PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a randomized controlled trial evaluating the effects of providing essential medicines at no charge: the Carefully seLected and Easily Accessible at No Charge Medicines (CLEAN Meds) trial
AUTHORS	Persaud, Nav; Lee, Taehoon; Ahmad, Haroon; Li, Winny; Taglione, Michael; Rajakulasingam, Yathavan; Umali, Norman; Boozary, Andrew; Glazier, Richard; Gomes, Tara; Hwang, Stephen W.; Jüni, Peter; Law, Michael; Mamdani, Muhammad; Manns, Braden; Martin, Danielle; Morgan, Steve; Oh, Paul; Pinto, Andrew; Shah, baiju; Sullivan, Frank; Thorpe, Kevin; Tu, Karen; Laupacis, Andreas

VERSION 1 - REVIEW

REVIEWER	Lars L Gustafsson Division of Clinical Pharmacology Department of Laboratory Medicine Karolinska Institutet Karolinska University Hospital SE-141 86 Stockholm Sweden
REVIEW RETURNED	07-Feb-2017

GENERAL COMMENTS	The authors aim to study if a limited list of essential medicines (200) freely accessible to primary care patients can improve adherence to medicines as well as affect a number of other medical parameters. This is a randomized control study with patients provided normal care as a control arm. The study is well-designed in many respects but a number of critical issues need to be clarified. The study protocol is a type of papers being accepted for publication in BMJ Open. The authors need to explain how the two arms are comparable in all respects except for free access to a basket of essential medicines. MAJOR ISSUES TO BE ADDRESSED 1. THE TITLE OF THE ARTICLE Preferably, the title can be shortened. I do not think that it is necessary to write that essential essential medicines are carefully selected. This should be self-evident if sound methods for evaluation and selection of medicines are applied. The title could be considered to be shortened like for example: “Protocol for a randomized controlled trial evaluating the effects of providing essential medicenes at no charge: the Carefully seLected and Easily Accessible at No Charge Medications (CLEAN Meds) trial” Throughout the manuscript the authors use the word medication. In many cases it seems more appropriate you use the word medicine that reflects that it is a unique pharmacological product that varies in characteristics across the pharmacotherapeutic field. Medication is a more passive process. Please, consider when and how the word

	medication and the word medicine should be used in the text. 2. The ABSTRACT should be adapted according to the comments given about the manuscript. The abstract should contain information about the number of essential medicines provided free of charge and ensure that the patients in the control arm only differ with the intervention patients in free access to medicines. 3. The section on STRENGTHS AND LIMITATIONS of the study (page 5 of 38) can be more specific. It needs to include a discussion on the limitations of the study. 4. The INTRODUCTION (page 5 to 8) is OK except that in the end (page 8) contains too much facts and too scarce comments on the need and potentials of improving adherence to medicines providng free access to essential medicines. It is an advantage if the Introduction is shortened slightly. Could the authors in the introduction comment about the availability of data and information on medical impacts of non-adherence among patients lacking financial resources? 5. In the section AIMS AND OBJECTIVES I do not find a clear description that the control group will be comparable to the intervention group except for free access to medicines. For example, if the intervention group easily can order medicines delivered to their homes delivery to the homes of medicines must be ensured. Throughout the manuscript comparability between groups have to be ensured if the study shall be conclusive. Have the authors considered that they have included too many secondary end points in the study? 6. In the section METHODS AND ANALYSIS (Page 7 and onwards) the authors should consider inclusion of a detailed description of the plan for analysis of results. A paragraph on strengths and limitations of the study is recommended. A study protocol is worth publishing if all aspects of the design and the study management are mentioned and discussed and not only reported as facts. a. Under SETTING the authors need to explain on what basis the three primary care districts have been chosen. It seems that there might be problems to include settings with such differences in population sizes. b. Under ELIGIBILITY CRITERIA the authors need to more carefully describe how the screening process is carried out. Are the study team planning to report both screened and included patients in the plan of analysis? c. Under the section INTERVENTION ARM the authors need to ensure that this group of patients do get similar type of care and handling as the intervention arm. See previous comments. I simply do not understand how patients in the control arm get easy access to medicines inte the same way as patients in the intervention arm. d. The description on the procedure for selection of 200 essential medicines should be more extensive. How is it ensured that the group selecting medicines have competence in critical drug evaluation methods that in particular clinical pharmacologists are experts in. In addition, pharmacotherapeutic experts need to be included in the panel selecting medicines. The team needs to follow a conflict of interest policy.

