CMAJ OPEN

Research

Publication of confirmatory studies required by Health Canada for drugs approved under a Notice of Compliance with conditions: a cohort study

Joel Lexchin MSc MD

Abstract

Background: Health Canada approves drugs based on limited data (Notice of Compliance with conditions [NOC/c]) and then requires companies to conduct confirmatory studies to validate the drugs' efficacy/effectiveness. The current investigation was carried out to determine whether these confirmatory studies are eventually published and are available to health care practitioners.

Methods: A list of drugs for which the confirmatory studies had been completed from 1998 to Sept. 30, 2014 was created from 2 published articles that listed NOCs/c and investigated whether they had been fulfilled, the NOC database and the NOC/c Web site. The confirmatory studies for these drugs were determined from Qualifying Notices, agreements between Health Canada and the drug companies. Possible publications from these studies were identified through a Web search, and companies were asked to confirm these publications. The time in days between fulfillment of the NOC/c and publication of the studies was calculated.

Results: There were 58 distinct confirmatory studies for 24 products made by 14 different companies. Eleven companies responded and identified 29 unique publications that reported on 31 studies. One company did not confirm a publication that was subsequently independently identified. Three companies did not respond, and in these cases another 18 publications were independently identified for an additional 19 studies. No publications were found for 7 studies. Thirty-one publications appeared a mean of 610 days before the NOC/c was fulfilled, and 17 appeared a mean of 572 days after fulfillment of the NOC/c.

Interpretation: Eighty-eight percent of the confirmatory studies were eventually published. Health Canada and drug manufacturers should take steps to ensure that knowledge about these publications is available to health care practitioners.

In an effort to ensure that promising therapies for serious illnesses can reach Canadians in a timely manner, Health Canada developed the Notice of Compliance with conditions (NOC/c) guidelines in 1998. The goal of this policy is to "provide patients suffering from serious, life threatening or severely debilitating diseases or conditions with earlier access to promising new drugs."[1] An NOC/c could used for drugs with trials with only surrogate markers, drugs with phase II trials that require confirmation with phase III trials, or drugs with a single small to moderately sized phase III trial that requires confirmation of the efficacy or the safety of the agent in question.[2] An NOC/c can be issued for a new drug or for a new indication for a drug already on the market.

A Qualifying Notice is the document that Health Canada sends to a drug sponsor indicating that the drug qualifies for an NOC/c. (Before February 2003, the Qualifying Notice did not exist, and a Letter of Understanding detailed the confirmatory studies. Henceforth, Qualifying Notice and Letter of Understanding will collectively be referred to as Qualifying Notice.) The Qualifying Notice outlines the additional clinical evidence to be provided in confirmatory studies, i.e., studies that definitively establish efficacy. When completed, these studies are submitted to Health Canada, and, if the studies are accepted, the product receives a full NOC. Should these post-market trials not provide sufficient evidence of clinical benefit, the NOC/c could be revoked and the product removed from the market.[3]

Competing interests: In 2015–2016, Joel Lexchin received payment for being a consultant to a project looking at indication-based prescribing and a project that determined what drugs should be provided free of charge by general practitioners. He also received payment for being on a panel that discussed establishing a pharmacare program in Canada. He is on the Foundation Board of Health Action International.

This article has been peer reviewed.

Correspondence to: Joel Lexchin, jlexchin@yorku.ca

***CMAJ Open* 2017. DOI:10.9778/cmajo.20170001**

Health Canada does not notify health care practitioners or the public that an NOC/c has been fulfilled except through the NOC/c Web site and, since September 2012, by including some information in the Summary Basis of Decision, a document that summarizes Health Canada's decision-making process in approving a new drug.[4] Health Canada does not release any details about the completed confirmatory studies. Therefore, if health care practitioners, guideline developers or other interested parties want information about the studies, they have to rely on the studies' being published.

The current study examined drugs for which the NOC/c was fulfilled (i.e., confirmatory studies had been completed and accepted by Health Canada) to determine whether the confirmatory studies were published as full journal articles and the time between fulfillment of the NOC/c and publication of the articles. Secondarily, I looked at how long it took between the time the NOC/c was granted and when it was fulfilled.

Methods

Sources of data

A list of all drugs with an NOC/c whose conditions had been fulfilled and the date the conditions were fulfilled, from the time that the program started (1998) until Sept. 30, 2014, was compiled from 4 sources: articles by Lexchin[3] and Law[5] that listed NOCs/c and investigated whether they had been fulfilled, the NOC database (http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp) and the NOC/c Web site (www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php). The latter Web site is updated when an NOC/c has been fulfilled, although Health Canada does not specify what the timeline is between fulfillment and posting of the information on the Web site. In addition, the date on which the NOC/c was granted, the generic and brand names of the drugs, and the names of the companies marketing them were recorded.

