Measuring and optimising patient-reported outcomes in eczema clinical trials through the use of online methods

Arabella Linda Baker

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Abstract

Background

Eczema is a chronic, inflammatory, itchy skin condition affecting 15-30% children and 2-10% adults. In randomised controlled trials (RCTs), patient-reported outcome measures (PROMs) are often used to evaluate interventions. The Harmonising Outcome Measures for Eczema (HOME) initiative developed a core outcome set (COS) consisting of four core domains to be included in all eczema trials, three of which are measured with PROMs. Implementing the COS helps to improve the consistency of outcome measures and the comparability of results across eczema trials. However, the optimum frequency of PROM assessments in eczema trials is unclear, which may hinder the uptake of the full COS.

Research aims

The overall aim of the research contained in this thesis was to inform the HOME initiative by addressing research priorities and filling validation gaps in relation to PROMs to help the implementation of the COS. In addition to improving the use of PROMs in eczema trials, this thesis aims to contribute to the field of trials methodology by evaluating a participant recruitment strategy used for an RCT.

The specific research aims for each study were as follows:

1. To establish the optimum frequency of patient-reported outcome assessments in eczema trials by conducting the Eczema Monitoring Online (EMO) RCT (Chapter 3)
2. To evaluate the social media recruitment strategy used for an online eczema trial (Chapter 4)
3. To fill the content validation gap of the Recap of atopic eczema (RECAP) instrument in young people (Chapter 5)
4. To aid the interpretability of RECAP change scores (Chapter 6)

Methods

Chapter 3 describes the EMO parallel group RCT, which was conducted entirely online. It included adults and children with eczema. The trial was 8 weeks long and compared the effect of weekly PROM assessments (intervention) with baseline and week 8 assessments (control). The primary outcome was change in eczema severity. Chapter 4 presents the efficiency and costs of both paid and unpaid social media recruitment methods used in the EMO trial. Chapter 5 contains a content validity study, which assessed the relevance, comprehensiveness and comprehensibility of RECAP. Semi-structured cognitive interviews with young people aged 8-16 years were conducted in the United Kingdom, Germany and the Netherlands. Chapter 6 determines the interpretability of RECAP scores by employing both anchor-based and distribution-based statistical methods to calculate the minimal important change score and the smallest detectable change. It provides a guide for the interpretation of change scores in RECAP.

Results

In the EMO trial (n = 296) the mean between group difference was -1.64 (95% CI -2.91 to -0.38; p = 0.01), demonstrating that weekly patient-reported symptom monitoring led to a small perceived improvement in eczema severity over 8 weeks. In 4 months, the social media campaign recruited 259 participants from diverse demographic backgrounds from Reddit (n = 121), Facebook (n = 43), Instagram (n = 88) and Twitter (n = 7) for a low cost with a retention rate of 82%. For the content validity study, findings indicate that RECAP is suitable for self-completion in children aged ≥12 years and using the proxy completed version for children younger than 12 years is advised. In terms of interpretability of RECAP, a change score of 1.9 or below is likely to be measurement error and the change in scores needs to be 2.0 points or greater before the change is considered clinically important and meaningful.

Conclusions

Based on the EMO trial results, reducing the frequency of PROM collection is recommended in future eczema trials. Using social media can be an effective tool for recruiting participants into trials. In addition, the RECAP patient-reported instrument performed well in both validation studies and appears to be fit for purpose for measuring the long-term control of eczema. The research in this PhD makes an original contribution to knowledge in the field of eczema and informs the HOME initiative in relation to the appropriate measurement of patient-reported outcomes in future eczema clinical trials.

Publications, presentations, prizes and awards arising from this work

I. Published journal articles

BAKER, A., MITCHELL, E. J., PARTLETT, C. & THOMAS, K. S. 2023. Evaluating the effect of weekly patient-reported symptom monitoring on trial outcomes: results of the Eczema Monitoring Online randomized controlled trial. *British Journal of Dermatology,* 189**,** 180-187.

BAKER, A., MITCHELL, E. J. & THOMAS, K. S. 2022. A practical guide to implementing a successful social media recruitment strategy: lessons from the Eczema Monitoring Online trial. *Trials,* 23**,** 905.

GABES, M., RAGAMIN, A., **BAKER, A.,** KANN, G., DONHAUSER, T., GABES, D., HOWELLS, L., THOMAS, K. S., OOSTERHAVEN, J. A. F., PASMANS, S. G. M. A., SCHUTTELAAR, M. L. & APFELBACHER, C. 2022. Content validity of the Recap of atopic eczema (RECAP) instrument in Dutch, English and German to measure eczema control in young people with atopic eczema: a cognitive interview study. *British Journal of Dermatology,* 187**,** 919-926.

- One additional manuscript, related to Chapter 6, is currently in preparation.

II. Published conference abstracts

BAKER, A., MITCHELL, E. J. & THOMAS, K. S. 2022. Symptom monitoring with patient-reported outcome measures: results of the Eczema Monitoring Online randomised controlled trial. *Acta Dermato-Venereologica,* 102**,** 1-65.

BAKER, A., HOWELLS, L., STUART, B., MITCHELL, E. J., & THOMAS, K. S. 2023. In pursuit of meaningful change: enhancing the interpretability of the Recap of atopic eczema (RECAP) instrument. *Acta Dermato-Venereologica,* 103**.**

III. Presentations, meetings, webinars and seminars attended

Date	Event attended	Location	Work presented
17 Oct 2020	Trials Methodology Research Partnership (TMRP) Annual PhD Student Meeting	Online	ORAL: Measuring outcomes in eczema clinical trials
26 May 2022	Eczema: an Evidence Based Update	Online	n/a
10 June 2022	School of Medicine Postgraduate Research Impact Forum	Nottingham, UK	ORAL AND POSTER: Measuring outcomes in eczema clinical trials
24 August 2022	Lifespan and Population Health (LPH) Research Skills Seminar	Online	ORAL: Using social media for participant recruitment
24 Sept 2022	Centre of Evidence Based Dermatology (CEBD) Patient Panel Day	Nottingham, UK	ORAL: Using social media for participant recruitment: lessons from the EMO trial
4-6 Oct 2022	6th International Clinical Trials Methodology Conference (ICTMC)	Harrogate, UK	ORAL: Evaluating the effect of regular symptom monitoring on trial outcomes: using electronic patient-reported outcome measures in an online eczema randomised controlled trial POSTER: Implementing a social media recruitment strategy: lessons learnt in the Eczema Monitoring Online randomised controlled trial
17-19 Oct 2022	12th Georg Rajka International Symposium on Atopic Dermatitis (ISAD)	Online	e-POSTER: Symptom monitoring with patient-reported outcome measures: results of the Eczema Monitoring Online randomised controlled trial
16 March 2023	TMRP-Health Data Research UK Patient-Reported Outcomes (PRO) Workshop	Online	ORAL: PRO monitoring as a healthcare intervention
24 March 2023	Sue Watson Postgraduate Presentation	Nottingham, UK	ORAL: Does weekly symptom reporting by patients affect clinical trial outcomes? Results of an

			online randomised controlled trial in eczema
17 April 2023	TMRP Webinar	Online	ORAL: Using social media in clinical trials
18-20 May 2023	European Academy of Dermatology and Venereology (EADV)	Seville, Spain	e-Poster: Evaluating the effect of weekly patient-reported symptom assessments on health outcomes: results of a randomised controlled trial in eczema
5 June 2023	University of Third Age (U3A)	Keyworth, UK	ORAL: Does weekly symptom reporting by patients affect clinical trial outcomes? Results of an online eczema trial
22 June 2023	7th UK Patient Reported Outcome Measures (PROMs) Research Conference	Sheffield, UK	ORAL: Is my instrument inclusive and accessible? Checking language variation and age appropriateness of an eczema patient reported outcome measure
31 Aug- 2 Sept 2023	13th Georg Rajka International Symposium on Atopic Dermatitis (ISAD)	Gdańsk, Poland	ORAL: In pursuit of meaningful change: enhancing interpretability of the Recap of atopic eczema (RECAP) instrument
10 Oct 2023	Harmonising Outcomes Measures for Eczema (HOME) XI Meeting	Berlin, Germany	ORAL: The impact of weekly patient-reported symptom assessments on trial outcomes: results from an online randomised controlled trial in eczema POSTER: Assessing language variation and age suitability of RECAP: an international content validity study

IV. Awards and prizes

- Best Student Oral Presentation Prize at the 6th ICTMC conference (6 Oct 2022)
- University of Nottingham Researcher Academy Conference Fund Award of £500 to attend the EADV conference in Seville, Spain (18-20 May, 2023)
- School of Medicine Doctoral Programmes Committee Funding Award of £500 to attend the 13th ISAD conference in Gdańsk, Poland (31 Aug – 2 Sept, 2023)

Acknowledgments

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I am sincerely grateful to my supervisors, Professor Kim Thomas and Dr Eleanor Mitchell for giving me the chance to pursue this PhD. Thank you for the support and guidance throughout my doctoral journey. I truly appreciate your intellectual generosity and kindness. Thank you for allowing me to engage with opportunities that aligned with my interests.

I am thankful to Dr Laura Howells for sharing useful insights and experiences about the PhD journey, which made this process easier. Thank you for checking on my wellbeing from the very beginning, your empathy and compassion provided reassurance in challenging times.

I would like to express my gratitude to Cydney Bruce for being there for me over the last three years. Our regular online calls at the height of the pandemic were instrumental in helping me tackle isolation. Thanks for the statistical advice in times of need. Most of all, thank you for your friendship and for the memorable professional and personal experiences.

I would like to thank the following individuals for their support and assistance: Dr Christopher Partlett and Professor Beth Stuart for statistical advice; Daniel Simpkins for database building; Dr Natasha Rogers for helping with website development; Centre of Evidence Based Dermatology Patient Panel members for their input on patient facing materials. Additional thanks goes to all the participants who took part in the studies contained in this thesis. It would not have been possible without you.

My appreciation goes to the Trials Methodology Research Partnership (TMRP). Thank you for organising unique training opportunities and networking events with fellow trials methodology students.

Dedication

I would like to dedicate this thesis to Szivecske. Thank you for inspiring me to undertake this PhD and for seeing my potential when nobody did. I am immensely thankful for your unwavering support, encouragement and mentorship. You have had a profound positive impact on my life and changed it for the better. I am deeply indebted to you and eternally grateful for everything.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

ADCT	Atopic Dermatitis Control Tool
API	Application Programming Interface
AUC	Area Under the Curve
BATHE	Emollient Bath Additives for Treating Eczema Trial
BEE	Best Emollients for Eczema Trial
CEBD	Centre of Evidence Based Dermatology
CDLQI	Children's Dermatology Life Quality Index
CDSS	Clinical Database Support Service
CI	Confidence Interval
COMET	Core Outcome Measures in Effectiveness Trials
COS	Core Outcome Set
ClinRO	Clinician Reported Outcome
CLOTHES	Clothing for the Relief of Eczema Symptoms Trial
CONSORT	Consolidated Standards of Reporting Trials
CONSORT-PRO	Consolidated Standards of Reporting Trials using Patient-Reported Outcomes
COSMIN	Consensus-based standards for the Selection of Health Measurement Instruments
COVID-19	Coronavirus
CS-COUSIN	Cochrane Skin-Core Outcome Set Initiative
CTIMP	Clinical Trial of an Investigational Medicinal Product
DLQI	Dermatology Life Quality Index
DOI	Digital Object Identifier
EASI	Eczema Area and Severity Index
ECO	Eczema Care Online
EMA	European Medicines Agency
EMO	Eczema Monitoring Online
EQ-5D-Y	EuroQol 5 Dimensions Youth

FDA	Food and Drug Administration
FLG	Filaggrin Gene
GCP	Good Clinical Practice
EUCTR	European Union Clinical Trials Register for Interventional Trials
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
HOME	Harmonising Outcome Measures for Eczema
HIV	Human Immunodeficiency Virus
ICC	Intraclass Correlation Coefficient
ICH	International Conference of Harmonisation of Technical Registration of Pharmaceuticals for Human Use
ID	Identification
IDQoL	Infant's Dermatology Quality of Life Index
IgE	Immunoglobulin E
IL	Interleukin
IMD	Index of Multiple Deprivation
IT	Information Technology
ISRCTN	International Standard Randomized Controlled Trial Number
MCID	Minimal Clinically Important Difference
MIC	Minimal Important Change
MID	Minimal Important Difference
NHS	National Health Service
NIHR	National Institute for Health Research
NICE	National Institute for Health and Care Excellence
NRS	Itch Numerical Rating Scale
ObsRO	Observer Reported Outcome
PGA	Patient Global Assessment
PIS	Participant Information Sheet
POEM	Patient Oriented Eczema Measure
PPI	Patient and Public Involvement

PRO	Patient Reported Outcome
PROM	Patent Reported Outcome Measure
PROMIS	Patient Reported Outcomes Measurement Information System
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RECAP	Recap of Atopic Eczema
REDCap	Research Electronic Data Capture
ROC	Receiver Operating Characteristic
RPE	Research Participation Effect
SAP	Statistical Analysis Plan
SEM	Standard Error of Measurement
SMS	Short Messaging Service
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SD	Standard Deviation
SDC	Smallest Detectable Change
SWET	Softened Water Eczema Trial
TARC	Thymus and Activation-Regulated Chemokine
TCS	Topical Corticosteroid
UK	United Kingdom
UKWP	UK Working Party Criteria
US	United States of America
UoN	University of Nottingham
WHO	World Health Organization

Statement of Contribution

This is to certify that the content of this thesis is a result of original research. This thesis was authored entirely by myself with feedback and comments provided by both supervisors: Kim Thomas (KT) and Eleanor Mitchell (EM). Additionally, other individuals were involved in various aspects of the projects contained in this thesis and, in most cases, they were co-authors on the publications related to this thesis. The specific contributions for each chapter are explicitly and comprehensively described below.

Chapter 3 - Online randomised controlled trial

Conceptualisation and study methodology was developed by me, KT and EM. I took a lead role in designing and registering the study protocol. I was responsible for setting up and managing the trial and undertook the following activities: ethics application, database development, website development, participant recruitment, project administration and data curation. KT and EM provided methodological input and support throughout the project. Daniel Simpkins, senior data manager, assisted with developing the database. Natasha Rogers (NR) helped to create the study website. I developed the statistical analysis plan, conducted the analysis and interpreted the findings with support from Christopher Partlett (CP), senior trial statistician. I drafted and finalised the manuscript. Co-authors: KT, EM and CP revised the manuscript, provided important intellectual input and approved the final manuscript. KT and EM reviewed this thesis chapter.

Chapter 4 - Retrospective analysis of social media recruitment strategy

I proposed the study idea, decided on the objectives and content of the study. I curated the relevant data, performed the analysis and decided on the structure of the study. I drafted and finalised the manuscript for publication. Co-authors: KT and EM revised the manuscript, provided important intellectual input and approved the final manuscript. KT and EM reviewed this thesis chapter.

Chapter 5 - Qualitative study to assess the content validity of RECAP

This was a collaborative study that was conducted simultaneously in three countries and the following researchers were involved:

- UK: myself, KT and Laura Howells (LH). Me and LH conducted the interviews.
- Germany: Michaela Gabes (MG), Christian Apfelbacher (CA), Gesina Kann (GK), Theresa Donhauser (TD), Daniela Gabes (DG). MG conducted the interviews.
- The Netherlands: Aviël Ragamin (AR), Suzanne GMA Pasmans (SP), Marie-Louise Schuttelaar (MLS), Jart AF Oosterhaven (JO). AR conducted the interviews.

The initial idea to conduct this study was suggested by the German researchers involved in this project, who contacted KT and the Dutch researchers to get involved. The study protocol, coding manual and interview guide was drafted by MG and TD and I contributed by reviewing the content of each and making suggestions for improvement.

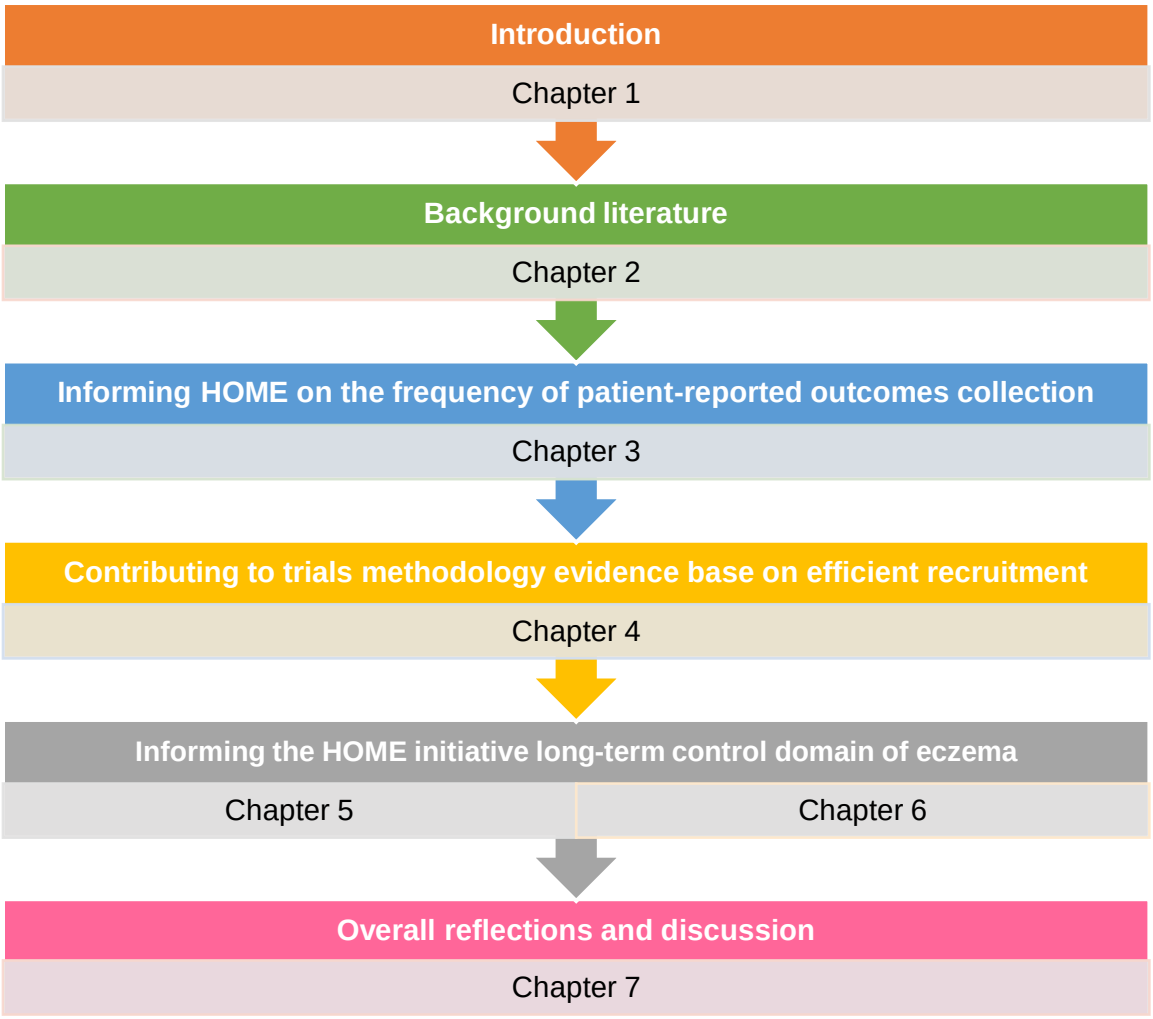
I was leading the UK side of the study and prepared the necessary documentation for ethics submission at the University of Nottingham. Since LH had ethics approval for a previous work related to RECAP, an ethics amendment request was made. I was responsible for participant recruitment in the UK, communicating with parents of potential participants and setting up the online interviews. LH conducted the first two interviews and I conducted the remaining five interviews. I transcribed the audio recordings and coded the transcripts independently alongside LH. Data analysis was conducted by myself, LH, GK, MG, AR, JO. I summarised the UK results. I was the third author on the paper and wrote up the abstract for the manuscript. All authors revised the manuscript for important intellectual content and approved the final manuscript. KT and EM reviewed this thesis chapter.

Chapter 6 - Validation study to assess the interpretability of RECAP

The idea was conceived by myself and KT. The study was designed by me, KT, LH, EM and Beth Stuart (BS). I took a lead role in developing the study protocol and selecting the calculation methods. I prepared the dataset, performed the statistical analysis and took a lead role in the interpretation of results. BS provided the statistical code for the receiver operating characteristic calculation method. KT and EM reviewed this thesis chapter.

Thesis Structure

Outcome measures are an integral part of clinical trials. Patient-reported outcome measures are increasingly used in eczema research, yet these outcomes have historically received limited attention. This thesis is comprised of four studies, three of which are focusing on improving how and when patient-reported outcomes are measured in eczema trials and one study is contributing to the evidence base on efficient participant recruitment strategies. The thesis is divided into seven chapters and the schematic outline below provides a visual overview of how the chapters are interconnected:



Chapter 1 introduces the rationale for the thesis and describes the aims and objectives of each of the four studies contained in this thesis.

Chapter 2 presents a comprehensive overview of the background literature that provided the underpinning motivation for the improvement and optimisation of patient-reported outcome measures in eczema clinical trials. This chapter sets the scene for the thesis and serves as a contextual foundation for the field, equipping the reader with insights into the research landscape in which the studies in this thesis are positioned.

Chapter 3 describes the core study within this thesis, which was an online RCT in eczema, called Eczema Monitoring Online (EMO), that evaluated the effect of weekly patient-reported symptom assessments on trial outcomes. This chapter describes the trial from conceptualisation to trial design and conduct as well as statistical analysis of results and the implication of findings. This work informs the Harmonising Outcome Measures for Eczema (HOME) initiative on the optimum frequency of patient-reported outcome collection in future eczema trials.

Chapter 4 consolidates the lessons learned from the EMO trial in relation to participant recruitment. In this chapter, the social media recruitment strategy is described in detail and the performance of unpaid posts and paid adverts and related costs is assessed. Since evaluating recruitment methods in clinical trials is of high importance in trials methodology research, this study serves as a valuable addition to the evidence base on efficient participant recruitment strategies.

Chapter 5 and Chapter 6 comprises two studies, one study per chapter, that helps to fill validation gaps in the long-term control of eczema domain in the HOME core outcome set for eczema clinical trials. Both studies examined various psychometric properties of the Recap of atopic eczema (RECAP) patient-reported instrument to ensure it is suitable for use in eczema trials.

Chapter 7 anchors the thesis through a reflective commentary, thereby establishing and confirming my original contribution to knowledge in the field, followed by the outline of potential future directions of research beyond the scope of this thesis.

Chapter 1 Introduction

1.1 Rationale for the thesis

RCTs represent the gold standard in evidence-based medicine for the evaluation of interventions. They are designed to mitigate bias, yet this goal can only be achieved if trial outcomes are selected and measured appropriately. Well-designed and conducted trials yield accurate and trustworthy evidence that can be used to inform the decision-making processes of healthcare professionals, patients, policy makers and funding organisations. However, the way outcomes have been historically measured in trials is far from evidence-based. In a recent editorial, Professor Hywel Williams (2022) who is a founding member of the HOME initiative, shed light onto the persisting disarray in outcome measures used in dermatology trials, marked by a profusion of unvalidated measures with questionable clinical interpretability. To remedy this ongoing problem, the use of core outcome sets is imperative in all trials, ensuring that trialists measure the same outcomes in the same way so that results can be compared and combined in a meaningful fashion.

The HOME core outcome set (COS) for eczema clinical trials is complete and can be readily used in upcoming trials (Williams et al., 2022). It consists of four core domains, three of which are measured by patient-reported outcome measures (PROMs) including: symptoms, quality of life and long-term control of eczema (Thomas et al., 2021). Numerous eczema trials have collected HOME-recommended PROMs weekly for various durations, however there is no consensus on the optimum frequency of PROM use in trials. In fact, this is a longstanding gap on the HOME research agenda. Furthermore, there is an emerging need for assessing the various measurement properties of RECAP to help HOME members make an evidence-based decision for selecting the most appropriate patient-reported instrument to measure the core domain of long-term control.

The aim of the work contained in this thesis was to inform the HOME initiative and contribute to their efforts on measuring outcomes in trials appropriately and at suitable intervals, thereby promoting the uptake of the HOME core set in eczema RCTs. This was achieved by: conducting a methodological RCT in eczema, focusing on evaluating the effect of weekly symptom assessments to help establish the optimum frequency of PROM collection; performing an international study with young people to assess the content validity of RECAP; aiding the interpretability of RECAP by calculating the minimal important change. Furthermore, the thesis provides a valuable addition to the field of trials methodology by enhancing the body of evidence related to efficient recruitment methods, thereby imparting new knowledge to the trials community.

1.2 Aims, objectives and study design

The primary aim of this thesis was to address research priorities and fill validation gaps for the HOME initiative to help the uptake of COS in eczema trials. In addition to improving outcome measures in eczema, this thesis aimed to contribute to the field of trials methodology by evaluating a participant recruitment approach used in an eczema RCT. Table 1.1 sets out the specific aims and objectives of each study contained in relevant chapters of this thesis, along with the chosen study design.

Table 1.1 Outline of aims, objectives and design for each study contained in the thesis chapters

Chapter	Aims	Objectives	Study design
3	**To establish the optimum frequency of patient-reported outcome assessments in eczema clinical trials**	To evaluate the effect of weekly patient-reported symptom monitoring on: 1. Eczema severity 2. Adherence to standard eczema treatment use 3. Data completeness	Randomised controlled trial
4	**To evaluate the social media recruitment strategy used for an online eczema trial**	1. To analyse the performance of paid social media adverts and unpaid posts 2. To comparatively assess the efficacy and cost of advertising on different social media platforms 3. To provide a practical guide for implementing a similar strategy	Retrospective analysis

5	**To fill the content validation gap of the Recap of atopic eczema (RECAP) instrument in young people**	1. To assess the content validity of the self-completed version of RECAP in young people with eczema in the UK, Germany and the Netherlands 2. To identify the most appropriate age cut-off for self-completion	Cognitive interview study
6	**To aid the interpretability of RECAP change scores**	1. To calculate the smallest detectable change for RECAP 2. To estimate the minimal important change (MIC) of RECAP using various calculation methods 3. To compare the MIC estimates provided by a single-item anchor and a multi-item anchor	Validation study

Chapter 2 Background

2.1 Clinical trials

Clinical trials are planned and structured investigations that form the cornerstone of modern medicine, providing the most valued empirical evidence in contemporary medical research. In essence, a clinical trial is a systematic inquiry that prospectively assigns human participants to medical, surgical or behavioural interventions in order to evaluate their safety and efficacy on health outcomes (Pocock, 1983, International Committee of Medical Journal Editors, 2021, WHO, 2021a). Trials represent a critical link between scientific innovation and the advancement of human wellbeing, enabling evidence-based decision making in healthcare. Rooted in rich historical legacy of medical exploration, clinical trials have evolved from initial rudimentary observations into intricately designed, conducted and analysed research studies that comply with stringent ethical and scientific principles. As the thesis embarks on the exploration of the different aspects of clinical trials, the subsequent section uncovers the historical background of trials.

2.1.1 Evolution of clinical trials

Clinical trials date back to ancient times and have evolved throughout the centuries (Nellhaus and Davies, 2017). The continuous evolution of clinical trials accounts for the high standards of medical research today and it has shaped regulatory and ethical frameworks in research (Nellhaus and Davies, 2017). Hence, exploring the key historical milestones helps to unfold the principles that have guided the advancement of clinical trials and cemented their crucial role in contemporary research.

An early resemblance of a clinical trial was described in the Bible (around 500 BC), comparing the effect of a diet of meat with legumes, using a concurrent

control group (Lilienfeld, 1982, Collier, 2009). In 1537, a manifestation of a trial was conducted comparing a standard treatment for battlefield wounds with a novel treatment, the latter was found to be superior (Packard, 1922). Although anecdotal events, the concept of evaluating interventions is demonstrated in both cases.

In 1747, James Lind conducted the first planned and recorded trial on a British ship to assess the effectiveness of nutritional interventions for scurvy, including citrus fruits (The James Lind Library, 2021). He allocated sailors into different treatment groups and was able to identify that citrus was effective for treating scurvy. This trial indicated the need for controlled experiments in research. Following the publication of Lind, the number of reported comparative studies increased, advancing the discipline (Dodgson, 2006).

The arrival of the placebo marked an important milestone in clinical trials. In 1863, the first placebo-controlled trial was conducted, comparing the active drug treatment for rheumatism, with placebo that was an inactive substance (Bhatt, 2010). No between group difference was found, highlighting the need for sound evaluation of positive effects of active drug treatments.

In the 1920s, Ronald Fisher developed randomisation techniques for treatment allocation for the design of research experiments (Armitage, 2003). However, it was not until 1946 that the first RCT was conducted, comparing streptomycin with placebo for the treatment of pulmonary tuberculosis (Medical Research Council, 1948). This trial was designed by Bradford Hill, a statistician who used randomisation to allocate participants to study groups. In addition, objective outcome measures and blinding to treatment allocation was also utilised (Hart, 1999). The streptomycin trial was considered a methodological landmark and led to the widespread application of randomisation, marking the era of modern clinical trials. Consequently, RCTs have become the gold standard for the evaluation of healthcare interventions (Bhatt, 2010). Sophisticated design and implementation techniques have been developed since the first RCT, the

principles of which originate from the work of Hill, indicating his great influence on trials methodology (Friedman et al., 2010).

More than two decades later, in 1964, the World Medical Association devised the Declaration of Helsinki framework, containing a set of essential ethical principles for the conduct of research involving human participants (World Medical Association, 1996). This fundamental document has shaped biomedical research ethics worldwide, protecting the rights and safeguarding the safety and wellbeing of study participants.

The emergence of adaptive trials in the 2000s was a further methodological milestone. Adaptive trials allow researchers to perform interim data analyses that can be used to modify the ongoing trial, enabling early stopping due to safety, futility or efficacy, without compromising data validity and integrity (Chow and Chang, 2008, Parmar et al., 2008, Park et al., 2020). Furthermore, the rising prominence of personalised medicine led to the development of biomarker-driven trials whereby participants are selected based on a specific biomarker information to identify those most likely to benefit from a given therapy (Hu and J., 2019).

Lately, the advent of the coronavirus (COVID-19) pandemic led to an unprecedented scientific effort worldwide to design and conduct clinical trials rapidly in an attempt to develop vaccines and treatments. The global rapid response to the pandemic and collaborative efforts showcased the adaptability of trial methodologies, resulting in the development and evaluation of multiple vaccines and treatments in a short time. In the wake of the pandemic, adaptive trial designs enabled the simultaneous evaluation of multiple interventions in COVID-19 trials in a perpetual fashion, allowing interventions to enter or leave the study according to a predefined decision algorithm (Woodcock and LaVange, 2017).

These remarkable milestones collectively represent a testament to the continued evolution of clinical trials throughout history. The aforementioned methodological

advancements have laid the foundations of scientifically sound research and have become an integral part of modern healthcare research (Nellhaus and Davies, 2017). The continuation of advances will undoubtedly pose new scientific challenges, requiring dynamic adaptations to enable rigorous clinical trial design and conduct in the pursuit of improving the health outcomes of patients.

2.1.2 Important elements of clinical trials

Clinical trials involve various important elements that enable the conduct of robust and ethical research. Since the main project within this thesis was an RCT, it is useful to explore the various aspects that underlined the conception and execution of the trial, as well as frameworks used for the design, analysis and dissemination of results.

2.1.2.1 Design

The initial step in the clinical trial design process is the development of the clinical trial protocol. The Medicines for Human Use (Clinical Trials) Regulations (2004) defines a clinical trial protocol as: *"A document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial."* The trial protocol plays a crucial part in the planning, conduct and reporting of the trial (National Institute for Health Research (NIHR), 2021). The protocol must comply with relevant ethical and legal requirements, such as the Declaration of Helsinki (World Medical Association, 2013) and Good Clinical Practice (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 2016). Creating a high quality, comprehensive protocol is crucial because deficiencies can result in protocol amendments causing the delay of the trial, poor trial conduct and insufficient reporting of findings (Getz et al., 2011). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 33-item checklist provides guidance for researchers in the development of a high quality protocol, facilitating

consistency, data integrity and transparency in trials, all of which help with reproducibility (Chan et al., 2013).

Trial registration is fundamental for promoting research integrity and transparency. It helps to mitigate publication bias, avoid unnecessary duplication and identify research gaps. The World Health Organization (WHO, 2021a) defines trial registration as the publication of a globally agreed amount of information about the design, administration and conduct of a clinical trial, which is recorded on a publicly accessible website managed by a registry. In 2005, the prospective registration of clinical trials was mandated by the International Committee of Medical Journal Editors (DeAngelis et al., 2005). Therefore, it is expected to prospectively register clinical trials on a trial registry prior to starting participant recruitment and data collection. Prospective trial registration reduces the incidences of unaccounted protocol alterations, helps to identify potential biases and prevents selective reporting.

Clinical trials can be prospectively registered on various widely used registries, including: International Clinical Trials Registry Platform (WHO, 2021b), International Standard Randomized Controlled Trial Number (ISRCTN, 2021), ClinicalTrials.gov (U.S. National Library of Medicine, 2021), European Union Clinical Trials Register (EUCTR, 2023) for interventional trials and the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT, 2021) for drug trials.

The number of prospectively registered trials are increasing. Nonetheless, a recent study reviewing 486 trials between 2010 and 2015 in high impact journals in the United States of America (USA) found that only 340 (77%) of trials were prospectively registered, 99 (23%) were retrospectively registered and 47 (10%) were unregistered (Gopal et al., 2018).

The trial protocol serves as a blueprint for researchers, in which the study design and setting is outlined. Within clinical trials, diverse designs exist but the most commonly used form is a parallel group RCT that consists of an intervention

group and a control group (Cook and DeMets, 2008). The baseline characteristics of the groups must be sufficiently similar, so that the differences in outcomes can be attributed to the effect of the intervention (ICH E10, 2000). This is achieved by the process of randomisation, which involves the allocation of participants to study groups based purely on chance (Altman, 1991, Grimes and Schulz, 2002). Randomisation reduces allocation bias, which refers to a systemic error in the assignment of participants that can occur when the participant allocation is influenced by the knowledge or prediction of the preceding allocation (Spenser et al., 2017). Another advantage is that randomisation is based on systematic mathematical algorithms, which eliminate random errors and help minimise bias, thus ensuring the validity of this technique (Shih and Aisner, 2016). Randomisation also enables to balance the number of participants in each study group and through the use of various randomisation techniques such as stratification, potential prognostic variables can be balanced as well.

Appropriately designed and conducted RCTs are the gold standard in evidence-based medicine (Feinstein and Horwitz, 1982) and have become the preferred study design for evaluating medical interventions (Schulz et al., 2010). Until the previous decade, RCTs were traditionally conducted face to face in clinical and research settings. However, the COVID-19 pandemic has initiated a significant paradigm shift towards decentralised clinical trials (Sacks, 2023). Decentralised trials frequently harness digital technology for the partial or full conduct of the study remotely, rather than being based at a trial site (Sommer et al., 2018). Internet-based RCTs are an example of a decentralised trial and are gaining momentum. These types of innovative trials allow participants to take part remotely for the entire duration of the trial. Although innovative trial methodologies are emerging, it is important to note that both traditional and internet-based trial designs have advantages and disadvantages that need to be considered when deciding the most appropriate option for answering the research question.

2.1.2.1.1 Traditional RCTs

Traditional RCTs involve the on-site conduct of the trial by the research team, consisting of trained researchers and healthcare professionals. This in-person approach enables increased interaction between the research team and participants, helping to foster trust and rapport which in turn aids participant recruitment and compliance with the study requirements. These factors are facilitators of effective communication between staff and patients and critically influence data quality.

Furthermore, in-person RCTs are more preferable for consenting procedures because staff can verify the participant through patient records and also record baseline data and eligibility screening truthfully, which helps to protect against individuals who might attempt to sign up multiple times or pose as a patient for mischievous purposes (Paul et al., 2005). Traditional trial methods typically embody a location-centric approach, which in itself has a bivalent consequence for these trials. On one hand, it is advantageous because it enables the inclusion of participants who have limited technological skills or experience such as the elderly. On the other hand, the disadvantage of this location-centricity, more precisely urban-centricity, lies within the limited generalisibility due to the potential lack of diversity in the trial population (Kennedy-Martin et al., 2015).

Notably, traditional trials may not be able to reach individuals living in rural areas or remote locations or those with mobility issues living far away from the trial site. Furthermore, traditional trials might have a reduced likelihood of accessing those who do not attend healthcare facilities regularly. Indeed, in-person trials are often criticised for poor representativeness stemming from the inclusion of a specific segment of the population. Thus, results might not be fully applicable to the general population (Kennedy-Martin et al., 2015). Additionally, traditional RCTs can be time-consuming and expensive to conduct and their stringently controlled and idealised environments may not completely represent real-world patient

experiences. These limitations have further prompted the emergence and implementation of alternative trial designs, such as internet-based trials.

2.1.2.1.2 Internet-based RCTs

Internet-based RCTs, also known as online, virtual, web-based or remote trials, utilise the internet and digital advancements for the recruitment, enrolment, data collection and management of the trial. In a fully internet-based trial, all processes occur remotely and participants engage with the trial related materials, intervention and data collection tools via web-based platforms (Mathieu et al., 2013).

The advantages of internet-based trials are multifaceted. They have a larger geographic reach, enhancing the opportunity to include participants from diverse demographic backgrounds. This improved inclusivity can lead to more generalisable and representative results. Furthermore, internet-based trials can save time as fewer steps are involved in the recruitment and data collection process, leading to reduced costs due to requiring fewer resources and staff time than traditional trials (Marks et al., 2001). The electronic data collection in these online trials enables real-time data validation, increases the speed of data acquisition and enhances data accuracy and quality.

Moreover, internet-based trials offer more convenience as people can take part from the comfort of their home, eliminating the burden of travel to a trial site (Mathieu et al., 2012). Participants can complete outcome measures at their own time and pace and this level of flexibility in participation can improve retention. Online trials may reduce social desirability, thus participants may feel more comfortable partaking remotely, especially anonymously, and may be more sincere and open in the self-reported questionnaires used in the trial (Joinson, 1999). The popularity of remote trials amongst participants is evident. Authors of an online survey assessing the perspectives of participants of an internet-based trial found that there was a notable preference towards internet-based trials for future participation compared to joining trials in other ways (Mathieu et al., 2012).

Despite the numerous benefits, challenges in internet-based trials also exist. Particular concerns may relate to data security and privacy as these trials may be more susceptible to data breaches that can compromise participant confidentiality (Paul et al., 2005). Ensuring data security is vital in online trials. However, even when sufficient security measures are taken, some individuals might refrain from taking part due to the online nature of the collection, transmission and storage of data. Furthermore, internet-based trials may inadvertently exclude individuals who do not have access to the internet and to an internet-enabled device or not comfortable with the use of digital technology (Mathieu et al., 2013). A further disadvantage of internet-based RCTs is the difficulty of confirming that participants meet the inclusion criteria due to the fact that online trials rely on self-reporting, which can inherently introduce uncertainties about eligibility.

Internet-based trials are a valuable and modern approach in trials methodology that capitalise on digital innovations, thereby advancing clinical research methods. With the ever evolving technological advancements, internet-based trials will certainly play a role in shaping the trajectory of trial designs. However, when deciding between online and traditional RCT designs, a trade-off should be considered regarding the pros and cons of each and a case by case approach is recommended. For some trials, a hybrid design incorporating elements of online and traditional approaches might be the most suitable option.

2.1.2.2 Conduct

Prior to approaching potential participants and conducting an RCT, ethical approval must be obtained from the relevant research ethics committee (REC) (Gelling, 2016). This is to protect the rights and well-being of participants and to ensure that the trial is conducted in a responsible and ethical fashion. Informed consent must be obtained from participants before enrolment into the trial (ICH, 2016). Informed consent refers to the process of providing information to potential participants about the purpose and key elements of the study and what

their role will involve (Health Research Authority, 2018). This information can be provided in the form of a participant information sheet (PIS) and a discussion with a member of the research team may also take place. Obtaining informed consent is imperative to the ethical conduct of research involving human subjects. Traditionally, paper consent forms were used but nowadays electronic methods for obtaining informed consent are also accepted. In 2018, the Health Research Authority (2018) endorsed the use of electronic consent in research and defined it as the: *"Use of any electronic media (such as text, graphics, audio, video, podcasts or websites) to convey information related to the study and to seek and/or document informed consent via an electronic device such as a smartphone, tablet or computer".*

When conducting RCTs, a wide range of potential challenges may arise, such as difficulties with recruitment, that can affect the progression of trials. Participant recruitment is central to the success of any trial, yet many reoccurring problems revolve around it, representing a prevalent issue in trials methodology research (Tudur Smith et al., 2014). In fact, recruitment remains a persistent and major challenge for the trial community (Healy et al., 2018, Treweek et al., 2018).

Recruitment is one of the most time-consuming aspects of clinical trials, which can take up to 30% of the overall research timeline and it is the leading contributor to missed trial deadlines (Bachenheimer and Brescia, 2007). Evidence suggests that many RCTs, regardless of specialty, face difficulties with recruiting participants and inadequate recruitment rates are often reported (Bower et al., 2007, Fletcher et al., 2012). A review of 114 publicly funded trials in the United Kingdom (UK) found that only 31% achieved the planned recruitment target and 53% required an extension (McDonald et al., 2006). In an updated review, Sully et al. (2013) reported that 45% of trials failed to meet recruitment goals and required a time extension. Insufficient recruitment can cause significant delays, leading to higher cost and increased length of the trial (Carlisle et al., 2014, Kasenda et al., 2014). Poor recruitment is oftentimes the most frustrating process in trials (Haidich and Ioannidis, 2001). The need for allocating

extra resources for extending the recruitment period may also affect the follow-up of already recruited participants as less resources might be available for ensuring participant retention, further jeopardising the outcome of the trial.

Failure to recruit participants to meet the target sample size, that is, the number of participants needed to meet the trial objectives, not only increases the risk of bias but also reduces the power of the trial to accurately detect the true effect of the intervention even if one exists (Julious, 2004, Friedman et al., 2010). In underpowered trials, clinically relevant changes may be considered statistically non-significant (Treweek et al., 2010). This can lead to a type II error or a false negative result, whereby the lack of statistical power prevents the detection of a real effect where one actually exists. However, in these cases it is important to consider the words of Altman and Bland (1995) stating that *"The absence of evidence is not evidence of absence."* A non-significant finding, that occurred due to insufficient recruitment, increases the risk of discarding an effective intervention before determining its true value.

