PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of antitussives, anticholinergics or honey versus usual care in adults with uncomplicated acute bronchitis: A study protocol of an open randomized clinical trial in primary care.
AUTHORS	Cots, Josep M.; Moragas, Ana; García-Sangenís, Ana; Morros, Rosa; Gomez, Ainhoa; Ouchi, Dan; Monfà, Ramon; Pera, Helena; Pujol, Jesus; Bayona, Carolina; de la Poza, Mariam; Llor, Carl

VERSION 1 - REVIEW

REVIEWER	Susan Smith RCSi Ireland
REVIEW RETURNED	18-Dec-2018

GENERAL COMMENTS	Thank you for asking me to review this protocol for a four-arm randomised control trial of symptomatic treatment for acute bronchitis. The protocol is very well presented with appropriate use of the SPIRIT reporting guidelines and checklist. I suggest the following minor revisions would improve the clarity of reporting: • The definition of acute bronchitis should be presented in the abstract as this is a controversial area with some authors using the cumbersome terminology of acute cough in which pneumonia is not suspected. • Abstract background: the related Cochrane review of over-the-counter cough medicines, referenced in the background section actually contains 29 studies and I would suggest that the evidence of benefit is lacking as opposed to being sparse • Background: line 44, page 6. Use of the term and non-systematic review is confusing here as the reporting seems to suggest the results from one study. Please clarify • The use of honey has been an interesting development in symptomatic treatment and the authors reference the related Cochrane review. I think it will be helpful if they stressed potential underlying mechanism as they propose to use natural honey which is quite different to much of the honey on the market which is essentially sweet and syrup. The latter may provide symptomatic relief but there is also a suggestion that real natural honey may have antimicrobial properties as well. • Allowing the honey to be placed into different drinks including yoghurts and herbal tea is may add additional potentially therapeutic agents into that arm and the use of the term ‘hot toddy’ needs to be clarified for an International readership

	• Aiming for a power of 80% should be recorded as a potential limitation and the power calculation does not seem to include any potential loss to follow-up which is likely in this patient population • The most important point I think to clarify is the use of antibiotics in the study population as this is not clearly specified in the patient inclusion criteria. While clinical guidelines do not recommend that antibiotics are used for acute bronchitis, in many countries they are still used and it is unclear whether using antibiotics would lead to exclusion as the criteria relating to pneumonia suggest that only patient with chest x-ray findings of pneumonia will be excluded. If the use of antibiotics is not an exclusion criteria the related Cochrane review indicates that antibiotics have a minimal but significant effect on recovery in acute bronchitis so the use of antibiotics should either be incorporated into the stratified randomisation or there should be a pre-planned subgroup analysis in patients using • The randomisation and allocation could be more clearly described and whether the investigator conducting these is independent • More detail on the primary outcome would be useful such as whether it has been previously used or validated in other studies • It is on clear in the description of the initial visit whether it is the GP him or herself who will collect consent and conduct all of the study data etc • I presume the diary is paper-based but this should be specified • The statistical analysis section lacks detail and should include potential subgroup analysis and potential confounder is for the regression models this would avoid any data driven analyses. In addition plans for dealing with missing data or not reported • The analysis refers to efficacy and says efficacy will be tested using intention-to-treat analysis. ITT analysis tests affectedness where as per protocol analysis tests efficacy. Please clarify this.

REVIEWER	Mina Bakhit Centre for Research in Evidence-Based Practice (CREBP), , Bond University, Australia
REVIEW RETURNED	29-Jan-2019

GENERAL COMMENTS	Summary Thanks for the opportunity to review this manuscript. It is an interesting and well-reported study protocol plan to evaluate pragmatically the effectiveness of different symptomatic therapies in patients with uncomplicated acute bronchitis. It is important because the current evidence (summarised well in a Cochrane review) leaves the efficacy of antitussives uncertain, recommending more high-quality randomised trials and trials evaluating honey for acute cough in adults are lacking [https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001831.pub5/full] The main weakness is the lack of a placebo (to address several potential biases, including the placebo effect). However, it is clear that this would be very difficult, expensive and possibly even unfeasible to mount. (It might even be helpful to report in the study limitations that patients who would use antitussives or anticholinergics treatments, could have a greater placebo effect than those who randomised to honey.

