, that ideally is a well interpretable measurement instrument, and a certain amount of change on this external criterion (i.e. change in a subgroup on the anchor measure) corresponds to a MIC on the measuring instrument of interest (11). Distribution-based approaches are based on the distributional characteristics of the sample (11). Both approaches have advantages and disadvantages; anchor-based approaches do not take the distribution of the sample into account, whilst distribution-based approaches have been criticised as not qualifying as MIC calculation as the importance of an observed change from the perspective of the patient (or it may be the carer in this instance) is not taken into consideration (11).

Current recommendations are that researchers use a range of methods using both anchor-based and distribution-based approaches and triangulate the results (4, 10, 12). Concurrent comparisons of methods to calculate the MIC for the POEM have begun in previous studies and to date three anchor-based approaches and two distribution-based approaches have been used, as far as we are aware. This study aims to expand on this current knowledge by repeating the methods used in previous samples as well as exploring the MIC using additional methods that have not as of yet been used to calculate the MIC for the POEM (See Table 1). We will use the visual method of integrating anchor-based and a distribution-based approach, which incorporates assessment of the distribution into an anchor-based method (ROC curve analysis). We will also use a new method that which uses a predictive modelling approach that has been demonstrated to be more precise than ROC curve analysis and takes into account baseline severity (13).

**Table 1: Methods used in MIC studies for the POEM**

Method	This study	Gaunt et al. (2016)	Schram et al. (2012)
Within patient mean change	x	x	x
Between patient mean change	x	x	
ROC curve analysis	x	x	x
Combined anchor and distribution based approach	x		
Predictive modelling approach	x		
Effect size estimate	x	x	
½ SD of the baseline distribution	x	x	



### Variation by anchor

The taxonomy describing responsiveness (types of changes or differences) by Beaton and colleagues emphasises the importance of defining whose perspective of change and whose perspective of the importance of that change an anchor is capturing (14). There is currently no consensus on the best anchor measure to use to calculate the MIC for a patient-reported outcome such as the POEM, therefore exploring anchors from different perspectives is important.

Schram and colleagues used a patient global assessment (PGA) of disease severity as an anchor. This anchor was prospective, which means patients reported a PGA of the severity of their disease at each time point the POEM was measured and the difference between the two scores was used as a measure of change. Gaunt et al. also used a PGA, but used a retrospective measure of perceived change where patients reported if their symptoms were worse, the same or better at follow up compared to baseline. Both previous studies used an anchor with a patient perspective of change, however it is suggested that MIC estimates should be based on both patient-based and clinical anchors (10). This study will use prospective anchors of change in a global rated assessment of severity using both the *patient* perspective of change and the *investigator* perspective of change (see Table 2 for details of these measures).

## **STUDY OBJECTIVES AND PURPOSE**

### **PURPOSE**

This study will provide further knowledge for understanding the MIC for the POEM to inform future clinical trial design and interpretation of clinical trial results.

### **OBJECTIVES**

- 1) To assess how the methods used (including both anchor- and distribution-based methods) influence the MIC estimates of the POEM.
- 2) To assess whether using a patient or investigator assessment as an anchor measure produces a different MIC for the POEM (which is a patient-reported outcome measure).

## **STUDY DESIGN**

### **STUDY CONFIGURATION**

This study will utilise the datasets available from the completed Clothes for the relief of Eczema (CLOTHES) trial (NIHR Health Technology Assessment Ref 11/65/01). The CLOTHES trial recruited children aged 1-15 years with moderate to severe eczema from secondary care settings and from the community. Secondary analysis of this existing dataset will be conducted.

### **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 January 2016 and be complete by January 2017.

## SELECTION AND WITHDRAWAL OF PARTICIPANTS

- **Recruitment**

There will be no recruitment for this study as it will use existing datasets for the CLOTHES trial.

### **Eligibility criteria**

All patients who were recruited for the CLOTHES trial will be included in the study if they have completed the measures needed for this analysis.

