Author's response to reviews

Title: EmPhAsIS: Empowering Pharmacists in Asthma management through Interactive SMS. Study protocol for a pragmatic, pharmacy-based, cluster randomized controlled trial.

Authors:

Mary A De Vera (mary.devera@ubc.ca)
Mohsen Sadatsafavi (mohsen.sadatsafavi@ubc.ca)
Nicole W Tsao (nicole_t@mail.ubc.ca)
Larry D Lynd (larry.lynd@ubc.ca)
Richard Lester (rlester@mail.ubc.ca)
Louise Gastonguay (louisega@mail.ubc.ca)
Jessica Galo (jessica.galo@ubc.ca)
J. Mark FitzGerald (Mark.Fitzgerald@vch.ca)
Penelope Brasher (Penny.Brasher@vch.ca)
Carlo A Marra (cmarra@mun.ca)

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Author's response to reviews: see over
November 06, 2014

Professors Doug Altman, Curt Furbert, and Jeremy Grimshaw
Editors-in-Chief
Trials

Dear Professors Altman, Furbert, and Grimshaw:

We thank you very much for your consideration of our manuscript “EmPhAsIS: Empowering Pharmacists in Asthma management through Interactive SMS. Study protocol for a pragmatic, pharmacy-based, cluster randomized controlled trial” (Manuscript ID: 1756907246139579) for Trials. We appreciate the time taken by the Reviewers and their comments and recommendations.

We outline below, point-by-point responses to these reviews. With each response, we also indicate the corresponding revision to the manuscript. Please note that to facilitate review of the revised manuscript, we have used the following guide:

• Yellow highlighted text Indicates text that we have edited/revised or added to address reviewer comments.

In addressing Reviewer comments’ we agree that they have contributed to an improved manuscript. We thank you again for your consideration of our study protocol in Trials.

Sincerely,

Mary De Vera, PhD (Corresponding Author)
Assistant Professor of Medication Adherence
University of British Columbia Faculty of Pharmaceutical Sciences
Arthritis Research Centre of Canada
2405 Wesbrook Mall
Vancouver, BC, V6T 1Z3
Tel: 604-827-2138
Fax: 604-207-4059
Email: mdevera@mail.ubc.ca
EDITORIAL REQUESTS

1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?____________: study protocol for a randomized controlled trial?
   
   Response: Yes we confirm that the title conforms to the journal style for study protocol articles.

2. Please include the date your study was registered with the trial registration number at the end of the Abstract.
   
   Response: We registered our trial through ClinicalTrials.gov on June 19th, 2014. We have revised the Abstract to include this information.

3. Please include a statement in your Methods section explaining that you obtained informed consent from each participant.
   
   Response: We included the following statement in the Methods section to indicate that we will obtain informed consent from each participant: (Revision, Methods, Participants, Patients, paragraph 1, page 9, included sentence: “Written informed consent will be obtained from eligible patients for enrollment into the study.”)

4. Please mention each author individually in your Authors? Contributions section. Currently 'RL' is missing. We suggest the following kind of format (please use initials to refer to each author's contribution): ?AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.?
   
   Response: We have revised this section to mention individual author’s contributions as follows:

   MDV designed the study and will lead all aspects as Principal Investigator.
   MS designed the study and will lead the economic evaluation of the study.
   NT participated in the design and coordination of the study.
   LL designed the study and will provide expertise in pharmaceutical outcomes research.
   RL designed the study and will lead the SMS component.
   LG participated in the design and coordination of the study.
   JG participated in the design and coordination of the study.
   JMF designed the study and will provide clinical expertise in asthma.
   PB designed the study and will provide expertise in statistical analyses.
   CM designed the study and will provide expertise in pharmacy practice research.
5. Please state clearly whether or not you have funding in the Acknowledgements section. If there is no funding, please state this.

Response: We included the following funding statement in the Acknowledgements section:

This study is funded by operating funds from the Canadian Institutes of Health Research and the College of Pharmacists of British Columbia and infrastructure support from the Canadian Foundation for Innovation.

6. Please include your figure title and legend section in the main manuscript document, below the reference list.

Response: We have revised the manuscript to include figure titles and legends below the reference list.

