Author's response to reviews

Title: Examining assumptions regarding valid electronic monitoring of medication therapy: development of a validation framework and its application on a European sample of kidney transplant patients

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Author's response to reviews: see over
Dear Mrs Puebla,

Please, find below the answers on the second review round. We thank the reviewers for the helpful comments. This cover letter contains a point-by-point response to the concerns of the reviewers. Do not hesitate to contact us if anything would be still unclear.

Sincerely,

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Reviewer: Andrew Vickers

I have been asked to review the statistics for this paper and I will restrict my comments to the statistical analysis (the paper involves a number of complex issues around compliance, and this are out of my area of expertise). In general, I think that the statistical approach is reasonable. However, some aspects of reporting could be improved. On page 12, the odds ratio is (presumably) per day, leading to statistically significant odds ratios that are difficult to interpret (e.g. 1.009). I suggest that the authors change the denominator to e.g. a 28 day period. The odds ratio will be something around 1.3, with an interpretation that the odds increased by about 30% for each 28 day period. In figure 4, don't give log odds on the y axis, just the probability. Include 0% on the y axis and use reasonable numbers (e.g. 5%, 10%, 15%) for tick marks. Also include the 95% C.I. for this figure.

1) We have changed the denominator for the variable 'exposure' to a 30 day period and have added a sentence on page 12: "The random-intercepts logistic regression analysis confirmed an increase in both taking and timing non-adherence over time (Table 3). The odds on non-adherence increased over one month by about 30% for taking (OR: 1.31; 95%CI: 1.17-1.46) and 25% for timing adherence (OR: 1.26; 95% CI: 1.17-1.35)."

2) The reason why log odds were presented in the figure was to be able to evaluate the nonlinearity of the lines, not in the first place to talk about the prevalence of non-adherence. An article about the prevalence has been published by our research group in the beginning of 2007 (Denhaerynck K, Steiger J, Bock A, Schäfer-Keller P, Küfer S, Thannberger N, De Geest S. Prevalence and risk factors of non-adherence with immunosuppressive medication in kidney transplant patients. American Journal of Transplantation 2007; 7(1):108-116). Predicted log odds regression in a logistic regression are straight. Estimating non-linearities using additive modeling, shows where non-linearities can be found. Detecting non-linearities would be much more difficult if the Y-axis shows probabilities instead of log odds, because one has to visually disentangle the non-linearities resulting from the sigmoidal logistic function and the empirical non-linear processes. If the reviewer insists that it is more informative for the reader to see a graph with probabilities, we are willing to deliver such a figure. At the moment, we left it as it is, as we think the reader is better served with a graphical presentation that that does not mingle two sorts of non-linearity. We also did not provide the 95% CIs, as we used this plot only for exploratory purposes, and did not do any post-hoc testing on this finding. Moreover, the GAM procedure in SAS does not calculate CIs’s for random-effects logistic regression analysis. Any CIs calculated with this procedure, would not he the correct ones. We therefore left the graph as it is.

Reviewer: Alistair W Stewart

Discretionary Revisions: In Table 3 the estimates and their errors (and odds ratios and CI’s) for 'Exposure' and 'Bottle size' are of little use. The scale of these variables is such that, using 3 decimal places, the important digits can not be seen. I would suggest both variables be scaled, bottle size could be measures as 100 cc rather than in cc’s and that the units of exposure be changed too (I was unable to see what units were being used).
We have changed the denominator for the variable 'exposure' to a 30 day period and have added a sentence on page 12: “The random-intercepts logistic regression analysis confirmed an increase in both taking and timing non-adherence over time (Table 3). The odds on non-adherence increased over one month by about 30% for taking (OR: 1.31; 95%CI: 1.17-1.46) and 25% for timing adherence (OR: 1.26; 95% CI: 1.17-1.35).” The variable Bottle size is calculated per 100 ml now (see Table 3).

Minor Essential Revisions: In Table 4 the rows entitled 'Self-report (1-7)' and 'Collateral Report (1-3)' are, at best confusing and may be wrong. If the 1-7 is the ranges of self-report then there is an error. Although self-report is referred to as a 7 point scale 8 points are used 0-7. In the table the mean is less than 1, the value given as the minimum point of the scale. For both measures using a mean and standard deviation to describe the data is quite uninformative. I suggest that the percentage in the most commonly used category be given as this contains almost all the information. (I was unable to find any combination of numbers participants having 1, 2 and 3 such that the mean was 1.12 and the sd was 0.35.)

Thank you for finding this inconsistence. The self-report and collateral report scales indeed started from 0 instead of 1, as was written in the variables and measurement section of the article. Regarding collateral report, the mean presented was that of patients' collateral report scores, which were in itself an average of all physicians and nurses' adherence evaluations within a patient. If more health care workers considered a patient as non-adherent, then his score was higher. The reviewer’s suggestion to present percentages of the most commonly used category is not possible for the collateral report, as the underlying values of this variable were averages per patient. However, we agree that means and standard deviations are not the ideal solution to summarize the data presented in table 4. We chose to calculate medians and inter-quartile ranges instead.