	An alternative enhancement for the investigators to consider is using a 4*4 factorial trial design to enable a cost-effective method of evaluating the treatment effects of the different interventions, and their possible interactions, simultaneously, [https://www.bmj.com/content/349/bmj.g5455] Recommendations: Accept +/- the suggestions

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Susan Smith

Institution and Country: RCSi, Ireland

Please state any competing interests or state 'None declared': None declared

Thank you for asking me to review this protocol for a four-arm randomised control trial of symptomatic treatment for acute bronchitis. The protocol is very well presented with appropriate use of the SPIRIT reporting guidelines and checklist. I suggest the following minor revisions would improve the clarity of reporting:

The definition of acute bronchitis should be presented in the abstract as this is a controversial area with some authors using the cumbersome terminology of acute cough in which pneumonia is not suspected.

Response: This is a pragmatic randomised clinical trial in which we wished to resemble the reality of primary care. However, we have better defined the inclusion criteria as follows: 'Potential participants who meet the following criteria will be included in this trial: (1) age 18 years or older, (2) symptoms of acute bronchitis, defined as an acute lower-respiratory-tract infection with cough as the predominant symptom, starting within 3 weeks before study inclusion, (3) patients who score ≥ 4 in either the daytime and/or nocturnal cough on a 7-point Likert scale, and (4) patients who consent to participate.

Abstract background: the related Cochrane review of over-the-counter cough medicines, referenced in the background section actually contains 29 studies and I would suggest that the evidence of benefit is lacking as opposed to being sparse

Response: Sorry for the misunderstanding. We have stressed the lack of benefit, as also mentioned by the authors of the systematic review.

Background: line 44, page 6. Use of the term and non-systematic review is confusing here as the reporting seems to suggest the results from one study. Please clarify

Response: Thank you for this comment. We have considered only review and deleted the word non-systematic.

The use of honey has been an interesting development in symptomatic treatment and the authors reference the related Cochrane review. I think it will be helpful if they stressed potential underlying mechanism as they propose to use natural honey which is quite different to much of the honey on the market which is essentially sweet and syrup. The latter may provide symptomatic relief but there is also a suggestion that real natural honey may have antimicrobial properties as well.

Response: This is a pragmatic clinical trial, which resembles general practice. As we mentioned on the paper, we will use wildflower honey which is the most common type of honey used in our country. In addition, there is no evidence about differences in the antimicrobial properties of different types of honey as mentioned in some papers that have been added to this new submission:

- Khan RU, Naz S, Abudabos AM. Towards a better understanding of the therapeutic applications and corresponding mechanisms of action of honey. Environ Sci Pollut Res Int 2017;24:27755–27766.

- Lusby PE, Coombes AL, Wilkinson JM. Bactericidal activity of different honeys against pathogenic bacteria. Arch Med Res 2005;36:464–7.

We have added this information in the text: ‘There is no clear evidence that some types of honey have superior antimicrobial properties to others as described in some papers [33,34].’

Allowing the honey to be placed into different drinks including yoghurts and herbal tea is may add additional potentially therapeutic agents into that arm and the use of the term ‘hot toddy’ needs to be clarified for an International readership.

Response: We totally agree with the reviewer. We have replaced the term ‘hot toddies’ by ‘herbal teas’. In fact, different drinks are allowed in all four arms of the study. Our aim is to reproduce usual care, where these therapeutic agents are available and used by some patients. We ask patients to register the concomitant therapies used in the diary, and we will consider them during analysis.

Aiming for a power of 80% should be recorded as a potential limitation and the power calculation does not seem to include any potential loss to follow-up which is likely in this patient population.

Response: We have clarified this section. The previous sentence ‘the drop-out rate is presumed to be 0.15' has been replaced by the clearer 'we expect a 15% of loss to follow-up.' On the other hand, 80% power is standard in most studies; obviously, increasing the sample size would help us reduce this error.

