Author's response to reviews

Title: Measuring adherence to antiretroviral therapy in northern Tanzania: feasibility and acceptability of the Medication Event Monitoring System

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Author's response to reviews:

To: Dr. Diana Boy (for Dr. Sabina Alam)

Senior Executive Editor

BMC Public Health

From: Ramsey Lyimo

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Moshi, 15 December, 2010

Dear Dr. Diana Boy and Dr. Sabina Alam,

We were very grateful to receive your positive response and valuable comments on our paper entitled: “Measuring adherence to antiretroviral therapy in northern
Tanzania: feasibility and acceptability of the Medication Event Monitoring System” (MS: 1137749058432002). We have made changes in the text accordingly (by using the ‘track changes’ function) as explained point to point below.

We hope that we have successfully addressed your concerns.

Yours sincerely,

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Comments of reviewer 1:

Discretionary Revisions

1.a. Since the authors are making the case for the feasibility of using MEMS in resource-limited settings, it might be nice to know how they were funded (i.e., how they obtained funding to purchase the MEMS caps). I know they mention their funding source in the Acknowledgements section, but perhaps briefly mentioning how they were funded in the text would be interesting.

1. b. Authors’ response:

As the reviewer suggests, we have now included the information about funding in the methods section (lines 125-127 of the revised version). It now reads as follows:
Financial support for this study was obtained from the ‘Innovation foundation health care insurers’ (RVVZ, the Netherlands) and from the ‘AIDS Foundation’ (the Netherlands).

2.a. Page 11, the authors report that four healthcare providers participated in the interviews. Were they asked the same questions as the patients? Very few results were presented from these professionals. Is there anything of interest from these interviews? If not, why include this detail in the paper? Also, it is not clear why the data clerk was interviewed, since that person may not have known much about the topics covered in the interviews (?)

2.b. Authors’ response:

We agree with the reviewer that this has not been systematically reported in the paper. Reviewing the manuscript, we decided that these interviews indeed do not really add valuable information to the manuscript. We have therefore removed the few remarks about these interviews from the manuscript.

Removed sentences:

Line 211-213 of the previous article” Apart from the participating patients, four health care providers at the ART clinic participated in the interviews; two clinicians, one dispensing nurse and a data clerk who downloaded the MEMS-data”

Line 226-228 of the previous article “One of the ART clinicians stated: “The users of the MEMS- bottles are quite happy. WE have no one who complained and returned back the bottle except the one truck driver who declined earlier in the study”
3.a. Page 14, paragraph 2: several patients reported that they did not travel with the MEMS bottle because of concerns about it being stolen. In these cases, did they put their medication into another bottle and take it with them? If so, why were they worried about the MEMS bottle being stolen but not their regular bottle of medication? Was it because of the potential expense of having to replace it? It would be nice if the authors could explain this a little more clearly.

3.b. Authors’ response:

Thank you for the observation. As we illustrated with several quotes in the manuscript (lines 251-258) of the current article, the patients feared the MEMS-device could be stolen, and therefore placed their medication in regular pill bottles and left the MEMS-caps at home. Apparently the patients considered the MEMS-device as valuable and therefore did not want to take the risk of it being stolen or loosing it.

In the discussion section, line 324-329 of the current article, we have added an additional clarification: “This fear of loosing the MEMS bottle on travel occasions was because patients perceived the MEMS-cap as a valuable device that could be stolen. This finding indicates the need of stressing patients that using the medication from the MEMS-caps when travelling is important and that the risk of it being stolen is acceptable and the responsibility of the researcher. This is especially important because adhering to the medication may be more challenging when travelling.

4.a. Page 15, paragraph 3: It is too bad that the clinic sometimes mismanaged the dispensation of medication so that patients did not have enough pills to get them through until their next visit. Do the authors have any recommendations for how
this could be handled better by clinic staff in the future?

4.b. Authors' response:

We agree that this was a very concerning finding and we discussed the problem and consequences for patients’ medication intake with the health care providers and the dispensing nurses. By now, they have adjusted their practices.