	e. Information is scanty for the CONTROL ARM as commented (Page 10 or 38). Would it be a good idea to present how comparability between the two arms are ensured in a Table. Would it be possible to summarize how much extra monitoring and care are included in the study as compared to ordinary care. It must crystal clear that the number of visits for the study arm are equal with the control to exclude that unknown “placebo effects into the intervention group. f. In the section OUTCOME MEASURES the authors need to explain how a composite measure determined by several variables can serve as a robust and valid primary measure of adherence. The authors needs to be more clear in the composite measure and argue why it will be valid. g. The section DATA COLLECTION (Page 13). Is it similar between groups? h. The section STATISTICAL ANALYSIS (page 14): no comments. As said, the primary outcome parameter seems to be composite. i. The section SAMPLE SIZE RATIONALE is important. To me it seems optimistic to expect that the intervention group will reach an adherence of 90%. The authors need to explain why there are so optimistic? 7. In the section METHODS AND ANALYSIS the authors need to discuss and summarize the strengths and weaknesses of the study design. They are adviced to discuss how they will ensure that the management of the study and the recruitment will work smoothly. It is a strength to mention how the study organization is set up and also how long it expected to take to complete the study. 8. The section AUTHORS CONTRIBUTION needs to be developed. As a reviewer I am not convinced that everyone has contributed equally to the efforts in designing and planning of the study. Please, be fair towards the different contributions to the study design. 9. It is good that the CONSENT OF PARTICIPATION is included as an appendix. The same is required for the list of essential medicines recommended to be used. It is necessary that the authors explain why the extensive information to patients should be used. With such a long text it might be difficult to recruit patients since the overall idea of the study and the safety are lost among thousands of words. I understand that the Ethics Review Board may require along consent form but still this is not sound information policy and scientifically doubtful. MINOR ISSUES TO BE ADDRESSED 10. Primary subject heading (1 of 38) is not general practice. It is about drug therapy. I would suggest ADCHERENCE TO MEDICINES IN GENERAL PRACTICE 11. Secondary subjective headings should be sorted in alphabetical order. 12. Key words should be sorted in alphabetical order. Consider, if not a key word about “costs for medicines” should be included as a key word. 13. Under the section PUBLIC INVOLVEMENT (Page 15 of 38) the study team met monthly with public sector representatives. For how long time? 14. Under ETHICS AND DISSEMINATION the study team describe various ways to disseminate the results. Should not publication in

	peer-reviewed international journals be mentioned as well? This is a powerful way of dissemination.

REVIEWER	Julie Lauffenburger Brigham and Women's Hospital (USA)
REVIEW RETURNED	09-Feb-2017

GENERAL COMMENTS	The authors describe a very interesting study that may advance knowledge about how cost-related non-adherence could be mitigated in a clinical setting. I have some concerns with the methodology and description of the study that are detailed below. Major comments: - Outcomes: How will outcomes be measured if patients are presenting with more than one of the chronic conditions? What is the expected percentage of patients presenting with the chronic conditions of interest for the secondary outcomes (to ensure adequate power for these outcomes)? - Adherence with pill monitoring: On Page 9, it sounds like every 7th patient will receive a medication-tracking device; however, on Page 11, it sounds like every other patient will receive a pill tracking device (100 per group). Please clarify. - Adherence measure: The authors' use of multiple methods of measuring adherence is commendable. However, please describe in more detail how these different methods of assessing adherence will be combined into one primary measure. In particular, how will electronic pill monitoring be combined if not all patients receive them? How will censoring or dropout be handled in the adherence measure? Presumably not all patients will return to the clinic (or move away) and not all patients will respond to self-reported adherence measurements at the end of follow-up. It is possible some of these could be differential (i.e., patients in the intervention group may be more likely to respond to telephone calls). - Adherence measure: Perhaps most importantly, which medications will be included in the adherence measure? All of their medications? If patients only receive one pill cap, it could not be used for all of their medications. Are the authors taking an average of the adherence? This has major implications for their assumptions in the sample size calculation. For instance, if patients take 3 medications and patients need to be adherent to all 3 for all 3 adherence measures, the baseline proportion of patients who will be adherent will be lower than anticipated as described on Page 14. - Sample size: As described above, the assumed baseline rate for non-adherence could change dramatically depending on how the authors are measuring adherence. Especially considering that drop-outs are considered "non-adherent", the baseline rate will likely be much lower than 40-60%. The authors are also likely overestimating the expected increase in adherence between the intervention and control group (10%) from this intervention. The MI-FREEE study cited in the background (which also provided evidence-based medications for free) observed absolute differences in adherence closer to 5%, which did result in clinically-meaningful differences in CV outcomes. This study will very likely be underpowered to observe the likely differences in the primary outcome and should power their study closer to 5%. Minor comments: - Intervention/Control: It sounds like there could several aspects to the intervention (i.e., free medications from the WHO essential medicines list and distribution from a different pharmacy than may

	be usual care), so it will be difficult to disentangle whether the authors are measuring whether adherence improves due to free medications or streamlined distribution. Please clarify how the dispensation process works (i.e., if all patients required to use the same pharmacy and whether control patients access medications via the mail as well). Will patients in both the intervention and control group receive calls from pharmacists after dispensation? - Self-reported cost-related non-adherence: Please provide a description of the procedures for how patients will be contacted within clinics or otherwise to be enrolled into the study. - Methods: A sense of timelines (i.e., when the study began) would be useful. - Randomization: Was blocking used for the randomization? Please provide a little more clarification. It sounds like some blocking was used (which characteristics?) for the primary arm randomization but not for the electronic monitoring device randomization. - Secondary outcomes: The usefulness of the average per person medication costs is unclear, especially as the usual care group will by definition be higher than the intervention group. What would be much more useful is average per person total costs or total costs from the payer perspective, which incorporates medical costs. - Secondary outcome measures: Please describe how the biometric values will be “adjusted for baseline”. Randomization should ensure balance between the two patient groups. The outcome could be measured as change from baseline, which would not require adjustment.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Lars L Gustafsson
Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
Competing interests: None declared

Please leave your comments for the authors below The authors aim to study if a limited list of essential medicines (200) freely accessible to primary care patients can improve adherence to medicines as well as affect a number of other medical parameters. This is a randomized control study with patients provided normal care as a control arm.
The study is well-designed in many respects but a number of critical issues need to be clarified. The study protocol is a type of papers being accepted for publication in BMJ Open. The authors need to explain how the two arms are comparable in all respects except for free access to a basket of essential medicines.
>>> We have clarified and improved the manuscript based on the peer reviewer comments as detailed below.

