PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Exploring a better treatment option for scabies using a tea tree oil-based gel formulation in remote-dwelling Australian Aboriginal children: Protocol for a randomised controlled trial
AUTHORS	Thomas, Jackson; Davey, Rachel; Peterson, Gregory; Carson, Christine; Walton, Shelley F.; Spelman, Tim; Calma, Tom; Dettwiller, Pascale; Tobin, Jacinta; McMillan, Faye; Collis, Paul; Naunton, Mark; Kosari, Sam; Christenson, Julia; Bartholomaeus, Andrew; McEwen, John; Fitzpatrick, Peter; Baby, Kavya

VERSION 1 – REVIEW

REVIEWER	Therese Kearns Menzies School of Health Research Charles Darwin University Australia I have co-supervised an international PhD student with Pascale Detwiller and worked in the same institution as Shelley Walton.
REVIEW RETURNED	07-Aug-2017

GENERAL COMMENTS	General comments - This is an exciting study that will provide alternative topical treatment options to what is currently available and recommended in CARPA. The protocol would benefit from revision by an experienced clinical trial person who has conducted studies in rural and remote Aboriginal communities as the methodological detail for how the project will be implemented was not clear and lacked some detail on how the study would be implemented. - Use of the word Indigenous is better abbreviated to Australian Aboriginal not ATSI if referring to Aboriginal and Torres Strait Islander people. If just referring to Aboriginal people in the NT then Aboriginal may be a more appropriate title. - Is your title accurate or are you exploring treatment options in Australian Aboriginal people living in the Katherine regions or NT? - Aboriginal Health Workers (AHWs) is very old terminology, for a considerable length of time now they have been known as Aboriginal Health Practitioners (AHPs). Introduction - The safety in pregnant women has been reported in several studies where it was given inadvertently but is not listed on the PI as suitable during pregnancy. - Review of sentence and paragraph structure would improve the clarity of the introduction. Setting, study sites and personnel - The setting has not been described or the population serviced by Wurli, which I believe is about 4500.

	- Is the project in Katherine or in surrounding communities or both, ie there are five communities in the area Wurli services, - What is the breakdown of population numbers ie 4000 in Katherine town and 500 in surrounding communities??? What is the distance between the communities and Katherine township and how are these communities accessed ie road or plane or boat? - You have said that Wurli staff members will screen for eligibility but have not included AHPs in the staff members. - The study personnel is very confusing, some researchers are doing some things and clinic staff are doing other things. You have not included all the study personnel in this heading e.g. there is a liason person under the participant heading, a researcher nurse under the clinical assessment heading, a research coordinator under the randomisation section, an Indigenous health worker in the compliance section and a study nurse in the compliance section. A table or flow chart outlining all the research and clinic staff and their roles would help to show how the study is going to be implemented in each community or Katherine township. Recruitment and Enrolment - There is no clear outline of how or when recruitment will occur, will it be done in the community clinics or in the town clinic? - Is recruitment only from clients that attend the health service or is the project planning on doing any home visits? - If recruitment is occurring in all locations how are you going to staff them with researchers to do the questions by the research nurse and randomisation by the research coordinator when scabies is diagnosed by clinic staff? - Make clear the process from recruitment to eligibility to enrolment and randomisation Participants - Once the clinic staff member has made the diagnosis and assessed eligibility then the protocol states that the research nurse will ask a set of questions, who is getting the informed consent should that not occur before the questions? - At the time of recruitment is this before or after they have consented? - What if they don't have a shower or phone, this is not included in the exclusion criteria? - Assent can be written from the age of 12 - It states that study staff (are they researchers for clinic staff) are doing the flipcharts is this before or after eligibility has been assessed, what if they say no, has their clinic experience been extended by hours? - A participant journey outline for the project would help to understand how the potential participants will be approached/recruited, assessed for eligibility (this is explained) obtaining informed consent for enrolment and randomisation to treatment. At the moment it appears that there are four different people involved in this process which could be a bit daunting for the participant and difficult to coordinate and staff in 5-6 different locations (if there are that many sites). - The protocol states that 'aboriginal,' should be Aboriginal liaison workers, will be employed for engagement with local communities. What does this mean, engagement for what, community consultation, recruitment, explain treatment???? Clinical assessment - After giving consent, it is not mentioned who has obtained this consent?

