Author's response to reviews

Title: Evaluation of the short-term short message service reminders on patient's medication adherence results of a random controlled study to assess the effects of and satisfaction with incoming messages

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Version: 3 Date: 7 July 2013

Author's response to reviews: see over
Dear Editor:

We are resubmitting a revised paper entitled “Evaluation of the short-term short message service reminders on patient’s medication adherence: results of a random controlled study to assess the effects of and satisfaction with incoming messages” according to the editor’s suggestion. We have followed the reviewers’ comments to adjust or correct our manuscript. We also provide the questionnaire to the reviewers in the attached file. The following pages are our replies to reviewers’ comments. We have marked with blue color for our any changes or adjustment in the revised manuscript.

Our manuscript has not previously been published in print or in electronic format and has not under consideration elsewhere. Besides, none of the authors has any conflict of interest in connection with this paper. We hope that you will consider our article for publication and look forward to hearing from you. Please let us know if any revisions are needed.

Sincerely yours,

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Reviewer's report
Title: Evaluation of the short message service reminders on patient's medication adherence results of a controlled study to assess the effects of and satisfaction with incoming messages
Version: 2 Date: 2 May 2013
Reviewer: Thyra E de Jongh
Reviewer's report:

Major Compulsory Revisions
Methods
1. It is unclear whether group assignment was random or not. Given that randomization is not explicitly mentioned, either in the title or in the methods, one is inclined to assume that this was not done. If indeed there was no randomization, it should be justified why this was not done. After all, given the controlled setting, this would have seemed entirely feasible and randomization would have eliminated a potential source of allocation bias.
Ans: Thank you for your comments. This study was designed to randomly assign patients into intervention group and control group. We designed that hospital’s pharmacists randomly and orderly recommended two patients assigned to the intervention group and one to the control group when the patients met the inclusion criteria. Since all patients were gradually recruited during several weeks, we hoped to send them the SMS as soon as possible after the patients agreed to participate in this study. We did not randomly assign patients into each group after we recruited all patients. Since all patients took medication daily and it would take several weeks or more than one month to recruit all necessary patients, if we sent the SMS after we finished recruiting all patients, it would take too long time. This is the reason why we designed to randomly assign patients when we recruited them.

2. It is not clear on what the allocation ratio of 2:1 was based. Was this somehow informed by a power calculation? Is it related to the fact that there were 3 hospitals involved, i.e. was there cluster randomization? This should be explained.
Ans: Since we focused on the effect of the SMS in the intervention group, this study purposely increase the sample size in intervention group. The sample size of intervention group and control group were allocated with ratio 2:1.

3. The outcome measures relating to adherence are insufficiently defined. For
instance, what is meant by a “delayed dose”: i.e. at what point is a dose considered delayed and when is it considered missed completely?

Ans: Thank you for your comments. If the patients did not take medication as prescribed either in timing or dosage, it was defined as “delayed dose”. If the patients did not take medication at all, it was defined as “missed dose”. (P.9)

Discussion and study limitations

4. Follow-up of only 7 days seems extremely short for an intervention that is supposed to aid in management of chronic disease. It is well known that interest in novel technologies such as SMS reminders wanes over time (E.g. Hanauer et al., Diabetes Technol Ther. 2009, 11(2):99-106) and that long-term adherence is much harder to foment than short-term adherence. This concern is especially relevant in light of the reported finding that the frequency of messages was already perceived as ‘too high’. Intervention fatigue is likely to be a limiting factor on the effectiveness of the intervention. Although this is recognized as a limitation in the discussion, it nonetheless raises questions about the relevance of this work in relation to management of chronic diseases. One could argue that the findings are more relevant to time-limited treatments, such as adherence to a course of antibiotics. This discussion needs to be worked out much better.

Ans: Thank you for your suggestion. We have added the discussion in page 16-17 and the limitation in page 21.