Poor recruitment may cause scientific, economic and ethical implications and creates research waste arising from lost staff time, participant time and financial resources (Gillies et al., 2019). Therefore, recruiting the target sample size, and also retaining it, is crucial to ensure the validity of the results and timely impact on patient care (Bower et al., 2014).

2.1.2.3 Analysis

Statistical methods and analyses influence trial conclusions, thus the adequate conduct and documentation of statistical analyses of clinical trial data is of paramount importance. The principal features of the planned statistical analysis of trial data should be well-described in the statistical section of the trial protocol (ICH E9, 1998). This section should outline the principal characteristics of the planned confirmatory analysis of the primary outcome and the proposed approaches to handling potential statistical analysis problems, such as missing

data (ICH E9, 1998). In exploratory trials, this section describes the statistical considerations in a more general fashion.

The sufficient and clear description of prespecified statistical methodology in the statistical section of the trial report is essential as it helps to reduce and detect bias, especially in relation to selective analysis (Hemming et al., 2020). However, the level of detail described in the statistical section does not allow full replication of the applied statistical methods (Hemming et al., 2020). Consequently, a separate statistical analysis plan (SAP) is often developed prior to database lock. The SAP includes a higher level of technical description of the data analysis features outlined in the trial protocol and contains detailed procedures for conducting the statistical analyses of primary and secondary outcomes and other trial data (ICH E9, 1998). In 2017, a SAP guidance document for RCTs was published (Gamble et al., 2017). This guidance standardises SAP content as it contains a minimum list of items that needs to be included when reporting statistical analysis details of RCTs (Gamble et al., 2017). The SAP guidance document promotes complete reporting and enhances transparency and reproducibility, reducing the risk of bias. Statistical considerations form the basis of treatment efficacy claims and the analysis of trial data requires expertise, therefore the involvement of a statistician in the design and analysis of trials is critical (ICH, 2016).

2.1.2.4 Reporting

Reporting of clinical trial methods and results is imperative as it enables critical appraisal, interpretation of findings and evidence synthesis (Chan et al., 2014). Many participants take part in trials for altruistic reasons to contribute to the generation of new knowledge and help other people, therefore reporting is an ethical obligation towards participants (DeVito et al., 2020). Adequate reporting allows evidence-based decision making about treatments and interventions, which ultimately improves patient lives. Availability of trial information, including the finalised study protocol, prevents unnecessary duplication and informs future

research. The CONsolidated Standards of Reporting Trials (CONSORT) statement outlines the fundamental minimum criteria for the reporting of clinical trials to ensure the availability of complete and transparent trial information, allowing readers to assess the validity of findings (Schulz et al., 2010). Trials are reported in trial registries, funder reports and journal publications, although the latter is the main route of dissemination of research to the scientific community. The Food and Drug Administration (FDA, 2007) has made clinical trial reporting a legal requirement, making it mandatory to report findings within one year of completion.

Despite legislations and guidelines, only less than 50% of clinical trials are reported (Chan et al., 2014, Zwierzyna et al., 2018, DeVito et al., 2020). Inaccessible research is detrimental to patient care because it can lead to the use of ineffective or harmful treatments (Chan et al., 2014). In addition, unreported trials waste valuable healthcare resources since they do not contribute to the medical knowledge base. Another significant issue in relation to reporting is that trials with positive or significant findings are more likely to be reported than negative or null findings, this is referred to as publication bias (Chan et al., 2014). Researchers need to realise that reporting of negative and inconclusive findings is important because it helps to maintain scientific integrity, avoid duplication of studies evaluating the same interventions and inform clinical practice by indicating that a particular intervention did not have a significant effect on outcomes (Zwierzyna et al., 2018). The Journal of Negative Results (2021) explicitly focuses on publishing research findings with negative or null results to counterbalance the issue of selective reporting. Timely reporting of results fulfils the ethical obligation to trial participants and prevents unnecessary duplication of research, helping to reduce research waste.

2.1.3 Trial effect

Clinical trials by their nature are conducted in unusual settings due to the use of various assessments, researcher involvement and increased medical

surveillance, potentially leading to unintended trial effects (McCarney et al., 2007). Participants are not passive partakers and the potential impacts of taking part are unlikely to be discernable in outcome assessments (MacNeill et al., 2016). Consequently, there have been longstanding concerns in the medical research community about how research participation might affect outcomes. This phenomenon is known as the trial effect that is based on the hypothesis that participants in clinical trials may experience better outcomes, regardless of group allocation, as opposed to patients who receive the same intervention outside of trials (Menezes, 2012). The trial effect is a multifaceted construct and an umbrella term used to indicate the broad effects of trial participation (Menezes, 2012). However, there is inconclusive empirical evidence in relation to the trial effect due to the lack of breath, quality and quantity of available studies.

In oncology, a widespread assumption exists that participation in trials improves outcomes, but reliable supportive evidence is scarce (Khoja et al., 2016). Peppercorn et al. (2004) assessed empirical evidence from mainly retrospective cohort studies in oncology that compared the outcomes of participants treated within and outside of trials. Upon analysis, little high-quality evidence was found to support the assumption that taking part in oncology trials improved outcomes. Furthermore, a recent retrospective cohort study compared the outcomes of 60 patients with ovarian carcinoma: 30 patients were treated with chemotherapy within a trial and 30 patients received the same treatment outside the trial (Khoja et al., 2016). This study found no significant difference between the outcomes of the two study groups, therefore did not support the existence of the trial effect in oncology trials.

On the contrary, Menezes et al. (2011) provided noteworthy evidence for the trial effect in human immunodeficiency virus (HIV) clinical trials. In this retrospective study, the virologic suppression was compared in 738 HIV infected patients who received the same antiretroviral therapy either in a trial or as a standard of care outside the trial. Results of the secondary analysis of continuous data demonstrated that the participation in HIV clinical trials improved outcomes

compared to standard of care outside of the trial. This was the first study that clearly demonstrated the existence of the trial effect in HIV trials (Menezes et al., 2011).

Researchers have attempted to investigate the effect of participation in trials from various angles. For example, a number of studies have focused exclusively on a specific type of trial effect, called the Hawthorne effect, which postulates that participation in research studies may cause behaviour change in participants (McCambridge and Kypri, 2011). This phenomenon has been extensively discussed in the scientific literature for nearly a century (Solomon, 1949, Sommer, 1968, Gillespie, 1991, Gale, 2004). However, McCambridge et al. (2014a) argues that the notion of the Hawthorne effect has been around for a long time without advancing knowledge and proposed a novel term instead, namely "*research participation effect"* (RPE). It is hoped that it will progress understanding and methodological issues arising from this unique construct. The RPE helps to examine the effect of participation in trials as well as its mechanism of action and magnitude. A recent systematic review supported the existence of the RPE, yet provided limited conclusions about its magnitude due to the heterogeneity of included studies (McCambridge et al., 2014b).

In recent years, several clinical trials in chronic diseases have been conducted with the aim to evaluate the effect of trial assessments on participant outcomes. For example, an RCT in dementia demonstrated that more frequent assessments (at baseline, 2, 4, and 6 months) resulted in better outcome than minimum assessments (at baseline and 6 months) (McCarney et al., 2007). Further evidence for the RPE was found in asthma. The School-Based Asthma Therapy RCT, looking at the effect of directly observed controller medication administration in schools, demonstrated that participants in the control group improved during the course of the trial despite the absence of any intervention (Halterman et al., 2011). However, monthly symptom assessments were completed by participants, which may have contributed to the improvement in outcomes. Similar findings were reported in the School-Based Telemedicine

Enhanced Asthma Management RCT, assessing the effect of enhanced asthma management in the form of supervised daily preventive asthma medication administration in schools (Halterman et al., 2018). This trial found that children in the control group who completed bi-monthly symptom assessments had notable improvements in their asthma severity and symptoms compared to baseline, indicating the potential impact of the frequency of symptom assessments on trial outcomes (Halterman et al., 2018).

A secondary analysis (*n* = 516) of the aforementioned two asthma RCTs and a pilot study of preventive asthma care in schools (Halterman et al., 2012) indicated that patient-reported symptoms significantly improved in the control groups without the presence of active interventions (Frey et al., 2020). This improvement may have been attributed to completing patient-reported questionnaires, which prompted behaviour change and enhanced self-management, increasing adherence to asthma control medications. Consequently, the study suggested that regular assessments were strongly associated with improved symptoms (Frey et al., 2020). Due to the lack of adequate information about participant adherence and self-management in this asthma study, reliable conclusions about behaviour change could not be drawn.

In terms of eczema, a recent systematic review and meta-analysis examined 24 placebo-controlled Phase II/III eczema trials, evaluating the effect of systemic and biologic treatments in adults with eczema, found that participation in clinical trials improved self-management (Andreasen et al., 2020). Authors reported increased adherence to topical treatment use in the placebo groups, resulting in improved disease severity (Andreasen et al., 2020). This improvement might have been related to the frequent monitoring of participants in the trial, which could have led to regular emollient usage in itself or in conjunction with topical corticosteroids, resulting in improved skin barrier and reduced eczema severity.

These findings are consistent with previous eczema RCTs, in which the control groups had improved outcomes. The softened water for eczema RCT tested the effect of ion-exchange water softener in children with eczema (Thomas et al., 2011). Although the results showed improved eczema severity in both study groups, more participants in the control group (56%) had improvement compared to the intervention group (52%). Another RCT, that evaluated the effect of silk garments on eczema in children, reported the improvement of eczema severity in both study groups (Thomas et al., 2017). Authors indicated that this improvement might have been due to the regular monitoring of eczema, leading to increased adherence to topical treatment use. Since weekly symptom assessments occurred for a period of 6 months in this trial, it is possible that the RPE effect emerged and masked the treatment effect (Thomas et al., 2017).

Hence, regular assessments may constitute an unplanned intervention that can unwittingly impact on trial outcomes, possibly leading to improvements occurring from the trial participation rather than the intervention. This scenario raises numerous concerns, such as: masking the intervention effect, threatening the validity of inferences and undermining the study objectives (McCambridge et al., 2014a). Further research is needed to explore whether the frequency of outcome assessments impacts on trial outcomes.

2.2 Outcome measures in clinical trials

Clinical trials evaluate the effect of interventions through the use of outcome measures that assess the health status of patients. The choice of outcome measure reflects how the researcher defined and operationalised the outcomes in the study (Coster, 2013). Consequently, the value of the study as a contribution to clinical knowledge is significantly reliant on the appropriateness of the chosen metrics. Thus, the selection of adequate outcome measures is a critically important element in the design of RCTs.

2.2.2 Increasing utility of patient-reported outcome measures

It is essential to measure what is important to patients because the development of new treatments encompasses not only disease cure and control, but also the subjective aspects of the disease (Fitzpatrick et al., 1998, Charman et al., 2003, Gooderham et al., 2018). The importance of the patient perspective is increasingly recognised by the healthcare sector. Over the past decade, a fundamental paradigm shift towards greater patient involvement has occurred, indicating the value of patient experience and the need for a patient-centred approach in both healthcare and research (Meadows, 2011). This shift was driven by various factors, including: a significant change in healthcare objectives with increased focus on the management of chronic conditions, increased patient involvement in decision-making, requirement for relevant and meaningful outcome measures that reflect patients' preferences and the need to adequately evaluate the benefits and cost-effectiveness of treatments to optimise the use of valuable healthcare resources (Fitzpatrick et al., 1998, Meadows, 2011). There is a growing appreciation of the value of PROM data in clinical trials and in recent years, many trials have incorporated PROMs especially in oncology (Lane et al., 2016, Safa et al., 2021).

In essence, PROMs are standardised questionnaires (also called scales) completed by patients that assess their perception of health status, wellbeing and quality of life (QoL). The standardised configuration contains a fixed series and order of questions and answer options, thus all respondents receive the questionnaire and its content in a prespecified identical format (Boynton and Greenhalgh, 2004). Each response option has an allocated score, allowing the generation of numerical data that enables the statistical analysis of responses (Gillham, 2000). This level of standardisation of questionnaires increases reliability by ensuring that the differences in results are due to genuine changes and not stemming from inconsistencies in the data collection method or other artifacts (Boynton and Greenhalgh, 2004). PROMs can be single-dimensional

examining a single health aspect, such as pain, or they can be multidimensional, assessing multiple health domains and symptoms.

Regarding the drug development process, the significance of incorporating the patient perspective by the use of PROMs is acknowledged by both the FDA and the EMA. Consequently, these regulatory authorities have attempted to standardise PROM use in trials by releasing PROM guidelines in relation to drug labelling claims (Bottomley et al., 2009). These regulatory initiatives provide a formal framework for the ratification of newly developed and existing PROMs in trials (DeMuro et al., 2013). Paradoxically, there has been a reduced acceptance from the FDA for the use of PROMs not directly related to symptoms, such as QoL and functioning, which has led to the rejection of some drug labelling claims (Bottomley et al., 2009). Although the FDA urges sponsors to include PROMs in drug development, but their guidance is viewed as restrictive with extensive requirements, some of which are prone to controversy (Bottomley et al., 2009). Conversely, the EMA guidance provides global advice in relation to PROM use (European Medicines Agency, 2005).

Given the mixed views and experiences about PROMs, the pharmaceutical industry traditionally has been reluctant towards employing PROMs as important endpoints and still predominantly relies on ClinROs in drug labelling claims, including for eczema (Barrett et al., 2019). However, recently PROMs measuring itch and QoL as key endpoints were included to support labelling claims for Dupilumab, a monoclonal antibody, for the treatment of moderate-to-severe eczema (Simpson et al., 2016). Notably, a degree of tension exists between the use of ClinROs and PROMs in RCTs as clinicians tend to regard the former as a source of more reliable, expert data based on accurate measurements. However, patients are experts in their own rights when it comes to their health condition and their perspectives and assessments are equally valuable.

According to the literature, discrepancies can occur between patient and clinician views of disease status and treatment effectiveness. It was found that some

clinicians reported fewer issues than patients and may underestimated the severity of the problems or overestimated the degree of treatment improvement (Copley-Merriman et al., 2017). For example, a study in rheumatoid arthritis reported that clinicians gave lower ratings for pain levels and higher ratings for health status compared to patients' ratings, indicating a lack of congruence between ratings (Suarez-Almazor et al., 2001). Furthermore, a study evaluating clinician and self-assessed severity measures in dermatology patients found very modest agreement between the patient and clinician assessments (Magin et al., 2011).

Notably, the historical preference towards ClinROs might be owed to the fact that PROMs are commonly criticised for being fully subjective measures, which is a misconception (De Vet et al., 2011). The scrutiny surrounding PROMs revolves around the need for personal judgement in the measurement process by a person without a clinical background which could be perceived as potentially influencing the responses. Indeed, PROMs rely on self-reported perspectives and there is a level of subjectivity involved but this does not undermine the value of PROMs. In fact, it highlights the importance and need for robust testing and evaluation of the psychometric properties of PROMs to enhance their credibility and utility in capturing health outcomes.

There is an erroneous assumption that ClinROs are objective measures as healthcare professionals still need to make a clinical judgment which involves a level of subjectivity (De Vet et al., 2011). For instance, the Eczema Area and Severity Index (EASI) is used by clinicians to evaluate the signs of eczema (Tofte et al., 1998). It requires the clinician to assess both the extent of eczema on four body regions (head and neck, trunk, upper limbs, lower limbs) and the intensity of eczema signs (erythema, oedema, scratching and skin thickening). For this assessment a clinical judgment is needed.

Moreover, some outcome measures that are deemed to be objective may require subjective interpretation. For example, imaging tests may appear to be objective

measures however clinical judgment and subjective interpretation is needed by a clinician to evaluate the images (De Vet et al., 2011). Including subjective measures in the form of PROMs in RCTs is necessary because they encapsulate aspects of health and illness that are relevant and important for patients. Therefore, outcomes should not be selected on the basis of assumed objectivity as it could exclude outcomes of high importance for patients.

Various international initiatives and consortia have developed guidance on PROM use across the research lifecycle, from trial conceptualisation to dissemination of results, including: writing of protocols (Calvert et al., 2018), selecting PROMs (Reeve et al., 2013), analysing patient-reported data (Coens et al., 2020), reporting findings (Calvert et al., 2013) and interpreting papers using PROMs (Wu et al., 2014). Additionally, the Patient-Reported Outcomes Measurement Information System (PROMIS) item bank contains over 300 validated, person-centred PROMs for a range of health conditions that is available for researchers wishing to use PROMs in their studies (Cella et al., 2010). Generally, there is a move towards standardising patient-reported instruments in medical research, which will help to improve the quality of the PROM evidence base and encourage clinicians and researchers to incorporate the patient perspective through the use of PROMs.

2.2.1 Types of outcome measures

There are four types of outcome measures, including: clinician-reported outcome measures, patient-reported outcome measures, observer-reported outcome measures and performance outcome measures (Powers et al., 2017).

Historically, clinical trials employed biomedical outcome measures, such as laboratory tests, because such data sources were viewed as scientifically robust and reliable (Feinstein, 1987, Fitzpatrick et al., 1998). However, Feinstein (1987) proposed a humanistic approach for collecting clinical data in trials, suggesting biomedical measures to be complemented by clinical examination. This is

referred to as clinician-reported outcome measure (ClinRO), whereby a healthcare professional assesses and reports on observable signs, symptoms, functional level or overall clinical status of patients (Powers et al., 2017). ClinROs may involve the assessment of disease severity based on strandardised criteria, but can also consist of quantifiable measures such as blood pressure readings and laboratory test results. Although ClinROs provide valuable clinical information, they might be unsuitable measures when symptoms are exclusively known to the patient, like pain intensity or itchiness in eczema (Charman et al., 2003, Powers et al., 2017). The latter concepts can only be measured by patient-reported outcome measures (PROMs) because they directly capture the experiences of patients in relation to symptoms, unobservable signs and health related quality of life (Au et al., 2010). Of note, PROMs and patient-reported outcomes (PROs) are synonymous terms and commonly used interchangeably. For consistency, PROMs will be used in this thesis to denote this concept.

The FDA (2009) defines a PROM as: *"Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."* PROMs can be either self-reported by the patient or completed by someone on behalf of the patient, known as proxy, provided that the response of the patient is accurately recorded without interpretation (FDA, 2009). Given that eczema affects many children, it is important to incorporate their perspectives in an age-appropriate manner, enabling them to comprehend the questions and provide meaningful answers independently if possible. For this purpose, the Children's Dermatology Life Quality Index (CDLQI) outcome measure is well suited as it uses a child friendly language that measures the impact of skin disease on important aspects of a child's life, including playing, doing sports and friendships (Lewis-Jones and Finlay, 1995).

By their nature, PROMs are patient-centred measures. Long and Dixon (1996) state that patient-centredness in outcome measures can be positioned on a two-dimensional spectrum. The patient end of the spectrum consists of patient

defined outcomes, whereby patient perspectives are incorporated into the content of the measure. Conversely, the other end of the spectrum contains outcomes defined by healthcare professionals based on clinical observations with no direct information from the patient (Long and Dixon, 1996). Available outcome measures can be located on different parts of this patient-centred spectrum.

However, there are instances when patients are unable to self-report and the use of PROMS is not plausible. In such cases, observer-reported outcomes (ObsRO) can be utilised instead. ObsROs are based on observable signs and behaviours related to the health condition of the patient, reported by an individual other than the patient or the clinician (Food and Drug Administration, 2016). ObsRO is a type of proxy-reported outcome measure that is commonly used across a range of age groups and clinical scenarios, including: young children, critically ill patients, those with cognitive impairments and elderly patients (Morrow et al., 2012, Li et al., 2015). The use of proxies makes the study more representative of the target population, nonetheless some argue that responses may be different from those obtained directly from the patient (Morrow et al., 2012). However, several studies comparing self-reported and proxy responses in children with chronic diseases found a high level of consistency between responses in relation to symptoms and disease control (Morrow et al., 2012, Barrett et al., 2013).

Another type of outcome measure is the performance-based outcome measure (PerfO), which is centered around standardised activities performed by a patient in accordance with a set of instructions (Bean et al., 2011). PerfOs are usually administered by a healthcare professional, for example a physiotherapist may use a stopwatch to measure how long it takes for the patient to complete a predetermined task or a geriatrician may use a word recall test to measure memory in elderly patients.

Beyond aforementioned outcome measures, some trials also utilise serum and plasma parameters, known as biomarkers, that measure a specific characteristic

in patients as an indicator of a biological response to an intervention (FDA-NIH Biomarker Working Group, 2016). For instance, serum thymus and activation-regulated chemokine (TARC) level can be used in eczema as a biomarker to assess disease severity and evaluate treatment response (Thijs et al., 2015).

2.2.3 Inconsistency in outcome measures

Clinical trial findings inform clinical practice, individual and public decision-making and healthcare policy (Tunis et al., 2003). With the high prevalence of eczema, research activity has exponentially increased and generated a significant volume of results. In order to make meaningful conclusions about the efficacy of treatments, study results need to be synthesised. This can be facilitated by systematic reviews that utilise explicit, rigorous and transparent methods to collate and compare empirical evidence according to a predefined criteria, which helps to minimise bias and random errors (Gough et al., 2020). Cochrane, a global organisation founded by a pioneer in evidence-based medicine, produces high quality systematic reviews on healthcare intervention studies (Cochrane, 2021). Systematic reviews often use statistical methods to synthesise and pool the results of several individual studies for the comparison and evaluation of findings, this method is referred to as a meta-analysis (Glass, 1976). Meta-analyses and systematic reviews, particularly that of RCTs, are considered to provide the highest level of evidence in medicine as illustrated in Figure 2.1.

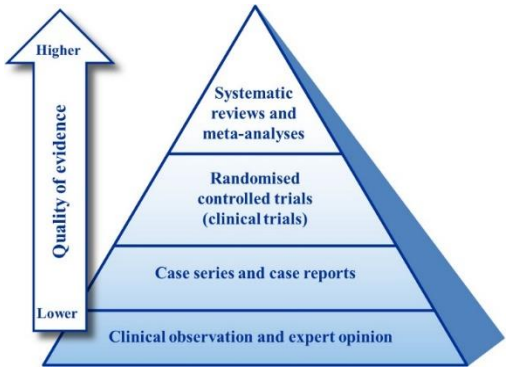


Figure 2.1 Hierarchy of evidence (James, 2017)

However, inconsistencies in outcome measures make it difficult, sometimes impossible, to conduct systematic reviews and meta-analyses. This is because clinical trials, across many disciplines, use a wide range of outcome measures that makes evidence synthesis difficult. For instance, a cross-sectional study in oncology highlighted that over 25,000 outcome measures were used in oncology trials (Hirsch et al., 2013). Furthermore, a comprehensive survey in schizophrenia reported that 2194 different instruments were used in controlled clinical trials (Miyar and Adams, 2012). A number of systematic reviews of eczema clinical trials have indicated significant inconsistencies in outcome measures (Charman et al., 2003, Schmitt et al., 2007, Rehal and Armstrong, 2011, Hill et al., 2016, Futamura et al., 2016). Diverse outcome measures in trials hinder the synthesis and systematic evaluation of results in health research. This diversity may stem from the lack of careful selection of outcome measures, which can be due to the lack of appropriate understanding or awareness and inadequate communication within the research team. These insufficiencies may lead to the use of suboptimal scales that lack evidence on the development process or the scales may contain inadequate measurement properties. Echoing these shortcomings, an early systematic review on outcome measures in eczema RCTs revealed that only 27% of the included trials employed a published severity scale and 59% used unnamed scales that lacked information on validity or reliability (Charman et al., 2003). In a more recent systematic review of 135 eczema RCTs, 62 different disease severity measures were identified but only 16 of them underwent validation (Hill et al., 2016, Chopra and Silverberg, 2018). Evidently, significant heterogeneity in eczema outcome measures remains.

The main problem with the wide variation of outcome measures in trials is that it jeopardises the accurate interpretation and comparison of findings. Even when properly validated and published outcome measures are used, it can be challenging to reach reliable conclusions about the effect of interventions if different outcome measures are employed. In order to be able to directly compare study results uniform and valid outcome measures are needed (Flohr,

2011). Beyond research, reliable outcome measures are also needed for routine patient care to be able to evaluate treatment success (Ingram, 2013).

Another issue associated with outcome measures is insufficient reporting of outcomes, which can give rise to bias. Hutton and Williamson (2000) recognised a distinct type of bias that occurred in trials and termed it as outcome reporting bias. This occurs when researchers do not report all the prespecified outcomes and select only a subset of the outcomes on the basis of knowing the results (Dwan et al., 2008). Moreover, outcome switching, misreporting and omission in trials is a serious, yet highly prevalent issue (Chan et al., 2004, Jones et al., 2015). A cohort study (Goldacre et al., 2019) reviewed 67 trials in the top 5 medical journals and found that 87% of the outcomes were not fully reported and 357 new outcomes were added, showing substantial discrepancy between registered and published outcomes. Furthermore, there is a significant body of empirical evidence suggesting that statistically significant outcomes are more likely to be fully reported than non-significant results (Dwan et al., 2008, Dwan et al., 2013).

Such distortions pose a major threat to the validity and correct inferences of findings. In a review of the effect of primary outcome change on the reported intervention effect size, Chen et al. (2019) found that the intervention effect size was 16% higher in studies that unreported or omitted the primary outcome. These spurious results provide misleading evidence for healthcare decision making and impacts on the pooled summary of systematic reviews. Besides inadequate reporting, a systematic review of 109 eczema RCTs reported that the description of primary outcomes was often insufficient and unclear (Nankervis et al., 2012). In this study, only 5 trials provided sufficient information for the authors to be confident that these studies did not have outcome reporting bias.

In 2009, Chalmers and Glasziou highlighted that bias and unusable reporting contributed to avoidable research waste. According to their conceptual framework illustrated in Figure 2.2, all research studies pass through 4 stages.

The authors emphasised that avoidable research waste typically occurred at stages 2, 3 and 4 and the cumulative research loss was estimated to be 85%, causing loss of benefit from billions of dollars invested in research due to resolvable problems (Chalmers and Glasziou, 2009).

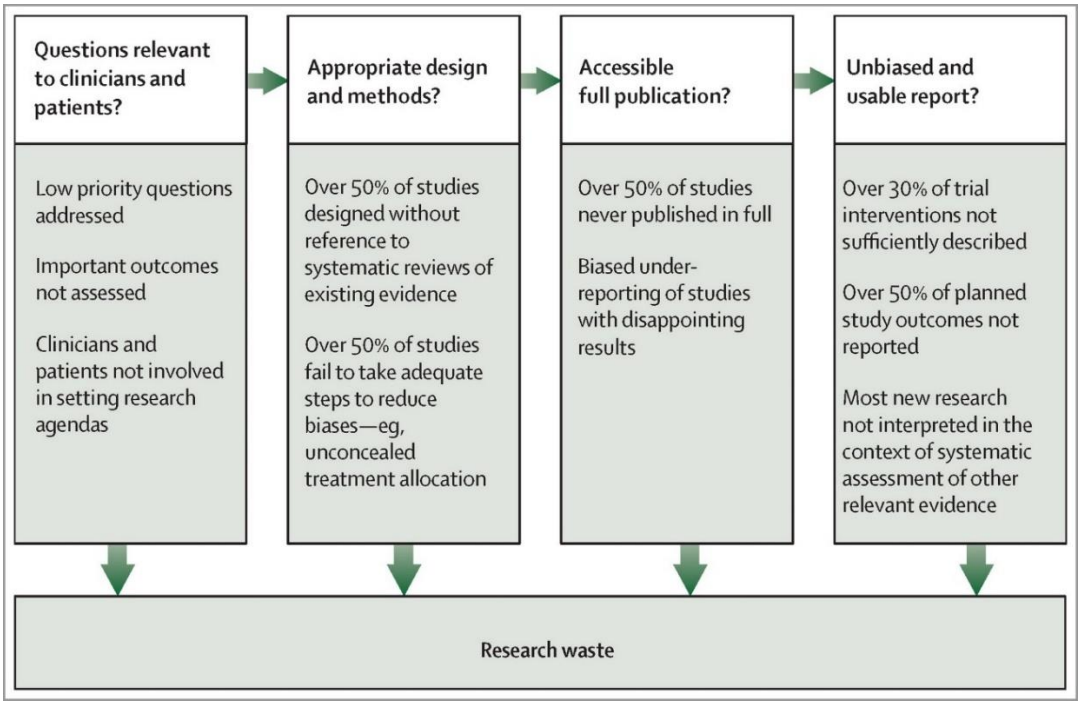


Figure 2.2 Stages of waste in the production and reporting of research evidence relevant to clinicians and patients (Chalmers and Glasziou, 2009)

To alleviate the problem of research waste, various key initiatives such as the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network, CONSORT and SPIRIT have all tried to improve the current state of play. Additionally, an increasing number of scientific journals have taken steps towards reducing research waste by mandating the prospective registration of trial protocols on a registry and requiring the completed CONSORT checklist as part of submission. However, these laudable efforts seem to have not reached the desired impact because bad health research is still a scandal (Glasziou and Chalmers, 2018). In fact, much of health research in general remains substandard (Yordanov et al., 2015, Van Calster et al., 2021). A paper published in 2022, including 1640 trials from 96 Cochrane reviews, highlighted that 56% of

participants were taking part in suboptimal trials that had a high risk of bias. The conservative estimate of these bad trials was £726 million, with high estimates exceeding £8 billion (Pirosca et al., 2022).

2.2.4 Core outcome sets

The development and use of core outcome sets provides a solution for the heterogeneity of outcomes used in clinical trials (Clarke, 2007). A core outcome set (COS) refers to a consensus-derived standardised set of outcomes that should be included and reported in all clinical trials in a specific health condition or clinical trial population (Williamson et al., 2012). COS reflects a predefined set of outcomes that should be included in trials. However, the existence of COS does not imply that only COS outcomes can be measured. Instead, it represents the minimum core outcomes that should be measured in a given trial, allowing for the possibility of exploring and including additional outcomes. Generally, in most trials the primary outcome is expected to be selected from the COS, where one exists.

The Core Outcome Measures in Effectiveness Trials (COMET) initiative promotes the uptake of COS in trials by providing both methodological guidance for researchers interested in COS and a platform for COS dissemination (Williamson et al., 2011). Since the debut of COMET, COS development and uptake has markedly increased. In 2019, 370 COS studies were available on the COMET database for a range of health disciplines (Gargon et al., 2021). Nonetheless, reviews of COS uptake in trials revealed varied, typically low, rates of use (Hughes et al., 2021, Matvienko-Sikar et al., 2022).

2.3 Validation of outcome measurement instruments

Measurement is a critical component of research and clinical practice. It serves as a basis for the evaluation of medical interventions, thereby informing decision

making about the application of treatments, diagnostic and prognostic tests and other health interventions (De Vet et al., 2011).

Although measurement instruments can be powerful tools, researchers should be certain that the chosen measure is appropriate for the intended purpose. Thus, firstly the outcome of interest (what to measure) should be defined as it dictates the selection of the suitable outcome measurement instrument (how to measure) (Mokkink et al., 2016). Prior to selecting adequate instruments, researchers must undertake a thorough literature search to identify, compare and contrast the quality and measurement properties of existing instruments for the chosen outcome (Streiner et al., 2015). Albeit, a plethora of instruments are available for nearly every disease and populations, a significant proportion have been inadequately developed or validated (De Vet et al., 2011). Consequently, researchers may conduct a validation study for the selected instrument before using it for measuring a predefined outcome. However, if no instrument is available to measure the chosen outcome, a new instrument may be developed. In the development of new instruments well-defined robust standards and iterative processes must be followed to ensure rigour and quality (McDowell, 2006, De Vet et al., 2011).

2.3.1 Measurement properties of outcome measurement instruments

The selection of outcome measurement instruments should be based on a critical literature review. However, significant insufficiencies have been noted in the literature, stemming from the lack of: clarity in terminology, outcome measurement definitions and evidence on measurement properties of instruments These deficiencies have led to the formation of the COSMIN (Consensus-based Standards for the selection of health Measurement Instruments) initiative, established by a global multidisciplinary team, with the aim to develop a consensus-based taxonomy and terminology on measurement properties (Mokkink et al., 2010a).

The COSMIN taxonomy (Figure 2.3) consists of three distinct quality domains: reliability, validity and responsiveness, wherein one or more subdomains are located that contain the measurement properties or aspects of measurement properties deemed to be relevant for any measurement instrument that is used in medicine (Mokkink et al., 2010b). This thesis will use measurement property terminology in accordance with the COSMIN taxonomy.

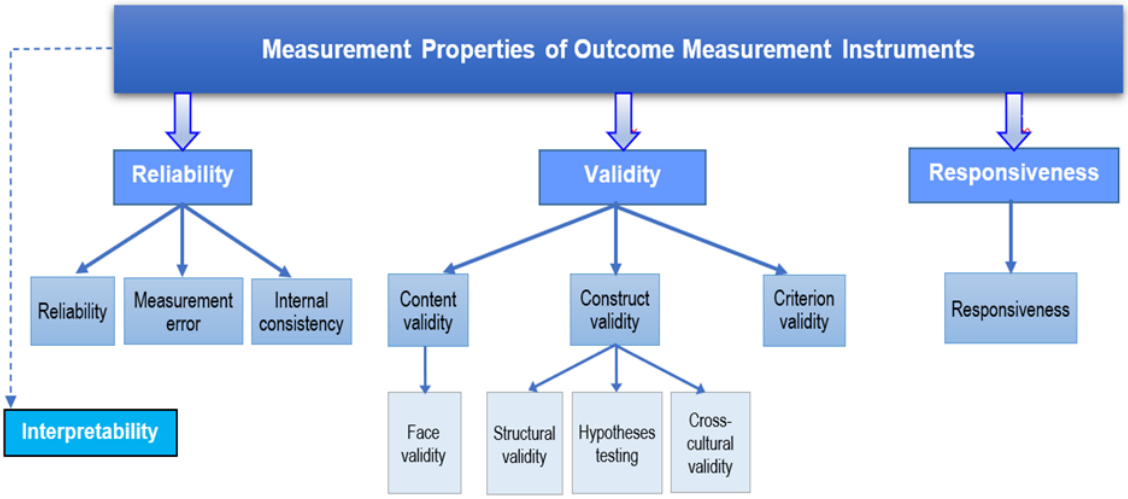


Figure 2.3 Measurement properties of outcome measurement instruments (COSMIN taxonomy)

Moreover, the COSMIN checklist has been also developed, providing methodological guidance for the assessment of the quality of studies on measurement properties of outcome measurement instruments (Mokkink et al., 2010b). The COSMIN initiative supports the standardisation of outcomes and the development of COS (Prinsen et al., 2016). Hence, a recent collaboration with the COMET initiative resulted in the development of a consensus-based practical guideline on the selection of measurement instruments for measuring outcomes included in a COS (Prinsen et al., 2016).

2.3.1.1 Reliability

A fundamental requirement of all outcome measurement instruments is to be reliable (De Vet et al., 2011). The first main domain in the COSMIN taxonomy is reliability, which is defined as the degree to which the measurement is free from measurement error (Mokkink et al., 2010a). Within the reliability domain the reliability subdomain is situated, which in this context refers to the proportion of the complete variance in the measurements that is due to 'true' differences between subjects (Mokkink et al., 2010a). The notion of 'true' in this situation is linked to the classical test theory (CTT), stating that an observed score consists of two components: a true score and error related to the measurement (Mokkink et al., 2010a). A true score represents the average score that would be acquired if the instrument was administered an infinite number of times (Mokkink et al., 2010a). However, reliability only refers to the consistency of the measurement scores and not representative of their accuracy (Streiner et al., 2015).

The second subdomain within the domain of reliability is measurement error, defined as the systematic and random error in the measurement score that is not associated with true changes in the construct of interest (Mokkink et al., 2010a). It is important to note that some degree of measurement error is inherent in any measurement. Moreover, measurement error and reliability are distinct, yet intertwined concepts (De Vet et al., 2011). Reliability represents both a measurement property of an instrument and the characteristic of an instrument used in a particular patient population (De Vet et al., 2011). Taking into account the latter, reliability is dependent on the heterogeneity of the population wherein measurements are made (Bartlett and Frost, 2008). For instance, if the instrument is employed in a heterogeneous population, the measurement error is low, thereby reliability is high as the discrimination between patients is scarcely affected by the errors (De Vet et al., 2011). However, the smaller variation among patients leads to reduced measurement error and this also causes lower reliability because patients have nearly identical values, making it difficult to distinguish between them despite the small measurement error (De Vet et al.,

2011). On the other hand, if measurement error is high in a heterogenous sample the reliability also becomes high due to the higher variation among patients in this situation, this occurs because the measurement error does not obscure the differences between patients (Bartlett and Frost, 2008).

The final subdomain within the reliability domain is internal consistency, that is the degree of interrelation among all the items in an instrument (Mokkink et al., 2010a). Internal consistency tests the CTT viewpoint that measurement items serve as causal indicators that tap into the same latent underlying construct (Streiner, 2003). Hence, this measurement property is not relevant to instruments that have been developed on the basis of formative models where items are not required to be interrelated (Prinsen et al., 2018).

2.3.1.2 Validity

Validity, a core domain in the COSMIN taxonomy, is the degree to which the instrument measures the construct it claims to measure (Mokkink et al., 2010a). Within the validity domain lies content validity, which is defined as the degree to which the content of an instrument is an accurate representation of the construct of interest (Mokkink et al., 2010a). Content validity is considered the most important type of validity measure (Krabbe, 2017). However, in order to appropriately evaluate the content validity of an instrument the construct of interest should be clearly specified and adequately described (De Vet et al., 2011). Before the detailed assessment of content validity is performed, a global assessment of the relevance and comprehensiveness of the instrument should occur, this is called face validity (Mokkink et al., 2010a, Krabbe 2017).

The core domain of validity contains construct validity that refers to the extent to which the scores of a measurement instrument are consistent with the theoretical hypotheses based on the assumption that the instrument validly measures the construct intended to be measured (Mokkink et al., 2010a). Evidence of construct validity includes the empirical and theoretical support for the interpretation of the construct. Hypotheses-testing is an aspect of construct validity, whereby the

performance of the instrument is tested and compared to other instruments (De Vet et al., 2011). Another element of construct validity is structural validity, defined as the degree to which the scores of an instrument are adequate representation of the dimensionality of the construct of interest (Mokkink et al., 2010a). Cross-cultural validity, a component of construct validity, is the degree to which the performance of the translated or culturally adapted instrument is an appropriate reflection of the performance of the original version of the instrument (Mokkink et al., 2010a). This measurement property is usually assessed after the translation of the instrument. The last subdomain within the main domain of validity is criterion validity, which refers to the degree to which the scores of an instrument are an adequate reflection of an existing gold standard (Mokkink et al., 2010a). In other words, this type of validity measure assesses the correspondence of the instrument with the available standard (De Vet et al., 2011).

2.3.1.3 Responsiveness

Responsiveness is described as the ability of an outcome measure to detect change over time in the construct to be measured (Mokkink et al., 2010a). Similarly to construct validity, responsiveness of an instrument is evaluated through hypotheses testing to assess whether the scale scores of individuals that are expected to change do result in change. In terms of clinical trials, the responsiveness of outcome measures is crucial as the primary purpose of clinical trials is to detect and adequately capture real change in health outcomes that occur as a result of the trial intervention.

2.3.1.4 Interpretability

Although the COSMIN taxonomy does not list interpretability as a measurement property, COSMIN still considers it to be a vital characteristic in the assessment of measurement instruments (Mokkink et al., 2010b). Interpretability refers to the extent to which qualitative meaning in the form of clinical or commonly used

connotations, can be assigned to the quantitative scores or change in scores of an instrument (Mokkink et al., 2010a).

2.4 Eczema

Eczema, synonymous with atopic dermatitis, is a chronic, itchy, inflammatory skin disease (Weidinger and Novak, 2016). It is a highly common skin condition that usually develops in early childhood, typically within the first two years of life (Williams and Strachan, 1998b, Herd et al., 1996, Wollenberg et al., 2016).

The global prevalence of eczema is approximately 20% in children and 3% in adults, although latest estimates suggest that 7% to 14% of adults are affected by eczema (Nutten, 2015, Abuabara and Langan, 2022). The largest eczema prevalence data originates from the International Study of Asthma and Allergies in Childhood (ISAAC) epidemiological studies, involving over 1 million children and adolescents with mild to moderate eczema in 97 countries (Williams et al., 1999). The ISAAC findings indicate that eczema has reached a level of public health concern globally, affecting both developed and low income countries (Odhiambo et al., 2009). Eczema appears to have reached a high plateau in industrialised countries with the highest disease prevalence, such as the UK and New Zealand (Mallol et al., 2013). Nonetheless, an increasing trend has been noted in Western Europe and regions of Northern Europe (Deckers et al., 2012) as well as in low-income countries, such as Latin America and South East Asia (Williams et al., 2008). Moreover, a comprehensive systematic review of 378 epidemiological studies from 1958 to 2017 also showed a general increase in eczema prevalence worldwide, especially in Africa, Asia and the USA (Bylund et al., 2020).

2.4.1 Clinical features, diagnosis and persistence of eczema

The main clinical features of eczema include intense itchiness (pruritus) and generalised skin dryness (xerosis). Eczematous lesions can become red or dark

depending on skin colour and cause symptoms such as: bleeding, oozing, swelling, cracking and flaking of the skin (Figure 2.4).

