PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	In patients with severe uncontrolled asthma, does knowledge of adherence and inhaler technique using electronic monitoring improve clinical decision making? A Protocol for a randomised controlled trial.
AUTHORS	Mokoka, Matshediso; Lombard, Lorna; MacHale, Elaine; Walsh, Joanne; Cushen, Breda; Sulaiman, Imran; Mc Carthy, Damien; Boland, Fiona; Doyle, Frank; Hunt, Eoin; Murphy, Desmond; Faul, John; Butler, Marcus; Hetherington, Kathy; FitzGerald, J Mark; Van Boven, Job; Heaney, Liam; Reilly, Richard; Costello, Richard

VERSION 1 - REVIEW

REVIEWER	Giorgio Walter Canonica Personalized Medicine Clinic: Asthma & Allergy - Humanitas Clinical and Research Center, Department of Biomedical Science, Humanitas University –Rozzano (Milano), Italy
REVIEW RETURNED	29-Dec-2016

GENERAL COMMENTS	This paper describes the protocol of a multi-centre, parallel group, prospective randomised controlled study aimed to verify if knowledge of adherence and inhaler technique improve clinical decision making. The protocol is clear and methodologically correct. The study will provide useful data for better menage patients with severe uncontrolled asthma.

REVIEWER	Konstantinos Votis Information Technologies Institute, Centre of Research & Technology - Hellas Greece
REVIEW RETURNED	19-Jan-2017

GENERAL COMMENTS	---------- Comments regarding the review checklist ---------- 4. Appendices are not included in the submission as they are referred in the text of the study 6. The proposed protocol is not clearly defined without details about the clinical decision pathway, the assessment of primary and secondary outcomes, the proposed statistical analysis design, indicative model of informed consent, etc. 7. The referenced appendix with the statistical analysis plan is not contained in the submission. 12. Study limitations are not described in a specific section with the

	only exception of the one limitation that is provided in page 4. --- Comments regarding the submitted study --- The current study proposes a protocol for a randomized controlled trial of clinical decision making versus knowledge of adherence and inhaler technique using an electronic monitoring device. More specifically the proposed protocol focuses primarily on two fundamental components of effective clinical support of patients, namely, the selection of the appropriate medication levels by the healthcare professionals and the maintenance of medication adherence by patients. Furthermore, the protocol has been designed to include a range of secondary outcomes covering clinical and economic outcomes as well as patient reported issues. Unfortunately the article appendices and figures are not included in the submission and as such it is suggested that the submission is revised and the full list of appendices with protocol details is included in the newer version. After the introduction of the problems and challenges that are stemming from the difficulties to accurate assess and control inhaled medication adherence for asthma patients, the authors provide the results of a related studies outlining the need and the requirements for the proposed study protocol. Unfortunately there is no comparison with previous work done in this field and how the current protocol addresses important components of the overall healthcare process that have not been covered by other protocols. It is suggested that the authors add one paragraph to the introduction when the current study is directly compared with similar studies such as the following publications: O'Dwyer, Susan Mary, et al. "The effect of providing feedback on inhaler technique and adherence from an electronic audio recording device, INCA®, in a community pharmacy setting: study protocol for a randomised controlled trial." Trials 17.1 (2016): 1. Sulaiman, Imran, et al. "A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in patients with poorly controlled severe asthma." BMJ open 6.1 (2016): e009350. Furthermore, the introduction should be clearly defining that the INCATM device can be used with only a specific type of inhalers, namely Diskus Dry Powder Inhaler. Unfortunately there is only one short mention in this requirement in the entire document (Page 8). Furthermore, a paragraph with a short introduction to other modern smart inhaler monitoring devices is also suggested that could provide a better understanding of the great technological and clinical research potential of this field. In page 5, the reference 10 is referring to a protocol rather that the analysis of digital audio recordings for the assessment of adherence and technique of inhaler use. In page 7 the referred Figure 1 is not available in the submission. In page 8, it is mentioned that the maintenance of actual adherence

