Author's response to reviews

Title: Comparison of pharmacy-based measures of medication adherence

Authors:

William M Vollmer (William.Vollmer@kpchr.org)
Maochao Xu (mxu2@ilstu.edu)
Adrienne C Feldstein (Adrienne.C.Feldstein@kpchr.org)
David H Smith (David.H.Smith@kpchr.org)
Amy Waterbury (Amy.Waterbury@kpchr.org)
Cynthia Rand (crand@welchlink.welch.jhu.edu)

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Author's response to reviews: see over
April 10, 2012

Dr. Mary Jo Pugh
Biomed Central Journal

Re: Manuscript #5415080026540249, Comparison of Pharmacy-Based Measures of Medication Adherence

Dr. Pugh:

Please find included our revised manuscript on comparison of pharmacy-based measures of medication adherence. We have attempted to address the reviewers’ concerns and to comply with your instructions regarding formatting. Hopefully you will find the revised manuscript acceptable in its current form. However, should you have any additional concerns we would be more than happy to attempt to address them as well.

Below is a point by point response to the concerns raised by the reviewers and the editorial staff. We were struck by the stark contrast in responses between the two reviewers; they could not have been more disparate. This posed a challenge in responding to their comments. The very parts of the text that reviewer #1 cited as particular strengths reviewer #2 did not seem to like. For instance, reviewer #1 noted that “strengths of this paper include its clear description of alternative measures (in formulas, in words, and in the helpful Table 1), its description of the relationship of these measures to prior literature, its balanced illustration of the tradeoffs between these measures in estimating adherence.” By contrast, reviewer #2 suggested that “much of the detailed Methods might be cut” and also felt that the text lacked “a good discussion of the strengths and weaknesses of these approaches.” Rarely have we encountered more disparate viewpoints.

Not surprisingly, we tended to agree with the comments of reviewer #1. Still, we have tried to address the concerns of reviewer #2 as best we can while retaining those aspects of the paper that so appealed to reviewer #1. We hope that you find our responses, as detailed below, acceptable.

We look forward to your response.

Sincerely,

William M. Vollmer, PhD
Senior Investigator
Center for Health Research

Kaiser Foundation Hospitals
3800 N. Interstate Avenue
Portland, 97227
Phone: 503-335-2400
Fax: 503-335-2424
Response to Reviewer and Editor Comments

Editor's comments

E1. The trial registration number should be included in the submission system and at the last line of the abstract of the manuscript.

We have included the clinicaltrials.gov number as the last sentence of the abstract and we also include this number in the journal’s submission system.

E2. Please check the instructions for authors to ensure that your abstract follows the correct structure for this journal and article type.

Done.

E3. Kindly provide specific names of ethics committees which approved your study in your manuscript.

At the end of the first paragraph of the Methods section we state “The study was approved by the Institutional Review Boards of each region and written informed consent was waived.” We assume this meets the journal’s requirements for level of detail, but please let us know if more information is required.

Associate Editor's Comments

Please make the following formatting changes during revision of your manuscript. Ensuring that the manuscript meets the journal’s manuscript structure will help to speed the production process if your manuscript is accepted for publication.

AE1. Structure: Please check the instructions for authors on the journal website to ensure that your manuscript follows the correct structure for this journal and article type.

We believe the article now conforms to current journal structure, which appears to have changed somewhat from the time of our original submission.

AE2. Tables: Please note that we are unable to display vertical lines or text within tables, no display merged cells: please re-layout your table without these elements. Tables should be formatted using the Table tool in your word processor. Please ensure the table title is above the table and the legend is below the table. For more information, see the instructions for authors on the journal website.

We have modified the tables in accordance with these instructions.
Reviewer #1 (John Steiner)

R1-1. *Strengths of this paper include its clear description of alternative measures (in formulas, in words, and in the helpful Table 1), its description of the relationship of these measures to prior literature, its balanced illustration of the tradeoffs between these measures in estimating adherence, and its demonstration of the dependency of several of these measures on the period of observation. The authors emphasize the important point that adherence measures (and adherence itself) typically decline over time – a covariate that is often ignored in papers in this field. In particular, CMA7 and CMA8 are novel measures, and while their applicability may be limited (as the authors note), these are creative additions to the set of possible adherence metrics.*

We are pleased to see the reviewer’s reaction was so positive.