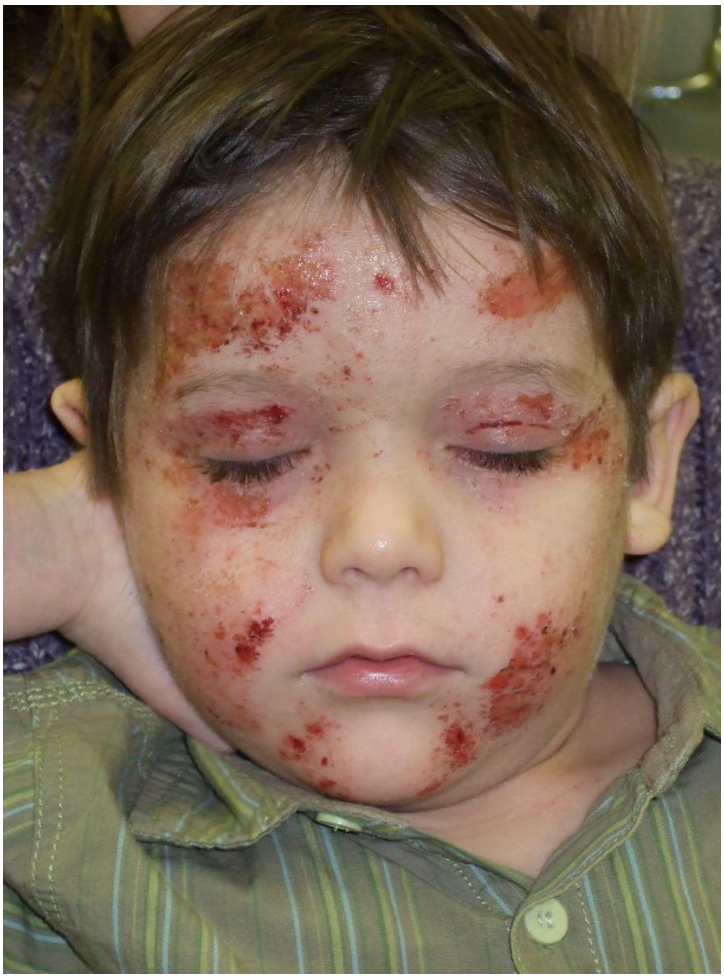


Figure 2.4 Clinical representation of severe eczema

Note. Used with permission.

Eczema is characterised by a waxing and waning disease course leading to periods of acute exacerbations, called flares, followed by relative remission (Wollenberg et al., 2016). Flares intensify pruritus that often triggers localised scratching (excoriation), which may result in thickening of the skin (lichenification) or skin damage at the affected area, increasing the risk of secondary infections.

A multitude of microbiota inhabit the epithelial surfaces in humans, including the Staphylococcus aureus bacteria that is present on healthy skin without causing

harm. However, the skin of patients with eczema has a decreased microbiome diversity with a relative abundance of Staphylococcus aureus that can colonise eczematous and pruritic lesions, resulting in infection (Weidinger and Novak, 2016). Bacterial colonisation contributes to the worsening of the disease (Rangel and Paller, 2018). Although eczema can affect any regions of the body, the appearance, location and distribution of lesions follow an age related pattern (Weidinger and Novak, 2016). In a systematic review and meta-analysis, it was found that paediatric patients typically had eczema on the eyelid, ear area and wrist, whereas adults usually exhibited eczema on the hand and foot (Yew et al., 2019).

Due to the lack of definitive laboratory and histological markers for the diagnosis of eczema, the diagnosis relies on past medical history combined with physical examination of clinical features. Hanifin and Rajka (1980) provided the first diagnostic criteria, listing the main clinical features for the diagnosis of eczema. The UK Working Party (UKWP) had empirically derived and simplified this criteria, creating a minimum set of reliable discriminators for the identification of eczema that can be applied in epidemiological and clinical research (Williams et al., 1994a).

Validation studies of the UKWP criteria indicate higher overall sensitivity and specificity compared to the original criteria (Williams et al., 1994a, Williams et al., 1996). According to a systematic review on eczema diagnostic criteria, the UKWP criteria has been the most extensively validated, warranting its use in interventional studies (Brenninkmeijer et al., 2008). This standardised criteria is often used in eczema clinical trials for eligibility screening. The UKWP diagnostic criteria includes the mandatory presence of an itchy skin condition, in addition to 3 or more of the following features: onset of the disease below the age of two, history of skin creases involvement, history of a generally dry skin in the preceding year, history of asthma or hay fever and visual flexural eczema (Williams et al., 1994a).

Eczema can be divided into the following severity strata: mild, moderate and severe. An early cross-sectional survey of 1760 children with eczema living in Nottingham reported the severity distribution of eczema in the community as follows: 84% mild, 14% moderate and 2% severe (Emerson et al., 1998). Subsequent studies confirmed predominant mild disease prevalence in children in the community (Kim et al., 2012). Results from a recent international cross-sectional survey of 8 countries, including the UK, highlighted that mild and moderate eczema severity was the most common presentation of eczema in adults (Barbarot et al., 2018). This study was among the few studies that looked at the severity distribution in adults.

There is a variation in eczema disease activity and persistence. Eczema is characterised by early age onset and it is estimated that 60% of cases in the UK are diagnosed in the first year of life. Eczema is considered to be a childhood disease and prevalence decreases with age, but the evidence is conflicting. Results of birth cohort studies (Williams and Strachan, 1998a, Eller et al., 2010, Ellis et al., 2012, Ballardini et al., 2012) and a population based follow-up study (von Kobyletzki et al., 2014) suggest spontaneous eczema resolution during childhood. Indeed, a recent systematic review and meta-analysis of 45 longitudinal studies concluded that in 80% of cases eczema resolved by age 8, although children with more severe eczema and later disease onset were likely to continue to have eczema in adulthood (Kim et al., 2016). However, this study may have underestimated eczema persistence because it did not evaluate disease activity following the initial period of disease clearance, which is an important assessment given the fluctuating nature of eczema. In other words, participants might have been in remission when assessments were performed, but later relapsed.

A cohort study, assessing 7157 patients from the US Pediatric Eczema Elective Registry of Pimecrolimus users, found that over 80% of patients across all age groups ranging from 2 to 26 years old had either persistent eczema or used treatments for it. Furthermore, only half of them achieved a six-month inactive

disease period by the age of 20 (Margolis et al., 2014). Other prevalence estimates also suggest that eczema is a lifelong condition that may persists throughout life (Silverberg and Hanifin, 2013, Mortz et al., 2015). Even if patients have outgrown the disease, they will likely to be prone to having sensitive, hyperreactive skin and might have eczema recurrences after long symptom free periods (Garmhausen et al., 2013). In addition, eczema is associated with the development of allergic chronic conditions, such as asthma, allergic rhinitis (hay fever) and food allergy (Gordon, 2011). This phenomenon is known as the atopic march.

2.4.2 Pathogenesis of eczema

The exact aetiology of eczema is not fully known, but is likely to be multifactorial involving a complex interrelated combination of genetic, environmental and immunological factors (Peng and Novak, 2015). The main features of eczema include skin barrier (epidermis) dysfunction and immune dysregulation characterised by altered immune responses (Brunner et al., 2018). A healthy epidermis provides physical and functional protection against exogenous pathogens. However, in eczema the epidermis is often compromised leading to: alterations in the lipid content of the skin, increased transepidermal water loss and raised skin pH. These factors make the skin vulnerable to the penetration of microbial pathogens, allergens and irritants leading to dry skin, itchiness and inflammation (Flohr et al., 2010).

Numerous genetic factors influence skin integrity in eczema, including mutations in the gene encoding the structural protein filaggrin (FLG) (Palmer et al., 2006). Loss-of-function FLG mutations represent the major genetic risk factor for developing eczema (Smith et al., 2006, Thyssen et al., 2013). FLG mutations are associated with early onset, increased eczema severity, more persistent disease and more frequent secondary skin infections (Rodríguez et al., 2009, Irvine et al., 2011, Margolis et al., 2012). FLG mutations are present in approximately 50% of European and 27% of Asian patients with eczema (Brown and Irwin McLean,

2012, Park et al., 2015). Whereas in African populations FLG mutations are less common (Winge et al., 2011) or even absent (Thawer-Esmail et al., 2014). While up to 50% of eczema patients carry a FLG mutation, not all individuals with FLG mutations develop eczema (Gupta and Margolis, 2020).

The role of immunological factors in the pathogenesis of eczema has gained momentum in recent years (Sullivan and Silverberg, 2017). Immune dysregulation marked by an overactive response in the skin can be present in some patients with eczema. In such cases, centralised T-helper 2 (Th2) immune response occurs causing the overproduction of cytokines. These cytokines are signaling proteins involved in the mediation and regulation of inflammation and immunity, particularly proinflammatory interleukin (IL)-4 and IL-13 (Guttman-Yassky and Krueger, 2017). This upregulation promotes skin inflammation, leading to reduced FLG expression that aggravates the epidermal defect, which results in increased sensitivity to allergens (Howell et al., 2009).

Consequently, elevated Immunoglobulin E (IgE) production may occur, causing allergic responses. The presence of IL-4 and IL-13 connects the skin barrier abnormalities directly to the immune system, showing that eczema can also develop as a result of cutaneous inflammation (Hanifin, 2009). Some patients are affected by immunological anomalies more strongly than by skin barrier defects and vice versa.

Twin studies suggest that genetic predisposition plays a significant role in eczema (Schultz Larsen et al., 1986, Schultz Larsen, 1993). The latest systematic review of population based twin studies has reported a significantly higher concordance rate for eczema in monozygotic (identical) twins (85%) than in dizygotic (non-identical) twins (21%) (Elmose and Thomsen, 2015). Furthermore, the heritability of eczema was approximately 75%, respectively (Elmose and Thomsen, 2015).

Demographic and environmental factors are considered to play a role in the development of eczema (McNally et al., 2000). An increased risk for eczema is

associated with higher socioeconomic status (Williams et al., 1994b, Apfelbacher et al., 2011, Ban et al., 2018), higher education level (Shaw et al., 2011) and black and Asian ethnicity (Lee and Lim, 2003, Shaw et al., 2011). Furthermore, living in an urban area is a substantial risk factor for eczema (Schram et al., 2010). Conversely, rural living is associated with the remission of eczema (von Kobyletzki et al., 2014). Accumulating evidence suggests a link between migration and eczema. Immigrants moving from developing countries to industrialised countries tend to acquire the eczema rate of the local population (Garcia-Marcos et al., 2014). These findings point towards the so called 'hygiene hypothesis' which posits that exposure to pathogens in early childhood can protect against eczema (Strachan, 1989). Results of a systematic review indicate that bacterial endotoxins, farm animals, dogs and day care attendance have a protective effect from eczema (Flohr et al., 2005). However, exposure to cats in the presence of FLG mutations is associated with the risk of developing eczema (Flohr and Yeo, 2011). Furthermore, a large birth cohort study in the UK found that having older siblings can have a protective effect against eczema (McKeever et al., 2002).

Lifestyle and dietary habits also play a role in the aetiology of eczema (Kantor and Silverberg, 2017). An analysis of ISAAC data found that paediatric eczema was linked to fast food, pasta and butter consumption, suggesting that Western diet may precipitate eczema (Ellwood et al., 2013). According to a systematic review and meta-analysis, smoking and exposure to passive tobacco smoke is strongly associated with childhood eczema (Kantor et al., 2016).

Moreover, the use of soap and detergents, especially fragranced personal care products, can further disrupt the impaired skin barrier causing worsened itch in people with eczema (Kantor and Silverberg, 2017). Many eczema patients anecdotally report flares in response to climate changes. A prospective cohort study found that high temperature, increased humidity and sun exposure resulted in poor disease control (Sargen et al., 2014). Further factors, such as: sweating, dust, shampoo and nylon clothing directly contribute to the deterioration of

eczema (Langan and Williams, 2006). In addition, certain foods, stress, house dust mite and seasonal factors can trigger eczema flares (Langan et al., 2009). It is clear that environmental exposures can contribute to the development of eczema, however the particular roles (protective or harmful) of different environmental factors is not fully understood (Thomas et al., 2014, Kantor and Silverberg, 2017).

2.4.3 Treatment of eczema

At present eczema cannot be cured, therefore the main focus is the effective management of the disease, consisting of various aspects such as: avoiding triggers, improving symptoms and skin hydration, protecting the skin barrier, decreasing disease severity, reducing inflammation and preventing the deterioration of eczema to achieve long-term disease control.

Numerous clinical trials have been conducted on the treatment and prevention of eczema. A scoping review identified 287 RCTs, conducted between 2000 and 2013, that evaluated 92 different treatments (Nankervis et al., 2016). In terms of eczema prevention studies, another systematic review found 39 clinical trials assessing potential interventions for preventing this chronic disease (Foisy et al., 2011). The most recent RCT looked at daily emollient application during the first year of life and found that it did not prevent eczema, food allergy, asthma or hay fever (Bradshaw et al., 2023).

In 2007, the National Institute for Health and Care Excellence (NICE, 2007) in the UK published a national guideline for the treatment of eczema in children younger than 12 years old. NICE recommends a holistic approach to eczema assessment that encapsulates disease severity alongside QoL and psychosocial wellbeing. It also promotes a stepwise approach to the management of eczema, whereby the treatment is tailored to disease severity (NICE, 2007). Emollients such as creams, ointments, lotions, gels, sprays and bath additives are considered the first line of treatment. Emollients help to repair the skin barrier,

improve skin texture and alleviate the itching caused by excessive dryness (Leung et al., 2004). Hence, emollients form the cornerstone of effective eczema management (NICE, 2007). The use of emollients is imperative in all disease severities, even when the eczema is clear and while using other eczema treatments. Whereas topical corticosteroids (TCSs) are considered the first line therapy for the treatment of flares. TCSs provide effective relief from symptoms, however their prolonged use carries potential safety issues, including cutaneous adverse events. Therefore, TSCs are intermittently used to manage exacerbations (NICE, 2007).

According to the severity of symptoms, NICE recommends the following treatments alongside emollients: for mild eczema mild potency TCSs; for moderate eczema moderate potency TCSs, topical calcineurin inhibitors and bandages; for severe eczema potent TCSs, topical calcineurin inhibitors, bandages, phototherapy and systemic therapy (NICE, 2007). Currently, NICE guidelines do not exist for the treatment of eczema in patients older than 12. However, the Scottish Intercollegiate Guidelines Network (2011) provides eczema management guidance for adults alongside children.

The successful management of eczema is based on the appropriate application of topical eczema treatments. However, following treatment regimens can be challenging and burdensome for patients, particularly for carers of children with eczema. Several studies have reported poor adherence to treatment use in paediatric patients (Ellis et al., 2011, Sokolova and Smith, 2015) and it remains the main reason for treatment failure (Santer et al., 2013). Barriers to treatment adherence are associated with a range of factors, including: doubts about the effectiveness of topical treatments, practical barriers to topical treatment use, worries about side effects, not considering eczema as a chronic condition that requires long-term treatment (Capozza and Schwartz, 2020, Teasdale et al., 2021). In fact, eczema is sometimes trivialised even by healthcare professionals, leading to the provision of conflicting and suboptimal advice about topical treatments (Teasdale et al., 2021).

In addition to topical treatments, other therapeutics such as phototherapy and systemic treatments play an important role in managing uncontrolled eczema (Sidbury et al., 2014). Phototherapy involves exposing the skin to different wavelengths of ultraviolet light and it is usually used when topical treatments do not provide improvement and relief for patients (Davis et al., 2023). On the other hand, systemic therapy is used in patients with moderate to severe eczema. Systemic therapy involves the administration of oral corticosteroids, immunosuppressants or monoclonal antibodies (biologics). Due to the risk of potential side effects, close monitoring by clinicians is recommended (Davis et al., 2023).

The majority of eczema cases are managed in primary care, often utilising the trial and error approach in the selection of treatments. However, this method is viewed by carers of children as frustrating, dismissive and unhelpful (Santer et al., 2012). The lack of sufficient personalised information and support can be perceived negatively by those living with eczema, resulting in involuntary autonomy that requires patients to self-manage eczema by default instead of working in partnership with healthcare professionals (Noerreslet et al., 2009). A person-centred approach is crucial in the treatment of eczema because it enables the effective management of this debilitating condition and alleviates the burden on people living with eczema and helps to improve their QoL.

2.5 Measuring outcomes in eczema clinical trials

The HOME initiative aims to develop and standardise a consensus-derived COS for eczema to be measured in clinical trials (Schmitt and Williams, 2010). In 2010, the first HOME consensus meeting (HOME I) was held as part of an eczema conference in Munich to determine whether the international eczema community was interested to establish a global collaborative group to perform outcomes research in eczema (Schmitt and Williams, 2010). The meeting indicated a genuine interest from international stakeholders to work together as part of HOME, making HOME a truly global initiative. HOME has over 400

members worldwide from relevant stakeholder groups, including: clinicians, methodologists, patients, regulatory bodies, journal editors and pharmaceutical industry representatives (HOME, 2022). The HOME initiative is also supported by a larger international collaboration, called the Cochrane Skin-Core Outcome Set Initiative (CS-COUSIN, 2014). To improve outcome measures in clinical trials, the CS-COUSIN aims to enhance the quality of COS in dermatology, which in turn strengthens the interpretability of dermatology systematic reviews, enabling evidence-based clinical decision making that ultimately improves patient care (CS-COUSIN, 2014).

In 2015, the HOME roadmap methodological framework was created as a guide to standardise the development of COS in dermatology (Schmitt et al., 2015). In developing this roadmap, the HOME multidisciplinary group drew on their experience and expertise in eczema outcomes research. According to the HOME roadmap the development of COS comprises of 4 distinct steps.

Step 1 of the HOME roadmap contains the definition of the scope and applicability of the COS, including the population of interest, setting and geographical area (Schmitt et al., 2015). It is important to identify and involve key stakeholders throughout the COS development process (Schmitt et al., 2015). For the development of COS in eczema, HOME involved all relevant stakeholders as described above. Step 2 of the roadmap requires a consensus process with stakeholders to decide on the domains that should be included in the COS (Schmitt et al., 2015). The application of the consensus process helps to prevent the potential dominance of individual stakeholders and allows others to express their views and make the decisions more representative. Before the HOME I consensus meeting took place, the HOME group conducted an online international Delphi exercise, reaching consensus on the inclusion of the following three domains in the COS: symptoms, clinical signs measured by a physician and long-term control of eczema (Schmitt et al., 2011). A discussion took place among stakeholders regarding the potential inclusion of QoL as a fourth domain in the COS. While clinical experts, journal editors and EMA

representatives advocated for the inclusion of QoL in the COS, surprisingly most patients (67%) were opposed to including it as a core domain (Schmitt et al., 2011) In 2011, the HOME II consensus meeting took place in Amsterdam with the aim to refine and confirm the COS domains derived through the Delphi process (Schmitt et al., 2012). Group discussion techniques and anonymous consensus voting occurred. The previously agreed core outcome domains of symptoms, clinical signs and long term control of eczema were confirmed by the stakeholders attending this meeting (Schmitt et al., 2011). During the group discussions it was evident that stakeholders, including patients, favoured the inclusion of QoL in the COS as it was considered an important outcome to be measured in upcoming trials. Consequently, 76% of stakeholders agreed to add QoL as a core domain. Broad consensus across the panel resulted in the recommendation of the following four domains: symptoms, clinical signs, long-term control of eczema and QoL. It was agreed that these domains should be measured in all future eczema clinical trials (Schmitt et al., 2012).

Step 3 of the HOME roadmap involves the identification, validation or, if necessary, the development of a suitable measurement instrument for every core outcome domain (Schmitt et al., 2015). This is a comprehensive iterative process that consists of five stages as outlined in Figure 2.5. For the clinical signs domain HOME members followed the methods described in step 3 of the roadmap, whereby a systematic review was conducted to identify instruments and their measurement properties (Schmitt et al., 2013). The results were presented at the HOME III consensus meeting in 2013, leading to the recommendation of the Eczema Area and Severity Index (EASI) instrument for the measurement of the clinical signs core domain (Chalmers et al., 2014).

<table>
<tr><th></th><th>Stage 1</th><th>Stage 2</th><th colspan="3">Stage 3</th><th>Stage 4</th><th>Stage 5</th></tr>
<tr><td>Task</td><td>Identify all instruments previously used to measure the domain.</td><td>Establish the extent and quality of testing of the identified instruments.</td><td colspan="3">Determine which instruments are good enough quality to be shortlisted for further consideration.</td><td>Carry out complementary validation studies on shortlisted instruments.</td><td>Finalise the core outcome instrument for the domain.</td></tr>
<tr><td rowspan="2">Methodology</td><td rowspan="2">Systematic review of instruments used.</td><td rowspan="2">Systematic review of validation studies of the identified instruments, highlighting validation gaps.</td><td colspan="3">Apply OMERACT filter:</td><td rowspan="2">Consensus discussion and voting to determine what validation studies will be conducted on shortlisted instruments.
Gaps in testing were highlighted in stage 2 (systematic review).
Appropriate methods used to fill the validation gaps.</td><td rowspan="2">Reapply the OMERACT filter with the results of the completed validation studies.
Consensus discussion and voting on core outcome to be recommended.</td></tr>
<tr><td>Truth:
“Is the measure truthful, does it measure what it intends to measure? Is the result unbiased and relevant?”</td><td>Discrimination:
“Does the measure discriminate between situations that are of interest?”</td><td>Feasibility:
“Can the measure be applied easily in its intended setting, given constraints of time, money and interpretability?”</td></tr>
<tr><td></td><td></td><td>Consensus discussion and voting on: face validity, content validity, construct validity and criterion validity.</td><td>Consensus discussion and voting on: reliability and sensitivity to change.</td><td>Consensus discussion and voting on: time take, cost and interpretability.</td><td></td><td></td></tr>
<tr><td>Output</td><td>Long list of all instruments previously used to measure the domain.</td><td>Summary of the quality and extent of testing of instruments.</td><td colspan="3">Shortlist of potential instruments that meet the requirements of the OMERACT filter.</td><td>Shortlist of fully tested instruments.</td><td>Recommended core outcome instrument for the domain.</td></tr>
</table>

Figure 2.5 Step 3 of the HOME roadmap, adopted from Schmitt et al. (2015)

In order to progress the patient-reported symptoms domain, a systematic review was performed to identify instruments that were used for assessing symptoms in eczema RCTs (Gerbens et al., 2016). A further systematic review evaluated the measurement properties of patient-reported symptoms instruments (Gerbens et al., 2017). This review was guided by the COSMIN checklist and taxonomy that helped to establish the methodological quality of the included studies and provided an overall conclusion on the quality of the measurement instruments (Gerbens et al., 2017). Consequently, at the HOME IV meeting in Malmö, POEM was selected as the core instrument to measure the patient-reported symptoms domain (Chalmers et al., 2016). However, it was highlighted that subsequent work with POEM was needed to address the remaining validation gaps.

For the long-term control of eczema domain, the first stage of step 3 of the HOME roadmap was used through a systematic review that assessed how long-term control was measured in published eczema RCTs (Barbarot et al., 2016). In 2018, the findings of this review were presented at the HOME V meeting in Nantes. These findings highlighted difficulties with measuring this domain, leading to a consensus to measure specific constructs as part of the long-term control domain (Chalmers et al., 2018). Moreover, it was recognised that determining the optimum frequency and timing of outcome assessments were important aspects of the COS that should be established by further work.

In 2019, the latest consensus meeting (HOME VII) was held in Tokyo, where the conceptual model for the construct of long-term control was demonstrated (Howells et al., 2020). Furthermore, two novel instruments were presented that were specifically developed to measure long term control, namely: Recap of Atopic Eczema (RECAP) and Atopic Dermatitis Control Test (ADCT) (Thomas et al., 2021). Both instruments were deemed to be of high quality and very similar in content, which made it difficult to choose between the two. Hence, it was agreed to include both instruments for the time being and either can be selected to measure the long-term control domain until further validation studies are conducted (Thomas et al., 2021).

In addition, results of an updated systematic review on measurement properties of QoL instruments for infants, children and adults with eczema were also presented (Gabes et al., 2020). It was acknowledged that existing QoL instruments for eczema were designed for different age groups and there was no available instrument that could be used in all ages. Based on evidence and discussion, consensus was reached on recommending the three well-validated and most frequently used instruments for measuring quality of life: for adults the Dermatology Life Quality Index (DLQI), for children the Children's Dermatology Life Quality Index (CDLQI) and for infants the Infant's Dermatology Quality of Life Index (IDQoL) (Thomas et al., 2021).

Previous HOME meetings have indicated that itch intensity should be measured within the patient-reported symptoms domain, in addition to POEM. At HOME VII, a systematic review on measurement properties of patient-reported outcome measures for itch intensity was presented followed by an updated systematic review on eczema symptoms, including itch (Gerbens et al., 2017). Based on the available evidence, guided by COSMIN methodology, the peak itch numerical rating scale (NRS)-11 past 24 hours was recommended for measuring the intensity of itch as part of the patient-reported symptoms domain. However, the peak itch NRS-11 is only applicable to those patients who can self-report, such as older children and adults, and cannot be used by proxy (Thomas et al., 2021).

At present, the COS for eczema clinical trials is complete (Williams et al., 2022). The agreed core outcome domains and instruments, shown in Figure 2.6, should be used in all future clinical trials and systematic reviews of eczema interventions. It should be noted that a COS is always regarded as preliminary, allowing new studies to inform the revision and refinement of the existing COS (Schmitt and Williams, 2010).

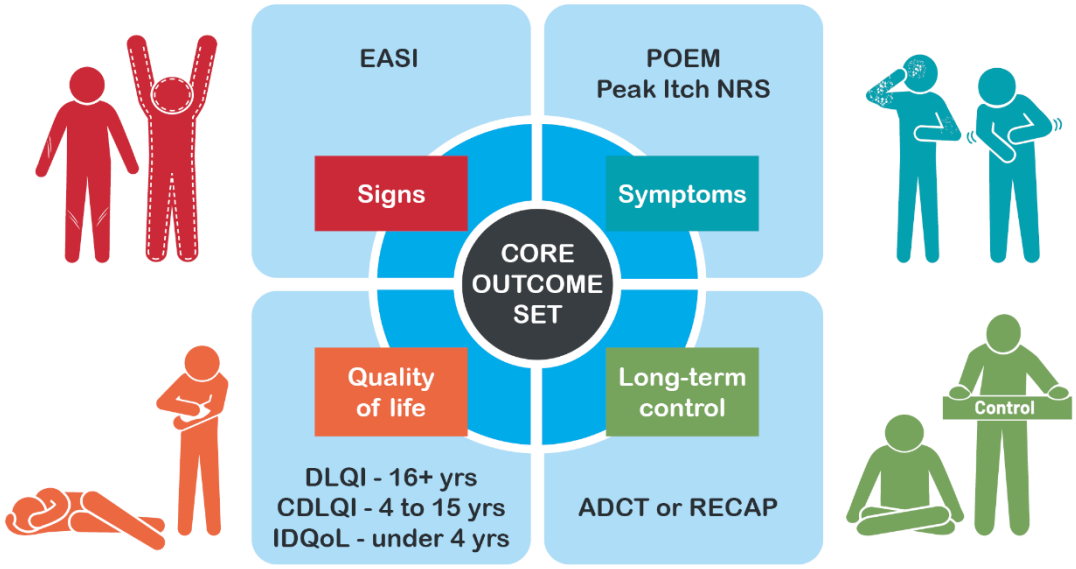


Figure 2.6 HOME recommended COS to be included in all eczema trials

Note. ©University of Nottingham (2023)

EASI= Eczema Area and Severity Index; POEM=Patient Oriented Eczema Measure; Peak Itch NRS=Peak Itch Numerical Rating Scale; DLQI= Dermatology Life Quality Index; CDLQI= Children's Dermatology Life Quality Index; IDQoL= Infant's Dermatology Quality of Life Index, RECAP=Recap of Atopic Eczema; ADCT: Atopic Dermatitis Control Tool.

Since the publication of the HOME roadmap, the COSMIN initiative in collaboration with COMET published a consensus-based stepwise guidance in relation to the selection of outcome measurement instruments for COS outcomes (Prinsen et al., 2016). Similar to the HOME roadmap, it recommends the selection of only one measurement instrument per COS domain (Prinsen et al., 2016). Therefore, additional validation work of the long-term control measurement instruments is needed to be able to decide which one should remain in the COS.

The HOME roadmap is crucial as it involves the dissemination and implementation of COS. The dissemination of COS recommendations in appropriate formats via various platforms is of high importance because it helps to reach all relevant stakeholders within the target field that enables the

implementation of COS, which in turn prevents research waste (Schmitt et al., 2015).

Vincent et al. (2020) assessed the uptake of HOME COS in 177 Phase III/IV eczema trials, conducted between 2005 to 2018, and found that only 33% trials included the full COS, 92% used EASI and only 17% used POEM. From 2018 to 2022, the use of EASI and POEM in RCTs increased to 94% and 60%, however the lack of appropriate reporting across studies hindered evidence synthesis (Lam et al., 2023). These findings highlight a challenge in COS implementation.

In 2021, the HOME IX virtual meeting identified key barriers related to implementation, including: stakeholder awareness and engagement, applicability of the COS across diverse populations, practicality and administrative burden associated with its use (Jacobson et al., 2023). During this meeting, working groups were formed and the HOME COS implementation project was launched (Jacobson et al., 2023). It became apparent that implementing the COS was a complex process, highlighting the need for guidance.

At the HOME X meeting, held in Montreal, the evidence-based HOME implementation roadmap was presented as demonstrated in Figure 2.7 (Leshem et al., 2023). It provides a pragmatic guide to implementing the HOME COS to enhance the consistent use of outcome measures in eczema RCTs. This framework enables the conduct of systematic reviews and meta-analyses, supporting therapeutic decision making and ultimately improving patient care.

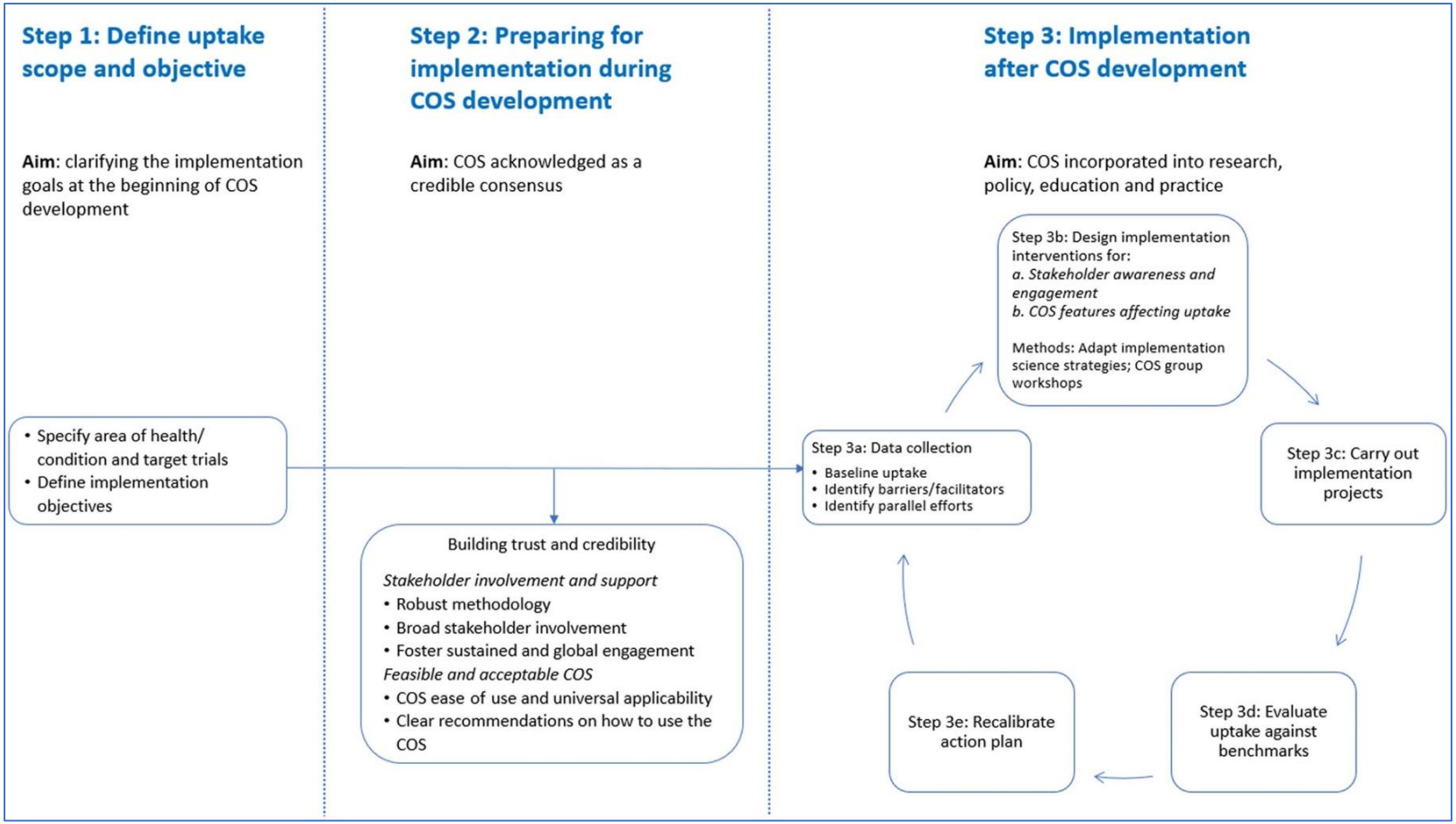


Figure 2.7 HOME implementation roadmap

COS=Core Outcome Set; HOME=Harmonising Outcome Measures for Eczema.

Chapter 3 Evaluating the effect of weekly patient-reported symptom assessments on trial outcomes: an online, parallel group, randomised controlled trial

This work has been published in the British Journal of Dermatology (Baker et al., 2023).

3.1 Introduction

This chapter reports the findings from the EMO trial that evaluated the effect of weekly symptom assessments on trial outcomes, using PROMs. The aim was to improve the design of future eczema trials, helping the accurate evaluation of interventions. Furthermore, as highlighted in Chapter 1, this RCT filled a longstanding research gap for the HOME initiative, whereby providing evidence on the optimum frequency of PROM assessment which aids consensus discussions on how often to measure PROMs in upcoming trials. This chapter provides the rationale for the study, followed by a detailed description of the methods and results. Next, the findings of the study are summarised and considered in the context of existing literature. Following that, a critical evaluation of the work is conducted, discussing the strengths and weaknesses. Lastly, the chapter explores implications for the design and conduct of future trials, offering recommendations for future research.

Chapter 2 of this thesis described the waxing and waning disease course of eczema that is characterised by periods of increased disease activity followed by relative remission (Weidinger and Novak, 2016). The fluctuating nature of eczema should be considered when designing clinical trials. In recent years, numerous RCTs in eczema have been conducted (Nankervis et al., 2017). Patient-reported outcome measures (PROMs) capture patients' perspectives and

are increasingly utilised in RCTs (Meadows, 2011). As detailed in Chapters 1 and 3 of this thesis, the HOME initiative recommends eczema symptoms, QoL and long-term control of eczema to be measured using PROMs. POEM (Charman et al., 2004) is a HOME-recommended instrument for measuring the patient-reported symptoms domain in the COS (Williams et al., 2022). Weekly assessment of POEM has been demonstrated to be feasible and acceptable to trial participants for up to 6 months (Thomas et al., 2017, Santer et al., 2018, Ridd et al., 2019) and monthly assessment for up to 12 months (Santer et al., 2018, Ridd et al., 2019). However, the potential effects of regular symptom monitoring is unknown. In this thesis, symptom monitoring refers to self-reported or proxy reported symptom assessments.

In the context of RCTs, regular patient-reported symptom monitoring may constitute an unplanned intervention and potentially serve as a therapeutic adjunct, which can mask the treatment effect and threatens the validity of inferences (McCambridge et al., 2014a). The positive effect of symptom monitoring on trial outcomes has been noted in other chronic conditions, such as asthma (Halterman et al., 2018) and cancer (Basch et al., 2016). A proposed mechanism of action of symptom monitoring is associated with participant behaviour change, which may lead to improved adherence to treatment use (McCambridge et al., 2014b, Andreasen et al., 2020) or it could be driven by paying more attention to how the eczema is changing over time.

Thus, regular symptom monitoring may prompt participants to enhance the self-management of eczema and increase standard topical treatment use that can lead to improvements in outcomes over time. Chapter 3 presents the EMO methodological RCT in eczema that aimed to assess the impact of weekly patient-reported symptom monitoring on trial outcomes. This RCT provided an original contribution to knowledge as it was the first trial to examine whether the frequency of PROM collection affected outcomes in eczema trials, thereby advancing understanding of this topic.

3.2 Aims and objectives

The aim of the study was to inform the HOME initiative about the optimum frequency of patient-reported outcome assessments in future eczema trials.

The objectives of the EMO trial were to evaluate the effect of weekly patient-reported symptom monitoring on:

1. Eczema severity
2. Adherence to standard eczema treatment use
3. Data completeness

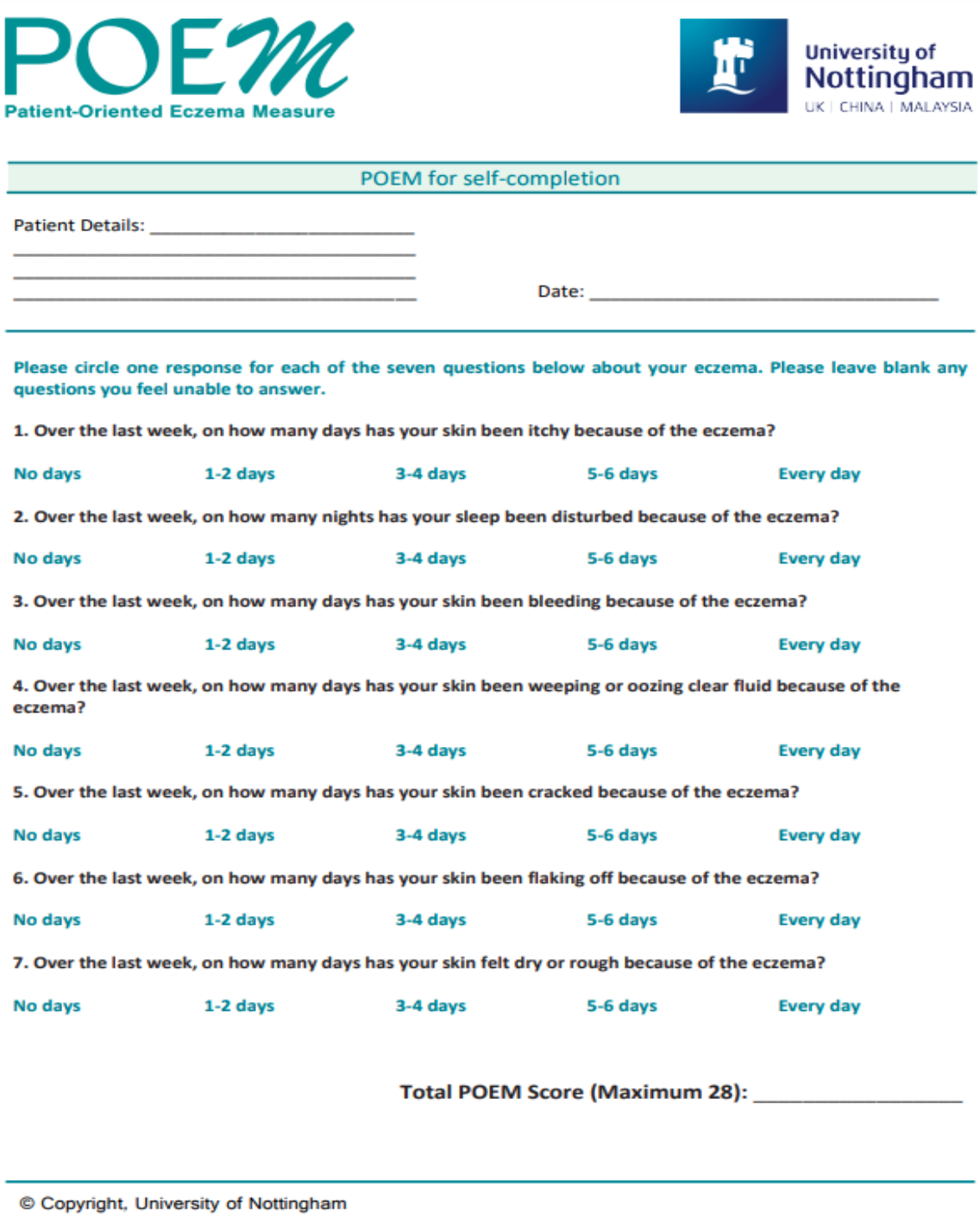
3.3 Methods

3.3.1 Study design

Online, parallel group, unblinded, RCT.

The EMO trial was an internet-based RCT that was 8 weeks long, recruiting mainly through online methods. Eligible participants were randomised to complete the POEM questionnaire online weekly for 8 weeks (intervention) or at baseline and follow-up only (control). In this uniquely designed methodological trial, POEM was both the primary endpoint and the intervention. The self-completed version of POEM is displayed in Figure 3.1. Since online PROMs are often used in eczema trials, this trial replicated the conventional approach that is usually employed in such research settings. Primary outcome data was collected at week 8 to minimise loss of data from the control group, who had no contact during this time, and to reflect the maximum period that most eczema trials would typically have between clinic visits. The EMO trial protocol was written in accordance with the SPIRIT guidelines (Chan et al., 2013). The study is reported in accordance with CONSORT guidelines for parallel group randomised trials

(Schulz et al., 2010) and per the CONSORT-PRO Extension, which is specific to trials using patient-reported outcomes (Calvert et al., 2013).



POEM
Patient-Oriented Eczema Measure

University of Nottingham
UK | CHINA | MALAYSIA

POEM for self-completion

Patient Details: _____
_____
_____
_____

Date: _____

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

2. Over the last week, on how many nights has your sleep been disturbed because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

3. Over the last week, on how many days has your skin been bleeding because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

5. Over the last week, on how many days has your skin been cracked because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

6. Over the last week, on how many days has your skin been flaking off because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

7. Over the last week, on how many days has your skin felt dry or rough because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

Total POEM Score (Maximum 28): _____

Figure 3.1 Self-completed version of the POEM questionnaire

3.3.2 Patient and Public Involvement (PPI)

The Centre of Evidence Based Dermatology (CEBD) has a Patient Panel that was established in 2009. Members of the panel are individuals affected by various skin conditions, including eczema, who want to help improve dermatology research by undertaking different activities related to projects to provide the patient perspective.

Before submission for ethical approval, I approached them via Dr Carron Layfield Patient and Public Involvement (PPI) coordinator, to gather feedback on: patient facing materials, social media adverts and wording of the treatment use secondary outcome question to ensure participants would understand it. Six PPI members provided detailed written comments on the materials and included suggestions for rewording and clarifications. For instance, in PIS it was advised to replace the word ‘trial’ with ‘study’ as it was felt that not every individual would know what a trial means. It was also suggested that the phrase ‘trial’ might have negative connotations, implying something would be tested on people and this could be discouraging in an online trial where there is no opportunity for the research team to explain concepts. Other suggestions that improved the quality of the PIS were: making the opening paragraph more engaging, using plain language, using the ‘You’ pronoun to address the reader directly to help to make it more personal. The latter was suggested for the social media adverts too. The involvement of PPI members proved to be very valuable because it provided crucial insights and new perspectives from the point of view of the target audience. By incorporating the feedback, the materials and adverts were improved in terms of clarity, relevance and inclusivity thereby allowing to foster better connection with the intended audience. An inconvenience allowance of £10 in the form of an Amazon voucher was given to each panel member as a token of appreciation for their kind contribution.