Until the confirmatory studies are completed and the product receives a full NOC, the Qualifying Notices are publicly available on Health Canada's Web site. Once the conditions have been met, the Qualifying Notice is no longer publicly available, and therefore I requested these from Health Canada through the Access to Information Act. The list and description of the confirmatory studies were abstracted from the Qualifying Notice. The Qualifying Notices were independently screened by 2 people (J.L. and a family physician), and disagreements were resolved by consensus. Only confirmatory studies that provided information about drug efficacy/effectiveness were identified, as these are the ones that health care practitioners would be most concerned about. Studies looking solely at pharmacokinetics or pharmacodynamics were not examined. Additional information about safety that Health Canada required typically took the form of enhanced reporting of adverse drug reactions or was an additional requirement of efficacy/effectiveness studies. There were no required confirmatory studies that focused solely on safety.

A Web search was performed in the first week of October 2014 and was repeated in the first week of December 2015 and in the first week of February 2017 to determine whether a possible clinicaltrials.gov identifier and/or journal publication(s) could be identified for each study listed in the Qualifying Notice. Matches between studies required in the Qualifying Notice and journal publications or trials registered in clinicaltrials.gov were made on the basis of 1 or more of the following characteristics: generic name, number and particulars of trial participants (e.g., women with breast cancer), primary outcomes and description of the treatment. If no journal publication was given in clinicaltrials.gov, I searched PubMed and Embase for a journal publication. Terms used in the search depended on the level of detail in the Qualifying Notice about the required study. (See Appendix 1, available at www.cmajopen.ca/content/5/2/E295/suppl/DC1, for an example of a search strategy.) Full journal articles published up to Feb. 6, 2017 were downloaded through the University of Toronto library Web site.

I then sent a letter to the drug manufacturers outlining the nature of the research, quoting a description of the confirmatory study or studies from the Qualifying Notices, giving the possible clinicaltrials.gov identifier (if one was found) and the possible publication (also if one was found), and asking the company to confirm that the publication corresponded to the study or, if not, to provide a citation to a publication. After 1 month, a single reminder was sent to nonresponders. In cases in which companies did not confirm that a publication was matched with a study required under the Qualifying Notice or companies did not respond, publications identified using the strategy described above were used.

Statistical analysis

I used descriptive statistics to report on the proportion of studies with corresponding publications. The time between when the conditions were met and journal publication was calculated in days, as was the time between granting and fulfillment of the NOC/c. The date of publication was as printed in the issue of the journal or the date published online. If only the month and year of publication were given, the publication date was deemed to be the midpoint between issues; for example, if a journal was published monthly, the day of publication would be the 15th of the month. Data are reported as means and were analyzed with the use of Prism 7.0 for Mac (GraphPad Software).

Ethics approval

The York University Ethics Review Board waived ethics approval for this study, as only publicly available material was being requested from companies.

Results

During the study period, there were 63 NOCs/c for 46 new drugs or new indications for existing drugs. Thirty-four NOCs/c were fulfilled for 26 products, 19 with an NOC/c for a single indication, 6 with 2 indications and 1 with 3 indications (Figure 1). The drugs were made by 15 different companies (range 1–3 drugs per company). The mean length of time between receipt of an NOC/c and fulfillment was 1390 (95% confidence interval 1160–1620) days.

Health Canada eventually supplied all the Qualifying Notices sought in the Access to Information Act requests, although in 1 case it took almost 20 months. Three Qualifying Notices (2 for different indications for amprenavir and 1 for nevirapine) had all the information about the confirmatory studies redacted, leaving the studies listed in 31 Qualifying Notices for 24 drugs made by 14 companies for analysis. These Qualifying Notices listed 1–7 confirmatory studies each. Health Canada sent only a single Qualifying Notice for delavirdine, although the product had received 2 separate NOCs/c and the letter from Health Canada acknowledged both NOCs/c. Therefore, I assumed that the 5 confirmatory studies in the Qualifying Notice for this product were the same for both NOCs/c. Two Qualifying Notices for 2 products (bortezomib and sunitinib) had 1 study in common. Thus, there were 58 distinct confirmatory studies that Health Canada required (Table 1).