We have added a few words about this in the discussion section (lines 340-346) “Finally, examining the MEMS-data in order to determine periods of non-adherence or non-MEM-use, patterns of missed doses were found prior to clinic visit because too few pills were being given to patients to bridge time between consecutive visits. Upon discussing the potential health consequences of this malpractice, the healthcare providers and dispensing nurse, acknowledging the necessity of a sufficient supply of medication, now provide patients with enough medication (including a buffer supply in case a patient is not able to visit the clinic on the appointed day)."

Minor Essential Revisions

5.a. Watch use of commas, misspelled words, and missing words. For example, in

the Background section, delete comma after "it" on line 5, paragraph 1 and after "ART" in line 8, paragraph 1. Page 5, last paragraph, insert "in" after "ART".

Results section: enrollment should have two ls, and "widow" should be "widowed". Conclusions paragraph: insert "a" after "given in" on line 4.

Define PLWHA the first time it is used (Background section, paragraph 2).

On page 6, paragraph 1, I think “proceeding” should be replaced with “preceding”
if the authors wish to convey that non-adherence comes before viral replication.

Page 7, paragraph 2: the sentence that starts “Patients were explained...” is not clear. It would be more clear to state “Patients were informed that...” or “The researcher explained that...”

5.b. Authors’ response:

Thank you very much; we have corrected the manuscript accordingly.

6.a. Page 8: in the Interview procedures and analysis section, were they any procedures implemented to ensure that the interviewers were relatively uniform in their administration of the questions?

6.b. Authors’ response:

There were three interviewers and they were all closely involved in the design of the interview guide. In addition, prior to commencement of the interviews, the 5th author organized an interviewer training in which the actual interview training was practiced. This preparation was considered to be sufficient to ensure uniform interview procedures. Also, the tape recordings did not reveal inconsistent interview procedures.

To clarify that the interviewers were trained, we rephrased the following sentence (line 164-166) of the previous article:

“All interviews were conducted in a private room at the ART clinic by researchers RL, EM, and DM.” into line (163-164) of the current article: “All interviews were conducted in a private room at the ART clinic by three trained interviewers (authors RL, EM, and DM).”
7. a. Page 16: sentence 5: I don’t think “fear for” should be in parentheses.

7.b. Authors’ response:

This has been changed accordingly.

8.a. Page 17, paragraph 1: I think this paragraph could benefit from more details.

When the authors note that the participants “did not mention any challenges”, could they be more specific about what they mean by “challenges”? Also, when the authors state that MEMS-data confirmed “that”, what is meant by “that”?

8. b. Authors’ response:

The aim of this paragraph was to explain that patients could use the MEMS without any problem or difficulty and that the MEMS data ascertained that there were no problems associated to proper use of MEMS such opening of the cap that was not associated with pill taking. However, upon re-reading that paragraph following the Reviewer comment, we decided these points were already made in other parts of the discussion (lines 307 and 313-315) of the current article. We therefore decided to remove this somewhat confusing paragraph (line 349-358) of the previous article.

9.a. Table 1: Age should not be included in the table because the table column presents N values and percentiles, not means. Present mean age in the text only.

9.b. Authors’ response:

We have followed the recommendation and removed Age from the Table. However, because of the skewed data, we present the median and interquartile
range (instead of mean and standard deviation) in the text only (line 192)

Major Compulsory Revisions

10.a. MEMS data analysis section, page 9: the authors describe examining data for

“periods of one week or more during which the MEMS cap registered no medication intake events”. I am not clear on why the authors chose one week as their time frame for this purpose, and think a shorter time frame would have been better. For example, if a patient had 4 days with no MEMS events registered, couldn't this indicate non-adherence or non-MEMS use? Please explain the rationale for this choice or shorten the time frame.

10.b. Authors’ response:

Thank you for the observation. We went back to our data to look for periods of >3 days (i.e. periods of 4-6 days. #7 days we already reported in the previous manuscript) of missing MEMS-data. We decided to not look for periods of 1-3 days since, in our opinion, looking back over a 3-month period and expect patients to reliably explain missing data of 3 days or less (“Was this non-adherence or non-MEMS-use?”) is not feasible.