3.3.3 Ethical approval

Ethical approval to conduct this RCT was obtained on 11th June 2021 from the University of Nottingham (UoN) Faculty of Medicine and Health Science Research Ethics Committee (reference number: 238-0421) (Appendix 1).

The four principles of medical ethics (autonomy, non-maleficence, beneficence and justice) were followed in the design, documentation and conduct of the EMO trial (Beauchamp and Childress, 2001). The PIS, accessed via the trial website, described the aims and full details of what participating in the trial entailed (Appendix 2, 3). It was stated that participation was voluntary and the potential participant may withdraw from the study at any time without any negative consequences. It was also explained that taking part would have no direct benefit for the participant, but would help to improve future eczema research. Prior to taking part, obtaining informed electronic consent was mandatory. Since this study was a methodological, non-therapeutic trial, regulations for Clinical Trial of an Investigational Medicinal Product (CTIMP) were not applicable. The trial management team (myself, supervisors and statistical advisor) possessed up to date Good Clinical Practice (GCP) training.

The EMO trial was prospectively registered on the ISRCTN registry (2021) prior to starting recruitment, reference number: ISRCTN45167024. Before recruitment started, the study protocol was also published on Figshare (Baker et al., 2021). Figshare, founded in 2011, is a free public domain that provides researchers the opportunity to store and share their work beyond traditional scientific publishing and is recommended for use by the Digital Research Team at UoN. Although Figshare does not include a peer-review process, it provides a digital object identifier (DOI) for each uploaded item that makes it discoverable and citable. The use of this platform helped me to make the protocol freely available in the public domain prior to the start of the trial. To further enhance visibility, the protocol was uploaded to the CEBD study protocol portal (2023).

3.3.4 Participants

In order to meet eligibility criteria, participants had to have a diagnosis of eczema by a healthcare professional, that was either self-reported or proxy reported. This approach for establishing the presence of eczema has been used in a previous eczema study (Howells et al., 2020). In addition, POEM was used to establish eczema severity, requiring a score of ≥3 to take part. This threshold was chosen to exclude very mild or inactive eczema to help avoid possible floor effects. Furthermore, it allowed those with a mild disease to potentially improve their severity scores.

Individuals ≥1 years were eligible to take part to help enhance generalisability. Due to lack of funding to employ translating services, the ability to read and understand written English was required. Furthermore, given the online nature of the study, it was necessary to have access to the internet and to an internet-enabled device. Individuals were excluded if they were unable to provide informed consent as this was a compulsory element. Those already taking part in another eczema clinical trial at the time of enrolment were not eligible, this was to eliminate confounding and limit questionnaire burden. The eligibility criteria are listed in Table 3.1.

Since this was an online trial, participation was not limited to the UK and individuals residing in other countries were allowed to join. However, the recruitment strategy mainly focused on targeting the UK population. Postcodes were collected from UK residents to link it with Index of Multiple Deprivation (IMD) data for establishing socioeconomic status of participants.

Table 3.1 Eligibility criteria for the EMO study

Inclusion criteria
Self-report or parent/carer report of eczema diagnosis by a healthcare professional (e.g. doctor or nurse)
Person aged ≥1
If under 16 years old, informed consent to participate to be provided by parent/carer
Able to read and understand written English
Have access to internet and to an internet-enabled device
POEM score ≥3 at eligibility screening
Exclusion criteria
Unable or unwilling to provide informed consent
Taking part in another eczema clinical trial at the point of eligibility screening

3.3.5 Data collection and enrolment

3.3.5.1 Database development in REDCap

Electronic patient-reported outcome measures (ePROMs) were collected through the Research Electronic Data Capture (REDCap©, Vanterbilt University) software, which is a secure web platform for building and managing online databases (Harris et al., 2019). REDCap is a well-established and tested software that is endorsed by the UoN Clinical Database Support Service and also used by the Nottingham Clinical Trials Unit. REDCap was the software of choice

as it encompassed all the necessary features that this online trial needed for the collection of high quality data, including:

- ✓ Standardised data capture
- ✓ Data entry validation
- ✓ Branching logic
- ✓ Calculated fields
- ✓ Mandatory fields
- ✓ Eligibility screening
- ✓ Audit trail
- ✓ Automation
- ✓ Blocked stratified randomisation
- ✓ Data transfer to statistical packages (e.g. Stata)
- ✓ Personalised email reminders

I was responsible for developing the trial database in REDCap and received guidance and practical support from Daniel Simpkins who was the senior data manager at the UoN Clinical Database Support Service. He provided me with a password and set up a project identification code. I was assigned the role of project administrator and was granted a set of permissions (custom user rights) that allowed me access to build the database independently. The project was in development status during the set up period, and real data could not be entered until it was moved to production status. Projects in REDCap are based on webpages, called data collection instruments, and they are built through tools and functionalities available in the project set up tab. This platform is highly flexible and allows the user to customise the dataset based on their preferences, including: how many instruments to be included, name for each tool, what data is captured in each, how that data is displayed for the participants and how it is stored afterwards. The number and order of instruments was an important consideration when building the database for this project and it was equally important how data was entered on each instrument.

The instruments were built and modified through both tools, the online designer and data dictionary, and refining the instruments was a key step in the development mode. These two methods of instrument development could be used interchangeably and REDCap updated both tools automatically each time a change was made to the instrument through either method. This was a key feature as possessing an up to date data dictionary was essential for performing the statistical analysis, discussed later in this chapter.

Each PROM tool was set up as a standalone instrument, leading to the use of multiple instruments which was a recommended method by the developers as it creates flexibility in data entry, modifications and helps to control user access. Every data collection tool reflected the exact content of the paper version of the validated eczema instrument. However, the layout of the data entry fields for the response options of the instruments had to be adjusted to accommodate the preferred vertical display mode on digital devices, as opposed to the usual horizontal layout used in the paper version of the respective questionnaires. In REDCap, a self-completed version (A) and a proxy completed version (B) was created for every instrument used in the EMO trial. The draft of each and all instruments could be previewed separately or together, allowing to view what the participant would see. In addition, the project administrator permission enabled the entry and submission of practice data that participants would see which reflected the real trial scenario. This helped the detection of occasional errors that went unnoticed.

REDCap automatically generated and allocated a unique study ID number for each participant, which de-identified the participant and ensured that the data was anonymised. Consent forms and personally identifiable information were automatically removed from the study dataset and were stored in a different location within REDCap. A secure hyperlink to the instruments was set up to be self-operating in the system, according to group allocation. Once participants received the unique link to their given email address or mobile phone number,

they were able to access the questionnaires through the link and securely complete them without the need to login. Another useful attribute of the software ensured that instruments could only be completed once per participant. Furthermore, REDCap provided a date and time stamp for each data entry, which helped to establish the typical signup and questionnaire completion time.

User testing the database was critical before the real data collection commenced and it was piloted by 20 people including friends and family, staff at CEBD and the Nottingham Clinical Trials Unit. Based on feedback, the major problem was that the eligibility screening malfunctioned, allowing individuals to proceed to the next page despite REDCap stating they did not meet the eligibility criteria. A few minor formatting issues were also flagged such as: order of questions in the outcome measures and asking for contact details at different pages instead of having it all at one place. All problems were addressed before the trial went live. Developing, piloting and finalising the database took me three months.

3.3.5.2 Website development

Given that participant recruitment and enrolment into this study occurred online, it was crucial to have a dedicated study website. Since the first impression of seeing the website was likely to be a deciding factor whether or not people wanted take part in the study, it was imperative to develop a professional looking, user-friendly and trustworthy website.

NR, the research communication specialist at CEBD, had experience in website development and suggested the use of the Xerte Online Toolkit that was available at UoN. It is a free bespoke software suitable for building websites, characterised by a suite of browser-based editable templates, access to JavaScript, ease of use and accessible content creation (Xerte, 2023). A website created in Xerte can be delivered to all devices as it consists of standards compliant with HTML5 and has a responsive template that can display content on both small and mobile screens as well as large desktop computers. The attributes of this platform matched the needs of the EMO trial and did not require

information technology (IT) background, thus could be used by non-technical individuals like myself. NR supported me with the start of website building, then I took over and created the final version of the EMO study website. This happened in parallel with the database development. Apart from these activities, a study specific domain name for the website was purchased at www.123-reg.co.uk that was called emostudy.org. Linking up the study website and domain with REDCap was the final step and for this purpose, usually an application programing interface (API) or other plug-in options are needed. Opportunely, the domain provider had a web forwarding option that allowed the REDCap public survey URL to be embedded into the website through the domain platform. To check if these intricate IT processes worked simultaneously and seamlessly, the website was also piloted during the database testing and no issues transpired.

3.3.5.3 Setting up reminders

Several methodological studies have demonstrated that email and text reminders are effective at increasing the completion of questionnaires in studies and have a positive impact on the timeliness of PROM submission (Archer, 2007, Pugh et al., 2021, Cureton et al., 2021, Papa et al., 2022).

REDCap has a feature that allows for sending automatic email reminders to participants who have not completed the overdue questionnaires yet. The frequency of reminders could be specifically set, including the number of days and time of day. For the EMO study, email reminders containing the first name of the participant were set up to be automatically sent if the week 8 follow-up questionnaires were overdue by 5 days and 7 days and the timing was set to replicate the exact hour and minute when the participant signed up for the study. The reminder contained a secure hyperlink to the non-completed set of questionnaires linked to the individualised record. Of note, reminders were only sent for incomplete follow-up questionnaires at week 8. No reminders were sent for the weekly questionnaires to avoid interference with the intervention and allow to observe completion rate trends without the use of reminders.

I regularly monitored the database to identify those participants who had not responded to the two email reminders. To encourage the completion of follow-up, a final text reminder was sent to those participants who provided their mobile phone number at enrolment. The text messages were personalised, containing the name of the participant and stating why it was important to complete the final questionnaire. For this purpose, a low-cost, web-based short messaging service (SMS) provider, called Text Marketer (2023) was used. It allowed for customised sender ID, thus people receiving the text saw that it came from the EMO study and not from a suspicious phone number. This text provider also presented delivery reporting on each text, enabling to view whether the message was delivered and also if it was opened by the receiver. Even though text messages could be sent worldwide, web-based messaging services were not supported in every country, resulting in the failure of delivering the text message. Therefore, some participants in non-UK countries did not receive the text reminder.

3.3.5.4 Recruitment and enrolment

The study flow is shown in Figure 3.2. Participant recruitment took place online, mainly via social media advertisements as shown in section 4.3.4 of this thesis. The detailed recruitment strategy has been published (Baker et al., 2022a) and will be discussed in Chapter 4. A weblink to the study website was displayed in the advert about the EMO trial. Interested individuals clicked on the link, which directed them to the study website (Eczema Monitoring Online, 2021). It displayed the summary of the aim of the research, eligibility criteria, full participant information, downloadable PIS and brief introduction of research team members. Individuals interested in taking part enrolled through the website by clicking on the SIGN UP button. There was a welcome message and a statement that made it clear that by clicking the NEXT button, they were agreeing to the information provided on the website.

Upon clicking the NEXT button, the online consent form was displayed, and potential participants were required to read and complete the form and they were

asked to type their name and provide an electronic signature. According to the Health Research Authority (2018), this was an appropriate electronic method to seek and document consent. If a child was below 16 years of age and wanted to participate in the study, the parent/carer was required to provide informed consent on behalf of the child. Potential participants were informed that by proceeding to submit the online consent form, they were agreeing that they had read and understood the information provided and were willing to voluntarily take part in this study.

A completed online consent form from each participant was always obtained prior to participating in this trial and a copy was automatically sent to the email address of the participant (Appendix 4, 5). All the electronic data (Appendix 6), including consent forms, was managed, stored and organised according to the prespecified data management plan of the study (Appendix 7). Upon providing informed consent electronically and completing eligibility checks, participants were randomised. After enrolment, participants received an automated welcome email explaining the frequency of data collection, according to their randomised allocation. For the completion of the week 8 follow-up questionnaires, participants could choose to enter an optional prize draw to win one of six £20 Amazon vouchers. The summary of data variables collected in the EMO study is presented in Table 3.2.

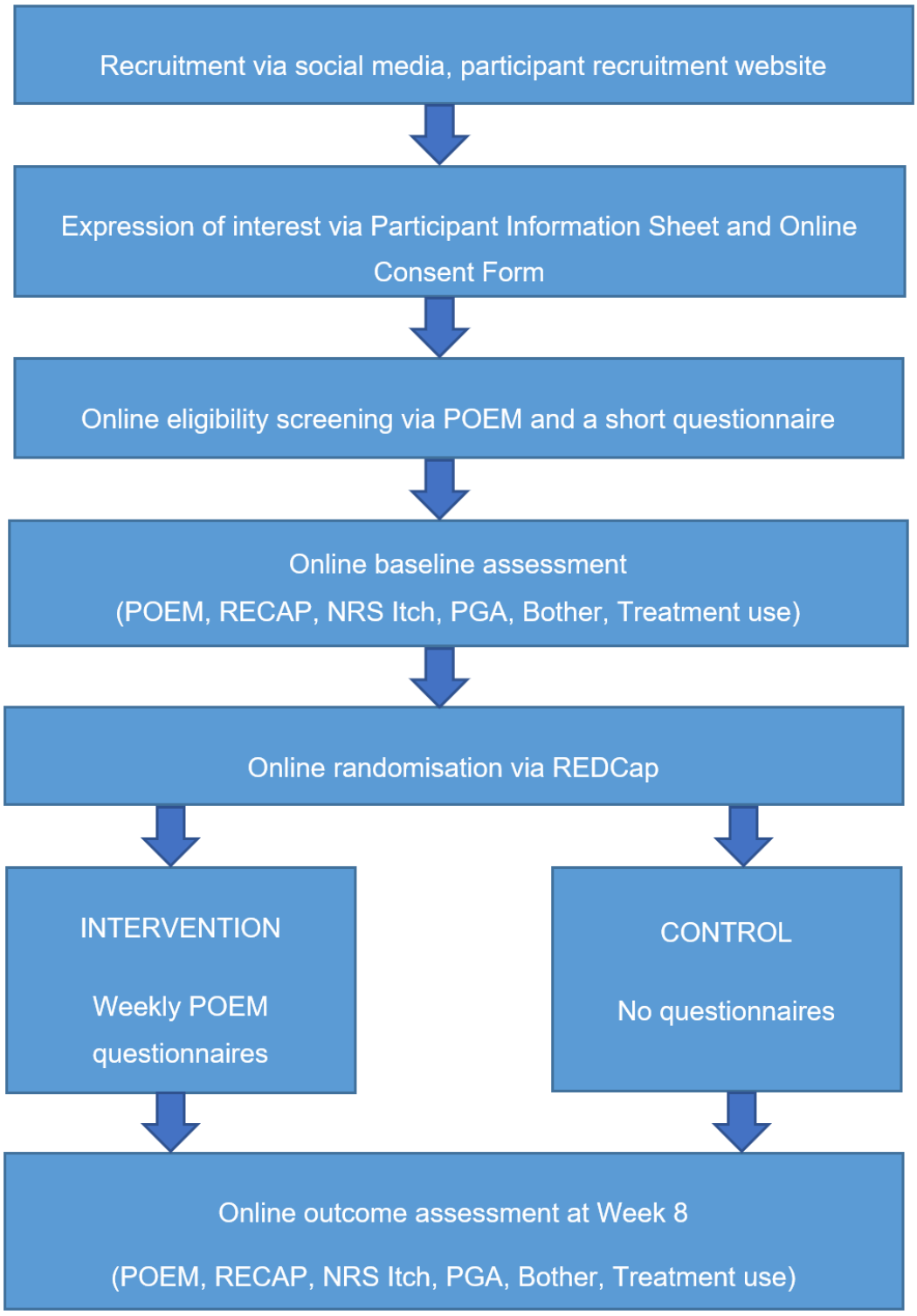


Figure 3.2 Study flow in the EMO trial

Table 3.2 Data variables collected during the EMO trial

Baseline characteristics
Age
Gender
Ethnicity
Country of residence
Postcode (UK only)
Clinical characteristics
Eczema symptoms: POEM score
Eczema control: RECAP score
Global eczema severity: PGA assessing how is the eczema on the day of sign up
Itch intensity over the last 24 hours assessed by NRS Itch (only for self-completers)
Bother caused by eczema over the last week
Emollient use over the last week
Emollient use over the last two months
Topical corticosteroid use over the last week
Topical corticosteroid use over the last two months

POEM=Patient Reported Outcome Measure; RECAP=Recap of Atopic Eczema; PGA=Patient Global Assessment; NRS Itch=Peak Itch Numerical Rating Scale.

3.3.6 Intervention

The intervention was weekly monitoring of eczema symptoms, using the POEM patient-reported questionnaire (Charman et al., 2004). The intervention group received a weblink to a weekly POEM questionnaire for 7 weeks. The control group did not receive any questionnaires during this time period. Participants were advised to use their treatments as usual.

3.3.7 Outcome measures

Two of the core domains of the HOME COS and the associated instruments were used in this trial, including the patient-reported symptoms domain measured by POEM and NRS Itch and the long-term control of eczema through using RECAP. The third PROM domain is quality of life, however this outcome was not assessed because the EMO trial was not long enough to allow for the appropriate assessment of this outcome.

3.3.7.1 Primary outcome measure

The primary outcome measure was the change in patient-reported eczema severity from baseline to week 8, measured by the POEM score (Charman et al., 2004). POEM was chosen as the primary outcome because it is a HOME recommended outcome measure and it has been extensively used in eczema clinical trials, often in online format (Santer et al., 2022). POEM is a seven-item questionnaire that assesses patient-reported symptoms over the last week, including: frequency of itch, sleep loss, bleeding, weeping/oozing, cracking, flaking and dryness (Charman et al., 2004). It provides a score from 0 to 28, with higher scores representing more severe eczema. It is a well-validated and reliable tool that demonstrates good validity, test-retest reliability and responsiveness to change and can be used to evaluate eczema severity in both children and adults (Charman et al., 2004, Gerbens et al., 2017). A reduction in the POEM score represents an improvement in eczema severity.

3.3.7.2 Secondary outcome measures

Secondary outcome measures included change in standard eczema treatment use from baseline to week 8, assessed by the number of days of emollient and topical corticosteroid use over the last week and by the frequency of treatment use over the last 2 months. The other secondary outcome was data completeness, measured as the proportion of fully completed follow-up questionnaires at week 8.

3.3.7.3 Schedule of trial assessments

The schematic representation of the schedule of trial assessments is shown in Figure 3.3, according to SPIRIT guidelines (Chan et al., 2013).

Timepoint	Week 0	From Week 1 to Week 7							Week 8
ENROLMENT:									
Eligibility Screening	✓								
Informed consent	✓								
Randomisation	✓								
GROUP ALLOCATION:									
Weekly POEM (Intervention Group)		✓	✓	✓	✓	✓	✓	✓	
No intervention (Control Group)									
ASSESSMENTS:									
Disease severity (POEM)	✓								✓
Eczema control (RECAP)	✓								✓
Itch intensity measure (NRS Itch)	✓								✓
Treatment use	✓								✓
Patient Global Assessment (PGA)	✓								✓
Global bother question	✓								✓

Figure 3.3 Schedule of trial assessments

3.3.8 Statistical analysis

3.3.8.1 Sample size

Appropriate sample size calculation is a critical aspect of clinical trial design and the following factors need to be considered:

- Statistical power: a statistical power of 80% or more is needed to ensure the detection of a true effect, if one exists
- Variability of the primary outcome variable: estimated by the means of the standard deviation (SD) of a continuous variable, a higher SD usually requires a larger sample size
- Significance level (α): 0.05 (5%) is a commonly used value
- Effect size: representing the magnitude of the difference between the study groups the trial aims to detect, generally for a smaller effect size a larger sample size is required to be able to detect a difference
- Attrition rate: accounting for this helps to preserve statistical power
- Clinical significance: established based on values of the primary endpoint in previous studies

With the involvement of Dr Christopher Partlett, statistical advisor for this project, the above statistical considerations were carefully taken into account for calculating the sample size of the EMO trial. Given that in this RCT eczema was not treated in any way, a relatively small effect size was assumed. This assumption was based on the fact that this was a non-treatment RCT with a minor intervention of weekly PROM completion. Since the study was powered for a 2.5 MCID of POEM, which was chosen to be sensitive to changes while exceeding the measurement error of 2.0 (Howells et al., 2018). This approach aimed to realistically evaluate the impact of the intervention in the context of the study design, participant population and objectives.

It was decided that even if a small between group difference was identified in the trial, it would be important for trialists to be aware of this finding due to its potential methodological implications for the design of future eczema clinical trials.

Determining the size of the trial on the basis of the primary endpoint is a commonly used approach in clinical trials. Thus, the sample size calculation was based on the ability to detect a small between group difference of 2.5 points in the primary outcome of POEM. This score is higher than the smallest detectable change of 2.13 points as calculated in a recent POEM validation study (Howells et al., 2018) and the lowest threshold of the minimal important change (MIC) for POEM. Previous validation studies have defined MIC for POEM as ≥3.0 points using trials with moderate to severe patients with eczema (Schram et al., 2012, Gaunt et al., 2016). Assuming a standard deviation of 6.5 in both groups, the estimated sample size to detect a between group difference of 2.5 points in POEM scores with 80% power and with a two-sided significance level of 5% was a total of 212 participants (106 per group). These statistical assumptions were congruent with a recent online eczema RCT that included a similar disease severity population for estimating sample size (Muller et al., 2021). Internet-based trials are more susceptible to lower retention rates than trials conducted with in-person contact. To account for this possibility, a 20% loss to follow-up was incorporated, leading to a target sample size of 266 participants (133 per group).

The Stata statistical software (StataCorp, 2021) was used to calculate the sample size. In order to learn the underlying methodology, I also performed the sample size calculation manually, using the following formula and assigned values:

$$n = \frac{2 * \delta^2 (\alpha + \beta)^2}{\mu_1 - \mu_2}$$

n = sample size in each group

μ_1 = mean in study group 1

μ_2 = mean in study group 2

$\mu_1 - \mu_2$ = the difference the trial aims to detect

δ^2 = population variance (SD)

α = significance level = 5% (0.05)

β = power = 80% (0.80)

When the significance level is set to 0.05 a value of 1.96 for α needs to be entered in the formula. Similarly, when β is chosen at 0.20 the value of 0.842 is required to be substituted for β in the formula. These values are the multipliers for conventional values for α and β (Noordzij et al., 2010). Entering the specified values into the formula yields: $2 \times 6.5^2 (1.96 + 0.842)^2 / 2.5^2 = 106.14$, which confirmed the Stata calculation that a sample size of 106 participants per group was necessary to answer the research question.

3.3.8.2 Randomisation and blinding

Participants were automatically randomised (ratio 1:1) through an online randomisation system in REDCap, installed by the senior data manager who provided support for the database building. The randomisation schedule was based on computer-generated random permuted blocks of randomly varying sizes of 2, 4 and 6. Randomisation was stratified by baseline disease severity (POEM scores: 3-7 (mild), 8-16 (moderate), 17-28 (severe)) and age (1 to < 5 years; 5 to < 16 years; ≥ 16 years). The blinding status of participants and the trial management group (TMG) is described in Table 3.3. The TMG consisted of myself, supervisory team and the statistical advisor with the purpose of designing, conducting, managing and overseeing the day-to-day activities and progress of the trial. Overall, meetings were held on a monthly basis to keep the group up to date and monitor progress to be able to identify problems at an early

stage. Since this was a low risk trial without involving a treatment intervention, having a trial steering committee was not required.

Table 3.3 Blinding in the EMO trial

Individuals involved in EMO	Blinding status and comments
Participants	**Not Blinded** Due to the nature of the intervention (weekly questionnaires) it was not possible to blind participants. We aimed to reduce contamination by not contacting participants until follow up questionnaires at week 8 were overdue.
PhD student (trial lead)	**Not Blinded** Since I dealt with all aspects of trial conduct and management, including answering participant queries and monitoring the database for discrepancies, it was not possible for me to be fully blinded. However, access to follow-up data was restricted until after database lock and the approval of the SAP.
Supervisory team	**Blinded** Unblinding occurred after database lock and the approval of the SAP.
Statistical advisor	**Blinded** The trial statistician did not any data when reviewing this SAP and did not see any unblinded data until after database lock and approval of the SAP occurred.

3.3.8.3 Analyses for the primary outcome

All analyses were performed in Stata version 17.0 (StataCorp, 2021) according to the pre-approved statistical analysis plan (SAP), which was developed by me with support from the statistical advisor. The primary analysis was based on complete cases, including only participants who completed POEM at both baseline and follow-up at 8 weeks. Descriptive statistics were used for comparing baseline characteristics of participants by randomised allocation. Estimates of the

intervention effect were presented with 95% confidence intervals (CI) and *p*-values. For the primary analysis, a linear regression model was used, adjusting for the continuous stratification variables of baseline disease severity and age. The primary outcome was based on adjusted results, but unadjusted results are also reported in this thesis.

To deal with missing data for the primary outcome, sensitivity analyses were performed by conducting imputation of missing POEM scores at week 8, using both 'best' and 'worst' case scenarios. For 'best' cases, participants were assumed to have either improved or not deteriorated scores and the best possible POEM score was given within their severity banding determined at baseline. For 'worst' cases it was assumed that participants either deteriorated or did not improve and the worst possible POEM score was allocated within their baseline severity banding. These assumptions allowed to assess the potential impact of outlined scenarios on the results and helped to explore whether these results were different from the primary analysis results. Sensitivity analyses included all randomised participants, with the exception of those who were excluded post-randomisation (n = 3).

In addition, subgroup analyses for the primary outcome were performed to explore whether the intervention effect was modified by baseline disease severity, age and socioeconomic status. Intervention effects were provided for the subgroups, but interpretation was based on the intervention-subgroup interaction, estimated by fitting an interaction term in the regression models.

3.3.8.4 Analysis for the secondary outcomes

For the analysis of the secondary outcome of treatment use, participants with missing treatment use data were excluded. Linear regression and descriptive statistics were used according to randomised allocation. For the data completeness outcome, all randomised participants were included and logistic regression was used.

3.3.8.5 Protocol deviations

The term *"Missing data"* was used to indicate the secondary outcome for data completeness in the protocol. This was subsequently replaced with the term *"Data completeness"* to avoid potential confusion relating to other types of missing data.

The impact of regular symptom monitoring on other HOME PROMs, including NRS Itch and RECAP, have been reported as exploratory findings, along with the global questions of Patient Global Assessment and eczema related bother. These instruments were originally included to inform a parallel methodological study looking at the MIC of RECAP (Chapter 6) and so were not included as named secondary outcomes.

3.4 Results

3.4.1 Participant recruitment and retention

Recruitment took place between 14 September 2021 and 16 January 2022, 400 people expressed interest in the study and 318 were assessed for eligibility. Of these, 19 did not fulfil inclusion criteria, 2 individuals were excluded due to duplicate enrolment and 1 person did not complete all baseline assessments. Thus, a total of 296 participants were randomised into the trial; 147 participants were allocated to the intervention group and 149 participants to the control group (Figure 3.5). Follow-up POEM (primary outcome) was completed by 81.7% of participants (*n* = 242/296), which helped to preserve the power of the study. The number of participants lost to follow-up due to not completing the final set of questionnaires was balanced between the groups, intervention group (*n* = 25) and control group (*n* = 29). The primary analysis included only participants who had completed the POEM at baseline and at week 8 (*n* = 242; 81.7%): 118 participants from the intervention group and 124 participants from the control group (Figure 3.4).

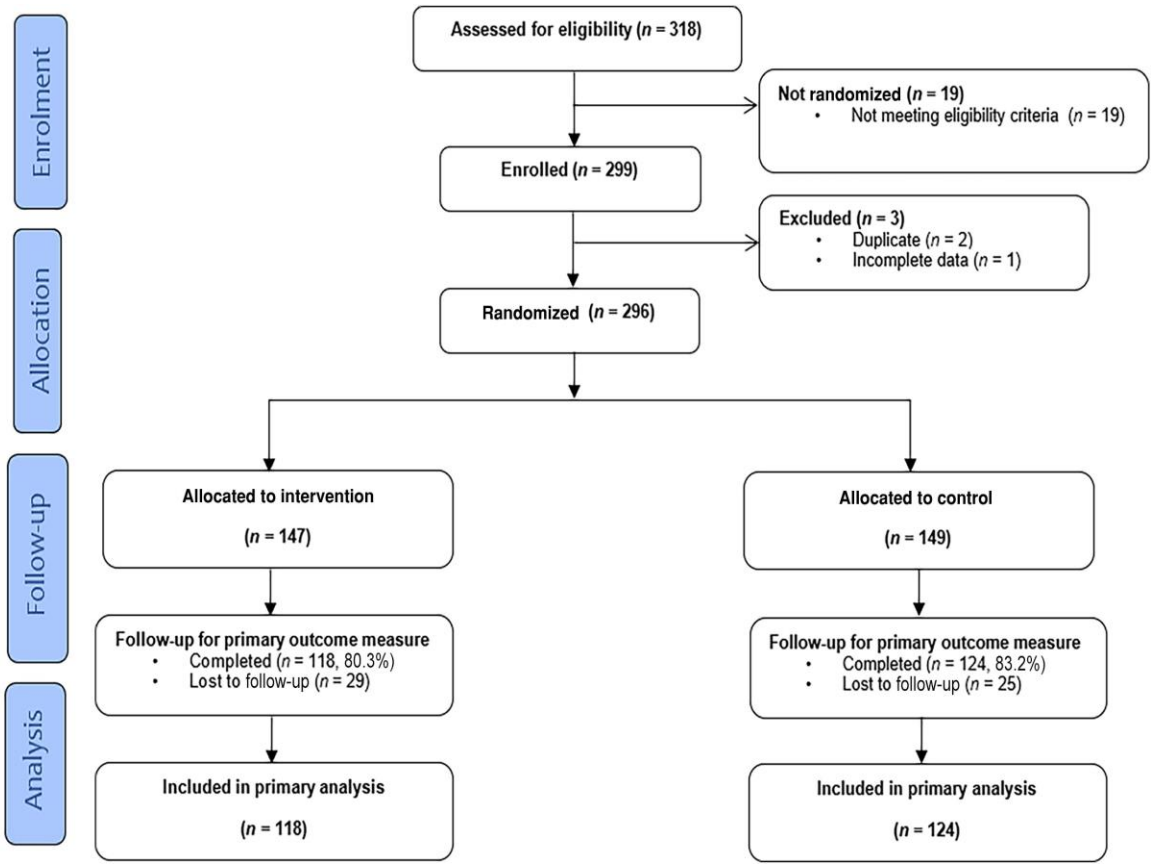


Figure 3.4 CONSORT flowchart

3.4.2 Baseline characteristics of participants

The baseline characteristics of randomised participants are summarised in Table 3.4. Participants came from diverse backgrounds, had a mean age of 26.7 years, 71% were female, 77% were white, 78% were UK residents. Baseline demographic and clinical characteristics were generally well balanced across the groups. The trial recruited mainly participants aged ≥16 (*n* = 276; 93.2%), despite being open to parents of children with eczema. Most participants had moderate (46%) or severe (42%) eczema and only 12% had mild eczema.

Table 3.4 Baseline characteristics of participants in the EMO trial

Participant characteristics	Intervention group (*n* = 147)	Control group (*n* = 149)	Total (*n* = 296)
Age (years)			
Mean (SD)	25.5 (13.1)	27.8 (15.1)	26.7 (14.2)
Range	2-73	2-74	2-74
Age groups, *n* (%)			
1-5	3 (2.0)	3 (2.0)	6 (2.0)
5 to <16	10 (6.8)	6 (4.0)	16 (5.4)
≥16	134 (91.1)	140 (93.9)	274 (92.6)
Gender, *n* (%)			
Male	37 (25.2)	40 (26.8)	77 (26.0)
Female	104 (70.7)	106 (71.1)	210 (70.9)
Other	3 (2.0)	0 (0)	3 (1.0)
Prefer not to say	3 (2.0)	3 (2.0)	6 (2.0)
Ethnicity, *n* (%)			
White	114 (77.5)	114 (76.5)	228 (77.0)
Asian or Asian British	17 (11.6)	19 (12.7)	36 (12.2)
Black, African, Black British or Caribbean	9 (6.1)	4 (2.7)	13 (4.4)
Mixed or multiple ethnic groups	5 (3.4)	10 (6.7)	15 (5.1)
Another ethnic group	2 (1.4)	2 (1.3)	4 (1.3)
Country of residence, *n* (%)			
UK	110 (74.8)	120 (80.5)	230 (77.7)
Other	37 (25.2)	29 (19.5)	66 (22.3)
Socioeconomic status (UK residents)[a], *n* (%)			
Lowest (most deprived)	24 (21.8)	18 (15.0)	42 (18.5)
Low	24 (21.8)	29 (24.2)	53 (23.3)
Middle	16 (14.5)	21 (17.5)	37 (16.3)
High	20 (18.2)	18 (15.0)	38 (16.7)
Highest (least deprived)	23 (20.9)	32 (26.7)	55 (24.2)
No postcode	3 (2.7)	2 (1.7)	5 (2.2)
Baseline POEM score[b], mean (SD)	15.27 (6.11)	14.38 (6.08)	14.82 (6.09)
Severity categories, *n* (%)			
Mild (3-7)[c]	18 (12)	18 (12)	36 (12)
Moderate (8-16)[c]	62 (42)	73 (49)	135 (46)
Severe (17-28)[c]	67 (46)	58 (39)	125 (42)

POEM=Patient Oriented Eczema Measure; SD=Standard Deviation; UK= United Kingdom. [a]Excluding participants who were not living in the UK as postcodes were not collected from non-UK residents (*n* = 66). [b]Higher values represent more severe eczema. [c]Stratification variables.

3.4.3 Primary outcome

Adjusting for the stratification variables of baseline disease severity and age, the mean between group difference was -1.64 (95% CI -2.91 to -0.38; $p = 0.01$), showing a small but statistically significant improvement in POEM scores in the intervention group (Table 3.5). Considering the minimal important change for POEM, 20% of participants (49/242) had a change score of ≥3.0 points on the POEM.

Sensitivity analyses for the primary outcome after imputation of missing data were broadly consistent with the primary analysis and showed the point estimate for the between group difference in POEM ranging from -1.38 (best case) to -1.18 (worst case) as shown in Table 3.6.

Table 3.5 Change in POEM score from baseline to week 8: primary analysis[a]

Measure	Intervention group (*n* = 118)	Control group (*n* = 124)	Unadjusted difference in means (95% CI)	Adjusted difference in means (95% CI)[b]	*p*-value
Week 0	15.42 (6.02)	14.28 (6.06)			
Week 8	12.00 (6.08)	12.94 (6.47)			
Change	-3.42 (5.42)	-1.34 (5.39)	-2.08 (-3.45 to -0.71)	-1.64 (-2.91 to -0.38)	0.01

Data are presented as mean (SD) unless otherwise stated. CI=Confidence Interval. [a]Based on participants who completed follow-up POEM at week 8. [b]Adjusted by stratification variables: age and baseline disease severity.

Table 3.6 Sensitivity analyses imputing missing values for the primary outcome

Measure	Intervention group (*n* = 147)	Control group (*n* = 149)	Unadjusted difference in means (95% CI)	Adjusted difference in means[a] (95% CI)	*p*-value
Change in POEM score from baseline to week 8: Sensitivity analysis for 'best case' scenario[b]					
Week 0	15.27 (6.11)	14.38 (6.08)			
Week 8	11.67 (6.07)	12.48 (6.34)			
Change	-3.61 (5.09)	-1.89 (5.21)	-1.72 (-2.90 to -0.54)	-1.38 (-2.47 to -0.29)	0.01
Change in POEM score from baseline to week 8: Sensitivity analysis for 'worst case' scenario[c]					
Week 0	15.27 (6.11)	14.38 (6.08)			
Week 8	13.44 (7.00)	13.98 (6.88)			
Change	-1.83 (6.06)	-0.39 (5.50)	-1.43 (-2.76 to -0.11)	-1.18 (-2.44 to 0.92)	0.06

Data are presented as mean (SD) unless otherwise stated. POEM=Patient Oriented Eczema Measure; CI=Confidence Interval. [a]Adjusted by stratification variables: age and baseline disease severity. [b]Imputation of missing values for those who did not complete POEM at week 8. [c]Imputation of missing values for those who did not complete POEM at week 8.

3.4.4 Secondary outcomes

After adjusting for stratification variables and baseline treatment use, there was no evidence of a difference between the groups in the number of days of treatment use over the past week at follow-up compared to baseline; mean change in emollient use was 0.09 days (95% CI -0.37 to 0.55; *p* = 0.69) and mean change in topical corticosteroid use was -0.22 days (95% CI -0.71 to 0.25; *p* = 0.35) (Table 3.7). No between group differences were found in the frequency of treatment use over the last 2 months (Figure 3.5). Analysis of data completeness showed that follow-up POEM was completed by 80.3% of participants (*n* = 118/147) in the intervention group and 83.2% participants (*n* = 124/149) in the control group (odds ratio 0.85, 95% CI 0.46-1.54; *p* = 0.59).

Table 3.7 Frequency of treatment use over the last week

Measure	Intervention (*n* = 118)	Control (*n* = 124)	Adjusted difference in means (95% CI)[a]	*p*-value
Number of days of emollient use over the last week				
Baseline	6.58 (2.41)	6.07 (2.52)		
Week 8	6.38 (2.41)	5.94 (2.65)		
Change	-0.20 (1.96)	-0.13 (1.77)	0.09 (-0.37 to 0.55)	0.69
Missing data	4	2		
Number of days of topical corticosteroid use over the last week				
Baseline	3.52 (2.27)	3.29 (2.24)		
Week 8	3.25 (2.29)	3.31 (2.48)		
Change	-0.27 (2.25)	0.01 (1.78)	-0.22 (-0.71 to 0.25)	0.35
Missing data	4	2		

Data are presented as mean (SD) unless otherwise stated. CI=Confidence Interval. [a]Based on participants who completed the Patient Oriented Eczema Measure (POEM) follow-up at week 8. [b]Adjusted by stratification variables.

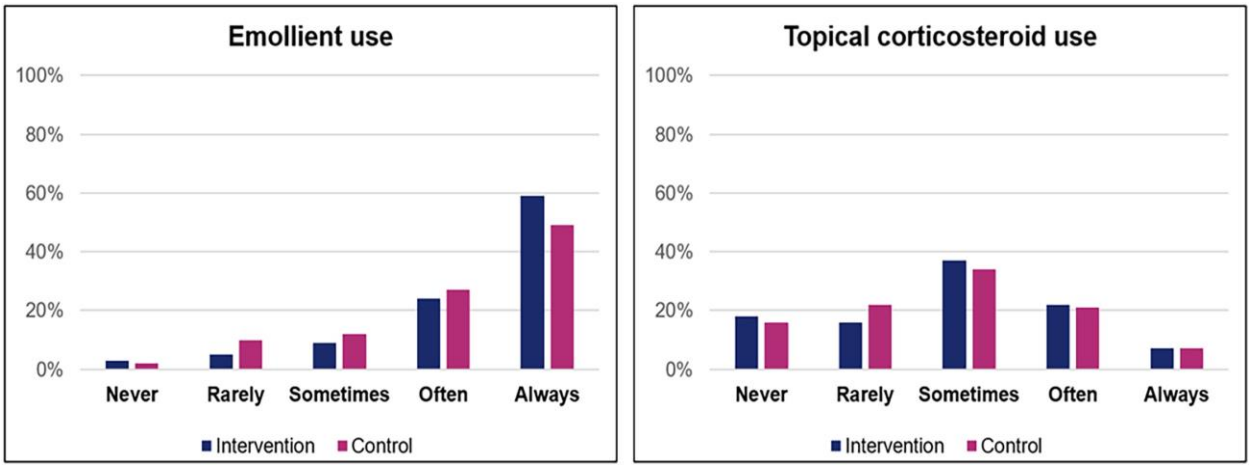


Figure 3.5 Frequency of treatment use over the last 2 months

3.4.5 Subgroup analyses

Subgroup analyses for the primary outcome indicated no evidence of differential treatment effect between the subgroups (Table 3.8). Since the trial was powered to detect overall differences between the groups rather than interactions of this kind, these subgroup analyses were regarded as exploratory.

Table 3.8 Subgroup analyses

Number of participants	Model coefficient (95% CI)[a]	*P*-value
Interaction between age and intervention (*n* = 242)[b]		
Baseline treatment effect	-0.64 [-3.30 to 2.02]	0.63
Interaction effect	-0.04 [-0.12 to 0.05]	0.40
Interaction between disease severity and intervention (*n* = 242)[b]		
Baseline treatment effect	-0.57 [-3.93 to 2.79]	0.73
Interaction effect	-0.07 [-0.28 to 0.14]	0.50
Interaction between socioeconomic status and intervention (*n* = 185)[b]		
Baseline treatment effect	-2.12 [-5.55 to 1.30]	0.22
Interaction effect	0.17 [-0.84 to 1.17]	0.75

CI=Confidence Interval. [a]Coefficients from a linear regression model, including a single interaction term for treatment effect and each continuous characteristic. The model also adjusted for stratification values.
[b]Based on participants who completed the follow-up Patient Oriented Eczema Measure (POEM) at week 8.

3.4.6 Exploratory analyses

Results for other patient-reported eczema outcomes, including the HOME-recommended outcomes for itch intensity and eczema control are shown in Table 3.9. Of the outcomes explored, only the PGA showed a between group difference similar to that observed for POEM; adjusted mean difference -0.30 (-0.55 to -0.05; $p = 0.01$).

