Article details	
Title	Postmarket safety of surrogate and clinical outcome drugs approved by Health Canada: a cohort study
Authors	Lexchin, Joel; Ahmed, Tareq
Abstract	Abstract Background: Health Canada approves drugs on the basis of clinical and surrogate outcomes. This study compares the postmarket safety of these two groups. Methods: Information about whether surrogate or clinical outcomes were used and the date of market approval came from the Summary Basis of Decision. Safety warnings and the dates they were issued were identified through advisories on the MedEffect Canada web site. Kaplan-Meier survival curves were calculated to determine the likelihood that drugs in the clinical and surrogate outcome groups would receive a serious safety warning. The time from market authorization until a first safety warning was compared for the two groups of drugs. Results: 124 drugs were approved using clinical outcomes compared to 114 with surrogate outcomes. There was no difference in Kaplan-Meier curves for the two groups (p = 0.8531). The median time between market authorization and a warning for clinical outcome drugs was 722 days versus 818 days for surrogate outcome drugs, difference 96 days (95% CI -295, 425). Interpretation: On two metrics used there is no difference in the postmarket safety of surrogate and clinical outcome drugs. At the same time, when surrogate outcome drugs are approved their benefit:harm ratio is not fully established arguing that these drugs should be used with caution until their benefits are better established.
Version 1	
Reviewer 1	
Name	Husereau, Don
Position	
Institution	University of Ottawa, Epidemiology and Community Medicine
Competing interests	
Date review returned	09-Mar-2015
General comments	Major point 1. My largest concern is the departure taken with the interpretation of the findings. Specifically, I don't follow the logic on P16 and in the interpretation section of the abstract. There is no evidence that drugs approved based on surrogate outcomes are more harmful then those approved based on clinical outcomes. I understand a clear benefit:harm ratio cannot established. But why demand post market studies if there is no cause for concern in re: harm? I get that it would make us more certain about beneficial clinical outcomes, which is great, but this does not follow the logic of this study. (i.e., concerns about harm) I'm not disputing post-marketing studies would be helpful for resolving clinical uncertainty. But your study would have to additionally show that surrogate outcomes consistently end up being poor predictors of

	clinical outcomes to draw this conclusion. As per our response to the editors and reviewer 1 we have deleted the last two sentences in the Interpretation section and have modified the Abstract. 2. My other major concern is that the authors have not adhered to STROBE or appropriate format for reporting cohorts, and as per journal guidance. I understand this is not a human cohort study, but would suggest that STROBE could be most easily adapted here. We have reviewed a number of published studies that report about postmarket safety of different drug cohorts and none of them use the STROBE format: Carpenter D, Zucker E, Avorn J. Drug-review deadlines and safety problems. New England Journal of Medicine. 2008;358:1354-61; Berlin R. Examination of the relationship between oncology drug labeling revision frequency and FDA product categorization. American Journal of Public Health 2008;99:1693-8; Arnardottir A, Hasijer-Ruskamp F, Straus S, Eichler H-G, de Graeff P, Mol P. Additional safety risk to exceptionally approved drugs in Europe. British Journal of Clinical Pharmacology. 2011;72:490-9; Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HGM, Egberts ACG. Safety-related regulatory actions for biologicals approved in the United States and the European Union. JAMA. 2008;300:1887-96; Heemstra HE, Giezen TJ, Mantel-Teeuwisse AK, de Vrueh RLA, Leufkens HGM. Safety-related regulatory actions for orphan drugs in the US and EU. Drug Safety 2010;33:127-137. Therefore, we have not made this change. Minor point 1. P6 Introduction Ln 6-11 – "Clinical outcomes" require definition here. For example, some may see HBA1C as a "clinical" outcome since it is used clinically to make decisions. You may just want to use the definition from your methods. In order to reduce the size of the Introduction we have removed the definition from that section and now define surrogate endpoints in the Methods. 2. "However for a surrogate outcome to be useful" – I think one of the main thrusts of the paper from Prentice is missing here – namely the surrogate response must be independently predictive (not simply correlated) of the final outcome response We have shortened the Introduction as per the instructions from the editors and have deleted the Prentice reference. 3. The authors may want to consider using the word "harm" instead of "safety" when appropriate (see Ioannidis CONSORT Harm Extension) We have elected to continue to use the word "safety" as that is the word commonly used in similar literature – see the titles of the articles in our response to the second major comment from this reviewer. 4. P8. "With different timelines" – these are "targets" but not necessarily met This phrase has been deleted. 5. The rationale for the secondary purpose of the study (time spent) is not clear As we state in the Introduction, one of the objectives behind using surrogate endpoints is to get new drugs to market more quickly. A

