Author’s response to reviews

Title: HATRIC: A feasibility study of Pelargonium sidoides root extract EPs®7630 (Kaloba®) for the treatment of acute cough due to lower respiratory tract infection in adults: study protocol for a double blind, placebo-controlled randomised trial

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Author’s response to reviews:

Dear Reviewers,

Thank you for your help and your time spent reviewing our manuscript. Please see below our responses to your comments, we hope that we have addressed them all to your satisfaction.
Thank you again,

The HATRIC Study Team.

Reviewer 1:

The investigators report on the protocol of a feasibility study of pelargonium sidoides compared to placebo for the treatment of acute cough due to lower respiratory tract infections in adults. I have the following feedback. Note that some of the comments cannot be used to modify the trial, given that it is ongoing in its current form, however, these concerns and limitations should be discussed/addressed in the published protocol.

1. The title should be rewritten to reflect the design better, i.e. double-blind, randomised placebo-controlled feasibility study instead of separating feasibility from the rest of the design.

We have moved the term feasibility from the beginning of the title to the trial description at the end

2. In the background, reference is made to the Department of Health. Please rephrase this for international readers.

We have now changed this to “Avoidance of unnecessary antibiotic prescriptions is one of the key components of the UK’s national action plan on tackling antimicrobial resistance (1).” This added reference is new; we have included it at the end of this document and added it into the paper itself.

3. The study participants and enrolment section is worded as instructions, rather than a description of future plans. Rephrase: "consent to enter the trial must be sought...." to "we will seek consent...."

We have reworded this section.

4. Other parts are written in the present tense. Please reword to future tense.

We have now corrected this throughout.
5. It is as though excerpts of text were lifted from the investigators brochure.

We feel that the background information on the herbal product is important for the understanding of this trial. If the reviewer requires parts of the text to be changed, please specify which parts.

6. Lack of data is insufficient justification to refuse participation or require contraception in women of childbearing age. Pregnant women get sick and sick women get pregnant. Reconsider explaining the risks and letting them decide.

There is no safety data for this patient group; therefore, we cannot explain the risks. The manufacturing authorisation in Germany for the Kaloba® preparation specifies that it must not be taken by women who are pregnant or breastfeeding. Therefore, Schwabe insisted on the absolute safest methods of contraception only being acceptable to prevent pregnant women entering the trial. These were based on the guidance on the FPA website. https://www.fpa.org.uk/sites/default/files/your-contraceptive-choices-chart.pdf. This guidance does actually specify that the COC and the POP are equally effective in routine use but a decision was made by the chief investigator that pregnancy could occur after a single missed POP and so the risks of pregnancy in acute illness may be higher.

We have added to the text: “There are no safety data available for pregnant women, and therefore the manufacturing authorisation in Germany for the Kaloba® preparation specifies that it must not be taken by women who are pregnant or breastfeeding. “

7. The investigators mention sites in the UK, but it is unclear in what parts of the UK this research will be conducted.

We have added, “Up to twenty health centres in the Wessex region of the UK will identify eligible patients and will invite them to participate in the trial”

8. Please replace "social demographic factors" with "sociodemographic" factors. Please add the word to your computer's dictionary.

We have changed this in the text.

9. Under "reasons for patient discontinuation", what does clinical decision entail and how it is different from recruiting physician's judgement? These should be operationalised with
examples to prevent questionable exclusions of participants. Under withdrawal, the wording is still odd: "Investigators should explain to patients…"

The following text has been added to the trial discontinuation section of the paper:

‘Recruiting physician’s judgement refers to the discontinuation of patients due to a clinical judgement made post-randomisation but while carrying out the recruitment and baseline trial processes for a patient. For example, if a patient is found to be ineligible while having their full history taken and examination carried out. At any other time within the trial a patient discontinued due to clinical judgement should be listed as a discontinuation due to a clinical decision. For example, if a patient develops symptoms that could be a side effect of the trial medication.’

We have also clarified the wording under the withdrawal heading.

10. Under withdrawal, the wording is still odd: "Investigators should explain to patients…"

This text has now been reworded.

11. The sample size justification is well done, but it is unclear what the target recruitment rate is? How many people will be approached, how many will be eligible and what proportion of the eligible participants is 160? Is recruitment here considered as number randomized?

We aimed to recruit 160 participants over the originally proposed 12-month recruitment period. The questions around how many people would need to be approached, how many would be eligible and what proportion of eligible patients would be randomised are major questions that are being addressed within this study.

These questions needed to be answered before a main definitive trial could be designed. As such, they are the feasibility objectives of this trial and the estimates of these will be the main results from this study.

As there was no estimate of these figures available before the study began the sample size justification uses a ‘statistical worst case scenario’ i.e. 50%, to show the widest possible resulting confidence interval for the given sample size.

