PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Findings from a Pilot Randomised trial of an Asthma Internet Self-management Intervention (RAISIN)
AUTHORS	Morrison, Deborah; Wyke, Sally; Saunderson, Kathryn; McConnachie, Alex; Agur, Karolina; Chaudhuri, Rekha; Thomas, Mike; Thomson, Neil; Yardley, Lucy; Mair, Frances

VERSION 1 - REVIEW

REVIEWER	Johanna L. van Gaalen Dept of Medical Decision Making Leiden University Medical Centre Leiden, the Netherlands
REVIEW RETURNED	29-Jul-2015

GENERAL COMMENTS	It is a well written paper, with good methodology, that describes an analysis on feasibility and effectiveness of an internet-based intervention aimed at improving patient self-management, with a particular focus on medication adherence. Results are describing that the website would be feasible to use. No major differences were identified between intervention and control group in terms of asthma control and asthma related quality of life. Comments P6 table 1 R24 A&E attendance (please describe in full) P6 Row 40 – 56: you do describe aims of the intervention but not how you are trying to target these aims, could you elaborate on this – just shortly – even though you are referring to another paper – in particular could you elaborate on how you are aiming to target medication adherence (p6 r29) as this is one of the key targets of your intervention and it would show the more or less dynamic content of your website - which is worth to point out! Furthermore could you add a printscreen of the website (addendum). P7 R11 allocation of concealment: did you try to balance categories, if so how, if not, why not P7R21-25 here you give some information on how the website worked P8: secondary outcomes: add 'barriers' as these do emerge in your discussion section. P9: ethnicity: blank ◊ Caucasian? P11 table 3 indicate range and interpretation of ACQ and AQLQ scores P17 r45: 'significant between group differences in improvement

	adherence' this is not shown in your result section, as the mean of MMAS scores (table 4, page 13) did not differ significantly. Only the number of patients with a mcid differed significantly. P17 r 47: feasibility of home-based spirometry: There are papers that do describe that electronic monitoring of lungfunction is feasible, (i.e. Reddel BMJ 2002. Analysis of adherence to peak flow monitoring when recording of data is electronic) P18 row 7 -10: recruitment targets were achieved, attrition rates were comparable to other studies. That's true. But the reach(r17) is still not enormous (as you wrote previously: response rate 4.6%, of whom 27% were randomised) as indeed has been shown in a variety of papers. P18 row 12: 'the fact that 42% …. And 95% impact on their lives' I do not understand what the meaning of this sentence. Maybe you should cut it in two as it are two items. P18, row 20: primary outcomes: there are no significant in between group differences in terms of asthma control and asthma related quality of life. I do believe you should mention this and then report on your other findings: … i.e. However there are some interesting findings in analysis , and..

REVIEWER	John Powell University of Oxford, UK
REVIEW RETURNED	12-Oct-2015

GENERAL COMMENTS	Thank you for asking me to review this study. It is interesting and well written. It addresses a topical area. It will be of interest to your readers. It describes a well designed study and has been conducted and analysed appropriately. My comments relate almost exclusively to how the results have been interpreted and presented in the paper. This is feasibility work but I feel the authors have perhaps made more of their between group 'efficacy' comparisons than is warranted. The abstract talks about "non-significant improvements" and "trends to improved outcomes". One could just as well say that for (most) of the outcomes there was "no significant difference". This is feasibility work, it was not powered to show these differences, and there was no placebo group. I think the authors therefore need to be much more cautious in presenting efficacy results and making between group comparisons. In my view they should restrict reporting of these between group differences within the abstract to just the two measures which were prespecified as primary outcomes (ACQ, AQLQ), and I would also say that they should report these differences as 'no significant difference'. I.e. in the abstract have something like "there was no significant difference in the pre-specified primary efficacy measures (ACQ and AQLQ)". I have similar comments about the main text, although at least within this there is more opportunity to put these numbers in context. However I still think how they are reported is potentially putting too positive a spin on these non-significant findings. In my view more caution is required in how these are presented in the results, and

	more cautious interpretation in the discussion, including the fact that the trial was not designed/powered to detect these differences and the possibility that these 'trends' to improvement occur by chance and actually there is no difference (but does this matter anyway as this was about feasibility). In the discussion I think the authors should reflect on the percentages achieving MCID for the two primary efficacy measures and the fact that these percentages (55%v48%, and 50%v36%) showed no difference (the authors may like to comment on the fact that quite a proportion of the 'standard care' control group achieved MCID with no intervention?). The usage data is one of the primary outcomes and more data should be given in the abstract. I would expect to see the summary measure and range in the abstract – and given that this is a primary outcome of this feasibility work I think the authors should give both minutes on site and number of logins. The authors have chosen to present mean numbers (in the main results) – why not medians? In studies of internet interventions the usage data is usually (in my experience) skewed. Can the authors justify using means rather than medians (with range)? Can the authors please present the data on a bar chart or graph where the distribution can be seen – I think this would be a valuable addition to the results. The authors conclude that the study showed feasibility and that a full trial is warranted. I think they should be a little more cautious. <1% of those invited took part. 24% of those who took part did not login. I appreciate that the authors have said that further work would be useful in optimizing the intervention. I think there needs to be discussion around engagement with the intervention and the plausibility of low actual usage being of benefit. I agree with the authors' comment that future work may explore use of other platforms (apps/smartphones etc). Should more feasibility work around these other platforms be proposed/undertaken? It would be interesting to know what the qualitative interview findings revealed in this regard. I think the qualitative findings would be more useful presented here in this paper than saved for a second publication – they are answering the same research question – is this feasible? What are the issues? I'd like to see the qualitative process evaluation findings added to this paper. The randomisaion is described as "using a third party interactive voice response system ensuring allocation concealment (ratio 1:1)". Can the authors elaborate a tiny bit on how the voice system generates its randomisation? The authors say the analysis was not blinded. I agree with them that this is a limitation. I do not see why the reason for this is that there were different numbers between groups? Many (most) randomised trials have different numbers between groups and manage to retain blinded analysis. I do not see why the trial statistician could not remain blinded to allocation or have I missed the point? This is a very good study and a valuable addition to the literature in this area.