Descriptions of the confirmatory studies in the Qualifying Notices were highly variable, ranging from minimal (e.g., "final results of the pivotal Phase 3 study") to very detailed (e.g., "a randomised, double-blind, comparative, parallel-group, multicentre trial to evaluate the safety and efficacy of abacavir versus placebo in combination with background antiretroviral therapy in HIV-1 infected antiretroviral therapy experienced subjects with CD4+ cell counts > 100 cells/mm^3 and plasma viral load between 400 copies/mL and 50 000 copies/mL"). At times, it was not clear whether the company was being asked to provide just a protocol for a study or the protocol and then the results; in these cases, I assumed that the companies were asked for the results of the studies. Some Qualifying Notices

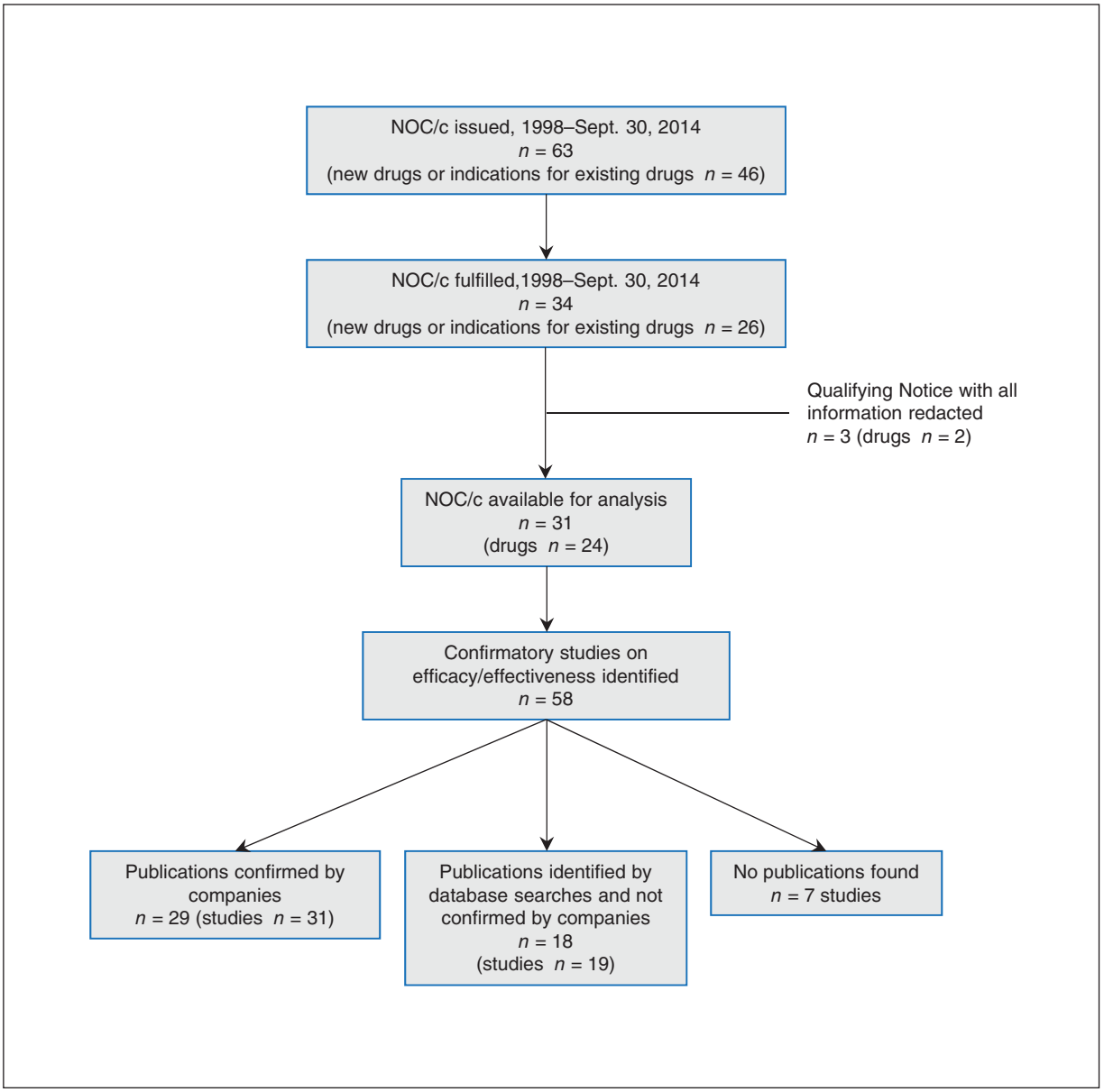

Figure 1: Numbers of Notices of Compliance with conditions (NOC/c), Qualifying Notices and resultant publications.