REVIEWER 1

1. Page numbers would be useful! The formula given in the section 'Sample size calculation' is wrong. The term 'beta/2' should actually be 'beta'.

Response: We have included page numbers in our manuscript and we thank Reviewer 1 for pointing out our typographic error. We have corrected the formula to reflect that it is 'beta' (page 15).

2. It is not clear why this formula has been chosen. It is the formula for comparing means when the primary outcome is binary. The authors should use the correct formula.

Response: We appreciate the reviewer's thoughtful concern on this. Given that MPR is the number of days with medication over follow-up time, it has an exact binomial distribution, but we agree that there will be enough samples within each arm with little to no incomplete follow-up, the distribution of the sample mean of MPR can well be approximated by the normal distribution to be in concordance with the sample size calculation formula. We have updated the analysis part accordingly.

Revision, Statistical analysis, Analysis for objective 1, page 17: To evaluate the impact of the EmPhAsIS intervention on our primary outcome of 1-year adherence as measured by the MPR, we will use a random effects GLMM, assuming an approximate normal distribution and specifying an identity link function.

3. It is essential that the authors report the power calculation in sufficient detail that it can be reconstructed. For example, although many ICC values are reported, it is impossible to find what value was actually used to determine the sample size.

Response: We drew from published ICC values based on adherence outcomes, medication-taking outcomes, and clinical outcomes. Based on this data, we determined a relevant ICC of 0.06 (as this was based on an adherence outcome evaluated in a prior
cluster RCT) which we applied in our sample size calculation. We have revised the sample size calculation section of the manuscript to include this information.

**Revision**, Methods, Sample size calculation, page 15: Based on these data, we applied an ICC of 0.06 and calculated the number of patients that will be required to detect a 10% improvement in adherence rate – deemed clinically significant in prior studies [47] and also relevant from a cost-effectiveness perspective based on our previous research [48] - with a power of 80%, significance level of 0.05 as 334.

More minor points which need to be addressed in greater detail:

4. Is it realistic for the study coordinator conducting telephone interviews to remain blinded to pharmacy allocation? Have the authors any pilot data to suggest that this can be maintained, and/or will it be explored in the trial itself?

**Response:** Both Reviewer 1 and 2 raised similar comments regarding blinding of study team members. The trial will be managed by a coordinator, that similar to pharmacists will not be blinded to pharmacy allocation, as they will be liaising with, and supporting pharmacists throughout the duration of the study. However, team members responsible for data collection and analyses will be blinded. Specifically, these include an interviewer whose sole responsibility will be to conduct telephone interviews and prospectively collect patient reported outcomes at 0, 6, and 12 months and the statistical analyst. We revised the manuscript as follows:

**Revision**, Methods, Randomization, page 10: It will not be possible for participating pharmacies to be blinded to which group they are assigned. However, while the trial will be managed by a coordinator who will also be unblinded, team members responsible for data collection (interviewer who will collect patient reported data at 0, 6, and 12 months) and analyses (statistical analyst) will be blinded to group allocation.

5. Under data collection, fax sounds rather a dead technology. Do pharmacies even have fax machines?

**Response:** Despite fax being a relatively older form of technology, it remains the predominant form of communication in community pharmacies for several reasons:

a. Faxed copies of documents are considered legal copies
b. Fax lines are secure and ensure the confidentiality of transmitted patient information
c. Fax machines are a minimum requirement of a pharmacy’s equipment as per policies of the College of Pharmacists of BC (http://library.bcpharmacists.org/A-About_Us/A-2_Governance/5003-PGP-PPP59.pdf); thus every pharmacy will have a fax machine.

6. Do authors have any data to suggest that they can maintain attrition rates as low as 10%. Is differential attrition likely, and if so, how will it be handled in the analysis?

**Response:** Given that our primary outcome is medication possession ratio calculated using BC PharmaNet data (administrative database), our primary analysis is in a sense
"protected" from attrition after participants are enrolled and have consented to the access of their de-identified PharmaNet data. Still, we are conservative and have estimated the attrition rate at 10% to account for any unanticipated changes in participant enrollment.