REVIEWER	Dermot Ryan

	University of Edinburgh, UK
REVIEW RETURNED	20-Oct-2015

GENERAL COMMENTS	This is a good start, but there is much to be learnt prior to proceeding into a further phase. In the introduction reference is made to new therapies. Omalizumab was introduced some 15 years ago. Bronchial thermoplasty still remains controversial. No mention has been made of mepolumizab. The referral to NRAD was somewhat glib. In those deemed to have either had asthma or died from asthma, there were avoidable factors. There are limitations to following the MRC complex intervention guidelines which merit some discussion: they may be unrealistic. In paragraph 2, reference is made to patients not having self management plans: this would be an opportunity to explain one the main factors was lack of professional knowledge and skills coupled with time pressures n the consultation.. No reference is made at all to the works of Victor Van der Meer (Improving Patient Care: Internet-Based Self-management Plus Education Compared With Usual Care in Asthma: A Randomized TrialAnn Intern Med July 21, 2009 151:110-120; doi:10.1059/0003-4819-151-2-200907210-00008) The essential feature being that patient education was given prior to trial entry, thus perhaps engaging the patient. A similar approach was undertaken in ref 27. Ref 11 is inaccessible thus unable to comment. Difficulties in recruitment were stated. There are descriptions which demonstrated similar obstacles (Malhotra et al, attached) The authors fail to highlight the fact that some 2/3 of participants had third level education and comment how this might affect engagement or outcomes. In the primary outcomes section, 50% of all patients achieved a chance in MCID: Is this simply due to the patients exhibiting some form of Hawthorn effect? What were the difference between this group and those who did not achieve such a difference? Did they have proven asthma? This non responding group merits further investigation. The authors state that blinding was not possible: might it not be possible to have some sort of dummy website? (although this in itself might be deemed an intervention) The authors seem to have taken on board the lack of a tablet or mobile phone app. Use of laps tops and PCs is falling of as exhibited by falling sales. These more convenient platforms might improve time and opportunity. In the discussion, I think that I would agree that further work is indicated , but substantial modifications to the existing structure need to be made. in particular patients need to be motivated or engaged to sign up to yet another task to perform in the context of a busy day. The benefits of participation need to be explained in the context of brief patient intervention at recruitment(This might not be given to the comparison group) I agree with the authors conclusions concerning spirometry. Any package needs to reflect real life, although the PIKO meter performs both PEF and FEV1 and may be a useful tool. Finally an aggregate of 90% of participants expressed doubts about the personal relevance of the website, were uncertain how to follow website advice or had symptoms too severe or were aggravated by website advice: this requires further investigation. This is a really good start: important lessons can and should be learnt to adapt and inform the next phase of your research in what is

	a notoriously difficult area of research. The reviewer also provided an attachment. Please contact the publisher for full details.

REVIEWER	Richard McNally Newcastle University, UK
REVIEW RETURNED	03-Dec-2015

GENERAL COMMENTS	GENERAL This is an interesting paper, reporting findings from a randomized trial of an asthma intervention. Generally it is well done. However, more detail on how this might inform a full trial is required. SPECIFIC COMMENTS 1. Some comment regarding the cost of the trial should be provided. 2. Would the full trial also involve patients from Glasgow or a wider area? Are there any foreseen problems in increasing recruitment?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Johanna L. van Gaalen Institution and Country Dept of Medical Decision Making, Leiden University Medical Centre

It is a well written paper, with good methodology, that describes an analysis on feasibility and effectiveness of an internet-based intervention aimed at improving patient self-management, with a particular focus on medication adherence. Results are describing that the website would be feasible to use. No major differences were identified between intervention and control group in terms of asthma control and asthma related quality of life.

Comments from reviewer 1:
P6 table 1 R24 A&E attendance (please describe in full)

- **AUTHOR'S RESPONSE:** This has been changed to 'Emergency Department attendance' to reflect the manuscript text, thank you. In our updated manuscript this can be found on page 5, table 1.

- P6 Row 40 – 56: you do describe aims of the intervention but not how you are trying to target these aims, could you elaborate on this – just shortly – even though you are referring to another paper – in particular could you elaborate on how you are aiming to target medication adherence (p6 r29) as this is one of the key targets of your intervention and it would show the more or less dynamic content of your website - which is worth to point out! Furthermore could you add a printscreen of the website (addendum).

    - **AUTHOR'S RESPONSE:** Thank you I am happy to add a few sentences to make this clearer (p5,r13), and have added a screenshot to the supplementary data file.
        - *"The website is interactive, aiming to engage the user in recognising that their asthma is uncontrolled, and illustrate the benefits via case vignettes (based on real life examples) of taking their medications as prescribed. The website is tailored based on their current use of preventer inhalers (never been prescribed; prescribed but don't really use; use regularly). There is a '4 week challenge' that users can sign up to, where they commit to taking their preventer regularly for 4 weeks, are guided through establishing their personal barriers to regular use (see screenshot in additional file for further illustration)and developing potential solutions to these barriers. "*
    - We are pleased to report that the development paper is now published and freely available for readers of this results paper to access at [1] http://www.biomedcentral.com/1472-6947/15/57

- P7 R11 allocation of concealment: did you try to balance categories, if so how, if not, why not
    - **AUTHOR'S RESPONSE:** The randomisation schedule was blocked (block length 4) to ensure near-equal numbers allocated to each group. As a pilot/feasibility trial, designed primarily to assess whether patients were amenable to randomisation etc., rather than to look at efficacy outcomes, the schedule was not stratified. In a larger study, stratification could be used to ensure balance between treatment groups, with respect to particularly important baseline characteristics. This is done in most large trials, so the feasibility of doing so was not considered as an important question for this study.

- P8: secondary outcomes: add 'barriers' as these do emerge in your discussion section.
    - **AUTHOR'S RESPONSE:** Barriers are included in the secondary outcomes in the last line (p6r33) when I describe the PETS questionnaire.
- P9: ethnicity: blank à Caucasian?
    - **AUTHOR'S RESPONSE:** We are not sure if the reviewer is suggesting that we should use the term 'Caucasian' rather than 'white' or that we should make more comment that 94% of participants were indeed white/Caucasian?

