Randomised Controlled Trial of 3% Kānuka Oil Cream vs Vehicle Control for the Topical Treatment of Eczema

Short Title	3% Kānuka Oil Cream for the Topical Treatment of Eczema (hk1)
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Principal Investigator	Alex Semprini
Co-ordinating Investigator	Nick Shortt
Investigators	Mike Armour, Kyley Kerse, Alex Martin, Marius Rademaker, Mark Weatherall, Richard Beasley
Sponsor	Hikurangi Bioactives Limited Partnership, 6434 Waiapu Road, RD1, Ruatoria
Funder	Hikurangi Bioactives Limited Partnership, 6434 Waiapu Road, RD1, Ruatoria
Primary Investigator Signature	
Disclosure statement	No conflicts of interest are reported for any listed investigators.
Confidentiality Statement	This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY TRIAL CONTACTS

Role	Contact Details
Principal Investigator	Dr Alex Semprini Medical Research Institute of New Zealand Level 7 CSB, Wellington Hospital, Riddiford Street, 6012, New Zealand Tel: +64 (4) 805 0260
Sponsor	Mr Manu Caddie Hikurangi Bioactives Limited Partnership 6434 Waiapu Road, RD1, Ruatoria, New Zealand Tel: +64 (274) 202 957
Clinical Trials Unit	Medical Research Institute of New Zealand Phone - (04) 805 0147 Fax – (04) 389 5707
Statistician	Mark Weatherall Mark.weatherall@otago.ac.nz

2. SYNOPSIS

Trial Title	Randomised Controlled Trial of 3% Kānuka Oil Cream vs Vehicle Control for the Treatment of Eczema
Short Title	3% Kānuka Oil Cream for the Topical Treatment of Eczema
Internal Reference Number	hk1
Clinical Phase	2
Trial Design	• Single blind • Parallel group • Randomised • Vehicle control
Trial Participants	• Participant has the ability and willingness to sign a written informed consent using a digital signature or paper form if back up is required • Participant is aged between 18 and 65 years of age, inclusive • Participant reported, Doctor diagnosis of eczema • Participant has a representative eczema lesion, located below the clavicle, that they are comfortable to have photographed. • Participant has a POEM category score of 'moderate or severe eczema' (8 to 24) • Participant is willing to stop all moisturisers and/or other skin barrier cream or emulsion treatments during the test period and replace with the investigational product assigned in this trial • Willing to replace their body wash and/or soaps with Aqueous cream as supplied at enrolment • Participant is able and willing to attend the follow up visit during the visit window • Participant is able and willing to complete the study and to comply with all study instructions
Planned Sample Size	80 participants
Treatment duration	Six weeks
Follow up duration	Eight weeks
Planned Trial Period	12 months

	Objectives	Outcome Measures
Primary	Improvement in subjective symptoms	Difference in POEM scores at Week Six.
Secondary	Efficacy of 3% Kānuka oil cream compared with vehicle control in the treatment of eczema	Proportion of participants with a ≥4 improvement in POEM score at Week Six compared to baseline.
		Difference in POEM scores at Week Six Analysed per protocol.
		Difference in PO-SCORAD at Week Six.
		Proportions of withdrawals for worsening eczema between groups.
		Proportions of treatment escalation between groups.
	Improvement in participant reported quality of life	A difference in DLQI score at Week Six.
	Acceptability of 3% Kānuka oil cream in the treatment of eczema	Participant acceptability of treatment as assessed by TSQM Version II[1]. Acceptability will be broken down as effectiveness, side effects, convenience and global satisfaction.
	Safety of 3% Kānuka Oil cream compared with vehicle control	Proportions of cutaneous and systemic adverse events between treatment groups.
	Assess inter-rater variability of SCORAD scoring between the blinded pharmacist investigators and the blinded study dermatologist	Comparison of intensity SCORAD scores (Part B) between blinded pharmacists.
		Comparison of intensity SCORAD scores (Part B) between blinded pharmacists and a blinded dermatologist.
IMP(s)	3% Kānuka oil cream	
Formulation	• 3% Kunzea Robusta (Kānuka) oil • Aqua (Water) • Prunus amygdalus dulcis (almond) oil • Glycerine • Cetearyl alcohol • Cetearyl glucoside • Sorbitan olivate • Xanthan gum • Benzyl alcohol • Dehydroacteic acid	

Dose	Liberal application at least twice daily, morning and night
Route of Administration	Topical Application

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CRF	Case Report Form
DLQI	Dermatology Life Quality Index
DMSC	Data Monitoring and Safety Committee
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigators Brochure
IMP	Investigational Medicinal Product
KO	Kānuka Oil
MRINZ	Medical Research Institute of New Zealand
PI	Principal Investigator
POEM	Patient Orientated Eczema Measure
PO-SCORAD	Patient Orientated Scoring of Atopic Dermatitis
PIS-CF	Participant / Patient Information Sheet and Consent Form
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCORAD	Scoring of Atopic Dermatitis
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSQM	Treatment Satisfaction Questionnaire for Medication

4. BACKGROUND AND RATIONALE

Eczema is a term encompassing a collection of inflammatory skin conditions with similar clinical characteristics[2,3] and typically presents as chronic, relapsing, itchy rash[4]. In a recent global burden of disease survey[5], eczema ranked second in disability-adjusted life-years when compared to other common skin conditions. Eczema primarily affects children[4] but can persist into (or develop in) adulthood[6]. From data obtained during the ISAAC study, New Zealand ranks high globally in terms of eczema prevalence in both children and adolescents[7] with disproportionately high numbers of Māori and Pasifika[8].

There is no current cure for eczema[3]. Instead treatments focus on symptom management, maintaining skin integrity and disease control[3,9,10]. Standard treatment approaches include moisturisers and topical corticosteroids[9,10]. Moisturisers act to maintain skin integrity while topical corticosteroids are the current first step treatment for the inflammation that occurs during symptom flares[3,4,10]. While efficacy of topical corticosteroids has been shown, they suffer from a poor patient perception of an undesirable side effect profile[9,10]. A 2011 study[11] found topical corticosteroid treatments for eczema had low compliance and patients reported high levels of anxiety associated with their use. 62% of patients surveyed responded that they would prefer a nonsteroidal treatment when given multiple treatment options[11].

Kānuka oil (KO) is derived from leaves of the Kānuka tree (*Kunzea Robusta*) and is obtained using steam distillation[12,13]. KO is characterised by high levels of α-pinene[12–14] and modest levels of sesquiterpenes[12]. In vitro KO has demonstrated a range of anti-bacterial[14–16], anti-fungal[15,16], and anti-inflammatory[15] properties.

The 3% KO cream being tested in this study has multiple properties that may help manage the symptoms of eczema. The cream vehicle which contains glycerine will act as a moisturiser[17,18], while the addition of the KO may confer anti-inflammatory[15] benefits, thereby reducing associated symptoms, and anti-bacterial[14–16] benefits which may reduce the risk of secondary infection.

If efficacy of KO in the treatment of eczema is demonstrated, it presents an opportunity to provide patients a new non-steroidal anti-inflammatory treatment option for eczema.

This study is a single blind, randomized, vehicle controlled trial of 80 adult participants with moderate to severe eczema through the New Zealand Pharmacy Research Network. The primary outcome measure is patient reported symptoms, with a secondary focus on validation of pharmacists completing measures of objective eczema signs.

The Harmonising Outcome Measures for Eczema (HOME) initiative established in 2010 has worked to develop a core outcome set for assessing eczema symptoms in clinical trials. Patient Orientated Eczema Measure (POEM) has been established as the preferred instrument to assess eczema symptoms[19]. POEM will be used as the primary outcome measure in this study to assess the patient reported symptoms of eczema.

The Scoring Atopic Dermatitis (SCORAD) measure is a validated outcome measure used to objectively assess the extent and severity of a patient's eczema. This study will involve the use of the patient orientated SCORAD (PO-SCORAD)[20], which has been validated and correlated with the original SCORAD[20,21], but allows self-reported data. In addition, study pharmacist investigators will assess the severity component of SCORAD and take a clinical photograph of a representative eczematous lesion for

blinded, remote assessment by the study dermatologist. This will allow interrater comparisons between both pharmacist investigators and pharmacists and dermatologist.

Quality of life will be assessed using the Dermatology Life Quality Index (DLQI)[22], an extensively validated[23–25] measure developed specifically for use in dermatology.

Treatment acceptability will be assessed using the Treatment Satisfaction Questionnaire for Medication Version II (TSQM Version II)[26]. The TSQM Version II has been validated in a pharmacy outpatient consumer population[26] and is a refinement of the original TSQM[27].

5. OBJECTIVES AND OUTCOME MEASURES

Table 1. Summary of Study Objectives

	Objective	Outcome Measure
Primary	Improvement in subjective symptoms	Difference in POEM scores at Week Six.
Secondary	Efficacy of 3% Kānuka oil cream vs vehicle control in the treatment of eczema	Proportion of participants with a ≥4 improvement in POEM score at Week Six compared to baseline.
		Difference in POEM scores at Week Six analysed per protocol
		Difference in PO-SCORAD at Week Six.
		Proportions of withdrawals for worsening eczema between groups.
		Proportions of treatment escalation between groups.
	Improvement in participant reported quality of life between groups	Difference in DLQI score at Week Six
	Acceptability of 3% Kānuka oil cream in the treatment of eczema	Participant acceptability of treatment as assessed by TSQM Version II. Acceptability will be broken down as effectiveness, side effects, convenience and global satisfaction.
	Safety of 3% Kānuka oil cream compared with vehicle control	Proportions of cutaneous and systemic adverse events between treatment groups.
	Assess inter-rater variability of SCORAD scoring between the blinded pharmacist investigators and the blinded study dermatologist	Comparison of intensity SCORAD scores (Part B) between blinded pharmacists.
		Comparison of intensity SCORAD scores (Part B) between blinded pharmacists and a blinded dermatologist.

6. TRIAL DESIGN

This study is a single blind, parallel group, vehicle controlled, randomised controlled trial. The study will be conducted within the New Zealand Pharmacy Research Network and coordinated from the MRINZ research office located in Wellington Hospital. A blinded dermatologist investigator will remotely score photographic outcome data. 80 participants will be enrolled and randomised 1:1 to receive 3% Kānuka oil cream or vehicle control. Study participation will include two pharmacy visits, five study diary entries (Appendix G), and one follow up survey (Appendix H) over an eight-week period. The protocol is designed to adapt to changing COVID-19 Alert levels in New Zealand and minimise contact between participants and study staff.

Alert Level 1:

The study will continue with face to face study visits. This will be conducted whilst adhering to the recommended distancing and healthcare consultation guidelines. For study sites, or participants, that request it, the study can be conducted in a way to limit contact between participants and pharmacy staff. To allow for this, components of the visits will be conducted by an investigator via telephone call.

