Author's response to reviews

Title: Using Novel Canadian Resources to Improve Medication Reconciliation at Discharge: A Cluster Randomized Trial

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Version: 5 Date: 4 April 2012

Author's response to reviews: see over
Reviewer 1

Major comments:

1. "Adverse drug events" is a term that is widely used but that poorly specifies the different things that it implies. Bates et al (JAMA 1995; 274: 29-34) originally defined an adverse drug event as "an injury resulting from medical intervention related to a drug", a definition that confusingly encompasses not only all adverse drug reactions, whether caused by medication errors or not, and harms other than adverse drug reactions caused by medication errors. However, the authors here use a different definition altogether: "Adverse drug events are defined as the occurrence of new signs and symptoms post-discharge that are judged to have a moderate to high probability of being drug-related." What they are therefore describing is not adverse drug events as originally defined, but suspected adverse drug reactions, which is the term that they should use, for the sake of clarity and avoidance of confusion. The FDA has defined a suspected adverse reaction as “any adverse event for which there is a reasonable possibility that the drug caused the adverse event”; in this definition "reasonable possibility" implies that there is "evidence to suggest a causal relationship between the drug and the adverse event" (http://edocket.access.gpo.gov/2010/pdf/2010-24296.pdf).

We appreciate the reviewer’s comments and agree that our terminology needs revision. We also appreciated having the opportunity to read the reviewer’s work in this area and have reflected on how we might improve the assessment of adverse drug events in a number of our other studies. For the study outlined in this manuscript, we have modified our definition to that used by Leape & Bates et al. for adverse drug events. We have chosen this definition for our primary outcome because we suspect that the major impact of discharge reconciliation will be to prevent two types of errors: 1) the failure to re-start a drug that was held at admission (e.g. anti-coagulants prior to surgery) that then leads to an adverse event (e.g. stroke), and 2) failure to notify community pharmacists and physicians of changes in treatment (e.g. a change in anti-hypertensive), that leads to unintended therapy duplication (e.g. the previous anti-hypertensive continues to be refilled) that results in a fall-related injury due to hypotension. As the first example would not be included as an adverse drug reaction, but would under Leape & Bates definition of adverse drug events, we have elected to use this broader definition and have modified the text accordingly.

2a. The authors say that "Reconciliation ... is critical in reducing the risk of preventable ADEs", but they do not specifically cite the evidence that that is so. Instead they quote papers about the accreditation requirement for reconciliation and papers that detail the challenges to implementation.

The reviewer points to a very important gap in the science supporting the need for medication reconciliation interventions. Although there is an abundant literature on the prevalence of discrepancies, there is a relative paucity of data on the impact of medication discrepancies (between community and hospital medication lists) on the occurrence of adverse events. Nevertheless, both Canada and the United States have adopted requirements that each and every patient needs to have their medications
reconciled at admission and discharge for a hospital to receive accreditation. One can certainly argue that there was premature adoption of a medication reconciliation accreditation policy, however that does not change current requirements or the considerable demand this places on hospitals to achieve this objective. A recent study (JAMA, 2011) suggests that these discrepancies may increase the risk of adverse events by 10%. We have cited this study in the background, and have modified the text to indicate that most “believe” that medication reconciliation is important.

2b. Nor do they refer to the possible downsides of reconciliation. For example, expense. There is some evidence of the cost-effectiveness of reconciliation (e.g. Karnon et al. J Eval Clin Pract 2009; 15(2): 299-306), but does that extend to the method that the authors propose? They quote the amount of money that might be saved, but do not mention the costs of the system. Adding value, as studied in the authors’ pilot study, or rather the perceived value according to physicians and nurses (Fig 2), is not enough; the added value has to be worth the cost.

In the background, we did acknowledge the expense of completing medication reconciliation as an important barrier to implementation (see Challenge #2). One of the reasons it is costly is the time required to obtain the community drug list. This study aims to reduce this time substantially by retrieving this information electronically from the provincial insurance agency. The article by Karnon is interesting. We appreciate you drawing it to our attention. However, the entire analysis of cost-effectiveness is based on the pharmacist using the “usual approach” for obtaining the community medication history, and the association between errors and adverse events is based on only one study (Bates), with 5 adverse events due to errors. The other cited study did not assess the association. As hospitals are currently required to invest resources in medication reconciliation, the question we are answering is whether or not there is a more efficient way to do so.

Another possible downside is the risk of adverse drug reactions that are due to reconciliation rather than despite it. If, for example, the community drug list specifies a drug that the patient was not in fact taking, even though it had been prescribed and dispensed, then reconciliation might introduce a drug that the patient was thought to be taking but had not in fact previously taken, one that might subsequently (even after discharge, with appropriate reconciliation with the hospital list) cause adverse reactions. One should not always assume that the community list must be replicated exactly. Thus, the term "current medicines" is inadequate; the authors need to distinguish between currently prescribed medicines and currently taken medicines and address the question of how accurately they can make that distinction.