Table 3.9 Response of additional eczema outcomes

Measure	Intervention group	Control group	Adjusted difference in means (95% CI)	*p*-value
Change in RECAP score from baseline to week 8				
n = 232	*n* = 112	*n* = 120		
Week 0	12.29 (6.14)	11.79 (6.30)		
Week 8	10.67 (5.66)	10.18 (5.86)		
Change	-1.62 (4.97)	- 1.62 (6.61)	0.39 (-1.07 to 1.84)	0.60
Change in NRS Itch score from baseline to week 8[a]				
n = 224	*n* = 107	*n* = 117		
Week 0	4.96 (2.47)	4.85 (2.44)		
Week 8	4.59 (2.48)	4.47 (2.29)		
Change	-0.37 (2.49)	-0.38 (2.50)	0.11 (-0.53 to 0.76)	0.72
Change in PGA score from baseline to week 8[b]				
n = 237	*n* = 115	*n* = 122		
Week 0	3.59 (0.95)	3.36 (0.97)		
Week 8	3.17 (0.97)	3.28 (0.93)		
Change	-0.42 (0.99)	-0.07 (0.98)	-0.30 (-0.55 to -0.05)	0.01
Change in bother score from baseline to week 8[c]				
n = 237	*n* = 115	*n* = 122		
Week 0	5.4 (2.50)	5.25 (2.49)		
Week 8	4.65 (2.42)	4.72 (2.39)		
Change	-0.74 (2.42)	-0.53 (2.56)	-0.09 (-0.72 to 0.53)	0.76

Data are presented as mean (SD) unless otherwise stated. CI=Confidence Interval. RECAP=Recap of Atopic Eczema; PGA=Patient Global Assessment [a]Measure of itch intensity: from 0 (No itch) to 10 (Worst itch imaginable): "How would you rate your itch at the worst moment during the previous 24 hours?" [b]Global assessment of eczema: *"How is your eczema today?"* response options: clear, almost clear, mild, moderate, severe, very severe [c]Disease related bother: *"How much bother has your eczema been over the last week?"* Response options range from 0 (No bother at all) to 10 (As much bother as you can imagine).

3.4.7 The importance of reminders

As discussed in chapter 3.3.6.3, the completion rate trends of the questionnaires were continuously monitored during the trial to gauge the level of participant engagement with the digital outcome measures. It also helped to compare the completion of follow-up at week 8 with and without reminders and ascertain the efficacy of reminders in those who did not complete follow-up without prompts. No reminders were sent for the weekly questionnaires, resulting in a weekly completion rate of 73.5% at week 1. A decreasing tendency in weekly completion was noted and as time progressed completion decreased to 59.2% by week 7 (Table 3.10).

Table 3.10 Completion rate of questionnaires

Measure of completion	Intervention group (*n* = 147)	Control group (*n* = 149)
Number of completed questionnaires during the study period, mean (SD)	6.47 (2.93)	1.82 (0.38)
≥4 weekly questionnaires completed[a]	108 (73.5)	0
Baseline	147 (100)	149 (100)
Week 1	108 (73.5)	0
Week 2	112 (76.2)	0
Week 3	95 (64.6)	0
Week 4	94 (63.9)	0
Week 5	95 (64.6)	0
Week 6	95 (64.6)	0
Week 7	87 (59.2)	0
Week 8 (data completeness at follow-up)[a]	118 (80.3)	124 (83.2)

Data are *n* (%) unless otherwise stated. SD=Standard Deviation. [a]Includes only participants who completed 4 out of 7 weekly questionnaires. [b]Secondary outcome, showing no between group difference: odds ratio 0.85 (95% confidence interval 0.46-1.54; $p = 0.59$).

Many participants required both email and text reminders. Of the 242 participants who completed week 8 follow-up, 110 required a reminder. Therefore, the completion rate without reminders would have been only 54.6%. The first email reminder was the most effective in enhancing completion, accounting for 49 extra follow-up responses. Closely following, text reminders prompted an additional 48 participants. The second email reminder, sent prior to the text reminder, was the least effective in motivating participants to engage with follow-up. The performance of reminders is summarised in Figure 3.6.

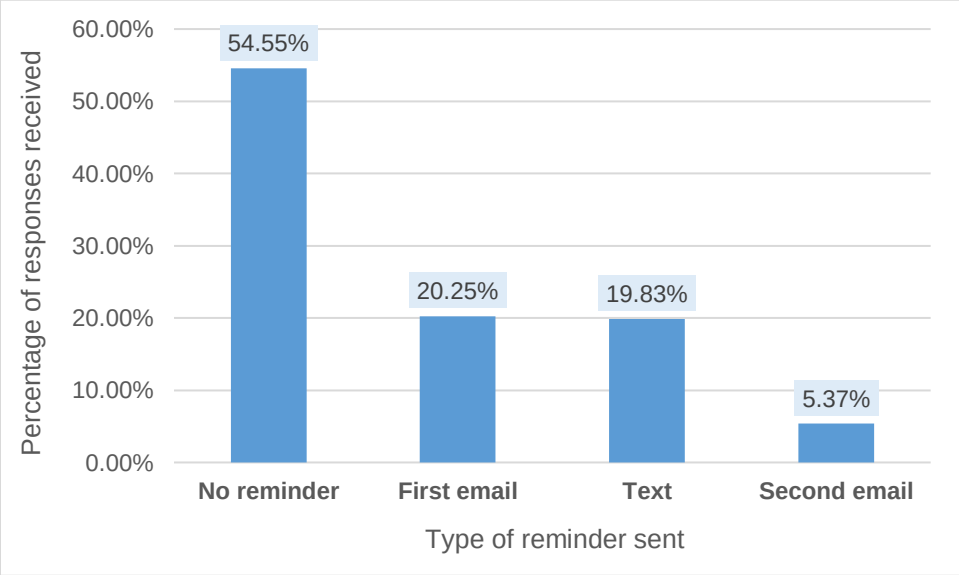


Figure 3.6 Reminders sent to participants to complete follow-up

3.5 Discussion

3.5.1 Summary of principal findings

The EMO trial assessed the effect of weekly symptom assessments on patient-reported outcomes to help establish the optimum frequency of PROM collection in upcoming eczema trials. The study found that weekly patient-reported symptom monitoring led to a small perceived improvement in eczema severity over a period of 8 weeks, compared to not recording symptoms weekly. There was no evidence to support the hypothesis that this improvement in eczema symptoms was mediated by a change in the frequency of standard topical treatment use (emollients and topical corticosteroids). Although, this may have been limited by the way in which participants were asked to record treatment use within the trial. It is also possible that unidentified psychologically driven effects may have resulted in the observed improvement in eczema symptoms, such as increased self-efficacy (Holloway and Watson, 2002),empowerment (Rappaport, 1987). Besides self-efficacy, positive reinforcement and motivation from regular monitoring causing increased self-awareness (Kamery, 2004) or social validation from being part of the study may have contributed to the observed improvement in symptoms.

There was no evidence that regular completion of weekly questionnaires increased participant retention in the trial, which is reassuring to trialists wishing to minimise the burden of data collection in trials. The use of reminders significantly increased follow-up at Week 8 and helped to gather a total of 110 additional responses resulting in a 45.4% boost in completion rate. Consequently, researchers should take advantage of this simple yet effective method for improving the completion rate of patient-reported questionnaires. Furthermore, using personalised text messages can be beneficial (Cureton et al., 2021) and likely had contributed to enhancing response rates in the EMO trial.

3.5.2 Generalisibility

The trial had reasonable external validity because participants were recruited from diverse ethnic and socioeconomic backgrounds and from different geographical locations. Moreover, the data collection instruments and their frequency mimicked what might typically happen in other eczema RCTs and this aided the generalisibility of results. Despite being open to all age groups, very few parents/carers of children with eczema took part. It is not known if these results are generalisable to children because the effects may be different in this population. A significant gender imbalance occurred in recruited participants (females 70.9% versus males 26.0%). This might have been due to the fact that signing up for a research study necessitates the disclosure of personal information and often requires the expression of socioemotional behaviours. Historically, these traits have been linked to women and may be contributing factors to their increased participation in research (Slauson-Blevins and Johnson, 2016). Consequently, the disparity in gender representation in the trial impacted on the generalisibility of findings to the male population.

Exploratory analyses of other eczema outcomes found similar effects to that of the primary outcome findings for the Patient Global Assessment, which improved by the end of the trial, but not for the other HOME recommended outcomes of patient-reported eczema symptoms (NRS Itch) and long-term eczema control (RECAP). Whether this is because these outcome instruments are less susceptible to bias or less sensitive to change is unclear.

3.5.3 Relevance to other studies

To date, this was the first RCT evaluating the effect of weekly patient-reported symptom monitoring in eczema. However, in asthma studies attempts have been made to assess whether more regular monitoring affects patient outcomes. For instance, a post-hoc analysis of three asthma RCTs with children was conducted to examine the influence of additional outcome assessments in control

participants (Frey et al., 2020). Depending on the trial, a combination of PROMs, phone calls or home visits were used for data collection and the number of planned assessments ranged from 4 (bi-monthly) to 10 (monthly) datapoints. Results indicated substantial improvement in symptoms with enhanced assessments, which may be linked to increased adherence with medication and other self-management behaviours initiated by the outcome assessments. Authors highlighted the need for reducing the number of assessments to optimise trial design and enable reliable interpretation of results.

Furthermore, a recent eczema study assessed the optimum frequency of data collection points in eczema trials that used repeated measures of weekly PROMs and reported the optimum number of datapoints to be approximately 5 (regardless of the duration of the trial). Having 5 datapoints would allow for maximum statistical efficiency whilst maintaining retention and minimising data collection burden (Stuart et al., 2018).

3.5.4 Strengths and limitations

The EMO study had several strengths. The trial protocol was written in accordance with SPIRIT guidelines (Chan et al., 2013), conducted and reported following CONSORT guidelines for parallel group RCTs and the CONSORT-PRO extension (Schulz et al., 2010, Calvert et al., 2013), making the trial suitable for inclusion in evidence synthesis studies. The primary endpoint was a well-validated and commonly used patient-reported outcome measure, often used in electronic format.

The trial was powered adequately. The prespecified SAP was followed during analysis, group allocation was concealed and the impact of missing data was analysed with suitable statistical methods. Bias was further mitigated by recruiting an appropriate sample size (n = 296), allowing for 20% loss to follow-up to account for the possible threat of losing participants that had the potential to jeopardise the power of the trial. Primary outcome data was available for 81.7% participants. This completion rate was considered high, especially in the

context of digital trials, which helped to maintain the statistical power and allowed to answer the research question.

The study also had some limitations. Blinding is vital for preserving integrity and validity of trial results. Due to the nature of this methodological trial, blinding to the intervention was not possible. Additionally, I managed all aspects of the trial, including: recruitment, data monitoring, sending text reminders and performing analysis. The lack of double-blinding may lead to an overestimation of treatment effect as it was demonstrated by a comprehensive review of 250 RCTs obtained from 33 meta-analyses, resulting in the exaggeration of odds ratios by 17% (Schulz et al., 1995). However, steps were taken in the EMO trial to eliminate ascertainment bias by creating the SAP before the trial finished and conducting sensitivity analyses to assess the impact of missing data on the primary outcome.

The trial was limited to 8-weeks of follow-up, which is a shorter duration than most eczema trials but is probably a reasonable estimate of the maximum time between study visits in the majority of eczema trials.

The observed between group difference of 1.64 points on the POEM is a small difference that may simply reflect measurement error (Howells et al., 2018). Nevertheless, this modest difference could be important if it masks small, but genuine treatment differences between eczema treatments being tested in intervention trials.

Finally, the wording used to record treatment use may have influenced the assessment of this secondary outcome. However, the wording for assessing treatment use was similar to the wording used in other eczema trials (Thomas et al., 2017).

3.5.5 Implications for design and conduct of future trials

This study investigated, through a series of online PROMs, the impact of weekly symptom monitoring on outcomes in an eczema trial. Based on the results,

reducing the frequency of patient-reported outcomes collection is recommended in future eczema trials (e.g. at monthly intervals in a 6 months trial or 2 monthly intervals in a 12 month trial). This would allow disease chronicity to be captured and trials designed efficiently (e.g. using repeated measures analysis), whilst minimising potential non-specific trial effects such as those observed in the current study.

In recent years in the field of dermatology, there has been a tendency towards capturing weekly progress for reporting trial data. These descriptive statistics are used to demonstrate clinical effect (Warren et al., 2020). When considering the frequency of data collection, it is important for researchers designing trials to consider the balance between collecting data for the evaluation of interventions and the potential burden on participants. In certain cases, and certainly in early phase trials, adopting longer assessment intervals may not be plausible for safety monitoring or other reasons. Thus in later phases of studies, such as phase III and beyond, reducing the collection of patient-reported data might be more appropriate. Applying longer data collection intervals could enhance the validity of results.

Overall, the reduction of the number of data collection points has a concurrent advantage of minimising responder burden and reducing the resources required for data collection and management, leading to beneficial scientific and societal impact. Sending reminders and incentivising participants to complete data points can help enhance retention rate.

In terms of future directions for research, exploring further the hypothesis of this study in clinical trials of pharmacological interventions could be an interesting area, given that effects similar to that of identified in the EMO trial have been reported. For example, in interventional trials improvement in the placebo group has been noted and the effect of increased frequency of PROM collection might be a contributing factor (Leshem et al., 2019, Lee et al., 2020). Consequently, it

would be valuable if future studies could investigate this phenomenon in the context of interventional trials that evaluate new therapeutics.

3.6 Conclusions

The EMO trial showed that weekly patient-reported symptom monitoring led to a small perceived improvement in eczema severity. The findings aim to inform the HOME initiative and researchers on the optimum frequency of outcome assessments to ensure appropriate design of future eczema trials, which will help to reduce systematic errors in trials. Beyond implications for future trial designs, this chapter also showcased the inception and implementation of a fully digital, decentralised trial whereby contributing to the existing body of evidence on online trial design and conduct. Chapter 4 reports the comprehensive recruitment strategy that was implemented in the EMO trial, using different social media platforms.

Chapter 4 Using social media for participant recruitment into clinical trials

This work has been published in the Trials journal (Baker et al., 2022a).

4.1 Introduction

The online RCT reported in chapter 3 revealed that social media can serve as a plausible and efficient method for participant recruitment, providing advantages such as speed and low cost. This chapter describes the social media recruitment strategy that was used for the EMO trial. The recruitment strategy consisted of both unpaid and paid social media adverts, with a subsequent analysis of their performance and cost. The chapter offers a practical guide for running social media campaigns, outlining the advantages and disadvantages associated with each platform used. Furthermore, it also provides information on retention rates per platform and describes the performance of email and text reminders.

Historically, participant recruitment for RCTs has often relied on clinician referrals and the performance of recruiting teams as mentioned in Chapter 2. Traditional recruitment methods include: approaching individuals in clinic, via mail and telephone by using health records and registers, newspaper advertisements, posters, flyers and media appearances in radio and television (Kakumanu et al., 2019). There are many caveats to traditional approaches, for instance, clinician referrals from a limited number of sites or print advertisements may not reach a sizeable audience to identify an adequate number of participants. This can lead to costly delays in recruitment that may endanger the success of the trial. Furthermore, traditional methods may not be able to fully provide the potential benefits that digital platforms and emerging technologies can offer such as cost-effectiveness and speed (Morgan et al., 2013, Moseson et al., 2020).

The number of internet users is growing globally and had reached 5.16 billion in April 2023 (Statista, 2023). The continuous increase in users, especially on social

media platforms, has made it inevitable for remote internet-based recruitment methods to enter health research. The growing popularity of online recruitment became apparent during the global COVID-19 pandemic, whereby traditional recruitment methods were reduced due to limited in-person contact. Accordingly, the use of social media rapidly accelerated as a modality of recruitment (Ali et al., 2020a). Herein, social media is defined as internet-based platforms that enable users to create, share and interact with user generated content as well as participation in social networking by interacting with fellow users.

Compared with conventional recruitment methods, social media has a potential for broad reach and capacity to target specific audiences based on age, gender, geographical location and interest, making it a potentially impactful advertising channel. Social media can help increase public awareness of the study, enhance diversity and improve trial efficiency (Darmawan et al., 2020). Studies using social media recruitment strategies have demonstrated that it is a viable approach for efficient participant recruitment (Ramo and Prochaska, 2012, Yuan et al., 2014, Jones et al., 2017, Watson et al., 2018). Consequently, social media as an emerging alternative recruitment method is causing a paradigm shift in trial recruitment towards innovative and unconventional digital approaches. However, it is important to assess whether these promising novel methods work, if so, how they can be implemented and operationalised in RCTs.

Despite the upsurge of social media recruitment strategies, adequate and comprehensive evaluation of these methods is scarce (Treweek and Briel, 2020). A significant proportion of studies evaluating RCT recruitment methods have focused on comparing traditional strategies with social media strategies (Admon et al., 2016, Frandsen et al., 2016, Moreno et al., 2016), in many cases opportunistically only after traditional methods failed to generate sufficient enrolments (Bowen et al., 2004, Adam et al., 2016). Moreover, studies have rarely utilised both unpaid and paid social media recruitment strategies in the same trial and little research has concurrently evaluated and compared the efficiency and cost implications of recruiting on different social media platforms.

Evaluating recruitment approaches to clinical trials has been highlighted as a priority topic for trials methodology research (Tudur Smith et al., 2014).

4.2 Aims and objectives

The aim of this study was to contribute to the trials methodology evidence base on efficient participant recruitment strategies. The objectives of the study were as follows:

1. To describe the social media recruitment strategy used for the EMO trial
2. To analyse the performance of paid adverts and unpaid posts
3. To comparatively assess the efficacy and cost of advertising on different social media platforms
4. To provide a practical guide for implementing a similar strategy

4.3 Methods

4.3.1 Study overview

Chapter 3 describes the EMO trial. In this chapter, the performance of the social media recruitment methods used in the EMO trial is evaluated. Regarding recruitment materials, as part of the ethics committee application, I submitted examples of texts and images that were planned to be used to advertise the study. It was highlighted that the content of the adverts were likely to be slightly adapted during the campaign to suit the different requirements of the individual social media platforms and tailor the content to the target audience.

4.3.2 Data collection and enrolment

The detailed data collection methodology is described in Chapter 3. Recruitment, consenting, randomisation and data collection was undertaken exclusively online

using REDCap (2022). I was solely responsible for participant recruitment and managed the related day-to-day activities. Recruitment occurred between 14 September and 16 January 2022 and it took 4 months, using various social media platforms (described below) for advertising. Individuals who clicked on the study advertisement link were directed to the study website at www.emostudy.org (Eczema Monitoring Online, 2021), which outlined the aims of the study, eligibility criteria and full participant information. Interested individuals signed up via the study website. Once the electronic consent form was signed, participants completed eligibility checks and were randomised. Randomised participants were sent an automated welcome email, based on their group allocation, immediately after enrolment explaining what happens next. Upon completion of the follow-up questionnaire, participants had the opportunity to be entered into a prize draw for a chance to win one of six Amazon vouchers worth £20 each.

4.3.3 Recruitment strategy

Since this was a low budget trial, it was important to enhance recruitment efficiency while minimising cost. Based on previous literature, social media appeared to be an affordable yet efficacious recruitment tool. For instance, an online feasibility study in postpartum women recruited 1083 participants in 13 days, demonstrating both time efficiency and low cost (Leach et al., 2017).Moreover, a scoping review including 33 studies examined the role of social media in enhancing recruitment to clinical trials found that social media can increase recruitment numbers and also reduce the cost per participant (Darmawan et al., 2020).

Therefore, it was decided to utilise an extensive social media advertising campaign that employed various social media platforms simultaneously. Given that the EMO trial was conducted entirely online, there was no restriction on geographical location of participants. The recruitment strategy broadly focused

on the UK, but individuals residing in other countries were able to join the study if they were eligible.

This social media based approach was augmented by using both unpaid and paid recruitment methods. Unpaid methods refer to advertising posts displayed on social media that did not require any monetary contribution to share with users, whereas the paid method denotes adverts that incurred financial costs to run the adverts and reach users. For unpaid advertising of the study Reddit, Instagram, Facebook and Twitter (X) social media platforms were used, incurring no direct advertisement costs. In addition, paid advertising was set up on Facebook.

The goal was to be inclusive to reach individuals with different demographics by utilising a range of social media outlets and implementing a recruitment strategy that took advantage of the different forms of content sharing avenues on each platform, including:

- Hashtags: categorising keywords to help discovery of content by users interested in the topic
- Stories: visual mode of content sharing of user-generated images/videos that disappear after 24 hours
- Reels: allowing the creation of short videos using pre-existing sound clips
- Tagging of followers: alerting users about updates
- Following relevant organisations

Of note, some of the participants (*n* = 37) learnt about the study by other recruitment modes that did not involve social media, including: word of mouth, web search, Callforparticipants.com, NHS website, poster, Mumsnet and email. Since this chapter is concerned with evaluating the effectiveness of social media recruitment methods, other modalities of recruitment will not be assessed and discussed in detail owing to a small percentage of recruited participants (13%).

Free advertising on social media platforms (unpaid methods)

Unpaid recruitment methods were used periodically for 63 days from 14 September to 18 November 2021. I produced the content for all adverts and posts, using a freely available graphic design software (Canva, 2022) and free images (Pixabay, 2022). At the design stage of the trial, six PPI panel members from CEBD provided feedback on some of the social media advertising materials as described in Chapter 3.3.2.

4.3.4 Social media platforms used for the unpaid recruitment methods

Instagram

Instagram is a photo and video sharing social media platform with over 1.3 billion users (We are Social & Hootsuite, 2021). Prior to study launch, a study specific Instagram account was set up. To build anticipation for the start of recruitment, 3 countdown posts indicating the number of days until the launch of the study, and a “Stories” post were shared. In addition, 3 days before the study opened to recruitment a 30-second video of me talking about the study, and a longer 51 seconds video with the same concept were released 1 day after study launch. During the recruitment period, altogether 3 written posts, 1 “Reels” post (15 seconds video clip) and 2 “Stories” posts were shared. In all forms of study publicity on Instagram, relevant hashtags (#eczema #eczemahelp #eczemasupport #eczemaresearch) were used to help reach the target audience.

Twitter (X)

Twitter, now known as X, is a social networking site with 436 million users as of 2021, where individuals communicate in short messages called “tweets” with a maximum character limit of 280 (We are Social & Hootsuite, 2021). Before the study went live, a Twitter account for the study was created using the study name

and logo. To raise awareness about the study and build an online network for advertising the study, organisations and charities affiliated with eczema and skin research were followed. Individuals were also followed if they were open about having eczema or being an eczema advocate. In anticipation for the study launch, 4 countdown tweets were shared. 1 day before the beginning of recruitment, the existing 30 second video was shared on this platform too. A total of 7 tweets were created using hashtags and sometimes the tagging function to add relevant organisations that might reshare the tweet and help to reach more people.

Facebook

Facebook is the most widely used social media platform worldwide with over 2.9 billion users (We are Social & Hootsuite, 2021). A Facebook page was created for the study with the use of the study logo. This page provided information about the study and contained the address of the University of Nottingham to build credibility with potential participants. I interacted with eczema organisations by 'liking' their pages. Altogether, 4 posts were shared prior to study launch, followed by 4 recruitment posts.

Reddit

Reddit is a social media platform that has 430 million users (Pew Research Centre, 2021). Reddit consists of a large collection of online forums divided by topics where users can share, rate and comment on content. An account for the study was created and I joined different forums, called subreddits, to advertise for recruitment, including: eczema groups, various local and regional cities and towns. For enhancing geographical coverage and representativeness, I also posted in the subreddits of the 4 UK countries.

Targeted paid advertising on Facebook (paid method)

Targeted paid advertising on Facebook was used for 16 days from 28 December 2021 to 16 January 2022. Facebook was selected for paid advertisement, as

opposed to search engine adverts such as GoogleAds, for its optimisation capabilities. Facebook allows for targeted advertising, flexible scaling of advert spend and advanced tracking of advert performance. The paid Facebook adverts ran separately from the rest of the social media recruitment campaign. Facebook owns Instagram and this configuration allowed for concurrent recruitment of participants from both platforms through the paid Facebook adverts.

In order to initiate the use of Facebook advertising, an existing post was 'boosted' (Boosted post 1). A boosted post on Facebook is a paid promotion of an already present post on the Facebook page. This advertising method requires payment to increase the reach of a selected post to a larger audience within a chosen budget and timeline (Facebook, 2022). Although a boosted post has limited customisation features, it allowed to enhance visibility and its simplicity made it an ideal tool for piloting the paid strategy and determine its feasibility, warranting the use of subsequent paid adverts. To avoid imbalance in age groups, I targeted varying ages with the paid adverts. Since the design of Boosted post 1 was more likely to appeal to a younger audience, this advert aimed to target 15-30 age groups. Another existing post was also boosted (Boosted post 2), targeting individuals 18 years and above.

The Facebook Ads Manager advertisement management platform was used to create 2 paid targeted adverts. The advanced customisation features in the Ads Manager allowed the adverts to be specific and tailored based on: goal (e.g. link clicks or increase the number of website visitors), target audience (e.g. age, gender, location), allocated budget and duration of the advert. The selection of automatic placements option enabled the adverts to be displayed across interconnected platforms, such as Instagram and Messenger. The Ads Manager facilitated the monitoring of advert performance, including link clicks. While the targeted paid adverts were running, performance statistics were regularly reviewed and spending limits were modified according to the performance of the individual advertisements.

The first advert was created with the goal of increasing website visitors. The automatic advert placement option was utilised, enabling the dissemination of the advert to a wide and potentially eligible population. The target audience initially consisted of people aged ≥14 years, any gender and living in the UK and Ireland. After 4 days, the audience of this advert was altered to specifically target men only to try to prevent substantial gender imbalance that started to occur in the trial. After 3 days, the target audience was reset to the demographics of the original advert, except for age which was raised to 16 years and above. The first Facebook advert ran periodically between 28 December 2021 and 16 January 2022 for 16 days in total.

The second advert was set up using a similar strategy to the first advert that included any gender, however, the location of the target audience differed to enhance ethnic diversity. Individuals from Birmingham (+40 km) and London (+40 km), where the population of ethnic minority groups is typically higher, were specifically targeted alongside the 4 UK countries and Ireland. Additionally, the Isle of Man was also targeted since it is an English speaking country and is located nearby. The second advert ran between 11 January and 16 January 2022 (6 days). Examples of Facebook adverts used for recruitment is illustrated in Figure 4.1.

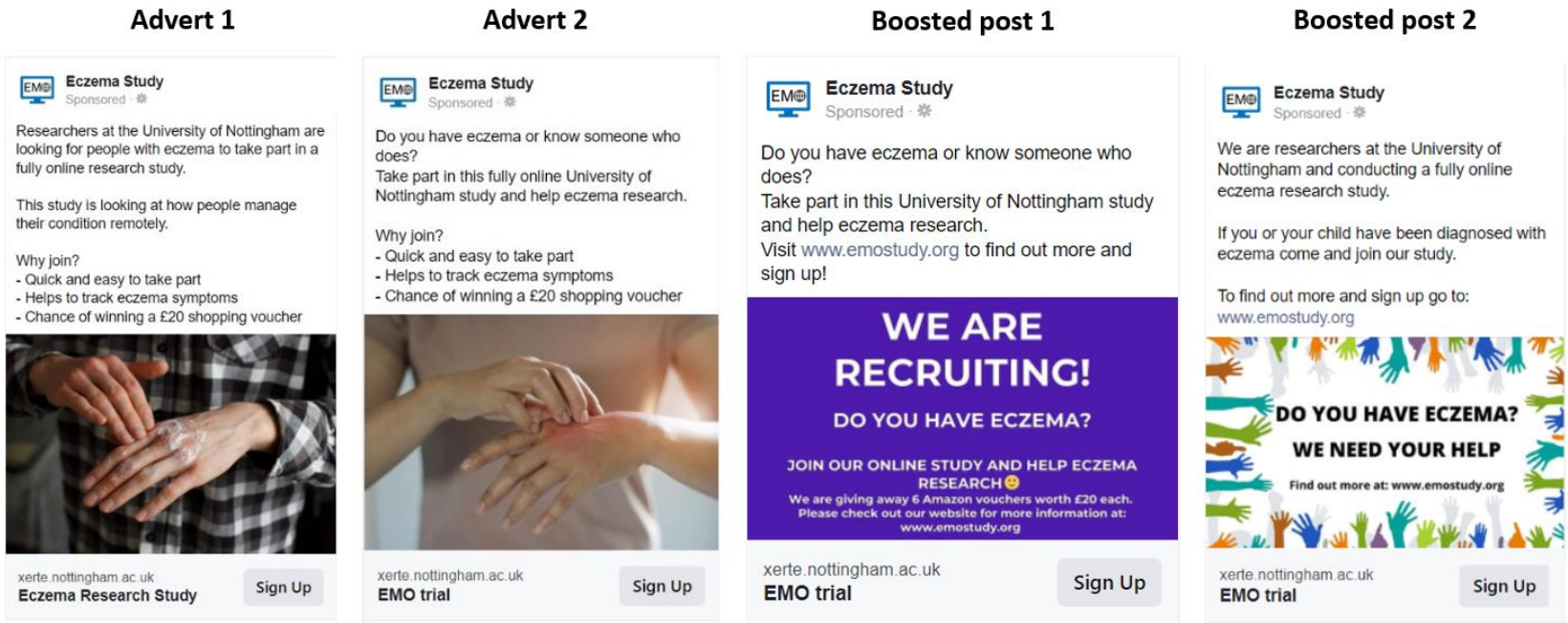


Figure 4.1. Adverts and boosted posts used in paid Facebook advertisements

4.3.5 Analysis

The performance of the unpaid and paid methods was assessed by calculating enrolment yield, defined as the proportion of enrolled participants out of those who expressed interest in the trial but did not reach enrolment. Descriptive statistics were used to report the baseline characteristics of participants, including age, gender, ethnicity and country of residence. The number of recruited participants was plotted by displaying the weekly enrolment rates of unpaid methods alongside the paid method throughout the study period. Retention was assessed by calculating the number of participants who completed follow-up at week 8 according to recruitment method.

Additionally, the performance of Facebook adverts was evaluated via the Facebook Ads Manager application that autogenerated metrics of engagement activity, providing a summary of the performance and cost of individual adverts. Measures for analysis included: (1) reach, which describes the number of people who saw the advert at least once; (2) link clicks, which indicates the number of clicks on the link displayed in the advert; (3) cost per link click, which refers to the average cost for each link click; (4) recruitment cost per participant, which is calculated by dividing advertising costs with the total number of enrolled participants. The direct advertising cost of each recruitment method was recorded.

Although the time spent on managing the different recruitment methods was not tracked, an estimate can be provided. Approximately 5 to 7 hours per week were spent on the unpaid recruitment methods, which involved written and visual content creation specific for the different social media platforms, posting in forums, dealing with queries of interested individuals and replying to comments. Whereas, operating paid Facebook adverts and tracking performance required approximately 4 hours per week.

4.4 Results

4.4.1 Participant characteristics

In 4 months, 400 expressions of interests were recorded for the EMO trial and a total of 296 participants were enrolled (Table 4.1). Unpaid methods accounted for 136 (45.9%) of participants and paid methods recruited 123 participants (41.6%).

Table 4.1 Number of expression of interest and enrolled participants using unpaid, paid and other methods of recruitment during the trial

Recruitment method	Number of expression of interest	Enrolment yield, *n* (%)
Paid method		
Facebook	55	41 (75)
Instagram	122	82 (67.2)
Total of paid method	177	123 (69.5)
Unpaid methods		
Reddit	152	121 (79.6)
Twitter (X)	11	7 (63.6)
Facebook	4	2 (50)
Instagram	8	6 (75)
Total of unpaid methods	175	136 (77.7)
Other methods		
Word of mouth	19	14 (73.6)
Callforparticipants.com	9	8 (88.8)
Web search	8	5 (62.5)
NHS website	6	6 (100)
Mumsnet	1	1 (100)
Email	1	1 (100)
Poster	2	2 (100)
PGR conference	1	0
Unknown	1	0
Total of other methods	48	37 (77)

Participants from diverse demographic backgrounds were recruited through social media (Table 4.2). The age of participants ranged from 2 to 74 years. Most participants were young, aged 14-19 years (35.5%) and were recruited mainly by paid Facebook adverts displayed on Instagram (*n* = 82). In contrast, those aged 20-29 (30.4%) primarily joined the trial from the unpaid method of Reddit (*n* = 67), while most participants 50 years old and above (9.3%) enrolled primarily via paid Facebook adverts (*n* = 23). Thus, paid advertisements predominantly attracted younger participants below the age of 20, whereas unpaid methods mainly drew in participants between 20-29 years of age (Table 4.2). Unexpectedly, very poor recruitment of parents of children with eczema occurred (*n* = 15).

Table 4.2 Baseline participant demographics and self-reported method of recruitment

Characteristic	Total, *n* (%)	Reddit	Facebook	Instagram	Twitter	Other[a]
Age range (years), *n* (%)						
0-13	15 (4.9)	2 (0.6)	2 (0.6)	1 (0.3)	4 (1.4)	6 (2)
14-19	104 (35.1)	14 (4.7)	2 (0.7)	81 (27.4)	0	7 (2.3)
20-29	90 (30.4)	67 (22.6)	3 (1)	4 (1.4)	1 (0.3)	15 (5.1)
30-39	43 (15)	30 (10.1)	7 (2.4)	2 (0.7)	0	4 (1.3)
40-49	16 (5.4)	5 (1.7)	6 (2)	0	2 (0.7)	3 (1)
50-59	13 (4.3)	3 (1)	9 (3)	0	0	1 (0.3)
60-69	10 (3.3)	0	9 (3)	0	0	1 (0.3)
70-74	5 (1.6)	0	5 (1.6)	0	0	0
Ethnicity, *n* (%)						
White	228 (77)	92 (31.1)	41 (13.9)	57 (19.3)	7 (2.3)	31 (10.4)
Asian	36 (12.1)	19 (6.4)	1 (0.3)	13 (4.4)	0	3 (1)
Mixed background	15 (5.1)	8 (2.7)	0	6 (2)	0	1 (0.3)
Black	13 (4.4)	0	0	11 (3.7)	0	2 (0.7)
Another ethnic group	4 (1.4)	2 (0.7)	1 (0.3)	1 (0.3)	0	0
Gender, *n* (%)						
Male	77 (26)	49 (16.6)	11 (3.7)	6 (2)	2 (0.7)	9 (3)
Female	210 (71)	69 (23.3)	32 (10.8)	76 (25.7)	5 (1.7)	28 (9.5)
Other	3 (1)	2 (0.7)	0	1 (0.3)	0	0
Prefer not to say	6 (2)	1 (0.3)	0	5 (1.7)	0	0

[a]Includes: word of mouth, web search, participant recruitment website, NHS website, Mumsnet, poster and email.

The geographical reach within the UK was noteworthy, enrolments occurred from all UK countries. Most participants were from England (*n* = 181), with the remaining residing in Scotland (*n* = 23), Northern Ireland (*n* = 16) and Wales (*n* = 14). 66 participants joined the study from 16 other, mainly English speaking countries, such as: Isle of Man (*n* = 17), USA (*n* = 16), Ireland (*n* = 13), Australia (*n* = 2) and Canada (*n* = 1). Due to its international coverage, Reddit recruited

most non-UK residing participants out of all social media platforms. The visual representation of country of residence of participants is shown in Figure 4.2.

Figure 4.2 Map of country of residence of recruited participants

4.4.2 Recruitment dynamics and trends

The number of recruited participants per day differed across the recruitment methods. The highest number of participants from unpaid methods (*n* = 9) joined the study on 28 September 2021 and from paid Facebook adverts (*n* = 25) on 3 January 2022. Differences in recruitment rate by the unpaid and paid methods were apparent throughout the study, which affected the overall recruitment rate as shown in Figure 4.3. Reasons for these fluctuations included periodic advertising via the unpaid methods and modifications made to paid Facebook adverts that was underpinned by intermittent pauses in advertising. During these advertisement pauses on Facebook, payment for the adverts stopped (between 8-11 January 2022), consequently recruitment completely stopped during this period. It is important to note that other methods recruited a few participants during these pauses, which slightly enhanced the overall recruitment rate of the trial. Advertising breaks affected recruitment but proved to be useful, allowing to

observe and evaluate the effect of temporary pauses of advertisements on recruitment rate.

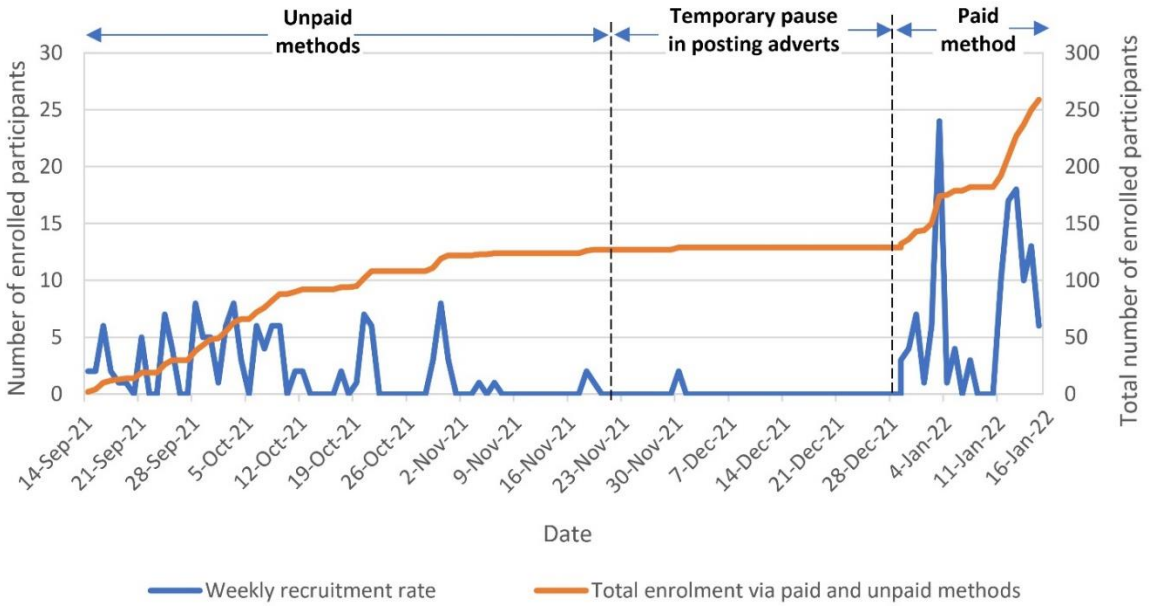


Figure 4.3 Weekly recruitment rate categorised by unpaid and paid methods and overall recruitment rate

Total social media/day excludes other recruitment methods, while total enrolment includes all recruitment methods.

In order to gauge information on recruitment timeline trends, the sign-up date and time of each participant by recruitment platform was tracked during the study. Most participants, regardless of recruitment platform, signed up after 5 PM (*n* = 138, 46.8%), especially during weekdays. Weekends and particularly Friday evenings usually generated increased traffic for the adverts, which in turn enhanced recruitment.

4.4.3 Cost and performance of paid Facebook advertisements

During a brief paid advertisement period of 16 days on Facebook, 123 participants were recruited for a total cost of £259.93. The average cost per link

click was £0.14 and the overall cost per enrolled participant arising from the paid advertisements was £2.11. Table 4.3 demonstrates the performance and itemised cost of each paid targeted Facebook advert.

Table 4.3 Summary of performance of paid adverts on Facebook

Advert type	Duration	Reach	Link clicks	Cost per link click	Advert cost
Advert 1	16 days	93,630	1,128	£0.16	£176.94
Advert 2	6 days	33,035	353	£0.17	£59.99
Boosted post 1	13 days	24,637	306	£0.06	£18.00
Boosted post 2	2 days	3,068	34	£0.15	£5.00
Total	*	154,370	1,821	£0.14	£259.93

*Data not available due to adverts running concurrently.

The aggregated reach of the Facebook advertisements was 154,370 individuals. Most adverts were placed on Facebook by default, reaching 94,096 individuals, while adverts displayed on Instagram reached 60,274 individuals. Even though paid adverts on Instagram reached fewer people, twice as many participants were recruited from Instagram (*n* = 82), compared to Facebook (*n* = 41).

4.4.4 Retention

Besides achieving the target sample size, retaining participants was also important for the success of this RCT. The completion rate of follow-up at week 8 was sufficient and slightly higher for the paid method (*n* = 103, 83.7%), compared with the unpaid method (*n* = 111, 81.6%). In terms of loss to follow-up by recruitment platform, participants recruited from Reddit had the highest dropout rate at 21% (25/121), followed by Instagram at 19% (17/88) and those from Facebook were the least likely to leave the study at 7% attrition (3/43).

4.5 Discussion

4.5.1 Summary of principal findings

The purpose of this chapter was to evaluate the performance and efficiency of social media recruitment approaches, using both unpaid and paid methods for the EMO RCT. The unpaid methods were the most effective in recruiting participants, resulting in 45.9% of total enrolments in approximately 2 months. These methods did not incur any advertising costs and recruited a diverse study population. On the other hand, paid adverts on Facebook were efficient in recruiting participants rapidly for a total cost of £259.99, recruiting 41.6% of participants in 16 days of active recruitment. Facebook provided flexibility to target specific audiences; though costs were incurred, a predetermined spending limit was set which could be regularly altered. This pragmatic feature is particularly useful for researchers working within financial constraints.

In order to minimise cost, I fully managed the social media campaigns throughout the trial by adopting an autodidact approach to learning the specifics of each platform and actively searching for free advertising opportunities on social media. Thus, the low recruitment cost was partly due to the fact that I found Reddit, which allowed free posting of adverts in forums. The use of Reddit helped to preserve the study budget and added novelty to the recruitment strategy as it has not been used for eczema RCTs. The results demonstrated the feasibility and versatility of Reddit posts in reaching a considerable sample of participants for free (*n* = 121, 40.8%), enhancing recruitment rate and demographic diversity with no advertising cost implications. These findings resonate with an online psychology study that successfully recruited participants through this unpaid method (Shatz, 2015). The success of the recruitment strategy may also be attributed to the high prevalence of eczema (Nutten, 2015) and people with this condition often search online for advice about the management of eczema (Santer et al., 2015).

Interestingly, there was a considerable difference in the recruitment pace of the unpaid methods and the paid recruitment method (Figure 4.3). In particular, Reddit was a post reactive platform where the number of recruited participants rapidly increased from the point of posting the advert that culminated at 2 days, followed by a drastic decrease and even a halt on recruitment afterwards. As depicted in Figure 4.3, when a longer period of break was applied, recruitment practically stopped. Therefore, this platform requires regular posting of adverts to allow for adequate recruitment.

Conversely, paid adverts on Facebook gradually reached potential participants, steadily increasing recruitment stream. Based upon this experience, I recommend running paid Facebook adverts for at least 7 days to take advantage of its streamlined algorithm that propagated the advert into the related social media networks to enhance the reach of the target audience. However, during this suggested advertising period, modifications to the advert should be avoided as it can interfere with the propagation and may cause temporary distraction to the performance of the advert. This was shown in the results, that indicated variations in the number of participants recruited during 28 December 2021 and 16 January 2022, which corresponded with modifications made to the existing adverts (e.g. daily cost, target audience and geographical location). In terms of timing of social media adverts, my findings indicate that for optimal results the adverts ought to be scheduled when people are likely to have spare time, such as upon finishing work and over the weekend. These timeframes provide a good window of opportunity for efficient recruitment.