	is defined as " the combination of the time of use, interval between doses and critical errors; which is calculated as the area under the curve". Please try to rephrase and provide details In page 10, the section "INCA device and analysis of audio data" should underline the fact that the device can be used for only a specific type of inhalers (Diskus Dry Powder Inhaler). Furthermore, the accuracy and precision of the audio analysis outputs of the device should be mentioned and references to related publications should be included. It would also be helpful to mention whether the automated outputs of the device were reviewed by a trained healthcare professional for evaluation. In page 10, the link to www.randomisation.com is not correct. Furthermore, it is suggested to include the link as a reference rather than a inline inclusion of the website address. In page 12 the details provided in the caption of the table are suggested to an additional table line under the timing of visits indicating whether type of the visit. In page 13, and the entire document in general, the referred appendices are not included in the submission. Please include all appendices in the following versions of the document. It is suggested that the inline reference to the educational video is changed to a formal reference with details about the publisher, the title of the video and its publication date. It is also suggested to publish the video from an institutional rather a personal account. Finally, the explanation of FeNO archetype was provided in page 11. A careful review to avoid multiple explanations of acronyms is therefore suggested. In Page 22, publications 25-28 are not referred within the text. One final suggestion to the authors is the rephrasing of the tile. --- Comments regarding SPIRIT 2013 Checklist --- Item 8: The figure and appendices are not included in the submission Item 11b: criteria to discontinuing or modifying interventions are not included despite the fact that in page 18 it is mentions the possibility of serious adverse events. A more detailed description is suggested as it also connected with items 21b and 22. Item 18a is addressed in pages 10-14 and not in pages 9-13 Item 19 is addressed in pages 18-20 and not in pages 18-19 Item 21b should be addressed in the submission. Please see comments for Item 11b. Item 22 should be addressed in the submission. Please see comments for Item 11b. Item 27 is addressed in pages 18-20 and not in pages 18-19

	Item 28 is addressed in page 18 and not in page 14 Item 28 is addressed in pages 18-20 and not in page 14 Item 29 is addressed in pages 18-20 and not in page 14 Item 30 is not addressed. Very short description should be included in regards to the final row of Table 2 (page 13) “Dispense prescription for inhaler without INCA device” Item 31a is addressed in page 20 rather than page 14 Item 15, 18a, 20a, 20b, 20c, 32 and 33 are not addressed within the submission as already mentioned above appendices are missing.

REVIEWER	Robert Morton University of Sheffield UK
REVIEW RETURNED	02-Feb-2017

GENERAL COMMENTS	An excellent study protocol investigating a very important issue. A few minor points which would in my opinion improve the study: Methods Could the authors give more detail about the primary outcome, and the definition of "appropriate" treatment. I presume this means appropriate with respect to the adherence level, but it would be useful for this to be clarified. My major concern with this study is that the control group is receiving many additional interventions and added clinician attention which is far removed from standard clinical practice. It is likely that with these additional interventions, both electronically monitored adherence and asthma control will be improved. With this increase in the control group, a between group difference for many of the specified outcomes may difficult to ascertain. Would it be reasonable to maintain care in the control group as close to "standard care" as possible? With the current protocol, the difference between 2 educational interventions is being compared, rather than comparing an innovative novel approach, to a true control group of standard existing care. Also, I think the follow up period of 32 weeks is too short to realise the true potential and effect of this promising intervention. Previous adherence studies have shown that the feedback of electronically monitored adherence data has a more enhanced effect compared to control over a prolonged period of time. At six months previous studies have failed to show a difference between groups, primarily because of the strong Hawthorne effect in the control groups. By one year, feedback of data and associated habit formation and behaviour change have led to a sustained improvement in adherence rates, which have waned in control groups. A study of this size and significant investment should aim to follow up participants for a year to determine the full effect and sustainability of the intervention.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This paper describes the protocol of a multi-centre, parallel group, prospective randomised controlled study aimed to verify if knowledge of adherence and inhaler technique improve clinical decision making.
The protocol is clear and methodologically correct.
The study will provide useful data for better manage patients with severe uncontrolled asthma.

Response: Many thanks, we appreciate your comments.

