Author's response to reviews

Title: Cost effectiveness of a computer-delivered intervention to improve HIV medication adherence

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Author's response to reviews: see over
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Adrian Aldcroft, Executive Editor
*BMC Bioinformatics and Medical Decision Making*

Dear Professor Aldcroft:

We thank you and the dedicated reviewers for their comments on the initial submission of our manuscript. We have responded to your and the reviewers’ comments as follows in the revision that accompanies this letter:

Editorial concerns:

1. We recommend that you copyedit the paper to improve the style of written English.

The paper has been thoroughly reviewed for stylistic issues.

Reviewer 1:

1. *What is the correlation between MEMS and actually taking the pills? What is the correlation between MEMS and changes in viral load?*

   The relation between any behavior and a measure of it can be complex; medication adherence is no exception. “Actually taking pills” is difficult to assess as any ethically acceptable strategy for measuring patient adherence may have effects on adherence. Most studies show a high correlation between MEMS data and unannounced pills counts, viral loads, and patient self-report.

2. *It appears that the intervention was a one-time only, one-hour sitting at the computer at a clinician’s office, and the effect was measured for only month after the intervention. Thus, extrapolating to one year seems a stretch. What happens to the cost effectiveness results when the effects are valid for a month only? (as there seems to be evidence of effectiveness only for that period)*

   We think that substantial data support the effectiveness of educational adherence interventions over longer periods of time. In this revision we have included calculations for a range of durations, costs, and levels of effectiveness. Results for one month are reported in the paper and included in more detailed supplemental tables now included with the revised MS.
3. What was the mean/median adherence rate of those with less than 85% adherence? Was the effectiveness measure 7% of that unmentioned average baseline? Or was it a 7-percentage-point reduction from that baseline? The distinction is very important as the results hinge on that number. If it is 7% of 85% mean adherence, then that would be a 5.95 percentage point difference. The details may be in the parent study, but the present paper should stand on its own.

In subsequent analyses for the paper recently published, we refined the original regression model on which the 7% effect was based by including number of years treated for HIV and the number of doses of medication taken per day. This model (reported in Neurobehavioral HIV Medicine; a copy of the paper accompanies this revisions as a supplement) showed a model-corrected (marginal mean) average adherence of 58.00% (SE 3.02) before and 68.58% (SE 4.320 after the intervention for participants with less than 85% at baseline. For this reason we now use 10% in the revised MS. The exact meaning of this value (as model-corrected group means before and after the intervention) is now clarified in the revision.

Also, what was the effectiveness when attrition was taken into account? Effectiveness rather than efficacy in an RCT may be the relevant number to use.

We agree with the reviewer’s observation, but note that the number of participants who left the study (6 of 124) is so small that changes in outcomes are very small. In the area of clinical trials, effectiveness (vs. efficacy) typically refers to an evaluation of the effects of an intervention in a typical clinical situation, not to an intent to treat analysis as suggested by the reviewer.

4. The authors need to be more specific about how exactly the total costs were reduced.

This information has been added.

Also, it would be informative the estimate the cost effectiveness leaving the research costs in.

Cost per QALY outcomes without reduction for research-related costs and for a range of development costs are now provided in supplementary tables.

Would the computer program have been developed in the absence of the research aims (and costs)?

We assume that since the US government has funded the study (and a number of similar studies), that in other circumstances those interested in public health and cost savings from improved health might have considered supporting its development.

What is meant by “real world”?

We mean a situation outside of a university clinic. Our meaning has been clarified.
From an economic point of view, who would produce this type of computer program? Presumably agents that could accrue the savings in avoided medical expenses…. Insurance companies?

The answer to the question is beyond the scope of this manuscript. In our experience the groups interested in improving medication adherence are pharmaceutical manufacturers and those in single payer systems, such as the National Health Service in the UK and the US Veterans’ Affairs systems of hospitals. The former are interested because of the potential for increasing sales, and the single payer systems because of the potential for reducing health care costs. Given the recent trends in healthcare finance in the US (i.e., the Affordable Healthcare Act) in which reimbursements are tied to prevention and actual clinical outcomes, interest has increased in cost-effective interventions that have the potential for improving patient health.