7. The proposed statistical analysis is appropriate, but will be opaque to most clinical/pharmacy readers. Are there plans to explore any more transparent approaches as sensitivity analyses, such as doing a t-test at pharmacy level, comparing mean adherence rates?

Response: In designing this trial, we sought to adhere to best practice standards in statistical analysis which in this case stipulates using the previously-mentioned statistical framework. We see little benefit in using statistical procedures that, while giving intuitive results, are incompatible with the structure of the data. However, we appreciate Reviewer 1’s concern and motivated by their suggestion in in being more transparent, we will do our best to provide intuitive interpretation of the findings in our knowledge translation and communication of results (e.g., textual interpretation of what the regression coefficient mean, reporting absolute and relative measures of treatment effect).

REVIEWER 2

Recommendations for overall improvements - voluntary

1. There are a few improvements that could be made to the background to set it into context, give more support to the study, and bring it up to date. The reference are quite old (over a decade), refs: 10, 12, 13,14 especially and the authors discuss “landmark studies in the 90's”. There is more up to date literature available which could be included to bring this up to date.

Response: We have updated some of the references to more recent citations, however, the older landmark studies are still relevant to asthma care and remain as key citations in guidelines and reports including the 2014 Global Strategy for Asthma Management and Prevention (GINA) report, so we have kept them in this paper.

2. The authors state mobile phone technology has had an impact on behavior change, and how this technology has been evaluated in other studies of asthma care but don't expand on this. It would be useful to report study outcomes and give examples of how this supports what the study aims to do - even though it is not delivered in pharmacy it would show application of the technology for asthma care in other health settings and state the potential applicability to pharmacy (refs 28 & 29).

Response: We have added a short description of study outcomes of a relevant clinical trial using short messaging service coupled with healthcare provider (nurse) follow up to improve medication adherence. This was added on page 7.

Mandatory revisions required to allow replication of the work
3. The study assistant (doing data collection via phone at 0, 6, 12 with participant) is blind to allocation - how will they keep this concealed & is it the same person collecting the data throughout? Are they blinding at analysis/statistician level? Further clarification is required.

**Response:** We respectfully refer Reviewer 2 to our response to comment #4 from Reviewer 1 who raised a similar question.

4. No time mentioned for recruitment of sites (n=74) this needs to be included

**Response:** We have clarified on page 7 that the total duration allotted for recruitment of participants (pharmacies and patients) is 12 months.

5. Recruitment of 5 participants, per site, over 12 months. This seems a long recruitment period for 5 people how is this justified?

**Response:** The 12 months recruitment period is for pharmacies and participants (see above response).

6. The authors identify a 12 month follow up period but no intervention period so are we to assume this is when the intervention is also delivered? This isn't clear and needs to be specified.

**Response:** We have clarified on page 7 that 12 month follow up period is indeed the period when the intervention will be delivered.

7. The authors do not include an overall timescale for the study anywhere in the paper so this needs to be included.

**Response:** We have indicated in the beginning of the Methods (Study design, page 7) that the study will be implemented from “2014 to 2016.” We have amended this to “2015 to 2018.” While we had targeted to launch the trial in November 2014, we had experienced delays in programming of the SMS platform, hence, we now target a launch in January 2015. While we had originally indicated a 2 year span (2014-2016) which takes into account the above aforementioned recruitment and intervention/follow-up period, we have revised to add an additional year to take into account completion of data collection, analyses, dissemination, and knowledge translation.

Taking comments 4 to 7 altogether, we have made the following revision:

**Revision.** Methods, Study design, page 7: This trial, known as EmPhAsIS, will be implemented from 2015 to 2018 in BC, Canada. It is a pragmatic cluster randomized trial of a community-pharmacist initiated, mHealth-supported adherence intervention (EmPhAsIS intervention) for asthma, with 12 months of participant (pharmacies and patients) recruitment and 12 months of follow-up over which the intervention will also be delivered.

**Pharmacy training**
8. Training components given to pharmacists aren’t described fully. The authors don’t mention giving training on the Asthma Control Test which will be administering at follow up. Some of the elements of the training (i.e. inhaler technique) are then not discussed elsewhere so it’s not clear if this is being done as part of the education or not.