	- The research nurse is asking questions after making the clinic staff decide on who they are including or excluding, where is consent obtained? - How does the clinic staff include the research nurse in asking the questions, are they sitting around in the clinic waiting to be called into the room? - Who is taking the photograph the clinic staff or research nurse, you have not explained that there will be a photographic procedure that says from what distance the photos will be taken etc…….. - Mild is <50 lesions, this is a huge amount of lesions considering most people only have 5-10 mites, where has this definition of classifying lesion numbers come from, are you wanting to know who has had more of a systemic reaction and who has a localised reaction? Randomisation - The randomisation process explained is for one site, how is this going to occur if there are several sites recruiting and enrolling? - Will the research nurse in each site, if there are going to be more than one site and more than one research nurse, ring the study coordinator to get the treatment allocation? - How are the treatments going to be divided between the different sites, if there is more than one site? - How are the day 1 and 7 treatments going to be numbered, are they going to be given out at the same time? Medications - Why does the protocol describe treatment of crusted scabies when they are excluded from the study? - If there is crusted scabies in the household in an adult how will you know this? - Are the day 1 and 7 medications given out at the same time? - The study medications will be stored in the clinic imprest (in how many locations?) and their supply will be supervised by the research nurse but upon recruitment the nursing staff will provide the sealed medication packs, why is it the clinic nurses and not the research nurse or the clinic staff member that diagnosed the scabies? - Long sleeve gowns and gloves are not part of routine care why are they being used in the trial when this will not happen in reality? - How will you know that the bed linen was changed, is this being provided by the study? - How is the application of treatment being monitored or are you just describing to parents/carers how to apply the medication? - Who is clipping the nails and making sure the medication gets under them? - How do you know clean clothing will be put on is this being supplied by the study? - How are you going to monitor reapplication of treatment if it is washed off? - Evening bath or shower or wash? - Where and how will the gloves and gowns be disposed of? Follow-up - What if the same clinic staff member are not available at follow-up. The protocol states the AHP will do the follow-up and then say the original staff member of whom an AHP is not listed in your first explanation of staff members making the diagnosis? - Are the study staff assisting in the follow-up process? - Why is the AHP comparing the body charts is this not for the person doing the analysis? Global outcome - Who is assessing cure, treatment failure and re-infestation?

	- Pruritis can continue past one week, why is it only being followed up at one week and not at the other follow-up times? Compliance - Who provides the participants with the tablet the research nurse, the clinic staff, the liason worker? - Where are the washing machines to be located? Who will be responsible for the maintenance and use of them? - Is the “Indigenous health worker” one of the researchers or a clinic staff member? - The gift vouchers appear to be excessive and coercive for a condition that requires treatment and follow-up in routine care. What if they only attend 1 or 2 follow-up visits are they still eligible for a gift voucher? - The “study nurse” is this the same as the “research nurse”? - Why is the “study nurse” going to phone about adverse events, use of treatment etc, when the “Indigenous health worker” is visiting every week in person? - Who is weighing the tubes, the “Indigenous health worker” visiting once a week or the AHP who does follow-up at week 1, 2 and 4 at the clinic, or the research nurse overseeing the supply stock of study medications? - Who sets up the sms is this the research nurse, research coordinator, AHP or clinic staff member that assesses for eligibility, is this different to the reminders in the tablets mentioned above? - Parents/carers will be reminded by nursing staff to return the formulations, which nursing staff and when, do you mean the research nurse, study nurse or the clinic nurses, why would it not be clinic staff or research staff? Monitoring of adverse events - Above you stated this was being done over the phone by the study nurse not on each visit? - Why is the study nurse ringing if there is a diary card being filled out? - What sort of adverse reactions would be expected and if severe when is it likely to occur ie on application or within a couple of hours Feasibility - I think that 15,000 people is misleading as they are not all eligible to be seen by Wurli. I think that the number is closer to 4500. - The prevalence of scabies diagnosed by Wurli health service has not been mentioned which makes it difficult to determine if 18 months is a reasonable timeframe to recruit 200 participants. Data analysis - There is no mention of adjusting for clustering of community or household participants - An explanation of why you are using the age groups of <12 and 12-16 years would be beneficial - What if other people in the house have scabies how are you going to record this other than reporting on if there are household members with an itch? Will this be important for your analysis? Study management - Are the CIs the same as the authors on the protocol, if so why are they called the clinical trial management group isn’t this what is expected of CIs? - Do you need a clinical governance group that does not include the CIs? - You mention a DSMB, but above in the adverse events section state that this will also be reviewed by a MO, are there two processes separate or is the MO part of the DSMB? - What child health indigenous reference group are you referring to?

	- Data sharing statement Why is this data not to be put in an open access repository?

REVIEWER	Buddhima Lokuge National Centre for Epidemiology and Population Health, The Australian National University, Australia
REVIEW RETURNED	24-Aug-2017

GENERAL COMMENTS	Checklist question 4. Details of the TTO formulation not discussed. 8. Include update relevant references (e.g. Related to TTO and skin sensitivity studies and TTO and efficacy in parasitic infestations/headlice). 12. Has not discussed why study population is only aged 5 -16. Burden of scabies is in children under 5 and this is the population where new scabies treatments are most needed. It would be a missed opportunity to miss this group is a study if there is not a strong safety or other reason why this population is being excluded. If so the reasons should be included in this protocol. 14. Conflicts of interest not stated. Especially ownership/patents over formulation being studied. None of the above comments should delay study or publication of study findings. This is a worthwhile study that should proceed and being conducted in a clinically and culturally sound way with governance and approvals by expert Aboriginal and Torres Strait Islander researchers and organisations.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1
General comments

1) This is an exciting study that will provide alternative topical treatment options to what is currently available and recommended in CARPA. The protocol would benefit from revision by an experienced clinical trial person who has conducted studies in rural and remote Aboriginal communities as the methodological detail for how the project will be implemented was not clear and lacked some detail on how the study would be implemented.