Reviewer: 2

Comments regarding the review checklist
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4. Appendices are not included in the submission as they are referred in the text of the study

Response: The appendices describing the clinical decision pathway, the assessment of primary and secondary outcomes, and the proposed statistical analysis plan were submitted with the manuscript as a separate tiff-formatted file, named 'figures and appendices'. We do appreciate that it would be difficult to read the manuscript if they are not accessible.The appedinces are now included as a separate file named appendices 1-10.

6. The proposed protocol is not clearly defined without details about the clinical decision pathway, the assessment of primary and secondary outcomes, the proposed statistical analysis design, indicative model of informed consent, etc.

Response: Figures and appendices (with details about the clinical decision pathway, the assessment of primary and secondary outcomes, the proposed statistical analysis plan) were submitted with the manuscript as a separate tiff-formatted file, named 'figures and appendices'. We do appreciate that it would be difficult to read the manuscript if they are not accessible. The study limitations have been reviewed and described as above. The appedinces are now included as a separate file named appendices 1-10. The figure 1 is now included as a separate file named Figure1 JPEG.

7. The referenced appendix with the statistical analysis plan is not contained in the submission.
Response: The referenced appendix with details of the proposed statistical analysis plan was submitted with the manuscript as a separate tiff-formatted file named 'figures and appendices'. See appendix 10 in the file named appendices 1-10.

12. Study limitations are not described in a specific section with the only exception of the one limitation that is provided in page 4.

Response:Study limitations have been described further, see page 4 of the manuscript.

Comments regarding the submitted study

The current study proposes a protocol for a randomized controlled trial of clinical decision making

versus knowledge of adherence and inhaler technique using an electronic monitoring device. More specifically the proposed protocol focuses primarily on two fundamental components of effective clinical support of patients, namely, the selection of the appropriate medication levels by the healthcare professionals and the maintenance of medication adherence by patients. Furthermore, the protocol has been designed to include a range of secondary outcomes covering clinical and economic outcomes as well as patient reported issues.

Unfortunately, the article appendices and figures are not included in the submission and as such it is suggested that the submission is revised and the full list of appendices with protocol details is included in the newer version.

Response: Figures and appendices (with details about the clinical decision pathway, the assessment of primary and secondary outcomes, the proposed statistical analysis plan) were submitted with the manuscript as a separate tiff-formatted file, named 'figures and appendices'. We do appreciate that it would be difficult to read the manuscript if they are not accessible.
The appedinces are now included as a separate file named appendices 1-10. The figure 1 is now included as a separate file named Figure1 JPEG.

After the introduction of the problems and challenges that are stemming from the difficulties to accurate assess and control inhaled medication adherence for asthma patients, the authors provide the results of a related studies outlining the need and the requirements for the proposed study protocol. Unfortunately, there is no comparison with previous work done in this field and how the current protocol addresses important components of the overall healthcare process that have not been covered by other protocols. It is suggested that the authors add one paragraph to the introduction when the current study is directly compared with similar studies such as the following publications:

O'Dwyer, Susan Mary, et al. "The effect of providing feedback on inhaler technique and adherence from an electronic audio recording device, INCA®, in a community pharmacy setting: study protocol for a randomised controlled trial." Trials 17.1 (2016): 1.
Sulaiman, Imran, et al. "A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in patients with poorly controlled severe asthma." BMJ open 6.1 (2016): e009350.

Response: Paragraph added in the introduction comparing this proposed trial with previous studies. See pages 5 and 6.

Furthermore, the introduction should be clearly defining that the INCATM device can be used with only a specific type of inhalers, namely Diskus Dry Powder Inhaler. Unfortunately, there is only one short mention in this requirement in the entire document (Page 8). Furthermore, a paragraph with a short introduction to other modern smart inhaler monitoring devices is also suggested that could provide a better understanding of the great technological and clinical research potential of this field.

Response: Addressed on page 5.

In page 5, the reference 10 is referring to a protocol rather that the analysis of digital audio recordings for the assessment of adherence and technique of inhaler use.

