Author's response to reviews

Title: Improving medication adherence in stroke patients through Short Text Messages (SMS4Stroke)-study protocol for a randomized, controlled trial

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Author's response to reviews: see over
Response to Reviewers:

MS: 2414997771369211 Study protocol: Improving medication adherence in stroke patients through Short Text Messages (SMS4Stroke)-study protocol for a randomized, controlled trial

We would like to thank our editorial staff and reviewers for their time; we have incorporated all their suggestions in the manuscript.

REVIEWER ONE:

Observation #1

The authors have planned a very carefully done study of a strategy to improve medication adherence following stroke, using text messaging. The problem is important, the idea is inventive, and the methods are original.

Response #1

We would like to thank the reviewer for his encouraging and positive comments on our efforts. We also would like to appreciate the detailed review and time given to our submitted manuscript.

Observation #2

There are a number of issues which the authors should address to achieve the maximum impact from the study, as well as the publication of the methodologies.

First, the authors have presumably considered but should detail in the manuscript, the strategies for SMS messages as a function of the number of medications and number of times patients take medications. If a patient, for example, is receiving all of a BID anticoagulant and once a day or BID beta blocker, ACE inhibitor or ARB, aspirin or other antiplatelet drug, statin, calcium channel blocker, as well as other non-cardiovascular therapies, will there be a separate and individual SMS message for every single drug at every time of day when indicated? Will the
SMS messages contain all of the drugs that are to be taken for example in the morning (presumably several drugs per message for some messages, and other drugs and fewer drugs per message for other messages?)

Response#2

We designed the tailored SMS based on the prescription provided to the participant. Reminder messages were designed and sent corresponding to the dosing frequency i.e. OD, BID and TID for all drug groups at a particular time. Thus they were sent for morning medications, afternoon, evening etc. and would cue/ nudge the participant to take their medications at that time. We have elaborated this strategy in the methods section now.

Observation#3

Will the message contain the name and dose of the individual drug? Or will it be a generic message: please remember to take your medication(s)? Exactly when will the messages be sent? ie: for the morning dose, early upon arising, later in the morning, mid-morning etc? is the precise time of day when the message to be sent specified per protocol or individualized for each patient? For medications taken at bedtime, will the message come after the patients are in bed and potentially asleep, or at some other time?

Response #3

The message is a generic message not specifying any drug name or class. Message timings are decided by observing individual prescriptions, hence usually at 8 am, 1:30 pm and 9 pm PST. We observed individual variations for those complex prescriptions that may have other timings e.g. 4pm, 5pm, early evening doses, but we do not send late night messages. Usually in Pakistan, dinner time is late around 930 to 10pm for most homes and bedtime is late around 11pm.

Observation#4

Do the authors have any information on whether the participants may find the potentially high frequency of messages intrusive, and choose to disable them? Is disabling the messages an option for the participants?

Response #4

Thank you for this observation. There is no disabling option to the receipt of SMS nudges and cues. However the participants have the right to withdraw at any moment during the study by contacting the study staff. After intervention close out, participants who received SMS will be asked to complete a survey on satisfaction and acceptability developed for the study and also
any further open comments that they feel may improve the program. We find that SMS is incredibly popular and acceptable in our region with Pakistani mobile phone users exchanging a staggering 315.7 billion text messages during July 2012 to June 2013 or 865 million SMS messages a day and prefer this mode of communication. Nonetheless, participant fatigue is a possible effect and we will be reviewing this at feedback and by monitoring withdrawal rates.

**Observation#5**

Will the reinforcing messages regarding the nature of the condition and the need to take medication be the same from day to day? Will they change during the duration of the study?

**Response#5**

Thank you for this observation. The health information messages cover information about disease, modifiable risk factors, drug information and importance of optimal drug adherence. These are 16 different messages, tailored to individual patients and will be sent over an 8 week period twice weekly. The set of messages for each patient will be selected at the time of recruitment and then sent at the scheduled timings by our IT staff. These messages change during the duration of the study for the participant based on their profile for e.g. a non-smoking participant is not to get a message about quitting smoking. However for the overall study these are standardized messages that have been worded and coded carefully; they have been added as appendix material.

**Observation#6**

How, specifically, do the authors plan to deal with medication changes? Will they depend on the patient volunteeringness?

**Response #6**

At entry into the study, we confirm that these are stable stroke patients most of them maintain the same prescription for long periods. If surgeries for e.g. CABG is expected and medications are likely to change rapidly, we would not offer enrollment into the study. Secondly yes, we do depend on patient volunteeringness to report any change in medication. Any reported change in medication will be however noted in the system and changes made to the reminder and health information messages both. This reporting is reviewed carefully with participants at consent, in addition, they are given free SMS text costing to report this to the SMS4Stroke Study Helpline at no cost. Additionally to reporting, since participants in the system are tagged as Clinical Trial Participants, all clinical encounters are tagged, thus triggering review of prescriptions in addition to reporting.
**Observation #7**

I have major concerns, as the authors mention and acknowledge, about the accuracy of the measurement of the primary endpoint ie: adherence. The availability heuristic suggest that even if patients wish to be “honest” in their responses, they may not remember or accurately remember the actual number of missed doses or frequency of adherence/non-adherence. In addition, since patients know that they are being “tested” for adherence, and the intervention obviously cannot be blinded, there is a high risk in my opinion that patients will answer in the affirmative to adherence questions even if they are not entirely adherent, or if they cannot remember. At a minimum, a validation sub-study must be done to verify the adherence reporting, for example using pill counts or some other measure.