Study team response: We thank the reviewer for considering our study exciting. As suggested, we have revised the protocol and manuscript to improve clarity and methodological detail. The team and CIA (Thomas, J) have had considerable experience running randomized controlled trials to completion (e.g. PMID: 19448254, ACTRN12614000946617, ACTRN12614001014640), and the specifics of the trial implementation process were designed with input from Wurli-Wurlinjang Health Service.

2) Use of the word Indigenous is better abbreviated to Australian Aboriginal not ATSI if referring to Aboriginal and Torres Strait Islander people. If just referring to Aboriginal people in the NT then Aboriginal may be a more appropriate title.

Study team response: Thanks. We agree with the reviewer's suggested change and have replaced all instances of ATSI with Australian Aboriginal or Aboriginal.

3) Is your title accurate or are you exploring treatment options in Australian Aboriginal people living in the Katherine regions or NT?

Study team response: We agree with the reviewer's comment and have changed the title of the manuscript to "Exploring a better treatment option for scabies using a tea tree oil-based gel formulation in remote-dwelling Australian Aboriginal children – Protocol for a pilot, randomised, controlled trial".

4) Aboriginal Health Workers (AHWs) is very old terminology, for a considerable length of time now they have been known as Aboriginal Health Practitioners (AHPs).

Study team response: We thank the reviewer for providing this insight and have replaced all instances of Aboriginal Health Worker with Aboriginal Health Practitioner, as suggested.

5) Introduction
The safety in pregnant women has been reported in several studies where it was given inadvertently but is not listed on the PI as suitable during pregnancy.

Study team response: We acknowledge the reviewer's comment, but consider it highly important that the safety of Ivermectin in pregnant women has not yet been adequately established to warrant listing on the PI or recommendation for use in pregnant women (PMID 12472363**). The PI does largely dictate prescribing, especially the medicolegal ramifications. We have added the word "adequately" to the relevant sentence which now reads "The safety of ivermectin (the sole oral therapy against scabies) has not been adequately established in the elderly, in patients with impaired liver function, in children aged <5 years or in pregnant women."

6) Review of sentence and paragraph structure would improve the clarity of the introduction.

Study team response: Numerous edits have been in the body of the manuscript to improve the flow and clarity of the content in the manuscript.

7) Setting, study sites and personnel

- The setting has not been described or the population serviced by Wurli, which I believe is about 4500.

- Is the project in Katherine or in surrounding communities or both, ie there are five communities in the area Wurli services,

Study team response: This has now been clarified in the text as follows: "The study will be performed in Katherine (NT, Australia) in collaboration with the Wurli-Wurlinjang, a community controlled Aboriginal Medical Service. The health service began in 1972, and based on conservative estimates, the Wurli-Wurlinjang Health Service has about 6400 regular Aboriginal clients. An additional 7,000 Aboriginal people who live in over 25 remote Katherine region communities are counted as occasional clients. Wurli also auspices Binjari Health Services, which has a population of around 300 Aboriginal people".

8) What is the breakdown of population numbers ie 4000 in Katherine town and 500 in surrounding communities??? What is the distance between the communities and Katherine township and how are these communities accessed ie road or plane or boat?

Study team response: The maximum distance between the participating communities and Katherine town is 90 kilometers. They will be accessed using Wurli-Wurlinjang Health Service vehicles (4WD).

9) You have said that Wurli staff members will screen for eligibility but have not included AHPs in the staff members.

Study team response: This has been amended in the text as follows: "Potentially eligible participants will be seen by a team of Wurli staff including Aboriginal Health Practitioners (AHPs) and general practitioners (GPs)…The study participants will be screened for eligibility by an AHP at the Wurli-Wurlinjang Aboriginal Health Service. … "
In the event of unavailability of the AHP responsible for patient recruitment and follow-up, another appropriately trained AHP from the Wurli team will perform these duties.

10) The study personnel is very confusing, some researchers are doing some things and clinic staff are doing other things. You have not included all the study personnel in this heading. e.g. there is a liason person under the participant heading, a researcher nurse under the clinical assessment heading, a research coordinator under the randomisation section, an Aboriginal health worker in the compliance section and a study nurse in the compliance section. A table or flow chart outlining all the research and clinic staff and their roles would help to show how the study is going to be implemented in each community or Katherine township.

Study team response: We have added a clarifying statement in the text as follows: "The study participants will be screened for eligibility by an AHP at the Wurli-Wurlinjang Aboriginal Health Service. Other study-related duties performed by this AHP will include patient recruitment, patient screening, patient clinical assessment, patient follow-up and site coordination, as well as coordination with other members of the study team (including interstate stakeholders)."
The roles of study personnel have also been included in the newly added trial progression algorithm (Figure 2).

11) Recruitment and Enrolment
There is no clear outline of how or when recruitment will occur, will it be done in the community clinics or
in the town clinic?

Study team response: Recruitment will occur at a single site, the Wurli-Wurlinjang Health Service in Katherine. This has now been clarified in the text under the new heading 'Recruitment and enrolment' as follows: "All participants will be recruited by an AHP while attending the Wurli-Wurlinjang Health Service. An outline of the recruitment and enrolment process is presented in Figure 2."

12) Is recruitment only from clients that attend the health service or is the project planning on doing any home visits?