5. Given that the medication adherence outcome data are purely reliant on self-reporting, there is a high likelihood of reporting bias. Many studies have shown that self-reported adherence rates tend to be overestimated as compared with findings from e.g. electronic pill-counting devices. This needs to be discussed and recognized as a limitation.

Ans: Thank you for your valued suggestions. Many studies have shown that the medication adherence outcome data were purely reliant on self-reporting, and there was a high likelihood of reporting bias. Since the overestimation might exist in both intervention and control group, this study designed including two groups (intervention vs. control) and had both pre-test and post-test, which tried to reduce the effect caused by reporting bias in two groups. We have added the limitation in page 21-22.

6. In the conclusion, it is mentioned that the PMP system may have sent more than one reminder to patients receiving several drugs from the clinical department at the time of recruitment. This implies that these patients would also have had to
show adherence to several drug regimes. How has this been treated in the analysis? Is there potential for clustering of data? No explanation of this is given at all.

Ans: Thank you for your comments. In this study, we asked the participants the situation of delayed dose or missed dose in previous three days. Each patient was treated as one sample in the analysis and there wasn’t potential for clustering of data.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Ans: We have corrected or adjusted the inappropriate or wrong terms in the text, tables or figure.

7. It is unclear what the data under the heading ‘demand for SMS' in Table 5 refer to. The categories used here are identical to those used under ‘satisfaction with SMS’ in the same table. Is this correct? Please confirm.

Ans: Thank you for your suggestion. We have adjusted the description of questions in table 5. In the questionnaire, we asked the participants’ satisfaction with the SMS, and also asked them about their demand for some specifications of message sent through SMS reminders.

8. The reporting of percentages throughout the text is somewhat inconsistent. Sometimes integers are used; other times one or even two digits. This needs to be made consistent.

Ans: Thank you for your comments. We have adjusted the number of decimals.

Discretionary Revisions
Methods

9. It is stated that the SMS content depended on “the extent of patient involvement in the text message medication reminder service”. What does this mean? How is the extent of patient involvement defined and in what way did this influence the SMS content?

Ans: Thank you for your comments. It was misunderstanding and incorrect translation when the manuscript was translated to English. We have corrected it to “The SMS content depended on the patient medication and frequency of medication use.” (in page 9)

10. Are all patients, both in the intervention and control group, users of the PMP
differing only in whether they receive the value-added SMS or is the PMP only used by those in the intervention group? If used by both groups, have there been any studies evaluating the effectiveness of the PMP without the SMS reminders already? If so, these should be discussed and referenced. If, however, the comparison is between ‘no PMP’ versus ‘PMP + SMS’, the availability of other adherence supporting features of the PMP should be discussed as a potential confounding factor.

Ans: In this study, medication reminders were sent to the patients by the PMP system via text messages only for the intervention group. The PMP did not provide any additional information or function to any participants in this study. Only the SMS was involved in this study.

11. Given that, according to Table 2, the denominator N is set to the number of participants in each group, rather than to the number of medication doses scheduled, I assume that the number of ‘delayed doses’ actually is the number of patients with a delayed dose (and similarly, the number of patients who missed a dose). This is in itself a justifiable choice, but it would also have been interesting to know if the number of delayed or missed doses per patient has decreased. In other words, even if a patient is still classified as ‘delayed/missed dose’, it is possible that his/her overall adherence has improved. Has this been considered as a possible outcome and if not, why not? After all, perfect adherence is often not required to achieve improved treatment effect.

Ans: In this study, as for patients having any improvement in decreases of delayed doses, there was 91.49% and 67.34% in the intervention group and control group, respectively. As for patients having any improvement in decrease of missed doses, there was 96.02% and 84.74% in the intervention group and control group, respectively. We have added this information of results into the result section in page 12-13. Since this study only asked the participants’ medication adherence in the past three days which was a short period of time, complete medication adherence might be a better measurement in this case. Thank you for your valued comments.