R1-2. *Major compulsory revisions: None*

Minor essential revisions:

R1-3. *Unless required by the journal, the methods section currently follows the conclusion, and should be moved to its usual location.*

The methods section has been moved, as suggested.

R1-4. *Refill measures are usually calculated for pills rather than inhalers. Additional description in the methods section about the adaptation of these measures for use with inhalers would be useful to readers who are unfamiliar with this variation on the standard approach.*

This detail is now provided in the second paragraph under “Adherence Measures” in the Methods section.

R1-5. *Table 1 is a nice summary of the differences between measures, but the column labeled “timing” in the table probably requires more description as a table footnote so that the table can stand alone.*

We have added a footnote to clarify the meaning of this term.
Discretionary revisions:

R1-6. While the authors are correct that many researchers cap these measures at 1.0 (p. 14), their statement that there is no theoretical reason why adherence can’t be > 1.0 is incorrect, and in fact they provide theoretical arguments for not truncating these measures on p. 7. Patients can certainly take an excessive number of inhalations; while this is less often a problem for inhaled corticosteroids, it has been a notorious problem with beta-agonist inhalers. Thus, the authors might provide a more critical assessment of measures CMA3 and CMA4, which may obscure important information in some circumstances. Their conclusion that CMA1 and CMA2 should not be used simply because researchers don’t generally consider the problem of “overadherence” seems like a weak argument given their own recognition of reasons why adherence >1 should not be ignored.

The reviewer makes a valid point and we have amended the text accordingly. Specifically, in what is now page 7 we modified:

“Because CMA1 and CMA2 may both be greater than 1, some researchers prefer to cap them at 1 (since adherence theoretically can’t be any greater than 100%).”

To read:

“Because CMA1 and CMA2 may both be greater than 1, some researchers prefer to cap them at 1 (since nominally adherence shouldn’t be any greater than 100%).”

In addition, in the Discussion section on page 13 (second paragraph), we have added the following:

“Nonetheless, further studies are needed to better understand patient factors associated with very high rates of dispensing, and whether such excessive dispensings are associated with adverse health outcomes. Reasons for this apparent over-adherence have been attributed to changes in directions not noted in the pharmacy record, intentional variable dosing, and stockpiling.”

R1-7. The decline in adherence over time can be interpreted in two ways. The authors define it as a source of bias, which is true if duration of observation is ignored in an analysis. However it may also be a valid measure of a change in the underlying behavior. The authors should note this in order to avoid conveying the impression that reduction of bias is the only rationale for prolonged observation of refill behavior.

We have done this in the Discussion section on page 16, last paragraph.
R1-8. At the top of p. 7, the authors distinguish between medication acquisition and “true adherence”. It would be more precise to use the term “medication-taking” rather than “true adherence”. Refill adherence measures are a highly valid measure of one behavior – obtaining refills from a pharmacy - and an imperfect measure of medication taking, but both are “true” behaviors.

We made this change as suggested, on what is now page 14.

R1-9. In the last 2-3 years, several papers have reported that a high proportion of patients never obtain the first fill of a medication ordered by their clinician. Since the authors so carefully identify other sources of bias in these common measures of refill adherence, the bias inherent in requiring even a single fill of a medication probably deserves at least brief mention in their discussion.

We have added a reference to this issue as part of a new limitations paragraph on page 17 (last paragraph).

Reviewer #2 (John Zeber)

R2-1. While a very interesting topic and well-intentioned study, I personally found the presented very complex, confusing, and with an unclear set of implications for either clinical care or advancing the research agenda. This perspective started with the abstract, an introduction that did not provide a sufficient review of the issues and prior work, and a lengthy but overly dense methods section. While I support many of the discussion points, I am unconvinced much of the audience will be able to utilize the significant amount of work comprising the analysis, as the description and overall presentation presents a challenge. Yet understanding the challenges of using pharmacy date and its limitations, I do encourage revision efforts to elucidate the issues raised here.

We try to address this reviewer’s concerns that follow, though clearly this reading of the paper stands in sharp contrast to those of reviewer #1.