Study team response: Recruitment will be only from clients who attend the health service (see new section 'Recruitment and Enrolment'). At this stage we do not intend to recruit participants through home visits. However, this may be considered in the future if we are unable to achieve the participant number targets.

13) If recruitment is occurring in all locations how are you going to staff them with researchers to do the questions by the research nurse and randomisation by the research coordinator when scabies is diagnosed by clinic staff?

Study team response: Recruitment will occur at a single site, the Wurli-Wurlinjang Health Service in Katherine.

14) Make clear the process from recruitment to eligibility to enrolment and randomisation

Study team response: Figure 2 has been included to further clarify the recruitment/enrolment process.

15) Participants

- Once the clinic staff member has made the diagnosis and assessed eligibility then the protocol states that the research nurse will ask a set of questions, who is getting the informed consent should that not occur before the questions?

- At the time of recruitment is this before or after they have consented?

Study team response: Informed consent will be sought from caregivers during the recruitment process (prior to eligibility assessment or enrolment) (see Figure 2).

16) What if they don't have a shower or phone, this is not included in the exclusion criteria?

Study team response: This question will be asked of participants/caregivers during recruitment. If participants do not have access to washing facilities or a phone, they will be excluded. This information has been included in the following text: "Caregivers will be expected to comply with the requirements of the protocol. This includes being able and willing to be contacted by telephone after the initial assessment, and being able to provide written informed consent. At the time of recruitment, the legally responsible caregiver will be asked whether the participating child will have access to regular shower facilities during the treatment course…"

17) Assent can be written from the age of 12

Study team response: We agree with the reviewer. Participants aged 12 or over will be given the opportunity to provide written assent. This has been clarified in the text as follows: "Further, a child's assent to participate in the trial will be confirmed verbally, or if aged ≥12 years will be asked for written assent."

18) It states that study staff (are they researchers for clinic staff) are doing the flipcharts is this before or after eligibility has been assessed, what if they say no, has their clinic experience been extended by hours?

Study team response: The flipcharts will be shown to participants before eligibility assessment. The whole recruitment process is estimated to take approximately 30 minutes, including the presentation of the information flipcharts. For clarity, the process has been outlined in Figure 2.

19) A participant journey outline for the project would help to understand how the potential participants will be approached/recruited, assessed for eligibility (this is explained) obtaining informed consent for enrolment and randomisation to treatment. At the moment it appears that there are four different people involved in this process which could be a bit daunting for the participant and difficult to coordinate and staff in 5-6 different locations (if there are that many sites).

Study team response: An outline of the trial process (including the participant journey) has been presented in a new figure, Figure 2.

20) The protocol states that 'aboriginal,' should be Aboriginal liaison workers, will be employed for engagement with local communities. What does this mean, engagement for what, community consultation, recruitment, explain treatment????

Study team response: This has been clarified in the text as follows: "The AHP will also collaborate with two Aboriginal elders/local champions (members of the Wurli-Wurlinjang board of directors) to undertake community engagement initiatives (extensive community consultations to promote study participation)."

21) Clinical assessment
After giving consent, it is not mentioned who has obtained this consent?

Study team response: Consent will be obtained by the Aboriginal Health Practitioner. This has been clarified in Figure 2.

22) The research nurse is asking questions after making the clinic staff decide on who they are including or excluding, where is consent obtained? How does the clinic staff include the research nurse in asking the questions, are they sitting around in the clinic waiting to be called into the room?

Study team response: The term 'research nurse' refers to the AHP. We have now replaced 'research nurse' with 'AHP' as a global change in the body of the manuscript. The duties of study personnel including AHP have been summarized in Figure 2, as noted earlier. "The study participants will be screened for eligibility by an AHP at the Wurli-Wurlinjang Aboriginal Health Service. Other study-related duties performed by this AHP will include patient recruitment, patient screening, patient clinical assessment, patient follow-up and site coordination, as well as coordination with other members of the study team (including interstate stakeholders."
The entire recruitment and enrolment and data collection process (including obtaining consent) will take place at the Wurli Health Centre (see Figure 2). After obtaining consent, the AHP will collect demographic information and perform the clinical evaluations.

23) Who is taking the photograph the clinic staff or research nurse, you have not explained that there will be a photographic procedure that says from what distance the photos will be taken etc.
Study team response: All clinical procedures, including photographs of target sites, will be carried out by the AHP. The study team will follow a previously published standardized photographic procedure as stated in the original manuscript: "At all evaluation times, the sites of lesions will be recorded on body diagram sheets and lesions will be photographed using a standardised protocol.34 "
- Reference 34: Bowen, A.C., Burns, K., Tong, S.Y., Andrews, R.M., Liddle, R., Irene, M.O., Westphal, D.W. and Carapetis, J.R., 2014. Standardising and assessing digital images for use in clinical trials: a practical, reproducible method that blinds the assessor to treatment allocation. PloS one, 9(11), p.e110395

24) Mild is <50 lesions, this is a huge amount of lesions considering most people only have 5-10 mites, where has this definition of classifying lesion numbers come from, are you wanting to know who has had more of a systemic reaction and who has a localised reaction?