**Response:** We recognize Reviewer 2’s comment regarding the training components and the clarity of presentation. In retrospect, having “inhaler technique” in the original description is not distracting. While the training webinar incorporates content to reinforce to pharmacists the importance of inhaler technique, it is not the key information to be conveyed which are study protocol, asthma, and medication adherence.

In addition to the overall trial webinar, pharmacists will also attend separate webinars (i.e., ‘intervention webinar’, ‘usual care webinar’) and receive written study manuals specific to whether they have been assigned to the EmPhAsIS intervention or usual care group. For example, pharmacists assigned to the EmPhAsIS intervention will be provided additional, relevant training on use of the WelTel SMS platform and administration of the Asthma Control Test.

The following are corresponding revisions:

**Revision** Methods, Participants, Pharmacies, page 9, revised to: All pharmacists will attend an online workshop (webinar) during which they will be trained on the study protocol and provided education on asthma and medication adherence as part of the study. Pharmacists will also attend separate webinars (i.e., ‘intervention webinar’, ‘usual care webinar’) and receive written study manuals specific to whether they have been assigned to the EmPhAsIS intervention or usual care group.

**Revision** Methods, Study groups, Intervention (EmPhAsIS) group, page 12, added: In the separate training provided to pharmacists in the EmPhAsIS intervention group, webinars will provide step-by-step instruction on use of the WelTel platform as well as administration of the ACT over the telephone. Patient responses to the ACT items will be entered into a survey system that will automatically score the questionnaire to facilitate this step for the pharmacist.

9. Pharmacists will be giving ‘counselling’ to the participants; what does this entail and who is training the pharmacist to be counsellors?

**Response:** Part of the responsibility of a pharmacist in providing pharmaceutical care involves counseling patients; this entails mainly education on the indication, efficacy, and safety of medications; medication use and storage; as well as education on the diseases being managed by the medications and other lifestyle advice. Pharmacists are trained in providing this counseling throughout their professional program, and we are not providing any additional training on this as part of this study.

10. How long will the training take?

**Response:** We summarize our pharmacists training plan below.
### Pharmacy Group | Trial Webinar | Intervention Group Webinar | Usual Care Group Webinar
--- | --- | --- | ---
Intervention | 2.0 hr | 1.0 hr | --
Usual Care | 2.0 hr | -- | 0.5 hr

11. What are the components of the action plan – these are not mentioned and need including

**Response:** Since submission of the manuscript, we have had on-going investigator meetings, consultations with pharmacists, and preliminary runs of the study procedures. Due to concerns regarding feasibility and workflow impediments, we have decided to drop the action plan from pillar 1 of the EmPhAsIS intervention. This is mainly due to the fact that in order for successful implementation of the asthma action plan, each pharmacy and patient participant will require a peak flow meter, and the feasibility of this is highly questionable. We have made the appropriate deletions in the manuscript.

**Participants**

12. Are there any issues related to taking consent in under 14s? The protocol requires further clarification on ethical issues relating to consent in children and then subsequently how they will manage the consent process as a result.

**Response:** As our age inclusion criterion is age 14 years or older, we do not anticipate any issues related to consent. According to the University of British Columbia Clinical Research Ethics Board Guidance Note, “An assent form is not normally required for legally incompetent minors who are aged 14-18, since they will usually be cognitively mature enough to read the consent form.”

13. What recruitment strategies will be used? Are participants recruited opportunistically/consecutively? Will the study monitor the number of non-eligible/non-consenting?

**Response:** We appreciate Reviewer 2’s comment on recruitment strategies and have made the following revision to address.

**Revision** Methods, Participants, Patients, page 10: We will utilize recruitment strategies as with our prior pharmacy practice studies including posters and self-talkers. We will also advertise the study through various communication channels available to our research team including the study website (emphasis.core.ubc.ca) and social media. We will also implement strategies for targeting recruitment, including working closely with participating pharmacies to establish recruitment targets that are appropriate for the community they service. Furthermore, we will also implement regular monitoring of recruitment including communication (e.g., site visits, telephone calls, emails) to discuss challenges and progress as well as offer on-going support.
14. The timing of the intervention is described as 'monthly'. Do we assume it is SMS monthly over the 12 month follow up period? This needs clarifying.