We found only 2 periods with of 4 consecutive days of missing MEMS-data. Both these periods were directly after distributing the MEMS-caps and were considered typical for patients first finishing their previous supply of medication. For the rest, there were no periods of 4-6 days of missed medication for any of the patients during the whole study period. Since we computed average monthly adherence levels ‘backwards’ (i.e., starting at the last study visit, and then using the 12 prior weeks to compute 3 monthly average adherence levels), and patients typically used the MEMS-cap for 13-14 weeks, these minor start-up issues were not part of the average adherence scores.
In order to indicate that our conclusion now apply to periods of >3 days of missing MEMS-data, we have made the following adjustments in the manuscript:

Line 175: “periods of one week or more” has been changed into “periods of >3 days”.

Line 270: “There were six patients whose MEMS-data showed periods of more than one week of missed medication.” was changed to “There were six patients whose MEMS-data showed periods of more than 3 days of missed medication.

11.a. In the same paragraph: the authors say that “interviews were examined for reports of interrupted MEMS use”. In describing the interviews in the previous section, this line of questioning was not described. Were all patients asked about interruptions in MEMS use as a standard part of the interview, regardless of MEMS data results?

11b. Authors’ response:

All patients had been interviewed about whether they used the MEMS-bottle according to the instructions, as we explain in the Methods section (lines 140), which includes the instruction to always take all pills from the bottle. Hence, we think we do describe that interviews focused on this point.

When we observed a period (previously of one week or more, now of >3 days) without pill bottle openings in the MEMS-data, we went back to the interview of that patient to look for self-reported non-MEMS-use. Six patients had non-monitored periods >3 days and two of these were coded as non-adherent adherence because patients did not collect their medication. Of the four of the other patients, three did report in the interviews to have left the MEMS-bottle at home when travelling. As we report in line 291, the 4th patient could not be traced.
12.a. Page 15, paragraph 1: monthly adherence scores were computed if at least 2 weeks of data was available. This makes it sound like the researchers calculated adherence scores for patients who had two weeks of data that was unaccounted for. Reporting a monthly adherence score for someone with two weeks of data for the month seems potentially misleading. How do the researchers know what happened during the missing two weeks? If someone were 100% adherent for two weeks (on MEMS), and non-adherent for the other two weeks of the month (with no MEMS data), you would be falsely representing that person’s adherence as 100%. I would recommend calculating adherence scores if someone had at least three weeks out of the month, or clarifying this methodology if I am not understanding it correctly.

12.b. Authors’ response:

Apologies for not writing this down more clearly, since we think there is a misunderstanding here. As we explained in our previous answer (11b), there were six patients with MEMS-data missing for periods of more than 3 days (in fact, all of these had periods of one week or more of missing data). From three of these, we could establish this was due to non-MEMS-use rather than non-pill use. Instead of assuming 100% adherence in case of non-MEMS-use, we set these periods to missing. This concerned three out of six patients with non-monitored periods greater than 3 days. Some of these three patients had monthly periods with less than two weeks of MEMS data in one month (since the rest was recoded to missing). We decided to include their average adherence
scores if they provided at least two weeks of data in a month, since two weeks of continuous data still gives a reliable estimate of their adherence behavior. Data from all other patients, regardless of whether there were data-gaps of two weeks or more in a month, were included because according to our procedure, these data really represented non-adherence rather than non-MEMS-use.

Please note that based also on feedback from Reviewer 2, we rewrote and simplified the quantitative section. In this simplified and shortened text (lines 302-308 [the results section on quantitative adherence data]) we now explain in relation to this comment:

“As a final step, we therefore explored patients monthly adherence scores, namely the percentage of doses taken (taking adherence) and the percentage of doses taken within a 9-15 hour interval (timing adherence), and explored whether adherence decreased over time also in this study. For the three patients who travelled and used their medication from another bottle, their period of non-MEMS-use was set to ‘missing’. Monthly adherence scores were only computed for these three patients if they provided at least two weeks of continuous MEMS-data.”