Study team response: The classification scheme above was adopted from previously published scabies trials; however, we agree with the reviewer that a more refined breakdown of lesion extent is warranted in this study. We have amended the protocol and manuscript as follows: "The extent of lesions will be recorded as mild (≤10 lesions), moderate (11–49 lesions) or severe (≥50 lesions).1,2"

References:
1. Haar K, Romani L, Filimone R, et al. Scabies community prevalence and mass drug administration in two Fijian villages. Int J Dermatol. 2014;53(6):739-745.
2. Elmogy M, Fayed H, Marzok H, et al. Oral ivermectin in the treatment of scabies. Int J Dermatol. 1999;38:926-928

25) Randomisation
The randomisation process explained is for one site, how is this going to occur if there are several sites recruiting and enrolling?

Study team response: Recruitment, enrolment and randomisation will all occur at a single site. This has been clarified in the manuscript and in Figure 2.

26) Will the research nurse in each site, if there are going to be more than one site and more than one research nurse, ring the study coordinator to get the treatment allocation? How are the treatments going to be divided between the different sites, if there is more than one site?

Study team response: There will not be more than one research site.

27) How are the day 1 and 7 treatments going to be numbered, are they going to be given out at the same time?

Study team response: The two treatments will be given out at the same time during the participant's first visit. This is stated in the manuscript under 'Medications, treatment' as follows: "Participant treatments for day 1 and day 8 will be provided concurrently at the first visit in well-labelled containers." The labels will make clear which treatment is to be used on day 1 and which is to be used on day 8. The second treatment will be applied on day 8, not day 7 as was indicated in the previous version of the manuscript.

28) Medications
Why does the protocol describe treatment of crusted scabies when they are excluded from the study? If there is crusted scabies in the household in an adult how will you know this?

Study team response: Crusted scabies will not be treated as a part of this trial. However, participants with household contacts showing symptoms of crusted scabies will be referred on for appropriate medical advice and treatment (to GP). This is described in more detail in the revised manuscript: "Crusted scabies-infested house contacts will be identified by questioning parents/carers, and parents/carers will be invited to refer household members with crusted scabies to a Wurli GP for appropriate medical therapy in conjunction with Katherine district hospital (NT0850; including hospitalization in an isolation ward)."

29) Are the day 1 and 7 medications given out at the same time?

Study team response: Yes, see above.

30) The study medications will be stored in the clinic imprest (in how many locations?) and their supply will be supervised by the research nurse but upon recruitment the nursing staff will provide the sealed medication packs, why is it the clinic nurses and not the research nurse or the clinic staff member that diagnosed the scabies?

Study team response: All study medications will be stored at a single location – Wurli Clinic, Katherine Town. As stated earlier, the AHP will have sole responsibility for recruitment, enrolment, treatment (including supply of trial medications) and follow-up.

31) Long sleeve gowns and gloves are not part of routine care why are they being used in the trial when this will not happen in reality?

Study team response: We acknowledge the reviewer's comment here; but this was an essential condition required by the human ethics committee to help prevent transmission.

32) How will you know that the bed linen was changed, is this being provided by the study?

Study team response: This pilot study does not at this stage have sufficient resources to provide bed linen for participants for the entire duration of the study. However, bed linen will be provided for use on the first day of treatment (day 1). Furthermore, pragmatic compliance strategies have been devised to encourage adherence to the protocol. Participants will be reminded by SMS to change their bed linen on the day of treatment (day 1 and day 8), and will be followed-up by telephone for 3 days post each treatment application. During these telephone calls participants will be reminded of the importance of personal hygiene and encouraged to change/clean/sun-dry clothes, bed linen and towels.

33) How is the application of treatment being monitored or are you just describing to parents/carers how to apply the medication?

Study team response: The application of treatment will not be directly monitored in this trial as it will be done at home by the carer and/or participant. We will inform the parents/carers of how to apply the medication, and then ask them if they did as instructed during the following clinic visit and during the telephone follow-ups. The AHP will address any difficulties or questions that arise for parents/carers during the telephone contacts made between the application of treatment 1 and treatment 2. Participants and carers will be reminded of treatment application requirements via SMS messages on the day of treatment.

34) Who is clipping the nails and making sure the medication gets under them?

Study team response: This will be done by the parent/carer (or participant if appropriate). This has been clarified in the text as follows: "Participants and carers will be instructed to clip the participant's fingernails and toenails, and apply the scabies formulations under nails."

35) How do you know clean clothing will be put on is this being supplied by the study?

Study team response: It is beyond the financial means of this pilot study to supply clean clothes to all participants. We will be instructing participants to put on clean clothes after treatment, but cannot guarantee that this will happen. In assessing compliance at clinic visits and over the telephone, carers and participants will be asked whether clean clothing was put on after treatment.

36) How are you going to monitor reapplication of treatment if it is washed off?

Study team response: Monitoring the reapplication of washed off treatment is not feasible and beyond the scope of this pilot study. Participants/carers will be instructed to reapply as necessary: "If the trial medication is washed off during hand washing, toileting, or perineal care, it must be reapplied"(by the carer or participant). During follow-up visits and telephone calls, participants will be asked whether washed-off treatment was reapplied as instructed. As stated in the 'Limitations' section at the beginning of the manuscript, it is possible that "Compliance to treatment protocol will be sub-optimal in an Aboriginal community setting in remote Australia."