5. Do we know anything about online program uptake and effectiveness?

Little is known about spontaneous uptake of online programs for medication adherence. When deployed in a number of interventions have demonstrated effectiveness in both HIV and other conditions. We have no data to answer this question specifically about the current intervention, but note that other studies of online interventions have had high levels of participation. For example the study of an online social participation intervention reported by Horvath et al. (paper presentation in June of 2012; available at http://iapac.org/AdherenceConference/presentations/ADH7_79984.pdf) had 87% retention of participants. We note that one popular Internet application for diet and fitness (www.myFitnessPal.com) reports 30 million downloads. Traffic statistics for their website (www.alexa.com accessed December 17, 2012) suggests that 0.059% of all Internet traffic was to its site showing that as many as several million persons accessed and used this site during the past week. We have thus addressed this issue in the discussion section.

The authors seem to be extrapolating from an in-office intervention and assuming that the uptake and effectiveness will be the same. More evidence should be presented for that assumption.

The reviewer is correct that this is an assumption. The purpose of the analyses we present is not to argue for the effectiveness of the intervention in various contexts, but to evaluate costs and benefits under the assumptions we have stated. As the content and interactions with the application would be the same whether the patient works through it in a clinician’s office or in another setting, we believe that the assumption is plausible. We have clarified this issue in the revised manuscript by emphasizing this limitation in the discussion.
6. Actually, it would be useful to see those results to see how the conclusions may change. In fact, I would suggest modeling a threshold effect: at what % increase in costs does the decision change?

These thresholds are now included.

7. For the same number of users as in the high utilization scenario in a clinician’s office (1,125 users annually), the cost per user for Internet delivery is $50." This volume of non-repeat patients may only be sustained in large urban centers with relatively high prevalence of HIV. It would be useful to have the results for clinics with lower volume of clients; especially since the authors suggest in the discussion that this computer programs may be useful in rural areas (where the volume of patients will be considerably lower).

This calculation is now completed with a smaller number of users for a shorter period of time reflecting the reviewer’s concerns about the duration of the intervention’s effectiveness.

8. There is an important selection and effectiveness interaction issue that has not been addressed: those patients with the most severe adherence problems usually also have drug, alcohol, mental health and/or housing issues, thus, it seems unlikely that they will have the ability . . .

Most of our participants met the criteria listed by the reviewer (current or past history of mental illness or substance abuse/dependence, housing instability), and all were able to complete not only the intervention but also an individually-administered cognitive testing battery and a series of computer-administered questionnaires at the end of the study visit. Participants completed a series of cognitive and psychosocial measures at the first study visit; only one chose to discontinue participation due to HIV-related fatigue. There is thus little question about their ability to complete the intervention. This issue has been addressed in the discussion section of the revised manuscript.

. . .and inclination to sit for an hour in front of a computer without receiving the participant incentive provided in the parent study (even assuming that the program is engaging, and that they have high speed Internet connection).

We agree that incentives may be an important way to improve patient participation in adherence interventions. As this is an issue that may be of even greater significance for in-person interventions (some of which require 7 to 10 in-person sessions), it is not unique to computer-based interventions. In fact, the convenience of the computer format and the potential for Internet delivery may make the issue of incentives less salient, although still important. We now provide additional consideration of this important issue in the discussion section.

Minor issues:
1. Need to add page numbers.

The template provided by the journal does not include page numbers and thus they may not be appropriate; in response to the reviewer’s request we have added them.

2. Section details on CD4 cell count levels and cutoff points on “Costs and utilities related to change in adherence” does not seem to correspond to figure.

The relevant sections have been reviewed and revised as suggested by this and other reviewers to improve their intelligibility.

3. “cost of $22 per sq feet” Please provide source.

The cost was based on the actual cost of the office space used in the project; in this revision in order to be more precise we have obtained a current estimate of the average cost per square foot of medical office space for our locale from a commercial real estate concern and now use this in analyses ($23.11/square foot in the second quarter of 2012).

4. “advertising costs increased by ten times” why? Based on what?

This was based on the 10 times greater costs for 10 times more users; it is an assumption. We have clarified this source in the revision.