- P11 table 3 indicate range and interpretation of ACQ and AQLQ scores
    - **AUTHOR'S RESPONSE:** Thank you, adding this information will make this table clearer, and I have done so. This comment has highlighted to me that adding similar explanations to the other tables would be helpful to the readers, so I have added explanations Tables 3, 4 and 5.

- P17 r45: 'significant between group differences in improvement adherence' this is not shown in your result section, as the mean of MMAS scores (table 4, page 13) did not differ significantly. Only the number of patients with a mcid differed significantly.
    - **AUTHOR'S RESPONSE:** Thank you. I will change this sentence (now located at p15,r27) to the following to make this clearer:
        - *"Significant between group differences in the numbers of patients showing a MCID improvement in adherence"*

- P17 r 47: feasibility of home-based spirometry: There are papers that do describe that electronic monitoring of lung function is feasible, (i.e. Reddel BMJ 2002. Analysis of adherence to peak flow monitoring when recording of data is electronic)
    - **AUTHOR'S RESPONSE:** Many thanks for this useful reference, and we agree that there is evidence that electronic measuring of peak flow (and even FEV_1) is indeed feasible by participants in their own home. In our discussion we are referring specifically to the limitation of trying to undertake full spirometry in participant's home by the researcher, as a baseline and follow up measure. Later in that paragraph we do suggest that using a device which only measures peak flow, such as that included in Reddel et al, would be a suitable alterative.
- P17 row 7 -10: recruitment targets were achieved, attrition rates were comparable to other studies. That's true. But the reach (r17) is still not enormous (as you wrote previously: response rate 4.6%, of whom 27% were randomised) as indeed has been shown in a variety of papers.
    - **AUTHOR'S RESPONSE:** It is true that only 4.6% of those who were invited responded positively. However given that asthma is very common with a prevalence of around 5%, and this standalone intervention is easy to roll out to very large numbers of people, it follows that it could still reach a large population with potential to benefit. Our low positive response rate is also a reflection of our recruitment strategy, which was refined after the first 4 months. We posted invites out to people identified from a GP practice list as having asthma in the appropriate age group. The criteria for 'coding' people as asthma can vary from practice to practice, and some

practices are more likely to 'code' people for asthma than others. The range of practice participants mailed ranged from 1.5% to 8.9%. Inevitably, we are inviting many people who are not really the target population of the website such as those with no symptoms who were very well controlled who correctly self-selected themselves out as not being in need of such an intervention.

- In response to this I have added a few sentences at p16,r19:
  - *"….. even taking into account our very broad recruitment strategy. Similar trials have reported comparable recruitment difficulties. [31] However given how common asthma is, improvements in even a small proportion of patients could lead to significant benefit overall , particularly with an intervention such as that trialled here which is entirely internet based and once developed is very economical to make available to large numbers of people. Therefore what seems like a low reach, can still improve outcomes for a large number of people. "*

- P18 row 12: 'the fact that 42% …. And 95% impact on their lives' I do not understand what the meaning of this sentence. Maybe you should cut it in two as it are two items.
  - **AUTHOR'S RESPONSE:** Thank you for pointing out that this sentence lacks clarity. I will alter this paragraph (p16,r4) so it now reads:
    - *"Lack of time and opportunity were the biggest barriers to using the website and providing the contents on a smartphone app or tablet would be worth investigating. During the introduction questions at the start of the website 95% of users agreed to statements which showed that asthma was negatively impacting on their lives. However at the end of the trial 42% of users doubted the personal relevance of the website, anecdotally reporting that the website would be more useful for people with symptomatic asthma. To be in the trial in the first place all users were symptomatic (as defined by ACQ score), so challenging this mismatch between users' perceptions and the reality would be warranted in future versions of such a mobile friendly digital intervention*."

- P17, row 20: primary outcomes: there are no significant in between group differences in terms of asthma control and asthma related quality of life. I do believe you should mention this and then report on your other findings: … i.e. However there are some interesting findings in analysis , and..
  - **AUTHOR'S RESPONSE**: Thank you, I have taken on board your comment here and altered this paragraph (p15,r9) so it starts:
    - "In terms of primary efficacy outcomes, *there were no significant between group differences in terms of ACQ and mini AQLQ, although it is important to note that this pilot trial was not powered to show such a difference. However there are some interesting findings in analysis, as both the ACQ and mini AQLQ demonstrate encouraging and consistent trends in favour of the intervention group, with one sub-domain of the AQLQ (activity limitation) reaching the MCID and statistical significance."*

Reviewer: 2 John Powell University of Oxford, UK

It is interesting and well written. It addresses a topical area. It will be of interest to your readers. It describes a well designed study and has been conducted and analysed appropriately. My comments relate almost exclusively to how the results have been interpreted and presented in the paper.

- This is feasibility work but I feel the authors have perhaps made more of their between group 'efficacy' comparisons than is warranted.
  - **AUTHOR'S RESPONSE:** With changes suggested by Reviewer 1's comments, and your own comments below, we have hopefully addressed this concern.

- The abstract talks about “non-significant improvements” and “trends to improved outcomes”. One could just as well say that for (most) of the outcomes there was “no significant difference”. This is feasibility work, it was not powered to show these differences, and there was no placebo group. I think the authors therefore need to be much more cautious in presenting efficacy results and making between group comparisons. In my view they should restrict reporting of these between group differences within the abstract to just the two measures which were prespecified as primary outcomes (ACQ, AQLQ), and I would also say that they should report these differences as ‘no significant difference’. I.e. in the abstract have something like “there was no significant difference in the pre-specified primary efficacy measures (ACQ and AQLQ)”.
    - **AUTHOR’S RESPONSE:** Thank you for this comment and we take on board your suggestions and have changed the abstract (p2,r20) so it now reads:
        - “*Recruitment target met. Fifty one participants randomised (25 intervention group). Age range 16-78 years; 75% female; 28% from most deprived quintile. 45/51 (88%) (20 intervention group) followed up. Nineteen (76% of the intervention group) used the website, for a mean of 23 minutes. There was no significant difference in the pre-specified primary efficacy measures of ACQ scores (-0.36; 95% confidence interval: -0.96, 0.23; p=0.225), or mini-AQLQ scores (0.38;-0.13, 0.89; p=0.136). Secondary outcomes showed increased patient activation and reduced reliance on reliever medications in favour of the intervention. There was no difference in other measures. No adverse events*.”