12. The approach to analysis of the effectiveness data is somewhat unclear. It is stated that: “McNemar’s tests were conducted to understand the distinct levels of improvement in the incidence of delayed or missed medication doses among the patient groups.” Presumably, this was only carried out within the groups, i.e. comparison of pre-test vs. post-test data, as this test cannot be used for comparison between the intervention and control groups. However, it is not
explained up front how the comparison between these two groups was done, whereas this is in fact the most relevant comparison. It appears that a simple odds ratio (OR) was used to describe the effect sizes. The methods section should mention this.

Answer: Thank you for your comments. We have adjusted the description for McNemar’s test in the data analysis section (in page 10). The odds ratio (OR) was used to describe the effect sizes (in page 11).

Discussion

13. The discussion into factors influencing adherence raises some questions. For instance, it is stated that “patients aged 65 years or older were significantly less likely to experience an improvement in the incidence of missed doses compared to the patients aged between 20 and 34 years”. The explanation given is interesting and grounded in literature, but it is striking that this same effect is not also seen for “delayed doses”. There the data show no significant effect at all, which sheds doubts on the explanation given. A similar lack of correlation between delayed and missed doses applies to the observation regarding military, civil servants, teachers and students.

Answer: Thank you for your good comments. We have added the explanation in discussion section (in page 17-18). Comparing the results in table 3 and table 4, when the senior patients neglected and delayed taking medication, after they received the SMS reminders, they would have higher likelihood to take the delayed medication than those who missed the medication. The reason might imply that if the senior patients neglected and failed to take medication on time, when they received the reminders, they would have higher likelihood to improve their adherence than those who did not have strong intention to take all medication and would still miss the medication. The similar situation happened in military, civil servants, teachers and students.

Answer: Thank you for your good comments. We have added the explanation in discussion section (in page 17-18). Comparing the results in table 3 and table 4, when the senior patients neglected and delayed taking medication, after they received the SMS reminders, they would have higher likelihood to take the delayed medication than those who missed the medication. The reason might imply that if the senior patients neglected and failed to take medication on time, when they received the reminders, they would have higher likelihood to improve their adherence than those who did not have strong intention to take all medication and would still miss the medication. The similar situation happened in military, civil servants, teachers and students.

14. There are quite a few studies that have used SMS reminders to impact medication adherence, e.g. for chronic disease management (e.g. asthma, diabetes, hypertension, HIV), adherence to oral contraceptives, or to chemoprophylaxis. This paper references a few of these studies [12, 13, 15, 16], though not necessarily the most appropriate. For instance, the reference by Da Costa TM 2010 [15] is a study centered primarily on appointment reminders rather than medication reminders. A better reference by the same authors would be: da Costa TM, et al. International Journal of Medical Informatics 81 (2012), 257-269. Similarly, the study by Kim et al. [16] uses SMS for supporting self-management
of diabetes, but does not actually use medication reminders. The authors should ground their findings better in existing literature and, in doing so, distinguish between short-term and long-term effectiveness.

**Ans:** Thank you for your comments. We have adjusted literature and discussed both short-term and long-term effectiveness (in page 16-17).

**General**

12. The English is a bit awkward at times and would probably benefit from some editing, but is generally acceptable.

**Ans:** Thank you for your comments. We will do our best to improve English in the text, and send it to do English edited again.
Reviewer's report
Title: Evaluation of the short-term short message service reminders on patient's medication adherence results of a controlled study to assess the effects of and satisfaction with incoming messages
Version: 2 Date: 13 May 2013
Reviewer: Brian Suffoletto

Reviewer's report:

Major Compulsory Revisions
1. Title: suggest adding "short-term" and "exploratory" as there does not appear to be an a priori hypothesis and sample size calculation.
   Ans: Thank you for your comments. We have adjusted the title with “Evaluation of the short-term short message service reminders on patient's medication adherence: results of a random controlled study to assess the effects of and satisfaction with incoming messages”.

