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Evaluating the effect of weekly patient-reported symptom monitoring on trial outcomes: results of the Eczema Monitoring Online randomized controlled trial

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Abstract

Background Patient-reported outcome measures (PROMs) are commonly used in eczema clinical trials. Several trials have used PROMs weekly for symptom monitoring. However, the increased frequency of patient-reported 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. This is concerning as weekly symptom monitoring may constitute an unplanned intervention, which may mask small treatment effects and make it difficult to identify changes in the eczema resulting from the treatment under investigation.

Objectives To evaluate the effect of weekly patient-reported symptom monitoring on participants' outcomes and to inform the design of future eczema trials.

Methods This was an online parallel-group nonblinded randomized controlled trial. Parents/carers of children with eczema and young people and adults with eczema were recruited online, excluding people scoring < 3 points on the Patient Oriented Eczema Measure (POEM), to avoid floor effects. Electronic PROMs were used for data collection. Participants were allocated using online randomization (1 : 1) to weekly POEM for 7 weeks (intervention) or no POEM during this period (control). The primary outcome was change in eczema severity based on POEM scores, assessed at baseline and week 8. Secondary outcomes included change in standard topical treatment use and data completeness at follow-up. Analyses were conducted according to randomized groups in those with complete data at week 8.

Results A total of 296 participants were randomized from 14 September 2021 to 16 January 2022 (71% female, 77% white, mean age 26.7 years). The follow-up completion rate was 81.7% [$n = 242$; intervention group, $n = 118/147$ (80.3%); control group $n = 124/149$ (83.2%)]. After adjusting for baseline disease severity and age, eczema severity improved in the intervention group (mean difference in POEM score –1.64, 95% confidence interval –2.91 to –0.38; $P = 0.01$). No between-group differences were noted in the use of standard topical treatments and data completeness at follow-up.

Conclusions Weekly patient-reported symptom monitoring led to a small perceived improvement in eczema severity.

What is already known about this topic?

- Weekly patient-reported symptom monitoring is commonly used in eczema clinical trials to capture repeated measures outcomes.
- Increased frequency of outcome assessments may constitute an unplanned intervention and improve eczema severity, but the effects of frequent monitoring of self-reported symptoms have not been evaluated.
- The optimum frequency of data collection to minimize nonspecific effects while maximizing statistical efficiency is unknown.

What does this study add?

- Weekly patient-reported symptom monitoring led to a small perceived improvement in eczema severity at week 8 compared to no symptom monitoring.
- Although small, this between-group difference in symptom scores has implications for future eczema trial designs.
- Trialists should reduce the number of data-collection timepoints.
- These results contribute to establishing the optimum frequency of outcome assessments in eczema trials and address a research gap for the Harmonising Outcome Measures for Eczema (HOME) initiative.

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Eczema (synonymous with atopic dermatitis) is a chronic inflammatory skin condition that causes itchiness, sleep loss and decreased quality of life (QoL); it affects 15–30% of children and 2–10% of adults.[1] Eczema is characterized by periods of increased disease activity followed by relative remission.[2] The fluctuating nature of eczema should be considered when designing clinical trials. In recent years, numerous randomized controlled trials (RCTs) in eczema have been conducted.[3] Patient-reported outcome measures (PROMs) capture patients' perspectives and are increasingly used in RCTs.[4] The Harmonising Outcome Measures for Eczema (HOME) initiative recommends that eczema symptoms, QoL and long-term control are measured using PROMs. The Patient Oriented Eczema Measure (POEM) is a HOME-recommended instrument for measuring the patient-reported symptoms domain in the core outcome set for eczema.[5,6] Recent RCTs have collected POEM weekly for various durations, including 12 weeks, 16 weeks and 6 months.[7–11] In the context of RCTs, regular patient-reported symptom monitoring may constitute an unplanned intervention, which masks the intervention effect and threatens the validity of inferences.[12]