- I have similar comments about the main text, although at least within this there is more opportunity to put these numbers in context. However I still think how they are reported is potentially putting too positive a spin on these non-significant findings. In my view more caution is required in how these are presented in the results, and more cautious interpretation in the discussion, including the fact that the trial was not designed/powered to detect these differences and the possibility that these ‘trends’ to improvement occur by chance and actually there is no difference (but does this matter anyway as this was about feasibility).
    - **AUTHOR’S RESPONSE:** We have added an additional sentence to the second paragraph as suggested by Reviewer 1, to make this clearer, (p15,r4).
    - I have changed the wording for the outcomes in the results sections in addition to remove references to terms such as ‘non-significant improvements’, and changed it to ‘no significant differences…’

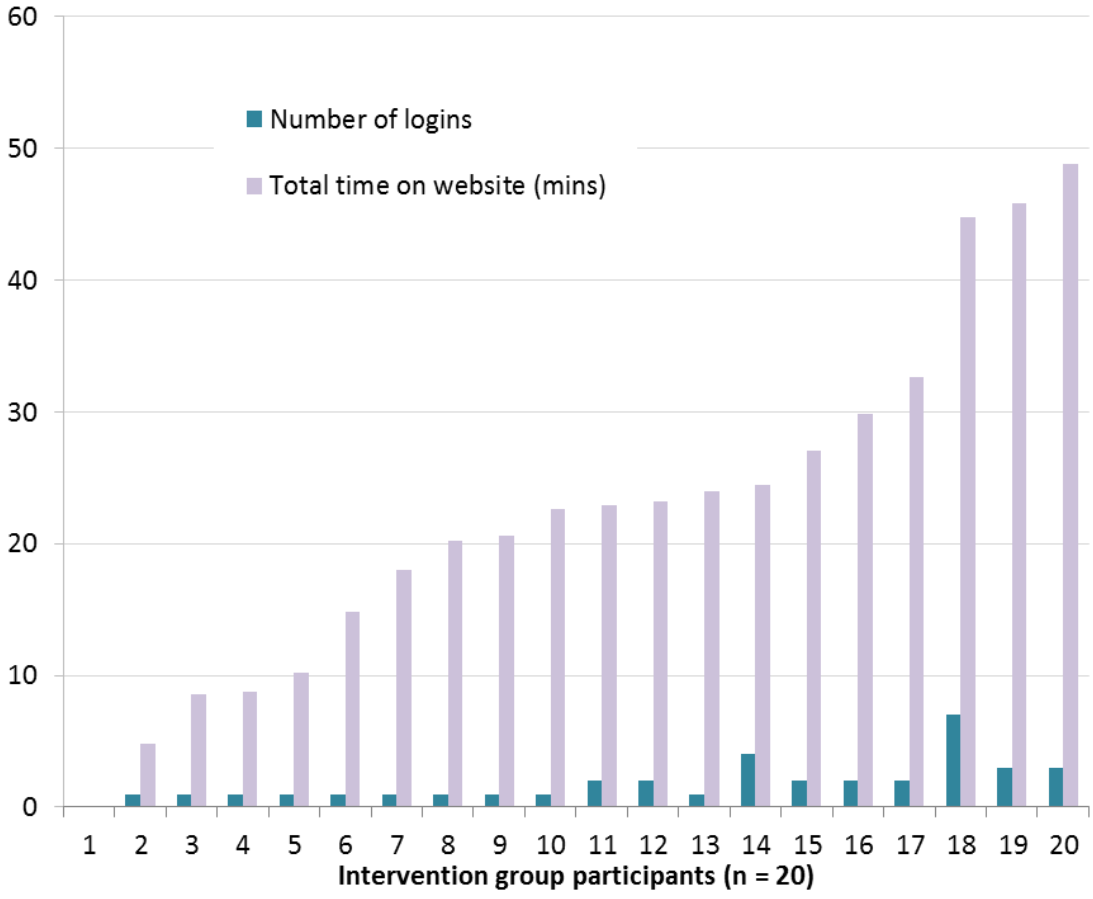
- In the discussion I think the authors should reflect on the percentages achieving MCID for the two primary efficacy measures and the fact that these percentages (55%v48%, and 50%v36%) showed no difference (the authors may like to comment on the fact that quite a proportion of the ‘standard care’ control group achieved MCID with no intervention?).
    - **AUTHOR’S RESPONSE:** Thank you. I have added the following sentence into p15,r13:
        - *“It is worth noting that for both primary efficacy outcomes, a proportion of those in the comparison groups demonstrated an improvement in MCID scores as well as the intervention group. This is often the case in unblinded complex intervention trials, and validates our approach of making this a pilot RCT, and not just a feasibility study. “*

- The usage data is one of the primary outcomes and more data should be given in the abstract. I would expect to see the summary measure and range in the abstract – and given that this is a primary outcome of this feasibility work I think the authors should give both minutes on site and number of logins.
    - **AUTHOR’S RESPONSE**: Thank you. We agree that this is interesting information to be shared with our readers as much as possible. Regarding the abstract the word limit is very tight for results when we have to include all the detail on methods as required by the consort statement. We chose to include the proportion of eligible users logging in, and the mean time spent on the website as the two most important

website usage results, as including any others would require removal of other words from the abstract.

- The authors have chosen to present mean numbers (in the main results) – why not medians? In studies of internet interventions the usage data is usually (in my experience) skewed. Can the authors justify using means rather than medians (with range)? Can the authors please present the data on a bar chart or graph where the distribution can be seen – I think this would be a valuable addition to the results.
    - **AUTHOR'S RESPONSE:** Again this is mainly to do with maximum tables allowed in the main manuscript. However, I will add some further explanation to the text, and update the table in the additional file to reflect your suggestions. Yes the data is skewed, and median and IQR would have been 1 (1,2) which we felt didn't illustrate the actual use fairly, hence our decision to opt for mean and range. I understand that omitting medians may raise a query with readers so will add this data as well, which would give a better description of the spread (p9,14).
        - *"The mean number of logins was 1.8 (range 0 to 7), median 1, (IQR 1,2), and the average time spent on the website during the study period was 22.6 minutes (range 0 to 48.9). More detail is shown in Figure A in the Supplementary File."*
    - In addition, we will add a further data table to the supplementary files to demonstrate the user patterns as requested (Figure A, Supplementary Data file), also shown below.