The eligibility criteria recruitment to the CLOTHES trial were:

#### **Inclusion criteria**

- Children aged 1 to 15 years at baseline
- Diagnosis of moderate to severe eczema (atopic dermatitis). Presence of eczema was confirmed using the UK Diagnostic Criteria for Atopic Eczema (Williams, Burney et al. 1994) and eczema severity judged using the Nottingham Eczema Severity Scale (NESS) (Emerson, 2000)
- Residents within travelling distance of a recruiting centre
- Children with at least one patch of eczema on the trunk or limbs
- Parent/legal guardian able to give informed consent

#### **Exclusion criteria**

- Children who have taken systemic medicine (including light therapy) or oral steroids for eczema within the previous three months
- Children who have started a new treatment regimen within the last month
- Children who have used wet/dry wraps  $\geq 5$  times in the last month
- Children who are currently using silk clothing for their eczema and are unwilling to stop using the clothing during the trial
- Children who are currently taking part in another clinical trial
- Children who have expressed a wish not to take part in the trial
- Only one child was enrolled per family. The choice as to which child becomes involved will be made by the parents and the children involved, taking into account the eligibility criteria above

### **Participant Withdrawal**

Any participants who were withdrawn from the original CLOTHES trial will not be included. However, since the CLOTHES trial is now complete there will be no necessary withdrawal of participants from the current study.

- **Informed consent**

Parents/legal guardians provided written informed consent prior to the CLOTHES study.

- **Criteria for terminating the study**

There are no foreseeable reasons why the study may need to be terminated.

On event of study termination, in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study.

## ANALYSES

- **Methods**

### Preliminary analyses

#### 1) Smallest detectable change

For a greater understanding of the usefulness of the POEM for detecting changes as small as the MIC value, it is important to understand if they are smaller or greater than the smallest detectable change (SDC). SDC is defined by COSMIN as a change beyond measurement error (11).

Calculate the SDC (11):

1. Calculate the standard error of measurement (SEM) =  $SD \times \sqrt{1 - ICC}$

ICC is the intra-correlation coefficient of the POEM.

2. Calculate the SDC =  $1.96 \times \sqrt{2} \times SEM$

We have used information from an article by Charman et al. (2004) that looked at the test-retest reliability of the POEM to calculate the ICC (15). We will report whether MIC estimates are greater than the SDC or not.

#### 2) Computing anchors to be used:

**Table 2: Measures used for anchors**

Measure name	Question	Response options (tick one box)	Completed by:	Times collected to be used for anchors:
Patient global assessment (PGA)	How is your / your child's eczema <u>today?</u>	Clear Almost clear Mild Moderate Severe Very Severe	Parent/legal guardian of child with eczema or child themselves if old enough (individual decision)	<b>Baseline 6 months</b>
Investigator global assessment (IGA)	How is the child's eczema <u>today?</u>	Clear Almost clear Mild Moderate Severe Very Severe	Research nurse (excluded measure when different nurse completed at different time points)	<b>Baseline 6 months</b>

IGA and PGA scores transformed into a change score to provide an anchor: Score at time point 1 (baseline) minus score at time point 2 (6 months) (See Table 3).

**Table 3: Anchors are the IGA and PGA change scores (11 pt scale)**

<i>Change scores for IGA and PGA</i>	<i>Interpreting the anchor change scores</i>
-5	Largest reported deterioration
-4	
-3	
-2	
-1	smallest reported deterioration
0	no change in score
1	smallest reported improvement
2	
3	
4	
5	largest reported improvement

### **3) Testing appropriateness of anchors**

For an anchor to be useful it must be at least moderately correlated with POEM change score ( $r \geq .3$ ) (10).

As part of the pilot work to ensure this study was worthwhile, this has been assessed and both prospective anchors (PGA change scores and IGA change scores) meet this minimum criteria (Table 4).

Table 4

Pearson's  $r$  correlations of change scores of POEM and anchors between baseline and 6 months:

	<b>PGA change scores</b>	<b>IGA change scores</b>
POEM change scores	0.55	0.46

### **4) Operationally defining MIC**

For our primary analysis we will consider a 1 point change to indicate a minimal important improvement or a minimal important deterioration in the respective directions. This was decided as a 1 pt. change indicates a change in severity banding (e.g. a change from moderate to mild scoring). It was considered that changes higher to this were unlikely to be sensitive enough to capture minimal changes, whilst any less would indicate no meaningful change has occurred. This is also the cut-off used by Schram and colleagues, therefore to maintain this cut-off will enhance our ability to compare results.