When using social media for recruitment, concerns may prevail about digital exclusion when only recruiting via internet-based methods, such as social media. However, according to the Office for National Statistics (2020), in 2019, 96% of UK households had internet access. In 2021, 53 million (77.9%) of the UK population were active social media users (Statista, 2021), with young people (aged 16–24 years) making up a high proportion, although adults in all age groups have shown a significant increase in social media presence. It is

important to highlight that the choice of recruitment approach must be determined on a per trial basis. There are situations where social media recruitment may not be suitable, and conversely, there are circumstances where it appears to be the most appropriate recruitment method.

Drawing upon personal experience of using several social media platforms in this study, Table 4.4 describes the advantages and disadvantages of each platform.

Table 4.4 Advantages and disadvantages of social media platforms used for advertising

Platform	Advantages	Disadvantages
Facebook (paid)	• Most social media users • User friendly • Interconnected with other platforms • Wide reach • Demographic targeting • Custom audiences • Performance tracking • Optimising capabilities	• Cost based on link clicks not on actual enrolments • Approval of advert may take 24 hours • Advert may be rejected by moderator • Digital skills required to craft a well performing advert • Adverts can be fatigued • Decreasing popularity with users
Reddit (unpaid)	• Simple to use • Diverse user base • Posting in forums is free • UK and international coverage	• Post reactive platform • Overflowing content in subreddits • Visibility of post decreases quickly • Requires regular posting • Time-consuming for researcher • Knowledge of Reddit-specific terminology is needed
Twitter (unpaid)	• Often used for recruitment • Free to post • Hashtags help the discovery of the posts by users interested in the topic	• Limited character count • Shorter content is needed • Reduced freedom in content creation • Poor organic reach • Time-consuming for researcher
Instagram (unpaid)	• Popular platform • A lot of active users • Free to post • Appealing interface • Organised layout of posts • Many creative and fun features for creating posts (emoji, music, filters) • Various content sharing formats (images, videos, short sound clips)	• Cannot target specific audiences • Poor organic reach • Only optimised for app use, its web-version is substandard • Requires capturing content • Limited insight into performance of posts • Creating different types of content formats can be time-consuming
Facebook (unpaid)	• Creation of study specific Facebook page, instead of profile, increases credibility • Free to post	• Difficult to gain followers • Poor organic reach • Cannot target specific audiences • Many features only available when paying for the adverts

4.5.2 Relevance to existing literature

Paid adverts on Facebook were efficient in recruiting participants into the EMO trial rapidly, for a total cost of £259.93 (£2.11 per participant). This cost was significantly lower than reported in previous eczema recruitment studies with a total spending of US$10,064,˜ £7,898 as of 11th January 2024 ($105 per participant, £82) for a non-interventional online feasibility study (Ali et al., 2021) and cost per participant of AUD$ 2,494 (£1312) for a placebo controlled, single centre RCT (Spada et al., 2021). The latter study reported major challenges in recruitment, despite employing recruitment agencies for running the social media advertising campaigns. It is important to note that hiring recruitment agencies has high cost implications, yet may not yield sufficient enrolments. Furthermore, using external agencies may hinder the ability of researchers to provide sufficient details on the day-to-day management and monitoring of these campaigns, which is vital for tracking recruitment rate and trial progress.

Moreover, enrolment yields in the EMO study were higher in contrast with other dermatology studies that utilised social media to recruit (Spada et al., 2021, Ali et al., 2020b). The recruitment duration for the EMO trial was relatively short, indicating that targeted social media campaigns have the potential for shortening the length of participant recruitment. These findings are consistent with the results of a recent eczema specific recruitment study for a phase III eczema RCT (Katz et al., 2019).

Despite eczema being a common skin condition in childhood, this trial only recruited 15 parents of children with eczema. The exceptionally low recruitment rate of this population was unanticipated and contradicts with other eczema studies that successfully recruited this demographic from social media (Bhanot et al., 2021, Howells et al., 2020). The reason for the low presence of children is unclear, but it could be related to the methodological nature of this RCT, wherein the intervention was online questionnaires rather than a treatment intervention. This might have decreased the interest of busy parents in taking part.

The social media adverts recruited mostly female participants who were overrepresented, by almost threefold. However, this level of gender imbalance commonly occurs in other eczema studies as well (Bhanot et al., 2021, Ali et al., 2020b). It might be related to gender differences in internet use whereby females are more likely to use the internet to communicate and exchange information, whereas males prefer to browse and seek information on the internet (Jackson et al., 2001). 4.5.3 Strengths and limitations

Regarding the strengths of the study, it provided comprehensive insights into the recruitment from different social media platforms. It also presented a combined approach to recruitment, including both unpaid and paid methods. Furthermore, the study included information on sign up initiation and enrolment yield per platform and conducted performance and cost analysis. It also condensed the advantages and disadvantages of each platform, offering a practical guide for researchers interested in using them for recruiting participants.

A limitation of this study is that the unpaid advertising posts on the social media platforms by default failed to provide information on how many individuals were reached by the adverts and how many clicked on the advert link. Facebook produced performance metrics only for paid adverts, hindering accurate response analysis and limiting comparison of the performance of unpaid and paid advertisements on the various social media platforms. Since exposure to the advertisements is associated with amount of time spent on social media, there is a natural tendency for a potential selection bias to occur. This means that recruitment may be skewed towards those who use social media frequently. Consequently, regular users of social media were more likely to come across my posts and adverts than those who spent less time on these platforms. This scenario was particularly pertinent to Reddit, where the visibility of the post was dependent upon potential participants being regularly online. Another limitation of this study is that time of developing and monitoring adverts was not tracked, yet it could have provided a more comprehensive and accurate overview. However, this was partly because a retrospective analysis of this recruitment strategy was

performed, prompted by its unexpectedly high effectiveness in reaching the target sample size in a short timeframe.

Lastly, given that social media recruitment methods were used at different times of the year, with unpaid adverts between September and November and paid adverts at the end of December and in January, direct comparison of the performance of the recruitment methods could not be made because these timings could have affected uptake. Indeed, Instagram was more successful in recruiting participants than Facebook. This might be due to the fact that adverts for the study were running during school term, when more people aged 14-19 were online, increasing their likelihood of coming across my adverts. Besides, the prize draw of Amazon vouchers might have played a role in attracting this particular audience from Instagram.

4.5.4 Implications and future directions for methodological research

Despite the continuous difficulties and uncertainties in recruitment into RCTs, there is a shortage of evidence for researchers to guide recruitment related decision making for optimal results (Healy et al., 2018). However, opportunities exist for clinical trialists and methodologists to learn from each other through sharing experiences. The current lack of transparent reporting about recruitment strategies do not allow for collaborative learning. In relation to this thesis I have read a lot of trial results related literature and noticed an the extremely narrow description of recruitment strategies in academic publications. The lack of transparent reporting, especially about recruitment related costs and timelines was striking. Then I turned to the methodology literature to find out whether my observations were accurate. A recent review of 88 ovarian cancer trials has clearly echoed my concerns and found that recruitment strategies were not reported in the included trials, which makes the evaluation of the applied strategies impossible (O'Sullivan Greene and Shiely, 2022). This deficiency can greatly inhibit the available evidence for systematic reviews to evaluate the

performance of different recruitment methods. Thus, collective reporting of detailed recruitment approaches is crucial to drive progress in this overseen area. Undoubtedly, recruitment strategies exist and are being used in trials, but they must be reported as part of the publication included a supplementary file at least, if not as a separate paper, so their effectiveness can be evaluated.

In terms of trials methodology research, there is a pressing need for high-quality evidence on recruitment strategies. Current literature on recruitment methods is highly variable with very little depth (Gardner et al., 2020). Trialists and the trials methodology research community are best placed at improving the evidence base for evaluating recruitment strategies (Treweek et al., 2018). With regards to eczema, further research is needed to establish the efficacy of social media for targeting parents of children with eczema. It might be also useful to conduct a systematic review to explore the current landscape of reporting about participant recruitment in eczema clinical trials.

4.6 Conclusions

Recruitment on social media was successful and cost-effective in recruiting participants with eczema for an online RCT. This study adds valuable data to the evidence base on the feasibility and efficiency of social media recruitment campaigns. The findings provide useful information on the practicalities and benefits of using social media for recruitment and has demonstrated that social media can be an efficient recruitment method tool that has a unique ability to transcend barriers to recruiting participants. Sharing of detailed recruitment approaches used in trials is crucial for enhancing understanding of efficient strategies. Continued effort, adequate evaluation and systematic reporting of recruitment strategies is required to enable researchers to select the most appropriate strategies for recruiting participants into RCTs.

Chapter 5 Content validity of the Recap of atopic eczema (RECAP) measure in young people: an international cognitive interview study

This work has been published in the British Journal of Dermatology (Gabes et al., 2022).

5.1 Introduction

As described in Chapter 2, eczema is a relapsing and remitting condition. High disease activity, called a flare, leads to uncontrolled periods that are associated with higher disease burden (Simpson et al., 2018). In addition to alleviating eczema related symptoms, treatments aim to reduce the intensity and number of flares. Therefore, assessing how well the eczema is controlled is an important outcome when evaluating the efficacy of treatments (Barbarot et al., 2016).

To assess eczema control, the Recap of atopic eczema (RECAP) has been developed (Howells et al., 2019, Howells et al., 2020). RECAP is recommended by the HOME initiative as part of the COS for eczema trials as mentioned in section 2.5 of this thesis (Thomas et al., 2021). This instrument consists of seven questions with five response options for each item. Currently, self-reported and proxy reported versions are available that were validated with adults and parents of children with eczema (Howells et al., 2020, Gabes et al., 2021, Bhanot et al., 2021, Bhanot et al., 2022). However, discrepancies between proxy and self-reported PROMs in young people has been described in the literature (Theunissen et al., 1998, Annett et al., 2003). The disparity is greater during periods of high symptom burden and in such cases carers tend to overestimate symptoms (Mack et al., 2020). Moreover, parents are often more likely to exhibit negativity towards the health-related outcomes of their child if the child has a chronic disease (van Summeren et al., 2018). Evidence suggests that reports of young people from

Canada, aged 8-17, typically correlate less closely to proxy reports (Verhey et al., 2009).

Self-reporting by young people could help better capture eczema control and would also help to improve engagement and treatment adherence as they learn to care for themselves and become partners in their treatment (Matza et al., 2013, Groot et al., 2021). For aforementioned reasons, self-completion of RECAP is preferred. However, respondents may have different conceptual and linguistic abilities and might be unsure of the intended meaning of particular words, presenting barriers to completion (Miller, 2003). It is unclear whether the self-reported version shows adequate content validity when it is completed by young people with eczema. The concept of content validity was introduced in chapter 1 and defined by Mokkink et al. (2010a) as “the degree to which the content of an instrument is an adequate reflection of the construct to be measured.” It encompasses relevance, comprehensiveness and comprehensibility of the patient-reported instrument for the target population, construct and context of use (Terwee et al., 2018a).

Content validity is considered as one of the most important measurement properties of a PROM because it ensures that the items of the instrument appropriately represent the construct it intends to measure (Mokkink et al., 2010a). Good content validity elevates the credibility and trustworthiness of the measurement tool and enhances the relevance of the instrument to the population under study, which in turn aids the generalisibility of findings to the broader population. The lack of content validity can compromise the accuracy and reliability of the instrument, potentially introducing bias and leading to erroneous results due to the instrument not measuring all the relevant aspects of the construct under study (De Vet et al., 2011). Conducting qualitative interviews with the target population is the most effective method to assess content validity.

With the increasing number of clinical trials in children and the movement towards the use of PROMs in clinical settings, it is important to use validated and reliable

outcome measures. The aim of this collaborative study was to fill the content validation gap of the English, German and Dutch version of the self-reported RECAP in young people with eczema, according to COSMIN guidelines that provide a systematic framework for assessing the measurement properties of instruments (Terwee et al., 2018b). Furthermore, the COSMIN reporting guideline for studies on measurement properties of PROMs was also followed (Gagnier et al., 2021).

5.2 Aims and objectives

The aim of this study was to fill the content validation gap of the Recap of atopic eczema (RECAP) instrument in young people. The study had the following objectives:

1. To assess the content validity of the self-completed version of RECAP in young people with eczema in the UK, Germany and the Netherlands
2. To identify the most appropriate age cut-off for self-completion

5.3 Methods

5.3.1 Study design

This was a qualitative study, consisting of semi-structured cognitive interviews with young people with eczema.

The study used a think-aloud method, which is a well-established qualitative research technique that provides insights into cognitive processes and decision-making whilst performing a task or answering questions (Fonteyn et al., 1993). Participants were asked to complete the RECAP questionnaire as they were reading out loud and saying what they were thinking about when trying to answer the questions. This method was appropriate for the study because it delved into thought processes and perceptions and generated rich qualitative data. It helped to identify the obstacles or challenges participants encountered by verbalising

their thoughts and working through the questions. This type of interviewing enhances participant engagement, contributing to a better understanding of their perspectives and experiences (Beatty and Willis, 2007).

Ethical approval to conduct this study in each country was obtained from the ethics committees of the participating institutions (UK: FMHS 18-1805; Netherlands: MEC-2020-0417; Germany: 19-1521-101). I was leading the UK side of the study. The self-completed version of the RECAP questionnaire is shown in Figure 5.1.

Figure 5.1 Self-completed version of the RECAP questionnaire

5.3.2 Translation of the RECAP questionnaire

Prior to starting this content validity study, the original English adult and proxy RECAP versions were translated into German and Dutch in the respective countries. To perform linguistic validation, forward and backward translation with a subsequent cognitive debriefing was carried out in Germany (Gabes et al., 2021) and the Netherlands. Due to the fact that German and Dutch children and young people are addressed differently from adults than in English, an 'informal' version of RECAP in German and Dutch was created by replacing the formal pronoun with its informal equivalent. This modification is not anticipated to have altered the main content of the instrument. Its sole purpose was to make the instrument more suitable for the target population.

5.3.3 Recruitment

In the UK, participants were recruited through existing mailing lists where people had previously provided consent to contact and through social media. If recruited through social media, self-report of eczema diagnosis by a doctor was used to confirm eligibility. In Germany and in the Netherlands, parents and primary caregivers of young people with eczema were recruited from dermatology clinics. Purposive sampling was used to ensure a range of different ages of young people were recruited. All participants, except for one German girl, were native speakers. The aim was to recruit at least five young people with eczema, aged 8-16 years, per language (English, German, Dutch). Many children aged ≥8 have the ability to read. For instance, the self-completed version of the widely used EuroQol 5 Dimensions Youth (EQ-5D-Y) health status instrument is appropriate for those aged 8-15 years, whereas for children aged 4-7, the proxy version can be used (EuroQol Research Foundation, 2020). In agreement with this, it was reasonable to target the 8-16 years population for this study.

5.3.4 Data collection

In the UK, five interviews were conducted by me and two interviews were performed by Laura Howells between 12th March and 17th April 2021. Laura had extensive experience in qualitative research methods and in cognitive interviewing and trained me on how to conduct interviews in this study. After observing the first two interviews she performed, I started conducting the interviews independently. As the interviews progressed, my interview technique developed and my experience expanded, increasing my confidence in probing and awaiting responses from participants. In Germany, researchers conducted the interviews and in the Netherlands a trainee dermatologist performed the interviews. Field notes were not taken.

A predefined interview guide, including probing techniques, was used to structure the interviews. Prior to conducting the interviews, written informed consent was obtained electronically from the parents or primary caregivers of the participating young people. Interviews were conducted by telephone or video call. A parent or caregiver was present during the interview and was instructed not to answer the questions on behalf of the child or disrupt the interview with their own views. However, they had the opportunity to share their thoughts during the debriefing once the interview was completed. At the start of the interviews, the background of the study was explained to the participants. It was emphasised that questions could be asked by the participants at any time during the interview. The duration of the interviews was approximately 20 – 30 minutes. The interviews were audio recorded. A voucher of £10 (or 10€) was offered to participants as an inconvenience allowance.

5.3.5 Interview guide

According to the COSMIN user manual for assessing the content validity of PROMs, there is a set of criteria that should be met to adequately rate the overall content validity of a patient-reported instrument (Terwee et al., 2018a). The

predefined criteria for good content validity consists of ten questions regarding the three imperative and distinctive aspects of content validity (relevance, comprehensiveness, comprehensibility) as depicted in Table 5.1. Questions to assess these aspects were incorporated in the interview guide, which is available in Appendix 8.

Table 5.1 Ten criteria for good content validity, adopted from the COSMIN user manual (Terwee et al., 2018a)

Relevance (all items in the PROM need to be relevant in the target population and context)
1. Are the included items relevant for the construct of interest? 2. Are the included items relevant for the target population of interest? 3. Are the included items relevant for the context of use of interest? 4. Are the response options appropriate? 5. Is the recall period appropriate?
Comprehensiveness (no key aspects of the construct should be missing)
6. Are no key concepts missing?
Comprehensibility (the items should be understood by patients as intended)
7. Are the PROM instructions understood by the population of interest as intended? 8. Are the PROM items and response options understood by the population of interest as intended? 9. Are the PROM items appropriately worded? 10. Do the response options match the questions?

5.3.6 Data processing and analysis

Transcripts were transcribed verbatim, in the UK by the UoN automated transcription service. The transcripts were anonymised by assigning a unique identifier and recordings were deleted. Analysis was conducted, using a problem-focused coding manual (Appendix 9). ATLAS.ti (2021), NVivo (2021) and/or Microsoft Excel (2021) were used to code the transcripts and summarise the results. After the transcripts were coded by two independent reviewers in each country, the data was analysed by six researchers (AB, LH, GK, MG, AR, JO). Data analysis was conducted in the same language as the interview took place. Themes were translated into English and compared across the three countries.

The comments of participants on the individual items of RECAP were evaluated and based on these findings, the items were assessed in relation to comprehensibility, comprehensiveness and relevance. If an issue with an item occurred, the reviewers classified it either as a minor or a major problem. When young people stated having problems with understanding specific words, but were able to complete the question by themselves it was rated as a minor problem since this issue was considered to be negligible. Issues with the items were only rated as a major problem if explicit comments about rewording were made and/or if participants had difficulty answering the question on their own. Additionally, the reviewers rated an issue as major when it was important to discuss the item with the research team before making a decision. All results were discussed within the research team prior to making final conclusions.

5.3.7 Researcher characteristics

This collaborative project involved 12 researchers from 3 different countries and diverse professional backgrounds, as listed in Table 5.2.

Table 5.2 Characteristics of researchers of the RECAP content validity study

Name of researcher	Professional role	Name of institution	Country
Arabella Baker (AB)	Year 1 PhD student Registered nurse	University of Nottingham	UK
Kim Thomas	Primary supervisor of AB Professor of applied dermatology research	University of Nottingham	UK
Laura Howells	Research fellow Health psychologist	University of Nottingham	UK
Michaela Gabes (MG)	Year 3 PhD student	Otto-von-Guericke University Magdeburg	Germany
Christian Apfelbacher	Supervisor of MG Professor of epidemiology and health systems research	Otto-von-Guericke University Magdeburg	Germany
Gesina Kann	Research assistant	Otto-von-Guericke University Magdeburg	Germany
Theresa Donhauser	Intern	Otto-von-Guericke University Magdeburg	Germany
Daniela Gabes	Paediatric linguist Primary school teacher	University of Regensburg	Germany
Aviël Ragamin (AR)	Year 2 PhD student Medical doctor	Erasmus MC University Medical Center Rotterdam	The Netherlands
Suzanne GMA Pasmans	Supervisor of AR Professor of paediatric dermatology	Erasmus MC University Medical Center Rotterdam	The Netherlands
Marie-Louise Schuttelaar	Dermatologist	University of Groningen	The Netherlands
Jart AF Oosterhaven	Researcher in dermatology Medical doctor	University of Groningen	The Netherlands

5.4 Results

5.4.1 Participant demographics

In total, 23 young people with eczema were recruited from the three countries: UK (*n* = 7), the Netherlands (*n* = 7) and Germany (*n* = 9) (Table 5.3). Overall, the mean age of participants was 10.7 years (SD = 2.65) ranging from 8 to 16 years. 43.48% (10/23) were female.

Table 5.3 Demographic characteristics of participants

	UK (*n* = 7)	**Netherlands (*n* = 7)**	**Germany (*n* = 9)**	**Total (*n* = 23)**
Age (years)				
8-11	5	3	7	15
12-16	2	4	2	8
Range	8-15	8-16	8-14	8-16
Gender				
Male	5	4	4	13
Female	2	3	5	10
Ethnicity				
White	5	3	Not collected	Not available
Asian	2	0		
Mixed	0	2		
Black	0	1		
Arab	0	1		

5.4.2 Relevance

All items in the RECAP questionnaire were considered to be relevant by the participants. In the UK, the response options were difficult for three young people because there were either too few options to choose from or they had problems in deciding what to answer. Furthermore, three participants stated minor problems with the following three items because they considered the items as overlapping or not related to eczema:

- Item 5: *“Over the last week, how much has your eczema been getting in the way of day to day activities?”*

- Item 6 “*Over the last week, on how many days has your eczema affected how you have been feeling?”*

- Item 7 *“Over the last week, how acceptable has your eczema been to you?”*

In the Netherlands, only one child stated that item 7 was not considered relevant, because *“this skin disease was not acceptable to anyone”*. In Germany, no problems regarding relevance were observed. Since these issues were minor and only occurred with a few participants, the reviewers reached a consensus against recommending the removal or modification of these items.

The recall period was also assessed, as part of relevance. The recall period of one week was considered to be appropriate by all participants. Furthermore, there were no issues during the think-aloud process regarding the recall period and participants were able to recall experiences over the last week, when answering the questions.

5.4.3 Comprehensiveness

Regarding comprehensiveness only one minor problem occurred. In the UK, one child suggested to include an additional question about ‘skin picking’, a disorder characterised by repetitive and compulsive scratching or picking at the skin, to which dermatological conditions such as eczema may contribute (Grant et al., 2012). In the Netherlands and Germany, noteworthy problems did not emerge for the comprehensiveness of RECAP. Since only one child expressed the need to add a question, the research team agreed that it was not necessary to recommend additional changes to the instrument.

5.4.4 Comprehensibility

In the UK, the interviews did not identify any issues that would warrant a recommendation of change to the original scale. However, the study did identify issues around comprehensibility that appeared to be age-related. Problems, both minor and major, occurred among participants aged <12 with items 6 and 7 (Table 5.4). Due to the recurring problems with item 6 and item 7 in the German interviews with younger participants, the research team concluded that these issues was age-related.

Table 5.4 Comprehensibility issues in the UK

RECAP items	Type of problem	Age (gender)	Examples
Instructions	Minor	8 years (female)	**Mother**: Did you understand this bit where it says the questions below provide a snapshot of your eczema. Do you understand that bit? **Participant**: No (female, 8 years)
Item 6	Minor	11 years (male) 13 years (male)	**Interviewer**: So, what is your answer? **Participant**: I'm not sure. (male, 13 years)
Item 7	Major	8 years (female) 11 years (male)	**Interviewer**: Do you know what it means? **Participant**: No (female, 8 years)

The results of the interviews in the Netherlands are depicted in Table 5.5. The title, item 3 (*"Over the last week, on how many days has your skin been intensely itchy because of your eczema?")* and item 5 were rated by the reviewers as minor problems. However, these problems were negligible, because only few young people had minor problems with understanding those, item 7 and the response

options were very difficult for the young people to comprehend. As already discussed for the UK data, item 7 was agreed to be an age-related problem and therefore a consensus was reached not to be altered. The response options were only problematic for item 7 because the participants did not understand the word "*acceptabel*" (acceptable). Since these problems only occurred for this specific item, it was decided that altering the response options was not necessary.

Table 5.5 Comprehensibility issues in the Netherlands

RECAP item	Type of problem	Age (gender)	Examples
Title	Minor	8 years (male) 15 years (female)	**Participant**: What is "atopic"? (male, 8 years)
Item 3	Minor	12 years (female)	Participant had difficulty estimating symptom severity (female, 12 years)
Item 5	Minor	9 years (male)	**Participant**: What are "*bezigheden*" (day to day activities)? (male, 9 years)
Item 7	Minor	8 years (male) 8 years (male)	Participant thinks, "*acceptabel*" (acceptable) is a difficult word (male, 8 years)
	Major	9 years (male)	Participant doesn´t know the meaning of "*acceptabel*" (acceptable) (male, 9 years)
Response options	Major	8 years (male) 9 years (male)	Participant does not know meaning of "*acceptabel*" (acceptable) (male, 8 years)

For Germany, the results of the interviews are depicted in Table 5.6. Some minor problems occurred with item 1 (*"Over the last week, how has your eczema been?"*), items 3 and 7. These problems were only stated by a few young people, thus these issues were felt insignificant. The young people had major issues understanding the title of the questionnaire, item 4 (*"Over the last week, how much has your sleep been disturbed because of your eczema?"),* item 5 and item 6. Regarding the title,

the gender-specific term “*Patient/innen*” (male and female patients) was difficult to understand for the young people. For this reason, the questionnaire was renamed as “*Fragebogen für Kinder und Jugendliche mit Neurodermitis*“ (“RECAP for children and adolescents with atopic eczema”). This alteration did not change the meaning, but it was more comprehensible for the young people. Since participants did not understand the translation of the word “disturbed” (item 4) this word was altered into “*gestört*”, which is a more easily understandable translation for “disturbed”. Regarding item 5, the translation of “getting in the way of” was slightly simplified. The same goes for item 6, as the word “affected” was changed into a more comprehensible expression in German. Of note, great attention was given to making these adaptations conceptually equivalent to the original version. All these changes were discussed within the German research team with the help of a primary school teacher and paediatric linguist. Therefore, these changes should now be more easily comprehensible for the majority of young people from the age of 8 years and the implemented adaptions should not affect the meaning of the items.

Table 5.6 Comprehensibility issues in Germany

RECAP item	Type of problem	Age (gender)	Examples
Title	Minor	9 years (female) 9 years (female) 10 years (male)	Participant stalled while reading "*Patient/innen*" (patients) and needed explanation from parent (female, 9 years)
	Major	8 years (male) 10 years (male)	**Participant**: I don´t know what "*Patient/innen*" means (male, 10 years)
Item 1	Minor	10 years (male) 10 years (male)	**Interviewer**: Do you know the word "*beurteilen*"? **Participant**: Not so well (male, 10 years)
Item 3	Minor	9 years (female) 9 years (female) 9 years (female)	Interviewer had to explain to the participant the difference between item 2 and item 3 (female, 9 years)
Item 4	Minor	9 years (female)	Participant had problems understanding the word "*beeinträchtigt*" (disturbed) (female, 9 years)
	Major	8 years (female)	**Interviewer**: What do you not understand? **Participant**: "*Beeinträchtigt*" (disturbed) (female, 8 years)
Item 5	Minor	9 years (female) 12 years (male)	Participant struggled with the word "*alltägliche Aktivitäten*" (day to day activities) but actually understood it very well (male, 12 years)
	Major	8 years (female) 8 years (male) 9 years (female) 10 years (male)	**Interviewer**: Do you know, what "*alltägliche Aktivitäten*" (day to day activities) means? **Participant**: No (male, 8 years)
Item 6	Major	8 years (female) 9 years (female) 10 years (male)	**Participant**: I don´t understand the word "*beeinflusst*" (affected) (female, 8 years)
Item 7	Minor	14 years (female)	Participant struggled with the word "*klarkommen*" (acceptable) (female, 14 years)

5.4.5 Combined results across the three countries

As demonstrated in Table 5.7, some major problems were identified across the three countries for young people between the ages of 8 and 11 years. RECAP is recommended for self-completion for children aged 12 and above and using the proxy completed version for children aged under 12 years is advised. Fewer difficulties were identified using the German translation for children in which the language was simplified. These findings suggest that this version may be suitable for completion by children as young as 8 years.

Table 5.7 Summary of major problems regarding the comprehensibility of RECAP

RECAP items	Age range	Number of participants	Examples
Title	8 – 10 years	2	**Participant**: I don´t know what "*Patient/innen*" means (male, 10 years)
Item 4	8 years	1	**Interviewer**: What do you not understand? **Participant**: "*Beeinträchtigt*" (disturbed) (female, 8 years)
Item 5	8 – 10 years	4	**Interviewer**: Do you know, what "*alltägliche Aktivitäten*" (day to day activities) means? **Participant**: No (male, 8 years)
Item 6	8 – 10 years	3	**Participant**: I don´t understand the word "*beeinflusst*" (affected) (female, 8 years)
Item 7	8 – 11 years	3	Participant does not know the meaning of "*acceptabel*" (acceptable) (male, 9 years)
Response options	8 – 9 years	2	Participant does not know meaning of "*acceptabel*" (acceptable) (male, 8 years)

5.5 Discussion

5.5.1 Summary of principal findings

This study assessed the content validity (relevance, comprehensiveness and comprehensibility) of the self-reported version of RECAP among young people with eczema across the UK, Germany and the Netherlands. No comprehensibility issues were reported in participants above the age of 12 years. These age groups only had minor problems with the questionnaire and were able to fully complete it by themselves. Children younger than 12 years old reported problems with several items of RECAP and were unable to complete the questionnaire by themselves. In addition, all items and response options were considered relevant. No problems with comprehensiveness were reported by participants of any age.

5.5.2 Linguistic comprehension and abstract thinking

Young people below the age of 12 reported difficulty understanding several terms, leading to an inability to complete RECAP without help. These terms included the terms “day to day activities” (item 5), “affected” (item 6) and “acceptable” (item 7). Interestingly, when explaining the terms “day to day activities” (item 5) or “affected” (item 6), participants could understand these items and were able to provide an answer. This may be due to vocabulary related issues rather than the construct of these items. Adding an example would probably aid children in understanding these items. However, including examples to the questionnaire would limit the intended construct that each item is trying to capture and is therefore not desirable. Since these items are purposely designed to leave room for individual interpretation, the inclusion of examples may restrict patients in doing so. Furthermore, the intention of the research team was to avoid issues related to cross-cultural validity by refraining from the addition of potentially inappropriate examples. A more pragmatic approach could be to encourage children and their caregivers to complete RECAP together. This provides children the opportunity to report their perspectives on eczema control, without restricting the measured

construct. Whereas, difficulties with the term “acceptable” (item 7) could be more complex as none of the children under 12 years old had a grasp of this term. Providing an explanation of the meaning of “acceptable” did not result in the ability to complete this item. The term “acceptability” could be a more intricate concept that requires a higher level of abstraction ability, which is usually not yet present in young children (Dumontheil, 2014). However, in the German version of RECAP which used a specific term “*klarkommen*” (get along, cope) for item 7, younger participants reported only minor difficulties. This indicated a problem with linguistic comprehension, instead of a problem in abstraction ability. Creating a new child version of RECAP could be an alternative. However, for uniformity purposes, a single version of RECAP that precisely captures the same construct in all age groups is preferred.

5.5.3 Reflexivity

In qualitative research, prior assumptions and experiences of the researcher may inevitably influence the collection and analysis of data (Geddis-Regan et al., 2022). Therefore, it is important to acknowledge the potential impact of the researcher through reflexivity (Berger, 2015). Reflexivity is a continuous self-reflective process, where the researcher critically examines how their experiences and preconceptions may influence the various stages of qualitative research. Reflexivity ensures that any undue impact or the influence of the researcher is transparently acknowledged and minimised.

I am a registered nurse and it is important to realise the potential impact of having a healthcare background. It was noted during the interviews that professional curiosity inevitably occurred, leading to wanting to know more about symptoms, treatments and how they affected the lives of participants. However, the prespecified interview guide played a vital role in preventing deviation from the study aims and objectives. The interview guide not only helped to minimise subjectivity of the interviewer, but provided a structured framework and a standardised approach to interviews. Adherence to the guide ensured

consistency in questioning, facilitated an open dialogue and allowed flexibility for participants for authentic self-expression.

5.5.4 Importance of involving young people

With the increasing number of potential treatment options available for young people with eczema, assessing effectiveness in ways that is important and meaningful to young people is essential (Chu, 2021). The importance of capturing self-reported outcomes of young people is well recognised in paediatrics and is emphasised by the FDA (Matza et al., 2013, Food and Drug Administration, 2009). In this study, it was found that young people ≥12 years had no problem with the self-completion of RECAP, whilst most younger children had difficulty with completing RECAP by themselves.

The use of RECAP is advantageous because it provides clinicians and researchers with enhanced insight into the perceived control over eczema. For children with eczema, it enables their care providers to offer more informed information on the perceived effectiveness of treatment options, thereby aiding the shared-decision process. In addition, self-completion promotes patient engagement and could lead to greater treatment adherence (Náfrádi et al., 2017, Groot et al., 2021).

In terms of clinical trials, it is important to maintain a consistent method for assessing the outcome, whether through self-completion or proxy reporting, and refraining from changing the assessment method during the course of the study is advised.

5.5.5 Strengths and limitations

A strength of this study is its multinational, multilingual approach to assessing the content validity of RECAP among young people. Additionally, in accordance with COSMIN criteria for good content validity studies, at least seven participants per language were included and a topic guide was used during the cognitive interviews, making the findings more robust (Terwee et al., 2017).

A limitation of the study was the lack of information on eczema severity (only collected in the UK), incomplete data on ethnicity (only collected in the UK and the Netherlands), educational level and socioeconomic status of included participants which may have potentially influenced both relevance and comprehensiveness. Consequently, the availability of partial data impeded the complete analysis of baseline characteristics and the ability to obtain a holistic view of participant demographic attributes. It was anticipated that recruiting from both dermatology clinics and the community ensured the inclusion of people from different backgrounds with a range of eczema severities. Another potential limitation was that this study only assessed the content validity of RECAP across the languages German, English and Dutch and further studies in other languages might be required.

5.5.6 Implications for research and clinical practice

In light of the increasing number of clinical trials in children and the movement of clinicians towards capturing patient-reported effectiveness of treatment in clinical settings (Naka et al., 2017, Leshem et al., 2020), the use of validated and reliable outcome measures is important. RECAP, alongside another patient-reported instrument called the Atopic Dermatitis Control Tool (ADCT) (Pariser et al., 2020), is recommended by the HOME initiative as a core outcome measurement instrument for the long-term control domain (Thomas et al., 2021). Based on the findings of this study, RECAP could be recommended as an outcome measure for assessing the long-term control of eczema in young people. Overall, the self-reported version of RECAP is likely to be appropriate for young people aged 12 years and above. Additionally, the German version is probably comprehensible to children of lower ages (≥8 years) due to the linguistic changes made.

Nevertheless, in all three languages, there might be some instances where the proxy-version is necessary for older children as well. Furthermore, considering that young people below the age of 12 encountered several comprehensibility issues with RECAP, the proxy version should be used for children younger than 12 years

or when they are unable to report their experience of eczema control. When employing the proxy version of RECAP, it is advised that caregivers should be encouraged to complete RECAP together with their child to ensure optimal assessment of perceived eczema control.

Further research is necessary to investigate the validity, responsiveness, reliability and interpretability of RECAP among different populations and age groups. The uptake of the HOME core outcome set is crucial for evidence synthesis, enabling the comparison and pooling of trial results in meta-analyses. In order to achieve the successful implementation of the HOME core outcome set, it is crucial for future clinical trials to incorporate HOME instruments, such as RECAP, into their design. Eczema clinical trials involving children and young people now have guidance available on which version of RECAP to use.

5.6 Conclusions

This study demonstrated that the self-reported version of RECAP is appropriate for use from the age of 12 years. The proxy version can be used in children younger than 12 years. These findings aim to expand the existing evidence on psychometric properties of RECAP, whereby enhancing the availability of information on validity. Hence, helping to increase the confidence in the ability of the instrument to provide meaningful and accurate data in the target population. Thus, aiding the adoption of RECAP in research and clinical practice in young people with eczema. Chapter 6 includes a validation study that assessed the interpretability of RECAP, aiding the understanding of change scores and providing additional data with the aim of helping to facilitate the uptake of RECAP in clinical trials.

Chapter 6 Aiding the interpretability of change in Recap of atopic eczema (RECAP) scores

6.1 Introduction

In section 2.3.1.4, the concept of interpretability was described whereby qualitative meaning, specifically clinical connotations, can be attributed to the quantitative scores or change in scores of an instrument (Mokkink et al., 2010a). A patient-reported multi-item instrument, like RECAP, initially provides a quantitative assessment of the construct under study by generating numerical scores. However, these raw scores might not be inherently interpretable by the users of the instrument, making it challenging to judge clinical significance and treatment effects.

Interpretability is a critical psychometric property as it defines what the clinical relevance of changes in RECAP scores are. It also helps the interpretation of study results in a way that is meaningful to users. Understanding what the score changes mean is critical for its adoption in both routine clinical practice and research settings.

6.1.1 Terminology used to establish interpretability

A well-known approach for improving the interpretability of an instrument is to assign meaning to the appeared change in scores. Establishing the meaning of changes in scores is particularly important in clinical trials, as statistically significant change in scores of a patient-reported instrument does not necessarily imply clinically relevant change (Mouelhi et al., 2020). This highlights the need to define the minimal change in outcome scores, which is perceived by patients as important and meaningful, called the minimal important change (MIC). This approach is regularly used for determining interpretability. COSMIN initially

defined MIC as: *"The smallest change in score in the construct to be measured which patients perceive as important"* (Mokkink et al., 2010a).

Despite, evidence suggests that inconsistency in the terminology used to explain the concept of MIC has occurred (King, 2011). Other commonly used terms are minimal clinically important difference (MCID) and minimal important difference (MID). The literature often erroneously interchanges these terms, even though they represent conceptually different types and magnitude of change (Beaton et al., 2001a). MIC refers to important changes within individuals, whereas MID considers the differences between individuals. Thus, it has been proposed to use MIC for longitudinal within-person changes in scores and MID to be used to denote cross-sectional between-person differences (De Vet et al., 2006a). In a recent systematic review of MIC terminology, Terwee et al. (2021) have provided conceptual clarification leading to a revised definition of MIC as: *"A threshold for a minimal within-person change over time above which patients perceive themselves importantly changed*". In accordance with these new recommendations on terminology, the term MIC will be used in this thesis in relation to interpretability.

To evaluate the effectiveness of an intervention, it is important to ascertain whether the improvement that resulted from the intervention is clinically meaningful. In clinical trials, MIC is used as a benchmark of important change against which the magnitude of improvement in PROM scores can be assessed (Jayadevappa et al., 2017). MIC emphasises the perspectives of patients on what constitutes a meaningful improvement or deterioration in their condition. In contrast, a clinically meaningful difference goes beyond the viewpoints of patients and it incorporates the clinical significance of observed changes by evaluating the practical importance or relevance of these changes in terms of treatment effectiveness and health outcomes (De Vet et al., 2011). A clinically meaningful difference is determined by the impact of change on symptoms, functioning and QoL. This concept is important for ensuring that observed

changes in clinical measures have real world significance. Since the minimal important change is more patient-centric and the clinically meaningful difference integrates both patient perceptions and clinical significance, these are different concepts and should not be used interchangeably.

Determining the MIC of RECAP is essential for clinical trials as a MIC estimate can be used to determine sample size and establish statistical power to detect a meaningful change or difference in the selected primary endpoint (Wright et al., 2012). Thus, ensuring that trials are designed appropriately, which in turn helps to prevent wasting resources on studies that would not yield meaningful results. Furthermore, MIC estimates provide the basis for the interpretation of clinical trial results that aid researchers, clinicians and patients to comprehend findings by assigning meaning to a change score on the instrument which helps to facilitate evidence-based decision-making.

Another useful concept used in relation to interpretability is the smallest detectable change (SDC). It is defined as the smallest amount of change in the score that can be detected by an instrument, beyond measurement error (De Vet et al., 2011). It is a statistical measure on the reliability of the instrument, providing a value that indicates the extent of the change in scores before a reasonable level of certainty in the occurrence of true change can be achieved. This information is important when establishing the MIC, as an MIC that is smaller than the SDC is not useful.

6.1.2 Approaches used to calculate MIC

Several MIC calculation methods exist to aid interpretability and each may yield slightly different results, however there is no consensus on the best single method as of yet (Mouelhi et al., 2020). Current recommendations suggest performing multiple methods in different datasets followed by the triangulation of MIC values (Copay et al., 2007, Revicki et al., 2008, Crosby et al., 2003, Terwee et al., 2021). While numerous MIC estimates could diminish the usefulness of a

standardised MIC threshold, investigating the potential variation of the MIC of RECAP is important to ensure it is meaningful within the applied context and population. Viewing MIC as a non-binary construct is encouraged, acknowledging its inevitable variation according to population, study design and interventions under investigation.

6.1.2.1 Anchor-based methods

Anchor-based methods assign meaning by relating change scores on the instrument to an external criterion, called an anchor, that is a well-interpretable and relevant outcome measure in itself (De Vet et al., 2007). An anchor can be derived from a patient-reported evaluation of change, such as the Patient Global Assessment (PGA); a certain level of change on the anchor corresponds with the MIC of the instrument (Rai et al., 2015). Notably, the selected anchor needs to relate to the underlying concept that the instrument under investigation is designed to measure. In this study, the anchors were measuring eczema severity that is a closely related notion to eczema control. Anchor-based methods incorporate minimal importance from the patient and clinician perspective, depending on the type of anchor (De Vet et al., 2011).

Using anchor-based methods, a prospective study has calculated the MIC of RECAP in a Dutch tertiary hospital in adults with eczema diagnosed by a dermatologist as per the UK Working Party Criteria (Zhang et al., 2023). Participants completed RECAP and anchor questions at baseline, after 1 to 3 days and 4 to 12 weeks. The PGA of atopic dermatitis control was used as an anchor to assess the overall perception of control by patients asking the following question: “What is your overall impression of your atopic dermatitis control over the last week?” with the following answer options: not at all, a little, moderately, mostly and completely controlled (Zhang et al., 2023). A further anchor of global rating of change scale was used to measure the degree of change in the perception of disease control in participants as follows: “Overall, has there been any change in the level of disease control of your atopic dermatitis since the last

time you completed the RECAP?" with the answer options: Yes/No. Two additional questions were asked if the answer was "Yes" leading to the following classifications: no important change, important improvement (much/moderate/minor improvement) and important deterioration (minor/moderate much deterioration) (Zhang et al., 2023). Results of this study will be discussed in section 6.5.2.