37) Evening bath or shower or wash?

Study team response: We have resolved the inconsistency with respect to washing method in the original manuscript and now refer to an "evening shower/bath" or "participants will be instructed to shower or bathe".

38) Where and how will the gloves and gowns be disposed of?

Study team response: Participants will be provided with a sealable easily-identifiable biohazard bag to dispose of gloves and gowns. They will be asked to return this bag to the clinic during their follow up visits for safe disposal.

39) Follow-up
What if the same clinic staff member are not available at follow-up. The protocol states the AHP will do the follow-up and then say the original staff member of whom an AHP is not listed in your first explanation of staff members making the diagnosis?

Study team response: This will be done by the AHP employed by the Wurli health services, as stated earlier. In the event of unavailability of the AHP responsible for patient recruitment and follow-up, another appropriately trained AHP from the Wurli team will perform these duties.

40) Are the study staff assisting in the follow-up process?

Study team response: No, the study staff will not assist in the follow-up process. This will be done by the AHP staff employed by the Wurli health services.

41) Why is the AHP comparing the body charts is this not for the person doing the analysis?

Study team response: Yes, the researchers doing the analysis will compare the body charts. This has been clarified by adding a new sentence to the 'Global outcome measurement' section as follows: "Cure and treatment failure will be assessed by the principal investigator or other coinvestigators by referring to target site photographs and marked body diagrams after data collection is complete."

42) Global outcome
Who is assessing cure, treatment failure and re-infestation?

Study team response: Cure, treatment failure and re-infestation will be assessed by the research staff after data collection is complete (see response above).

43) Pruritis can continue past one week, why is it only being followed up at one week and not at the other follow-up times?

Study team response: We thank the reviewer for noticing this error. Pruritis will in fact be followed up in participants at all 3 follow-up appointments. The manuscript text has been amended to read “All participants will be followed up for three weeks post-intervention to assess pruritus.”

44) Compliance
Who provides the participants with the tablet the research nurse, the clinic staff, the liason worker?

Study team response: As stated earlier, all study-related procedures involving participants will be carried out by the AHP.

45) Where are the washing machines to be located? Who will be responsible for the maintenance and use of them?

Study team response: The following detail about the washing machines has been added to the text: “These washing machines will be kept in a location agreed upon by the community elders and maintained by the community.” During the course of the trial, all maintenance costs will be borne by the study team.

46) Is the “Indigenous health worker” one of the researchers or a clinic staff member?

Study team response: The indigenous health worker (now AHP as per the reviewer’s earlier comment) who is performing home visits is a dedicated clinical staff member employed by Wurli.

47) The gift vouchers appear to be excessive and coercive for a condition that requires treatment and follow-up in routine care. What if they only attend 1 or 2 follow-up visits are they still eligible for a gift voucher?

Study team response: The use of these gift vouchers has been approved by the human research ethics committee and Indigenous sub-committee who approved this study and agreed to by staff at Wurli. Participants will receive the vouchers only if they attend all follow-up visits. This has been clarified in the revised manuscript as follows: “gift vouchers (e.g. prepaid telephone cards and grocery vouchers) will be given to participants who attend all follow-up visits to compensate for patient transport to the study centre for follow-up assessments.”

48) The “study nurse” is this the same as the “research nurse”?

Study team response: We agree with the reviewer that there was a lack of clarity and consistency in the terms used to describe staff involved in this trial. In the original manuscript, study nurse and research nurse were used as equivalent terms, but we have now replaced ‘study nurse’ with AHP. The AHP will review participants by phone, which has been updated in the revised text as follows: “An experienced and appropriately qualified AHP will review each participant by phone.”

49) Why is the “study nurse” going to phone about adverse events, use of treatment etc, when the “Indigenous health worker” is visiting every week in person?

Study team response: Home visits will only take place for participants who cannot be successfully contacted by phone. The revised manuscript now states: “In cases where telephone follow-up is not successful, the AHP will undertake healthcare home visits to enhance patients’ adherence to the treatment and/or protocol.

50) Who is weighing the tubes, the “Indigenous health worker” visiting once a week or the AHP who does follow-up at week 1, 2 and 4 at the clinic, or the research nurse overseeing the supply stock of study medications?

Study team response: As stated earlier, the AHP will undertake all trial-related duties except data analysis. This includes weighing the tubes.

51) Who sets up the SMS is this the research nurse, research coordinator, AHP or clinic staff member that assesses for eligibility, is this different to the reminders in the tablets mentioned above?

Study team response: The AHP will set up the SMS. This is different to the preset reminders in the tablets.

52) Parents/carers will be reminded by nursing staff to return the formulations, which nursing staff and when, do you mean the research nurse, study nurse or the clinic nurses, why would it not be clinic staff or research staff?

Study team response: As stated earlier, the AHP will undertake all trial-related duties except data analysis.

53) Monitoring of adverse events
Above you stated this was being done over the phone by the study nurse not on each visit?

Study team response: Adverse events will be monitored both during face-to-face visits and over the phone to ensure that appropriate measures are taken in the event of any adverse reactions.

54) Why is the study nurse ringing if there is a diary card being filled out?