Alert Level 2:

Study sites will be contacted and MRINZ investigators will ensure that each site is still willing to continue recruitment at the current Alert Level. If required, recruitment will be suspended at individual study site on a case by case basis.

Alert Levels 3 and 4:

Recruitment of participants will be suspended, those already enrolled in the study will be able to do Visit Two remotely. However, the photograph of the representative lesion and SCORAD (part b) will be excluded.

Data will be collected using secure REDCap data capture software[28]. Both visits and study diaries will be completed electronically. Paper versions of case report forms and study diaries will be available as a back-up. Electronic data capture will be used to minimise monitoring queries and ensure timely analysis of data once the study has concluded.

Table 2. Summary of Study Procedures

Visit	Visit 1	Treatment Period					Visit 2	Follow Up Survey
Day	**0**	**7**	**14**	**21**	**28**	**35**	**42 (+3)**	**56**
Informed Consent	X							
Inclusion / Exclusion Criteria	X							
Demographic data collection	X							
POEM	X	X	X	X	X	X	X	
PO-SCORAD	X						X	
SCORAD (Part B)	X*						X*	
DLQI	X						X	

Eczema Photo	X*						X*	
Randomisation	X^							
Dispense Medication	X^							
Study Diary (weekly) – electronic or paper		X	X	X	X	X		
Text reminder (weekly)		X	X	X	X	X	X	
Treatment Compliance		X	X	X	X	X	X	
Adverse event collection		X	X	X	X	X	X	X
TSQM Version II							X	

*will only occur if the participant is able to attend the pharmacy.
^will be done by pharmacy investigators only.

7. PARTICIPANT IDENTIFICATION

Trial Participants

80 participants with moderate to severe eczema will be enrolled from the general population. Participants will be enrolled on presentation to a participating pharmacy.

Inclusion Criteria

- Participant has the ability and willingness to sign a written informed consent using a digital signature or paper form if back up is required
- Participant is aged between 18 and 65 years of age, inclusive
- Participant reported, Physician diagnosis of eczema
- Participant has a representative eczema lesion, located below the clavicle, that they are comfortable to have photographed.
- Participant has a POEM category score of 'moderate or severe eczema' (8 to 24)
- Participant is willing to stop all moisturisers and/or other skin barrier cream or emulsion treatments during the test period and replace with the investigational product assigned in this trial
- Participant is willing to replace their body wash and/or soaps with aqueous cream as supplied at enrolment
- Participant is able to attend a follow up visit 6 weeks after they enrol in the study. This will take place at a participating pharmacy or via telephone call if required.
- Participant is able and willing to complete the study and to comply with all study instructions

Exclusion Criteria

- Current requirement for prescription of antibiotics or corticosteroids for the treatment of any condition (with the exception of inhaled and intranasal corticosteroids)
- Use of antibiotics, corticosteroids, calceneurin inhibitors, or antihistamines within the last four weeks (with the exception of inhaled and intranasal corticosteroids)
- Cutaneous mycotic or bacterial disease requiring a topical or systemic therapy
- Other skin condition which may affect the assessment of eczema severity
- History of allergy or hypersensitivity to the ingredients of the study treatments
- Participation in a clinical trial involving an investigational product during the last three months
- Participant is pregnant or planning to become pregnant during the study
- Known contact with PCR confirmed or probable diagnosis of COVID19 within the last 28 days.
- Cold/flu like symptoms, fever, or unexplained shortness of breath in the past 14 days.
- Any other condition which, at the investigators' discretion, it is believed may present a safety risk or impact upon the ability of the participant to complete the study.

8. TRIAL PROCEDURES

Recruitment

Potential participants will be approached upon presentation to a participating pharmacy. Pharmacists will identify individuals seeking topical treatments for eczema and offer the study to them. Advertising within participating pharmacies and on mainstream / social media will be used as a recruitment tool, the content will only be based on HDEC approved material from the Participant Information Sheet and Consent Form (PISCF).

Screening

Prior to the informed consent process potential participants will be screened using a predefined summary statement and the POEM score to determine suitability for the study. Potential Participants will be read a statement detailing the treatment being studied, the condition being studied, and the main exclusion criteria for the study. This statement will also inform the participant that the POEM data used for screening will be collected anonymously and if they don't meet the inclusion criteria (POEM score ≥8 and ≤24) no further information will be captured. If potential participants are happy to continue after this statement has been read they will continue to the POEM score. If their POEM score is within the study criteria they will proceed to informed consent.

The screening statement is as follows:

"This study is looking at the effect of Kanuka Oil cream on the treatment of eczema.

To be eligible for the study you must have a doctors diagnosis of eczema, be aged between 18 and 65 years, and have a POEM score criteria of moderate or severe eczema.

You will be ineligible for this study if you are taking steroids (either tablet or topical), taking antibiotics, or you are pregnant/breastfeeding.

If you are happy to proceed the next step is filling out the POEM questionnaire to determine your eligibility for this study. This data will be collected anonymously. Identifying information will only be collected if you meet the POEM eligibility score.

If you are eligible for the study this process will take between 15 and 30 minutes and you will need to return to the pharmacy in six weeks for a second visit."

Screening may take place remotely by telephone call. If screening is taking place remotely, an investigator will request a telephone number from a potential participant and organise a time to conduct the screening at a time convenient to the participant.

Participants screened remotely will be sent a link to the POEM questionnaire (on REDCap) via secure messaging or email. Responses will be available in real time to investigators. Participants who are eligible, as determined by their POEM score, will move on to Informed Consent.

Informed Consent

An electronic, written version of the PIS-CF will be presented to the participants detailing: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Informed consent for the study will be undertaken prior to any physical examination or study-related procedures. This will be conducted according to ethical and GCP guidelines by an appropriately trained and PI authorised investigator.

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed. This will be in an electronic form in the first instance, with a consenting criterion agreeing the signature delivered to an eCRF digitally or via stylus pen, is equivalent to their paper signature. A copy of the signed Informed Consent will be emailed to the participant. The original signed form will be retained securely on the study database. In the event of systems failure, a paper back-up facility will be provided.

Participants will be considered 'enrolled' at the time the inclusion and exclusion criteria have been met and the study specific consent form has been completed by both the Participant and Study Investigator.

Remote Consent: participants will be sent an electronic copy of the participant information sheet during the screening process to ensure they have as much time as possible to decide whether or not they wish to participate. When going through the informed consent process for the study the investigator will discuss the consent over the phone with the participant and answer any questions they have about the study. The investigator will record details of this conversation in the text box provided on the electronic consent form. The investigator will then sign the consent form and send it to the participant to sign as well. Upon signing the consent form, a PDF of the consent will be saved into REDCap and the participant will be able to download a copy of the consent (or receive an email with a copy of the consent).

Eligibility Assessment

Immediately after Informed Consent is obtained, a trained investigator will go through all inclusion and exclusion criteria apart from the previously completed POEM score. If the participant meets all eligibility criteria the investigator will proceed with enrolment. If not, the ineligible participant will have a screening ID which was created during the screening process.

If Visit One is conducted remotely, then eligibility will be assessed by the remote investigator and confirmed by the onsite investigator when the participant presents to the pharmacy.

Randomisation, blinding and code-breaking

Randomisation of participants takes place at the pharmacy. A statistician generated block randomisation schedule, using a block size of four, will be uploaded by a member of the MRINZ informatics team to the REDCap randomisation module and will be used to randomise participants electronically. The

randomisation schedule will use stratification to ensure equal allocation of treatment between those presenting with moderate eczema and those with severe eczema. A POEM score of 8 - 16 denotes moderate eczema while a score of 17 - 24 denotes severe eczema. Each site will have its own site code and randomisation schedule which may be increased if initial allocation codes are exhausted. Participants will be randomised 1:1 to receive either 3% Kānuka oil cream or vehicle control. Pharmacists and blinded investigators will have no access to the randomisation schedules. The randomisation section will only be made available when consent has been completed and all inclusion / exclusion criteria have been checked and auto validated by the REDCap system. If necessary, a non-blinded investigator will break the code for a single participant and will report to a designated study doctor.

This is a single blind study in which investigators who obtain consent are not aware of the randomised treatment. Participants will not be informed of their treatment allocation, however Kānuka oil has a distinctive odour which will be apparent on opening and use of the dispensing pump. Participants are therefore considered unblinded.

A central study pharmacist will label the treatments prior to delivery to the MRINZ PI office for onward distribution at site initiations.

Pharmacy investigators will be blind to treatment allocation, with the IMP delivered in masked and non-descript dispensing systems labelled A or B with application instructions only.

The PI, and study investigators will remain blinded until the data analysis phase, or an adverse event or safety event requires unmasking.

A blinded dermatologist investigator will be provided baseline and 6-week standardised photographs (in random order) taken using an iPad.

Visit One

Screening, informed consent and eligibility assessment will be completed first followed by recording of demographics, medical history, concomitant medications, and contact details. The Participant will then score their eczema using the PO-SCORAD. After this the investigator will assess the participant's eczema using the intensity questions from the SCORAD assessment and will photograph the representative eczema lesion using the iPad. Participants will then be asked to complete the DLQI. As a final step before randomisation the investigator will book in a follow up visit for six weeks (+3 days) post baseline with the study scheduling system.

Once all data has been collected, and the second visit booked, the investigator will randomise the participant and dispense the assigned treatment. Post randomisation the participant will be instructed on use of their assigned study treatment and how to complete the weekly diaries.

Medical history includes, but is not limited to, clinically significant diseases and surgeries, and reproductive status.

Demographic data will include age, sex and self-reported race/ethnicity. Race/ethnicity is recorded because of the potential contribution of this variable to difference in observed response to treatment.

Remote Visit One: visit one is able to be conducted remotely with the exception of the SCORAD (part b), photograph of the representative lesion, randomisation, and dispensing. Remote data collection will be done by a trained investigator who will contact the participant by phone. General data will be collected over the phone while the PO-SCORAD and DLQI will be sent to the participant for electronic completion. The investigator will stay on the phone while the participant answers the questionnaires, in case they need clarification. Once the remote data has been collected, the participant will be instructed to present at the pharmacy on the same calendar day to complete the visit. Upon presentation to the pharmacy an investigator on site will confirm eligibility, complete the SCORAD (part b), photograph the representative lesion, randomise the participant, and dispense the study treatment.

Weekly Diaries

Participants will complete a weekly electronic diary and will be provided with a paper diary for back up use or in the absence of available suitable technology or data connection. The diaries will be sent to the participant via email and text message weekly (Appendix F). Each diary will assess treatment compliance, POEM score, adverse events, and concomitant medications. If a diary is not completed on the day it is received the participant will receive a daily reminder for up to five days or the diary entry is completed (whichever occurs first). These reminders may be via phone, text message, or email. Electronic diary entries that are not completed within the five-day window will be considered missing data and not analysed.