6.1.2.2 Distribution-based methods

Distribution-based methods are based on the distributional characteristics of the outcome scores in the study population, providing a means for evaluating change beyond some level of random variation to gauge a standardised metric (Guyatt et al., 2002). A commonly used distribution-based method to interpret change is the effect size which is a statistical parameter, standardised mean difference, that relates change to the variability of the sample (Cook, 2008, Beaton et al., 2001a, Copay et al., 2007, Wright et al., 2012). Cohen (1988) devised standard thresholds for interpreting effect sizes, stipulating that 0.2 represents a small effect, 0.5 a medium effect and 0.8 denotes a large effect. Furthermore, a systematic review found that an effect size of 0.5 often closely corresponded with MIC scores of health-related quality of life instruments used in patients with chronic disease (Norman et al., 2003). In contrast, others opposed to this parameter suggesting that an effect size of 0.2 would be more appropriate because MIC is typically viewed as a small effect size (Beaton, 2003). However, a recently published meta-analysis pointed out that higher effect sizes may occur for certain self-reported outcome measures, such as pain (Swinton et al., 2023). In general, the effect size is not a universally applicable parameter as it is dependent upon various characteristics such as the type of outcome measure, patient population and context. Nonetheless, using the 0.5 baseline standard deviation (SD) for effect size is a commonly used method to enhance the interpretability of change in PROM scores due to its calculation simplicity in the available dataset.

The major limitation of distribution-based methods is that they only offer statistical properties and do not convey the importance of the observed change, thus fail to provide direct MIC estimates and for this reason are not deemed as true MIC calculations (De Vet et al., 2011). Consequently, anchor-based methods are viewed as superior and provide primary evidence for the MIC. Nevertheless, distribution-based methods can complement these MIC estimates by providing supporting evidence for the proposed MIC (Revicki et al., 2008). In fact, Crosby et al. (2003) recommended the combination of distribution-based and anchor-based methods, allowing for a more comprehensive interpretatability as it takes into account both the measure of variability and the selected external criterion. This blended approach has been widely adopted for calculating MIC.

In terms of RECAP, there is limited evidence on the MIC values and SDC in different populations and settings. Therefore, this study aimed to establish the MIC of RECAP through a variety of calculation methods using the readily available dataset of the Eczema Monitoring Online trial, as described in Chapter 3. The results of this study will further aid the interpretation of data from RCTs and will help the adoption of this patient-reported instrument in future clinical trials.

6.2 Aims and objectives

The aim of this study was to aid the interpretability of RECAP change scores, thereby helping the interpretation of clinical trial results and filling a validation gap for the HOME initiative. The study had the following objectives:

1. To calculate the smallest detectable change for RECAP
2. To estimate the MIC of RECAP using various calculation methods
3. To compare the MIC estimates provided by a single-item anchor and a multi-item anchor

6.3 Methods

6.3.1 Study design

This was a validation study, performing secondary analysis on the EMO trial dataset, described in Chapter 3, to establish the interpretability of RECAP.

The study design adhered to the COSMIN guidelines (Mokkink et al., 2019). The study protocol was prospectively registered on 1st February 2023 on Figshare (Baker et al., 2022b). The EMO trial was described in chapter 3. To conduct this study RECAP, PGA and POEM scores were derived from the existing dataset. Since in the ethics application of the EMO trial it was mentioned that this subsequent study will be conducted, seeking further ethical approval was not necessitated.

6.3.2 Outcome measures

RECAP is a seven-item instrument that captures patient-perceived eczema control over the preceding week, as illustrated in Chapter 5 (Howells et al., 2020). Each item carries equal weight and rated between 0 and 4 points; providing a total score from 0 to 28, with higher scores indicating less eczema control. To calculate the total RECAP score, the scores from each item were summed. If one item was unanswered, the total score was calculated, if two or more items were unanswered the total score was not calculated and it was assumed to be missing as per instrument developers' recommendation. This study used baseline and week 8 scores for RECAP, PGA (single item anchor) and POEM (multi-item anchor) (Table 6.1).

Table 6.1 Measures used as anchors for calculating MIC

Outcome measure name (anchor)	Single-item anchor: PGA	Multi-item Anchor: POEM
Question(s)	1. How is your eczema today?	1. Over the last week, on how many days has your skin been itchy because of your eczema? 2. Over the last week, on how many nights has your sleep been disturbed because of your/their eczema? 3. Over the last week, on how many days has your skin been bleeding because of your eczema? 4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema? 5. Over the last week, on how many days has your skin been cracked because of your eczema? 6. Over the last week, on how many days has your skin been flaking off because of your eczema? 7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?
Response options	• Clear • Almost clear • Mild • Moderate • Severe • Very Severe This results in a 5 point scale.	• No days • 1-2 days • 3-4 days • 5-6 days • Every day This results in a 28-point scale with a published MIC value of ≥3.0 points (Howells et al., 2018, Gaunt et al., 2016, Schram et al., 2012)
Recall period	On the day of assessment	Past week
Completer	Participants aged ≥14	Participants aged ≥14
Data collection timepoints	Baseline Week 8	Baseline Week 8

6.3.3 Statistical analysis

EMO trial participants with completed paired measurements for RECAP, PGA and POEM scores at baseline and follow-up were included in this study (*n* = 219), which appears to be adequate as a minimum of 100 participants are recommended to be included for validation studies (Mokkink et al., 2010b, Mokkink et al., 2019). Parents of children were excluded from the analysis due to the insufficient number of participants (*n* = 15), allowing for a more precise estimation of the MIC for self-completers (≥14 years). For each paired measurement, change scores were computed prior to performing the analyses. Since this study used an already completed trial dataset, formal sample size calculation was not performed. Analyses were conducted in Stata statistical software, version 17.0 (StataCorp, 2021).

6.3.3.1 Computing the smallest detectable change

To be able to calculate SDC the intraclass correlation coefficient (ICC) needs to be derived by conducting a test-retest reliability of the instrument under investigation. This assessment should be performed with at least 50 participants and ideally within 24 hours of the initial assessment (De Vet et al., 2011). Until now, two studies have performed test-retest reliability of RECAP in adults with eczema (Bhanot et al., 2021, Zhang et al., 2023). The first was an online survey study in the UK, using a two weeks test-retest window with a lower sample size (*n* = 44, ICC = 0.85, CI 0.7451, 0.9166). Whereas the newest study in the Netherlands, used a 1-3 days assessment period for test-retest reliability with sufficient sample size (*n* = 112, ICC = 0.988, CI 0.983, 0.992).

Given that test-retest evaluations are usually not performed in every study, especially in RCTs, it is a common practice to use ICC values from a different study that involved a similar population. Since the EMO trial dataset did not contain this data, the ICC from the Dutch study was used to calculate the SDC for RECAP. Furthermore, having the ICC value also allowed to calculate the

standard error of measurement (SEM) for RECAP that describes the error related to the measure (Wyrwich et al., 1999). SEM is needed for calculating the SDC. Beyond having MIC values, the SDC and SEM values are useful as they can serve as further benchmarks for the interpretation of RECAP scores.

The SDC was derived, using the following formula (De Vet et al., 2011):

$$SDC = 1.96 \times \sqrt{2} \times SEM_{agreement}$$

$\mathrm{SEM}_{\mathrm{agreement}}$ was calculated as:

$$SEM = SD_{pooled} \times \sqrt{1 - ICC}$$

The following formula was used for SD_{pooled}:

$$SD_{pooled} = \sqrt{\frac{SD_1^2 + SD_2^2}{2}}$$

SD_1 = baseline RECAP scores (6.1)

SD_2 = follow-up RECAP scores (5.7)

Taking the $ICC_{agreement}$ score from the Dutch study (Zhang et al., 2023) was considered appropriate as there was a similar variability in baseline RECAP scores: EMO trial $SD_{baseline}$ = 6.12, mean = 12.0 versus Dutch study $SD_{baseline}$ = 8.0, mean = 11.5.

6.3.3.2 Computing the minimal important change

6.3.3.2.1 Anchor-based methods

In this study, 4 anchor-based methods were used to establish MIC values. The PGA was the selected anchor due to its simplicity, common use and widespread recognition as a meaningful external anchor (Schram et al., 2012). PGA scores range from 0 (clear) to 5 (very severe), higher scores represent more severe eczema. To obtain a scale where higher scores represent less severe eczema, scores were reversed and positive change scores represented improvement. To provide a single item anchor, PGA scores were converted into a change score using the following formula:

$$PGA_{change\ score} = PGA_{baseline\ score} - PGA_{follow-up\ score}$$

Since MIC anchor-based methods contrast two prespecified groups, therefore analysis of change can focus on one direction at a time (improvement or deterioration). Following this suggestion, this study exclusively focused on improvement and excluded deteriorated participants (De Vet et al., 2011). The two adjacent groups used were the minimum important improvement and not importantly changed (stable) groups (Figure 6.1).

Thus, the change scores for PGA ranged from 0 (no change) to 1 (smallest improvement) where a positive 1.0 point change on the PGA indicated a meaningful improvement, denoting a change in severity banding.

	Change scores for PGA	Interpreting the anchor change scores	Change scores for POEM
Cut off	0	No change in score (stable)	-1, 0 , 1
	1	Smallest reported improvement	3

Figure 6.1 Definition of the stable and improvement groups needed for the anchor-based methods

Prior to performing analyses, the suitability of PGA as an anchor was gauged by assessing its linear relationship with the RECAP change scores. For this purpose, the Pearsons' r correlation was used and a moderate correlation (r = 0.62) was noted. This was greater than the preferable correlation criterion of r = 0.50 (Revicki et al., 2008), thus PGA was a suitable anchor in this study. Figure 6.2 illustrates the correlation between the RECAP change score and PGA anchor.

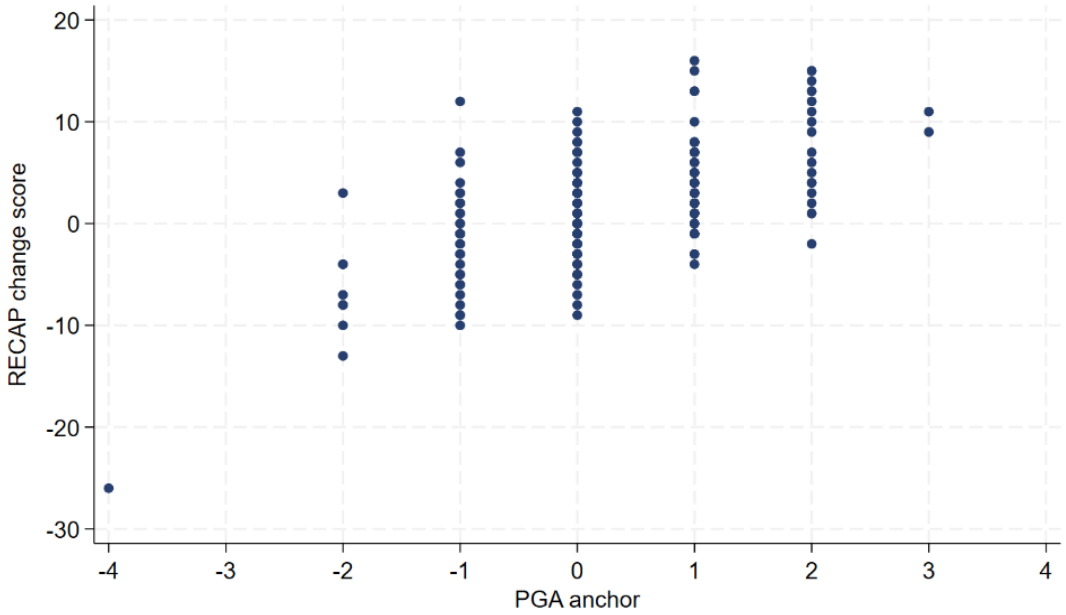


Figure 6.2 Scatterplot of correlation between RECAP change score and PGA anchor

POEM was used as a multi-item anchor to allow to compare the findings of this study with other validation studies using the HOME core outcome set to establish the interpretability of RECAP. The change scores were computed to provide an anchor as follows:

$$POEM_{change\ score} = POEM_{baseline\ score} - POEM_{follow-up\ score}$$

POEM scores range from 0 (clear) to 28 (very severe eczema), a decrease in scores represents less eczema severity. Similarly to the PGA anchor, POEM scores were reversed so that positive change scores represented improvement. POEM has an established MIC value of ≥3.0 points (Schram et al., 2012, Gaunt et al., 2016) and the SDC for POEM is reported as 2.0 points (Howells et al., 2018). Considering these established values, POEM change scores in this study were prespecified as +1, 0, -1 point change (stable) and a positive 3.0 point change (smallest improvement) as shown in Figure 6.1. These categories ensure the inclusion of those who importantly changed, thus providing more precise estimates. Moderate correlation between the POEM anchor and the RECAP change score was noted r = 0.68, indicating the suitability of POEM as an anchor. The scatterplot in Figure 6.3 represents the correlation between RECAP change score and the POEM anchor.

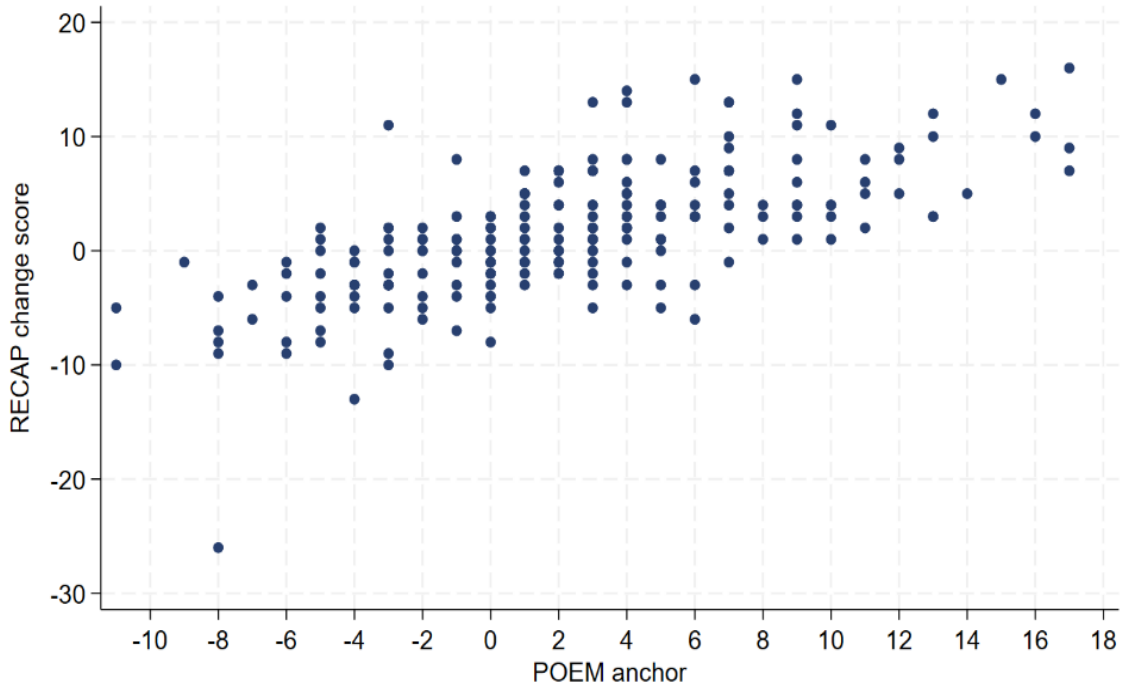


Figure 6.3 Scatterplot of correlation between RECAP change score and POEM anchor

Two anchor-based methods used the mean change approach to calculate the MIC:

- Within-person change method, involves the mean change in RECAP scores of the group with a minimum important improvement on the anchor.
- Between-patient change method, based on the mean difference in RECAP change scores between two adjacent subgroups on the anchor, namely: the minimum important improvement and the no change groups.

The receiver operating characteristic (ROC) curve method was the third anchor-based approach used in this study. The area under the curve (AUC) of the ROC curve analysis was utilised to obtain the optimal cut-off point for the RECAP change scores. This cut-off point serves as a discriminating factor between the improved group (change scores of PGA ≥1 and POEM ≥3) and the stable group (PGA = 0 and POEM = -1, 0, 1). The optimal ROC cut-off point denotes the MIC

of RECAP, which maximises the Youden's J statistic of sensitivity-(1-specificity) (Copay et al., 2007). To calculate a MIC score with 95% confidence interval (CI), the nonparametric bootstrapping method was used as suggested by Terluin et al. (2015).

The fourth and final anchor-based method was the predictive modelling method. This method uses logistic regression analysis with dichotomous outcomes to predict whether a participant belongs to the improved or stable group. The change in RECAP scores served as the primary predictor, whereas the improvement in the respective anchors was the dependent variable (Terluin et al., 2015). MIC is determined by finding the RECAP change score that corresponds to a likelihood ratio of 1. This method is advantageous as it provides greater precision than the ROC curve analysis and allows for adjustment of baseline disease severity, if required (Terluin et al., 2017). The MIC was estimated using the following formula:

$$\mathrm{MIC}_{\mathrm{pred}} = \frac{\ln(\mathrm{odds}_{\mathrm{pre}}) - \mathrm{C}}{\mathrm{B}}$$

MIC_{pred} = MIC value

C = Intercept

B = Regression coefficient of RECAP changes from logistic regression

$$\ln(\mathrm{odds}_{\mathrm{pre}}) = \frac{\text{Proportion improved on anchor}}{1 - \text{Proportion improved on anchor}}$$

According to Terluin et al. (2015) when looking at improvement then $odds_{pre}$ are 1, and the $\ln(odds_{pre}) = 0$ using the following formula to calculate the MIC for this method:

$$\mathrm{MIC_{pred}} = \frac{(0 - \mathrm{C})}{\mathrm{B}}$$

If the proportion of improved does not equal to 50%, it might be necessary to calculate an adjusted MIC (Terluin et al., 2017). Since the proportion of improved on the PGA anchor was 36% and on the POEM it was 46%, the adjusted MIC (MIC_{adj}) was calculated, using the following formula:

$$\mathrm{MIC_{adj}} = \mathrm{MIC_{pred}} - (0.090 + 0.103 \times \mathit{Cor}) \times \mathrm{SD_{change}} \times \ln(\mathrm{odds_{pre}})$$

6.3.3.2.2 Distribution-based methods

This distribution-based method is a measure of variability, whereby the variation among a group of scores is assessed. This approach solely relies on the distribution of baseline RECAP scores without relating it to an anchor for assessing the degree of change. The value of 0.5 SD of baseline RECAP scores corresponds to the MIC (Norman et al., 2003). To estimate the MIC, the baseline SD of baseline RECAP scores was calculated.

6.4 Results

A total of 219 participants with eczema completed RECAP, PGA and POEM at baseline and follow-up. The demographic and clinical characteristics of participants included in the study is displayed in Table 6.2. The distribution of baseline RECAP scores is demonstrated in Figure 6.4.

Table 6.2 Characteristics of included participants

Participant characteristics	*n* (%)
Age (years)	
Mean (SD)	28.48 (14.14)
Minimum, maximum	14-74
Gender	
Male	52 (23.7)
Female	162 (74.0)
Other	1 (0.5)
Prefer not to say	4 (1.8)
Ethnicity	
White	167 (76.3)
Asian or Asian British	28 (12.8)
Black, African, Black British or Caribbean	10 (4.6)
Mixed or multiple ethnic groups	11 (5.0)
Another ethnic group	3 (1.3)
PGA, mean (SD)	3.4 (0.9)
Clear	2 (0.9)
Almost clear	34 (15.5)
Mild	70 (32.0)
Moderate	86 (39.3)
Severe	23 (10.5)
Very severe	4 (1.8)
POEM, mean (SD)	14.9 (5.9)
Mild (3-7)	27 (12.3)
Moderate (8-16)	95 (43.4)
Severe (17-28)	97 (44.3)
RECAP scores used for MIC calculation	**Mean (SD)**
Baseline	12.0 (6.12)
Week 8	10.6 (5.71)
RECAP change scores	1.4 (5.6)

SD=Standard Deviation; PGA=Patient Global Assessment; POEM=Patient Oriented Eczema Measure; RECAP=Recap of Atopic Eczema; MIC=Minimal Important Change.

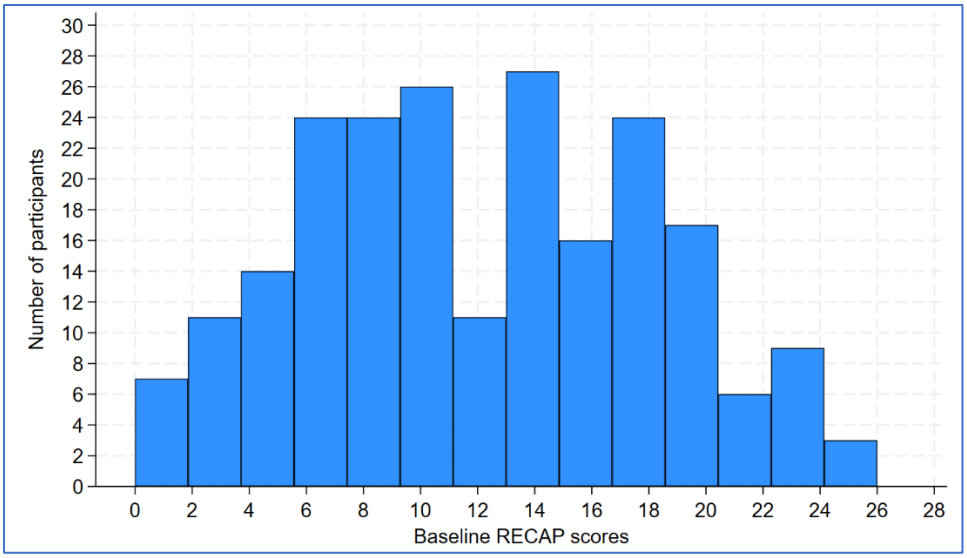


Figure 6.4 Distribution of baseline RECAP scores

6.4.1 Smallest detectable change

The ICC was 0.988 and the SD_{pooled} was 4.91, resulting in the $SEM_{agreement}$ = 0.64.

Based on these results, the SDC was computed as follows:

$$\text{SDC} = 1.96 \times \sqrt{2} \times 0.64 = 1.7739$$

Therefore, the SDC in the EMO trial dataset was 1.77 points for RECAP.

6.4.2 Minimal important change

6.4.2.1 Anchor-based methods

Prior to starting the analysis, the anchors were operationally categorised as demonstrated in Tables 6.3 and 6.4.

It can be seen in Table 6.3 that for the PGA anchor the mean RECAP change score was 0.42 for the stable group (*n* = 96) and 3.94 (*n* = 58) was for the minimum important improvement group (PGA = 1). Accordingly, for the within-patient score change method the MIC equals to 3.94 (95%CI 2.80, 5.08) whereas for the between-patient score change approach the MIC was 3.52 (95%CI 2.14, 4.90).

Table 6.3 Mean PGA anchor sores of RECAP for participants categorised according to change on the anchor

Change in score on PGA	*n* (%)	Mean RECAP change score (SD)
-4	1 (0.5)	-26 (n/a)
-2	8 (3.7)	-6.37 (4.80)
-1	34 (15.5)	-1.44 (4.87)
0	96 (43.8)	0.42 (3.92)
1	58 (26.5)	3.94 (4.33)
2	20 (9.1)	7.75 (5.30)
3	2 (0.9)	10 (1.41)

SD=Standard Deviation; PGA=Patient Global Assessment; RECAP=Recap of Atopic Eczema.

As shown in Table 6.4, when using POEM as the anchor, the mean RECAP change score was 0.27 in the stable group (*n* = 45) and 2.33 for the minimum important improvement group (*n* = 18). Thus, the within-person change method provided a MIC value of 2.33 (95% CI 0.16, 4.50) and the between-person MIC was 2.06 (95% CI 0.28, 4.37).

Table 6.4 Mean POEM anchor sores of RECAP for participants categorised according to change on the anchor

Change in score on POEM	*n* (%)	Mean RECAP change score (SD)
-11	2 (0.9)	-7.5 (3.53)
-9	1 (0.5)	-1 (n/a)
-8	5 (2.3)	-10.8 (8.70)
-7	2 (0.9)	-4.5 (2.12)
-6	5 (2.3)	-4.8 (3.56)
-5	8 (3.7)	-2.87 (3.72)
-4	9 (4.1)	-3.66 (3.84)
-3	13 (5.9)	-1.69 (5.31)
-2	9 (4.1)	-1.44 (2.92)
-1	11(5.0)	-0.18 (3.86)
0	19 (8.7)	-1.21 (2.83)
1	15 (6.8)	1.66 (3.03)
2	19 (8.)	1.57 (3.20)
3	18 (8.2)	2.33 (4.36)
4	16 (7.3)	4.5 (4.56)
5	11 (5.0)	1.63 (3.58)
6	10 (4.5)	3.5 (5.62)
7	11 (5.0)	6.90 (4.32)
8	3 (1.4)	2.66 (1.52)
9	9 (4.1)	7.11 (4.70)
10	5 (2.3)	4.6 (3.78)
11	4 (1.8)	5.25 (2.5)
12	3 (1.4)	7.33 (2.08)
13	4 (1.8)	7 (4.69)
14	1 (0.5)	5 (n/a)
15	1 (0.5)	15 (n/a)
16	2 (0.9)	11 (1.41)
17	3 (1.4)	10.6 (4.72)

POEM=Patient Oriented Eczema Measure; RECAP=Recap of Atopic Eczema; SD=Standard Deviation.

The ROC curve anchor-based method provided an acceptable area under the curves for the PGA anchor (Figure 6.5) and the POEM anchor (Figure 6.6). The Both anchors led to a MIC score of 1.0 , PGA (95% CI -0.65, 3.65) and POEM (-1.20, 2.20).

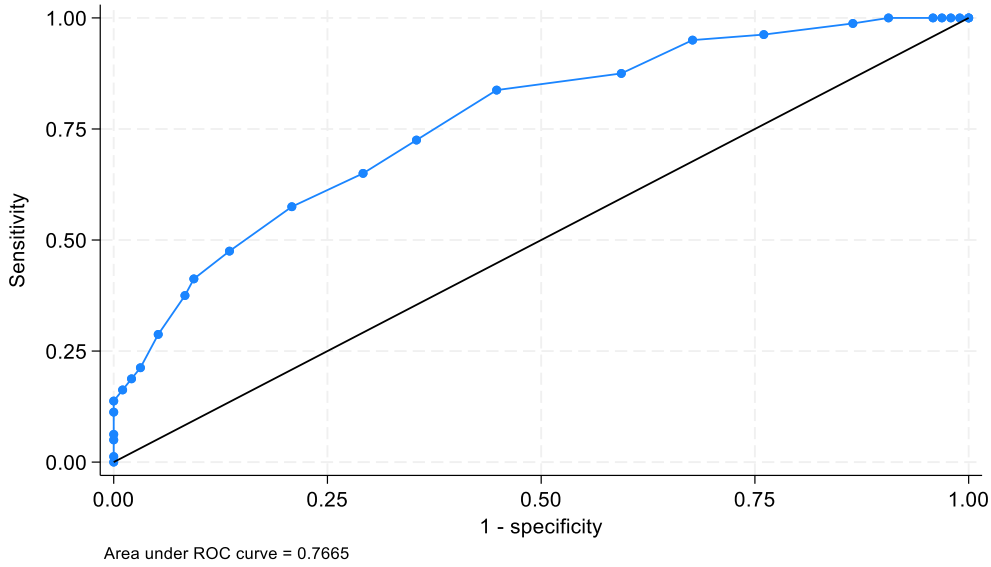


Figure 6.5 Area under ROC curve for the PGA anchor

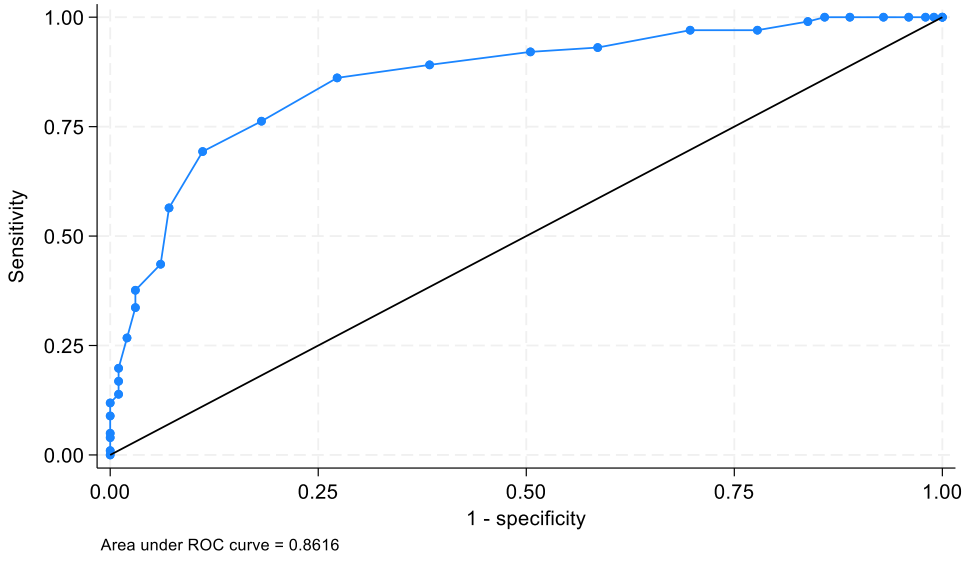


Figure 6.6 Area under ROC curve for the POEM anchor

Table 6.5 presents the summary of the results of the logistic regression analysis for performing the predictive modelling analysis. The PGA anchor provided a MIC estimate of 4.36, after adjusting by baseline disease severity the MIC estimate was 1.92. Whereas the POEM anchor yielded a MIC value of 2.08 and the result for the adjusted MIC was 1.38.

Table 6.5 Summary of logistic regression results used for the estimation of MIC in the predictive modelling analysis

Measure	PGA	POEM
$odds_{pre}$[a]	0.56	0.85
C (SE)	-1.09 (0.19)	-0.67 (0.18)
B (SE)	0.25 (0.04)	0.32 (0.47)
Correlation of RECAP change score and PGA anchor	0.48	0.54
SD of RECAP change score	5.64	5.64

C=Intercept; SE=Standard Error; B=Regression coefficient of RECAP changes from the logistic regression; RECAP=Recap of Atopic Eczema; PGA=Patient Global Assessment; POEM=Patient Oriented Eczema Measure [a]Odds of improvement according to the anchor only.

6.4.2.2 Distribution-based method

As presented in Table 6.1, the SD of RECAP scores at baseline was 6.12. Using the 0.5 SD of baseline scores resulted in a MIC of 3.06 (95%CI 5.60, 6.41).

The different MIC estimates derived from the calculation methods are summarised in Figure 6.7.

Calculation method	MIC values using PGA as anchor (single-item anchor)	MIC values using POEM as anchor (multi-item anchor)
Within-person score change	3.94	2.33
Between-person score change	3.52	2.06
Predictive modelling	4.36	2.08
Predictive modelling (adjusted)	1.92	1.38
0.5 x SD baseline RECAP scores	3.06	3.06
ROC method	1.0	1.0

Figure 6.7 Summary of MIC estimates according to calculation methods

6.5 Discussion

6.5.1 Summary of principal findings

This study helped the interpretability of RECAP change scores by calculating the smallest detectable change and also establishing MIC values in the EMO clinical trial dataset of 219 participants with eczema. These results contribute to the improvement of the design of clinical trials and the interpretation of results when using RECAP for measuring outcomes. Furthermore, it helps to fill a validation gap for the HOME initiative whereby aiding the uptake of the full core outcome set in trials.

The smallest detectable change on RECAP was 1.77 in this study population, indicating that MIC values above this value are likely to be a change beyond measurement error. In the EMO trial, the MIC estimates ranged between 1.38 (predictive modelling adjusted for baseline disease severity) and 4.36 (predictive modelling). Owing to the fact that the choice of calculation method impacts on the MIC estimates, as noted in the present study, due consideration should be given

in the interpretation of published MIC values. Notably, there is an ongoing debate in the field of clinimetrics on the most appropriate and optimal MIC calculation methods, posing a challenge in the selection of approaches. The anchor-based methods are superior as they provide more theoretically sound estimations than the distribution-based methods, while the latter are practical and also provide statistical thresholds for the margins of error. Consequently, multiple calculation methods were employed in this study which allowed to gain a more comprehensive interpretation and understanding of the MIC of RECAP.

Anchor-based methods are preferred due to explicitly measuring the importance of the change (De Vet et al., 2006b). Findings of this study support the stance by Turner and colleagues (2010) that 0.5 SD is a good approximation of MIC. Amongst anchor-based approaches, the calculation methods are gradually evolving and becoming more advanced. Initially, this was evident with the emergence of the ROC method for calculating MIC followed by a more recent development of the predictive modelling method. The latter method is preferred by COSMIN because it is more precise than the ROC method (Terwee et al., 2021).

In this study, the PGA and POEM anchors provided a range of MIC estimates for the different calculation methods. In general, the PGA yielded higher unadjusted MIC values between 3.52 and 4.36 whereas the POEM anchor produced values around 2.06 and 2.33. This inconsistency in estimates was likely related to the fact that both single-item and multi-item anchors were used, which required to define the minimum improvement groups slightly differently (PGA =1, POEM = 3). Thus, a change of 3.0 points in POEM is likely to be smaller than a change of 1.0 points in PGA, leading to smaller MIC values. Furthermore, the different sample sizes in the predefined groups on the two anchors may have caused further variability. For instance, there was 45 participants whose POEM scores did not change from baseline to follow-up (stable group) compared to 96 participants who remained stable on the PGA.

The ROC method yielded a MIC value of 1.0 and it is unclear why this result was such an outlier, but may be due to the skewed distribution of the dataset. Since it falls below the smallest detectable change, this value was discounted as being potentially clinically important.

The results of this study demonstrated that MIC is not a fixed value and a single, undisputed MIC estimate cannot be assigned. In fact, it has been shown that the MIC is a variable concept and its value depends on different factors, including: choice of anchor, calculation methods, disease severity, type of intervention and setting, resulting in varied MIC estimates (Wright et al., 2012, Cook, 2008).

Findings in this chapter resulted in recommendations on how to interpret changes on RECAP as represented in Table 6.6.

Table 6.6 A guide for enhancing interpretation of change on RECAP

Change in RECAP score	Suggested interpretation
0 to 1.9 points	Likely to be measurement error
2.0 to 2.9 points	Small improvement, likely to be beyond measurement error, but unclear clinical relevance
3 to 3.9 points	Improvement that is likely to be clinically important
4+ points	Improvement that is very likely to be clinically important

RECAP=Recap of Atopic Eczema.

6.5.2 Relevance to other studies

RECAP is a relatively new instrument, initial testing in the UK indicated good psychometric properties (Howells et al., 2020) and good validity, reliability and responsiveness (Bhanot et al., 2021). However, there is limited evidence on interpretability. As described in section 5.1, , a Dutch study has calculated the MIC of RECAP in adults with eczema (Zhang et al., 2023). Authors used anchor-based methods that provided MIC values ranging from 3.5 points (ROC method)

to 4.1 points (within-person change score). The authors concluded that an improvement of ≥4.0 points is considered as a clinically important improvement.

The results presented in this chapter are broadly consistent with the findings of the Dutch study, nonetheless the results are not directly comparable for multiple reasons. The studies were conducted in different populations, consisting of self-referring participants into an online trial versus more severe patients in secondary care. Although both studies used a global assessment of change as an anchor, but the anchors measured different constructs (eczema severity versus eczema control) and at different timepoints. Thus, findings from these studies cannot be synthesised yet due to the varied methodology used. Further validation studies are needed to make firm conclusions on MIC values.

Additionally, substantial difference between the smallest detectable change values were noted, for this study it was 1.77 points whereas for the Dutch study it was 3.2 points. This disparity is likely to be related to the use of prespecified groups used for calculating this measurement property. Including all participants at baseline for this calculation is a conventional approach and was done in this study, however the Dutch study only included unchanged patients from the test-retest reliability method. In essence, these variations may have led to the varied estimates.

Zhang et al. (2023) further aided the interpretability of RECAP by assigning meaning to single scores. As illustrated in Figure 6.8, authors proposed a range of banding categories for RECAP scores that indicate the different levels of eczema control. Having these distinct categories helps to identify controlled and uncontrolled disease states for individual participants.

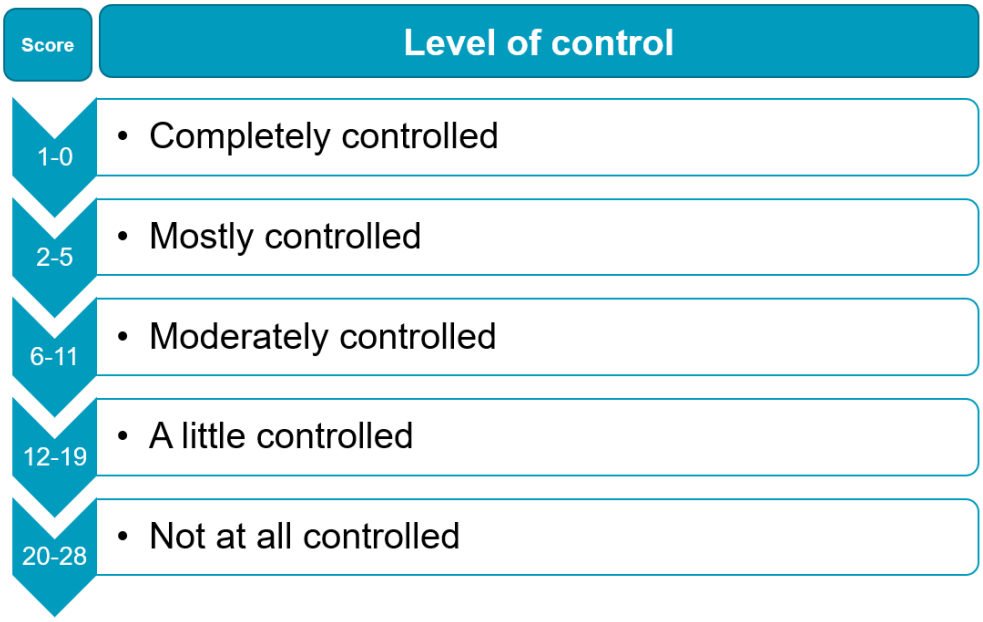


Figure 6.8 Eczema control banding categories for RECAP, proposed by Zhang et al. (2023)

6.5.3 Strengths and limitations

A notable advantage of this study is that it estimated the MIC of RECAP in accordance with COSMIN guidelines (Mokkink et al., 2019). Moreover, the use of well-interpretable anchors and the inclusion of all disease severities as well as the sample size further enhanced the robustness of the results.

Another strength was the fact that the anchors in this study measured change on the day of assessment (PGA) or over the preceding week (POEM). This made the anchors used in this study more advantageous compared to other studies that used a retrospective measure of change for the anchor (Bhanot et al., 2021a). Retrospective self-reports may be prone to recall bias and typically reflect present state rather than baseline state (Crosby et al., 2003, Revicki et al., 2008, Kamper et al., 2009).

Furthermore, best practice was followed in this study by using a range of anchor-based methods and also included a distribution-based method to provide a more extensive assessment of interpretability.

A limitation of this study lies in its use of only one trial dataset, which may have led to limiting the generalisability of findings beyond adults. This study, as well as the Dutch study, estimated the MIC for RECAP only in adults (Zhang et al., 2023) and the MIC of RECAP in children is currently unknown.

Furthermore, the anchors in this study did not assess the importance of change from the viewpoint of participants, though this is a reoccurring criticism of the anchors typically used for calculating MIC values (Terwee et al., 2010).

6.5.4 Implications and future directions

The study included in this chapter enhances the interpretability of change scores of RECAP, helping the understanding of users in both clinical trials and routine clinical practice. Since the existing studies assessed the MIC of RECAP in adult populations only, it would be beneficial if further studies would include children. To address this pressing need, the calculation methods used in this study will be performed in the Eczema Care Online (ECO) datasets. The ECO trial consisted of two independent, pragmatic online RCTs involving children (0-12 years) and young people (13-25 years) (Santer et al., 2022). A few anchor-based methods calculations have been conducted and the preliminary results are similar to that of the results of the study presented in this chapter. Final analyses for all calculation methods are underway.

Overall, it will be useful to provide a range of MIC estimates based on three clinical trial datasets that included wide age ranges in the same setting (0-74 years). It would be also helpful if the test-retest reliability of RECAP within 24 hours would be assessed in children to be able derive the ICC value that is needed to calculate the smallest detectable change in this population.

Interpretability is just one of the psychometric properties to be examined in the future and there are other validation gaps that remain in the HOME COS, especially around cross-cultural validity.

6.6 Conclusions

This validation study has enhanced to the interpretability of RECAP by calculating the MIC, using different methods. Results of this study indicate that a change score of ≤1.77 points reflects a measurement error and changes in scores ≥2.0 points are likely to be considered clinically important with different degrees of certainty. These results help the understanding of users of the instrument, aid the interpretation of trial results and clinical significance, facilitate evidence-based decision making and supports the integration of RECAP into clinical trials and routine practice. Ultimately leading to improving the uptake of the HOME core outcome set, which is one of the major aims of this thesis.

Chapter 7 Conclusions and future plans

The methodology and detailed findings of each study presented in this thesis has been discussed and concluded, respectively. Consequently, this chapter focuses on summarising the following: key findings and overall conclusions of the thesis as a whole, outline of future directions for research and personal reflection.

7.1 Summary of thesis findings and contributions

The online RCT used a series of online PROMs to examine their effect on trial outcomes (Chapter 3) and has found that weekly symptom assessments contributed to a small perceived improvement in eczema severity due to the frequency of patient-reported outcome collections. This thesis recommends to collect PROMs at approximately five timepoints in future eczema trials, allowing for efficient trial designs. Chapter 3 hopefully prompts trialists to consider the interval of patient-reported outcomes collections as weekly data collection is burdensome for participants, yet might not provide additional value. In most eczema trials, monthly or bi-monthly outcome assessments would be sufficient. The thesis informed the HOME initiative on the optimum frequency of the collection of patient-reported outcomes. The takeaway message is being disseminated through the HOME initiative, consisting of over 400 members worldwide.