MAJOR ISSUES TO BE ADDRESSED
1. THE TITLE OF THE ARTICLE
Preferably, the title can be shortened. I do not think that it is necessary to write that essential essential medicines are carefully selected. This should be self-evident if sound methods for evaluation and selection of medicines are applied. The title could be considered to be shortened like for example: “Protocol for a randomized controlled trial evaluating the effects of providing essential medicenes at no charge: the Carefully seLected and Easily Accessible at No Charge Medications (CLEAN Meds) trial”

>>>We have made this change to the title. We have used “medicines” instead of “medications” as suggested below.

Throughout the manuscript the authors use the word medication. In many cases it seems more appropriate you use the word medicine that reflects that it is a unique pharmacological product that varies in characteristics across the pharmacotherapeutic field. Medication is a more passive process. Please, consider when and how the word medication and the word medicine should be used in the text.
>>>We have made this change. We now use “medicines” instead of “medications”.

2. The ABSTRACT should be adapted according to the comments given about the manuscript. The abstract should contain information about the number of essential medicines provided free of charge and ensure that the patients in the control arm only differ with the intervention patients in free access to medicines.
>>>We have added both of these points to the abstract.

3. The section on STRENGTHS AND LIMITATIONS of the study (page 5 of 38) can be more specific. It needs to include a discussion on the limitations of the study.
>>>We have added several important limitations to this summary.

4. The INTRODUCTION (page 5 to 8) is OK except that in the end (page 8) contains too much facts and too scarce comments on the need and potentials of improving adherence to medicines providng free access to essential medicines.

It is an advantage if the Introduction is shortened slightly. Could the authors in the introduction comment about the availability of data and information on medical impacts of non-adherence among patients lacking financial resources?
>>>We have added a summarizing comment about the potential of the intervention. We have also added a brief comment about the potential impact of non-adherence.

5. In the section AIMS AND OBJECTIVES I do not find a clear description that the control group will be comparable to the intervention group except for free access to medicines. For example, if the intervention group easily can order medicines delivered to their homes delivery to the homes of medicines must be ensured. Throughout the manuscript comparability between groups have to be ensured if the study shall be conclusive.
>>>We have specified that control participants have “usual access to medicines and usual access to care” and that the intervention group has “otherwise usual care”. We have also added a sentence that indicates that participants in both groups will be treated the same apart from the intervention.

Have the authors considered that they have included too many secondary end points in the study?
>>>There are six secondary outcomes and the first two are the constituents of the primary outcome. So there are four secondary outcomes that are separate from the primary outcome. Of these four, three measure control of particular conditions and one is an economic outcome. We think that each secondary outcome is reasonable and that the total number is reasonable. We will clearly report all secondary outcomes as secondary outcomes.

6. In the section METHODS AND ANALYSIS (Page 7 and onwards) the authors should consider inclusion of a detailed description of the plan for analysis of results. A paragraph on strengths and limitations of the study is recommended. A study protocol is worth publishing if all aspects of the design and the study management are mentioned and discussed and not only reported as facts.
>>>We have added a paragraph about strengths and weaknesses. We have addressed each of the points below.

a. Under SETTING the authors need to explain on what basis the three primary care districts have been chosen. It seems that there might be problems to include settings with such differences in population sizes.
>>>We have added an explanation of why the sites were selected.

b. Under ELIGIBILITY CRITERIA the authors need to more carefully describe how the screening process is carried out. Are the study team planning to report both screened and included patients in the plan of analysis?
>>>We have added details about how patients are recruited at the sites. We will report information about screened individuals who do not consent that is allowed by the Research Ethics Board (e.g. numbers and basic demographic information)

c. Under the section INTERVENTION ARM the authors need to ensure that this group of patients do get similar type of care and handling as the intervention arm. See previous comments. I simply do not understand how patients in the control arm get easy access to medicines inte the same way as patients in the intervention arm.
>>>We have clarified that care is otherwise unchanged. Patients in the control group continue to get their medicines from the usual pharmacy in the usual way.

d. The description on the procedure for selection of 200 essential medicines should be more extensive. How is it ensured that the group selecting medicines have competence in critical drug evaluation methods that in particular clinical pharmacologists are experts in. In addition, pharmacotherapeutic experts need to be included in the panel selecting medicines. The team needs to follow a conflict of interest policy.
>>>We have provided these details and also provided a reference to a recently published paper that describes the development of the list.

e. Information is scanty for the CONTROL ARM as commented (Page 10 or 38).
Would it be a good idea to present how comparability between the two arms are ensured in a Table. Would it be possible to summarize how much extra monitoring and care are included in the study as compared to ordinary care. It must crystal clear that the number of visits for the study arm are equal with the control to exclude that unknown “placebo effects into the intervention group.
>>>We have added these clarifications.

f. In the section OUTCOME MEASURES the authors need to explain how a composite measure determined by several variables can serve as a robust and valid primary measure of adherence. The authors needs to be more clear in the composite measure and argue why it will be valid.
>>>We have added to our discussion of the validity of the measures an explanation of why the composite is valid.

g. The section DATA COLLECTION (Page 13). Is it similar between groups?
>>>Yes it is the same and we have now stated this.

h. The section STATISTICAL ANALYSIS (page 14): no comments. As said, the primary outcome parameter seems to be composite.
>>>Yes it is a composite. See above.

i. The section SAMPLE SIZE RATIONALE is important. To me it seems optimistic to expect that the intervention group will reach an adherence of 90%. The authors need to explain why there are so optimistic?
>>>We have now explained the difference between adherence to the invtervention (that is used for

the sample size calculation as usual and adherence to medicines (that is an outcome of the study to be measured). The sample size calculation is based on 90 % adherence to the intervention and a 10 % difference in the primary outcome.