2. No abstract was included. Please include.
   Ans: We have included abstract in the manuscript.

Background:
3. Overall, needs more concision. PP 1 should summarize of med adherence difficulties in patient populations. PP2 should summarize prior interventions. PP3 should discuss prior interventions using SMS for med adherence (consider adding reference to Suffoletto et al., 2013. A mobile phone text message program to measure oral antibiotic use and provide feedback on adherence to patients discharged from the emergency department.)
   Ans: Thank you for your comments. We have reduced the background text and became more concise.

4. A priori hypotheses need to be explicitly stated at end of background. i.e. "The primary aim of this study was to determine the effect of SMS medication reminders on number of delayed doses and missing doses of medications. Secondary aim includes determining the satisfaction and demand for an SMS-based intervention."
   Ans: We have adjusted the text in the background section. Thank you for your suggestions.

Methods:
5. How patients were allocated to control and intervention exposure needs to be discussed.

Ans: We planned to recruit participants from three medical centers according to the outpatient volume in each hospital. Since we focused on the effect of the SMS in the intervention group, this study purposely increase the sample size in intervention group. The sample size of intervention group and control group were allocated with ratio 2:1. Finally, in this study, the intervention group and control group had 780 and 460 participants at the pretest, respectively. The number of valid participants who completed 2 surveys was 763 in the intervention group and 435 in the control group. In total, we obtained 1,198 questionnaires from the 3 study hospitals. In each hospital, we collected 188, 225, 350 for intervention group and 117, 118, 200 participants for control group, respectively. We have added the description in page 8 and 11.

6. Authors need to specify how they assessed and defined delayed or missing doses at baseline (for inclusion) and at follow-up. Please include samples of actual questions used. Are they validated tools?

Ans: Thank you for your comments. If the patients did not take medication as prescribed either in timing or dosage, it was defined as “delayed dose”. If the patients did not take medication at all, it was defined as “missed dose”. This study used a self-designed questionnaire involving a pretest and a posttest as the research tools. We have added the definition of delayed doses and missed doses in page 9. The questionnaire was attached in the appendix file.

7. Authors need to clarify whether the SMS system was part of clinical care or research.

Ans: The SMS system was only for research and was not a part of clinical care in this study.

8. Please provide actual content of messages.

Ans: The following text was one example of content of messages for the first message sent to the patient:

“A warm reminding! You visited xx Clinics at xx Hospital on 2010/3/15. We remind you to follow your prescription, which included taking Panadol® one tablet each day for 7 days, Lasix® 0.5 tablet once each day immediately after meal for 7 days, and Lontex® 0.5 tablet once each day for 7 days. Please remember to take medicine on time. Wish you a prompt recovery.”

After we sent the first message to the patient, we would regularly sent the
message which included each medication name, doses, medication time, before/after meal etc. to remind patients according to the prescription schedule.

Results
9. Please specify how many participants came from each hospital.
   Ans: In each hospital, we collected 188, 225, 350 for intervention group and 117, 118, 200 participants for control group, respectively. We have added this information in page 11. Thank you for your suggestion.

10. Authors should refrain from using term "medication" as this has different connotations in US. Try "medication"
    Ans: We have changed the term. Thank you.

11. Authors need to specify what medications were used. This is critical and should be available.
    Ans: In this study, we did not specify the patients. This study recruited patients who might suffer from different diseases such as diabetes or hypertension. The following table provides the example for some diseases.

    | Disease                  | Medication Name | Dose       | Dosing frequency                        | Duration |
    |--------------------------|-----------------|------------|-----------------------------------------|----------|
    | Hypertension             | Adalat ®        | one tablet | once each day immediately after meal    | 28 days  |
    | Hypertension             | Hyzaar ®        | one tablet | once each day immediately after meal    | 28 days  |
    | Heart disease            | Cordarone ®     | 0.5 tablet | once each day immediately after meal    | 28 days  |
    | Hyperlipidemia           | Lipitor ®       | 0.5 tablet | each day                                | 28 days  |
    | Diabetes                 | Januvia ®       | one tablet | once each day immediately after meal    | 28 days  |
    | Menyal or psychiatric disease | Erispan ®    | one tablet | twice each day immediately after meal   | 14 days  |