Visit Two

At week six (+3 days) participants will attend a final scheduled appointment with the pharmacist investigator who will obtain a second photo of the representative lesion, POEM score, SCORAD (intensity only) score, PO-SCORAD score, DLQI score, TSMQ Version II score, and collect information on adverse events and concomitant medications. Participants will be reminded of this visit by email and/or text message. All reasonable attempts should be made to ensure the participant attends Visit Two.

At Alert level 3 & 4 (or if the participant is unable to attend the pharmacy), Visit Two, for already enrolled participants, will be conducted remotely. If a Visit Two occurs remotely, the SCORAD (part b) and second photo of the representative lesion will not be able to be completed. This will not constitute a protocol deviation.

Follow Up Survey

At week eight participants will receive a survey (Appendix G) via email (or if necessary, in the form of a phone call from a study investigator). This survey will be used to assess any adverse events that have occurred since the participant stopped their treatment, confirm reimbursement information, and get general comments about the study itself. If the participant reports an adverse event, a study investigator will get in contact to collect a more detailed description of the event.

Other visits

If required for reasons of incomplete data, safety or other unforeseen study related issues the MRINZ based investigator team may contact the participant via telephone, email, text message, letter or other medium during the study period and the post study period with a justifiable time frame. All contact will be logged within a dedicated participant communications REDCap instrument.

Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Previously undisclosed or new information resulting in ineligibility
- Significant protocol deviation or violation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Withdrawal of Consent
- Loss to follow up

Withdrawal from the trial will not result in exclusion of the data provided up to that point. The participant's data will be included in the intention to treat analysis.

The reason for withdrawal will be recorded in the eCRF.

If the participant is withdrawn due to an adverse event related to the study drug, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised as per the opinion of the study physician.

Definition of End of Trial

The end of trial is the date of the last visit of the last participant.

GP Notification

Participants general practitioners (GPs) will be notified of study participation with a letter containing a summary of the study, details about study treatment and length of participation, and contact information for the study PI. GPs will also be sent a letter in the event that a participant withdraws from the study.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

IMP Description

The treatments involved in this study are 3% KO cream and a vehicle control. Both treatments are applied topically, twice daily, morning and night, with liberal application. Investigator Brochures are detailed in Appendix C. The treatments will be supplied by the Sponsor (Hikurangi Bioactives Limited Partnership) as a cream in 500g dispensers. The kānuka oil is collected and distilled by Hikurangi Bioactives Limited Partnership.

Ingredients	
3% Kānuka Oil Cream	**Vehicle Control**
Kānuka oil	
Water	Water
Prunus amygdalus dulcis (almond) oil	Prunus amygdalus dulcis (almond) oil
Glycerine	Glycerine
Cetearyl alcohol	Cetearyl alcohol
Cetearyl glucoside	Cetearyl glucoside
Sorbitan olivate	Sorbitan olivate
Xanthan gum	Xanthan gum
Benzyl alcohol	Benzyl alcohol
Dehydroacteic acid	Dehydroacteic acid

3% KO is likely to be well tolerated as a previous study[29] found good tolerance of 20% KO with no serious adverse events.

Both 3% KO Cream and Vehicle Control will be labelled according to Good Manufacturing Practices, Annex 13. Manufacture of Investigational Medicinal Products (Appendix D).

Labelling of IMP

Treatments will be kept in separate marked containers and vehicle control will be labelled with a non-descriptive label of “Treatment A” or “Treatment B” and application instructions.

Storage of IMP

KO cream and Vehicle Control will be stored below 25 degrees Celsius in the pharmacies and central MRINZ facility. A temperature logger will be used to monitor treatment temperature within MRINZ. Given the pharmacy locality environment, all IMP will be kept in the medicine storage area and therefore adequate storage conditions can be assumed.

Compliance with Trial Treatment

Participants will be asked about compliance in a weekly diary (Appendix G). Compliance will be broken down into daily uses of assigned treatment with the following options for a given day: 0, 1, 2, 3, 4, >4. This will be monitored by study investigators on REDCap to ensure compliance.

Accountability of the Trial Treatment

An electronic stock log in REDCap will be created for each site to document the number of KO cream and vehicle control present at each site. The stock log will be completed at the conclusion of Visit One and is immediately available to the MRINZ monitoring team who may visit the site in person if required. A central stock log will be kept at the MRINZ, who will receive and onward courier IP for site initiation and restocking purposes.

Concomitant Medication

The following concomitant medications are prohibited during the study:

- All moisturisers and/or other skin barrier cream
- All emulsion treatments
- Topical or systemic antibiotics
- Topical or systemic steroids
- Topical or systemic immunomodulatory agents (such as calcineurin inhibitors, methotrexate)
- Any newly started treatment that the study Doctor considers would impact the validity of study data.

Should any of the above medications be taken the PI will determine if the participant should continue taking the IMP. If the PI advises the participant to cease the IMP, the participant will remain in follow-up and data will continue to be collected. If the PI advises that the participant may continue on the IMP they will complete the study as per protocol.

Participants that use any of these treatments during the study will be included in the intention to treat analysis but not the per protocol analysis.

Participants will be instructed to return any unused treatment and/or empty treatment containers to the pharmacy when the participant attends their final visit.

IMP Disposal

All remaining IMP will be disposed of by the study pharmacies after reconciliation by a study monitor as per usual industry procedure. This will be recorded on the study stock log. Remaining MRINZ stock will be disposed of by a local pharmacy research network pharmacy or via the Wellington hospital medicines destruction service.

10. SAFETY REPORTING

Definitions

Term	Description
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”.

Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Causality Term	Description
Certainly Related	Occurred in a reasonable time sequence to administration of the drug, and cannot be explained by concurrent disease or other drugs or chemicals.
Probably Related	Occurred in a reasonable time sequence to administration of the drug, and unlikely to be attributed to concurrent disease or other drugs or chemicals
Possibly Related	Occurred in a reasonable time sequence to administration of the drug, but could also be explained by concurrent disease or other drugs or chemicals.
Unrelated	There is evidence of a clear alternative explanation or non-plausibility.
Unknown	There is insufficient information or the information available is contradictory. The information available cannot be supplemented or verified.

Procedures for Recording Adverse Events

All AEs occurring during the trial that are reported by the participant, will be recorded on the eCRF, whether or not attributed to trial medication.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale:

Severity Term	Description
Grade 1 Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3 Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**.

Grade 4 Life-threatening	Urgent intervention indicated.
Grade 5 Death	Related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Grades 4 and 5 constitute a SAE and be reported using the guidelines described below.

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Principal Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

If a participant attends the pharmacy with a suspected cutaneous allergic reaction, the pharmacist will take a photo using the tele-dermatology app. The photograph will be assessed by the blinded dermatologist as a part of the overall safety analysis. Participants will be instructed to see their usual health care provider and will be followed up by study staff as part of the normal AE follow up process.

Reporting Procedures for Serious Adverse Events

All SAEs must be reported on the SAE reporting form to the MRINZ / Sponsor Safety Monitoring Committee within 24 hours of the Site Study Team becoming aware of the event. The MRINZ / Sponsor Safety Monitoring Committee will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. All SAE information must be recorded on an SAE form and retained at the MRINZ site. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and supplied to the MRINZ / Sponsor Safety Monitoring Committee and the sponsor.

Expectedness will be determined according to the Investigators' Brochure.

SUSAR Reporting

All SUSARs will be reported by the PI to Medsafe and to the HDEC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported in accordance with current guidelines. Treatment codes will be un-blinded for specific participants.

Safety Monitoring Committee

The MRINZ/Sponsor will appoint an independent monitoring committee to conduct a review of all SAEs for the trial reported after the first 10 participants.

The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

11. STATISTICAL ANALYSIS PLAN

Description of Statistical Methods

Table 3. Summary of Study Objectives and Associated Statistical Analysis

	Objective	Outcome Measure	Statistical Analysis
Primary	Improvement in subjective symptoms	Difference in POEM scores at Week Six.	ANCOVA with baseline POEM score as a continuous co-variate, treatment escalation as a categorical covariate, and randomised treatment as a categorical variable of interest.
Secondary	Efficacy of kānuka oil cream vs vehicle control in the treatment of eczema.	Proportion of participants with a ≥4 improvement in POEM score at Week Six compared to baseline.	Estimation of relative risk Associated confidence interval.
		Difference in POEM scores at Week Six analysed per protocol.	ANCOVA with baseline POEM score as a continuous covariate, and randomised treatment as a categorical variable of interest
		Difference in PO-SCORAD at Week Six	ANCOVA with baseline PO-SCORAD score as a continuous co-variate and randomised treatment as a categorical variable of interest.
		Proportions of withdrawals for worsening eczema between groups.	Estimation of relative risk Associated confidence interval.
		Proportions of treatment escalation between groups.	Estimation of relative risk Associated confidence interval.
	Improvement in participant reported quality of life	Absolute change in DLQI score at Week Six compared to baseline.	ANCOVA with baseline DLQI score as a continuous co-variate and randomised treatment as a categorical variable of interest.
	Acceptability of kānuka oil cream in the treatment of eczema	Participant acceptability of treatment as assessed by TSQM Version II. Acceptability will be broken down as effectiveness, side effects, convenience and global satisfaction.	t-test or if normality assumptions are strongly violated Mann-Whitney test Hodges-Lehmann estimator of location.

	To evaluate the safety or 3% Kānuka oil cream compared with vehicle control	Proportions of related and probably related cutaneous and systemic adverse events between treatment groups.	Estimation of relative risk and associated confidence interval.
	Inter-rater variability objective SCORAD scoring between the blinded pharmacist investigators and the blinded study dermatologist	Comparison of intensity SCORAD scores (Part B) between blinded pharmacists.	Intra-class correlation Bland-Altman plots and Limits of agreement.
		Comparison of intensity SCORAD scores (Part B) between blinded pharmacists and a blinded dermatologist.	Intra-class correlation Bland-Altman plots and Limits of agreement.

In addition to the above analyses, general statistics including mean and standard deviation will be calculated for baseline and weekly POEM scores as well as baseline and Week Six PO-SCOARD scores.

Primary analysis will be "Intention To Treat" (ITT) as described by Fisher et al. ITT will include all randomised participants.

Supporting analysis will be "Per Protocol" (PP). PP will include all participants who: were eligible for the study; didn't withdraw / get withdrawn from study; provided data at every time point; adhered to treatment instructions (as measured by ≥50% adherence); and didn't use any concomitant medication.

A sub analysis will be conducted to compare the POEM scores at Baseline and Week 6 between participants recruited before and after the start of the COVID-19 pandemic. This will be done to determine any difference that increased handwashing and sanitiser use had on POEM scores.