The effect of symptom monitoring on trial outcomes has been noted in other chronic conditions, such as asthma and cancer.[13,14] In this study, symptom monitoring refers to self-reported or patient/carer-reported symptom assessments. A proposed mechanism of action of symptom monitoring is associated with participant behaviour change, which may lead to improved adherence to treatment use.[15,16] Thus, weekly symptom monitoring may prompt participants to enhance the self-management of eczema and increase standard topical treatment use, which can lead to improvements in outcomes over time. To date, no eczema study has evaluated the impact of symptom monitoring on patient-reported outcomes. The Eczema Monitoring Online (EMO) RCT had three main objectives that aimed to evaluate the effect of weekly patient-reported symptom monitoring on: (i) eczema severity; (ii) adherence to standard eczema treatment use; and (iii) data completeness. The results will inform the design of future eczema trials and also contribute to establishing the optimum frequency of outcome assessments in eczema trials, addressing an existing research gap for the HOME initiative.[17,18]

Patients and methods

Study design

The EMO trial was an online parallel group nonblinded RCT with an 8-week follow-up period. Participants were randomized to complete the online POEM weekly for 7 weeks (intervention) or at baseline and follow-up only (control). The primary outcome was collected at week 8, to minimize 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 study was designed to assess the potential impact of collecting outcomes from patients more frequently. Before starting recruitment, the study was prospectively registered (ISRCTN45167024) and the trial protocol was made publicly available (Appendix S1; see Supporting Information).[19] Ethical approval to conduct this trial was obtained from the University of Nottingham Research Ethics Committee (reference number: 239-0421). The study is reported according to the CONSORT guidelines.[20,21]

Data collection and enrolment

Electronic PROMs were used. All trial processes were carried out online, including recruitment, eligibility screening, consent, randomization and data collection through the Research Electronic Data Capture (REDCap©; Vanderbilt University, Nashville, TN, USA), which is a secure online platform for managing trial data.[22] Recruitment took place online, mainly via social media. The detailed recruitment strategy has been published previously.[23] Individuals who clicked on the advert link were directed to the study website (www.emostudy.org),[24] which included the study aims, eligibility criteria and full participant information. Individuals interested in taking part enrolled via the website. Upon providing informed consent electronically and completing eligibility checks, participants were randomized. After enrolment, participants received an automated welcome email explaining the frequency of data collection, according to their randomized allocation. Email reminders were sent after follow-up questionnaires were overdue by 5 days and 7 days and, if still incomplete, a final text reminder with a hyperlink to the questionnaires was sent. For the completion of the follow-up questionnaires, participants could choose to enter an optional prize draw to win one of six £20 Amazon vouchers.

Participants

In order to meet the eligibility criteria, participants had to have a self-report or proxy report of eczema diagnosis; be ≥ 1 year old; have a POEM score of ≥ 3, to exclude very mild or inactive eczema (to avoid possible floor effects); be able to read and understand written English; and have access to the internet and an internet-enabled device. Individuals were excluded if they were unable to provide informed consent or were already taking part in another eczema clinical trial at enrolment, to eliminate confounding and limit questionnaire burden. As this was an online trial, participation was not limited to the UK; individuals living in other countries were allowed to join. However, postcodes were collected from UK residents to link it with Index of Multiple Deprivation (IMD) data, to establish the socioeconomic status of participants.

Intervention

The intervention was weekly monitoring of eczema symptoms using the POEM patient-reported questionnaire.[5] Participants in the intervention group were sent a hyperlink to a weekly POEM questionnaire for 7 weeks. The control group did not receive any questionnaires during this time period. All other eczema treatments remained as per usual practice.

Outcomes

The primary outcome was the change in participant-reported eczema severity from baseline to week 8, measured by the POEM score.[5] POEM was chosen as the primary outcome measure because it has been extensively used

for outcome assessments in eczema clinical trials, often in an online format.[25] 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. 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.[5,26] A reduction in the POEM score represents an improvement in eczema severity.