7. In the section METHODS AND ANALYSIS the authors need to discuss and summarize the strengths and weaknesses of the study design. They are adviced to discuss how they will ensure that the management of the study and the recruitment will work smoothly. It is a strength to mention how the study organization is set up and also how long it expected to take to complete the study.
>>>We have added a paragraph about the strength and weaknesses. We have added a section on management. We have included an expected duration of the study.

8. The section AUTHORS CONTRIBUTION needs to be developed. As a reviewer I am not convinced that everyone has contributed equally to the efforts in designing and planning of the study. Please, be fair towards the different contributions to the study design.
>>> We have clarified the statement.

9. It is good that the CONSENT OF PARTICIPATION is included as an appendix. The same is required for the list of essential medicines recommended to be used. It is necessary that the authors explain why the extensive information to patients should be used. With such a long text it might be difficult to recruit patients since the overall idea of the study and the safety are lost among thousands of words. I understand that the Ethics Review Board may require along consent form but still this is not sound information policy and scientifically doubtful.

>>>We have provided a url for the list of essential medicines that, as per the protocol, may change. We agree that the informed consent form is long and this is indeed required by the Research Ethics Board. We have added the length of the informed consent form as a limitation.

MINOR ISSUES TO BE ADDRESSED
10. Primary subject heading (1 of 38) is not general practice. It is about drug therapy. I would suggest ADCHERENCE TO MEDICINES IN GENERAL PRACTICE
>>>There are only a small number of general primary subject headings and the suggestion is not one of them.

11. Secondary subjective headings should be sorted in alphabetical order.
>>>The list is ordered by the online submission system.

12. Key words should be sorted in alphabetical order. Consider, if not a key word about “costs for medicines” should be included as a key word.

>>>We have re-ordered the key words and added costs.

13. Under the section PUBLIC INVOLVEMENT (Page 15 of 38) the study team met monthly with public sector representatives. For how long time?
>>>We have added this.

14. Under ETHICS AND DISSEMINATION the study team describe various ways to disseminate the results. Should not publication in peer-reviewed international journals be mentioned as well? This is a powerful way of dissemination.
>>>We have added this.

Reviewer: 2
Julie Lauffenburger
Brigham and Women's Hospital (USA)
Competing interests: None declared

Please leave your comments for the authors below
The authors describe a very interesting study that may advance knowledge about how cost-related non-adherence could be mitigated in a clinical setting. I have some concerns with the methodology and description of the study that are detailed below.
Major comments:
- Outcomes: How will outcomes be measured if patients are presenting with more than one of the chronic conditions? What is the expected percentage of patients presenting with the chronic conditions of interest for the secondary outcomes (to ensure adequate power for these outcomes)?
>>>The primary outcome can be measured for all participants regardless of condition. The sample size calculation is based on the primary outcome. The secondary outcomes related to particular conditions will only be assessed for participants with those conditions. We have clarified this.

- Adherence with pill monitoring: On Page 9, it sounds like every 7th patient will receive a medication-tracking device; however, on Page 11, it sounds like every other patient will receive a pill tracking device (100 per group). Please clarify.
>>>Only a subset will receive the tracking device. We have re-iterated this in the text.

- Adherence measure: The authors' use of multiple methods of measuring adherence is commendable. However, please describe in more detail how these different methods of assessing adherence will be combined into one primary measure. In particular, how will electronic pill monitoring be combined if not all patients receive them? How will censoring or dropout be handled in the adherence measure? Presumably not all patients will return to the clinic (or move away) and not all patients will respond to self-reported adherence measurements at the end of follow-up. It is possible some of these could be differential (i.e., patients in the intervention group may be more likely to respond to telephone calls).
>>>We have clarified in the text that we will use the lowest reported adherence. We will assume patients with missing data are non-adherent. Since patients in the control group may be more likely to have missing data, we will perform and report a sensitivity analysis to determine the effect of missing data.

- Adherence measure: Perhaps most importantly, which medications will be included in the adherence measure? All of their medications? If patients only receive one pill cap, it could not be used for all of their medications. Are the authors taking an average of the adherence? This has major implications for their assumptions in the sample size calculation. For instance, if patients take 3 medications and patients need to be adherent to all 3 for all 3 adherence measures, the baseline proportion of patients who will be adherent will be lower than anticipated as described on Page 14.
>>>All medications except medications taken on an "as needed" basis will be included in the primary analysis. Patients will get one tracking device for each medicine. The unit of analysis is the number of prescribed medications.

- Sample size: As described above, the assumed baseline rate for non-adherence could change dramatically depending on how the authors are measuring adherence. Especially considering that drop-outs are considered "non-adherent", the baseline rate will likely be much lower than 40-60%. The authors are also likely overestimating the expected increase in adherence between the intervention and control group (10%) from this intervention. The MI-FREEE study cited in the

background (which also provided evidence-based medications for free) observed absolute differences in adherence closer to 5%, which did result in clinically-meaningful differences in CV outcomes. This study will very likely be underpowered to observe the likely differences in the primary outcome and should power their study closer to 5%.
>>>This study includes primary care patients who are at a much lower risk of adverse events compared with participants in the MI-FREEE study (who had all had an MI). Thus we have chosen clinically important difference of 10 %. Also, other studies have shown improvements in adherence that are larger than the 5 % seen in the MI-FREEE study: 21 % (86 % versus 65 %) in Thom et al (2013), 22 % (67% versus 45 %) in Farooq et al 2011)
Thom, S., et al., Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. JAMA, 2013. 310(9): p. 918-29.
Farooq, S., et al., Schizophrenia medication adherence in a resource-poor setting: randomised controlled trial of supervised treatment in out-patients for schizophrenia (STOPS). Br J Psychiatry, 2011. 199(6): p. 467-72.