Specific Comments: major

R2-2. abstract: a little clarification here is needed re: what measures require “dispensing to be calculated” vs those that do not – consider providing a short example of each; this lack of definition is only clarified later in the text, plus some information in table 2. I am also confused and disagree with the statement that administrative pharmacy data measures cannot be defined well for large populations. Instead, such approaches are frequently used in population studies of large healthcare cohorts using administrative pharmacy databases. This includes, from what I understood, your own study.

Space constraints for the abstract prevent us from providing the types of illustrative examples to which the reviewer alludes. Most of the existing measures of adherence in common use require a dispensing event to be calculated. We have revised the manuscript by deleting the sentence, “In
addition, they often cannot be defined for large numbers of individuals.” from the abstract and by (hopefully) clarifying our discussion of this issue in paragraph 2 of the Discussion.

R2-3. *one major problem I experienced with understanding this study was the fact that, in my copy, the Methods section followed the discussion. This is perhaps an issue with uploading the file, but admittedly colored my initial perspective and led to some confusion.*

See our response to R1-3.

R2-4. *not sure I agree there is little published information on comparing pharmacy measures, and would suggest citing 1-2 papers that used a few of your 8 measures (MPR / PDC is frequently used, with increasing work on gaps in general), whether validated against some objective outcome. A summary of noted strengths and weaknesses of these approaches would be useful to the reader as well; as noted below, much of the detailed Methods might be cut to allow room for such information. Otherwise, simply presenting a detailed review on measure construction, even with the practical RCT example, seems to push this paper towards being quite theoretical and not sure it could significantly improve upon past pharmacy research.*

We agree and have amended the first paragraph of the background section to state that “relatively” few studies have systematically compared the properties of competing pharmacy-based measures of adherence, and also have added two of the reviewer’s suggested references.

R2-5. *contributing to a more theoretical (and naturally methodological) appearance of this paper, the Methods section is very long and complex in describing the different measures. Though I am perhaps misreading the journal audience, I suggest moving much of the detailed information, including the measure formulas, to an appendix (with article or online supplement). Another option is presenting all 8 measures in a flow chart format, listing the variables for time (t), dispensing length (n) and so forth in a more visual, graphical manner. The same would work for continuous and gap measures.*

We wholeheartedly agree with reviewer #2 when he states that this is a methodological paper. That is clearly our intent. We believe, and reviewer #1 clearly agrees, that this is useful content that would be helpful to anyone contemplating the use of such measures. As noted in our response to R2-4, the literature is very confused in its use of terminology. We believe that a paper that takes the time to lay out the subtle distinctions between these measures in their computation and illustrates the impact such differences have on measured adherence is needed and will be a useful contribution to the literature. If the editors would like us to restructure the paper to move much of the current Methods to an appendix we can certainly do so. As noted above, reviewer #1 cited these very details as a strength of this paper.

We were intrigued by the idea of creating some sort of graphic, as suggested by the reviewer, but are having a hard time visualizing what this might look like and still be intelligible.
R2-6. how did the authors, using any of the measures (though more important for
continuous ones rather than gaps), account for inpatient lengths of stay? This can be
an issue since long admissions reduce the likelihood of outpatient pharmacy days
covered, and is therefore often addressed in MPR/PDC type studies.

We did not make any attempt to adjust for inpatient stays and now acknowledge this as a
potential limitation of the study on page 17 (last paragraph). However we also note that we think
any biases associated with this would likely be comparable across the measures and hence have
minimal impact on our general conclusions.

R2-7. to be honest, despite several runs through the analysis section, I am not sure what
information Table 2 presents, and the Results text does not clarify it well. It would
appear that the means represent MPR equivalents, but not sure what percentiles
indicate. “Upward bias” is also perhaps a slightly inaccurate term without defining
what a gold standard of accurate adherence measurement should be.

We have used a footnote to clarify what is represented in Table 2. We believe Table 2 makes two
main points, and that these are clearly described in the text. Paragraph 1 of Results comments on
the fact that, because CMA1/3/5 all require two dispensing events to be calculated, they are
missing for 68% of the population. Similarly CMA2/4/6, which all require at least one
dispensing event, can only be defined for 83% of the population. By contrast, CMA7 and CMA8
are definable for the full population whom we believe should be taking these medications.
Paragraph 2 of Results comments on the relative biases between the measures. We don’t claim
to know which is the true gold standard for measuring adherence, and so were careful to use the
term “relative” in describing these biases. We include the various percentiles since collectively
they give a good picture of the shape of the distributions. For example, we note in the text that,
“the even more pronounced relative upward bias in CMA1 and CMA2, which is reflected in their
means and standard deviations but not their more robust interquartile ranges, results from the
extreme skewness in the right-hand tail of these measures.” Thus the added detail provided by
this information (as opposed to simply means and standard deviations), provides greater
understanding into the behavior of these measures and hence, we believe, should result in greater
understanding of the behavior of these measures.