5. The % efficacy scenarios were based on any literature or empirical evidence?

We regret any lack of clarity, as we believed that this issue was addressed in the original version of the manuscript. The percent efficacy scenarios are based on assumptions we think are conservative. These sections have been rewritten to emphasize the reasoning that underlies the assumptions that are an inevitable aspect of this study in the absence of definitive data on precisely how increased adherence would change the number of patients with specific CD4 counts.

6. “analyses presented here show that even under the most pessimistic projections…” The most pessimistic projection assumptions do not really seem to have been considered.

The reviewer does not state what he might consider “the most pessimistic projections.” If he means that we should revise the sentence to avoid a reader construing it literally, we have done so.

7. “did not attempt to calculate the economic benefit of returning ill persons to the workforce…” Note that a non negligible portion of non-adherent patients are often unemployed, underemployed or earning less than minimum wage.
We appreciate the reviewer’s comment and agree that this is an important issue. As noted in our response other reviewers, only 22 of our participants reported that they were employed. Given the complexity of the factors beyond health status that might affect a patient’s return to employment (e.g., difficulties in finding employment, financial incentives to remain on disability, problems in finding childcare), it is clear that a number of factors in addition to immune status might have an impact on return to work. In this revision we have used data from a study on return to work in persons with HIV to complete estimates of the possible impact of some participants’ return to work on the net cost of the intervention, including lost salary and wages during development and increased productivity resulting from return to work.

8. “This may be particularly relevant in delivery of services to persons in rural areas”
Again please consider patient volume and age. . .

We note that the intervention, when deployed on the Internet, is not geographically limited so that the volume of users could still be high whether they are in urban or rural locations. One server, for example, could accommodate users in many places including a large number of users in rural communities.

Rural persons’ access to high speed Internet connections is limited, however, so that it may be more likely that they would access it at clinician’s offices. Although this might be accomplished as part of other office visits, in this revision we have calculated estimated transportation costs for rural participants that would be associated with deployment of the intervention based on data describing rural patients’ average distance from physicians and cost of automobile transportation per mile. These calculations are incorporated in supplementary tables that accompany this revision.

Older patients may be reluctant to use the computers.

We do not know what the reviewer intends by “older” patients; persons aged 50 to 65 are quite different from those who are much older. While it is true that persons aged 65 years and older are less likely than younger individuals to use computers and the Internet, the majority of persons with HIV infection are younger than 65 years of age. Research, including our own (Ownby RL et al. [2008] Cognitive abilities that predict success in a computer-based training program. The Gerontologist, 48, 170-180) has shown that individuals 65 years of age and older can successfully use computers when provided with appropriate instruction. We note that the majority of persons treated for HIV infection are younger than 65 years of age (for example, only 4% of new HIV infections in 2010 were in persons aged 65 and older; data from the CDC at [http://www.cdc.gov/hiv/topics/surveillance/basic.htm#hiv aidsage](http://www.cdc.gov/hiv/topics/surveillance/basic.htm#hiv aidsage)). We thus believe the intervention most appropriately targets persons aged 65 years or younger and note that 76% of persons aged 55 to 64 report using the Internet ([Generations Online. Pew Internet and American Life Project. Report available at [http://www.pewinternet.org/~/media/Files/Reports/2010/PIP_Generations_and_Tech10.pdf](http://www.pewinternet.org/~/media/Files/Reports/2010/PIP_Generations_and_Tech10.pdf)]. The percentages of persons younger than 55 who use the Internet are much greater.
Through our development process (now more fully explained in response to reviewers’ comments) we sought to ensure that the intervention would be maximally user friendly. As is now more fully explained in response to other reviewers’ concerns, interacting with the application only required touching the computer screen, and the application’s usability was thoroughly evaluated prior to beginning the study. We understand the reviewer’s concerns on this issue but believe that for the reasons outlined here that they are not likely to have a large impact on the intervention’s use. This issue is briefly addressed in the introduction.

*Do we know what the most common use for Internet is? Retail? Increased risk behaviors? (i.e., pornography and search of sex partners)?*

We do not understand the relevance of these comments to the manuscript but would refer the reviewer to data on these issues from the Pew Internet and American Life Project (http://www.pewinternet.org).