Minor comments:
- Intervention/Control: It sounds like there could several aspects to the intervention (i.e., free medications from the WHO essential medicines list and distribution from a different pharmacy than may be usual care), so it will be difficult to disentangle whether the authors are measuring whether adherence improves due to free medications or streamlined distribution. Please clarify how the dispensation process works (i.e., if all patients required to use the same pharmacy and whether control patients access medications via the mail as well). Will patients in both the intervention and control group receive calls from pharmacists after dispensation?
>>>We have made the fact that the intervention has several components more clear and we have described our inability to disentangle the effects of the different components as a limitation.

- Self-reported cost-related non-adherence: Please provide a description of the procedures for how patients will be contacted within clinics or otherwise to be enrolled into the study.
>>>We have added this information.

- Methods: A sense of timelines (i.e., when the study began) would be useful.
>>>We have added this information about the timeline and the registration details will also be updated.

- Randomization: Was blocking used for the randomization? Please provide a little more clarification. It sounds like some blocking was used (which characteristics?) for the primary arm randomization but not for the electronic monitoring device randomization.
>>>Yes we have clarified that block randomization by site was used.

- Secondary outcomes: The usefulness of the average per person medication costs is unclear, especially as the usual care group will by definition be higher than the intervention group. What would be much more useful is average per person total costs or total costs from the payer perspective, which incorporates medical costs.
>>>We have added other healthcare costs to this outcome.

- Secondary outcome measures: Please describe how the biometric values will be “adjusted for baseline”. Randomization should ensure balance between the two patient groups. The outcome could be measured as change from baseline, which would not require adjustment.
>>>Any difference between groups in baseline values (despite randomization) could be associated with the a difference in the outcomes so we will use the final value and adjust for baseline. For example, analyzing change from baseline does not protect treatment comparisons from regression to

the mean. Adjusting for baseline by including it as a covariate in a linear regression model provides and estimate of the treatment effect that is protected from regression to the mean phenomena.

VERSION 2 – REVIEW

REVIEWER	Lars L Gustafsson Division of Clinical Pharmacology (C1:68) Department of Laboratory Medicine Karolinska Institutet Karolinska University Hospital SE-141 86 Stockholm Sweden
REVIEW RETURNED	15-Mar-2017

GENERAL COMMENTS	The authors have in this version made some important but minor revisions but it is still unclear what the objective is of the study. MAJOR ISSUES 1. The major issue is if the authors really want to pursue a study with 1. an intervention group that is provided BOTH FREE ACCESS TO ESSENTIAL MEDICINES and EASY AND CONVENIENT DELIVERY OF THOSE MEDICINES AT THEIR HOMES and 2. a control group that BOTH HAS TO PAY FOR MEDICINES AND ARE NOT SUBJECT TO HOME-DELIVERY. I would like to know if the authors really want to study the value of both free access to essential medicines and smooth home-delivery? In my view it is self-evident and most likely that the results of the study may to a major part with likely increased adherenece to medicines may be explained by the smooth home-delivery. Please, explain more the thinking behind the study and be more clear in the presentation of the objectives of the study. 2. If the choose continue to argue that the study aims to study both the value of free access to essential medicines and of smooth delivery, the title needs to be changed. Presently (in the revised version) the title only tells that the study aims to investigate the value of free access to medicines. The title does not tell the truth. 3. i am not convinced (page 49 in revised manuscript) that the study is enough powered to address potential differences in main aoutcome between rural and urban areas . Please, provide statistical data supporting that you only need half population in rural as compared to urban areas for the study. 4. Throughout their answers to raised questions, the authors provide general answers with lack of clarity such as "...we have added several important point ", "....we have added these clarifications ....". They do not specify where changes have been carried out in the manuscript. 5. I can not find that the authors have added information on the

	selection process of medicines and clarified how conflict of interest policy for involved experts. Please, consult with point 6d in the previous review.

REVIEWER	Julie Lauffenburger Brigham and Women's Hospital, US
REVIEW RETURNED	03-Mar-2017

GENERAL COMMENTS	Thank you for the opportunity to review a revision of this manuscript. My largest remaining comment is regarding with the powering for an absolute improvement in those adherent of 10% or greater. This difference is quite large compared with many other interventional studies in the literature (especially those of financial incentives), and smaller differences would still be clinically meaningful (as has also been demonstrated in the literature). The authors run the risk of being underpowered in their current design and should provide some statement of potential limitations for their study. In addition, given that the outcome is non-rare (e.g., adherence rates of 40-60%), the analysis plan should clarify exactly how the outcomes will be compared as logistic regression via odds ratios will not approximate the relative risk if the outcome is non-rare.