The most important point I think to clarify is the use of antibiotics in the study population as this is not clearly specified in the patient inclusion criteria. While clinical guidelines do not recommend that antibiotics are used for acute bronchitis, in many countries they are still used and it is unclear whether using antibiotics would lead to exclusion as the criteria relating to pneumonia suggest that only patient with chest x-ray findings of pneumonia will be excluded. If the use of antibiotics is not an exclusion criterion the related Cochrane review indicates that antibiotics have a minimal but significant effect on recovery in acute bronchitis so the use of antibiotics should either be incorporated into the stratified randomisation or there should be a pre-planned subgroup analysis in patients using.

Response: Thank you for this comment. Certainly, the benefit of antibiotic therapy for this condition is negligible as the reviewer points out. We have included the usage of antibiotics as a sub-analysis study. However, since this is randomised clinical trial, we do not expect the percentage of utilisation of antibiotics to differ across the four arms.

The randomisation and allocation could be more clearly described and whether the investigator conducting these is independent.

Response: We have described this point more in depth as suggested. The outcome assessment

Randomisation

Patients will be assigned sequentially as they enter the study. Randomisation of patients will be performed by registering the patient in an electronic CRF during the index visit. Patients will be stratified based on the previous duration of symptoms (≤ 1 week; > 1 week). Once a patient is

included in the trial and the randomisation has been centrally made, the investigator will provide the assigned treatment and record the dispensing and medication code in the electronic CRF. Since this is a multicentre study, a block procedure will be performed to assign patients to each of the health centres at a 1:1:1:1 ratio.

Blinding

This is an open study. Neither physicians nor patients will be blind to the patient's assignment to the study group. The open nature of the clinical trial ensures that the results obtained in this study are very close to the reality of primary care, considering that both the participating GPs and the patients with uncomplicated acute bronchitis will be aware of the treatment given. However, the main outcome will be assessed by the patients themselves.

More detail on the primary outcome would be useful such as whether it has been previously used or validated in other studies.

Response: We will use validated questionnaires, which have also been used in a previous recently published (reference number 35) randomised clinical trial about the efficacy and safety of delayed prescribing of antibiotics for the same RTIs. We have added this information at the bottom of the Primary outcome paragraph in the Outcome measures section, as follows: ‘We will use validated questionnaires, which have also been used in a previous study.’

It is on clear in the description of the initial visit whether it is the GP him or herself who will collect consent and conduct all of the study data etc

Response: We have better described that GPs are responsible for collecting the informed consent and collect the data: ‘The patients will receive information on the study by the participating GPs, and if they are interested in participating, they will be provided with an informed consent form to read and sign. A maximum length of 10-15 minutes is expected for the interview, randomisation and the introduction of the data. The participating GPs will explain the study scheme and the visit programme to the patient (Table 1).’

I presume the diary is paper-based but this should be specified.

Response: Yes. We have added the term paper-based symptom diary to the text.

The statistical analysis section lacks detail and should include potential subgroup analysis and potential confounder is for the regression models this would avoid any data driven analyses. In addition, plans for dealing with missing data or not reported.

The analysis refers to efficacy and says efficacy will be tested using intention-to-treat analysis. ITT analysis tests affectedness whereas per protocol analysis tests efficacy. Please clarify this.

Response to both comments: Thank you for this comment. We have modified this statistical section as suggested:

Statistical analysis

The characteristics of the study population will be described using frequencies for categorical variables and mean and standard deviation for quantitative variables. To compare the different strategies with the usual treatment, we will use the chi-square tests for categorical variables and the Student t-test and variance analysis for continuous variables. Effectiveness evaluation will be primarily based on intention-to-treat (ITT) analysis in such a way that any event in any patient will be included in the group to which the patient was randomised, and per protocol (PP) analysis will be used as a secondary analysis. ITT analysis will be conducted in all subjects randomised, and PP analysis will be conducted in those who complete the entire trial without violating the protocol.