The Number of Participants

Based on a minimum clinically important difference (MCID) of 3.4 and standard deviation (SD) of 4.8 for the change in POEM score[30], each treatment group would require 32 participants. Accounting for an assumed dropout rate of 20% in such a community-based study, 40 participants would be required per arm (80 total) having 80% power at 5% two-sided alpha.

Criteria for the Termination of the Trial

The trial may be terminated by the Sponsor at any time, except for reasons of commercial interest. The trial may be terminated for safety concerns and/or clear inability to recruit as deemed by the PI and Sponsor.

Procedure for Accounting for Missing, Unused, and Spurious Data.

No additional statistical imputation or last value carried forward methods will be used in the case of missing data points.

Inclusion in Analysis

This study will be analysed by both intention-to-treat and per protocol analysis. All participant data will be included in the study analysis, up to the point of withdrawal.

Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations from the original statistical plan will be reported to the relevant HDEC, and to ANZCTR prior to the revised statistical analysis being undertaken.

12. DATA MANAGEMENT

Source Data

eCRF entries will be considered source data if the eCRF is the site of the original recording (e.g. there is no other written or electronic record of data). Paper back-ups will be considered source data if used instead of the eCRFs. All documents will be stored securely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

Access to Data

Direct access will be granted to authorised representatives from the Sponsor/MRINZ and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Data Recording and Record Keeping

All trial data will be entered into REDCap[28] data capture software or paper CRFs. The participants will be identified by a unique trial specific number and/or code in any database. At conclusion of the study the electronic database will be archived and stored for 15 years in accordance with MRINZ Policy and GCP. Paper source documents will also be stored for 15 years. All pharmacy research network localities will retain a USB copy of their electronic site file on site for 15 years and be provided access to any archived paper data upon request to MRINZ.

13. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP and the monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor/MRINZ must be contacted within 1 working day. In collaboration with the PI, the serious breach will be reviewed by the Sponsor/MRINZ and, if appropriate, the Sponsor/MRINZ will report it to HDEC.

15. ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the responsible Health and Disability Ethics Committee (HDEC), for written approval. An application will also be made to MEDSAFE for regulatory approval of the study.

The Investigator will submit and, where necessary, obtain approval from the HDEC and Medsafe for all substantial amendments to the original approved documents

Reporting

The PI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to HDEC, and the Sponsor. Six monthly reports will also be sent to SCOTT. In addition, an End of Trial notification and final report will be submitted to HDEC, host organisation and Sponsor.

Participant Confidentiality

All reasonable efforts will be made to ensure that participant's confidentiality and privacy is maintained. All study staff will comply with current and future New Zealand legislation.

Expenses and Benefits

Participants will receive free study investigational product and be reimbursed for travel, and other study related expenses and inconvenience over the two scheduled visits and data collection points at a fixed $200 on completion of the study.

Pharmacies will be reimbursed at a fixed rate of $300 per visit ($600 per participant), accounting for all pre-initiation training, site initiation, participant visits, monitoring visits, study close out and potential loss of sale of relevant over the counter eczema products.

Reimbursement will be paid according to the MRINZ internal SOP RP.001.

Other Ethical Considerations

No other ethical considerations.

16. FINANCE AND INSURANCE

Funding

The study is fully funded by Hikurangi Bioactives Limited Partnership, 6434 Waiapu Road, RD1, Ruatoria, New Zealand

Insurance

All participants will be informed as to the potential for ACC non-payment whilst participating in a clinical trial, should a harmful event occur. Full sponsor insurance will be in place prior to study commencement. As a contractual requirement with the MRINZ, the Sponsor must agree to abide by the current Medicines New Zealand Guidelines on Clinical Trials Compensation for Injury Resulting From Participation in an Industry-Sponsored Clinical Trial.

17. PUBLICATION POLICY

The study findings will be published by MRINZ, in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations. The Investigators listed on page one will be listed as authors, in recognition of their contribution to the design, implementation and oversight of the study.

Results of the study will be sent to participants on request (once available) and will be made available on a publicly available trial registry website, recognised by the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) as a Primary Registry.

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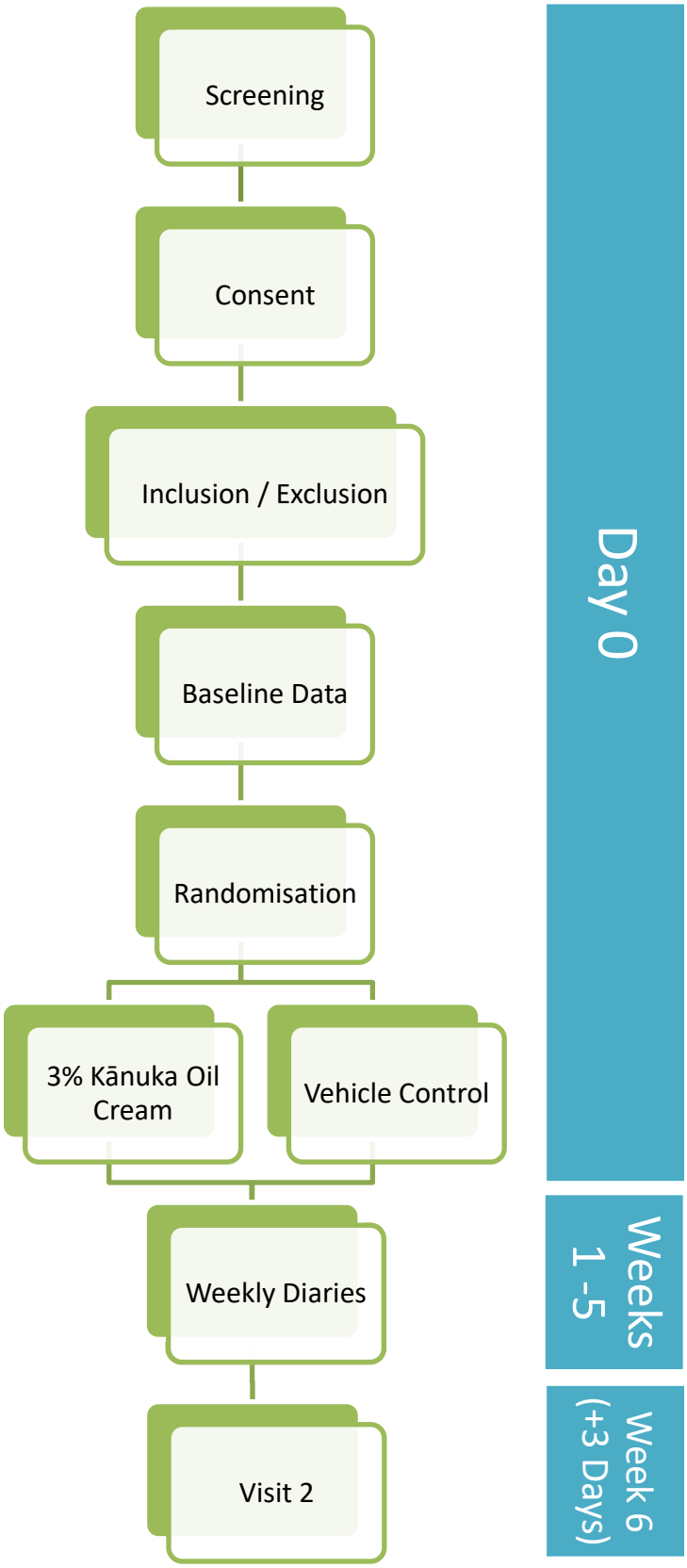
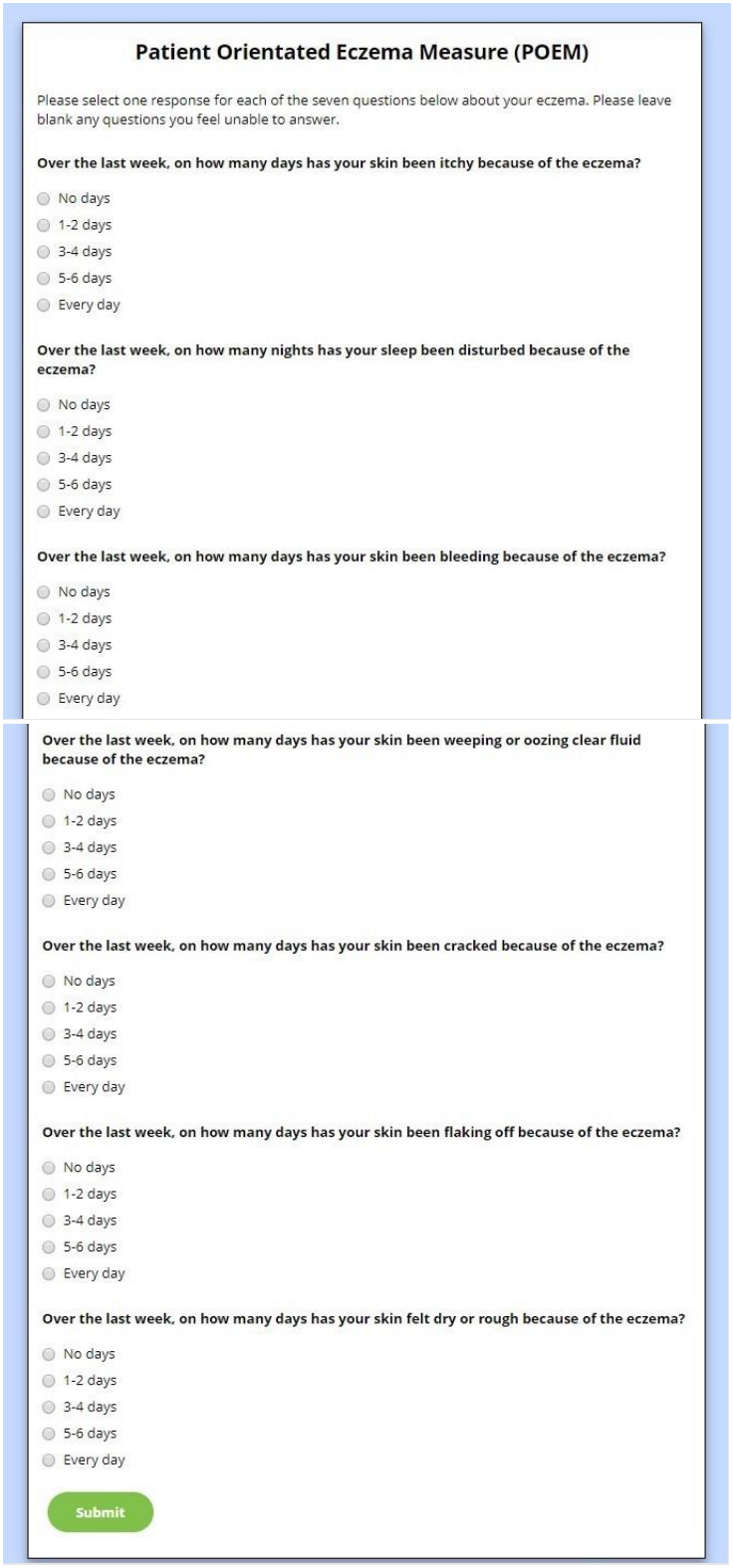
19. APPENDIX A: TRIAL FLOW CHART



20. APPENDIX B: POEM



Patient Orientated Eczema Measure (POEM)

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

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

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

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

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

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

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

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

Submit

21. APPENDIX C: DLQI

DLQI

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK.