Study team response: In a remote Aboriginal setting it is likely that compliance with the diary card will be low, and using multiple strategies to record/review adverse events will improve patient adherence and safety.

55) What sort of adverse reactions would be expected and if severe when is it likely to occur ie on application or within a couple of hours

Study team response: This comment has been addressed by including more detail in the ‘Monitoring of adverse events’ section as follows: “This will be done using a pre-specified list of adverse events (AEs) including local adverse reactions (swelling, stinging/burning, itching, induration (lumps), erythema, sore eyes or conjunctivitis) and systemic adverse reactions (fever, nausea, vomiting, headache, dizziness).” These adverse reactions, if there are any, are likely to occur within a couple of hours following application.

56) Feasibility
I think that 15,000 people is misleading as they are not all eligible to be seen by Wurli. I think that the number is closer to 4500.

Study team response: This comment has been addressed by an amendment of the text as follows: “The Katherine region is a uniquely suitable site at which to perform this proof-of-concept trial because of its proximity to Aboriginal communities. The region is home to about 15,000 Aboriginal residents, 5000 of whom are regular clients at the Wurli-Wurlinjang Health Service.”

57) The prevalence of scabies diagnosed by Wurli health service has not been mentioned which makes it difficult to determine if 18 months is a reasonable timeframe to recruit 200 participants.

Study team response: The exact prevalence of scabies diagnosed by Wurli health services in the relevant age bracket (5-16 years) is not known. Conservative estimates based on extensive consultation with Wurli staff and community members indicate that four randomisations per week is feasible. We intend to extend the study beyond 18 months if it proves impossible to recruit the participants within this timeframe.

58) Data analysis
There is no mention of adjusting for clustering of community or household participants.

Study team response: The proposed study has not been designed as a cluster randomization. . At this stage it is not clear that how many children from the same community and/or house hold will be recruited and commencing treatment. However, the authors acknowledge that subjects belonging to the same household may increase (or decrease) the event risk for all household members. Given the magnitude and presence of any clustering effect is at present uncertain, it was decided to manage any such clustering at the level of the data analysis (e.g. by including the household and/or the community as a cluster variable), rather than imposing a cluster design on the trial which may have significantly increased the requirement for additional sample and associated cost for, potentially, marginal gain.

59) An explanation of why you are using the age groups of <12 and 12-16 years would be beneficial.

Study team response: Inclusion 5-16 age bracket is likely to provide additional comparative data on scabies incidence in communities between grade-schoolers (5-15) and tweens (12-18).

60) What if other people in the house have scabies how are you going to record this other than reporting on if there are household members with an itch? Will this be important for your analysis?

Study team response: The presence of other people in the house with scabies will be determined only by asking participants/parents/carers. It is outside the scope of this study to investigate scabies in non-participants any further.
Study management

61) Are the CIs the same as the authors on the protocol, if so why are they called the clinical trial management group isn't this what is expected of CIs?

Study team response: The authors PC, AB, JcM, KB are AIs (associate investigators) or have contributed significantly to the study design and formulation of this manuscript, and these authors won't be directly involved in the trial management.

62) Do you need a clinical governance group that does not include the CIs?

Study team response: The study steering group will include the following members (please see below). This will mostly include clinical staff from the Wurli Clinical Service, and this is different to the authors on this manuscript.

The study steering committee/trial management group will have the following members

- Karen Rosas, Manager for Child and Maternal Health at Wurli Wurlijang
- Dr Peter Fitzpatrick, Director of Medical Services, Wurli-Wurlinjang Health Service
- Dr Megan Cope, Senior GP, Wurli-Wurlinjang Health Service
- Dr Jackson Thomas (Pharmacist, Principal Investigator, University of Canberra)
- Mr Patrick Ahkit, Coordinator Stron Bala Clinic
- Ms Bridgette Hutchinson, Coordinator Outreach Clinic
- Mr Peter Gazey, Clinic Manager

The study steering committee members have rich clinical expertise amongst them, and have been endorsed by the approving ethics committees. Further, the current steering committee includes only one CI, providing a balanced composition to the committee. To maintain delivery of the best possible care to its regular clients and also to maintain an integrated risk management framework, the Wurli Health Services has a "clinical governance" group. The proposed scabies clinical trial will be overseen by this group.

63) You mention a DSMB, but above in the adverse events section state that this will also be reviewed by a MO, are there two processes separate or is the MO part of the DSMB?

Study team response: These are two processes. In the event of any solicited or unsolicited adverse drug reactions, the events will be reviewed by GPs at the trial site (i.e. Wurli Health Services). The events will also be referred to the Data Safety Monitoring Board.

The Data Safety Monitoring Board will comprise of the following members.

A. Professor Andrew Bartholomaeus (former chief toxicologist and consultant to FDA and TGA)
B. Professor John McEwen (Pharmacist, Medical Doctor, and former Chief medical advisor for TGA)
C. Adjunct Associate Professor Raymond Wilson (former chief regulatory scientist (new pharmaceuticals), TGA).
D. Dr Kavya E Baby (Medical Practitioner, Physician Trainee, TCH, Canberra, ACT)

Members "B" and "D" are medical practitioners with considerable experience.

64) What child health indigenous reference group are you referring to?