**Quality of written English:** Needs some language corrections before being published.

The paper has been reviewed for possible language problems; as the reviewer does not indicate what his concerns were, we have not been able to correct specific problems.

**Reviewer 2**

*The problem is that the intervention is not adequately described or referenced.*

We regret that in our effort to make the manuscript a manageable length we did not provide sufficient information. We now include a more extensive description of the intervention and references to a recently-published article (available via open access and provided as a supplement for review) as well as to a presentation with illustrates that provides even more information on the application, its development, and its efficacy. A walk-through of the intervention with images from the computer screen has also been included as an appendix, also as suggested by the reviewer (below).

*A better article would be an analysis of the intervention itself, or at least reference where the intervention (and computer program) can be fully described, and its efficacy discussed. At the very least, please reference the program itself or maybe put in as an appendix, so that readers can better appreciate the program.*

Through changes in the revised MS, the referenced article, and the appendix we now provide the requested information.

2. Another issue is that I am not convinced that the cost data reflects what would be required for a non-research clinic to develop the program. It is not justified well in the text.
While the reviewer’s comments make it clear he is unsure of the accuracy of the cost data, it is not clear to us why he thinks this might be true. The costs, if anything, are inflated by the development of the application in a university setting with salaries for staff who would not typically be involved in so extensively (e.g., a professor in a medical school). These increased costs would result in a lower probability of a positive cost effectiveness, making these cost estimates if anything more conservative.

We agree that the costs might be different in another setting but have no data to use in what would be a hypothetical situation (at least for this application, we know what the actual costs were – we would just be guessing at costs in another setting). We also note that reviewer 1 expressed concerns about decreases in the budget to eliminate research-related concerns.

We have attempted to address this issue in the revised manuscript, by completing cost-related sensitivity analyses of costs reduced by 50%, and increased to 150% of actual costs derived from the adjusted actual costs in order to evaluate outcomes with different development costs and effectiveness estimates. These analyses are now included as supplemental data tables. In response to reviewer 1’s suggestion, cost thresholds have been calculated for each scenario and are reported in the results section.

I think using the budget from the study is a clever concept, but I am uncertain that it’s accurate. For example, saying the participation incentive of $50 covers lost wages is not necessarily accurate, or even likely. The authors need to provide more rationale/data to support the cost data used.

Twenty-two participants were employed. Based on the average income of persons in each of their educational levels we calculated lost wages based on transportation time and two different levels of participation (only for the intervention and for the entire study). Total lost wages for the entire study, as described in the revised manuscript, were $2,595 when calculated for the entire study (three study visits with an average time for transportation of 30 minutes each way for the 22 participants who reported regular employment). Participants were provided with $18,656 in compensation for study visits and for travel reimbursement.

Loss of salary and wages during the development process is now included in development costs; participant compensation was previously included in development costs. Lost wages for one visit are now also included in deployment costs, and these calculations are now discussed in the revision.

In the response to reviewer 1 on how costs were reduced, additional information has been provided on costs and what they represent.

3. Further, the adherence improvement is based on one month pre-/post-.. This is so short term for a long term therapy, that the QALY analysis becomes suspect. It would be far better to have longer term adherence data and determine benefit and cost-effectiveness on that data.
We agree that data from such a study would be valuable; unfortunately we were funded
to do a brief developmental study and do not have the data requested by the reviewer.
As noted above, we have now provided cost-effective calculations for different time
periods, cost estimates, and levels of effectiveness. We would hope to be able to obtain
funding to evaluate the effectiveness of the intervention over time as well as the
possible effects of booster sessions. In response to this and other reviewers’ concerns,
the QALY analyses now assume only a six-month period of effectiveness.

This is especially so as the authors assert that an increase in adherence is related to
higher costs due to higher medication costs (reasonable), but they don’t take into
account the higher costs of care of hospitalizations and emergency care, etc.,
associated usually with poorer adherence and poorer immune status. If these costs are
accounted for, that needs to be made more explicit or if implied in the different costs by
immune status that should be noted also.