REVIEWER	Michael Grayling MRC Biostatistics Unit Cambridge UK
REVIEW RETURNED	30-Mar-2017

GENERAL COMMENTS	Report (Statistical) This paper discusses a protocol for a randomised controlled trial to evaluate the effect on appropriate adherence of providing a selection of essential medicines at no cost, within three primary care sites in Ontario. The sample size justification is complete, itemizing all aspects required for its replication. In addition, the proposed analyses are given in detail for both the primary and secondary endpoints. Overall, the paper is written and structured well, which makes it very easy to read. As stated, the statistical methods and analyses are explained clearly and I have no major concerns over the proposed design and analysis procedures. I do however have some comments/suggested revisions which are given below. Major Comments 1.1.The trial is to be run in three site; one urban, and two rural. On ~line(L)22 of page(P)8 it is stated that the 'sites were selected…both urban and rural settings'. However, there is no further mention in the paper of how/whether this will be achieved. The analyses discussed do not mention, for example, inclusion of fixed/random effects for site, and there is no mention of secondary analyses on the data from each site. Is this assessment to be undertaken? And if so, how? 1.2.Could you offer some further insight as to why exactly you have defined your primary endpoint as adherence to appropriately prescribed medicines? You go on to define adherence and appropriate prescribing as separate secondary endpoints, which you do not correct for multiplicity for. Consequently, the paper reads as though this is an attempt to prevent having to correct for multiple

	testing. I'm sure this isn't the case, and the stated primary endpoint is what is truly of interest, but I think some statisticians may find this curious as currently written. 1.3. In the 'Sample size rationale' section you discuss how you plan to take any dropouts as non-adherent. In many realistic scenarios this would be a conservative approach, which is preferable, but it would not be conservative if for example those who drop out in the control arm are generally adherent. Since you only expect 5% dropout this likely won't be a great issue for the trial, but some indication as to how large an effect this could have upon the estimated relative risk difference would be helpful. This should be tied to the discussion of the planned sensitivity analyses. Minor Comments 2.1. In 'Outcomes' starting on ~L41 of P7, the Secondary outcomes listed do not match those from ~L18 on P12. 2.2. It may be helpful to clarify what open label means in this context, i.e., that patients obviously are aware whether they are receiving the medication for free (c.f. ~L3 of P8). 2.3.Greater clarification could be provided as to the allocation procedure. Overall there is 1:1 randomisation, is this also achieved at the site level? I didn't feel this was obvious (c.f. ~L17 of P9). 2.4. In ~L21 of P9 you state that 'every 7th patient' will receive the electronic medical tracking device. However then on ~L30 of P11 you state '100 participants, half from each treatment group' will receive them. Given there are to be 392 patients in each arm, unless I'm missing something these figures do not add up. 2.5.You are to 'report adherence rates by each of the three measures' as per ~L51 of P11. There is no mention of performing analyses according to these three measures separately. I feel, unless you are strongly against this, that this may be a helpful secondary analysis to assess the trial's results. 2.6.How are the HbA1c, blood pressure and LDL cholesterol measures to be taken (c.f. ~L22-28 on P12)? I'm guessing it is by standard methods. 2.7.You state that you will 'also record comments' on ~L42 of P12. Is this by telephone recording or a written questionnaire? 2.8. It would be helpful to be clear about whether you are talking about a two-sided or one-sided test in the 'sample size rationale'. Typographical/Grammatical Comments The authors may find the following proposed typographical and grammatical revisions helpful: 3.1.A set of round brackets are opened on ~L14 of P7 but never closed. 3.2. I believe the word 'prescribing' is missing after 'appropriate' on ~L21 of P7. 3.3. I think ~L28 of P8 should read 'aged 18 years or older who self report'. 3.4. It seems the 'electronic medicine tracking device' mentioned on ~L23 of P9 is the 'electronic bill bottle' then noted immediately after. I thought these sentences were slightly confusing as to whether these were the same/different things. A reference as to how this device works would also be helpful here I feel. 3.5.There is a full stop missing before '[25, 26]' on ~L53 of P9. 3.6.Should ~L14 of P11 read 'as for diary reports[31]' rather than 'as diary reports[31]'?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Julie Lauffenburger
Brigham and Women's Hospital (USA)
Competing interests: None declared
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Thank you for the opportunity to review a revision of this manuscript.
My largest remaining comment is regarding with the powering for an absolute improvement in those adherent of 10% or greater. This difference is quite large compared with many other interventional studies in the literature (especially those of financial incentives), and smaller differences would still be clinically meaningful (as has also been demonstrated in the literature). The authors run the risk of being underpowered in their current design and should provide some statement of potential limitations for their study.
***AUTHOR RESPONSE: We agree with the reviewer and we have added this as a limitation. See the bottom of page 16.

In addition, given that the outcome is non-rare (e.g., adherence rates of 40-60%), the analysis plan should clarify exactly how the outcomes will be compared as logistic regression via odds ratios will not approximate the relative risk if the outcome is non-rare.

***AUTHOR RESPONSE: We have clarified the plan at the bottom of page 13. We will indeed report the odds ratio as this is the appropriate way to test the primary hypothesis. We agree with the reviewer that the odds ratio will not approximate the relative risk and we do not plan to provide an estimate of the relative risk. We will report the (absolute) risk difference as described on page 13.

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Reviewer: 1
Lars L Gustafsson
Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
Competing interests: None declared
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The authors have in this version made some important but minor revisions but it is still unclear what the objective is of the study.

MAJOR ISSUES
1. The major issue is if the authors really want to pursue a study with 1. an intervention group that is provided BOTH FREE ACCESS TO ESSENTIAL MEDICINES and EASY AND CONVENIENT DELIVERY OF THOSE MEDICINES AT THEIR HOMES and 2. a control group that BOTH HAS TO PAY FOR MEDICINES AND ARE NOT SUBJECT TO HOME-DELIVERY.