Figure A. Total time logged in and number of logins per participant (in order of length of time on website).



- The authors conclude that the study showed feasibility and that a full trial is warranted. I think they should be a little more cautious. <1% of those invited took part. 24% of those who took part

did not login. I appreciate that the authors have said that further work would be useful in optimizing the intervention. I think there needs to be discussion around engagement with the intervention and the plausibility of low actual usage being of benefit.

- **AUTHOR'S RESPONSE:** Although our uptake was low I have explained to reviewer 1 why for this type of intervention which can be made available to large numbers of people quickly and economically it is less of an issue, and should not be considered as a barrier to progression to further roll out.

- I agree with the authors' comment that future work may explore use of other platforms (apps/smartphones etc). Should more feasibility work around these other platforms be proposed/undertaken?
  - **AUTHOR'S RESPONSE:** Yes we agree that following any changes to the resource as it is currently, for example developing an app version would warrant further qualitative work, but I believe that further pilot evaluation would not be necessary, if the changes to the underlying function of the intervention were similar.
  - Colleagues in Southampton are currently developing the website, and their end result will be quite different compared to that trialled here (additional modules, health professional involvement). As a result they intend to undertake further qualitative work, and further piloting, given the resource has been changed significantly.

- It would be interesting to know what the qualitative interview findings revealed in this regard. I think the qualitative findings would be more useful presented here in this paper than saved for a second publication – they are answering the same research question – is this feasible? What are the issues? I'd like to see the qualitative process evaluation findings added to this paper.
  - **AUTHOR'S RESPONSE:** We too discussed having the qualitative work included, but decided this was not feasible for many reasons. Firstly the analysis and writing up of this separate piece of work is only just nearing completion and manuscript at present is 6000 words. All reviewers have requested additional explanation and data to be included in this manuscript; therefore it is clear we would not have the word limit or space to do justice to both pieces of research. We will consider asking BMJ Open if they would consider publishing our qualitative paper as a companion piece.

- The randomisation is described as "using a third party interactive voice response system ensuring allocation concealment (ratio 1:1)". Can the authors elaborate a tiny bit on how the voice system generates its randomisation?
  - **AUTHOR'S RESPONSE**: We have added the following text (p6,r9)to clarify:
    - *"The randomisation schedule was generated in advance of the study by the Robertson Centre for Biostatistics, in a 1:1 ratio, using the method of randomised permuted blocks of length 4, without stratification. Access to the randomisation schedule was restricted to those within the Centre with responsibility for provision of the IVRS."*

- The authors say the analysis was not blinded. I agree with them that this is a limitation. I do not see why the reason for this is that there were different numbers between groups? Many (most) randomised trials have different numbers between groups and manage to retain blinded analysis. I do not see why the trial statistician could not remain blinded to allocation or have I missed the point?
  - **AUTHOR'S RESPONSE:** The first author (D Morrison) is a PhD student, and was involved initially in recruitment, and then also undertaking the analysis. There was no separate trial statistician. When recruitment was completed D Morrison was informed that there were 26 in the control group and 25 in the intervention group. Therefore when it came to the analysis she knew which each group represented by the number of participants in it. There was unfortunately no way for D Morrison to be blinded to the group allocations as the data once recruitment numbers was known.
  - I have added the following to the manuscript so this sentence (p 16,r22) now reads:

- *"Blinding to group allocation during analysis was not possible due to the different numbers in each group being known by the researcher undertaking the analysis."*

- This is a very good study and a valuable addition to the literature in this area.
  - **AUTHOR'S RESPONSE**: Thank you very much, and we appreciate your comments.

Reviewer: 3 Dermot Ryan University of Edinburgh, UK

- This is a good start, but there is much to be learnt prior to proceeding into a further phase.
  - **AUTHOR'S RESPONSE:** Thank you.

- In the introduction reference is made to new therapies. Omalizumab was introduced some 15 years ago. Bronchial thermoplasty still remains controversial. No mention has been made of mepolumizab.
  - **AUTHOR'S RESPONSE**: While these therapies have been around for some years, they could be considered as 'new' compared to inhaled corticosteroids which have been available for 40 plus years.
  - We will change the word 'new' to 'newer' to reduce the impact of the sentence (p4r3), and will add a reference to mepolumizab (p4,r3) [2]. While the Cochrane review on bronchoplasty (referenced in the manuscript) was not definitively in its favour (neither was the Cochrane review for Mepolizumab [3]), it is still a new treatment option available to some individuals with severe asthma, and therefore we feel is acceptable to mention here.

- The referral to NRAD was somewhat glib. In those deemed to have either had asthma or died from asthma, there were avoidable factors.
  - **AUTHOR'S RESPONSE**: I appreciate that when reviewing patient notes it is often the case that there are factors present which appear avoidable, however it is not possible to be 100% sure that in real life these factors were indeed truly avoidable for a given individuals' circumstances and therefore we feel it is not inappropriate to report these factors as *potentially* avoidable.

- There are limitations to following the MRC complex intervention guidelines which merit some discussion: they may be unrealistic.
  - **AUTHOR'S RESPONSE:** Many guidelines and frameworks have limitations, but it was felt that this particular document provided the best available evidence for guiding our development process, and we personally found it very useful for this project, as is detailed in our development paper [1]. Unfortunately, we do not have the space to debate the merits, or otherwise, of the framework in this RCT results paper.