Table 1: Drugs with completed Notice of Compliance with conditions and number of confirmatory studies per drug

Generic drug name	Company	Date of NOC/c (d/mo/yr)	Date NOC/c fulfilled (d/mo/yr)	Time from NOC/c to fulfillment, d	No. of unique confirmatory studies listed in Qualifying Notice	No. of confirmatory studies with publications		
						Based on company response	Based on database search*	No publication identified for study
Company responded								
Abacavir	GlaxoSmithKline	04/06/1999	10/09/2001	829	3	3	NA	
Alteplase	Hoffmann-La Roche	16/02/1999	26/01/2005	2171	2	2	NA	
Anastrozole†	AstraZeneca	30/06/2004	02/12/2008	1616	3	1	1	1
Bortezomib	Janssen-Ortho	27/01/2005	11/09/2007	957	1‡	1‡	NA	
		24/04/2006	11/09/2007	505	1‡	1‡	NA	
Capecitabine	Hoffmann-La Roche	07/12/2005	23/10/2008	1051	1	1	NA	
Darunavir	Janssen-Ortho	28/07/2006	11/02/2009	929	2	2	NA	
Dasatinib	Bristol-Myers Squibb	26/03/2007	19/11/2009	969	2	2	NA	
Exemestane	Pfizer	12/05/2006	06/06/2008	756	3	3	NA	
Gefitinib	AstraZeneca	17/12/2003	18/12/2009	2193	4	3§	NA	
Lenalidomide	Celgene	17/01/2008	06/06/2013	1967	1	1	NA	
Levodopa/ carbidopa	AbbVie	01/03/2007	12/03/2014	2568	2	2	NA	
Pregabalin	Pfizer	09/11/2007	29/06/2010	963	1	1	NA	
Recombinant factor VIIa	Novo Nordisk	12/02/1999	19/03/2006	2319	1	1	NA	
Riluzole†	Sanofi-Aventis	30/08/2000	29/11/2007	2647	1		NA	1
Sorafenib	Bayer	28/06/2006	12/06/2009	1050	3	2§	NA	
Sunitinib	Pfizer	17/08/2006	23/04/2010	1345	3‡	3‡	NA	
		01/05/2008	23/04/2010	722	1‡	1‡	NA	
Zanamivir	GlaxoSmithKline	02/11/1999	26/08/2003	1393	1	1	NA	
Total no. of distinct confirmatory studies/publications					34 studies	29 publications (31 studies)	1 publication (1 study)	2 studies
Company did not respond								
Aztreonam	Merck (Gilead)	17/06/2009	17/05/2011	669	1	NA	1	
Delavirdine	ViiV Healthcare	22/07/1998	22/07/2003	1826	5¶	NA	1‡	4¶
		25/04/2000	22/07/2003	1183	5¶	NA	1‡	4¶
Imatinib	Novartis	20/09/2001	29/12/2004	1196	7	NA	6	1
		08/10/2003	17/06/2010	2444	1	NA	1	
		24/05/2007	21/02/2013	2100	1	NA	1	
Letrozole	Novartis	01/04/2005	17/12/2010	2086	2	NA	2	
		06/10/2006	17/12/2010	1533	1	NA	1	
Nilotinib	Novartis	09/09/2008	30/11/2011	1177	1	NA	1	
		22/07/2010	18/08/2011	392	1	NA	1	
Raltegravir	Merck	27/11/2007	04/03/2009	463	2	NA	1§	
Tenofovir	Merck (Gilead)	18/03/2003	20/07/2005	855	2	NA	2	
Total no. of distinct confirmatory studies/publications					24 studies	NA	18 publications (19 studies)	5 studies

Note: NOC/c = Notice of Compliance with conditions.
*No company response or publication not confirmed by company.
†Company responded but did not confirm all studies.
‡One study or publication in common.
§Two studies in 1 publication.
¶All studies or publications in common.

gave the trial number of the study, some did not, and in some cases it was redacted. Only 1 Qualifying Notice included a clinicaltrials.gov identifier for 1 study. Similarly, only 1 Qualifying Notice listed a specific deadline for filing the results of the confirmatory studies.

Of the 14 companies contacted, 11 responded (17 products) and 3 did not respond (7 products) (Table 1). The companies that responded were responsible for 34 studies and identified a total of 29 unique publications that reported on 31 of these studies. For 2 products (gefitinib and sorafenib), a single publication reported on 2 studies. Finally, for 2 products (anastrozole and riluzole), studies were described in the Qualifying Notices, but the response from the companies did not address whether publications existed for some or all of the studies. No publications could be found for 1 study required for each product, and 1 publication was identified through database searches for anastrozole (Table 1).

