PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial
AUTHORS	Maricoto, Tiago; Correia-de-Sousa, Jaime; Taborda-Barata, Luís

VERSION 1 – REVIEW

REVIEWER	Timothy H. Self University of Tennessee Health Science Center, USA
REVIEW RETURNED	13-Mar-2018

GENERAL COMMENTS	hank you for conducting this study! I suggest that you enroll all COPD patients OR all asthma patients unless you have a larger patient population. Analyze by COPD or asthma and other variable including age and comorbidities. Also, analyze data for perhaps ages 65-75, 75-85, and >85 years (or some level of stratification). Have roughly the same number of DPIs and MDIs. Add to variables how long each patient was using devices prior to the study as well as previous inhaler education, including demos and observation of patient's technique. Cite and briefly discuss the following references: Strayhorn-Smith V, Tolley E, Demirkan K, Self T: Metered dose inhaler - spacer technique in hospitalized geriatric patients: Effect of patient education by a pharmacist. Hosp Pharm 35:162-4, 2000. (attached) Sanchis J et al. Chest 2016 (August);150:394-406. Dolovich M et al. Chest 2005;127:335-71. Self TH et al. Ann Allergy Asthma Immunol 2016;117:101-2. (guidelines vs. manufacturer directions for MDI) Thomas RM et al. Respir Care 2017;62:1412- Blasi F et al. COPD 2016;13:367-71

REVIEWER	Richard Dekhuijzen Radboud umc, Nijmegen, the Netherlands
REVIEW RETURNED	16-Mar-2018

GENERAL COMMENTS	Important clinical problem and well designed study. Some suggestions: 1. Include the Critikal study (Crystyn 2017). 2. Explain why you chose this training method and schedule. 3. Explain why you did not include electronic measures of adherence and inhalation technique.

REVIEWER	Valerie Press University of Chicago, USA
REVIEW RETURNED	19-Mar-2018

GENERAL COMMENTS	This is an important topic. There are several concerns with this manuscript that need addressing: 1. Is the research question or study objective clearly defined? The objective should be written more clearly to identify the PICO statement. 2. Is the abstract accurate, balanced and complete? The abstract discussion states this is the 'first study to..."--it is not clear that is the case. A more thorough review of the literature could clarify how this study is different from other studies. This systematic review notes several studies with interventions linked to outcomes: Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes; Omar Sharif Usmani1Email author, Federico Lavorini2, Jonathan Marshall3, William Christopher Nigel Dunlop3, Louise Heron4, Emily Farrington4 and Richard Dekhuijzen5 Respiratory Research201819:10 3. Is the study design appropriate to answer the research question? The use of usual care is tricky because it is not necessarily reproducible or quantifiable. Further, since inhaler misuse is so widespread, it is not clear that it is warranted. Did the authors consider a comparator arm other than control and how/why was usual care chosen? Single -blinded may not accurately describe the study. While the patients were blinded (or masked which is a preferable term), were not others involved in the study also masked? The investigators? Statistician? Etc? 4. Are the methods described sufficiently to allow the study to be repeated? see above re: usual care 7. If statistics are used are they appropriate and described fully? The hypothesis is not written correctly--the null and alternative hypotheses are flipped. The statistical analysis should include a GEE model to account for the longitudinal design, chi-square is not sufficient for this methodology. 8. Are the references up-to-date and appropriate?

	see above for systematic review citation--there are significant numbers of intervention studies on this-the authors need to better clarify the novel aspects of their study. 11. Are the discussion and conclusions justified by the results see above for abstract 12. Are the study limitations discussed adequately? Any issues that cannot be changed in the methods identified above should be addressed. 15. Is the standard of written English acceptable for publication? Several areas could be strengthened.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Timothy H. Self
Institution and Country: University of Tennessee Health Science Center, USA
Competing Interests: none

Thank you for conducting this study!
• I suggest that you enroll all COPD patients OR all asthma patients unless you have a larger patient population. Analyze by COPD or asthma and other variable including age and comorbidities. Also, analyze data for perhaps ages 65-75, 75-85, and >85 years (or some level of stratification).
Author:
We thank the reviewer for the suggestion. In order to broadly include all potentially eligible patients, we decided to re-write the last paragraph of the “exclusion criteria” in page 5, as follows:
“We will exclude patients who do not need inhaler medication on a daily basis, since such patients are less susceptible to the full impact of intervention. In addition, these are mostly patients with intermittent asthma, as well as COPD patients with mild obstruction (GOLD stage I), and tend to have a low frequency of disease exacerbations, which would hamper our ability to detect a true outcome effect”.
We also have re-written the middle section of “statistical analysis” in order to include more sub-group analysis, as suggested:
“Subgroup analysis will be performed according to secondary variables, such as diagnosis, age (including stratification into the following categories: 65-75, 75-85, and >85 years), sex, years of diagnosis, disease classification/stage, comorbidities, previous teaching of inhaler technique and device type.”

• Have roughly the same number of DPIs and MDIs.
Author:
We thank the reviewer for the comment. However, it is difficult to predict an exact balance between DPIs and pMDIs users during the enrolment of patients from the general population, since there are differences in the prevalence of their use. In Portugal, for instance, DPIs are more frequently used. On the other hand, pMDIs with a spacer are only now starting to be used in a more widely manner, due to the recent issue of specific guidelines by the National Directorate of Health. For these reasons, we find it very difficult to ensure a correct balance between both types of inhalers, unless we opted to set up a type of restriction method, in the inclusion phase.

However, we believe that restricting the inclusion in order to achieve this balance would bias the results away from the real value. If we allow the inclusion process to include DPIs and pMDIs users according to a more “realistic” prevalence in the general population, we also will enable the study to achieve a better estimation of the real intervention impact, since it is probably related to device types.

• Add to variables how long each patient was using devices prior to the study as well as previous inhaler education, including demos and observation of patient's technique.
Author:
As requested, we have added the following statements to the “Other variables collected at baseline” section:
“• Previous teaching of inhaler technique, specifying the education type (placebo device, video, leaflet, multimedia, etc.).
• Years of use with current device.”