I would like to know if the authors really want to study the value of both free access to essential medicines and smooth home-delivery?

In my view it is self-evident and most likely that the results of the study may to a major part with likely increased adherenece to medicines may be explained by the smooth home-delivery.

Please, explain more the thinking behind the study and be more clear in the presentation of the objectives of the study.

***AUTHOR RESPONSE: The intervention is comprised of three elements (1) free access, (2) a short list of essential medicines and (3) convenient access to medicines (patients do not have to go to a pharmacy because medicines are either present in the clinic or mailed to patients). We designed the intervention this way because it is efficient and scalable. This trial is meant to inform public policy in Canada and other jurisdictions where free and convenient access to essential medications is not available and the intervention could be scaled up to provide medicines to millions of people. The intervention may or may not improve adherence. If the intervention improves adherence – and if it is deemed important to do so – future studies could determine the relative contributions of the three components of the intervention to the change in adherence. Alternatively, the intervention could be scaled up. If the intervention does not improve adherence, other approaches might be needed. The limitations of multifaceted intervention are described on page 16 in the paragraph on limitations.

2. If the choose continue to argue that the study aims to study both the value of free access to essential medicines and of smooth delivery, the title needs to be changed.Presently (in the revised version) the title only tells that the study aims to investigate the value of free access to medicines. The title does not tell the truth.

***AUTHOR RESPONSE: The title includes the term “Easily Accessible” which refers to the medications being delivered to patients in a convenient way and also to the certain medications that need to be started quickly being present in the clinic. The abstract also describes access as “free and convenient” and the intervention is described in detail in the manuscript.

3. i am not convinced (page 49 in revised manuscript) that the study is enough powered to address potential differences in main aoutcome between rural and urban areas .

Please, provide statistical data supporting that you only need half population in rural as compared to urban areas for the study.

***AUTHOR RESPONSE: The study is powered to detect a difference between the control and intervention groups with respect to the primary outcome. We will also report any differences between urban and rural sites as results of exploratory analyses that might generate new hypotheses that can be tested in future studies.

4. Throughout their answers to raised questions, the authors provide general answers with lack of clarity such as "...we have added several important point ", "....we have added these clarifications ....". They do not specify where changes have been carried out in the manuscript.
***AUTHOR RESPONSE: We have provided page numbers in this response. We have also provided a tracked changes version that shows each change made.

5. I can not find that the authors have added information on the selection process of medicines and clarified how conflict of interest policy for involved experts. Please, consult with point 6d in the previous review.
***AUTHOR RESPONSE: From the previous review, point 6d was: “The description on the procedure for selection of 200 essential medicines should be more extensive. How is it ensured that the group selecting medicines have competence in critical drug evaluation methods that in particular clinical pharmacologists are experts in. In addition, pharmacotherapeutic experts need to be included in the panel selecting medicines. The team needs to follow a conflict of interest policy.” At the bottom of page 8, under the heading Intervention arm, we include the following description: The list of essential medicines was adapted from the 2013 WHO Model List of Essential Medicines [23] using a four-step interdisciplinary, clinical peer review process. Additional medicines were added or removed from the list based on clinician suggestions, pharmaceutical industry suggestions and retrospective prescribing data. [24] A panel of clinician-scientists who are free of financial conflicts of interest convenes every

three months to evaluate the evidence and votes on recommended changes to the list using a modified nominal group technique [25, 26] For medicines removed from the list throughout the duration of the study, patients who were initially prescribed these medicines upon enrollment will remain on these medicines." We have also added a citation to a paper describing the development of the list (reference 24).

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Reviewer: 3
Journal: BMJ Open
Manuscript ID: bmjopen-2016-015686.R1
Article Type: Protocol
Date Submitted by the Author: 28th February 2017
Reviewer: Michael Grayling
Data Review Submitted: 30th March 2017
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Report (Statistical) This paper discusses a protocol for a randomised controlled trial to evaluate the effect on appropriate adherence of providing a selection of essential medicines at no cost, within three primary care sites in Ontario. The sample size justification is complete, itemizing all aspects required for its replication. In addition, the proposed analyses are given in detail for both the primary and secondary endpoints. Overall, the paper is written and structured well, which makes it very easy to read. As stated, the statistical methods and analyses are explained clearly and I have no major concerns over the proposed design and analysis procedures. I do however have some comments/suggested revisions which are given below.

Major Comments

1.1.The trial is to be run in three site; one urban, and two rural. On ~line(L)22 of page(P)8 it is stated that the 'sites were selected…both urban and rural settings'. However, there is no further mention in the paper of how/whether this will be achieved. The analyses discussed do not mention, for example, inclusion of fixed/random effects for site, and there is no mention of secondary analyses on the data from each site. Is this assessment to be undertaken? And if so, how?

***AUTHOR RESPONSE: We agree that this is an important issue and we have added an explanation at the bottom of page 13. We do not plan to include a term for site in the primary analysis model. Since we have randomized within sites, site is not a confounder. This will generate a population level estimate that is appropriate to inform public policy. Adjusting for site makes the result conditional upon the particular sites studied. As the reviewer suggests, we will also report the site-specific odds ratios in a descriptive way that may generate hypotheses that can be tested in future studies.

1.2.Could you offer some further insight as to why exactly you have defined your primary endpoint as adherence to appropriately prescribed medicines? You go on to define adherence and appropriate prescribing as separate secondary endpoints, which you do not correct for multiplicity for. Consequently, the paper reads as though this is an attempt to prevent having to correct for multiple testing. I'm sure this isn't the case, and the stated primary endpoint is what is truly of interest, but I think some statisticians may find this curious as currently written.