R2-8. so 1/3 of these patients only had 1 fill (as suggested by 3 of the measures), and 17%
ever had a prescription? Most studies would exclude the latter patients completely.
Again, it is still not clear at this point what “needs dispensings to calculate …”

One point our study aspires to highlight is the trade-offs associated with the decision to exclude
patients without a prescription. If you are trying to assess adherence in a population and wind up
throwing out 1/6 to 1/3 of the data because individuals who have been prescribed the medication
and should be taking it were totally nonadherent during your observation window, you will
clearly overestimate true population level adherence. If in addition you wish to compare the
impact of some intervention on adherence, then throwing out nonadherers as the reviewer
suggests further biases such a comparison if one treatment arm is more effective in promoting
medication use. An intention to treat analysis says you should analyze everyone you randomize.
We have added a new paragraph to the Discussion (para 2) that tries to further clarify this point. We realize the Discussion is already on the long side, but we wanted to try and clarify these issues for the reviewer.

**R2-9.** *perhaps equally important from a research perspective, as noted by the authors, one major problem with any adherence study is not knowing truly when a patient was prescribed a medication, when they truly stopped taking it during a defined period, not to mention the actual adherence behavior of taking filled prescriptions. All, this uncertainty often overwhelms the distinctions between measurement approaches and “bias”.*

We respectfully disagree. Although we acknowledge the salience of the reviewer’s points, these issues are in play for all of our measurements and yet we see striking differences between them in estimated adherence, and the magnitude of these differences are highly dependent on the length of observation (Table 3). So it is hard to see how the reviewer can say the uncertainty “overwhelms the distinctions between measurement approaches”.

**R2-10.** *these significant concerns (or at least confusions regarding the approach) aside, such examinations are important as adherence research continues to evolve, along with how such research relates to improving clinical care and monitoring must be further addressed in the literature. The Discussion section is well written, the clearest of all parts of this paper, and does indeed cover the most salient issues. However, it is also long and wanders through a variety of points related to the 8 measures. Although some key points are summarized nicely (e.g., window length important, need to understand what we are measuring), I am having difficulty seeing the overall utility and application of these findings to either research or clinical practice. Granted, much of this might be attributable to my lack of complete understanding of the specific methods.*

We have tried to edit the Discussion to better clarify the utility and application of the findings.

**Other suggested discretionary or other comments:**

**R2-11.** *further support of the study significance might be made concerning the of pharmacy databases is increasingly essential in examining adherence issues in large health care systems (HMOs, VA, Medicaid and Medicare, etc.). The first part of the introduction addresses some of this, but most pharmacoepidemiological research absolutely depends of such databases and systematic adherence measures.*

We fully agree, however, space limitation restricted our elaboration on this point. If the editor would like, we can expand on this more in the Background section.
**R2-12.** save any commentary about the findings until the Discussion; e.g., early in the Results the authors note “two points are worth noting”.

We generally agree with the reviewer’s point. However we feel that the nature of the results requires some level of comparative discussion. We have, however, modified the text somewhat to attempt to reduce commentary in the Results.

**R2-13.** given the length of this paper, not sure how much detail is needed regarding the RCT and intervention itself, since the primary objective is the adherence measures, though some detail is helpful for context.

The main outcome results from this study have now been published and we have added a reference to the findings in the Methods section. Should the editor wish us to add some more description of the parent study and results we will be happy to do so.

**R2-14.** I strongly suggest adherence not be capped at 1.0 for any study – our own work and that of others have demonstrated that patients with very high values are a special subset of sicker or more unstable individuals that need to be monitored carefully (i.e., values above 1.0 are important to capture).

Please see our response to R1-6.

**minor points: [all minor, perhaps subject to journal’s formatting requirements]**

**R2-15.** check for comma used following e.g., / i.e.,

Done.