• Cite and briefly discuss the following references:
Strayhorn-Smith V, Tolley E, Demirkan K, Self T: Metered dose inhaler - spacer technique in hospitalized geriatric patients: Effect of patient education by a pharmacist. Hosp Pharm 35:162-4, 2000. (attached)
Sanchis J et al. Chest 2016 (August);150:394-406.
Dolovich M et al. Chest 2005;127:335-71.
Self TH et al. Ann Allergy Asthma Immunol 2016;117:101-2. (guidelines vs. manufacturer directions for MDI)
Thomas RM et al. Respir Care 2017;62:1412-
Blasi F et al. COPD 2016;13:367-71
Author:
We have made some adjustments in the “Introduction” section, in order to include the suggested references. Some of them were extremely important to reinforce and reorganise the rationale of the study, and we thank the reviewer for the important additional references.

Reviewer: 2
Reviewer Name: Richard Dekhuijzen
Institution and Country: Radboud umc, Nijmegen, the Netherlands
Competing Interests: None declared

Important clinical problem and well designed study.
Some suggestions:
1. Include the Critikal study (Crystyn 2017).
Author:
We thank the reviewer for this additional and important reference, and have included it in the “introduction” section (Page 4, 2nd paragraph). Furthermore, we have included critical errors as a new variable to be explored in the subgroup analysis, in the “statistical analysis” section (Page 8).

2. Explain why you chose this training method and schedule.
Author:
In order to better this important question, we have made some adjustments in the “Introduction” section (namely in Page 4, paragraphs 2, 3 and 4) in order to include some suggested references from reviewer no1. Some of these references are extremely important to reinforce and reorganise the rationale, mainly the aspect regarding this particular question. In addition, by establishing interim evaluations at 3 and 6 months, we may more adequately assess which of these may be the most optimal time point for inhaler review. Furthermore, such time-lapse was chosen in accordance with

the principal recommendations regarding general clinical control of patients (such as the GINA guidelines for Asthma).

3. Explain why you did not include electronic measures of adherence and inhalation technique.
Author:
We thank the reviewer for this very important request, and have included a paragraph in the Discussion section (Page 8). Electronic measures of adherence and inhalation techniques are a very useful approach to monitoring real world adherence to inhaler therapy. In fact, these electronic measures overcome the bias seen with self-report and other problems observed with objective medication checks such as pharmacy reconciliation, or prescription refill rates. However, most electronic measures of adherence do not measure timing of device activation but rather the overall number of activations performed. However, this measure does not mean that medication was taken on a regular basis (patients may just activate the inhaler several times, prior to handing over the device) (it is not until recently that a new device has been studied, which seems to overcome this problem, but it is not widely available – INCA device; Moran et al. Psychol Health 2017; 32: 10). Nevertheless, these devices are expensive and their use could not be implemented in our study. We therefore decided to use the best suitable tools in Portugal, which have, in fact, been used in many studies worldwide. In fact, the adherence questionnaire (BMQ) is a well-validated tool in several languages worldwide, and also in Portuguese. Furthermore, it is a very simple and easy method to detect non-adherence, which also allows separating sub-domains of adherence, which could be important in our patients. Thus, it is a good tool for assessing adherence in our study involving the general population of asthma and COPD patients, although we mention its limitations due to possible report biases.
Regarding inhalation technique, we decided to use regular checklists, since they are the most widely method used in other studies, thereby allowing further comparisons. They are also easy to use and allow detection of critical errors in each device.

Reviewer: 3
Reviewer Name: Valerie Press
Institution and Country: University of Chicago, USA
Competing Interests: None declared

This is an important topic. There are several concerns with this manuscript that need addressing:

1. Is the research question or study objective clearly defined?
The objective should be written more clearly to identify the PICO statement.
Author:
We thank the reviewer for this very important comment, and have re-written the “specific aims and hypothesis” section (Page 5), as follows:
“Our objective is to test the impact of an inhaler technique education programme on the risk of exacerbations in elderly patients with Asthma or COPD.
The main hypothesis is that regular education of inhaler technique using a placebo device-based approach in elderly patients can reduce the exacerbation risk by 50%.”

2. Is the abstract accurate, balanced and complete?
The abstract discussion states this is the 'first study to..."--it is not clear that is the case. A more thorough review of the literature could clarify how this study is different from other studies.
Author:
We thank the reviewer for this relevant remark. In fact we have removed the discussion section from the abstract, in order to fully comply with the BMJ Open guidelines. However, in reply to your

comment, we have added some new references to the “introduction” section that will reinforce the rationale of the study (Page 4, paragraph 4):
“Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk with inhaler education programmes, but none has yet addressed inhaler review alone or in a regular education programme”.
We have also re-written the sentence that you mention on the “discussion” section (Page 9), in order for the meaning to be better clarified, as follows:
“This is the first study designed to test this specific intervention on inhaler education performance in elderly patients with a regular education programme, and it was…”

This systematic review notes several studies with interventions linked to outcomes:
Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes; Omar Sharif Usmani1Email author, Federico Lavorini2, Jonathan Marshall3, William Christopher Nigel Dunlop3, Louise Heron4, Emily Farrington4 and Richard Dekhuijzen5 Respiratory Research201819:10
Author:
We thank the reviewer for this comment. This systematic review has included both interventional and observational studies, in order to identify and define critical errors and their association with clinical control We have collected the most relevant studies including interventions in elderly patients and included a brief discussion on them in the “introduction” section to improve our rationale (Page 4, paragraph 2). We have also included critical errors as a new variable to be explored in the subgroup analysis, in the “statistical analysis” section (Page 8).