Please select one option for each question.

Over the last week, how itchy, sore, painful or stinging has your skin been?

Over the last week, how embarrassed or self conscious have you been because of your skin?

Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?

Over the last week, how much has your skin influenced the clothes you wear?

Over the last week, how much has your skin affected any social or leisure activities?

Over the last week, how much has your skin made it difficult for you to do any sport?

Over the last week, has your skin prevented you from working or studying?

Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?

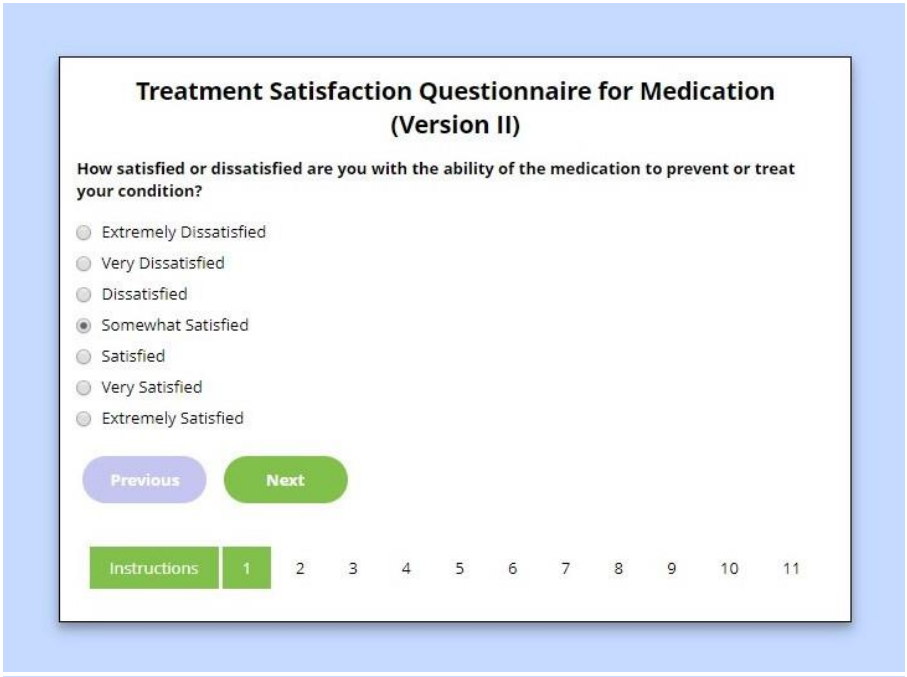
Over the last week, how much has your skin caused any sexual difficulties?

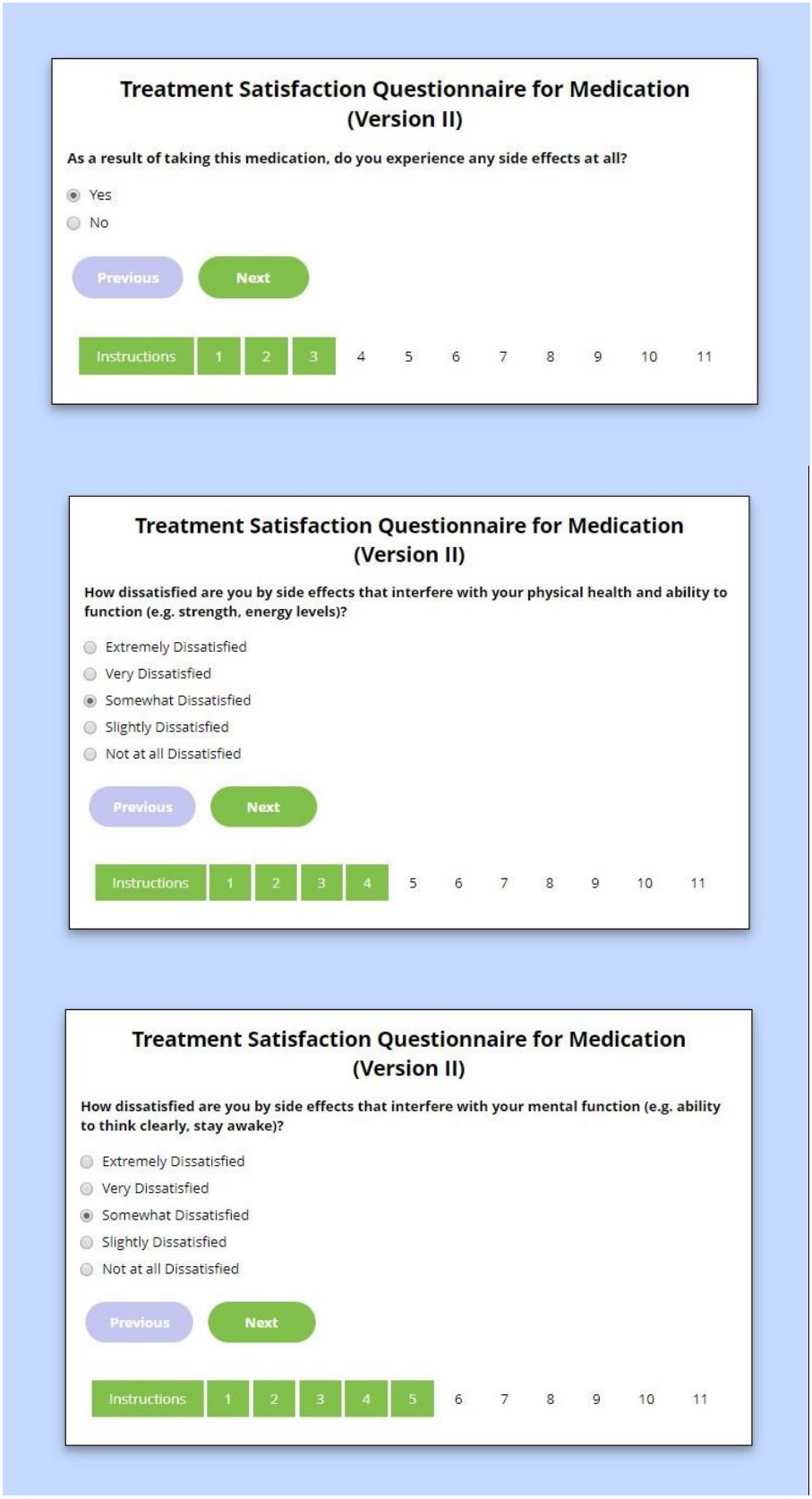
Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?

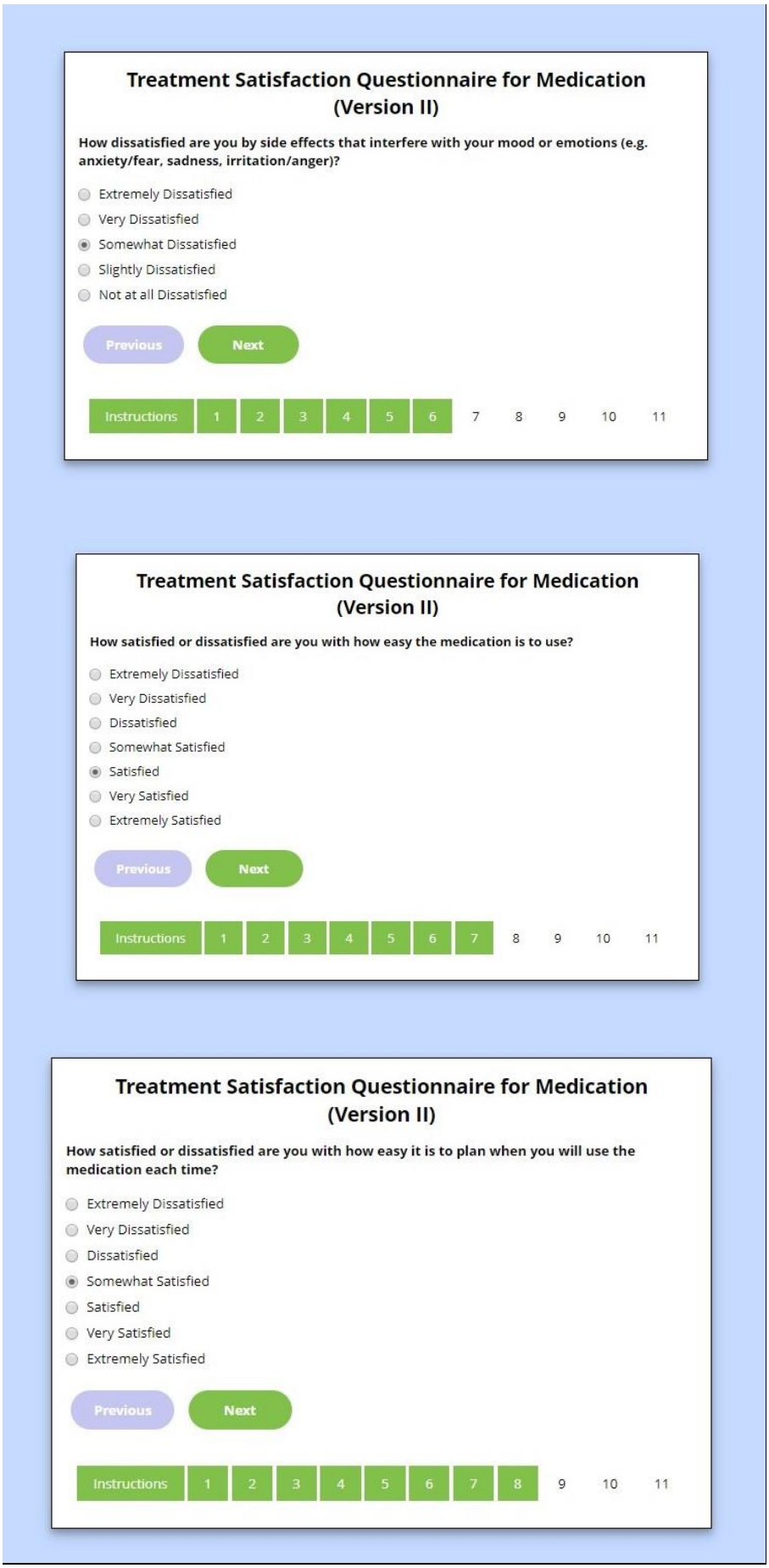
Please check you have answered EVERY question. Thank you.