- In paragraph 2, reference is made to patients not having self management plans: this would be an opportunity to explain one the main factors was lack of professional knowledge and skills coupled with time pressures n the consultation.. No reference is made at all to the works of Victor Van der Meer (Improving Patient Care: Internet-Based Self-management Plus Education Compared With Usual Care in Asthma: A Randomized Trial Ann Intern Med July 21, 2009 151:110-120; doi:10.1059/0003-4819-151-2-200907210-00008) The essential feature being that patient education was given prior to trial entry, thus perhaps engaging the patient. A similar approach was undertaken in ref 27.
  - **AUTHOR'S RESPONSE:** I agree Van der Meer's excellent RCT is relevant to our own work. However our intervention was developed with the aim being simple and practical to implement into current NHS practice, with little or no additional resources required. Therefore it was a conscious choice NOT to provide additional pre-intervention education as we felt this would limit its implementability in the long term, and making it prohibitively expensive to provide to large numbers of people. For a comparatively basic intervention

like this, aimed at those with mild to moderate asthma, the individual benefit could only be expected to be modest, but across a population could lead to significant improvement in outcomes.

- Ref 11 is inaccessible thus unable to comment.
    - **AUTHOR'S RESPONSE:** I apologise there has been miscommunication here, as the contents of this reference (a submitted manuscript describing the development of the website) was provided to BMJ Open as a supplementary file to be made available to peer reviewers, and should have been available to you. The paper has now been published and is accessible at www.biomedcentral.com/1472-6947/15/57 [1]

- Difficulties in recruitment were stated. There are descriptions which demonstrated similar obstacles (Malhotra et al, attached).
    - **AUTHOR'S RESPONSE:** Many thanks for providing the pdf of this article describing in detail the difficulties you experienced with recruitment which were indeed very similar to our own, and I will take the opportunity to cite this, as it further illustrates our similar recruitment difficulties (p16,r20).

- The authors fail to highlight the fact that some 2/3 of participants had third level education and comment how this might affect engagement or outcomes.

    - **AUTHOR'S RESPONSE:** By third level education we included any qualification beyond secondary school, for example apprenticeships where college attendance was required. Numbers vary but at least a half of school leavers go on to further education, with data from England in 2013 suggesting that 64% of school leavers are in further or higher education (https://www.gov.uk/government/news/government-publishes-destination-data-for-the-first-time). We appreciate that this figure is much higher than say 20 years ago when many of our participants were at school leaving age, but we do not think that this is a significant issue. Given that so few studies report similar data it is difficult to compare to other trials.

- In the primary outcomes section, 50% of all patients achieved a chance in MCID: Is this simply due to the patients exhibiting some form of Hawthorn effect? What were the difference between this group and those who did not achieve such a difference? Did they have proven asthma? This non responding group merits further investigation.
    - **AUTHOR'S RESPONSE:** Thank you, these are interesting thoughts and comments, and may be investigated in further analysis of our data, but is beyond the scope of this specific paper. As per reviewer two I have added a reflection on this in the discussion (p15,r13):
        - *"It is worth noting that for both primary efficacy outcomes, a proportion of those in the comparison groups demonstrated an improvement in MCID in scores as well as the intervention group. This is often the case in unblinded complex intervention trials, and validates our approach of making this a pilot RCT, and not just a feasibility study. "*

- The authors state that blinding was not possible: might it not be possible to have some sort of dummy website? (although this in itself might be deemed an intervention) The authors seem to have taken on board the lack of a tablet or mobile phone app. Use of laps tops and PCs is falling of as exhibited by falling sales. These more convenient platforms might improve time and opportunity.
    - **AUTHOR'S RESPONSE:** Thank you and yes we agree. At the time of development LifeGuide software was not compatible with tablets or smartphones, but is now, and further iterations of the website will be accessible on these platforms. Other internet interventions have had participants blinded by directing those in the control group to a

static website, without interactive material aimed at behaviour change. This is an option to be considered for future evaluations.

- In the discussion, I think that I would agree that further work is indicated , but substantial modifications to the existing structure need to be made. in particular patients need to be motivated or engaged to sign up to yet another task to perform in the context of a busy day. The benefits of participation need to be explained in the context of brief patient intervention at recruitment(This might not be given to the comparison group)
    - **AUTHOR'S RESPONSE:** We do agree that further development work is required before moving on to a full trial. An app version of the website as it is could be generated fairly easily, and would require qualitative work before proceeding to a full scale trial, to address some of the engagement issues, and challenging the mismatch between perception of control and reality. I will add a few words to this effect at p16r8:
        - *" To be in the trial in the first place all users were symptomatic (as defined by ACQ score), so challenging this mismatch between users' perceptions and the reality would be warranted in future versions of a mobile friendly digital intervention. "*

- I agree with the authors conclusions concerning spirometry. Any package needs to reflect real life, although the PIKO meter performs both PEF and FEV1 and may be a useful tool.
    - **AUTHOR'S RESPONSE:** Yes we agree the PIKO meter might have been a useful option to have considered. However we were attempting to

      a) minimise the 'intervention burden' trying to get the best possible outcomes for our participants with the least amount of work, and we felt that daily monitoring would possibly shift this balance towards too much work, especially as it is unlikely to be replicated in any real life use post trial;
      b) we were trying to make the intervention (and trial) as close to real life as possible, and felt that asking people to use monitors daily did not reflect what was happening in real life at present (rightly or wrongly!) However, we could have used the PIKO metre to have recorded the PEF and FEV1 at baseline and follow-up which would likely be a preferred option for any full scale trial.

- Finally an aggregate of 90% of participants expressed doubts about the personal relevance of the website, were uncertain how to follow website advice or had symptoms too severe or were aggravated by website advice: this requires further investigation.
    - **AUTHOR'S RESPONSE:** This PETS outcome can be reported in two ways. The first is the way we have done in this manuscript where results are dichotomised into either 'no barrier identified' (e.g. strongly disagreeing the stated barrier, i.e. score of 1) or 'some barrier identified'(any other response, including slightly disagreeing with the stated barrier), and then for each domain the percentage of people identifying with a barrier can be presented. I do not think it is a fair representation to aggregate these scores, as it may be the same individuals who were reporting barriers across the domains. Also within each domain there were between 2 to 4 statements, so even just one statement within that domain being identified as a barrier would flag this whole domain up as a barrier. This method reflects the assumption that only one reason, no matter how strongly felt, may be a sufficient threshold to reduce or prevent adherence, and could be seen as being very sensitive to detecting barriers. The other way is the original way the PETS was used [4] where the average score within each domain is calculated, and the median (IQR) of these are presented. This was is shown in the table below (and in the updated Supplementary Data file):

Table A. Problematic Experiences of Therapy (PETS). Barriers to following website advice, range 1-5. Intervention group only (n = 19).