3. Is the study design appropriate to answer the research question?
The use of usual care is tricky because it is not necessarily reproducible or quantifiable. Further, since inhaler misuse is so widespread, it is not clear that it is warranted. Did the authors consider a comparator arm other than control and how/why was usual care chosen?
Author:
We thank the reviewer for this very important observation. We should, thus, clarify that we believe that a pure placebo arm without any kind of intervention would be unethical, since there is enough evidence and recommendations on regular inhaler review as the standard of care. For that reason we could only use “usual care” as the main comparator or some other type of intervention. To control for potential bias in this arm of the study, we designed well-structured interim evaluations, including all endpoints just as in the intervention arm. Moreover, the “usual care” group will also receive usual education on inhaler technique at any moment, by the family doctor, and such procedures, if implemented as “usual care”, will be recorded in order to be controlled in statistical analysis. Moreover, establishing this “usual care” group will truly represent real-life practice, and thus, will enable precise conclusions about the effect of intervention. That is mentioned at the end of “Predictors/Intervention” section (Page 6), and is also explained at the middle of the “discussion” section (Page 9, 3rd paragraph).
In fact we have discussed the possibility of using several arms with different intervention types, but that would significantly increase sample size estimation of the trial, and would hamper its feasibility. Moreover, as there is growing evidence that a face-to-face placebo device training programme could be the most efficient approach, we decided to focus this study on that intervention alone. We believe the need now is to clarify the impact on inhaler performance itself and as an isolated factor, and that has not yet been reported.

Single -blinded may not accurately describe the study. While the patients were blinded (or masked which is a preferable term), were not others involved in the study also masked? The investigators? Statistician? Etc?
Author:

In fact the blinding applies to the secondary investigator (who will collect data from both groups) and also to the statistician. The primary investigator will only deliver inhaler education to the intervention arm, and for that reason, will not be blinded to allocation.
We clarified this in the main text, in the “discussion” section (Page 9; 2nd paragraph), with the following adjustment:
“On the other hand, the control group (“usual care”) will maintain their usual care in their own family doctors, who are completely free from any influence of the study design. For this reason, the control group (“usual care”) participants will not receive any intervention from the primary investigator. They will only contact with the secondary investigator in order to collect endpoints and outcome data, and who is completely blinded to randomisation. With this approach, the Hawthorne effect will not contaminate the control group, and will represent a real life usual care. On the other hand, the Data Safety Monitoring Board will be composed of two external investigators who will, together with the statistician, be blinded to the endpoints and outcomes (PROBE setting).”

4. Are the methods described sufficiently to allow the study to be repeated?
see above re: usual care
Author:
We thank the reviewer for this additional query. We will answer it in line with our reply to the previous question. We believe that the information provided about “usual care” definition is enough to be replicated.

7. If statistics are used are they appropriate and described fully?
The hypothesis is not written correctly--the null and alternative hypotheses are flipped.
The statistical analysis should include a GEE model to account for the longitudinal design, chi-square is not sufficient for this methodology.
Author:
We would like to thank the reviewer for this important comment. We have corrected the order of the hypotheses, which were indeed flipped.
We strongly agree upon adding a generalised estimating equation model, since that is a good alternative to the likelihood–based generalised linear mixed model to handle unmeasured dependence between outcomes, which is a very reasonable phenomenon to be taken into account here. We have added that on the “statistical analysis” section (Page 8).

8. Are the references up-to-date and appropriate?
see above for systematic review citation--there are significant numbers of intervention studies on this- the authors need to better clarify the novel aspects of their study.
Author:
As we have previously mentioned, we made significant changes in the “introduction” section, in order to include important references and strengthen the rationale of the study. We believe that these inclusions have made the study clearer and the references up-to-date and appropriate.

11. Are the discussion and conclusions justified by the results
see above for abstract
Author:
We have addressed this issue, which was also raised regarding the abstract, and corrected the text as requested. We now believe that the current version is more adequately written regarding this issue.

12. Are the study limitations discussed adequately?
Any issues that cannot be changed in the methods identified above should be addressed.
Author:

We thank the author for this comment. We have corrected all aspects mentioned above, introduced new aspects, and now believe that all major study limitations have been addressed.

15. Is the standard of written English acceptable for publication?
Several areas could be strengthened.
Author:
After the changes we have carried out during this review, we have submitted it to an Academic English editing service.

VERSION 2 – REVIEW

REVIEWER	Valerie Press University of Chicago, USA
REVIEW RETURNED	29-May-2018

GENERAL COMMENTS	1. The abstract needs to explain what the intervention is. 2. The intervention is described in the text and sites teach-to-goal but should cite the teach-to-goal literature (M. Paasche Orlow AJRCCM 2005; V Press JGIM 2011). It needs to be better described- are you starting by evaluating their baseline technique then teaching to goal? 3. The reasoning for the justification for why health care outcomes will be improved in TTG vs. UC at 3, 6, and 12 months need to be made. Both the AJRCM 2005 article above and V Press JGIM 2011 showed deceased acute care utilization by 30 days but not 90 days and V Press AnnalsATS 2016 showed that inhaler technique worsened by 30 days and health care outcomes were better for TTG at 30 days but not at 90 days. So there are not good data on the long lasting effect of TTG on skills. This is a critical factor that needs addressing. To be clear, in my prior questioning I was not recommending placebo--that would be entirely unethical and I don't even know what that would mean? here usual care is not ethical because it is not enough--usual care fails (see the 100's if not 1000's of articles showing this). Although 'real life' is important you will need to justify in the manuscript not just real life but how it is ethical. Having teach to goal vs. usual care or teach to goal vs. alternative intervention (even something like a handout) would have the same power. 4. The ethics of testing usual care needs to be justified. Since inhaler misuse is so pervasive and inhaler teaching is generally not provided or not provided well, how can you justify usual care as the comparator? 5. chi square is not sufficient for the longitudinal analysis you would need GEE or other statistical anlyses 6. you acknowledge video/web formats but do not reference the virtual teach-to-goal platform (V Press JACIP 2017; M Wu JACIP 2017) 7. It is still an overstatement to say this is the first study --'isolated manner' is not clear -what do you mean by that? 8. will you re-provide education after the one session? 9. I think there are many other limitations that need to be acknowledged--including usual care not be standardized 10. this statement is not correct:

	"Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk with inhaler education programmes, but none has yet addressed inhaler review alone or in a regular education programme [21 30-33]." Look up VG Press, read her articles and then rephrase this statement. Althuogh the setting is in the hosptial, patients have both asthma/COPD and include elderlypatients and is specifically on inhaler teaching using teach to goal and other methods. 11. please re-review prior comments in first review there are several things not fully addressed in this revision. 12. please re search the literature, there is a great deal of references missing some of which are noted above that directly influence this project 13. the hypothesis is not clear enough-- reduces risk at what time point? 3 months? adjusting for baseline misuse? GEE is now mentioned but not sufficiently; chi square is not sufficient for the primary analysis

VERSION 2 – AUTHOR RESPONSE

Answer to the Reviewer no3

Reviewer: 3

Reviewer Name: Valerie Press

Institution and Country: University of Chicago, USA

Competing Interests: None declared

1. The abstract needs to explain what the intervention is.

Author:

In order to clarify that we have re-written the following sentence on the “Methods and Analysis” section of the abstract:

“A multicentre single-blinded RCT will be set up, comparing an inhaler education programme with placebo-device training versus usual care, with a one-year follow-up, in elderly patients with Asthma or COPD”

2. The intervention is described in the text and sites teach-to-goal but should cite the teach-to-goal literature (M. Paasche Orlow AJRCCM 2005; V Press JGIM 2011). It needs to be better described- are you starting by evaluating their baseline technique then teaching to goal?

Author:

We thank the reviewer for such observation. We have added the references in the introduction section on the last paragraph. We also have clarified that issue on the “Predictors/Intervention” section and have re-written the second sentence:

“We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used, repeating all correct steps as many times as needed in order for patients to perform them correctly. This will be performed at each follow-up evaluation”

3. The reasoning for the justification for why health care outcomes will be improved in TTG vs. UC at 3, 6, and 12 months need to be made. Both the AJRCM 2005 article above and V Press JGIM 2011 showed deceased acute care utilization by 30 days but not 90 days and V Press Annals ATS 2016 showed that inhaler technique worsened by 30 days and health care outcomes were better for TTG at 30 days but not at 90 days. So there are not good data on the long lasting effect of TTG on skills. This is a critical factor that needs addressing. To be clear, in my prior questioning I was not recommending placebo--that would be entirely unethical and I don't even know what that would mean? here usual care is not ethical because it is not enough--usual care fails (see the 100's if not 1000's of articles showing this). Although 'real life' is important you will need to justify in the manuscript not just real life but how it is ethical. Having teach to goal vs. usual care or teach to goal vs. alternative intervention (even something like a handout) would have the same power.

Author:

Dear reviewer, we thank you for your observation and we are aware of such references. However, there are, in fact many studies addressing inhaler education programmes, but most of them, just like the one from V Press JGIM 2011, include more adult than elderly volunteers. There are few randomised studies addressing elderly patients exclusively, which is our main objective. As you may also notice, we cite 3 of these studies (Khdour MR 2009; Rootmensen GN 2008; Tommelein E 2014), which showed a decrease in exacerbation rates, after intervention, in different follow-up measures, such as 3, 6 and 12 months. That is why we chose to perform such interim evaluations.

To clarify this, and to reinforce our decision, we added the following sentence in the middle section of “Predictors/Intervention”:

“…to assess outcomes, since there is dissenting evidence about the timeline to achieve significant exacerbation risk reductions”

Regarding the issue about using “usual care” as the main comparator instead of using another intervention method (such as a leaflet/ handout), we believe that whatever the other method we would use, it would minimise the potential effect detection of our intervention (teach-to-goal placebo device training). This is particularly important, since all method have shown some degree of efficacy in clinically relevant outcomes, as we mentioned in the introduction. For instance, delivering written information can also lead to reductions in exacerbation rates in elderly patients (Khdour MR, 2009, Bourbeaus J 2003). That is why we believe the only way to test the true effect of a placebo device training programme is using “usual care” as comparator. Moreover, all of the randomised studies that we mention also used “usual care”, which will be important when comparing them with our results. We have, however, guaranteed that all participants in “usual care” arm will receive inhaler education if they show any event during the follow-up, if they ask for that, or if their own family doctor decides so.

To support and justify this, we have added this rationale in the beginning of “ETHICS AND DISSEMINATION” section:

“We decided to use “usual care” as the main comparator instead of another intervention method, since all methods have shown some degree of efficacy in clinically relevant outcomes, as previously mentioned. Using other education method would minimise the effect detection of our intervention. Moreover, all of the randomised studies performed in elderly patients also used “usual care”, which will be important when comparing them with our results.”

4. The ethics of testing usual care needs to be justified. Since inhaler misuse is so pervasive and inhaler teaching is generally not provided or not provided well, how can you justify usual care as the comparator?

Author:

We believe the previous answer applies here.

5. chi square is not sufficient for the longitudinal analysis you would need GEE or other statistical analyses.

Author:

This was already corrected in the first review round. We have added the following sentence at the end of the “statistical analysis”:

“As an alternative approach, generalised estimating equation models will be used to handle unmeasured dependence between outcomes.”

6. you acknowledge video/web formats but do not reference the virtual teach-to-goal platform (V Press JACIP 2017; M Wu JACIP 2017)

Author:

We thank the reviewer for that suggestion. We have added such information in the introduction.

7. It is still an overstatement to say this is the first study --'isolated manner' is not clear -what do you mean by that?

Author:

Most randomised studies performed in elderly patients addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers. And none have tested yet, a placebo device training programme alone.

To clarify this, we have re-written the first sentence of the “STRENGTHS AND LIMITATIONS” section:

“This is the first study to address a specific placebo device education programme alone, without any other aspects, in elderly patients with Asthma or COPD.”

We also have re-written the following sentence in the 3rd paragraph of the “Inhaler technique” sub-section of “introduction”:

“Some of these studies have shown significant reductions in exacerbation risk with inhaler education programmes, but most of them addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers.”

8. will you re-provide education after the one session?