Secondary outcomes included change in standard eczema treatment use from baseline to week 8, assessed by the number of days of emollient and topical corticosteroid (TCS) use over the last week, and by the frequency of treatment use (never, rarely, sometimes, often, always) over the last 2 months; and data completeness, measured as the proportion of fully completed follow-up questionnaires at week 8.

Sample size

The sample size calculation was based on the ability to detect a small difference in POEM (2.5 points) based on published data on the minimal clinically important difference (MCID) for this outcome instrument.[27] Assuming a standard deviation of 6.5 in both groups, the estimated sample size to detect a between group difference of 2.5 in POEM scores with 80% power and with a two-sided significance level of 5% was 212 participants (106 per group). Allowing for 20% loss to follow-up, the total sample size was 266 participants (133 per group). These statistical assumptions are congruent with a recent online eczema RCT that included a similar disease severity population for estimating sample size.[28]

Randomization and blinding

Participants were automatically randomized (1 : 1) via an online randomization system in REDCap. The randomization schedule was based on computer-generated random permuted blocks of randomly varying sizes of 2, 4 and 6. Randomization 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; $\geq$ 16 years). Given that the intervention was weekly questionnaires, it was not possible to blind participants. As the lead researcher (A.B.) dealt with all aspects of trial conduct and management, she could not be fully blinded. However, access to follow-up data was restricted until after database lock and the final statistical analysis plan (SAP) was approved. The rest of the trial management group, including the statistician, was fully blinded to allocation.

Statistical methods

Analyses were performed in Stata version 17.0 according to the preapproved SAP.[29] Descriptive statistics were used to compare the baseline characteristics of participants by randomized allocation. The primary analysis was based on complete cases, including only participants who completed the POEM at both baseline and follow-up. For the analysis of treatment use, participants with missing treatment use data were excluded. For the data completeness outcome all randomized participants were included.

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

Sensitivity analyses were performed by imputing 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.

For the secondary outcome of treatment use, linear regression and descriptive statistics were used by randomized allocation. For the analysis of data completeness, logistic regression was used. Subgroup analyses explored 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.

Deviations from the protocol

The term 'missing data' was used to indicate our secondary outcome for data completeness in the protocol (Appendix S1). This was subsequently replaced with the term 'data completeness' to avoid potential confusion related to other types of missing data.

The impact of regular symptom monitoring on other HOME PROMs [24 h itch intensity numerical rating scale (NRS) and Recap of atopic eczema (RECAP)] are reported as exploratory findings, along with the global questions of Patient Global Assessment (PGA) and eczema-related bother (Table S1; see Supporting Information). These instruments were originally included to inform a parallel methodological study looking at the minimum important change (MIC) of HOME outcomes and so were not included as named secondary outcomes.

Results

Participants

Recruitment took place between 14 September 2021 and 16 January 2022, and follow-up was completed by 14 March 2022. A total of 296 participants were randomized: 147 were allocated to the intervention group and 149 to the control group (Figure 1). Follow-up POEM (primary outcome) was completed by 81.7% of participants ($n = 242$), which helped to preserve the power of the study. The number of participants lost to follow-up was balanced between the groups: 25 from the intervention group and 29 from the control group. The primary analysis included only participants who had completed 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 1). Participants came from diverse socioeconomic backgrounds; they had a mean age of 26.7 years, 71% were female, 77% were white and 78% were UK residents (Table 1). Baseline demographic