Discussion
12. Authors need to discuss limitations more thoroughly. i.e. The problem with med adherence is largely related to long-term medications for chronic diseases.
    A 7-day interventions will not be relevant to chronic diseases. Also, we need to know about what meds were prescribed and the dosing regimen and length of prescriptions.
    Ans: (1) We have added more discussion or limitation in the text in page 16, 17, and 21. (2) In this study, we did not specify the patients. This study recruited patients who might suffer from different diseases. So, there were many kinds of
medication used in this study. Here we only provide some information the same as those in last question. Thank you for your comments.
Reviewer's report

Title: Evaluation of the short message service reminders on patient's medication adherence results of a controlled study to assess the effects of and satisfaction with incoming messages

Version: 2 Date: 1 June 2013
Reviewer: Marcia Vervloet

Reviewer's report:

Minor Essential Revisions

1. Figure 1 appears to be incomplete; some of the text appears to be invisible (e.g. in the block “Assigned to the intervention and control” and the block “Intervention”).
   Ans: We have adjusted the figure. Thank you for your comments.

2. Table 6, first sentence (“preferred text message to be sent before time medication should be consumed”) needs rewriting as it is not clear what is meant by this.
   Ans: We have adjusted it to “Preferring time to receive text messages before medication taken”. This sentence would like to ask the patient “If we want to send an SMS reminder to patients before medication taken, when would be better for you?”

3. What is meant by the term ‘phone monitoring’ (p.3)?
   Ans: Thank you for your comments. ‘phone monitoring’ has been changed to “phone follow-up”.

4. The term ‘demand for text message reminders’ is a bit confusing. What exactly do the authors wish to assess? The three statements with which ‘demand’ is assessed (“The SMS clearly described the frequency…, the method… and drug dose”) are also used to assess patients’ satisfaction with the SMS (which is indeed more appropriate in my opinion).
   Ans: We have adjusted the description to distinguish “demand for” and “satisfaction with” in table 5. In the questionnaire, we asked the participants’ satisfaction with the SMS, and also asked them about their demand for some specifications of message sent through SMS reminders.

5. It would be interesting to know whether patients could choose the times at which the medication reminder would be sent. The authors only mention that the reminders were sent at ‘specific times’. If patients were able to choose the times
themselves, they might be more positive about or satisfied with the reminders than when the times were set for them by the hospital pharmacists.

**Ans:** In this study, the patients could not choose the times at which the medication reminder would be sent. But we have asked the participants when would be your preferring time to receive the text message in the questionnaire, which would provide better information for future application.

6. It would be interesting to know what the specific text of the SMS reminder could be. Maybe the authors can provide some examples? The authors state that “the SMS content depended on the extent of patient involvement in the text message reminder service”. What exactly is meant by this statement? Does the content differ between patients regarding the amount of information given? Or how specific the information was?

**Ans:** Thank you for your comments. (1) The following text was one example of content of messages for the first message sent to the patient:

“A warm reminding! You visited xx Clinics at xx Hospital on 2010/3/15. We remind you to follow your prescription, which included taking Panadol ® one tablet each day for 7 days, Lasix ® 0.5 tablet once each day immediately after meal for 7 days, and Lontex ® 0.5 tablet once each day for 7 days. Please remember to take medicine on time. Wish you a prompt recovery.”

After we sent the first message to the patient, we would regularly sent the message which included each medication name, dose, medication time, before/after meal etc. to remind patients according to the prescription schedule.

(2) It was misunderstanding and incorrect translation when the manuscript was translated to English. We have corrected it to “The SMS content depended on the patient medication and frequency of medication use” (in page 9).

7. I would recommend being consistent in reporting percentages concerning the number of decimals (now sometimes none, sometimes one or sometimes two decimals are used).