Author:

Yes, one of the objectives is precisely to test the efficacy of a regular teaching programme. As mentioned above, we have clarified that issue in the “Predictors/Intervention” section and have re-written the second sentence:

“We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used, repeating all correct steps as many times as needed in order for patients to perform them correctly. This will be performed at each follow-up evaluation”

9. I think there are many other limitations that need to be acknowledged--including usual care not be standardized

Author:

“Usual care” will be evaluated at every follow-up visits, just like in the intervention group, regarding the same endpoints. However, we decided not to standardise any kind of intervention in these patients, in order to maintain the true real care effect in this arm of the study.

10. this statement is not correct:

"Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk with inhaler education programmes, but none has yet addressed inhaler review alone or in a regular education programme [21 30-33]."

Look up VG Press, read her articles and then rephrase this statement. Althuogh the setting is in the hosptial, patients have both asthma/COPD and include elderlypatients and is specifically on inhaler teaching using teach to goal and other methods.

Author:

Dear reviewer, the study that you suggest includes participants with a mean age of 51.7 years, and that is why we have decided not to include such reference as being a study on elderly patients. We have added such reference in the paragraph after this one, and re-written the following sentence:

“Nevertheless, some studies including also adult patients suggest that the most efficient method seems to be using a teach-to-goal approach with placebo device demonstration and training provided in person”

11. please re-review prior comments in first review there are several things not fully addressed in this revision.

Author:

Dear reviewer, we believe we have answered all the suggestions and remarks presented in the previous review. If there is any other concern you may have, besides the ones here presented, please inform us.

12. please re search the literature, there is a great deal of references missing some of which are noted above that directly influence this project

Author:

The main text has already more than 60 references, including the most important studies addressing this issue. To avoid overcoming the journal limits furthermore, we decided to only add the references we already have mentioned above.

“Our.”

13. the hypothesis is not clear enough-- reduces risk at what time point? 3 months? adjusting for baseline misuse? GEE is now mentioned but not sufficiently; chi square is not sufficient for the primary analysis.

Author:

Dear reviewer, the main hypothesis refers to the end of the follow-up, after one year. To clarify that we have re-written the main hypothesis to the following:

“The main hypothesis is that regular education of inhaler technique using a placebo device-based approach in elderly patients can reduce the exacerbation risk by 50% after a one-year follow-up.”

In addition, and regarding our statistical plan, as you may notice almost all similar studies used the same statistical approaches that we mention. In fact, we have decided to include some quite robust methods to adjust non-regular distributions and patterns, such as GEE, mixed effects models for repeated measures and Poisson regression models. None of the similar studies has addressed the outcomes with such robust approaches.

Nevertheless, a professional statistician graduated by the Harvard medical School reviewed our statistical plan, and we decided to reorganise the “Statistical Analysis” section, in order to make it clearer.

VERSION 3 – REVIEW

REVIEWER	Valerie Press University of Chicago, USA
REVIEW RETURNED	05-Jul-2018

GENERAL COMMENTS	re Q1/response: Abstract- when I suggested explaining the intervention, I meant explain the actual intervention-- "inhaler education programme" is not an explanation of what the intervention is, just that there was some sort of programme that was different from usual care.

	re Q2/response: mostly responsive changes--but it is still not clear that you understand what teach to goal is as it is not explicitly described in this sentence--did the patients at any time in the 'as many times as needed' teachback? how was 'as many times as needed' assessed? if you are going to call your intervention teach to goal, then it needs to actually be teach to goal and be described accurately; if it is not teach to goal, then do not call it teach to goal. If it is teach to goal-- use this information to address Q1 above. Q3/response: You are still not addressing the issue here. Your response addresses that you think your elderly population (the age definition of this needs to be added to abstract by the way) is different from other programs identified by the reviewer--but your 3 examples cited for 'elderly' do not have the same age criteria as your study. Do your other references that focus on elderly patients only provide inhaler teaching (no) and do they use the teach-go-goal intervention (none of them state what their education is)?--therefore, can you use them as comparators? Could their effects on exacerbation be attributed to other parts of their intervention? These studies did not use the same age criteria as you did, did not just focus on inhaler teaching, did not necessarily use the inhaler education you provided, provided additional sessions and/or program elements. Therefore, this response is not sufficient to justify why your inhaler education program would by itself without other components lead to decreased acute care utilization given the information in my prior review about inhaler education x 1 session not leading to sustained skills at 2 weeks (Paasche-Orlow AJRCCM) or 30 days (Press AnnalsATS) and only showing decreased acute care use at 30 days but not at 90 days (Press AnnalsATS). Notes from your references: Tommelein E 2014: This has more than inhaler education, uses two sessions, the inhaler education is not teach-to-goal--and the age group if over 50 years (not 65 years as in your study). Khdour MR 2009: This was also an intervention that included more than inhaler teaching including an action plan; the mean age was 67-but there is no clear identification that this study was intended for 'elderly' patients and almost certainly included a significant proportion of patients <65 years; they received reinforcement every 6 months and received telephone calls. Rootmensen GN 2008: multi-component program including pulmonary physician, medication teaching was only one of many parts of this study and what the teaching was is not provided; the mean age is 60/61 so again, not the same age group. Regarding usual care-- creating a scenario where you want the most effect is not a sufficient justification for using usual care, nor is 'others did it' if there is ample evidence to suggest that usual care is not sufficient care. Your response says that "all methods have shown some degree of efficacy" --you mean the usual care would be included in this? Is this true? What if usual care is no care (no teaching)--as is common? This response is insufficient currently to address my concern. Q4/response--see above. Q5/response-fine. Q6/response-fine.