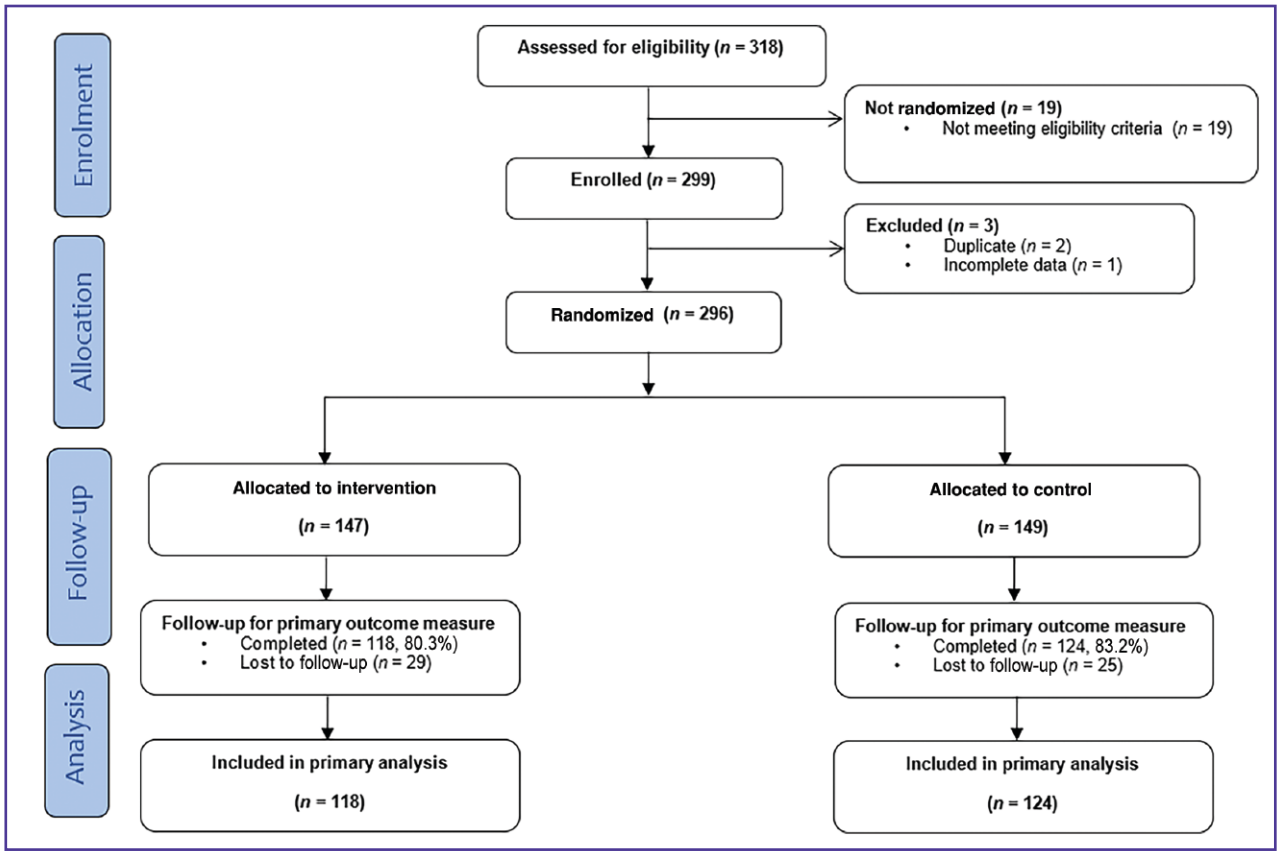

Figure 1 CONSORT flowchart.

and clinical characteristics were generally well balanced across the groups. The trial recruited mainly people aged ≥ 14 years (n=281; 94.9%), despite being open to all age groups. Most participants had moderate (46%) or severe (42%) eczema.

Primary outcome

After adjusting for stratification variables (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 2).

Sensitivity analyses for the primary outcome after the imputation of missing data were broadly consistent with the primary analysis and showed a point estimate for the between-group difference in POEM score ranging from –1.38 (best case) to –1.18 (worst case), as shown in Table S2 (see Supporting Information).

Subgroup analyses indicated no evidence of a differential treatment effect between subgroups (Table S3; see Supporting Information).