These costs were included in analyses reported in the previous version of the
manuscript. We regret that this was not evident and have made this clearer in the
revised manuscript. For example, these costs and are now explicitly included in the new
figure and table suggested by reviewers 4 and 3, who suggested that their addition
might help readers better understand analyses. These are now included in the revision
as Figure 1 and Table 1.

4. Further, the assumption of only 5% movement/improvement of treatment effect from
say <50 cells/µL to the next level is too low. That would imply fairly ineffective therapy,
and not consistent with today’s treatments.

We regret that this issue may not have been clear in the original MS. The assumption
was not that the institution of antiretroviral therapy would only increase CD4 cells by 5%
but that the effect of the adherence intervention would only move a small percentage of
patients from one CD4-based group to another. The 5% estimate was only one of those
used in order to provide a sensitivity analysis of a range of possible intervention effects
from very small to much larger.

5. The discussion section is well-written. The conclusions, though, need work, as
I’m not sure that as written they are justified by the data. The cost-savings argument
needs revision, especially as some of the assumptions made to fit the model (noted
above) are questioned.

We have rewritten the discussion section in light of the reviewer’s concerns and hope
that by addressing his concerns about the assumptions underlying the analyses our
conclusions are now justified.

Reviewer 3
The authors find evidence to suggest computer based interventions, delivered in a clinical setting or via the internet, have the potential to be more cost effective than existing in-person medication adherence interventions. The paper makes a unique contribution to the literature, and these types of economic analyses are much needed in the field of technology based HIV prevention.

1. The authors should further explain and attempt to place a monetary value on the costs to participants of using an office based versus internet based intervention. Using the internet has several advantages over delivering a computer based intervention in a physician’s office, such as reduced travel time and greater convenience. The cost difference between the internet and office based delivery may therefore be overstated by not accounting for the participant costs. This is especially true in rural areas, where a computer kiosk in a physician’s office may be located a great distance away.

We have calculated corrected costs of the kiosk-delivered intervention for rural users by using data for the average distance from a patient’s home to a medical specialist reported in Rosenthal et al. (2005) and the average cost per mile of driving a medium-sized sedan reported by the American Automobile Association. Costs are included for the lowest estimate of effectiveness and for a range of costs and time periods in the supplementary tables and are reported in the results section.

2. The authors cite a 7 percent improvement in adherence resulting from the intervention. However, the citation provided is not a published manuscript, so relying on that estimate as the basis of a cost-effectiveness analysis might be premature.

Since the submission of this manuscript we have published additional data on the application’s effects in peer-reviewed journal; these are now reviewed in this revision and a reference to the publication is provided.

The follow up period of the study was 1 month, so it is not clear whether this effect remains for a longer period following the intervention.

We agree that this is an important limitation; it has been addressed by providing data on a shorter period of effect as requested by reviewer 1. We also provide citations on the duration of other interventions’ effects.

The authors undertake sensitivity analyses of the intervention’s effectiveness, but this limitation should be stated explicitly.

We regret the lack of clarity and have rewritten the relevant section of the manuscript to make this clearer (under the heading “sensitivity analyses”).

Minor revisions

1. The abbreviation “ARV” is used in the body of the paper before being introduced.
This problem has been addressed.

2. *The first 2 sentences of the “Results” section were already stated in the “Methods” section and can be deleted.*

These sentences have been deleted.

3. *The results presented in Tables 5 & 6 warrant further description in the “Results” section. Authors should, at a minimum, provide the range of costs per QALY for each delivery approach.*

The results section has been edited to include the information suggested by the reviewer.

4. *The tables need additional notes. The reader should be able to understand the table without having to refer to the text.*

In response to this reviewer as well as reviewer 4, explanatory footnotes have been added to the table.

**Discretionary revisions**

1. *A table or figure summarizing the advantages/disadvantages of clinician, computer, and internet delivered interventions would help to clarify arguments presented on pages 1-2.*

A summary table incorporating the reviewer’s excellent suggestion is now provided and incorporated in the conclusion section as Table 8.

2. *A table summarizing the parameter values assumed for the baseline analysis and sensitivity analyses would be useful to inform the reader of the necessary components of a cost-effectiveness analysis (most readers are likely not economists) and the values assumed. The source of the values (parent study or published literature) should also be stated in the table.*

The table the reviewer suggests as well as a figure (as suggested by reviewer 4) are now included to address this concern as Table 1 and Figure 1.