***AUTHOR RESPONSE: The primary outcome is based on the premise that it is only good to improve adherence to medicines if they are appropriately prescribed. Improving adherence to medications that are inappropriately prescribed may actually be harmful. Some readers may be interested in the effects of the intervention on adherence or appropriateness separately and so we will report them separately in a secondary analysis.

1.3.In the 'Sample size rationale' section you discuss how you plan to take any dropouts as

nonadherent. In many realistic scenarios this would be a conservative approach, which is preferable, but it would not be conservative if for example those who drop out in the control arm are generally adherent. Since you only expect 5% dropout this likely won't be a great issue for the trial, but some indication as to how large an effect this could have upon the estimated relative risk difference would be helpful. This should be tied to the discussion of the planned sensitivity analyses.
***AUTHOR RESPONSE: Based on the interim data available, the dropout rate is 1.8 % and dropouts are balanced between groups (54 % control, 46 % intervention). So this will unlikely be an issue. There is also no reason to believe that dropouts in the control group would be more adherent than dropouts in the intervention group.

Minor Comments
2.1.In 'Outcomes' starting on ~L41 of P7, the Secondary outcomes listed do not match those from ~L18 on P12.
***AUTHOR RESPONSE: We have revised these to make them align.

2.2.It may be helpful to clarify what open label means in this context, i.e., that patients obviously are aware whether they are receiving the medication for free (c.f. ~L3 of P8).
***AUTHOR RESPONSE: We have added: "The trial is open label as participants are told their allocation group immediately after randomization."
2.3.Greater clarification could be provided as to the allocation procedure. Overall there is 1:1 randomisation, is this also achieved at the site level? I didn't feel this was obvious (c.f. ~L17 of P9).
***AUTHOR RESPONSE: Allocation is balanced at the site level. The top of page 8 states that randomization is "stratified by site using permuted blocks of varying sizes".

2.4.In ~L21 of P9 you state that 'every 7th patient' will receive the electronic medical tracking device. However then on ~L30 of P11 you state '100 participants, half from each treatment group' will receive them. Given there are to be 392 patients in each arm, unless I'm missing something these figures do not add up.
***AUTHOR RESPONSE: We have corrected page 10 to 112.

2.5.You are to 'report adherence rates by each of the three measures' as per ~L51 of P11. There is no mention of performing analyses according to these three measures separately. I feel, unless you are strongly against this, that this may be a helpful secondary analysis to assess the trial's results.
***AUTHOR RESPONSE: We do not plan to test hypotheses for the three different measures. We do plan to report these but we do not think it is necessary to describe these as secondary outcomes. The results may or may not be importantly different from the primary outcome. In subsequent work, we may prepare Bland-Altman plots to compare the measures. But we do not believe that exploring the differences between these measures is important when reporting the results of the trial.

2.6.How are the HbA1c, blood pressure and LDL cholesterol measures to be taken (c.f. ~L22-28 on P12)? I'm guessing it is by standard methods.
***AUTHOR RESPONSE: Yes, these will be performed as part of usual care in laboratories using standard methods and subject to stringent quality control procedures.

2.7.You state that you will 'also record comments' on ~L42 of P12. Is this by telephone recording or a written questionnaire?
***AUTHOR RESPONSE: We have clarified this on page 11 to "transcribe"

2.8.It would be helpful to be clear about whether you are talking about a two-sided or one-sided test in the 'sample size rationale'.
***AUTHOR RESPONSE: We have clarified that this is two sided at the bottom of page 13.

Typographical/Grammatical Comments The authors may find the following proposed typographical and grammatical revisions helpful:
3.1.A set of round brackets are opened on ~L14 of P7 but never closed.
***AUTHOR RESPONSE: Corrected with thanks.

3.2.I believe the word 'prescribing' is missing after 'appropriate' on ~L21 of P7.
***AUTHOR RESPONSE: Corrected with thanks.

3.3.I think ~L28 of P8 should read 'aged 18 years or older who self report'.
***AUTHOR RESPONSE: We removed the hyphen.

3.4.It seems the 'electronic medicine tracking device' mentioned on ~L23 of P9 is the 'electronic bill bottle' then noted immediately after. I thought these sentences were slightly confusing as to whether these were the same/different things. A reference as to how this device works would also be helpful here I feel.
***AUTHOR RESPONSE: We have simplified this by only using the term "electronic monitoring device" and we have explained how they work on page 10.

3.5.There is a full stop missing before '[25, 26]' on ~L53 of P9.
***AUTHOR RESPONSE: Corrected with thanks.

3.6.Should ~L14 of P11 read 'as for diary reports[31]' rather than 'as diary reports[31]'?
***AUTHOR RESPONSE: We changed this to "like".

VERSION 3 – REVIEW

REVIEWER	Julie Lauffenburger Brigham and Women's Hospital, USA
REVIEW RETURNED	15-Apr-2017

GENERAL COMMENTS	I have no further comments after this revision.

REVIEWER	Michael Grayling MRC Biostatistics Unit, UK
REVIEW RETURNED	19-Apr-2017

GENERAL COMMENTS	In my review of the previous version of this paper, I expressed a small number of concerns regarding the content. In particular, I felt clarifications around the randomisation scheme and the analyses planned to address the fact that the trial consists of three sites were required. The authors have now addressed these points, and the others I made well. Consequently, I have no further concerns regarding the manuscript.