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 vs. baseline; mean change in emollient use was 0.09 days (95% CI –0.37 to 0.55; P=0.69) and mean change in TCS use was –0.22 days (95% CI –0.71 to 0.25; P=0.35) (Table 3). No between-group differences were found in the frequency of treatment use over the last 2 months (Figure 2). 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 4).

The completion rate of weekly questionnaires was 73% on week 1; however, it decreased to 59% by week 7 (Table 4).

Exploratory analyses

Results for other patient-reported eczema outcomes, including the HOME-recommended outcomes for itch intensity and eczema control, are provided in Table S1. Of the outcomes explored, only the PGA showed a between-group difference similar to that observed for POEM (adjusted mean difference –0.30, 95% CI –0.55 to –0.05; P=0.01).

Discussion

This 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 those not recording symptoms weekly. We found 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

Table 1 Baseline characteristics of participants enrolled in the Eczema Monitoring Online 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
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			
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			
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			
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]			
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, mean (SD)[b]	15.27 (6.11)	14.38 (6.08)	14.82 (6.09)
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)

Data are presented as *n* (%) unless otherwise stated. POEM, Patient Oriented Eczema Measure. [a]Higher values represent more severe eczema. [b]Excluding participants who were not living in the UK as postcodes were not collected from non-UK residents (*n* = 66). [c]Stratification variables.

Table 2 Change in Patient Oriented Eczema Measure score from baseline to week 8: primary analysis[a]

	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 Frequency of treatment use over the last week

Measure	Intervention (*n* = 118)	Control (*n* = 124)	Adjusted difference in means (95% CI)[a]	*P*-value
No. 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		
No. of days of TCS 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; TCS, topical corticosteroids. [a]Adjusted by stratification variables (age and baseline disease severity) and by baseline treatment use.

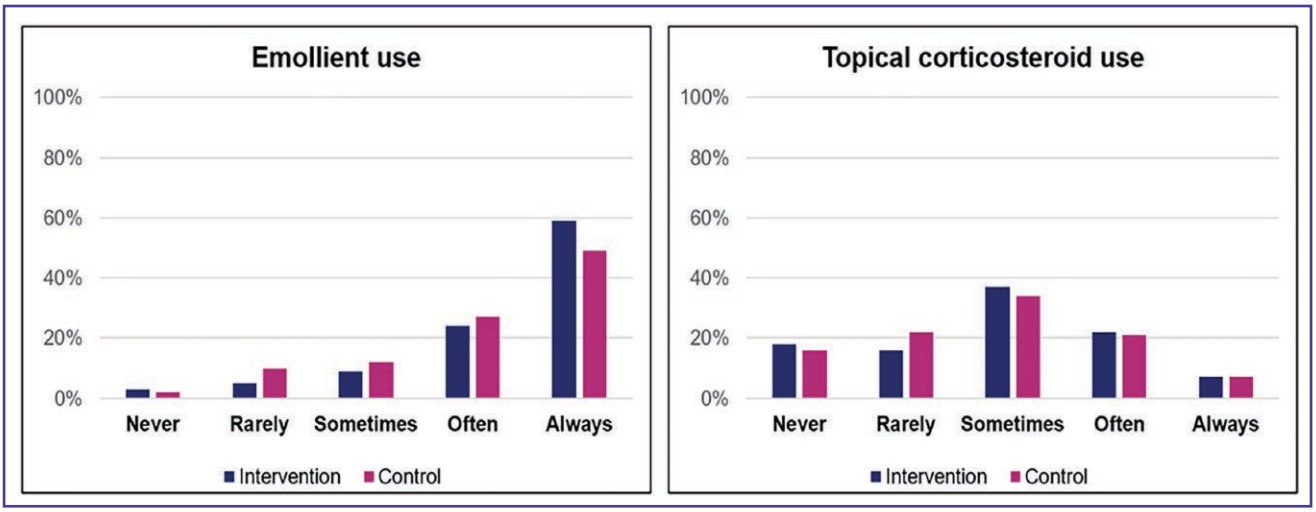

Figure 2 Frequency of treatment use over the last 2 months.

and TCS), 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 or empowerment,[30,31] which warrant further investigation in future studies.