To avoid the effect of potential confounders, the effectiveness of each treatment with respect to the usual clinical practice will be analysed through Cox proportional risk survival analysis, reporting both crude and adjusted relative risk. The effect of the treatment will be adjusted for variables collected at baseline (demographics, previous treatment, initial progression of the disease...), variables collected during the follow-up (concomitant drug, adherence, adverse events...) and other variables that are considered relevant (clinically or statistically) in the evolution of the symptoms.

Censoring and missing data

Those who discontinue, miss follow-up or, for whatever reason, are not evaluated for the main variable will be considered censored at the last follow-up date. In addition, patients who do not show symptoms of improvement along the study will also be censored at the last day of follow-up. We do not plan to make imputation of missing data.

Sub-analysis

To assess the consistency of the data collected by telephone (in subjects not attending the visit of the 15th and 29th), a sub-analysis will be carried out using only the data from the diary. A sub-analysis with the patients taking antibiotics will also be studied.

All the analyses will be done with the statistical software R (version 3.2 or higher) and the level of significance will be 0.05.

Reviewer: 2

Reviewer Name: Mina Bakhit

Institution and Country: Centre for Research in Evidence-Based Practice (CREBP), Bond University, Australia Please state any competing interests or state ‘None declared’: None declared

Thanks for the opportunity to review this manuscript. It is an interesting and well-reported study protocol plan to evaluate pragmatically the effectiveness of different symptomatic therapies in patients with uncomplicated acute bronchitis.

It is important because the current evidence (summarised well in a Cochrane review) leaves the efficacy of antitussives uncertain, recommending more high-quality randomised trials and trials evaluating honey for acute cough in adults are lacking [https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001831.pub5/full]

The main weakness is the lack of a placebo (to address several potential biases, including the placebo effect). However, it is clear that this would be very difficult, expensive and possibly even unfeasible to mount. (It might even be helpful to report in the study limitations that patients who would use antitussives or anticholinergics treatments, could have a greater placebo effect than those who randomised to honey.

Response: We fully agree with the reviewer that placebo is essential when assessing efficacy. We considered the possibility during the design of the study but, as our aim is to conduct a pragmatic trial and evaluate the effectiveness of the treatments in usual care conditions, in which the main outcome is assessed by the patient, we finally decided that placebo was not necessary.

An alternative enhancement for the investigators to consider is using a 4*4 factorial trial design to enable a cost-effective method of evaluating the treatment effects of the different interventions, and their possible interactions, simultaneously, [https://www.bmj.com/content/349/bmj.g5455]Accept +/- the suggestions

Response: Thank you for this comment. Our aim is to evaluate the individual effect of adding each of the interventions (dextromethorphan, ipratropium or honey) to the standard treatment of the condition (usual clinical practice). We think the best design for this is to include usual clinical practice in the 3 interventions and to compare them with a usual clinical practice group (control group), being usual clinical practice the control group.

VERSION 2 – REVIEW

REVIEWER	Susan Smith RCSI Ireland
REVIEW RETURNED	01-Mar-2019

GENERAL COMMENTS	Very minor issues outstanding: 1. The title should read antitussives, anticholinergics OR honey. Otherwise looks like you could be giving all three together 2. Ideally the analysis plan should identify the planned variables in the analysis models rather than saying it will be based on what is significantly related to outcomes 3. you just state the the primary outcomes uses a validated measure but don't give any reference to the study that validated it - maybe you mean a measure you have used in previous studies than a formally validated measure?

VERSION 2 – AUTHOR RESPONSE

Very minor issues outstanding:

1. The title should read antitussives, anticholinergics OR honey. Otherwise, looks like you could be giving all three together

Response: Done. We have replaced this in the title and in the abstract section.

2. Ideally the analysis plan should identify the planned variables in the analysis models rather than saying it will be based on what is significantly related to outcomes.

Response: We have better explained this as suggested.

3. you just state the the primary outcomes uses a validated measure but don't give any reference to the study that validated it - maybe you mean a measure you have used in previous studies than a formally validated measure?

Response: We have added a reference.