13.a. Page 18, paragraph 1: the authors suggest that future studies should ensure that

participants know their MEMS data is anonymous so that adherence does not increase as a result of being monitored. Wouldn’t that be a positive impact of MEMS caps? There is no way to prevent the effects of being monitored, even if the patients are told that their clinician will not be told of the results. Similarly, it sounds funny to say in the last sentence that MEMS instructions should be “given in a way that it does not instigate patients to improve their adherence.” Even if just for research purposes, I would wonder about the ethics of attempting to avoid having the patients’ adherence improve. Perhaps the authors could revise
this paragraph with this thought in mind.

13.b. Authors’ response:

Thank you for this relevant observation. We agree that a monitoring or measurement effect can always occur in studies, but if it is large it can also distort the study and limit the chance of finding, for example, existing relations between medication beliefs and adherence behaviors. In clinical practice, on the other hand, it is beneficial. To better clarify these points, we altered the following text:

Lines 378-380 of the previous text: “Future studies that aim to measure adherence should ensure that their instructions concerning anonymity of the data are sufficiently clear to participants” now replaced with a new text line 340-346 “Finally, although beneficial in clinical care or adherence supporting interventions, the reported effects of MEMS-monitoring on adherence could introduce noise and threaten research outcomes. Careful instructions about anonymity, and a period of adjustment to MEMS-monitoring are therefore recommended.”

Comments by reviewer 2:

Major revisions

14.a. In the MEMS data analysis, it is unclear why only “periods of one week or more” were examined to explore non-MEMS use. Why was this not done for single days when no MEMS cap use was detected?

14.b. Authors’ response:

This comment was also raised by reviewer 1 (comment 10.a). Please see our response 10.b.

15.a. Pg 9, “taking adherence” is an awkward phrase. I would instead call it “pill adherence”
15.b. Authors’ response:

Kindly note that “taking adherence” is a formal term for the percentage of prescribed doses actually taken (Vrijens & Goetghebeur. Controlled Clinical Trials. 1997;18:197-203). We suggest maintaining this terminology to be in agreement with this literature.

16.a. An important finding is that patients did not take their MEMS bottle while traveling because of fear that it might be lost or stolen. If you can say more in the results about where that fear is coming from (e.g., protection of the MEMS bottle, perception that they might get in trouble if they lost it, etc) that would be helpful. Also, it would be good to say more about the implications for this finding in the discussion section (e.g., “patients should be assured that they will not be penalized for losing the bottle or having the bottle stolen.”)

16.b. Authors’ response:

Please see our response 3.b. to reviewer 1 who commented similarly.

17.a. Table 2: There is clinical reason why you might be interested in the proportion of patients who achieve at least 95% pill adherence. However, there is no justification why you need to look at 95% adherence for dosing or timing. I would remove those. Reference in the text (pg 15) should then be updated.

17.b. Authors’ response:

We agree with the reviewer that only for taking adherence the norm of 95% has been established. We removed the 95% adherence for the other measures. Moreover, also in relation to the next comment, we have excluded the 95% adherence levels from the Table. The 95% scores for Taking adherence are now reported in the text only.

Please note that based on this comment, and some remarks from Reviewer 1, we rewrote and simplified the quantitative section.

In relation to updating the reference in page 15 of the previous article, we have now placed an appropriate reference;
Gross, Robert; Bilker, Warren B.; Friedman, Harvey M.; Strom, Brian L: Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. AIDS: 2001, 9 November 2001 - Volume 15 - Issue 16 - pp 2109-2117

18.a. Only mean and SD are necessary to present. Median (IQR) make the table confusing

18.b. Authors’ response:

We agree that the Table was confusing and that most authors are report Mean (SD) adherence values. However, adherence data (and our data as well, especially in Month 3) is often strongly left-skewed. It is therefore relevant to report Median (IQR) values as well. We decided to re-design the Table and hope to have accurately addressed this comment.