**Ans:** Thank you for your comments. We have adjusted the number of decimals in the text.

8. When presenting results regarding medical history, it is confusing that the authors mention patients without diseases or patients without a disease (p.11): they probably mean patients without that specific disease, as they do have other diseases for which they take medication?
Ans: Thank you for your suggestion. We have changed it to ‘without this disease’.

**Major Compulsory Revisions**

1. The abstract is missing!
   **Ans:** We have provided the abstract in the manuscript. Thank you for reminding.

2. The background lacks a clear aim. Is the aim of this study to establish a ‘personal medication management system’ (as was stated as the aim by the authors), or to improve medication adherence by sending patients SMS reminders for medication intake, or to improve patients’ satisfaction and loyalty towards health care institutions? In addition, more studies using SMS reminders to improve patients’ medication adherence have been conducted over the past years, which are not acknowledged in the background section.
   **Ans:** Thank you for your valued comments. We have added more literatures in background section, and also rewrote the study aims in the end of background.

3. It is unclear whether patients might receive SMS reminders for more than one type of medication. If patients use multiple medications, do they receive reminders for each medication? This may be an important factor! Especially when the authors state in the discussion (these are actually results that are not included in the result section!) that patients reported the frequency of the text messages was too high / the number of messages was excessive. This annoyance with the reminders can have an impact on adherence.
   **Ans:** In this study, if patients used multiple medications, they would receive one reminder for all medications at the same. For instance, if one patient had to take two medications at morning after the meal, the system would send the message including information for two medications to remind the patient at one message sent. Since some patients might need to take medications 3-4 times daily including 3 medications before/after meals and one time before sleeping, they would receive 3-4 times reminders daily. Some patients might take some medications with different kinds of schedule, which would become more complicate. These situations might cause patients to feel uncomfortable.

4. It is unclear whether all patients, thus also the patients in the control group, had access to the PMP system during the intervention period? Through this platform, patients could obtain information regarding their medication use, medication history and free professional medical consultations (as was stated by the authors at p.6). If all patients had access to this platform during the SMS-intervention, this
might have influenced the results? As the authors also state that “this service can enhance medication adherence”. A large improvement can be observed in the control group for both delayed (46.4%) and missed (60.1%) doses. Can this also be a result of use of the PMP system, but then without the SMS reminder service? 

Ans: In this study, in order to clarify the SMS effect on medication adherence, the patients in the control group and intervention group could not access the PMP system during this study. Medication reminders only were sent to the patients by the PMP system via text messages for the intervention group. Thank you for your comments.

5. Table 1 shows significant differences between the groups concerning education level, occupation, income, marital status and medical history. This is not consistent with the authors stating that “analyses of basic information indicated that no significant differences existed between groups” (p.10)?

Ans: Thank you for your comments. We have adjusted the description of results in page 12.

6. As also mentioned in my third comment: the discussion includes presents new results. Another example is the subgroup analyses with 54 patients (p.17). The authors may want to move these results to the results section, and keep the discussion section for reflecting on these results.

Ans: We have moved them to the results section in page 15 and also kept discussion in page 20. Thank you for your suggestion.

7. Similar to my comment concerning the background section, the discussion section seem to lack relevant references to previous studies employing SMS reminders to improve adherence. There are much more studies being conducted in the past years! In addition, ref 13 is referred to as an article showing similar results as this study, but is a study protocol. In addition, some explanations given by the authors are not supported with any reference. The authors might want to search for more relevant literature to add to the discussion for a better reflection of their results.

Ans: Thank you for your comments. We have added some related literature in background section and discussion section. In discussion section, we tried to explain our findings with previous literatures, but some of them were not easily to find previous studies’ findings to support our argument.

8. An important limitation of the study, which is not mentioned, is that a self-report measure is used to assess medication adherence. Self-report is generally
acknowledged as a less reliable method, as patients tend to overestimate their adherence. In addition, the short follow-up might also be a limitation. Patients received reminders for only seven days.

**Ans:** Thank you for your comments. We have added limitation in page 21 according to your suggestion.