Reviewer: Ruairidh Milne

1. “After a goodly amount of hemming and hawing...” The authors make a good case in their response for the validity and usefulness of the patient information methods (collected from contemporaneous notes and later interview). These points do not appear with the same clarity in the paper. I would suggest that they
   a) break up and better structure the very long para on p7/8 in which these are described
   b) include a brief comment on the validity of these methods in the discussion
   c) consider explicit mention of these two methods in the abstract

   a) We divided the long paragraph by adding a sub-title: “Adherence to the EM instructions.” We also started a new paragraph where we made the transition from explaining the notes to introducing the interview.

   b) On page 14, in the discussion section, we have added the following paragraph: “We are aware that our attempts to estimate the adherence of patients to the EM instructions rely on patient self-reports, which is not a highly sensitive measurement method. However, in the case of the patient reports we used to supplement missing or correct phantom registrations, recall bias could not have been a large problem because the notes were recorded at the time of each event or not long thereafter. The interview at
the end of the measurement period asked for a general impression of the use of the bottle and the notes form, not for detailed adherence information. Even if less reliable than other sources, this kind of patient report may result in a more accurate measurement than simply not correcting the data with information given by the patient. When a patient for instance assures that during a holiday period the monitor was left at home while medication was taken from another source, it would be less accurate to discard this information and rely blindly on the monitor’s records than to use this information to interpret the missing data in the EM records. Future studies should be clear about how they dealt with issues of non-adherence to the EM system. Few studies to date report on these issues.”

c) We have added extra information in brackets on the patient self-report measurements in the abstract: “Internal validity was determined by assessing the prevalence of nonfunctioning EM systems, the prevalence of patient-reported discrepancies between cap openings and actual intakes (using contemporaneous notes and interview at the end of the study), and by exploring whether adherence was initially uncharacteristically high and decreased over time”

3. "There is no indication in the present paper..." The authors’ response finishes "We showed that an intervention effect may occur" and this is true. But it would seem reasonable to ask them to include brief mention of this possible limitation in the discussion. 7. "The question of observer bias...” As mentioned above under #3, it would be reasonable to ask the authors to include brief mention of this possible limitation in the discussion. The fact that this 'does not diverge from standard practice' explains what they have done, but does not of course eliminate possible biases.

We have addressed this issue by adding some sentences in the discussion on page 15-16.: “The fact that our researchers were not blinded may also have influenced the occurrence and strength of the intervention effect. The found significant difference in patient’s timing adherence between two of the researchers (Table 3), may be an indication of this influence. Differences could occur if patient recruitment was accompanied by stressing on the importance of being adherent to the immunosuppressive regimen.”

Reviewer: Jesse Berlin

Dr. Urquhart provides an explanation for increasing adherence over time, whereas the authors noted a very slight increase in non-adherence over time. I wasn't quite sure where that discussion was going, but agree completely with Dr. Urquhart that the changes over time were so small that they could be considered of trivial clinical importance. The authors make this point, but should probably strengthen that part of their discussion to better reflect this acknowledgement. Their statement on page 14, that "A subsequent increase of non-adherence probably reflects the waning of the adherence-enhancing effect of introducing EM to patients' daily lives", I believe is a bit of an overinterpretation of those very small changes.

We agree that the clinical importance of this intervention effect is not that large. Violations to the second guideline have more impact on the measured adherence prevalences. We therefore have added a more balanced statement to the mentioned sentence: “A subsequent increase of non-
adherence probably reflects the waning of the adherence-enhancing effect of introducing EM to patients' daily lives, although our sensitivity analysis showed that omitting the first month did not lead to a large increase of the prevalence of non-adherence, implying that the observed intervention effect had only minor clinical relevance in our sample.”

Page 11, first paragraph: “Thirty-four (12%) patients were excluded from the analyses because they failed to adhere to the EM guidelines.” What does this mean? What was the nature of the failure? What distinguishes these violations from the sort of discrepancies that were captured on the forms for patients who remained in the study?

We have extended the sentence by adding how we defined failure to adhere to the EM guidelines: Thirty-four (12%) patients were excluded from the analyses because according to the data quality assessment outlined in the methods section and illustrated in figure 2, they failed to adhere to the EM guidelines (scores 4 and 5).

Page 12, first paragraph: Similar point for the 23 patients who had “defined periods of non-adherence to the guidelines of correct EM use.” What constitutes one of these periods?

We again referred to figure 2: “Twenty-three patients (9.2%) had defined periods of non-adherence to the guidelines of correct EM use the according to the used data quality algorithm (figure 2).”