19.a. There is an inconsistency in your discussion, where your qualitative results suggest that MEMS technology increases adherence, but your MEMS data findings actually show adherence decreasing over time. I would consider downplaying your MEMS data findings – in particular, because it reflects some patients having poor use (not using the device while traveling) and running out of pills because of improper scheduling by the clinic. I would attribute less of that change over time to the decline in the impact of MEMS monitoring (as you suggest on pg 17)

19.b. Authors’ response:

We agree with the reviewer that these findings are tentative. In response to the specific points above, first: the assumption in adherence trials that monitoring has increased adherence is because after e.g. 1 month MEMS-monitoring there is a drop in adherence. In studies with treatment-experienced patients, this drop of e.g. 5-10% taking/pill adherence is commonly attributed to an improved adherence during the first period of monitoring, and then returning to routine adherence levels after e.g. 1 month. Hence, the pattern that we have observed here is similar to this.

Second, please note that data from patients with ‘established’ non-use of MEMS were excluded from these analyses (i.e., recoded to missing; see also our reply 12b for Reviewer 1) and that running out of pills because of clinic malpractice was not related to month 1, 2 or 3 of the study. It is thus unlikely that the
decrease in adherence rates can be attributed to these causes.

Following this comment, however, we have ensured that all comments in relation to this point are phrased tentatively.

20.a. In the discussion, I would be more explicit that MEMS technology has potential application for both research and for monitoring in the clinical setting.

20.b. Authors’ response:

We have followed the recommendation and have added a paragraph in the discussion section (lines 347-354): “This study showed that MEMS-devices have potential application in adherence research and monitoring of adherence in clinical practice in resource-limited settings. Although attention has to be paid to accurate MEMS-use, both at the time of instruction as well as at the moment of data interpretation, we did not observe some of the typical hurdles related to MEMS-use in resource-rich settings. For example, patients did not experience problems with the MEMS-design. In the absence of financial resources for regular viral load or CD4 testing, regular monitoring of adherence with the MEMS-cap may be possible and thus provide clinicians with valuable information to support patients’ medical treatment and medication adherence.”

21.a. The abstract should state in the methods section that qualitative in-depth interviews were conducted.

21.b. Authors’ response:

We have followed the recommendation. It now reads as follows: “Thereafter, qualitative, in-depth interviews about the use of MEMS were conducted with patients and healthcare providers. MEMS-data were used to corroborate the interviews results.”

22.a. Pg 6, when stating the cost of MEMS technology, “if obtained per 100” does not make sense.

22.b. Authors’ response:
Our point here may not have come across well. Since we wanted to explain that although MEMS-caps cost money, the costs are modest as compared to viral load and CD4 counts, we wanted to report the prices if obtained on a large scale. Instead of just reporting the costs per 100, there should also have been text showing how much they would cost per e.g. 5,000. This information is relevant in relation to the argument that MEMS-caps could be a valuable tool in clinical practice in this setting.

We have now included the detailed prices (lines 98-99): “(30 USD for one year of data if obtained per 100 and 22 USD per 5,000), and these costs could - in theory - be less than 10 USD per year if mass-produced.

23.a. Pg 6, the first time PLWHA is used, it needs to be spelled out

23.b. Authors’ response:

We have now spelled it out in line 65 where it is mentioned for first time.

24.a. Pg 12, “practicability” is an awkward word. Would “feasibility” be a better word here and more consistent with your title?

24.b. Authors’ response:

We have followed your recommendation and changed the word into “feasibility”.

25.a. Pg 14, you conclude the section on corroborating interviews by saying that 4 patients did not use the MEMS cap during long distance travels. However, from the data presented it seems like there were only 3 patients.

25.b. Authors’ response:

We acknowledge your observation; indeed there were only three patients of whom it was confirmed that they left the MEMS bottle at home on travel occasions. We have corrected the number accordingly in Line 270.
26.a. There are some minor typos:

a. Pg 5, “the possible bias”, delete “the”

b. Pg 5, “ART developing countries”, missing “in”

c. Pg 6, “such as importance”, missing “the”

d. Pg 7, “three-months period” does not need the s in months

26.b. Authors’ response:

We have corrected the text as required.