	Q7/response--given your response here, you need to significantly consider whether you can hypothesize that your particular program can impact health outcomes--since you are saying there are no comparators. The closest comparators (inhaler only) are in younger patients but were not successful, why would your elderly population do better? What are the studies that have shown "significant reductions in exacerbation risk with inhaler education programmes"? Q8/response- see item #2 above re ensuring that your instruction actually is teach to goal. This sentence here about follow-up visits needs to clearly state at what time points. You may be able to use the multiple education sessions in conjunction with GOLD guidelines and Paasche Orlow/Press literature on inhaler education programs to justify your hypothesis. 9/response- you do not acknowledge that this study has many other limitations than what is in your manuscript; the limitations around usual care are 1) it is not sufficient for good patient outcomes and is questionable as a comparator at all and 2) that it is not standardized-- even if you use usual care you need to adequately address these limitations in your limitations section and note the effects these limitations could have on your results/findings/conclusions. Q10/response- ok -but see notes above Q11- see notes throughout this review q12-ok if there are limits on references but be certain you have chosen the best 60 q13-the hypothesis should meet PICOTS criteria--population, intervention, comparator, timing, setting: Something like: "We hypothesize that among elderly patients with COPD our placebo device-based educational provided [where] [how often] {?teach to goal] intervention will reduce exacerbation risk by 50% compared to usual care at one years post the initial educational session."

VERSION 3 – AUTHOR RESPONSE

Answer to the Reviewer no3

Reviewer: 3
Reviewer Name: Valerie Press
Institution and Country: University of Chicago, USA
Competing Interests: None declared

Q1.
ROUND2 - The abstract needs to explain what the intervention is.
Author:
In order to clarify that we have re-written the following sentence on the “Methods and Analysis” section of the abstract:

“A multicentre single-blinded RCT will be set up, comparing an inhaler education programme with placebo-device training versus usual care, with a one-year follow-up, in elderly patients with Asthma or COPD”
ROUND3 – Abstract- when I suggested explaining the intervention, I meant explain the actual intervention-- "inhaler education programme" is not an explanation of what the intervention is, just that there was some sort of programme that was different from usual care.
Author:
Dear reviewer, he have added to that sentence the following:
“A multicentre single-blinded RCT will be set up, comparing an inhaler education programme with a teach-to-goal placebo-device training versus usual care”

Q2.
ROUND2 - The intervention is described in the text and sites teach-to-goal but should cite the teach-to-goal literature (M. Paasche Orlow AJRCCM 2005; V Press JGIM 2011). It needs to be better described- are you starting by evaluating their baseline technique then teaching to goal?
Author:
We thank the reviewer for such observation. We have added the references in the introduction section on the last paragraph. We also have clarified that issue on the “Predictors/Intervention” section and have re-written the second sentence:
“We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used, repeating all correct steps as many times as needed in order for patients to perform them correctly. This will be performed at each follow-up evaluation”
ROUND3 – mostly responsive changes--but it is still not clear that you understand what teach to goal is as it is not explicitly described in this sentence--did the patients at any time in the 'as many times as needed' teachback? how was 'as many times as needed' assessed? if you are going to call your intervention teach to goal, then it needs to actually be teach to goal and be described accurately; if it is not teach to goal, then do not call it teach to goal. If it is teach to goal-- use this information to address Q1 above.
Author:
Dear reviewer, we have clarified that in the following sentence:
“We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used with correction of identified errors. Then we will ask patients to demonstrate the inhaler technique, and again, committed errors will be corrected by demonstration. We will repeat all correct steps as many times as needed in order for patients to perform them correctly”

Q3.
ROUND2 - The reasoning for the justification for why health care outcomes will be improved in TTG vs. UC at 3, 6, and 12 months need to be made. Both the AJRCM 2005 article above and V Press JGIM 2011 showed deceased acute care utilization by 30 days but not 90 days and V Press Annals ATS 2016 showed that inhaler technique worsened by 30 days and health care outcomes were better for TTG at 30 days but not at 90 days. So there are not good data on the long lasting effect of TTG on skills. This is a critical factor that needs addressing. To be clear, in my prior questioning I was not recommending placebo--that would be entirely unethical and I don't even know what that would mean? here usual care is not ethical because it is not enough--usual care fails (see the 100's if not 1000's of articles showing this). Although 'real life' is important you will need to justify in the manuscript not just real life but how it is ethical. Having teach to goal vs. usual care or teach to goal vs. alternative intervention (even something like a handout) would have the same power.
Author:
Dear reviewer, we thank you for your observation and we are aware of such references. However, there are, in fact many studies addressing inhaler education programmes, but most of them, just like

the one from V Press JGIM 2011, include more adult than elderly volunteers. There are few randomised studies addressing elderly patients exclusively, which is our main objective. As you may also notice, we cite 3 of these studies (Khdour MR 2009; Rootmensen GN 2008; Tommelein E 2014), which showed a decrease in exacerbation rates, after intervention, in different follow-up measures, such as 3, 6 and 12 months. That is why we chose to perform such interim evaluations.
To clarify this, and to reinforce our decision, we added the following sentence in the middle section of "Predictors/Intervention":
"…to assess outcomes, since there is dissenting evidence about the timeline to achieve significant exacerbation risk reductions"
Regarding the issue about using "usual care" as the main comparator instead of using another intervention method (such as a leaflet/ handout), we believe that whatever the other method we would use, it would minimise the potential effect detection of our intervention (teach-to-goal placebo device training). This is particularly important, since all method have shown some degree of efficacy in clinically relevant outcomes, as we mentioned in the introduction. For instance, delivering written information can also lead to reductions in exacerbation rates in elderly patients (Khdour MR, 2009, Bourbeaus J 2003). That is why we believe the only way to test the true effect of a placebo device training programme is using "usual care" as comparator. Moreover, all of the randomised studies that we mention also used "usual care", which will be important when comparing them with our results. We have, however, guaranteed that all participants in "usual care" arm will receive inhaler education if they show any event during the follow-up, if they ask for that, or if their own family doctor decides so.
To support and justify this, we have added this rationale in the beginning of "ETHICS AND DISSEMINATION" section:
"We decided to use "usual care" as the main comparator instead of another intervention method, since all methods have shown some degree of efficacy in clinically relevant outcomes, as previously mentioned. Using other education method would minimise the effect detection of our intervention. Moreover, all of the randomised studies performed in elderly patients also used "usual care", which will be important when comparing them with our results."
ROUND3 – You are still not addressing the issue here. Your response addresses that you think your elderly population (the age definition of this needs to be added to abstract by the way) is different from other programs identified by the reviewer--but your 3 examples cited for 'elderly' do not have the same age criteria as your study. Do your other references that focus on elderly patients only provide inhaler teaching (no) and do they use the teach-go-goal intervention (none of them state what their education is)?--therefore, can you use them as comparators? Could their effects on exacerbation be attributed to other parts of their intervention? These studies did not use the same age criteria as you did, did not just focus on inhaler teaching, did not necessarily use the inhaler education you provided, provided additional sessions and/or program elements. Therefore, this response is not sufficient to justify why your inhaler education program would by itself without other components lead to decreased acute care utilization given the information in my prior review about inhaler education x 1 session not leading to sustained skills at 2 weeks (Paasche-Orlow AJRCCM) or 30 days (Press AnnalsATS) and only showing decreased acute care use at 30 days but not at 90 days (Press AnnalsATS).
Notes from your references:
Tommelein E 2014: This has more than inhaler education, uses two sessions, the inhaler education is not teach-to-goal--and the age group if over 50 years (not 65 years as in your study).
Khdour MR 2009: This was also an intervention that included more than inhaler teaching including an action plan; the mean age was 67-but there is no clear identification that this study was intended for 'elderly' patients and almost certainly included a significant proportion of patients <65 years; they received reinforcement every 6 months and received telephone calls.
Rootmensen GN 2008: multi-component program including pulmonary physician, medication teaching was only one of many parts of this study and what the teaching was is not provided; the mean age is 60/61 so again, not the same age group.
Regarding usual care-- creating a scenario where you want the most effect is not a sufficient justification for using usual care, nor is 'others did it' if there is ample evidence to suggest that usual