Response: Reference 10 has been removed to avoid confusion.

In page 7 the referred Figure 1 is not available in the submission.

Response: Figures and appendices (with details about the clinical decision pathway, the assessment of primary and secondary outcomes, the proposed statistical analysis plan) were submitted with the manuscript as a separate tiff-formatted file, named 'figures and appendices'. We do appreciate that it would be difficult to read the manuscript if they are not accessible.
The figure 1 is now included as a separate file named Figure1 JPEG.

In page 8, it is mentioned that the maintenance of actual adherence is defined as "the combination of the time of use, interval between doses and critical errors; which is calculated as the area under the curve". Please try to rephrase and provide details.

Response: Further details are provided, see introduction second paragraph on page 5.

In page 10, the section "INCA device and analysis of audio data" should underline the fact that the device can be used for only a specific type of inhalers (Diskus Dry Powder Inhaler).

Response: This is already addressed in the introduction on page 5.

Furthermore, the accuracy and precision of the audio analysis outputs of the device should be mentioned and references to related publications should be included. It would also be helpful to mention whether the automated outputs of the device were reviewed by a trained healthcare professional for evaluation.
Response: These are included, see section "INCA device and analysis of audio data" on page 10.

In page 10, the link to www.randomisation.com is not correct. Furthermore, it is suggested to include the link as a reference rather than an inline inclusion of the website address.
Response: The link www.randomisation.com has been removed because it is not necessary, the randomisation process has been clearly described on page 10.

In page 12 the details provided in the caption of the table are suggested to an additional table line under the timing of visits indicating whether type of the visit.
Response: This has been updated please see table 2 on page 11.

In page 13, and the entire document in general, the referred appendices are not included in the submission. Please include all appendices in the following versions of the document.
Response: Figures and appendices (with details about the clinical decision pathway, the assessment of primary and secondary outcomes, the proposed statistical analysis plan) were submitted with the manuscript as a separate tiff-formatted file, named 'figures and appendices'. We do appreciate that it would be difficult to read the manuscript if they are not accessible.
The appedinces are now included as a separate file named appendices 1-10.

It is suggested that the inline reference to the educational video is changed to a formal reference with details about the publisher, the title of the video and its publication date. It is also suggested to publish the video from an institutional rather a personal account.
Response: The educational video has been changed to a formal reference and it is no longer published from a personal account.

Finally, the explanation of FeNO archetype was provided in page 11. A careful review to avoid multiple explanations of acronyms is therefore suggested.
Response: The explanation of FeNO has been removed from the previous page 11 (now page 10).

In Page 22, publications 25-28 are not referred within the text.
Response: These publications are cited in the appendices, and they have been removed and

referenced in the supplementary file named appendices 1-10.

One final suggestion to the authors is the rephrasing of the tile.
Response: Tittle rephrased.

Comments regarding SPIRIT 2013 Checklist

Item 8: The figure and appendices are not included in the submission
Response: Figures and appendices (with details about the clinical decision pathway, the assessment of primary and secondary outcomes, the proposed statistical analysis plan) were submitted with the manuscript as a separate file, named 'figures and appendices'. We do appreciate that it would be difficult to read the manuscript if they are not accessible.
The appedinces are now included as a separate file named appendices 1-10. The figure 1 is now included as a separate file named Figure1 JPEG.

Item 11b: criteria to discontinuing or modifying interventions are not included despite the fact that in page 18 it is mentions the possibility of serious adverse events. A more detailed description is suggested as it also connected with items 21b and 22.

Response: Item 11b and 21b are not applicable because in this study we are not studying an investigational medicinal product (IMP). This is a behavioral change study using an INCA device which will be attached to two established IMPs (in this case salmeterol/fluticasone and salbutamol). As per good clinical practise guidelines we plan to report any possible adverse events, including serious adverse events during the study as mentioned on page 18. In this study, we have not planned any interim analyses and we don't anticipate to discontinue or modify allocated interventions and hence we don't have any stopping guidelines because this study does not involve studying a new IMP.
However, for data quality assurance we plan to conduct an interim analysis of clinical outcome data for efficacy and data analysis for expected and unexpected adverse events for safety once 50% of total patient recruitment is achieved. See section "Team Organization and Data Quality Assurance" on page 19. Item 18b: has been addressed on page 10, see section "Enrolment, run-in phase and randomisation".