#### **MIC calculation methods**

##### ***Anchor-based approaches***

##### **1) Within-patient mean change:**

The mean change score of the smallest reported improvement group will be the MIC estimate. This score should be larger than the mean change score in the no difference group and larger than the SDC.

1) Between-patient mean change:

There is controversy in the literature over whether MIC estimates should use the mean change method described above or assess mean change by calculating the mean POEM change score of smallest improved group minus mean POEM change score of no difference group. Since trials report on the difference between groups, this method may be more useful in the interpretation of trials than the within patient mean change method as it looks at relative change (combines between person differences and within person changes).

2) ROC curve analysis:

The area under the curve (AUC) of the ROC curve can identify the cut-off point on the POEM change scores that most optimally distinguishes between POEM scores with no difference and POEM scores with minimal improvement. The cut-off used to provide an MIC estimate will maximise the Youden J statistic: sensitivity- (1-specificity).

3) Combined distribution and anchor based approach:

We also plan on using the combined anchor and distribution method, which is based on the ROC curve method but plots the distribution of the change scores using proportionate frequency instead of using absolute numbers (16). This has the advantage of allowing us to have a measure of variability incorporated into an anchor-based method (16).

4) Predictive modelling approach

This method will use logistic regression analysis to identify the change score associated with a likelihood ratio of 1 as the MIC (13). This method has the advantage of being more precise than ROC curve methods, which improves the statistical power. Using this method we are also able to control for baseline severity (13).

***Distribution-based approaches***

5) Effect size (ES) estimate:

This method is a standardised measure of change that is obtained by dividing the difference in scores from baseline and follow-up time point by the SD of the baseline scores.

For this study:

$$\text{ES estimate} = \frac{\text{POEM score at 6 month} - \text{POEM score at baseline}}{\text{SD of POEM score at baseline}}$$

6) Half standard deviation of the baseline distribution of POEM scores:

It has been found that a value of 0.5SD has corresponded to the MIC for a variety of studies, therefore 0.5 SD has been suggested as an estimate of the MIC.

- **Sample size and justification**

As this study is using secondary analysis, the sample size is pre-determined by the sample size of the dataset available to us (n=273). As far as we are aware there are no guidelines for sample size required for MIC studies. COSMIN recommend a minimum of 100 participants for other validation studies such as construct and criterion validity (11)

## **ETHICAL AND REGULATORY ASPECTS**

### **1. Anonymity**

Anonymity will be maintained as the datasets we are given will be in an anonymised format.

### **ETHICS COMMITTEE AND REGULATORY APPROVALS**

The CLOTHES trial was granted ethics approval by NHS Health Research Authority, NRES Committee East Midlands – Nottingham 1, and the respective NHS Research & Development (R&D) departments for participating sites (Nottingham University Hospitals NHS Trust; Barnet and Chase Farm Hospitals NHS Trust, Cambridge University Hospitals NHS Foundation Trust, Portsmouth Hospitals NHS Trust and Isle of Wight NHS Trust) prior to start of recruitment. The trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

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**

Informed consent was a requirement of the CLOTHES study. Since this study will be based on secondary analysis, the informed consent process used for the CLOTHES study will suffice for this study.

### **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. The CRF will only collect the minimum required information for the purposes of the study. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password protected. Access will be restricted by user identifiers and passwords.

Any medical information provided will be kept confidential.

## **QUALITY ASSURANCE & AUDIT**

### **RECORD RETENTION AND ARCHIVING**

In accordance with the University of Nottingham (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. This will include anonymised transcripts and database of participant information.

#### 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.

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 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 as part of the PhD of Laura Howells.

- **Participant stipends and payments**

N/a

## SIGNATURE PAGES

Signatories to Protocol:

**Chief Investigator:** Prof. Kim Thomas\_\_\_\_\_

Signature: KT Thomas

Date: 04/01/2017



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