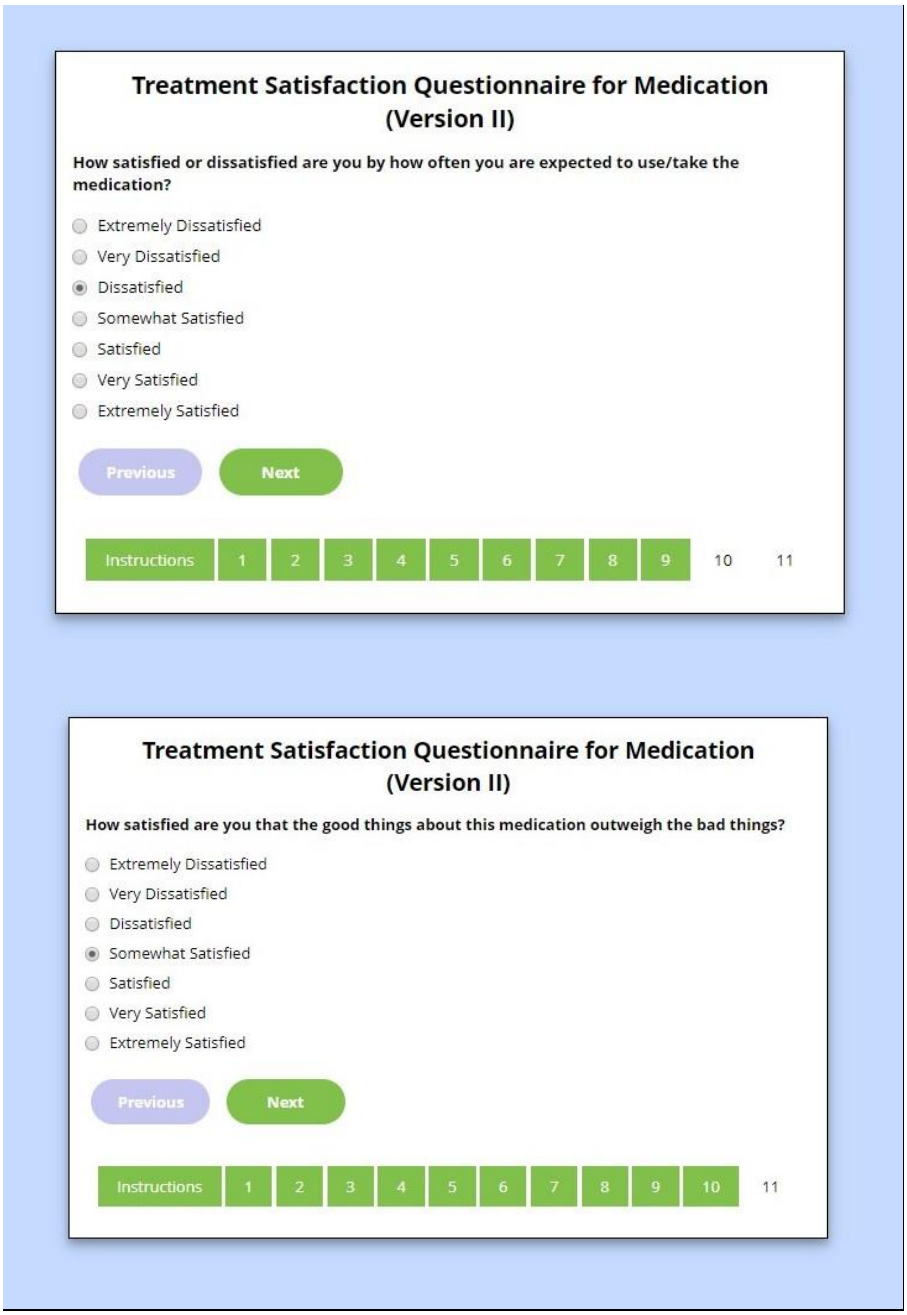
Save & Exit Form

22. APPENDIX D: TSQM VII




Treatment Satisfaction Questionnaire for Medication (Version II)
As a result of taking this medication, do you experience any side effects at all?
Yes
No
Previous
Next
Instructions 1 2 3 4 5 6 7 8 9 10 11
Treatment Satisfaction Questionnaire for Medication (Version II)
How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g. strength, energy levels)?
Extremely Dissatisfied
Very Dissatisfied
Somewhat Dissatisfied
Slightly Dissatisfied
Not at all Dissatisfied
Previous
Next
Instructions 1 2 3 4 5 6 7 8 9 10 11
Treatment Satisfaction Questionnaire for Medication (Version II)
How dissatisfied are you by side effects that interfere with your mental function (e.g. ability to think clearly, stay awake)?
Extremely Dissatisfied
Very Dissatisfied
Somewhat Dissatisfied
Slightly Dissatisfied
Not at all Dissatisfied
Previous
Next
Instructions 1 2 3 4 5 6 7 8 9 10 11

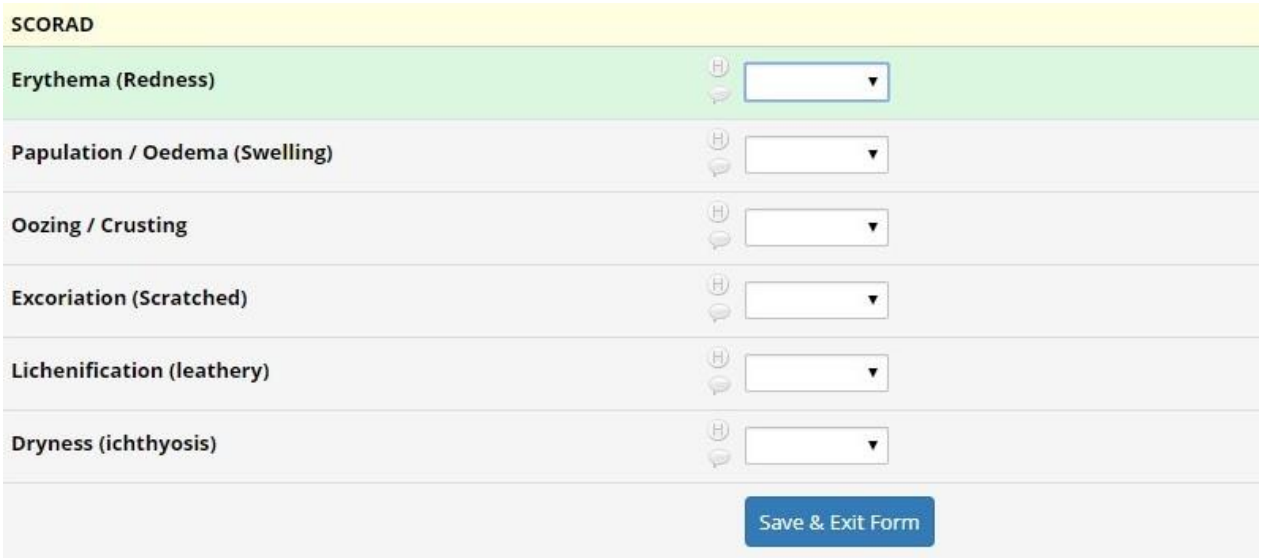

Treatment Satisfaction Questionnaire for Medication (Version II)
How dissatisfied are you by side effects that interfere with your mood or emotions (e.g. anxiety/fear, sadness, irritation/anger)?
Extremely Dissatisfied
Very Dissatisfied
Somewhat Dissatisfied
Slightly Dissatisfied
Not at all Dissatisfied
Previous
Next
Instructions 1 2 3 4 5 6 7 8 9 10 11
Treatment Satisfaction Questionnaire for Medication (Version II)
How satisfied or dissatisfied are you with how easy the medication is to use?
Extremely Dissatisfied
Very Dissatisfied
Dissatisfied
Somewhat Satisfied
Satisfied
Very Satisfied
Extremely Satisfied
Previous
Next
Instructions 1 2 3 4 5 6 7 8 9 10 11
Treatment Satisfaction Questionnaire for Medication (Version II)
How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?
Extremely Dissatisfied
Very Dissatisfied
Dissatisfied
Somewhat Satisfied
Satisfied
Very Satisfied
Extremely Satisfied
Previous
Next
Instructions 1 2 3 4 5 6 7 8 9 10 11


Treatment Satisfaction Questionnaire for Medication (Version II)
How satisfied or dissatisfied are you by how often you are expected to use/take the medication?
Extremely Dissatisfied
Very Dissatisfied
Dissatisfied
Somewhat Satisfied
Satisfied
Very Satisfied
Extremely Satisfied
Previous
Next
Instructions 1 2 3 4 5 6 7 8 9 10 11
Treatment Satisfaction Questionnaire for Medication (Version II)
How satisfied are you that the good things about this medication outweigh the bad things?
Extremely Dissatisfied
Very Dissatisfied
Dissatisfied
Somewhat Satisfied
Satisfied
Very Satisfied
Extremely Satisfied
Previous
Next
Instructions 1 2 3 4 5 6 7 8 9 10 11


Treatment Satisfaction Questionnaire for Medication (Version II)
Taking all things into account, how satisfied or dissatisfied are you with this medication?
Extremely Dissatisfied
Very Dissatisfied
Dissatisfied
Somewhat Satisfied
Satisfied
Very Satisfied
Extremely Satisfied
Previous
Submit
Instructions
1
2
3
4
5
6
7
8
9
10
11

23. APPENDIX E: SCORAD & PO-SCORAD

SCORAD

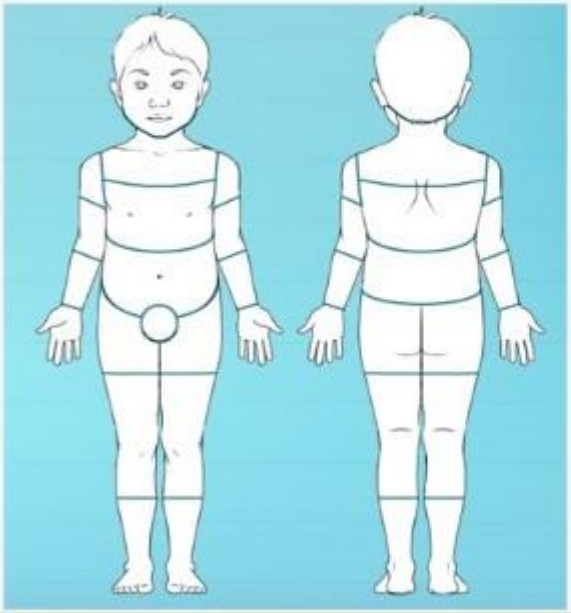


POSCORAD

1st Step

Spread of the eczema

Extent



2nd Step

Different symptoms to evaluate

Is the skin dry?

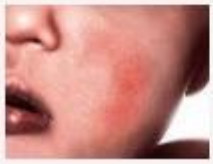
(Examine the skin not affected by eczema)

Moderately dry ▼

Not at all	Slightly dry	Moderately dry	Extremely dry
			

Are there red areas on the eczema patches?

Extremely red ▼

Not at all	Slightly red	Moderately red	Extremely red
			

Are the eczema-affected areas swollen? Moderately swollen

Not at all | Slightly swollen | Moderately swollen | Extremely swollen

Are there scabs or oozing areas on the eczema patches? A few

Not at all | A few | A moderate number | Several

Are there scratch marks on the areas affected by eczema? A few scratch marks

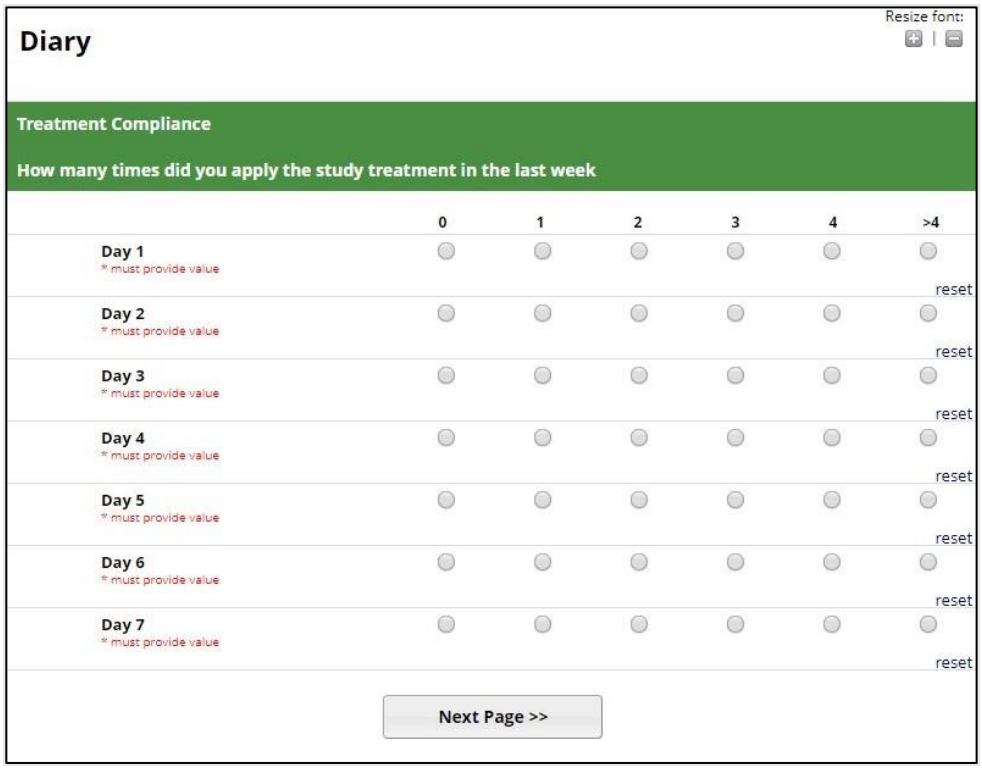
Not at all | A few scratch marks | A moderate number of scratch marks | Several scratch marks

Have you noticed any thickening of the skin on the areas affected by eczema? Moderate thickening

Not at all | Slight thickening | Moderate thickening | Significant thickening


3rd Step
Itching and trouble sleeping
(average for last 48 hrs)
Have you been bothered by itching?
No Itching
Unbearable itching
reset
Have you had trouble sleeping?
No Trouble Sleeping
A lot of Trouble Sleeping
reset

24. APPENDIX F: WEEKLY DIARY



Diary

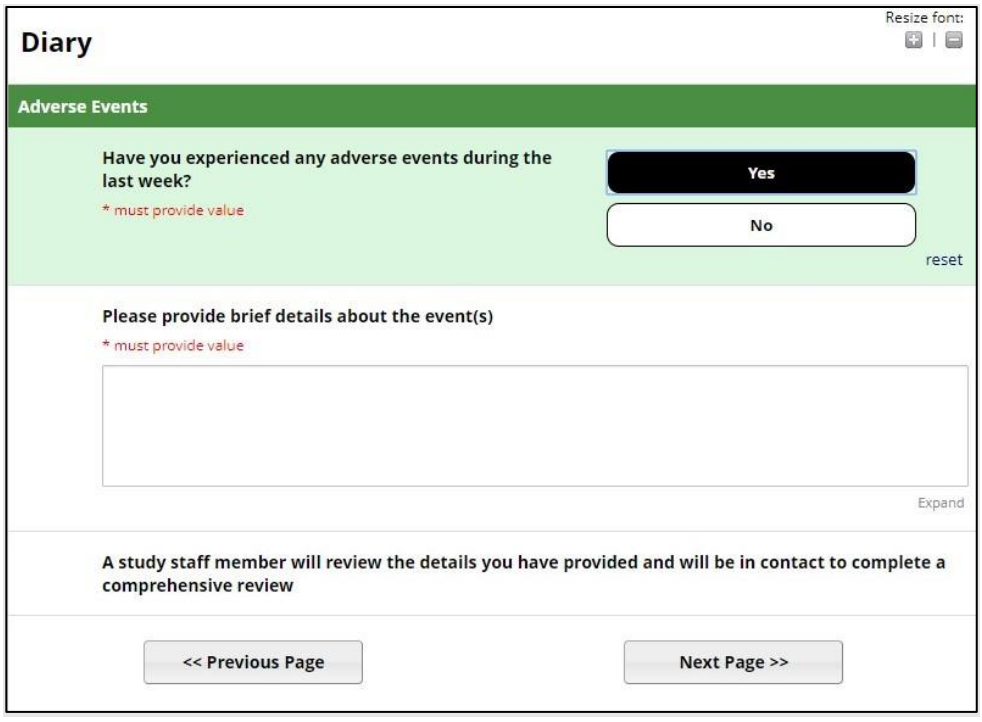
Resize font:

Treatment Compliance

How many times did you apply the study treatment in the last week

	0	1	2	3	4	>4	
Day 1 * must provide value	○	○	○	○	○	○	reset
Day 2 * must provide value	○	○	○	○	○	○	reset
Day 3 * must provide value	○	○	○	○	○	○	reset
Day 4 * must provide value	○	○	○	○	○	○	reset
Day 5 * must provide value	○	○	○	○	○	○	reset
Day 6 * must provide value	○	○	○	○	○	○	reset
Day 7 * must provide value	○	○	○	○	○	○	reset

Next Page >>



Diary

Resize font:

Adverse Events

Have you experienced any adverse events during the last week?

* must provide value

Yes

No

reset

Please provide brief details about the event(s)

* must provide value

Expand

A study staff member will review the details you have provided and will be in contact to complete a comprehensive review

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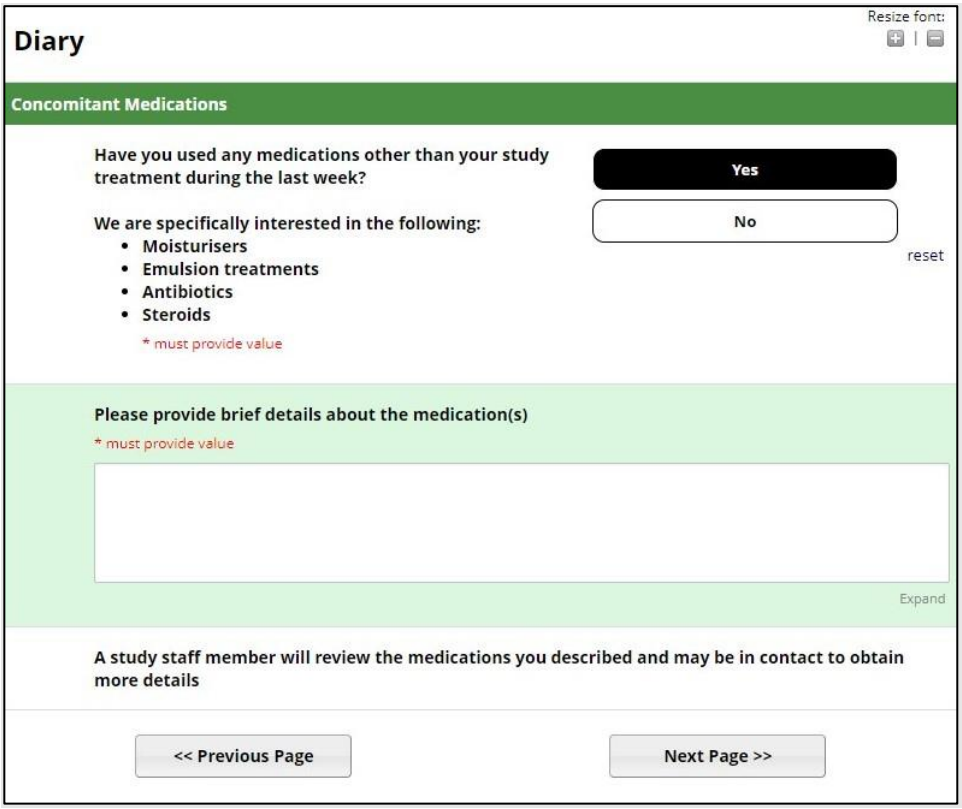
Resize font:
Diary
Concomitant Medications
Have you used any medications other than your study treatment during the last week?
Yes
No
reset
We are specifically interested in the following:
Moisturisers
Emulsion treatments
Antibiotics
Steroids
* must provide value
Please provide brief details about the medication(s)
* must provide value
Expand
A study staff member will review the medications you described and may be in contact to obtain more details
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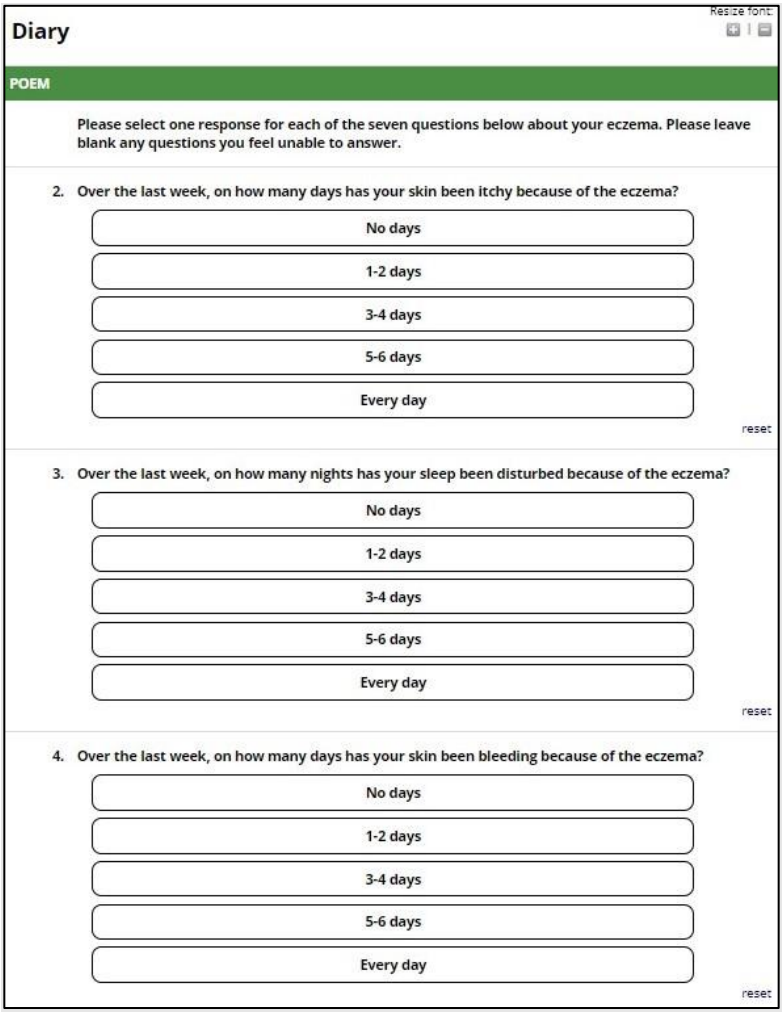