Response: Yes, that is correct. The EmPhAsIS intervention involves monthly SMS over the 12 month intervention/follow-up period. We added this information in the description of the SMS-based monthly assessment as follows:

**Revision** Methods, Study groups, Intervention (EmPhAsIS) group, page 10, added highlighted text: **b) SMS-based monthly assessment of adherence to controller therapies:** The principal component of the intervention is monthly text messages, delivered over the 12 month follow-up, by which patients are asked to disclose their level of agreement with the following statement:

15. The authors show a flow chart for the steps of the intervention but don't mention how many repeated attempts they will use for follow up phone contacts and at what point they will record missing data / attrition – this needs to be included.

Response: As this is a pragmatic pharmacy practice trial, it is important to be mindful of how this may affect workflow in participating pharmacies. In our training materials, we recommend that pharmacists attempt up to at least 2 follow-up telephone calls. As pharmacists will be asked to log all telephone calls and responses/non-response, we will have a record of missing data points. We have revised the manuscript to include this as follows:

**Revision** Methods, Study groups, Intervention (EmPhAsIS) group, page 13: Pharmacists will log telephone calls including response and non-responses and in instances of non-responses, at least 2 follow-up attempts will be made.

16. Pharmacists follow up the SMS, in 24 hours, if participant scores high on the screening questions as advised by an electronically generated report. Will this report tell them which parts of the AAAQ the participant scored high on so they can adjust their telephone 'counselling' accordingly? (the AAAQ looks at why someone doesn't adhere i.e. side effects, cost, forgot, severity of asthma) This needs to be addressed and clarified.

Response: Yes, that is correct. Based on the responses, WelTel will generate an AAAQ adherence report which will identify potential barrier(s) to help facilitate and guide the follow-up telephone call. We have made the following revision to clarify this:

**Revision** Methods, Study groups, Intervention (EmPhAsIS) group, page 11: Based on the responses, WelTel will generate an AAAQ adherence report that identifies potential adherence barrier(s) (e.g., cost, fear of side effects) to help facilitate and guide the pharmacist's follow-up telephone call with the patient.
17. What happens if pharmacist can't respond within 24 hours?

Response: The 24 hours response window is a guideline provided to pharmacists. However, given that it is a pragmatic trial we anticipate that there may be instances where pharmacists are unable to respond within that window. Pharmacists are asked to log all telephone calls so we will be able to see the variability in response time.

18. If they refer to physician how will this activity be captured, will attendance at the physicians be monitored and what if repeated referrals are made? Repeated attendance at a physician may have an impact on improving adherence rather the intervention so how will this be handled in the analysis?

Response: Pharmacists will be asked to log instances when they have made a referral for patients to see their family physicians. However, we will not have information on whether patients actually saw their physicians or not, nor will we have information on what transpired during the physicians’ visits (there could have been discussions about medication adherence or not). We feel that this is beyond the scope of the current study.

Usual care

19. Sites in the control arm will receive the educational plan so that they can assess the "impact of the intervention itself" assuming they mean the SMS? But the authors don't account for the impact of the follow up phone call which may also be monthly depending on scores from the AAAQ. How will the effect of the SMS be isolated or is the follow up phone call also part of the overall intervention? Will acceptability of delivering the intervention be measured?

Response: On page 10, it states that the EmPhAsIS intervention consists of three main pillars: a) patient education, b) short-messaging-service (SMS)-based monthly assessment of adherence to controller therapies, and c) follow-up of non-adherent individuals by community pharmacists. We appreciate Reviewer 2’s question regarding whether we will assess the acceptability of delivering the intervention. While this is not part of the main trial, this may certainly provide an opportunity for a graduate student interested in assessing humanistic perspectives and outcomes.

20. Usual care participants will have had 1 contact with pharmacist in 12 months. The intervention is up to 12 contacts (and potential referrals to a physician) depending on AAAQ results. Will this be accounted for in the analysis?

Response: Usual care participants will typically have 3-4 contacts with the pharmacist over a 12-month period because prescription dispensations rarely exceed 3-month intervals in usual practice. We will take into account in the cost-effectiveness analysis the
additional pharmacist time required for follow up and counseling related to the AAAQ results, as well as additional referrals to physicians.