	more rapid review could lead to more safety problems in the postmarket phase and therefore we felt it was necessary to examine how long each group of drugs takes in the review process. 6. "Surrogate outcomes were no different" (appears a few times) – this is slightly inaccurate. They were different, but significant differences using statistical testing and a threshold did not demonstrate detectable differences. We have changed the phrase to "surrogate outcomes were not statistically different". 7. Paragraph "At the same time…that of surrogate outcome drugs" suggests we know everything about harm when clinical outcomes are reported which may not be true. We have removed the phrase "At the same time". 8. P15. "The continued use of surrogate outcomes… diabetes" – should spell out why rather than simply provide a reference We have added the reason – that a reduction in the concentration of glycated hemoglobin does not corrected with cardiovascular mortality. 9. P15. "Surrogate outcomes are reasonable" – this is a bit subjective. You may want to rephrase that using clinical outcomes becomes a significant barrier when… We have made this change.
Author response	
Reviewer 2	
Name	Light, Donald
Position	
Institution	University of Medicine and Dentistry of New Jersesy, Psychiatry
Competing interests	
Date review returned	09-Mar-2015
General comments	This is a professional, lucid report and analysis of a study that compares the postmarket safety of drugs approved by Health Canada based on surrogate versus clinical outcomes. The methods are appropriate, and it complements related articles by Lexchin that fill out a valuable contribution to strengthen the need for full review and better postmarket surveillance to protect the public from harmful side effects. There is an important need to measure the number of people affected and the seriousness of the harms that the authors discuss at the end of the paper.
Author response	This is a professional, lucid report and analysis of a study that compares the postmarket safety of drugs approved by Health Canada based on surrogate versus clinical outcomes. The methods are appropriate, and it complements related articles by Lexchin that fill out a valuable contribution to strengthen the need for full review and better postmarket surveillance to protect the public from harmful side effects. There is an important need to measure the number of people affected and the seriousness of the harms that the authors discuss at the end of the paper. We thank the reviewer for his comments.
Reviewer 3	
Name	Rotstein, Dalia
Position	

Institution	St. Michael's Hospital, Neurology
Competing interests	
Date review returned	20-Feb-2015
General comments	This is one of the first papers to investigate the interesting issue of whether there is a difference in patient safety outcomes for drugs approved based on clinical outcomes versus surrogate outcomes. It is notable that the authors did not find any difference in the rate of serious safety warnings or time to serious safety warning. This finding is reassuring given concerns over the use of surrogate outcome measures in clinical trials. The analysis and interpretation of the data by the authors are quite clear and cogent. Major points: Was this study under-powered? The reported confidence intervals are quite wide. It would be nice to include a power calculation. Are there data available prior to 2005? (presumably not online) One of the major limitations of this study is that it does not probe the question of whether all surrogate outcome measures are created equal. However, the authors acknowledge this and do a good job in the discussion of explaining why it is difficult to classify these outcome measures based on validity. Another limitation is that the authors discuss drug approval and safety warnings only with respect to the Canadian context. However, at times our national approval process lags behind that of other jurisdictions like the United States which may mean drugs with postmarketing safety issues are not approved here in the first place. Are there any data concerning rejection rates for drugs with clinical trials using surrogate vs. clinical outcomes? Have similar studies been performed in other jurisdictions and what were their findings? It would be important to report any similar studies in the discussion, or, if there are none, to acknowledge that these findings may be of limited generalizability. Minor points: p. 8 Were there any trials which used a combined endpoint which incorporated both clinical and surrogate outcomes? If so, how were they dealt with? p. 14 – Why is the use of surrogate endpoints reasonable for ALS, but not for certain cancers, as the authors seem to imply, which may also be uniformly fatal? p. 16 – Last 2 sentences – this seems like an overly editorial point as a conclusion to the piece. Arguably, if Health Canada were to require this the use of many drugs could be limited because drug companies may not be willing to fund studies like the authors suggest for the Canadian market alone, which is quite small.
Author response	Major points: 1. Was this study under-powered? The reported confidence intervals are quite wide. It would be nice to include a power calculation. [Editor's note: A post-hoc power calculation may not be necessary, so long as confidence intervals are provided] Are there data available prior to 2005? (presumably not online) Power calculations were not done because this was a study of the entire population of drugs approved during this period. Summary

	Basis of Decision documents only started to be used in 2005 and so prior to this date there was no way of determining if a drug was approved using clinical or surrogate endpoints. 2. One of the major limitations of this study is that it does not probe the question of whether all surrogate outcome measures are created equal. However, the authors acknowledge this and do a good job in the discussion of explaining why it is difficult to classify these outcome measures based on validity. As the reviewer notes we discuss this limitation in the Interpretation section. Deciding on whether all of the surrogate endpoints used were or were not validated would have involved a major review of the literature for each endpoint and that was not possible given the resources available. 3. Another limitation is that the authors discuss drug approval and safety warnings only with respect to the Canadian context. However, at times our national approval process lags behind that of other jurisdictions like the United States which may mean drugs with postmarketing safety issues are not approved here in the first place. Are there any data concerning rejection rates for drugs with clinical trials using surrogate vs. clinical outcomes? Have similar studies been performed in other jurisdictions and what were their findings? It would be important to report any similar studies in the discussion, or, if there are none, to acknowledge that these findings may be of limited generalizability. Health Canada does not release any information about drugs that it has declined to approve and therefore rejection rates are not available. Based on our knowledge of the medical literature and on a PubMed search no similar studies have been done in other jurisdictions. The question of generalizability has been added to the limitations. Minor points: 1. p. 8 Were there any trials which used a combined endpoint which incorporated both clinical and surrogate outcomes? If so, how were they dealt with? As we point out in our response to the editors there is a statement about this question at the start of the first paragraph on page 6. 2. p. 14 – Why is the use of surrogate endpoints reasonable for ALS, but not for certain cancers, as the authors seem to imply, which may also be uniformly fatal? We have added the phrase “or some forms of cancer” after “amyotrophic lateral sclerosis”. 3. p. 16 – Last 2 sentences – this seems like an overly editorial point as a conclusion to the piece. Arguably, if Health Canada were to require this the use of many drugs could be limited because drug companies may not be willing to fund studies like the authors suggest for the Canadian market alone, which is quite small. These sentences have been deleted.