**Reviewer 4**

*Presentations of cost analyses with this level of complexity are challenging and one area that could improve the potential impact of this manuscript would be to find a way to escort the reader a bit more through the process. Possibilities for this may include providing a bulleted list of assumptions, adding a figure of input/output,*

A new figure (Figure 1) has been provided to address this suggestion.
and better labeling and explanation of tables and figures (noted in specific comments below).

We have revised the MS in response to the reviewer’s comments, as described below.

Larson (J Am Med Inform Assoc 2006) used some figures to highlight sources of costs of development of a computer intervention, but to this reviewer, a better approach would be to place in a single figure all status “quo” estimated (with no intervention, costs of medication and costs of Tx are estimated at X per person or per year) and then adding in the information specific to implementation (at low or high utilization).

We consulted the article by Lairson and have revised the manuscript in response to the reviewers’ suggestions, including adding a new figure and table (as mentioned above in the response to reviewer 3).

This would allow the reader to easily see the scenario in place for no intervention and how this picture changes when an intervention is introduced. Creating a graphic or comprehensive table that allows single-view, versus flipping through multiple tables, is no small task and would require a fair amount of innovation from the authors given that there is really very little guidance out there in terms of how to do this successfully.

The figure and table have been added to attempt to address this issue.

However, given that presently there is substantial burden on the reader, it would be worth trying to find a way to consolidate inputs and outputs more efficiently.

We agree that the presentation is complex and have tried to follow the reviewer’s suggestion to make the presentation clearer and more user friendly.

**ABSTRACT**

Consider using past tense on results from previous study…”…but it was not clear that the benefits…”

This has been corrected.

Consider changing wording for “…a favorable cost per QALY” – Could this be stated as “cost savings”?

In this context “favorable” refers to a value of $50,000 or less. The use of this criterion is more clearly explained in the text.

**BACKGROUND**
In noting that effective interventions are not widely available, consider pulling in citations to support this statement. While the literature is fairly silent on overall rates of uptake and availability of behavioral interventions to promote ART adherence in the “real world” there are some data that suggest that indeed behavioral support is not commonly available [Amico (JIAPAC 2011) has a snap-shot of standard of care for a select group of respondents, as does Harmon (AIDS Care 2005)].

References to these sources have been added and the relevant portion of the MS has been rewritten.

The authors may want to make the point here that we are not certain of this in the US [deBruin’s meta analysis looking at control arms in RCTs of behavioral interventions would actually suggest that there are ample behavioral intervention components in “SOC”]—however there is good enough reason to believe that implementation of effective behavioral interventions is not presently “common” or at least not perceived as “sufficient” among care providers.

A reference to deBruin’s excellent meta-analysis has been added and the relevant section of the MS has been rewritten.

Despite the authors noting that computer interventions are not intended to take over or replace clinicians, this is in fact a real concern- if adherence is assumed to be “covered” by the software, would we expect clinicians to completely abandon conversations about one’s adherence? We would like to say no, but the current phrasing of the argument does leave the reader wondering.

We recognize concerns that the availability of a computer-based intervention might have a negative effect on the amount of time clinicians spend on adherence-related issues. In the introduction and later in the discussion this issue is reviewed, and we note that some research suggests that better informed patients are actually more active participants in their care.

It may be important here in also include the likely possibility that the ad-hoc discussions that clinicians have with patients regarding adherence are indeed pressed for time and can be derailed by the need to focus on pressing medical issues, but also that most clinicians providing care would not have the breadth of behavior-related information or motivation enhancement strategies that would be feasibly housed in a computer software. A software program has added advantages of standardized use of strategies and content that tailor and target. The time-savings is critical for implementation and cost effectiveness. Adding some foreshadowing for how it may also be advantageous in promoting quality of life would be a good opportunity here.

The introduction has been revised to include the reviewer’s suggestions.
The sentence “Previous evaluations of interventions for ARV adherence have shown that the cost-effectiveness of interventions is highly dependent on their costs.” seems too obvious to be worth stating.