Study team response: We have amended the sentence to indicate that the Child Health Indigenous Reference Group referred to is affiliated with the Wurli-Wurlinjang Health Service: "The independent data monitoring and safety committee will consist of at least one independent paediatric infectious disease clinician, a pharmacist, a statistician and a representative from the Child Health Indigenous Reference Group (Wurli-Wurlinjang Health Service)."

65) Data sharing statement
Why is this data not to be put in an open access repository?

Study team response: The de-identified data will be made available in an open access repository after publishing the study results.

REVIEWER 2

Checklist question
1.Details of the TTO formulation not discussed.

Study team response: The 5% TTO gel contains approximately 14% poloxamer 407 gel in addition to other excipients such as formulation stabilisers and preservatives.

2. Include update relevant references (e.g. Related to TTO and skin sensitivity studies and TTO and efficacy in parasitic infestations/headlice).

Study team response: We have now updated the introductory content as suggested. The updated content is given below.
“TTO has been shown to possess insecticidal, acaricidal and repellent properties against a range of medical and veterinary pests, such as house dust mites,26 Demodex mites,27 28 swine mites,29 30 and head lice.31 In vitro testing of TTO against human scabies mites demonstrated a superior result (60 min median survival time with 5% TTO) in comparison with standard treatments (150 min with ivermectin 100 µg/g; 120 min with permethrin 5%).4 32 TTO has also been used as a regular adjunct treatment (Royal Darwin Hospital, treatment protocol) in combination with benzyl benzoate and oral ivermectin for the management of crusted scabies.4 33 Additional information on the therapeutic potential of TTO for scabies can be found in a recent review.21”

- 4. Walton SF, McKinnon M, Pizzutto S, et al. Acaricidal activity of Melaleuca alternifolia (tea tree) oil: in vitro sensitivity of sarcoptes scabiei var hominis to terpinen-4-ol. Archives of dermatology 2004;140(5):563-6. doi: 10.1001/archderm.140.5.563 [published Online First: 2004/05/19]
- 21. Thomas J, Carson CF, Peterson GM, et al. Therapeutic Potential of Tea Tree Oil for Scabies. The American journal of tropical medicine and hygiene 2016;94(2):258-66. doi: 10.4269/ajtmh.14-0515 [published Online First: 2016/01/21]

26. Williamson EM, Priestley CM, Burgess IF. An investigation and comparison of the bioactivity of selected essential oils on human lice and house dust mites. Fitoterapia 2007;78(7-8):521-5. doi: 10.1016/j.fitote.2007.06.001 [published Online First: 2007/07/31]

- 27. Gao YY, Di Pascuale MA, Elizondo A, et al. Clinical treatment of ocular demodecosis by lid scrub with tea tree oil. Cornea 2007;26(2):136-43. doi: 10.1097/01.ico.0000244870.62384.79 [published Online First: 2007/01/26]
- 28. Gao YY, Di Pascuale MA, Li W, et al. In vitro and in vivo killing of ocular Demodex by tea tree oil. The British journal of ophthalmology 2005;89(11):1468-73. doi: 10.1136/bjo.2005.072363 [published Online First: 2005/10/20]
- 29. Mägi E, Järvis T, Miller I. Effects of different plant products against pig mange mites. Acta Veterinaria Brno 2006;75(2):283-87.
- 30. Sherry E, Sivananthan S, Warnke PH, et al. Topical phytochemicals used to salvage the gangrenous lower limbs of type 1 diabetic patients. Diabetes research and clinical practice 2003;62(1):65-6. [published Online First: 2003/10/29]
- 31. Di Campli E, Di Bartolomeo S, Delli Pizzi P, et al. Activity of tea tree oil and nerolidol alone or in combination against Pediculus capitis (head lice) and its eggs. Parasitology research 2012;111(5):1985-92. doi: 10.1007/s00436-012-3045-0 [published Online First: 2012/08/01]
- 32. Walton SF, Myerscough MR, Currie BJ. Studies in vitro on the relative efficacy of current acaricides for Sarcoptes scabiei var. hominis. Transactions of the Royal Society of Tropical Medicine and Hygiene 2000;94(1):92-6. [published Online First: 2000/04/05]
- 33. Davis JS, McGloughlin S, Tong SY, et al. A novel clinical grading scale to guide the management of crusted scabies. PLoS neglected tropical diseases 2013;7(9):e2387. doi: 10.1371/journal.pntd.0002387 [published Online First: 2013/09/27]

3. Has not discussed why study population is only aged 5 -16. Burden of scabies is in children under 5 and this is the population where new scabies treatments are most needed. It would be a missed opportunity to miss this group is a study if there is not a strong safety or other reason why this population is being excluded. If so the reasons should be included in this protocol.

Study team response: We acknowledge the reviewer's suggestion. However, the proposed pilot study will be confined to patients aged between 5 and 16 years, whose legally responsible caregiver is willing for their child to participate. While there is a particularly high burden of scabies among children aged less than 5 years, the safety of TTO in this age group has not been adequately established to include them in this trial.

4. Conflicts of interest not stated. Especially ownership/patents over formulation being studied.

Study team response: The conflicts of interest statement was included in the original submission. However, for clarity --there are NO competing interests to declare regarding the development of trial formulations.