The retrospective analysis of social media recruitment strategy (Chapter 4) showed that the use of internet-based methods can be an efficient and cost-effective tool for recruiting participants from diverse backgrounds. Since social media platforms are commonly used, often on a regular basis, they have a broad national and international reach that can transcend geographic barriers and increase awareness of ongoing trials that are open for recruitment. The thesis demonstrates that online recruitment approaches are plausible and can augment traditional recruitment methods.

Regarding the psychometric properties of the RECAP patient-reported instrument, the studies in this thesis assessing content validity (Chapter 5) and interpretability (Chapter 6) showed that it is suitable for measuring eczema control. The thesis posits a cut-off age for self-completion, suggesting that the self-reported version of RECAP is appropriate for use from the age of 12 years, whereas the parent-reported version shall be used in children below 12 years of age. Additionally, the thesis has improved the interpretation of RECAP scores by establishing that a change score of 1.77 or below is likely to be consistent with measurement error and the change in scores need to be 2.0 points or greater before the change is considered clinically important and meaningful.

7.2 Future plans

I plan to continue conducting research about various aspects of patient-reported instruments, especially with regards to the HOME core outcome set in order to aid the refinement and implementation of the full set. Regarding the RECAP instrument, the further assessment of reliability, validity and interpretability in different populations (e.g. age, ethnicity, eczema severity) and in different settings (e.g. clinical trials, routine practice) is required to improve understanding about the performance and appropriateness of the instrument in varied contexts. In order to promote the uptake of the core set globally, cross-cultural validity needs to be assessed to check whether the items on a translated or culturally adapted version of RECAP accurately represent the performance of the items in the original version of RECAP.

In relation to the long-term control of eczema core domain, currently both RECAP and ADCT are recommended instruments. However, further work on measurement properties is required to assess which instrument should remain in the core outcome set in the future. This dual inclusion of instruments conflicts with COSMIN and COMET guidance, which advocate for selecting one instrument per core domain as this enhances the ability to synthesise trial results (Prinsen et al., 2016). Even though the HOME roadmap does not prohibit the

inclusion of multiple instruments within a core domain, it does suggest that having one well-validated instrument is the preferred scenario.

At present, the itch question is redundant in the HOME core set as it is asked five times by four different patient-reported instruments as shown in Figure 7.1. Thus, further research is required to explore whether all of the itch related questions are necessary to include. Currently, a study is being developed to establish if the identical questions contained in POEM and RECAP are sufficiently similar to be collected only once as part of the core outcome set. The overlap between content was also noted at the HOME VII meeting and there is an increasing need for a single item global assessment for eczema, helping to reduce patient burden and improve trial design (Thomas et al., 2022).

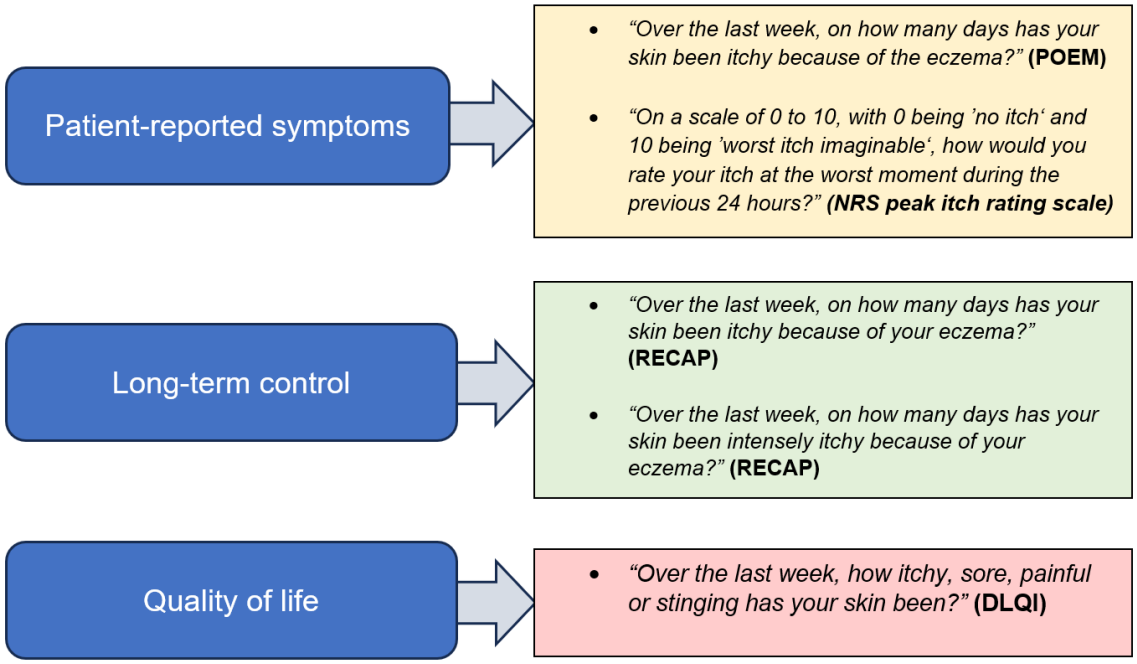


Figure 7.1 Patient-reported instruments measuring itch in the HOME core outcome set

In terms of outcomes research, there is a need to explore the views and opinions of patients on patient-reported outcome collection. Currently, I am involved in a TMRP and HDR UK collaborative project, which is a scoping review of existing literature with the aim of examining current evidence of patient understanding and engagement of patient-reported outcomes.

7.3 Personal reflections on the PhD

My doctoral journey has been both an academic and personal pursuit, providing me with a transformative experience. Coming from primary care, working as a practice nurse with limited prior research experience, embarking on this endeavour was challenging. Especially, starting in the middle of the pandemic presented unexpected adversities. However, my genuine interest in improving patients' lives through research and making a positive impact remained a driving force throughout the difficult times.

Each study in this PhD has provided distinct learning opportunities, enabling me to develop an array of invaluable skills. I have obtained essential academic competencies in quantitative and qualitative study design, ethics process, study management, statistical analysis, effective communication, leadership and co-ordination of research efforts. Furthermore, presenting my work at conferences allowed me to engage with fellow methodologists, scholars and experts from around the world. These interactions have broadened my perspectives and fostered collaborative and interdisciplinary thinking in me that I will carry forward into my professional career. This PhD has equipped me with the skills, mindset and network of like-minded individuals that will allow me to thrive in academia and beyond. On a personal note, this PhD has had a positive impact on my self-perception. It has enabled me to realise my full potential through hard work, dedication, perseverance and a genuine desire to help others. This journey has been nothing short of extraordinary and I am immensely grateful for the privilege of embarking upon it.

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Appendices

Appendix 1 Research ethics committee approval to conduct the EMO trial

University of Nottingham
UK | CHINA | MALAYSIA

Faculty of Medicine & Health Sciences
Research Ethics Committee
Faculty Hub
Room E41, E Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham, NG7 2UH
Email: FMHS-ResearchEthics@nottingham.ac.uk

11 June 2021

Arabella Baker
PhD Student in Clinical Trials Research
Centre for Evidence Based Dermatology
School of Medicine
University of Nottingham, King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Dear Ms Baker

Ethics Reference No: FMHS 239-0421 – **please always quote**	
Study Title: Eczema Monitoring Online via Questionnaires (EMO)	
Chief Investigator/Supervisor: Kim Thomas, Professor of Applied Dermatology Research, Centre for Evidence Based Dermatology, School of Medicine.	
Lead Investigators/student: Arabella Baker, PhD Student in Clinical Trials Research	
Other Key investigators: Eleanor Mitchell, Assistant Professor of Clinical Trials, Nottingham Clinical Trials Unit, School of Medicine.	
Proposed Start Date: 01.06.2021	**Proposed End Date:** 28.02.2023

Thank you for submitting the above application which was considered at the meeting on 23 April 2021 and the following documents were received:

- FMHS REC Application form and supporting documents version 1.0: 10.04.2021

These have been reviewed and are satisfactory and the project has been given a favourable ethics opinion.

A favourable ethics opinion has been given on the understanding that:

1. The protocol agreed is followed and the Committee is informed of any changes using a notice of amendment form (please request a form).
2. The Chair is informed of any serious or unexpected event.
3. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

Dr John Williams, Associate Professor in Anaesthesia and Pain Medicine
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

Appendix 2 Participant information sheet for adults EMO study

Research Team: Arabella Baker, PhD Student, Centre of Evidence Based Dermatology (CEBD), University of Nottingham (UoN); Professor Kim Thomas, Lead Supervisor and Chief Investigator, CEBD, UoN; Eleanor Mitchell, Co-supervisor and Co-investigator, Nottingham Clinical Trials Unit, UoN.

Study Website: www.emostudy.org Study Email: eczema@nottingham.ac.uk

Study Title: Eczema Monitoring Online via Questionnaires

PARTICIPANT INFORMATION SHEET (ADULT)

Research Ethics Reference: FMHS 239-0421

Final Version 1.0 Date: 09/04/2021

Thank you for your interest in taking part in this online study. Before agreeing to take part, please take time to read the following information carefully.

Please note "You" refers to adults with eczema and parents/carers of children under 16 years of age with eczema.

What is this study about?

Eczema is an itchy skin condition that affects both children and adults. In eczema research studies, participants often complete questionnaires to tell us about their symptoms and treatment. In this study we would like to evaluate how eczema changes over time by asking participants to complete online questionnaires. This will help to improve how future eczema research is conducted.

Why am I being invited to take part?

You are being invited to take part because you have eczema, or you are the parent or a carer of a child with eczema.

To take part:

- You (or your child) must have been diagnosed with eczema by a health professional (e.g. doctor or nurse)
- You need to be able to and willing to provide informed consent
- You need be able to read and understand written English
- You need to have access to the internet and to an internet-enabled device (e.g. phone, tablet or computer)
- If participating on behalf of a child with eczema, the child should be aged 1-year or older

Do I have to take part?

No. It is up to you to decide if you want to take part in this research study. Even if you do agree to take part, you may withdraw from the study at any time without giving a reason and without any negative consequences, by advising the researchers of this decision via the study email address (above). If you do withdraw, we will keep the research data that you have already provided. This information may be used in the analysis. All data will be reported anonymously.

What will I need to do?

If you choose to take part, you will be asked to complete an online questionnaire during the study. It takes about 10 minutes to complete and you will be in the study for 8 weeks in total. How often you're asked to complete the questionnaire will vary. Some people will be asked to complete the questionnaire every week for a period of 8 weeks, and some people will be asked to complete it at the beginning and end of the study only. If you are completing the questionnaire on behalf of a child with eczema we would encourage you to discuss the answers with the child.

We will request an email address from you to enable us to send a link to you for the questionnaire. We will also request a mobile phone number from you as we might contact you for the final questionnaire. Upon return of the final questionnaire after 8 weeks, you can choose to be entered into an optional prize draw for a chance to win one of six £20 vouchers as a thank you for taking part. When you have completed the final questionnaire, your participation in this study ends. Your personal data will be kept confidential and will NOT be shared with third parties.

Are there any risks in taking part?

There are no anticipated risks to your eczema from taking part. You will be able to use your normal eczema treatment throughout this research study.

Are there any benefits in taking part?

There will be no direct benefit to you from taking part, but your participation will help to improve future eczema research. Taking part in this study will allow you to track your eczema symptoms at home, which you may find useful and interesting.

What happens to the data provided?

Once you consent to the study, a unique code/ID will be generated to protect your personal data. All data are kept on password-protected databases sitting on a restricted-access computer system at the University of Nottingham with only the research team having access to the research data. All research data will be kept for a minimum of 7 years after publication of the research. You can find out more about how we use your

information and read our privacy notice at:
https://www.nottingham.ac.uk/utilities/privacy.aspx/

Who will have access to your data?

Your data will be used for research purposes only. Under UK Data Protection laws the University is the data controller, which means legally responsible for data security. The Chief Investigator of this study (Prof. Kim Thomas) manages access to the data and responsible for protecting your information and ensuring it is used properly. Responsible members of the University of Nottingham may be given access to data for monitoring and/or auditing of the study to ensure we are complying with guidelines.

What will happen to the results of this study?

The research team will write up the research and publish the results in scientific journals and present at conferences. The research will be also submitted for the doctoral work of Arabella Baker. At the beginning of the study, you will be asked if you'd like to receive a copy of the results. If you agree to this, you will be sent a summary of the results via email. All data will be reported anonymously.

Who has reviewed this study?

This study has been reviewed and given favourable opinion by the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee (REC ref number: FMHS 239-0421).

What if I have more questions or concerns?

If you have any questions about this project, you may contact the research team.

Email: eczema@nottingham.ac.uk If you remain unhappy and wish to make a formal complaint, please contact the FMHS Research Ethics Committee Administrator. Email: FMHS-ResearchEthics@nottingham.ac.uk

Appendix 3 Participant information sheet for teenagers EMO study

Research Team: Arabella Baker, PhD Student, Centre of Evidence Based Dermatology (CEBD), University of Nottingham (UoN); Professor Kim Thomas, Lead Supervisor and Chief Investigator, CEBD, UoN; Eleanor Mitchell, Co-supervisor and Co-investigator, Nottingham Clinical Trials Unit, UoN.

Study Website: www.emostudy.org Study Email: eczema@nottingham.ac.uk

Study Title: Eczema Monitoring Online via Questionnaires

PARTICIPANT INFORMATION SHEET (TEENAGER)

Research Ethics Reference: FMHS 239-0421

Final Version 1.0 Date: 09/04/2021

Thank you for your interest in taking part in this online study. Before agreeing to take part, please take time to read the following information carefully.

What is this study about?

Eczema is an itchy skin condition that affects both children and adults. In eczema research studies, participants often complete questionnaires to tell us about their symptoms and treatment. In this study we would like to evaluate how eczema changes over time by asking participants to complete online questionnaires. This will help to improve how future eczema research is conducted.

Why am I being invited to take part?

You are being invited to take part because you have eczema.

To take part:

- You must have been diagnosed with eczema by a health professional (e.g. doctor or nurse)
- Your parent or carer needs to be able and willing to provide informed consent for you to take part
- You need be able to read and understand written English
- You need to have access to the internet and to an internet-enabled device (e.g. phone, tablet or computer)

Do I have to take part?

No. It is up to you to decide if you want to take part in this research study. Even if you do agree to take part, you may withdraw from the study at any time without giving a reason

and without any negative consequences, by advising the researchers of this decision via the study email address (above). If you do withdraw, we will keep the research data that you have already provided. This information may be used in the analysis. All data will be reported anonymously.

What will I need to do?

If you choose to take part, you will be asked to complete an online questionnaire during the study. It takes about 10 minutes to complete and you will be in the study for 8 weeks in total. How often you're asked to complete the questionnaire will vary. Some people will be asked to complete the questionnaire every week for a period of 8 weeks, and some people will be asked to complete it at the beginning and end of the study only.

We will request an email address from you to enable us to send a link to you for the questionnaire. We will also request a mobile phone number from you as we might contact you for the final questionnaire. Upon return of the final questionnaire after 8 weeks, you can choose to be entered into an optional prize draw for a chance to win one of six £20 vouchers as a thank you for taking part. When you have completed the final questionnaire, your participation in this study ends.

Are there any risks in taking part?

There are no anticipated risks to your eczema from taking part. You will be able to use your normal eczema treatment throughout this research study.

Are there any benefits in taking part?

There will be no direct benefit to you from taking part, but your participation will help to improve future eczema research. Taking part in this study will allow you to track your eczema symptoms at home, which you may find useful and interesting.

What happens to the data provided?

Once you consent to the study, a unique code/ID will be generated to protect your personal data. All data are kept on password-protected databases sitting on a restricted-access computer system at the University of Nottingham, with only the research team having access to the research data. All research data will be kept for a minimum of 7 years after publication of the research. You can find out more about how we use your information and read our privacy notice at:
https://www.nottingham.ac.uk/utilities/privacy.aspx/

Who will have access to my data?

Your data will be used for research purposes only. Under UK Data Protection laws the University is the data controller, which means legally responsible for data security. The

Chief Investigator of this study (Prof. Kim Thomas) manages access to the data and responsible for protecting your information and ensuring it is used properly. Responsible members of the University of Nottingham may be given access to data for monitoring and/or auditing of the study to ensure we are complying with guidelines.

What will happen to the results of this study?

The research team will write up the research and publish the results in scientific journals and present at conferences. The research will be also submitted for the doctoral work of Arabella Baker. At the beginning of the study, you will be asked if you'd like to receive a copy of the results. If you agree to this, you will be sent a summary of the results via email. All data will be reported anonymously.

Who has reviewed this study?

This study has been reviewed and given favourable opinion by the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee (REC ref number: FMHS 239-0421).

What if I have more questions or concerns?

If you have any questions about this project, you may contact the research team.

Email: eczema@nottingham.ac.uk

If you remain unhappy and wish to make a formal complaint, please contact the FMHS Research Ethics Committee Administrator. Email: FMHS-ResearchEthics@nottingham.ac.uk

Appendix 4 Consent form for adults EMO study

Research Team: Arabella Baker, PhD Student, Centre of Evidence Based Dermatology (CEBD), University of Nottingham (UoN); Professor Kim Thomas, Lead Supervisor and Chief Investigator, CEBD, UoN; Eleanor Mitchell, Co-Supervisor and Co-Investigator, Nottingham Clinical Trials Unit, UoN.

Study Title: Eczema Monitoring Online via Questionnaires

CONSENT FORM (Adult)

Final Version 1.0 Date: 09/04/2021

Research Ethics Reference: FMHS 239-0421

Please, tick each statement to continue:

1. I confirm that I have read and understood the participant information sheet and have had the opportunity to ask questions.
    - o I agree
2. I confirm that I am 16 years old or older.
    - o I agree
3. I understand that my participation is voluntary and I am free to withdraw at any time without giving any reason. The information collected prior to withdrawal may still be used in the study analysis.
    - o I agree
4. I understand that my answers are anonymous (so that you could not be identified).
    - o I agree
5. I agree to take part in the above study.
    - o I agree

I would like to receive information about the study results (optional).

- o Yes
- o No

I would like to be entered into the free prize draw for a chance to win one of six £20 vouchers upon completion and submission of the 8-week online questionnaire (optional).

- o Yes
- o No

Name:
Email address:
Date:

I have read and understood the above information and consent form, I confirm that I am 16 years old or above and by clicking the NEXT button to begin the eligibility screening form, I indicate my willingness to voluntarily take part in the study.

NEXT – I consent to take part EXIT - I do not give consent

Thank you for participating in this study!

The EMO Study Team
eczema@nottingham.ac.uk

Appendix 5 Consent form for parent/carer of under 16 year olds EMO study

Research Team: Arabella Baker, PhD Student, Centre of Evidence Based Dermatology (CEBD), University of Nottingham (UoN); Professor Kim Thomas, Lead Supervisor and Chief Investigator, CEBD, UoN; Eleanor Mitchell, Co-Supervisor and Co-Investigator, Nottingham Clinical Trials Unit, UoN.

CONSENT FORM (For parent/carer of a child under 16 years of age)

Final Version 1.0 Date: 09/04/2021

Research Ethics Reference: FMHS 239-0421

Please, tick each statement to continue:

1. I confirm that I have read and understood the participant information sheet and have had the opportunity to ask questions.
   - o I agree
2. I confirm that I am the parent/carer of the participant.
   - o I agree
3. I understand that my child's participation is voluntary and he or she is free to withdraw at any time without giving any reason. The information collected prior to withdrawal may still be used in the study analysis.
4. I understand that my child's answers are anonymous (so that your child could not be identified).
   - o I agree
5. I agree for my child to take part in the above study.
   - o I agree

I would like to receive information about the study results (optional).

- o Yes
- o No

I would like to be entered into the free prize draw for a chance to win one of six £20 vouchers upon completion and submission of the 8-week online questionnaire (optional).

- o Yes
- o No

Name:
Email address:
Date:
I have read and understood the above information and consent form, I confirm that I am the parent/carer of the participant and by clicking the NEXT button to begin the eligibility screening form, I indicate my willingness for my child to voluntarily take part in the study.

NEXT – I consent to take part EXIT - I do not give consent

Thank you for participating in this study!

The EMO Study Team
eczema@nottingham.ac.uk

Appendix 6 Questionnaires used in the EMO trial in order of appearance for participants

Page 1: Start form

What is the age of the person with eczema? [numerical value was entered]

Who is completing the questionnaire:

- I am 16 years old or above and have eczema.
- I am less than 16 years old and have eczema.
- My child has eczema. I am completing this questionnaire on behalf of my child.

Your email address:

(we need this to send you links to the questionnaires)

Confirm your email address:

How did you find out about this research study?

- Twitter
- Facebook
- Instagram
- Reddit
- Callforparticipants.com
- Web search (e.g. Google)
- Friend/family/colleague
- Other (please specify)

Would you like to hear about our other eczema research studies in the future?

- Yes
- No

Page 2: Participant information sheet and consenting

- Participant information sheet
- Consent form
- I have read and understood the above information and consent form. I confirm that I am the parent/carer of the participant and by clicking the NEXT button to begin the eligibility screening form, I indicate my willingness for my child to voluntarily take part in the study
- NEXT – I consent to take part
- EXIT – I do not give consent

Page 3: Participant demographics and screening

Gender:

- Male
- Female
- Other
- Prefer not to say

Ethnicity:

- Asian or Asian British (includes any Asian background, for example, Bangladeshi, Chinese, Indian, Pakistani)
- Black, African, Black British or Caribbean (includes any Black background)
- Mixed or multiple ethnic groups (includes any Mixed background)
- White (includes any White background)
- Another ethnic group (includes any other ethnic group, for example Arab)
- Prefer not to say

Which country do/your child you live in?

- UK
- Other (please specify)

Have you/your child been diagnosed with eczema by a health professional (e.g. doctor or a nurse)?

- Yes
- No

Are you/your child taking part in another eczema clinical trial?

- Yes
- No

Page 4: POEM questionnaire

Please select one response for each of the seven questions below about your/**your child's** eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your/**your child's** skin been itchy because of your/**their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

2. Over the last week, on how many nights has your/**your child's** sleep been disturbed because of your/**their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

3. Over the last week, on how many days has your/**your child's** skin been bleeding because of your/**their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

4. Over the last week, on how many days has your/**your child's** skin been weeping or oozing clear fluid because of your/**their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

5. Over the last week, on how many days has your/**your child's** skin been cracked because of your/**their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

6. Over the last week, on how many days has your/**your child's** skin been flaking off because of your/**their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

7. Over the last week, on how many days has your**/your child's** skin felt dry or rough because of your**/their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

Page 5: Eligibility screening with POEM

Eligibility was calculated by the REDCap software based on the answers to the POEM questionnaire. If the POEM score was less than 3, then the person was not eligible to take part in the study.

After this randomisation took place in REDCap, which determined group allocation of participants (intervention group or control group).

If the person was eligible, contact details were asked.

Your email address:

Your mobile phone number:

(we need this in case we need to contact you in relation to the study)

What is your postcode? (UK only)

IMPORTANT: please make sure to add eczema@nottingham.ac.uk to your Favourites email folder otherwise the follow-up emails may appear in your Junk/Spam/Clutter folder.

The participant was automatically notified with the following text:

Intervention Group:

Dear (Participant's first name automatically appeared),

Thank you for taking part in this study.

Please follow the link to complete the questionnaire.

We will send you a link to the questionnaire weekly for eight weeks via email for you to complete.

Best wishes

The EMO Study Team

Control Group:

Dear (Participant's first name automatically appeared),

Thank you for taking part in this study.

Please follow the link to complete the questionnaire.

We will send you a link to another questionnaire in eight weeks' time via email for you to complete.

Best wishes

The EMO Study Team

Page 6: Treatment use questions

Over the last week, have you/your child used any moisturisers (emollients) for their eczema? (for example: Diprobase, Doublebase, Epaderm, E45, Aveeno cream)?

- Yes
- No

Over the last week, on how many days have you/your child used moisturisers (emollients) for your/their eczema?

- 1 day
- 2 days
- 3 days
- 4 days
- 5 days
- 6 days
- 7 days

Over the last 2 months, roughly how often have you/your child used moisturisers (emollients) for their eczema?

- Never
- Rarely
- Sometimes
- Often
- Always

Over the last week, have you/your child used any flare-control creams (topical steroids) for their eczema? (for example: Hydrocortisone 1%, Clobetasone butyrate (Eumovate), Mometasone furoate (Elocon), Bethamethasone valerate 0.1% (Betnovate)

- Yes
- No

Over the last week, on how many days have you/your child used flare-control creams for your/their eczema?

- 1 day
- 2 days
- 3 days
- 4 days
- 5 days
- 6 days
- 7 days

Over the last 2 months, roughly how often has your/your child used flare-control creams for their eczema?

- Never
- Rarely
- Sometimes
- Often
- Always

Page 7: PGA, NRS Itch and bother assessment scale

How is your/your child's eczema today?

- Clear
- Almost clear
- Mild
- Moderate
- Severe
- Very Severe

On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your at the worst moment during the previous 24 hours? (appeared for self-completers only)

- 0 - No itch
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10 - Worst itch imaginable

How much bother has your/your child's eczema been over the last week?

- 0 - No bother at all
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10 – As much bother as you can imagine

Page 8: RECAP questionnaire

The questions below provide a snapshot of how your/your child's eczema has been over the last week from your point of view. Please only select one response for each question. Try and respond to every question, but if you are unable to respond then leave it blank.

1. Over the last week, **how has your/your child's eczema been?**

- Very good
- Good
- Ok
- Bad
- Very Bad

2. Over the last week, on how many days has your/**your child's** **skin been itchy** because of your/**their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

3. Over the last week, on how many days do you think your/**your child's** **skin has <u>been intensely itchy</u>** because of your/**their** eczema?

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

4. Over the last week, how much do you think your/**your child's** **sleep has been disturbed** because of your/their eczema?

- Not at all
- A little bit
- Quite a bit
- A huge amount
- Completely

5. Over the last week, how much has your/**your child's** eczema been **getting in the way of day to day activities?**

- Not at all
- A little bit
- Quite a bit
- A huge amount
- Completely

6. Over the last week, how many days do you think your/**your child's** eczema **affected how you/they have been feeling?**

- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

7. Over the last week, **how acceptable** has your**/your child's** eczema been to you?

- Completely acceptable
- Mostly acceptable
- Quite acceptable
- Not very acceptable
- Not at all acceptable

Page 9: Debrief

Thanks ever so much for taking part in this study and completing the questionnaires.

This text appeared for the Intervention group:

We will be sending you an email every week for 8 weeks, with a link for you to open to complete a short questionnaire.

This text appeared for the Control group:

We will send you an email in 8 weeks-time, with a link for you to open to complete a short questionnaire.

If taking part in this study has raised any concerns or questions for you or if you require support, please do not hesitate to visit your general practitioner (GP) to discuss these issues. You can also receive support in a various ways via the National Eczema Society: https://eczema.org/information-and-advice/eczema-helpline/

Appendix 7 Data management plan for the EMO study

Eczema Monitoring Online via Questionnaires

Data description

This is an online, randomised controlled trial in eczema.

We will generate quantitative data from online questionnaires. Participants with eczema will be randomised to complete online questionnaires weekly (Intervention group) or at the beginning and end of study (Control group).

The REDCap (Research Electronic Data Capture) software will be used to collect research data.

Questionnaire responses will be downloaded into Excel files in .xlsx file format and stored on a password protected restricted access Microsoft Teams channel that can only be accessed by the research team.

At the start of the study, personally identifiable information about participants such as: name, email, mobile phone number will be collected. A unique identification number will be assigned to the participant at the beginning of the study to anonymise their personal data so that the participant cannot be personally identified. Consent forms will be stored separately, using the identification number. All data will be stored in accordance with the General Data Protection Regulation (GDPR). The data is expected to be collected from 266 participants.

Data collection / generation

Data will be collected using the REDCap (Research Electronic Data Capture) software, which is a University of Nottingham supported platform. REDCap allows for standardised data capture/ data entry validation, which ensures consistency and accuracy in data collection, allowing high quality data to be collected.

Data will be initially stored in REDCap, whilst questionnaire responses are being collected. In REDCap, all research data will be de-identified with a participant number/ID, which will be automatically generated to protect individuals from being identified and ensure the data is anonymised. Once all data is collected, it will be downloaded to an Excel spreadsheet and kept anonymised with the same unique study identification number. The data will be then uploaded for analysis to Stata, which is a statistical data analysis software.

Personally identifiable information such as name, email address, mobile phone number will be removed from the study data and will be stored in a different, securely protected study folder. The mobile phone number will be used to contact the participant for the follow up questionnaire, if necessary. The email address will be used to send a link to the questionnaire and also for the optional prize draw, if the participant chose to be entered. Winners will have 60 days from the date they were notified of winning to claim the prize. All research data, including consent forms and personal data will be password protected and stored securely on the servers provided by the University of Nottingham.

Data storage and security

Data will be captured using REDCap, which is a safe platform that provides a secure web connection with authentication and data logging. REDCap can be fully personalised to meet local data management and security policies. The University of Nottingham Clinical Database Support Service (CDSS) will provide support for the PhD student with REDCap, which will help to ensure compliance with regulatory requirements.

We will use a restricted access Microsoft Teams channel for our working data. Microsoft Teams is an ISO 27001 information security management compliant service that allows secure and controlled sharing of data amongst the research team. Microsoft Teams encrypts data both in transit and at rest and complies with the University's Handling Restricted Data Policy. Access to Microsoft Teams will be restricted by user identification and passwords. All research data including consent, email address and personal data will be password-protected and stored securely on secure servers provided by the University of Nottingham.

Data management, documentation and curation

All data will be managed according to the University of Nottingham's Data Management Policy (accessible to University staff through the library website): https://www.nottingham.ac.uk/library/research/research-data-management/index.aspx;https://uniofnottm.sharepoint.com/sites/DigitalResearch/SitePages/Research-Data-Management-Policy.aspx) with specific focus on policy statement 3.1.

This is the policy of the University of Nottingham, which requires that all research data be managed in a manner that supports its authenticity, reliability, security, discoverability and, where appropriate, accessibility for re-use.

Data will be generated using the REDCap software, which is an established and secure platform for data capture and a University of Nottingham supported software. REDCap is fully personalisable, to enable compliance with local data management standards and requirements, including GDPR.

Ethics & Privacy

Personal data will be collected during this project, and the project has considered ethical and legal implications in its data storage, as well as appropriate security of personal data. All participants will agree to data collection and long term retention and archiving their anonymised data.

All data will be fully anonymised and stored securely within REDCap during data collection. Only members of the research team will have access to any anonymised and non-anonymised data (e.g. consent forms). To protect the privacy of participants, only members of the research team will have access to the data unless an individual is requested and required access by the University. Email addresses and mobile phone numbers will be gathered from participants, this information will not be used for data analysis or in publications. These identifiable details will be removed from the study data and will be transferred to another securely protected folder.

Research will follow standard ethical procedures of the Faculty of Medicine and Health Sciences and the University of Nottingham. Specific aspects will be considered by the Faculty Research Ethics Committee as appropriate.

Participants will be informed that they can withdraw their participation at any stage during the study. We will be working with only personal data, there will not be any special category data involved in this study. As we will be working with personal data, we will adhere to the Data Protection Act 2018, including GDPR requirements. This will include the provision of relevant privacy information for participants in the PIS. We will ensure that appropriate safeguards for storage and handling of data are in place.

Data preservation

Anonymised research data created by the project will be deposited in the UoN research data archive, https://rdmc.nottingham.ac.uk/

For each published dataset, a DataCite DOI is issued facilitating the ability to cite the data in associated research outputs. The UoN data archive is underpinned by commercial digital storage which is audited on a twice-yearly basis for compliance with the ISO 27001 standard. UoN will retain and preserve research data in line with UoN requirement for a minimum of 7 years, but data will be retained for longer periods of time where it is of continual value to users. No cost has been charged to this project for data archiving as we anticipate that the amount of data generated for long-term retention will not exceed 50GB (the capacity provided free by the University).

Data sharing and access

All data processing and sharing will be abided by the GDPR and University of Nottingham Data Protection Policy. All data processing and sharing will adhere to the University of Nottingham Data Protection Policy (https://www.nottingham.ac.uk/governance/records-and-information-management/data-protection/data-protection-policy.aspx).

Our anonymised dataset does not contain any personal or commercially sensitive information and thus will be shared via the University of Nottingham data archive under a CC-BY license. There will be no need to update the data past the project period. All published outputs will contain a Data Availability Statement including the datacite DOI, which directs to the relevant data set. Data will be released at the same time as any published outputs which are underpinned by the data or by 1 year from the end of the project at the latest.

Roles & responsibilities

The PhD student (Ms Arabella Baker) will be responsible for the management, security and quality of data during this study. The chief investigator (Professor Kim Thomas) will be responsible for overseeing the data management, security, and quality of data during and after the study. The co-investigator (Eleanor Mitchell) will also have access to the research data. The overall responsibility of data security lies within the remit of the University of Nottingham's Chief Information security officer. Data will be accessible to the members of the study team both during the study and in the analysis stage via the restricted access channel in Microsoft Teams, which allows for team members based at different locations to still have access to the dataset. All study team members will abide by all the relevant data management and data security policies.

Relevant policies

The University of Nottingham adheres to the GDPR. Under the UK Data Protection regulation the University is the Data Controller and legally responsible for data security. We will ensure that our research aligns with the requirements of the University's Research Data Management Policy, Information Security Policy, Code of Research Conduct and Research Ethics. As we are working with personal data, we will abide by the Secure Data Handling Policy and Data Protection Policy. All third party commercial data or new data that may be suitable for commercial exploitation will be protected by the University's Intellectual Property policy.

IPR

The University will have ownership of the copyright and intellectual property of any data generated during this study.

Budgeting

Participants will have the opportunity to enter an optional prize draw for a chance to win one of six £20 vouchers to thank them for taking part in this study.

We don't anticipate any costs associated with storing and archiving of data.

Appendix 8 Topic guide for semi-structured interviews with young people

	Questions	Prompts
Introduction	Thank you very much for your time. With this interview, you are supporting a project of … We would like to investigate whether the questions of the subsequent questionnaire are easily understood and feel relevant to you when describing how well controlled your eczema is. Atopic eczema often flares and then improves again. This questionnaire has been designed to measure how well you feel your eczema is controlled. However, this questionnaire is new in … (language) and with these interviews, we would like to ask you about your thoughts when trying to complete the questionnaire.	You said that ... Did I understand correctly that… Could you explain that to me? Could you tell me more about that? Can you give me an example?
	The interview will be recorded. Data will be assessed anonymized, thus conclusions on personal data won't be possible. (DECLARATION OF CONSENT & START RECORDING).	
	Before we start I would like to mention that there are no right or wrong answers. This interview is about your views and thoughts whilst completing	

	the questionnaire, not about knowledge. I am guiding you through the interview. However, please feel free to add any additional thoughts that you might have along the way. I would ask you now to respond to the questions of the questionnaire. Please read the single questions out loud and ‘say out loud what goes through your mind as you read it. Participants complete the 7-items of the RECAP scale.	
General impression of the questionnaire	How was your impression of the questionnaire? - What did you think when completing the questionnaire? - What did you feel when completing the questionnaire?	Unsure/glad to tell something about this topic /overstrained, ….
Comprehensibility	How easy to understand were the instructions for you? How easy to understand were the questions for you? How easy to understand were the response options for you? Were there any questions which should have been formulated differently? For each question, did you know what it was aimed at?	

Relevance	In your opinion, were there any questions which you think are redundant, double or very similar? In your opinion, are the response options appropriate? In your opinion, is the recall period of "*last week*" appropriate?	
Comprehensiveness	In your opinion, are there any key concepts missing in the questionnaire?	
Suggestions for improvement	Do you have any suggestions for improvement for the questionnaire?	
Conclusion	Is there anything you would like to add? Is there any important aspect which have not been mentioned until now?	You have already said… Are there also …?
	This is the end of the interview. Thank you very much for your time.	

Appendix 9 Coding manual for the RECAP content validity study

	No problem	No problem, but interesting to note	Minor problem	Major problem	**Notes and illustrative quotes**
Comprehensibility					
Title	☐	☐	☐ Ambiguous meaning ☐ Lack of clarity in wording ☐ Obscure or difficult language ☐ _____	☐ Ambiguous meaning ☐ Lack of clarity in wording ☐ Obscure or difficult language ☐ _____	
Instruction	☐	☐	☐ Ambiguous meaning ☐ Lack of clarity in wording ☐ Obscure or difficult language	☐ Ambiguous meaning ☐ Lack of clarity in wording ☐ Obscure or difficult language	
Item 1	☐	☐	☐ Ambiguous meaning ☐ Lack of clarity in wording ☐ Obscure or difficult language ☐ Lacked information to answer the question ☐ _____	☐ Ambiguous meaning ☐ Lack of clarity in wording ☐ Obscure or difficult language ☐ Lacked information to answer the question ☐ _____	
Item 2	☐	☐	☐ Ambiguous meaning ☐ Lack of clarity in wording ☐ Obscure or difficult language ☐ Lacked information to answer the question ☐ _____	☐ Ambiguous meaning ☐ Lack of clarity in wording ☐ Obscure or difficult language ☐ Lacked information to answer the question ☐ _____	

Item 3	□	□	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language □ Lacked information to answer the question □ _____	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language □ Lacked information to answer the question □ _____	
Item 4	□	□	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language □ Lacked information to answer the question □ _____	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language □ Lacked information to answer the question □ _____	
Item 5	□	□	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language □ Lacked information to answer the question □ _____	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language □ Lacked information to answer the question □ _____	
Item 6	□	□	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language □ Lacked information to answer the question □ _____	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language □ Lacked information to answer the question □ _____	
Item 7	□	□	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language	□ Ambiguous meaning □ Lack of clarity in wording □ Obscure or difficult language	

			☐ Lacked information to answer the question ☐ _____	☐ Lacked information to answer the question ☐ _____	
Response options	☐	☐	☐ Undefined or vague ☐ Unclear what they referred to ☐ Not clearly distinguishing frequency from intensity ☐ _____	☐ Undefined or vague ☐ Unclear what they referred to ☐ Not clearly distinguishing frequency from intensity ☐ _____	
Relevance					
Items	☐	☐	☐ Not relevant or applicable (redundant, double or very similar) Which ones: _____ ☐ Item had made assumptions Which ones: _____ ☐ Not related to eczema Which ones: _____ ☐ Related to eczema, but not to the concept we are trying to capture Which ones: _____ ☐ Raised concerns Which ones: _____ ☐ Wording was too sensitive Which ones: _____ ☐ Desirability bias likely to occur Which ones: _____	☐ Not relevant or applicable (redundant, double or very similar) Which ones: _____ ☐ Item had made assumptions Which ones: _____ ☐ Not related to eczema Which ones: _____ ☐ Related to eczema, but not to the concept we are trying to capture Which ones: _____ ☐ Raised concerns Which ones: _____ ☐ Wording was too sensitive Which ones: _____ ☐ Desirability bias likely to occur Which ones: _____	

			☐ Difficulty recalling information required Which ones: _____ ☐ High level of detail required Which ones: _____ ☐ Shortage of cues Which ones: _____ ☐ Uncertainty about the aims of the questions Which ones: _____	☐ Difficulty recalling information required Which ones: _____ ☐ High level of detail required Which ones: _____ ☐ Shortage of cues Which ones: _____ ☐ Uncertainty about the aims of the questions Which ones: _____	
Response options	☐	☐	☐ Inappropriate units ☐ Overlapping categories ☐ Missing categories ☐ Complex estimation to decide upon a judgement/evaluation ☐ Participant had to use heuristics to provide answers ☐ _____	☐ Inappropriate units ☐ Overlapping categories ☐ Missing categories ☐ Complex estimation to decide upon a judgement/evaluation ☐ Participant had to use heuristics to provide answers ☐ _____	
Recall period	☐	☐	☐ Too short ☐ Too long ☐ _____	☐ Too short ☐ Too long ☐ _____	
Comprehensiveness					
Is anything missing?	☐	☐	☐ _____ ☐ _____ ☐ _____	☐ _____ ☐ _____ ☐ _____	

Other					
General impression	□	□	□ _____ □ _____	□ _____ □ _____	
Layout	□	□	□ _____ □ _____	□ _____ □ _____	

Appendix 10 Research ethics committee approval to conduct the content validity study in the UK

University of Nottingham
UK | CHINA | MALAYSIA

Faculty of Medicine & Health Sciences
Research Ethics Committee
Faculty Hub
Room E41, E Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham, NG7 2UH
Email: FMHS-ResearchEthics@nottingham.ac.uk

19 February 2021

Dr Laura Howells
Research Fellow/Trainee Health Psychologist
Centre of Evidence Based Dermatology
University of Nottingham
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

Dear Dr Howells

Ethics Reference No: FMHS 18-1805 – **please always quote**
Study Title: Developing a patient-reported outcome measure of eczema control (ICE)
Chief Investigator/Supervisor: Professor Kim Thomas, Professor and Deputy Director, Centre for Evidence Based Dermatology, School of Medicine.
Lead Investigators/student: Arabella Baker, PhD, School of Medicine
Other Key Investigators: Dr Joanne Chalmers, Senior Research Fellow, Dr Natasha Rogers, Dr Laura Howells, Research Fellow, Centre for Evidence Based Dermatology, Mr Tim Burton, Ms Lynita Howie, Kate Sykes, PPI Representatives, Professor Christian Apfelbacher, Professor Medical Sociology, University of Regensburg, Dr Alison Sears, Clinical Research Fellow, King's College London, Prof Phyllis Spuls, Dermatologist University of Amsterdam, Dr Laura Von Kobyletszki, Dermatologist, Karlstad University, Sandra Lawton, Nurse Consultant Dermatology, Rotherham NHS Foundation Trust, Dr Matthew Ridd, GP and Senior Lecturer, University of Bristol.
Proposed Start Date: 01/05/2018 **Proposed End Date:** 31/12/2021

Thank you for notifying the Committee of amendment no 3: 02.02.2021 to extend the cognitive interviewing stage to capture older children and young people as detailed and the following documents were received:

- FMHS REC Notice of Amendment form No 3: dated 02.02.2021
- Online Version Young Person Participant Consent Form v1.2
- PIS Young Person Participant_v1.1
- Young People - Recruitment social media and email text v1 02.02.21
- Screening tool
- interview guide - Young People
- Data management plan for RECAP Content Validity Study

These have been reviewed and are satisfactory and the project amendment no 3: 02.02.2021 is approved.

Approval is given on the understanding that:

1. The protocol agreed is followed and the Committee is informed of any changes using a notice of amendment form (please request a form).
2. The Chair is informed of any serious or unexpected event.
3. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely

pp

Dr John Williams, Associate Professor in Anaesthesia and Pain Medicine
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee