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STUDY PROTOCOL

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Mānuka oil based ECMT-154 versus vehicle control for the topical treatment of eczema: study protocol for a randomised controlled trial in community pharmacies in Aotearoa New Zealand

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Abstract

Background Eczema is a chronic, relapsing skin condition commonly managed by emollients and topical corticosteroids. Prevalence of use and demand for effective botanical therapies for eczema is high worldwide, however, clinical evidence of benefit is limited for many currently available botanical treatment options. Robustly-designed and adequately powered randomised controlled trials (RCTs) are essential to determine evidence of clinical benefit. This protocol describes an RCT that aims to investigate whether a mānuka oil based emollient cream, containing 2% ECMT-154, is a safe and effective topical treatment for moderate to severe eczema.

Methods This multicentre, single-blind, parallel-group, randomised controlled trial aims to recruit 118 participants from community pharmacies in Aotearoa New Zealand. Participants will be randomised 1:1 to receive topical cream with 2% ECMT-154 or vehicle control, and will apply assigned treatment twice daily to affected areas for six weeks. The primary outcome is improvement in subjective symptoms, assessed by change in POEM score. Secondary outcomes include change in objective symptoms assessed by SCORAD (part B), PO-SCORAD, DLQI, and treatment acceptability assessed by TSQM II and NRS.

Discussion Recruitment through community pharmacies commenced in January 2022 and follow up will be completed by mid-2023. This study aims to collect acceptability and efficacy data of mānuka oil based ECMT-154 for the treatment of eczema. If efficacy is demonstrated, this topical may provide an option for a novel emollient treatment. The community-based design of the trial is anticipated to provide a generalisable result.

Ethics and dissemination Ethics approval was obtained from Central Health and Disability Ethics Committee (reference: 2021 EXP 11490). Findings of the study will be disseminated to study participants, published in peer-reviewed journal and presented at scientific conferences.

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Trial registration Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12621001096842. Registered on August 18, 2021 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=382412&isReview=true).

Protocol version 2.1 (Dated 18/05/2022).

Keywords Eczema, Emollient, Botanical therapy, Pharmacy-based research network, Decentralised

Background

Eczema is a common, chronic or recurrent inflammatory skin condition, characterised by acute flares of pruritic lesions [1, 2]. Although prevalence is highest in children, for many it can persist into, or even develop in, adulthood [3–6]. Aotearoa New Zealand has a high prevalence of disease, with Māori and Pacific populations having a greater disease burden than New Zealand Europeans [7, 8]. Eczema represents a significant individual and societal financial burden, and contributes to a strain on healthcare resources [9–11]. Additionally, patient quality of life is significantly affected due to persistent itch, pain, disturbance of sleep, and emotional distress [12, 13].

Eczema is caused by complex interactions of genetics, environmental factors, and immune activation [14, 15]. The primary mechanisms for the pathophysiology include skin barrier dysfunction and immune dysregulation [16, 17]. Filaggrin is a key protein in epidermal barrier function, preventing water loss and entry of allergens and infectious organisms [18]. Two common loss-of-function mutations in the gene encoding Filaggrin can lead to an epidermal barrier defect, and have been strongly linked to the development of eczema [19, 20]. This reduction of epidermal integrity can cause allergen and microbe introduction, leading to activation of the immune system and inflammatory response [21]. The immune response in patients with eczema is associated with $CD4^+$ T cells (Th) and upregulated expression of Th2 and Th22 cytokines, resulting in chronic inflammation [22–24].

Skin colonisation by *Staphylococcus aureus (S. aureus)* is common among patients with eczema, at a carriage rate much higher than the general population [25–27] *S. aureus* is associated with disease pathogenesis, and symptom flares which can result in loss of skin microbiota diversity, further allowing *S. aureus* to dominate which can lead to significant secondary infections [28–30].

There is currently no cure for eczema, treatment instead focuses on symptom management, including identification and avoidance of irritants that exacerbate symptoms [31–33]. The primary strategy for symptom management includes the regular use of emollients to maintain and restore skin barrier function [34]. Topical corticosteroids or calcineurin inhibitors effectively reduce inflammation and are often used to treat symptom flares, or used prophylactically to maintain disease control [32, 33, 35]. However, up to 80% of eczema patients report fears around topical corticosteroids use, with concerns of side effects leading to low treatment adherence, a major contributing factor in treatment failure, and consequent poor disease control [36–38].

Prevalence of use and demand for plant-derived botanical therapies for eczema is high worldwide, [39, 40] however high quality clinical evidence for the efficacy of such products is limited. ECMT-154 is a formula comprising β-triketone rich mānuka oil and palmarosa oil, both of which demonstrate anti-inflammatory and antimicrobial activity [41–44]. In vitro, mānuka oil reduces lipopolysaccharide-induced release of inflammatory cytokine TNF-α [41]. The geraniol component of palmarosa oil has also demonstrated inhibition of various inflammatory pathways in vitro and in vivo [42, 45–47]. β-triketone rich mānuka oil and geraniol are also both effective agents against gram-positive bacteria, such as *S. aureus* [44, 48–50]. The anti-inflammatory effects may be effective in relieving eczema symptoms when lesions develop while anti-staphylococcal activity may be beneficial by reducing eczema severity and lower the risk of secondary infections. This randomised controlled trial (RCT) is designed to investigate whether in vitro evidence may translate to clinical benefit, through reduction of symptoms in patients with eczema.

This study aims to assess efficacy of a novel, non-steroidal topical emollient cream containing 2% ECMT-154 via an RCT in community pharmacies.

Methods and analysis

Study design

This study is a parallel-group, superiority, assessor-blinded RCT assessing the efficacy of 2% ECMT-154 compared with vehicle control in the topical treatment of moderate to severe eczema in adults. The trial protocol has been developed in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [51].

Trial setting and recruitment

This study will be conducted using the Medical Research Institute of New Zealand (MRINZ) Pharmacy Research Network (PRN), an established network of over 80 research trained community pharmacists in Aotearoa New Zealand overseen centrally by researchers at the

MRINZ [52, 53]. Between 10–15 pharmacies will recruit participants and undertake study related procedures. Pharmacies were selected based on previous recruitment success and capacity to complete study procedures. Adults presenting to a PRN pharmacy seeking advice for eczema will be screened for eligibility. Advertising within participating pharmacies and on mainstream or social media will be used as a recruitment tool.

Screening and selection

An anonymous pre-screening survey will be available for potential participants to self-screen against eligibility criteria (Table 1). At the pharmacy participants will be screened using a predefined statement to determine suitability for the study, followed by anonymised assessment of Patient Oriented Eczema Measure (POEM) score [54]. If participants decline participation or do not meet the inclusion criteria of POEM score (≥ 8 to ≤ 24), no further information will be collected. Moderate to severe eczema is required to prevent a floor effect, and increase the likelihood of detecting a significant change in POEM score. Willing participants provide written informed consent, and undergo assessment of eligibility.

Randomisation and masking

Participants are randomised 1:1 to receive a 2% ECMT-154 cream or vehicle control. Participants will be block randomised, block size four, and randomisation will be stratified according to site. A computer-generated randomisation number sequence will be created by the study statistician. Randomisation of participants takes place at the pharmacy, electronically within REDCap. Participants will be randomised by pharmacy investigators who have no access to the randomisation schedule. Manufacturing and labelling of interventional treatments will be conducted by an external compounding pharmacist, licensed to complete such activities and assessed according to Good Manufacturing Practice guidelines. Active treatment and vehicle control will be labelled as "Treatment G" and "Treatment H" in non-descript packaging for the purpose of blinding. Study investigators at the pharmacies and MRINZ will be blinded. Participants will not be told if they receive the active or control cream, however due to the distinctive smell of ECMT-154 compared to control, participants are assumed to be unblinded therefore this study will conservatively be classified as single blind rather than double blind.

Interventional treatments

Study intervention, and vehicle control are expected to provide emollient benefits from ingredients in the base cream, comprised of polyethylene glycol (300 and 3350), water, white soft paraffin, stearyl alcohol, propylene glycol, and sodium lauryl sulphate. Treatments are identical in formulation, with the exception of 2% ECMT-154 added to interventional cream. Participants will be dispensed two 500 gram tubs of study treatment for liberal application to affected areas twice daily, morning and night, for six weeks. In addition, three 500 gram tubs of aqueous cream (Boucher, India) will be supplied to replace participants usual soap and body wash. Adherence to randomised treatment will be collected in weekly

Table 1 Eligibility criteria

Inclusion criteria	• Participant is willing and able to provide written informed consent • Participant is aged between 18 and 65 years, inclusive • Participant reported, doctors diagnosis of eczema • Patient has a representative eczema lesion, located below the clavicle that is in an area they are comfortable having photographed • Patient has a POEM score of 'moderate to severe eczema' (8 to 24) • Participant is willing to stop all moisturisers and other skin barrier cream or emulsion during the treatment period and replace it with the investigational product assigned in this trial. Usual facial regimens and application of sunscreen is permitted • Participant is willing to replace their body wash/soap with aqueous cream as supplied at enrolment • Participant is able to attend a follow up visit six weeks after they enrol in the study. This will take place at a participating pharmacy or via telephone call if required due to COVID restrictions or unanticipated inability to attend in person • Participant is willing and able to comply with the study and comply with all study procedures
Exclusion criteria	• Current requirement for antibiotics or corticosteroids for the treatment of any condition (with the exception of inhaled and intranasal corticosteroids) • Use of topical and/or oral antibiotics, corticosteroids, or antihistamines within the last two weeks (with the exception of inhaled and intranasal corticosteroids) • Use of immunomodulatory medications taken for eczema within the past four weeks • Cutaneous mycotic or bacterial disease requiring a topical or systemic therapy • Other skin condition which may affect the assessment of eczema • History of allergy or hypersensitivity to study treatment ingredients • Participation in a clinical study involving an investigational product during the last three months • Participant is pregnant/breastfeeding or planning to become pregnant during the study • Cold/flu like symptoms, fever, or unexplained shortness of breath in the past 14 days • Any other condition which, at the investigators' discretion, is believed may present a safety risk or impact upon the ability of the participant to complete the study

diaries with participants asked how many times they used their treatment each day over the past week.

Participant timeline

Upon presentation to the pharmacy, consent, demographic data, eligibility, and baseline data are collected, followed by a clinical photograph of a representative eczema lesion, chosen by the participant. The participant is randomised, and the appropriate treatment is dispensed by the study pharmacist along with the aqueous cream. Over the six-week interventional period, participants complete a weekly digital diary to report POEM, treatment adherence, adverse events, and use of concomitant medications (Table 2). Participants return to the pharmacy for a second face to face visit at week six including a second clinical photograph of the representative lesion. A final electronic follow up survey is completed at week eight to collect any adverse events following the cessation of study treatment. The study flow is depicted in Fig. 1.

Retention

Participants are reimbursed $200 (NZD) in recognition of travel and time. Reminders for weekly study diary completion are sent to non-responders once daily for five days, after which the diary window is closed.

Permitted and prohibited concomitant treatment

No other eczema treatments or moisturisers will be permitted during the trial. Participants can continue with all other prescribed medication. Concomitant medication usage will be collected in the weekly participant diaries, which ask asked if participants have used any medications other than their study treatment in the last week, prompts them to leave details and MRINZ investigators will contact the participant directly to complete concomitant medication forms based on C-DASH standards. It is recognised that minor exacerbations of eczema are expected, therefore the usage of topical corticosteroids habitually used by the participant, for a duration of less than or equal to seven days, is permitted without requiring withdrawal from the study. The requirement for escalated treatment will be recorded and compared between treatment groups.

Data capture

All study related data, including informed consent, will be captured using e-source via REDCap-based case report forms [55]. REDCap is a secure, United States Health Insurance Portability and Accountability Act 1996 (HIPAA) compliant web-based application designed to support data capture for research studies. CDASH-compliant structures are used to collect standard data types required for this study. Data is entered into tablet devices at pharmacy sites. Online study diaries and questionnaires completed by study participants are accessed via a link unique to each participant for each time point. The usage of electronic data capture allows for data validation using data entry ranges, required data fields, and logic checks. Study data is stored on secure password protected servers and only accessible by trial staff and

Table 2 Summary of study procedures

	Visit 1	Treatment Period					Visit 2	Follow Up Survey
Day	**0**	**7**	**14**	**21**	**28**	**35**	**42 (+ 5)**	**14 days post Visit 2 (+ 5)**
Eligibility screen	X							
Informed consent	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							
Electronic study diary		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	
Acceptability NRS							X	

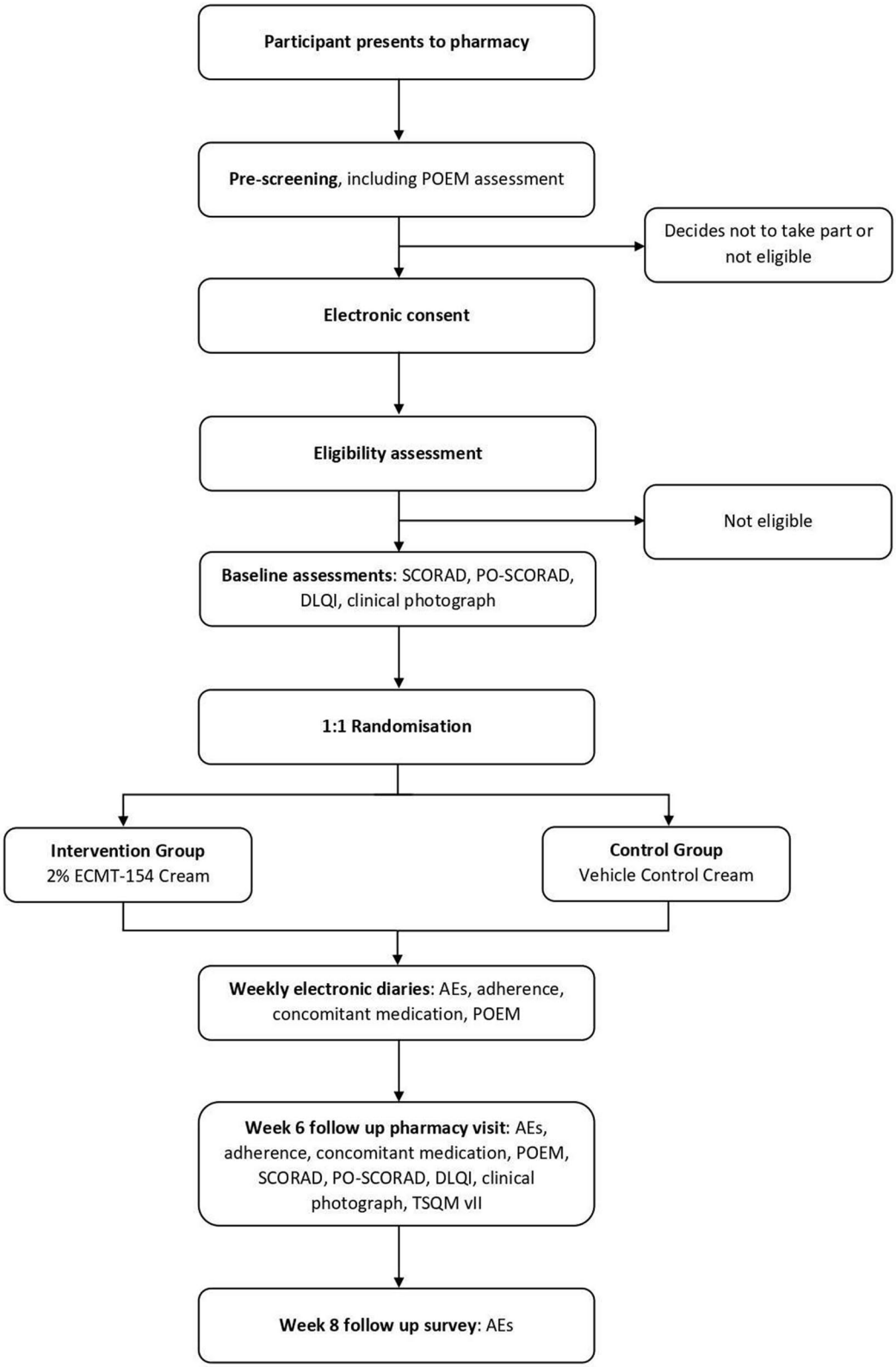

Fig. 1 Study flow diagram

independent study auditors, investigators will retain access to the final trial dataset.

Monitoring

A study monitoring plan, independent from the Sponsor, is in place to ensure all study conduct complies with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice and New Zealand ethical guidelines. All substantial protocol deviations and violations will be reported to the New Zealand ethics committee as per approval requirements.

Outcome measures

Primary

Primary outcome is severity assessed by subjective symptoms over six weeks, measured by change in POEM scores, adjusted for baseline. The POEM tool assesses severity of eczema by capturing self-reported frequency of symptoms over the previous seven days [54]. Scores can range from 0 to 28, with higher scores indicating a higher severity of disease. The following bandings have been established: Clear or almost clear (0–2); Mild eczema (3–7); Moderate eczema (8–16); Severe eczema (17–24); Very severe eczema (25–28).

Secondary

Secondary outcome measures include participants who had a four or greater reduction in POEM score (termed 'responders' [56]); the difference in POEM scores analysed per protocol; the difference in POEM scores; the difference in Patient Oriented SCORing Atopic Dermatitis (PO-SCORAD) [57]; the difference in pharmacist-assessed SCORing Atopic Dermatitis (SCORAD) score (part B only) [58]; withdrawals due to the exacerbation of eczema; the proportion of treatment escalation between groups; the difference in Dermatology Life Quality Index (DLQI) [59, 60]; participant acceptance of the treatment measured by Treatment Satisfaction Questionnaire for Medication (TSQM) Version II [61]; Numerical Rating Scale (NRS) of the acceptability of the treatment; the proportion of cutaneous and systemic events between the treatment groups; the difference in SCORAD scores between blinded pharmacist and blinded dermatologist; and the difference in SCORAD scores between pharmacists. For full schedule of interventions and assessments see Table 2.

Statistical analysis

Primary outcome analysis, and analysis of secondary POEM, PO-SCORAD, and DLQI outcomes will be by ANCOVA with baseline POEM score as a continuous covariate, and randomised treatment as a categorical variable of interest. Analysis of proportions will be by estimation of relative risk and associated confidence intervals. Participant acceptability will be assessed by t-test, or if normality assumptions are strongly violated by Mann–Whitney test with Hodges-Lehmann estimator of location. Comparison of SCORAD scores between pharmacists and between pharmacist and dermatologist will be by linear mixed model with participant treated as a random effect.

Analysis will be separated by intention-to-treat (ITT) and per protocol set (PPS), with ITT as the primary analysis. ITT population is all participants randomised. PPS is all participants with at least 80% completed data, including primary outcome with no significant protocol deviations determined to influence POEM score. For inclusion in PPS, participants should adhere to treatment instructions, measured by > 80% daily adherence. Missing outcome data will not be imputed. No interim analyses are planned and SAS will be used for analysis.

Power calculation

The sample size calculation is based on a minimal clinically important difference (MCID) of 3.4 [62] and pooled standard deviation (SD) of 6.0 for the change in POEM score [52]. With 80% power, and 5% two-sided alpha, each treatment group would require 50 participants. Allowing for 15% withdrawal and loss to follow up, 118 participants total are required for this study.

Participant safety

A study specific safety plan is in place for the trial. AEs will be identified by participant diaries, at pharmacy visits, or by ad-hoc contact from participants to the study team. Participants are prompted in their weekly diary with an open question asking if they have experienced any changes in their health or if they have experienced worsening eczema in the last week in order to capture all a wide-variety of adverse events. Any affirmative response results in contact from central MRINZ investigator for formal AE collection. All AEs are reviewed by the study doctor and coordinating team within 24 hours. An Independent Data and Safety Monitoring Committee (DSMC) is appointed to monitor all adverse events on a three-monthly basis, and will be informed of any SAEs within 72 hours. If safety concerns are expressed by the DSMC, unblinded study data may be made available to them on request. The DSMC may advise the study should be halted or terminated in the case of significant concerns for the safety of participants. AEs will be reported every six months to Medsafe, the New Zealand Medicine and Medical Devices Safety Authority. Indemnity insurance is in place for study sponsor for claims resulting from trial participation.

Discussion

There is increasing demand worldwide for effective botanical therapies for eczema as an adjunct to conventional treatment. This community-based randomised controlled trial will determine if in vitro evidence for mānuka oil based ECMT-154 translates to clinical benefit.

This decentralised study will use direct electronic data capture, allowing real-time remote monitoring of study visits. Weekly follow up of participants through electronic diaries allows the study team to maintain safety oversight throughout participation in the study.

Community pharmacies are well positioned to facilitate trial participation for individuals with that may otherwise be faced with barriers accessing clinical trials [63, 64]. It is anticipated this study design will provide a more generalisable result than if recruitment was conducted at a single study site, which could otherwise introduce bias on ethnicity or socioeconomic status.

A secondary outcome of this study will assess pharmacist capability for SCORAD scoring, a tool typically used by trained dermatologists. Training will be provided to pharmacists and SCORAD scores will be compared to remote dermatologist assessment. Results may help inform appropriate selection of outcome assessments for future research conducted in community pharmacies.

In conclusion, this trial will provide high quality safety and efficacy data on mānuka oil based ECMT-154 for the topical treatment of eczema. If efficacy is demonstrated, this novel topical treatment may provide a steroid-sparing emollient option for individuals with eczema.

Trial status

At the time of submission, participant recruitment began in January 2022. Enrolment is anticipated to continue through to mid-2023. Current protocol version 2.1 dated 18th May 2022.

Abbreviations

AE	Adverse Event
DLQI	Dermatology Life Quality Index
DSMC	Data and Safety Monitoring Committee
HDEC	Health and Disability Ethics Committee
ITT	Intention-to-treat
MCID	Minimal Clinically Important Difference
NRS	Numerical Rating Scale
PO-SCORAD	Patient-Oriented SCORing Atopic Dermatitis
POEM	Patient-Oriented Eczema Measure
PPS	Per Protocol Set
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SCORAD	SCORing Atopic Dermatitis
SCOTT	Standing Committee on Therapeutic Trials
TSQM	Treatment Satisfaction Questionnaire for Medication

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Authors' contributions

The protocol was designed by GS, AS, NS, KK, SH, and AE. With later input from MA, MR, NL, BB, GB, STP, BK, and LR. AS and GS are co-chief investigators with overall responsibility for the trial. GS, GB, AM, and BK manage the study participants and data. AE provided statistical expertise. NS built and maintains REDCap trial database. This manuscript was drafted by GS, all authors were involved in manuscript revision and final approval.

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Availability of data and materials

Study results will be submitted for publication to an appropriate academic peer-reviewed journal, and will be presented at relevant conferences. Results will be shared with participant and all recruiting pharmacy sites. Findings will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement.

Declarations

Ethics approval and consent to participate

This study has been approved by Central Health and Disability Ethics Committee (HDEC reference: 2021 EXP 11490). National Standing Committee on Therapeutic Trials (SCOTT) approval has been obtained (21/SCOTT/118), as required for all clinical trials investigating a new medicine under Aotearoa New Zealand legislation [65]. Written informed consent to participate will be obtained from all participants. All methods have been performed in accordance to guidelines and regulations set forth by HDEC and SCOTT.

Consent for publication

Not applicable.

Competing interests

SH is the inventor of ECMT-154 (as described in International Publication Number WO2022/234340 A1) and a shareholder of Manuka Bioscience. SH is also a contractor (R&D Strategist) at Manuka Bioscience. SH had input into protocol development, but is not involved in study conduct or data analysis. AS and GS declare funding from Manuka Bioscience to the MRINZ for the submitted work. There are no other conflicts of interest to declare.

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