care is not sufficient care. Your response says that "all methods have shown some degree of efficacy" --you mean the usual care would be included in this? Is this true? What if usual care is no care (no teaching)--as is common? This response is insufficient currently to address my concern.
Author:
Dear reviewer, we have corrected the abstract:
“in patients above 65 years of age with Asthma or COPD”
Regarding the cited references that we have mentioned, we totally agree with your observations. It is, in fact, due to that inconsistency in the literature that our trial is needed and of major importance. We believe we will contribute towards clarifying those issues. For that reason, we have corrected the following information in the “ethics and dissemination” section:
“We decided to use “usual care” as the main comparator instead of another intervention method, since all interventional methods have shown some degree of efficacy in clinically relevant outcomes, as previously mentioned. We thus believe that comparing with other education methods would minimise the effect detection of our teach-to-goal placebo-device intervention. Moreover, all of the randomised studies that included mostly elderly patients also used “usual care” as a comparator, which will be important when comparing them with our results. However, we highlight the fact that those studies did not use the same age criteria as we are using, since they also included non-elderly adult patients in their samples. In addition, they did not just focus on inhaler teaching, since they provided additional sessions with other program elements, such as self-management care. There is, thus, insufficient evidence about the efficacy of inhaler education as an isolated intervention, and for that reason, our approach will be novel and will significantly contribute towards clarifying those issues.”
Moreover, we have added the following information in the “predictors/intervention” section, to clarify the controlling factor for usual care:
“At any appointment, if the patient asks for or if the clinician decides to teach inhaler technique, that will be recorded, since it will be important to analyse and control for the true effect size of intervention.”

Q4.
ROUND2 - The ethics of testing usual care needs to be justified. Since inhaler misuse is so pervasive and inhaler teaching is generally not provided or not provided well, how can you justify usual care as the comparator?
Author:
We believe the previous answer applies here.
ROUND3 – see above

Q5.
ROUND2 - chi square is not sufficient for the longitudinal analysis you would need GEE or other statistical analyses.
Author:
This was already corrected in the first review round. We have added the following sentence at the end of the “statistical analysis”:
“As an alternative approach, generalised estimating equation models will be used to handle unmeasured dependence between outcomes.”
ROUND3 – fine

Q6.
ROUND2 - you acknowledge video/web formats but do not reference the virtual teach-to-goal platform (V Press JACIP 2017; M Wu JACIP 2017)
Author:

We thank the reviewer for that suggestion. We have added such information in the introduction.
ROUND3 – fine

Q7.
ROUND2 - It is still an overstatement to say this is the first study --'isolated manner' is not clear -what do you mean by that?
Author:
Most randomised studies performed in elderly patients addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers. And none have tested yet, a placebo device training programme alone.
To clarify this, we have re-written the first sentence of the “STRENGTHS AND LIMITATIONS” section:
“This is the first study to address a specific placebo device education programme alone, without any other aspects, in elderly patients with Asthma or COPD.”
We also have re-written the following sentence in the 3rd paragraph of the “Inhaler technique” sub-section of “introduction”:
“Some of these studies have shown significant reductions in exacerbation risk with inhaler education programmes, but most of them addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers.”
ROUND3 – given your response here, you need to significantly consider whether you can hypothesize that your particular program can impact health outcomes--since you are saying there are no comparators. The closest comparators (inhaler only) are in younger patients but were not successful, why would your elderly population do better? What are the studies that have shown "significant reductions in exacerbation risk with inhaler education programmes"?
Author:
Dear reviewer, you are completely right. Our sentence is not clear enough and would suggest a wrong claim. We have corrected it, based upon the findings of the studies whose references are given, namely the RCT by Tommelein, which showed in mostly elderly patients (mean age = 68+9.6 yr; although inclusion age was above 50 years of age, as you previously mentioned) that, at the end of their study, there was a significant decrease in the estimated mean severe exacerbation rate in the intervention (various approaches) group versus the usual care group:
“Some of these studies have shown significant reductions in exacerbation risk, but most of them addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers.”