Item 18a is addressed in pages 10-14 and not in pages 9-13
Response: Pages numbers amended to reflect suggestion.

Item 19 is addressed in pages 18-20 and not in pages 18-19
Pages numbers amended to reflect suggestion.

Item 21b should be addressed in the submission. Please see comments for Item 11b.
Response: Please see response above under comment for 11b.

Item 22 should be addressed in the submission. Please see comments for Item 11b.
Response: Item 22 has been already addressed in the manuscript please see section "Data collection, safety and confidentiality" on page 18.

Item 27 is addressed in pages 18-20 and not in pages 18-19
Response: Pages numbers amended to reflect suggestion.

Item 28 is addressed in page 18 and not in page 14
Response: Pages numbers amended to reflect suggestion.

Item 29 is addressed in pages 18-20 and not in page 14
Response: Pages numbers have been amended to reflect suggestion.

Item 30 is not addressed. Very short description should be included in regards to the final row of Table 2 (page 13) “Dispense prescription for inhaler without INCA device”
Response: These have been addressed under section “Post-trial Care” on page 20.

Item 31a is addressed in page 20 rather than page 14
Response: Pages number has been amended to reflect suggestion.

Item 15, 18a, 20a, 20b, 20c, 32 and 33 are not addressed within the submission as already mentioned above appendices are missing.
Response: Figures and Appendices (with details about the clinical decision pathway, the assessment of primary and secondary outcomes, the proposed statistical analysis plan) were submitted with the manuscript as a separate tiff-formatted file, named ‘figures and appendices’. We do appreciate that it would be difficult to read the manuscript if they are not accessible.
The appedinces are now included as a separate file named appendices 1-10. The figure 1 is now included as a separate file named Figure1 JPEG.

Reviewer: 3

An excellent study protocol investigating a very important issue.

A few minor points which would in my opinion improve the study:

Methods
Could the authors give more detail about the primary outcome, and the definition of "appropriate" treatment. I presume this means appropriate with respect to the adherence level, but it would be useful for this to be clarified.
Response: This has been further clarified, please see text under section “primary outcome” on page 8.

My major concern with this study is that the control group is receiving many additional interventions and added clinician attention which is far removed from standard clinical practice. It is likely that with these additional interventions, both electronically monitored adherence and asthma control will be improved. With this increase in the control group, a between group difference for many of the specified outcomes may difficult to ascertain. Would it be reasonable to maintain care in the control group as close to "standard care" as possible? With the current protocol, the difference between 2 educational interventions is being compared, rather than comparing an innovative novel approach, to a true control group of standard existing care.

Response: We appreciate the comment and we acknowledge that the control group is receiving additional care than standard clinical practice which would result in an improvement in adherence and clinical outcomes for both control and active groups. We accept that this is a limitation in our study. It is worth noting that, current standard clinical practice is suboptimal and hence there is a need for these interventions such as PEFR, FEV1, FeNO, and AQLQ to be assessed routinely on a day to day practice in management of patients with severe uncontrolled asthma.

Also, I think the follow up period of 32 weeks is too short to realise the true potential and effect of this promising intervention. Previous adherence studies have shown that the feedback of electronically monitored adherence data has a more enhanced effect compared to control over a prolonged period of time. At six months, previous studies have failed to show a difference between groups, primarily because of the strong Hawthorne effect in the control groups. By one year, feedback of data and associated habit formation and behavior change have led to a sustained improvement in adherence rates, which have waned in control groups. A study of this size and significant investment should aim to follow up participants for a year to determine the full effect and sustainability of the intervention.

Response: We appreciate that the 32-week period is too short to appreciate the true potential and effect of this INCATM intervention and accept that this is one of the limiting factor in this study. This is now addressed in the manuscript please see section “Strengths and limitations of this study” on page 4.