	Median (IQR)
Symptoms too severe to follow website advice, or symptoms aggravated by website advice	1.0 (1.0 to 1.0)
Uncertain how to follow the website advice	1.0 (1.0 to 2.0)
Doubt about personal relevence of website advice	1.0 (1.0 to 1.7)
Practical obstacles to following website advice (e.g time, opportunity)	3.3 (2.0 to 4.0)

1 = strongly disagree with statement; 5 = strongly agree with statement

- Presenting the data this way demonstrates the most people really did not strongly identify with these barriers, with the exception of the final one. Thank you for highlighting that the way we were presenting this data initially was ambiguous, and seemed to be giving the impression that patient feedback was more negative than it was. I will present this alternative table instead.

- This is a really good start: important lessons can and should be learnt to adapt and inform the next phase of your research in what is a notoriously difficult area of research.
  - **AUTHOR'S RESPONSE:** Thank you, we appreciate you taking the time to review our article and for your constructive comments.

Reviewer: 4 Richard McNally Newcastle University, UK

This is an interesting paper, reporting findings from a randomized trial of an asthma intervention. Generally it is well done. However, more detail on how this might inform a full trial is required.

SPECIFIC COMMENTS FROM REVIEWER 4

- Some comment regarding the cost of the trial should be provided.
  - **AUTHOR'S RESPONSE:** Once up and running we anticipate that annual intervention costs would be about £2500 to cover server maintenance.

- Would the full trial also involve patients from Glasgow or a wider area? Are there any foreseen problems in increasing recruitment
  - **AUTHOR'S RESPONSE:** Recruitment strategies for the future trial have not decided. We anticipate that we would undertake a 'traditional' RCT with participants recruitment from Glasgow, and decision about a second site has not yet been made. Ideally we would also like to run a parallel online trial where recruitment and data collection is carried out remotely (online and via postal data collection) which would allow us to recruit Scotland wide.

1. Morrison D, Mair FS, Chaudhuri R, et al. Details of development of the resource for adults with asthma in the RAISIN (randomized trial of an asthma internet self-management intervention) study. BMC Med. Inform. Decis. Mak. 2015;**15**(1):57 10.1186/s12911-015-0177-z
2. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. N Eng J Med 2014;**371**(13):1198-207 doi:10.1056/NEJMoa1403290

3. Powell C, Milan SJ, Dwan K, Bax L, Walters N. Mepolizumab versus placebo for asthma. The Cochrane database of systematic reviews 2015;**7**:CD010834 10.1002/14651858.CD010834.pub2
4. Yardley L, Kirby S. Evaluation of Booklet-Based Self-Management of Symptoms in Meniere Disease: A Randomized Controlled Trial. Psychosom. Med. 2006;**68**(5):762-69

VERSION 2 – REVIEW

REVIEWER	Johanna L van Gaalen Department of Medical Decision Making, Leiden University Medical Centre, Leiden, the Netherlands.
REVIEW RETURNED	01-Feb-2016

GENERAL COMMENTS	Interesting paper tthat describes issues relevant for studies in today's clinical practice.

REVIEWER	John Powell University of Oxford
REVIEW RETURNED	05-Feb-2016

GENERAL COMMENTS	Thank you to the reviewers for the various changes they have made. I still have some issues. Firstly I still think there is a general point with how they are presenting efficacy findings in what is a feasibility study. The primary results are the feasibility ones and the abstract could still better reflect this (I asked for more inclusion of usage data in abstract as this is primary outcome – I would still like this – if they need 'more words' they could drop the secondary efficacy results from the abstract). I find Figure A misleading – it only includes 20 participants. For a true presentation of participant usage it must include all participants including participants who had zero logins, zero time on site – surely this is a very important feasibility finding? This relates to my previous point about using medians for skewed usage data – the reader must be able to understand the distribution of usage. I note the authors' response but my preference is that this paper include the qualitative findings as they are also looking at the same research question. I think more caution is still required in next steps – I am not convinced the next step is a large trial. I think there is a good argument for more work on refining the platform, and working on issues of uptake and engagement with the intervention.

REVIEWER	Dermot Ryan University of Edinburgh UK
REVIEW RETURNED	21-Jan-2016

GENERAL COMMENTS	This probably does not need a formal review: I think it is worth stating that the website was available on computer/lap top earlier on. This may be one of the factors for the limited access.People may

	have accessed the website when not otherwise occupied had it been available in a mobile phone/tablet format.

REVIEWER	Richard McNally Newcastle University, England, UK
REVIEW RETURNED	20-Jan-2016

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Johanna L van Gaalen
Department of Medical Decision Making, Leiden University Medical Centre, Leiden, the Netherlands.
Interesting paper that describes issues relevant for studies in today's clinical practice.