Resize font:
Diary
POEM
Please select one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.
2. Over the last week, on how many days has your skin been itchy because of the eczema?
No days
1-2 days
3-4 days
5-6 days
Every day
reset
3. 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
reset
4. 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
reset

5. 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

reset

6. 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

reset

7. 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

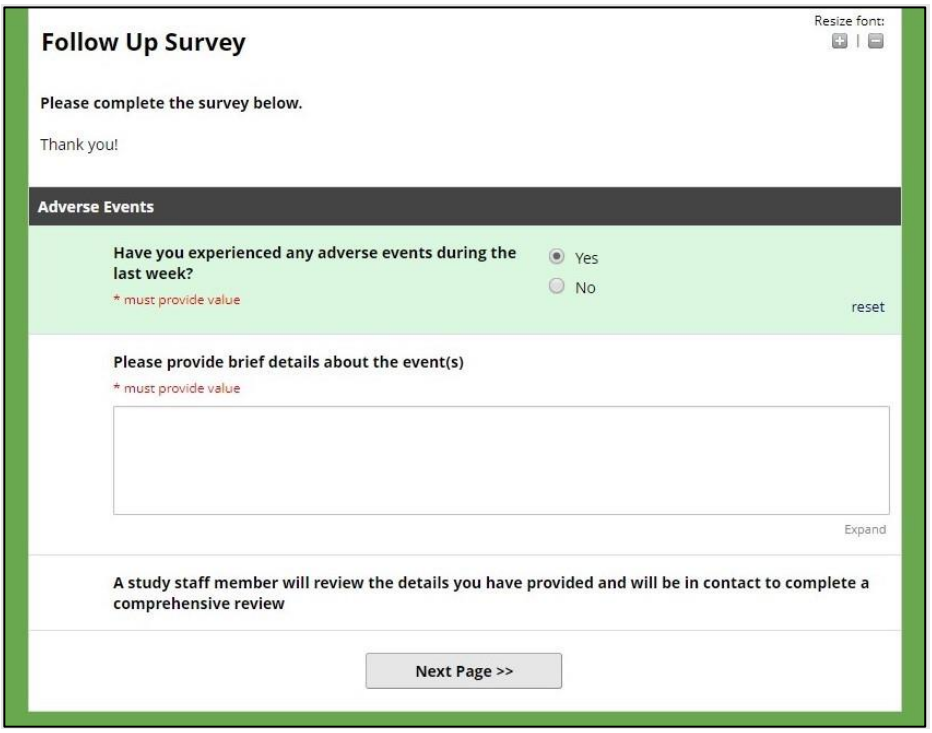
reset

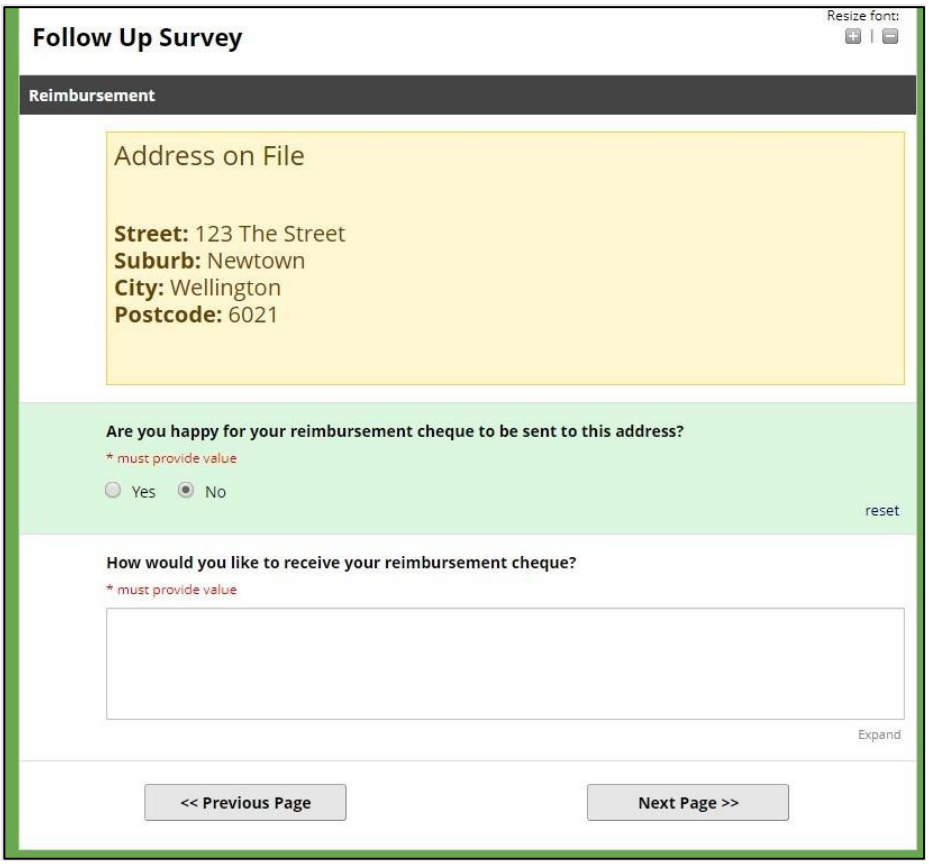
8. Over the last week, on how many days has your skin felt dry or rough because of the eczema?

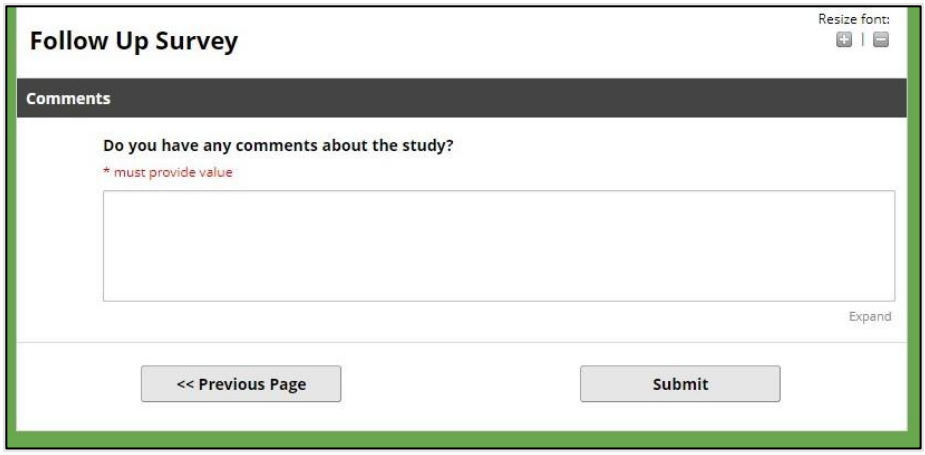
- No days
- 1-2 days
- 3-4 days
- 5-6 days
- Every day

reset

25. APPENDIX G: FOLLOW UP SURVEY






Follow Up Survey
Resize font:
Comments
Do you have any comments about the study?
* must provide value
Expand
<< Previous Page
Submit

26. APPENDIX H: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	23/10/2018	Nick Shortt	In Section 8. under the Trial Visits heading the following addition was made: A follow up survey taking place at week eight. In Section 7. under the Inclusion Criteria heading the following addition was made: An inclusion criteria stating the following "Participant has a representative eczema lesion, located below the clavicle, that they are comfortable to have photographed.".
2	2.1	17/01/2019	Nick Shortt	General Changes: Mentions of "patient" changed to "Participant" Follow up duration adjusted from 6 weeks to 8 weeks Section Specific Changes: Appendix G & H added In Section 8. under the Screening heading, the text has been updated to reflect the inclusion of a screening statement. In Section 8. (Informed Consent) the text has been updated to remove reference to a verbal version of the PIS-CF In Section 8. (Visit 1) the flow of the visit has been adjusted to reflect the intended process. In Section 8. (Weekly Diaries) the text has been adjusted to reflect the reminder process.

				In Section 8. (Follow Up Survey) the test has been adjusted to reflect the content of the survey. In Section 9. (Compliance with Trial Treatment) the section has been updated to reflect the new compliance questions. In Section 10. (SUSAR Reporting) the text has been adjusted to reflect current Medsafe guidelines.
2	2.2	21/02/2019	Nick Shortt	Changed mentions of "DermEngine" to "Epitomyze" Made some small grammar changes.
3	2.3	14/03/2019	Nick Shortt	In Section 8. (Randomisation, blinding and codebreaking) the text has been updated to reflect the change to a stratified randomisation approach.
4	2.4	16/08/2019	Nick Shortt	In Section 8. (Visit One) the text has been updated to include a REDCap file upload field for photo capture.
5	3.0	07/05/2020		Updated outcome measures and statistical analysis plan to reflect the addition of treatment escalation between groups as a secondary outcome measure. Added in the ability for investigators to complete visit 2 over the phone if the participant is unable to attend the pharmacy. Adapted protocol based on changing COVID19 Alert levels. Added the ability for parts of screening, Visit One, and Visit Two to be conducted by telephone to reduce unnecessary contact between staff and participants.
6	3.1	24/08/2020	Nick Shortt	Removed references to epitomyze for photo capture.
7	3.2	07/10/2020	Nick Shortt	In section 8. (Weekly Diaries) the text has been updated to define that weekly diaries will be set to expire after 5 days. In section 9. (Concomitant Medications) the text has been updated to provide greater clarity about what occurs when a participant reports concomitant medication use.