This sentence has been deleted.

Typo: “actually reduce total net costs [9], but even with these costs savings adherence interventions may not be widely deployed because of lack of trained personnel.. Further, adherence interventions”

This error has been corrected.

Consider adding to the argument on page 6/34 that computer interventions available via internet can also provide intervention support “in real time” and “as-needed” for the growing number of PLWH who have regular internet access, rather than having to wait until you return to clinic.

We agree that this is a valuable point and thank the reviewer for the suggestion. We have included it as recommended.

Consider adding mention of Fisher et al’s [AIDS and Beh 2011] LifeWindows project results to the background.

A reference to the study has been included.

*Please clarify if the intervention was single session and provide date for reference 11.

This information has been added.

**METHOD**

*Add footnote to Figure (label it as Figure 1) to inform reader of meaning of p, t and x, as well as numbers within the circles for the Health Utilities portion.

The suggested footnote has been added to what is now Figure 2 in the revision.

*Define in text the two levels of utilization used in analyses in first methods paragraph.

The definition has been added.

*Provide a clear definition/operationalization of ‘utilities’ and ‘health state utilities’ if that is different.

The concept of utilities is more fully described.
*Provide greater detail on Table 1. Not clear in table what ‘average’ is or what x refers to. If referring to the strata of CD4 and movement from that strata to next higher, this could be explained far more clearly. Provide CD4 values for each group and change situation.

A footnote to this table has been added to clarify these issues.

*Text makes it confusing regarding cost estimates- which is in the table, estimate 1 or estimate 2? If estimate 1, it would seem more appropriate to include estimate 2 as that is what was used in subsequent analyses.

This issue has been clarified.

Is the 44.8% the indirects charged off the grant costs? Is there reason to believe that in practice or real world deployment that this would be as high?

The 44.8% administrative costs is the agreed-upon rate used by our institution. Other reviewers expressed concerns about the accuracy of costs, and more extensive sensitivity analyses are now included to address this issue.

*In description of utilization scenarios it seems that the intervention would be used only for new patients. If that is the case, framing the intervention as specifically for new patients entering care early in the manuscript would be important. In any case, given that “eligibility for intervention” is frequently referred to, stating who the intervention targets and who is eligible early on would add clarity to the text. Also- is it anticipated that each person would use the intervention once or is it repeatedly over the course of a year?

These issues have been addressed in revisions to the introduction.

In determining medication costs, why was 70% adherence used as starting adherence values?

This value has often been found in studies of adherence in persons with HIV, as in the referenced studies. This has now been further explained.

*Text states that the difference between states 1 and 2 is $14,964. Does that mean that the numbers of the circles are the savings or is this a typo and should state 2 be valued at a cost of $14,964 producing a cost savings of 33,007 – 14,964? In any case, isn’t 33,007 – 14,198 = 18,809? Please clarify.

We thank the reviewer for this observation and apologize for the error. It has been corrected.

*Define in table 1 and Figure 1 the time line for these improvements- would it be a 5% chance of moving up over the course of a year? Also, confirm in these scenarios that
people are not estimated to move down-backwards in groups, or are those individuals incorporated in the odds?

These issues have been addressed in the text in the methods section. It was assumed that the effect of the intervention would only be to improve adherence and increase the likelihood of patients moving from one CD4 group to another. Although in actual practice some patients might have lower adherence over time, this effect was not modeled as it was assumed that it would not be related to the intervention’s effects.

*Check numbers in Table 5 and in text (eg., $323,5230 in table, and $20,542 in text vs $20.541 in table).

All values in the relevant tables and text have been recalculated and changed.

DISCUSSION

*Text “Even with a low probability of change in CD4 count for a small number of patients” reads awkwardly. Should this be ‘Even in scenarios where the low probability of change in CD4 count resulted in improved CD4 counts for a small number of patients..’?

We appreciate the reviewer’s suggested revision and have incorporated it.

Consider adding that the cost savings are at the societal level in the discussion sentence below: “With higher probabilities of effects and wider deployment, the intervention would result in net cost savings.”

We thank the reviewer for the suggestion and have incorporated it in several places in the revised manuscript.