**Response #7**

*Yes, agreed, we do acknowledge the limitation of our endpoint measure of self-reported adherence. However, the tool we are employing is a locally validated version of the Morisky Medication adherence scale and we acknowledge and discuss its limitation. To counter check self-reported adherence we will triangulate phone verified data in those in the intervention arm to adherence scores. Additionally, a larger study is planned to check effect of adherence on physiological endpoints like Blood pressure and lipids as they are harder outcomes to capture. A pill count sub study would be outside our resource and logistics at this time. It would require transportation of disabled participants and their caregivers across the city and we would not be able to do so, at this time. We acknowledge this limitation in our protocol.*

**Observation #8**

The statistical description can be shortened substantially. The primary outcome should, in my opinion, be simply rephrased as “the difference between overall adheres in the first two months of therapy between the control and intervention groups”. Since prior to the study, the patients may be less aware of or keeping track of their adherence, I am not sure how much the “delta MMAS score” will be useful.

**Response #8**

*We have made changes in statistical section in accordance with the above recommendations.*
**Observation #9**

The section of on participant timeline could be very substantially shortened or placed in an appendix.

**Response #9**

*The section has been substantially shortened.*

**Observation #10**

As a minor point, the section on pilot studies is in the present tense, and some of the other sections are in the past or future tense. Presumably if the study has not been performed yet, all statements everywhere in the manuscript should be in the future tense (unless some of the pilot testing is already complete).

**Response #10**

*The tense has been corrected and made uniform.*

**Observation #11**

Presumably important covariates in the usefulness of the adherence program will be patient age, the severity of their stroke, and the number of medications they are required to take. At a minimum, it may be useful to stratify the randomization by “able to take medications independently”, and or by “number of pills required daily” (divided into two arbitrary groups) to ensure a balance in these potential confounders.

**Response #11**

*Thank you for this observation, since the study had a limited timeline for recruitment, stratifying randomization would create problems in achieving sample size. However, the analysis plan would incorporate sensitivity analysis using the above mentioned variables if they are found strikingly different in the two groups. We have made these changes in the analysis plan and clarified this point.*
REVIEWER TWO:

We would like to thank the reviewer for their time and attention to our manuscript. We respond to their observations.

Observation #1

The reviewer asks that the authors consistently use either the present or the past tense throughout the manuscript

Response #1

*We have corrected this throughout the manuscript.*

Observation #2

Please define SMS at first use

Response #2

*We have corrected this usage.*

Observation #3

Are there preliminary data specific to the use of mobile phones in this particular population? It is usually the case that older patients use these devices less regularly.

Response #3

*Yes, there is data from Pakistan that elderly use mobile phones less frequently than younger age groups. However our study population included those who possessed a mobile phone themselves or their primary caregiver (usually a younger person from family) who possessed a mobile phone, we plan to reach these stroke survivors and caregiver dyads in their homes even if one can be reached. This is regionally important as Pakistan doesn’t have a single long stay rehab center; we have to work with families within communities.*
**Observation #4**

Do the authors anticipate loss to follow-up? That is, are most patients expected to complete their post-stroke care at the intervention clinic?

**Response # 4**

Yes, we anticipate some lost to follow up and we have inflated the sample by 15% to accommodate for it. However, most patients are expected to complete their post stroke care at the stroke follow up clinic.

**Observation#5**

How will the authors know that their medication reminders explain the variability in outcomes with the addition of SMS for medication education and lifestyle advice to the intervention arm? Did the authors consider using the latter for the control condition?

**Response #5**

This is a very important observation. We do not know which component of the intervention will have the effect. However, we targeted SMS to cover both intentional non adherence (due to lack of knowledge, or myths, or attitude, which is the educational SMS) and unintentional non adherence (due to cognitive issues, forgetfulness etc., which is the reminder SMS). These issues are discussed in the clinic but there is usually not enough time and not enough reminders and presence to reinforce these messages, thus we have not aimed to target one kind of SMS over the other, but to try to increase adherence via SMS by targeting both components of non-adherence through SMS.

**Observation #6**

Are caregivers required to provide informed consent if they will be responding on behalf of the patient/participant?

**Response #6**

Yes, whoever (Patient/Caregiver) will receive the SMS is required to sign the informed consent.
**Observation #7**

Is the patient satisfaction "tool" a survey? What will be the "predecessor innovations" that the SMS will be compared to?