In this case, recruitment is considered to be the number of patients randomised into the trial. We have clarified this within the text: ‘this sample size allows us to predict the recruitment rate (number of eligible patients randomised into the trial)’
12. The statistical analysis section is incomplete. At very least, you must conduct analyses to determine if you haven’t your feasibility thresholds. How many must you recruit to determine that larger trial is feasible? How many must you retain to determine that a larger trial is feasible? How is "delivery" measured? Table 1 is helpful in understanding what you are looking for in terms of feasibility, but it does not tell us how you will interpret this information. Set thresholds that will inform whether a larger trial is feasible.

Although it is now commonplace for these types of trial to be designed with set progression criteria for moving to the main trial. This trial was funded and REC approved without these having been set.

There are many factors that will feed into the feasibility or infeasibility of a definitive trial for this study, some we may have considered beforehand and others not.

‘Consideration will be given to all of the experience and knowledge gained from running the HATRIC trial including, the trial team experience and the qualitative data as well as the quantitative data to make a conclusion about the feasibility of the main trial. The results of the trial will be reported in accordance with the CONSORT extension for pilot and feasibility trials. (2)’. This paragraph has also been added to the text. Including the new reference, which we have included at the end of this document and added it into the paper itself.

13. Exclusion criteria number 6, ability to speak English is also a questionable one. Make efforts to accommodate "all" the people who show up for care.

We are unable to change this criterion as it has already been approved by the ethics committee and operationalised in the conduct of the trial. We did not have resources to translate the information sheet into multiple languages. This has been added to the limitations section at the end of the document.

Reviewer 2:

Thank you for the opportunity to read your manuscript. I found it to be a well-written and clearly described protocol for your feasibility study. I have just a few questions and observations of a generally minor nature.

14. Page 2, line 39 - should there be some additional punctuation between "preparation)" and "additionally"?

We have updated the text.
15. Page 7, line 136-7 - "time allowed for consideration" - can you expand briefly on this?

This section of the text has been reworded.

16. Page 7, line 154 - can you comment on why the various other forms of effective contraception have been omitted from this list?

Please see above comment on use of contraception within the trial (Feedback point 6).

17. Page 13, line 295-6 - the dosage regime seems to place something of a burden on the patient to remember to take the trial medicine three times daily, 30 minutes before food. Do you have any information about acceptability?

The dosage regime and method was approved by South Central – Berkshire B Research Ethics Committee. This trial is a feasibility study looking at the possibility for a full definitive trial; how this should be carried out including the acceptability to patients. A parallel qualitative study interviewing patients is being carried out alongside the HATRIC trial; this will provide some indication on the acceptability of the trial and the medication to patients. The results of the feasibility study presented here in this protocol and the qualitative study will be used to design the planned main definitive trial.

18. Page 14, line 308 - can you expand on the reasons for recommending a delayed antibiotic prescribing strategy in preference to a no antibiotic or combined delayed or no antibiotic recommendation?

We have added the following explanation to the text: “because it reduces use of antibiotics while maintaining patient satisfaction (3)”

19. Page 17, line 375 - I see that the trial is not regarded as a CTIMP on the basis that outcomes do not include treatment efficacy (page 18, line 402). The analysis plan does indicate that the analysis will be "mainly descriptive" and that "no formal comparison between groups will take place". Are you able categorically to state that there will be no comparison at all of clinical outcomes between groups?

We have deleted the word mainly from the description of the analysis – there will be no formal comparison of groups. The analysis of the trial will address the original objectives of assessing
eligibility, recruitment, randomisation, retention, compliance, patient preference, collection of health economic outcomes, acceptability, the success of the delayed antibiotic strategy and estimating parameters for the future sample size calculation. We have expanded the analysis section of the text to include more details surrounding the analysis.

20. Page 18, line 385 - can you clarify what you mean by underlined conditions?

We have now changed this to ‘Societal costs will be collected through the patient diary on out-of-pocket spending related to lower respiratory tract infection’.

21. Page 24, lines 512-4 - I didn't quite follow this as written. Can it be amended for clarity?

We have amended the text.

22. Page 31, exclusion criterion number 2 - can you provide a reference for the choice of <91% oxygen saturation (NICE CKS for example use <94% https://cks.nice.org.uk/chest-infections-adult#!diagnosisSub)

This was based on evidence from a systematic review (not yet published) which found that although a threshold of <94% predicts radiographic pneumonia, a threshold of <91% predicts poor prognosis and the need for hospital admission. Papers by Carusone et al. (2007) and Mehr et al. (2001) were identified during the systematic review, they show that sats of <91% are associated with a worse prognosis in adults with lower respiratory infections. (4, 5) There were no studies showing a worse prognosis in adults with other cut-offs.

We have also added these references to the eligibility criteria table in the paper.

Editorial:

23. We appreciate that some of these changes may not be possible to the protocol due to commitments to funders. In these instances, please discuss mitigation strategies or whether these are limitations.

We have added a limitations section to the text discussing the potential impact of both excluding non-English speakers and women at risk of becoming pregnant.
References


