Reviewer comments from Original Submission (see supplemental info): 2015-0036

Title: Do routinely collected health data complement randomized evidence? A survey	
Authors: Lars G. Hemkens MD MPH, Despina G. Contopoulos-Ioannidis M, John P.A. Ioannidis MD DSc	
Reviewer 1: Ian Shrier, The SMBD-Jewish General Hospital, Centre for Clinical Epidemiology and Community Studies	**Author response**
Comments to the Author The authors have submitted a thoughtful paper on the motivations authors use to justify RCD studies. The writing is clear, the methods sound, and the results reasonable and not surprising. I really only have two comments that the authors might wish to comment on.	
1. First, as the authors are aware, an ITT analysis in an RCT study evaluates the effect of treatment assignment. In general, RCD studies aim to evaluate the effect of treatment. These are different, and the difference should be one of the motivations for investigators to choose a particular study design, even if they don't state this themselves. I think adding this thought might help future investigators explain themselves more appropriately, or even choose to design their RCD studies differently. For example, some argue the effect of treatment assignment is the more appropriate effect of interest (especially in public health studies). Other times, the effect of treatment is of more interest (patients want to know what will happen if they take or do not take the treatment, not a diluted effect that represents the effect when lots of people don't take the treatment). RCD studies can be designed to address either question. Although some forms of analyses in RCT studies attempt to evaluate the effect of treatment, they all require assumptions that are usually just as believable or non-believable as a fully observational study. Therefore the RCT does not provide much advantage unless the specific assumptions are more likely to be true than those of a fully observational study, and that is very study specific.	We absolutely agree on the importance to differentiate between ITT and the actual 'per protocol' (PP) effects. Differences between ITT and PP would be caused by time-varying effects (e.g. treatment switch). We have added this in the Discussion section.
2. Second, I think the overall message of this paper is simply that authors should focus on areas where knowledge gaps are the largest. From a population and grant funding agency perspective, this is almost a truism. I think commenting on, or proposing solutions that will overcome current obstacles to ensuring this happens could improve the paper. As I see it, researchers are going to focus on what interests them the most, and their own perceived current gaps in knowledge, magnitude of the problem, severity of the condition, and most important, what they can get funded.	These are very interesting and important thoughts which we address in more detail in an accompanying analysis paper for the CMAJ. Detailed analysis of these issues is beyond the scope of our work.

Researchers often have a direct conflict of interest to studying where knowledge gaps exist. Although the motivation (grant funding, publications, peer recognition) is different from pharmaceutical companies (profit), it is likely just as strong. Funding comes from grant committees. By their nature, grant committees have non-experts reviewing submissions by experts in the field. The experts are often well acquainted with the literature, but spin the literature review to maximize the perceived impact of the study, and the relevance of their own particular expertise (which includes methods, population, etc). It is only once published, and after analyses of the type conducted in this paper, that we find out how much spin was actually applied. I would be interested in reading how the authors think this paper will help promote solutions, and what the solutions would be. If this is beyond the scope of their paper, I would suggest CMAJ consider having one of their editors write an accompanying editorial when the paper is published.	

Reviewer 2: Comments to the Author Summary of comments This is a simple, descriptive study that identifies scientific studies that used routinely collected data (RCD) (such as from a registry) to compare mortality outcomes of interventions, searches for RCTs on the same comparisons, documents the reasons for the RCD study if a similar RCT exists (based on a retrospective review of the published text of the RCD study, rather than direct inquiry), and examines the citation impact of the RCD studies. The results call into question the general perception that RCD studies are performed when RCTs are unethical or difficult to perform. It confirms that a common motivation is to perform a "real world" analysis. The methods appear adequate and are for the most part clearly explained. The findings are interesting, appear to be novel and at times are unexpected. The main limitation of the study methods are that they hinge on the quality of the literature search methods and on interpreting published text to categorize and quantify the results. The main limitation of the article itself is the writing style.	./.

Major comments 1. The constructions, grammar and choice of words do not always display fluency in English. Examples: First sentence of the Interpretation section in the abstract (page 2), 1st sentence of Methods, 9th section of introduction (page 3), last sentence on page 9 continuing onto page 10, first sentence of Discussion, sentences 4 and 5 of paragraph 2 on page 11, sentences 3 and 5 of paragraph 2 on page 12, sentence 4 of paragraph 2 on page 13; last sentence of Discussion on page 13.	These are now rephrased.
2. Second paragraph of introduction: is there a context for these questions? Are the authors, for example, coming from the perspective of decision-making, or research into epidemiological methods?	We mention the context for these questions in the prior paragraph in the Introduction: "This may improve the reliability of RCD-studies and thus their value for decision-making in situations where clinical trial evidence is inadequate or lacking."
3. Did the search period start at inception of PubMed? (otherwise, when was the start year?) Was the study selection itself also performed by only one reviewer? This should be clearly stated. Study selection would have been strengthened if at least a subset of articles (say 10%) were tested for selection by 2 independent reviewers.	We have now clarified that we searched from inception in the methods section and it is now clarified that only one reviewer selected the studies.
4. The reasoning behind the 2nd last sentence on page 11 is not clear: why does it follow that the citation record of previous RCTs by RCD studies may be better?	This is now rephrased.
5. The explanation regarding the 4th limitation (page 12) is difficult to follow. Should the second last sentence on page 12 start with "notably" rather than "preliminarily"?	These are now rephrased.
The "subsequent RCTs" are from what time period? I assume this finding (n=19) arises from the parallel project being performed by the investigators? On the top of page 13, "in the current circumstances" is vague.	This is now rephrased and it reads: "Thus far, we found very few RCTs published after the RCD-study (only for n=18 topics covered by RCD-studies). "
6. Web appendices are very complete.	./.
7. Table 2 should present the categories in the same order as in the text on page 9 (lines 16-48), as is already the case for Table 3.	We have revised the table accordingly.
8. The discussion would benefit from some consideration of the possible effect of publication bias on the sample of studies examined; the results reflect the associations between RCD and RCT studies among published studies (and not among all investigations performed which may not make it into the published literature).	We have added this in the Discussion section.

9. The discussion would benefit from some consideration of whether choosing RCTs published up until a year before publication of the RCD study might influence the results. What if an RCT was published only a month before the RCD: couldn't this be considered a prior trial, since the RCD authors may be aware of other work before it is actually published?	We found only 3 cases were a RCT was published in the same year as the RCD and the RCD authors did not cite/mention them. Therefore we don't think that this would have influenced the results.
Minor comments 1. First paragraph of introduction is too long, should be split into two. 2. Typographical errors: "RCD-data" is redundant sentences should not end with "or not" "also already" is awkward "to-date" and "effect-modifications" are not hyphenated "conversely" seems to be used incorrectly (page 4) "juxtaposed to" is an incorrect formulation "these" is superfluous in sentence 5, page 13 "worthy their effort" should be "worth the effort"	These are now rephrased.