There was no evidence that regular completion of weekly questionnaires increased participant retention in the trial, which is reassuring to triallists wishing to minimize the burden of data collection in trials. The use of email and text reminders was successful in ensuring a high completion rate (81.7%) of the follow-up questionnaires at week 8.

To our knowledge, no RCTs have evaluated 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.[32] Depending on the trial, a combination of PROMs, telephone calls or home visits were used for data collection, and the number of planned assessments ranged from 4 (bimonthly) to 10 (monthly) data points. The results indicated substantial improvement in symptoms with greater contact, which may be linked to increased adherence with medication and other self-management behaviours initiated by the outcome assessments, highlighting the need to reduce the number of assessments to optimize trial design and enable reliable interpretation of results.

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 data points to be approximately five (regardless of the duration of the trial), as this would allow for maximum statistical efficiency while maintaining retention and minimizing data collection burden.[33]

We mitigated bias by recruiting a large sample size, concealing treatment allocation and analysing the impact of missing data, but it was not possible to blind the intervention or trial outcomes due to the nature of the online trial. This may have contributed to the observed effect. The trial was also limited to 8 weeks of follow-up, which is shorter than most eczema trials but is probably a reasonable estimate of the maximum time between study visits in the majority of eczema trials.

Table 4 Questionnaire completion rates

Measure of completion	Intervention group ($n=147$)	Control group ($n=149$)
No. of completed questionnaires during the study period, mean (SD)	6.47 (2.93)	1.82 (0.38)
$\geq$ 4 weekly questionnaires completed	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)[a]	118 (80.3)	124 (83.2)

Data are *n* (%) unless otherwise stated. [a]Secondary outcome, showing no between-group difference: odds ratio 0.85 (95% confidence interval 0.46–1.54; $P=0.59$).

The observed between-group difference of 1.64 points on the POEM score is a small difference that may simply reflect measurement error.[27] Nevertheless, this small difference could be important if it masks small but genuine treatment differences between eczema treatments being tested in intervention trials.

The trial has reasonably good external validity because participants were recruited from diverse ethnic and socioeconomic backgrounds, and from various geographical locations. Despite being open to all age groups, we did not recruit many parents/carers of children with eczema, so it is not known if these effects are generalizable to those age groups. For trials with proxy reporting on behalf of a child with eczema, the effects may be different. Exploratory analyses of other eczema outcomes found similar effects for PGA but not for the other HOME-recommended outcomes for capturing eczema symptoms (NRS itch intensity) and eczema control (RECAP). Whether this is because these outcome instruments are less susceptible to bias or less sensitive to change is unclear.

We recommend reducing the frequency of PROM collection. This would allow disease chronicity to be captured and trials designed efficiently (e.g. using repeated measures analysis), while minimizing potential nonspecific trial effects such as those seen in the current study. Reducing the number of data collection timepoints also has the advantage of reducing responder burden and reducing the resources required for data collection and management, leading to beneficial scientific and societal impact.

This trial evaluated the effect of weekly patient-reported symptom monitoring, which led to a small perceived improvement in eczema severity. The findings aim to inform researchers on the optimum frequency of outcome assessments to ensure the appropriate design of future eczema trials.

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Conflicts of interest

K.S.T. is a member of the Harmonising Outcome Measures for Eczema (HOME) Executive Group.

Data availability

The dataset of this trial is available from the corresponding author upon reasonable request.

Ethics statement

Ethical approval to conduct this study was obtained from the University of Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee on 11 June 2021 (reference number: 239-0421).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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