We agree with the reviewer; errors can arise if a patient is not using the medications dispensed as they were prescribed. This is why we indicated, in the description of the intervention, that “...the admitting team and pharmacist will verify the list with the patient, add any other drugs including over-the-counter and herbal products...”. The
software has been designed to assist the clinician to verify how the patient is taking their medication.

3. The authors intend to use the Naranjo criteria for judging the probability of a suspected adverse drug reaction. This is fraught with difficulties, as indeed are all algorithms for assessing such reactions. They would do well to consider using more than one such method, as a cross-check, such as the UMC's method (http://www.who-umc.org/graphics/4409.pdf) and the method of Bégaud et al (Eur J Clin Pharmacol 2005; 61(3): 169-73), although other methods are possible (see the systematic review by Agbabiaka et al. Drug Saf 2008; 31(1): 21-37). The fact that the Naranjo method is the most widely used, as the authors point out, is no recommendation. Nor does achieving a consensus among three clinicians guarantee an accurate assessment of the probability that an adverse event is an adverse reaction, if they are all using the same faulty tool. Reproducibility is no guarantee of reliability.

We agree that these algorithms have problems, as do all assessments requiring expert judgment of causality, including the approach outlined by Begaud. Agbabiaka also acknowledges that there is no universally accepted method. However, at present most pharmacotherapy-related journals require use of the Naranjo criteria for publication. We may not publish in these journals but we want to keep the door open. As outlined in response to earlier comments, we have modified our approach to use both the Leape-Bates assessment method for adverse drug events, and the Naranjo criteria.

Minor comments:
4. The data that the authors quote (numbers of admissions associated with suspected adverse drug reactions, etc) are largely drawn from the US literature. Although it is likely that they apply equally to Canadian practice, they should make that assumption clear. Are the dollar costs that they quote US or Canadian dollars?

We have added that this is a US dollar estimate. While most articles are based on US studies, one author completed the same type of study in both the US and Canada (Forster), producing almost identical results.

5. For the sample size calculation, the authors would do better to use a worst case scenario and plan to randomize more than their current estimate (say 4000-4500 patients), particularly because of the risks of introducing bias that they discuss.

We agree that increasing the sample size will improve precision contributed by random errors in measurement that produce unexplained variability, but not systematic errors (bias). As this study is already funded, we have funds for 3,714 patients only.

6. CPOE is better expanded as "computerized prescriber order entry", since in some places others besides physicians are empowered to prescribe.
Reviewer 2
This is an interesting methodology paper for a randomized cluster trial of a computerized system to retrieve patients’ hospital and out-of-hospital (private practice) medication prescriptions or medication lists, to make sure all persons involved known what is prescribed.
There are two aspects: one is purely methodological, and there is nothing much to say about what is a relatively classical method of cluster randomization for non-blindable intervention, with blinded adjudication of adverse events.
The other is the study's background hypothesis, that most adverse drug reactions are related to a mismatch in knowledge of what has been prescribed to a patient. This is an interesting hypothesis, but I'm afraid the authors might be in for some disappointment here. But then it would be nice to know.

In the response to reviewer #1, we outlined the main types of errors that might be addressed by medication reconciliation. A recently published paper in JAMA reports that these types of discrepancies may increase the rate of adverse events by 10% (See Bell, C, JAMA, 2011), a reference that has now been added to our background.

A) no major issues except for the basic premise, but that is of no concern here except that the authors might introduce some degree of moderation ("among the many factors involved in avoidable drug reactions, misunderstanding or incomplete information about actual medication history or drug use in hospital or out of hospital might be a contributing factor..."
there are many other factors such as prescriber incompetence in the choice of drugs or doses and duration, misdiagnoses, patient non-compliance (over or under-compliance), in addition to genetic variations in drug metabolism or activity.

We agree that these are all factors that contribute to adverse events. As outlined in the analysis, we are testing a hypothesized set of modifiers of the intervention effect.

minor comments
b) the pages are not numbered
Page numbers were added
c) in biases and blinding the authors mention treatment assignment, which does not seem appropriate here, and is probably from another protocol...
We were simply acknowledging that treatment teams are not blinded to the treatment assignment.

Reviewer 3

This well written paper presents a trial protocol. The goal of this randomized cluster trial is to determine if an electronically-enabled discharge medication
reconciliation intervention reduces the risk of adverse drug events. The primary outcome is the occurrence of an adverse drug event within 30 days after the discharge.

Adverse drug events are one of the lead preventable health problems, especially among older patients. Evaluations of the interventions that aim to reduce this burden are thus relevant.

Methods are well described and relevant with respect to the objective.

Does this study currently recruit participants? The beginning date should be specified.

*The trial was delayed by the need to have the provincial privacy commission approve the electronic transmission of the community-based prescribing physician information so they could be notified of change in drug therapy during hospitalization. We expect that recruitment will begin in June, 2012.*

Concerning the form: the figures are not really useful (especially figures 1 and 2).

*We have eliminated Figure 1 and 2.*