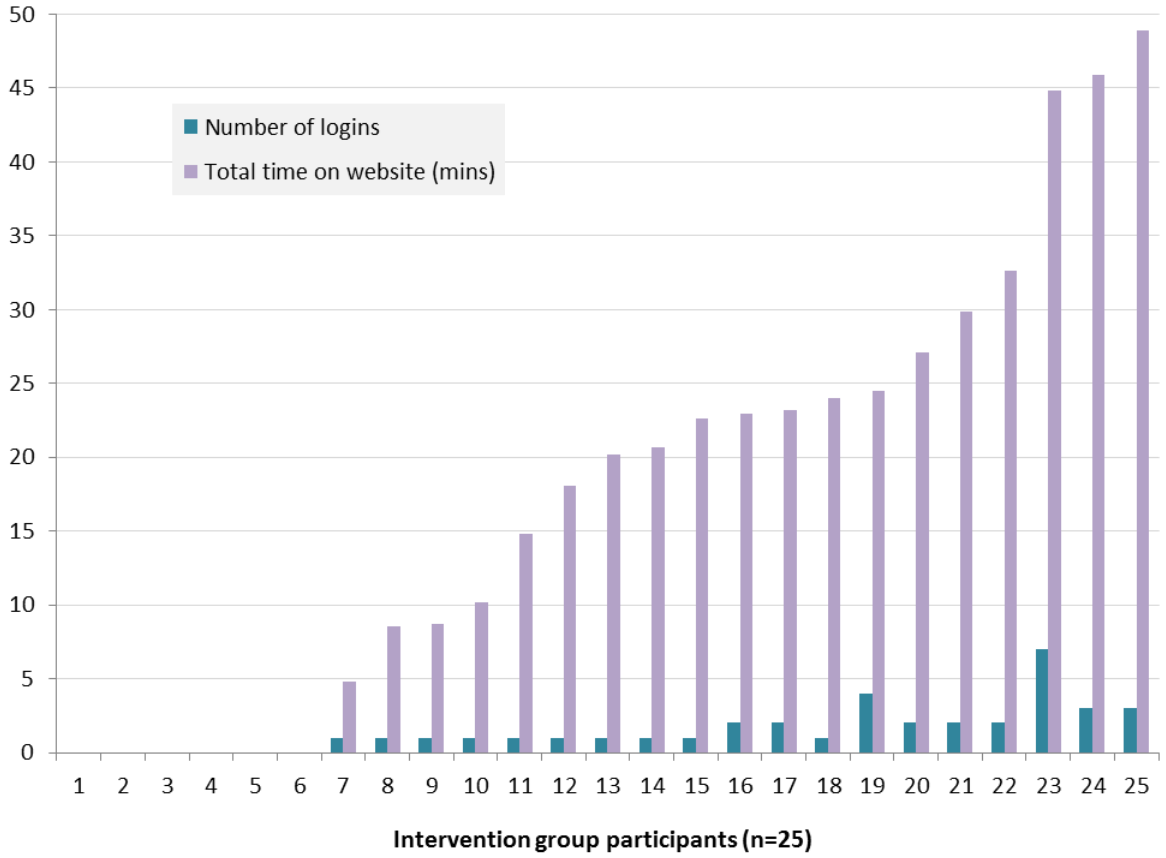
Reviewer: 2
John Powell
University of Oxford
Thank you to the reviewers for the various changes they have made. I still have some issues. Firstly I still think there is a general point with how they are presenting efficacy findings in what is a feasibility study. The primary results are the feasibility ones and the abstract could still better reflect this (I asked for more inclusion of usage data in abstract as this is primary outcome – I would still like this – if they need 'more words' they could drop the secondary efficacy results from the abstract).

- Thank you for your input again. I appreciate your suggestion to remove the secondary outcomes in the abstract to free up more words and have added further usage data. In addition I take on board your comment about the usage data only including the 20 participants who had completed the study. I had missed this point from the original comments, and have amended this so that usage data calculations include the 5 participants who did not complete the study. This leads to a drop in the mean time on website from 23 to 18 minutes and I have updated this here in the abstract below and also in the text (page 9, line 14).
    - Recruitment target met. Fifty one participants randomised (25 intervention group). Age range 16-78 years; 75% female; 28% from most deprived quintile. 45/51 (88%) (20 intervention group) followed up. Nineteen (76% of the intervention group) used the website, for a mean of 18 minutes, (range 0,49). Seventeen went beyond the two 'core' modules. Median number of logins was 1 (interquartile range 1,2, range 0,7). No significant difference in the pre-specified primary efficacy measures of ACQ scores (-0.36; 95% confidence interval: -0.96, 0.23; p=0.225), and mini-AQLQ scores (0.38;-0.13, 0.89; p=0.136). No adverse events.

I find Figure A misleading – it only includes 20 participants. For a true presentation of participant usage it must include all participants including participants who had zero logins, zero time on site – surely this is a very important feasibility finding? This relates to my previous point about using medians for skewed usage data – the reader must be able to understand the distribution of usage.

- As above thank you for reiterating this point, I had missed it from the earlier comments and I agree that this is misleading, it was not deliberate. I have redone the graph to include the participants who did not complete to provide a truer picture, and added further usage data to the abstract.

Figure A Total time logged in and number of logins per user (in order of length of time on website.



I note the authors' response but my preference is that this paper include the qualitative findings as they are also looking at the same research question.

- As before this is not possible.

I think more caution is still required in next steps – I am not convinced the next step is a large trial. I think there is a good argument for more work on refining the platform, and working on issues of uptake and engagement with the intervention.

- I think I have not been as explicit as I could l have been that we do indeed plan to undertake further work refining the platform, and investigating strategies for streamlining recruitment before we would progress to a trial. We have undertaken qualitative interviews with intervention group participants and along with our own conclusions from this study we will refine this current version, and understand that further user testing of this refined version will be required. However, we are confident that the results of this will not change our overall conclusion that ultimately a full scale RCT is indeed warranted. I have made some changes to the text (page 2, line 31; page 15 line 4,25-6; page 17, lines7-13) to reflect this and our final paragraph now reads:
    - We have shown that evaluating the Living Well with Asthma intervention was feasible and resulted in encouraging trends in clinical outcomes. Further qualitative work to understand usage patterns with intervention group participants has been completed and will inform a future version of the resource. To overcome the 'practical barriers' to using the intervention future versions need to be mobile and tablet compatible, and will require further user testing . Following this development work on the resource, these findings suggest that a large scale Phase III RCT is merited, with some exploration of recruitment strategies and minor modification to outcome measurement methods. Low intensity digital interventions that are easier to deliver at scale may be a more successful strategy, particularly in those with mild to moderate asthma.

Reviewer: 3
Dermot Ryan
University of Edinburgh
This probably does not need a formal review: I think it is worth stating that the website was available on computer/lap top earlier on. This may be one of the factors for the limited access. People may have accessed the website when not otherwise occupied had it been available in a mobile phone/tablet format

- Thank you, I have added this to the abstract, on line 13

Reviewer: 4
Richard McNally
Newcastle University, England, UK
None

VERSION 3 - REVIEW

REVIEWER	John Powell University of Oxford, UK
REVIEW RETURNED	20-Apr-2016

GENERAL COMMENTS	Thank you for making the changes. I think the qualitative findings will be interesting to see.