**Response #7**

Yes, it is a survey. SMS is compared to usual care that employs counseling and use pill boxes etc. SMS will also be reviewed as an innovation in terms of acceptability, user response, repeatability, perceived benefits (This is a tool that looks at SMS via the Rogers Diffusion of Innovations Theory Framework to elaborate its characteristics for diffusion). We have clarified this in the manuscript.

**Observation #8**

Primary and secondary outcomes are likely to vary by the number of medications patients are taking. Did the authors consider a sub-analysis among patients managing a long list of medications versus only a few?

**Response #8**

Yes, agreed. We plan to adjust the results according to confounding variables like number of pills taken daily and frequency of medicine dosing.

**Observation #9**

It would be interesting to report patient "adherence" to responding to the text messages - particularly over time. "Alert fatigue" is documented among providers receiving clinical decision support alerts via the electronic health record. I think that patients who take a lot of medications may be less likely to respond to SMS over time.

**Response #9**

Yes, we plan to assess adherence to responding messages over the study duration and monitor alert fatigue.
**Observation #10**

It is a safety issue to depend on patients to alert the SMS programmers about medication changes. The healthcare provider should be the one to confirm any medication changes so that the patients are reminded to take the correct dose at the correct time. Similarly, will the detailed interviews with the patients re: medications be confirmed by the provider / clinic notes? How will adverse events be documented/addressed? Is there a DSMB?

**Response # 10**

Yes, the research team intends to follow patients on their scheduled appointments and note all changes in prescriptions. Yes, the patients are asked for their prescription and the staff notes down the details of the prescriptions and reviews charts and clinic notes to confirm prescription details. An adverse event reporting is to the Ethical Review Committee of the Aga Khan University which functions also as a DSMB for this study. All Trial participants are tagged as a Clinical Trial Participant in the system and all adverse events, hospital clinical visits are tagged and team is informed about all events.

**Observation #11**

Is this intervention scalable to other healthcare settings / conditions? What are some future directions for this work?

**Response #11**

Yes, it is capable of being used by other similar settings with minimal support from IT staff due to its clear frameworks and Open Access Program to modify it for other settings. Chronic health conditions which need improvement in medication adherence can also utilize this intervention. Also this intervention can be used for the masses after some modifications for stroke prevention and be tested in a larger scale trial with longer follow ups.
REVIEWER THREE

Observation #1

This is a protocol paper describing a randomized, controlled, assessor blinded study testing use of SMS texts to support adherence to medications for secondary stroke prevention in patients recruited from a Stroke clinic. This study is very well-written and addresses an important problem: adherence to medications (antiplatelet, anti-lipid and anti-hypertensives) aimed at secondary stroke prevention in Pakistan. Authors describe a promising technique for improving adherence in resource-strapped nations. Their description of study protocol is thorough, vigorous, detailed and they cite several appropriate theoretical underpinnings to their intervention development. Their description of Frontline SMS (a free and open source software which they will use for their intervention) and their inclusion of study materials will help others reproduce their efforts.

Response #1

We would like to thank the reviewer for their positive feedback and encouragement.

Observation #2

On page 13 authors say that special care is taken to maintain confidentiality of patient’s disease and diagnosis will not be mentioned. Yet examples of texts (p9) included references to Stroke happening again and “Please take your blood pressure medicine” and the texts listed in SMS templates do reference smoking, blood pressure pills, cholesterol lowering meds, etc. Please clarify the comment on page 13.

Response #2

Yes, thank you, we note this and since these messages are templates we will be able to change the face of the SMS message. Thus it will not state for e.g. This message is for Mr X Stroke clinic patient on its User / Face interface. The participants will be counseled to understand not to consider the message as an urgent message and that they have to necessarily open it in traffic, company etc., they can read it in relative privacy. These are also user safety considerations besides confidentiality concerns.

Observation #3

It would be interesting to see if there are differences in acceptability of SMS texts between those patients already receiving SMS appointment reminders vs. those not yet accustomed to
any SMS communication from medical center. Would also be interesting to see if those for
whom caregivers have the phone have different response rates to intervention.

Response#3

This is a very interesting observation and it would be testable in a multicenter study where all
centers may not be using SMS for appointment reminders. All participants receive appointment
SMS reminders from the hospital at our center but they occur only once before their follow up
visit usually once every 3 months. Thus, in the environment of this study, it is impossible to
identify patients within the hospital who are not exposed to such reminders.

Observation #4

Would also be interesting to see if those for whom caregivers have the phone have different
response rates to intervention.

Response#4

Thank you for this observation, yes, we plan to do sensitivity analysis for the above to evaluate
difference in response rates to the intervention.

Observation#5

Is the recording of patient response to texts automatic or is there a person monitoring this and
handling the phone follow up?

Response#5

The IT staff assigned to the study is personally responsible for recording the follow up
responses to the nudges and cues in medications and informs the investigator of any
irregularity / drop out in participant responses.

Editorial Observations

Please revise the methods section of your manuscript to include the name of the ethics
committee that approved your study.

Response

Thank you, we have done so.
We thank the reviewers and the staff for their help and careful observations that have greatly improved our manuscript.

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