Q8.
ROUND2 - will you re-provide education after the one session?
Author:
Yes, one of the objectives is precisely to test the efficacy of a regular teaching programme. As mentioned above, we have clarified that issue in the “Predictors/Intervention” section and have re-written the second sentence:
“We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used, repeating all correct steps as many times as needed in order for patients to perform them correctly. This will be performed at each follow-up evaluation”
ROUND3 – see item #2 above re ensuring that your instruction actually is teach to goal. This sentence here about follow-up visits needs to clearly state at what time points. You may be able to use the multiple education sessions in conjunction with GOLD guidelines and Paasche Orlow/Press literature on inhaler education programs to justify your hypothesis.
Author:

Dear reviewer, we have clarified the time point for follow-up visits, in the following sentence of "predictor/intervention" section:
"This intervention will be performed at baseline, 3 and 6 months. Outcomes will be assessed at baseline and after 3, 6 and 12 months, since there is dissenting evidence about the best timeline to achieve significant exacerbation risk reductions"

Q9.
ROUND2 - I think there are many other limitations that need to be acknowledged--including usual care not be standardized
Author:
"Usual care" will be evaluated at every follow-up visits, just like in the intervention group, regarding the same endpoints. However, we decided not to standardise any kind of intervention in these patients, in order to maintain the true real care effect in this arm of the study.
ROUND3 – you do not acknowledge that this study has many other limitations than what is in your manuscript; the limitations around usual care are 1) it is not sufficient for good patient outcomes and is questionable as a comparator at all and 2) that it is not standardized-- even if you use usual care you need to adequately address these limitations in your limitations section and note the effects these limitations could have on your results/findings/conclusions.
Author:
Dear reviewer, in order to recognize those limitations in the manuscript, we have added that in the "discussion" section. However, we maintain our intention to use usual care as our main comparator for all the reasons we have mentioned.
"Using usual care as the comparator arm also brings some limitations to consider, because it is not a perfect comparator due to its nature. It is not sufficient for good patient outcomes and it is not standardized. This aspect is due, for instance, to the fact that patients on usual care can receive interventions on inhaler education and self-management tools from other uncontrolled sources. To overcome that we will retrospectively query patients in this arm and their own family doctor for any type of interventions that may have been delivered during the study period."

Q10.
ROUND2 - this statement is not correct:
"Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk with inhaler education programmes, but none has yet addressed inhaler review alone or in a regular education programme [21 30-33]."
Look up VG Press, read her articles and then rephrase this statement. Althuogh the setting is in the hosptial, patients have both asthma/COPD and include elderlypatients and is specifically on inhaler teaching using teach to goal and other methods.
Author:
Dear reviewer, the study that you suggest includes participants with a mean age of 51.7 years, and that is why we have decided not to include such reference as being a study on elderly patients. We have added such reference in the paragraph after this one, and re-written the following sentence:
"Nevertheless, some studies including also adult patients suggest that the most efficient method seems to be using a teach-to-goal approach with placebo device demonstration and training provided in person"
ROUND3 – ok -but see notes above

Q11.

ROUND2 - please re-review prior comments in first review there are several things not fully addressed in this revision.
Author:
Dear reviewer, we believe we have answered all the suggestions and remarks presented in the previous review. If there is any other concern you may have, besides the ones here presented, please inform us.
ROUND3 – see notes throughout this review

Q12.
ROUND2 - please re search the literature, there is a great deal of references missing some of which are noted above that directly influence this project
Author:
The main text has already more than 60 references, including the most important studies addressing this issue. To avoid overcoming the journal limits furthermore, we decided to only add the references we already have mentioned above.
ROUND3 – ok if there are limits on references but be certain you have chosen the best 60

Q13.
ROUND2 - the hypothesis is not clear enough-- reduces risk at what time point? 3 months? adjusting for baseline misuse? GEE is now mentioned but not sufficiently; chi square is not sufficient for the primary analysis.
Author:
Dear reviewer, the main hypothesis refers to the end of the follow-up, after one year. To clarify that we have re-written the main hypothesis to the following:
“The main hypothesis is that regular education of inhaler technique using a placebo device-based approach in elderly patients can reduce the exacerbation risk by 50% after a one-year follow-up.”
In addition, and regarding our statistical plan, as you may notice almost all similar studies used the same statistical approaches that we mention. In fact, we have decided to include some quite robust methods to adjust non-regular distributions and patterns, such as GEE, mixed effects models for repeated measures and Poisson regression models. None of the similar studies has addressed the outcomes with such robust approaches.
Nevertheless, a professional statistician graduated by the Harvard medical School reviewed our statistical plan, and we decided to reorganise the “Statistical Analysis” section, in order to make it clearer.
ROUND3 – the hypothesis should meet PICOTS criteria--population, intervention, comparator, timing, setting: Something like: "We hypothesize that among elderly patients with COPD our placebo device-based educational provided [where] [how often] {?teach to goal] intervention will reduce exacerbation risk by 50% compared to usual care at one years post the initial educational session."
Author:
Dear reviewer, we have re-written that:
“The main hypothesis is that, among elderly patients with Asthma or COPD, a regular education of inhaler technique using a teach-to-goal placebo device-based approach, and delivered by family doctors at baseline, 3 and 6 months can reduce the exacerbation risk by 50% after a one-year follow-up, when compared to usual care.”

VERSION 4 – REVIEW

REVIEWER	Valerie Press University of Chicago, USA
REVIEW RETURNED	17-Sep-2018

GENERAL COMMENTS	This is NOT the first study to test the teach-to-goal intervention in older patients as a stand alone. Other studies have studied this though some patients were not 'older', many were. This sentence remains misleading.

VERSION 4 – AUTHOR RESPONSE

Answer to the Reviewer no3

Reviewer: 3
Reviewer Name: Valerie Press
Institution and Country: University of Chicago, USA
Competing Interests: None declared

ROUND 4:
This is NOT the first study to test the teach-to-goal intervention in older patients as a stand alone. Other studies have studied this though some patients were not 'older', many were. This sentence remains misleading.

Author:
Dear reviewer, we have re-written that on both “STRENGTHS AND LIMITATIONS OF THIS STUDY” and “DISCUSSION” sections, in order to clarify the originality of this study:
“This study is innovative because it includes exclusively elderly patients with Asthma or COPD, addressing, in a one-year follow-up, a specific placebo device education programme, alone, without any other aspects.”