The companies that did not respond were responsible for 24 of the studies. A total of 18 publications for 19 studies (1 publication reported on 2 studies of raltegravir) were identified through searches of clinicaltrials.gov, PubMed and Embase. No corresponding publication was found for 5 studies (Table 1).

If all the publications identified through database searches and not confirmed by the companies involved were correct, 51 (88%) of the 58 confirmatory studies were eventually published, as 48 full journal articles. Of the 48 articles, 31 (65%) (19 confirmed by companies and 12 identified through database searches) were published before the NOC/c was fulfilled, with a mean of 610 (95% confidence interval 439–780) days. Seventeen publications (35%) (11 confirmed by companies and 6 identified through database searches) appeared after the NOC/c was fulfilled, with a mean of 572 (95% confidence interval 338–805) days (Table 2).

Table 2: Time between fulfillment of Notice of Compliance with conditions and publication of confirmatory study*

Drug	Time, d	
	Between publication and NOC/c fulfillment	Between NOC/c fulfillment and publication
Abacavir	87, 187, 238	
Alteplase	1260	104
Anastrozole	1431	1311
Aztreonam		487
Bortezomib	817	
Capecitabine		1048
Darunavir	585	124
Dasatinib	1024	210
Delavirdine	979	
Exemestane	479	1335, 1364
Gefitinib	212, 391, 1511	
Imatinib	58, 184, 380, 424, 689, 912	655, 708
Lenalidomide	280	
Letrozole	1041	160, 308
Levodopa/carbidopa	82	339
Nilotinib	19, 269	
Pregabalin		320
Raltegravir	223	
Recombinant factor VIIa		813
Sorafenib		28, 405
Sunitinib	265, 1198, 1416	
Tenofovir	371, 687	
Zanamivir	1198	
Overall mean (95% CI)	610 (439–780)	572 (338–805)

Note: CI = confidence interval, NOC/c = Notice of Compliance with conditions.
*Riluzole omitted from table because no publication found.

Interpretation

Based on the assumption that the publications identified through database searches and not confirmed by the companies were correct, 88% of the confirmatory studies on efficacy/effectiveness were eventually published. Sixty-five percent of those published appeared a mean of 1.7 years before Health Canada declared that the NOC/c had been fulfilled. The remaining 35% of the publications appeared, on average, 1.6 years after NOC/c fulfillment. Up to 12% (7/58) of confirmatory studies may not be published at all, and in these cases the detailed information in the studies about the efficacy of the product will not be available to health care practitioners. The reasons for nonpublication are not clear. Since the studies were performed to fulfill the requirements of the NOC/c, it is highly likely that they were favourable, and therefore negative results are probably not an explanation. Companies may not have felt it necessary to submit the studies for publication since the drugs were already approved, or the studies may have been rejected by journals. Interestingly, 5 of the 7 confirmatory studies for which no publication was identified came from the 3 (out of 14) companies that did not respond to the request for information.

The average time from granting of an NOC/c to its fulfillment in the current study was 1390 days, or 3.8 years. The conditional approval mechanism of the European Medicines Agency also requires confirmatory studies. From the inception of this pathway, in 2006, until April 2014, 21 medicines requiring 59 confirmatory studies were approved; the studies were expected to take a median of 575 (interquartile range 204–1287) days (1.6 yr) to complete.[6] Twenty-six of these studies were completed, but it took a median of 275 (interquartile range 121–773) days (0.8 yr) longer than expected.[6] There are a number of possible explanations why completion of confirmatory studies may be different in the different jurisdictions. The type of studies required may be different (e.g., randomized controlled trials v. observational studies), the European Medicines

Agency may be more diligent in monitoring the status of the studies, and the drugs requiring studies may be different; in fact, there were only 4 drugs in common between the 2 agencies. Hoekman and colleagues[6] did not give the time to fulfill the marketing conditions for individual drugs, so times for these 4 could not be compared.

Limitations

Three companies responsible for 24 of the 58 confirmatory studies failed to respond, and, therefore, there is uncertainty about whether the 18 publications for 19 of these studies were correctly identified, especially since in many cases confirmatory studies were often vaguely described, which makes it difficult to construct precise search strategies. In other cases, publications may have been missed, as the grey literature was not searched on the grounds that these publications would not have been readily available to health care practitioners.

Conclusion

Most confirmatory studies were eventually published, but publication does not necessarily translate into access. Health care practitioners need to be provided with information to allow them to appropriately prescribe medications. To this end, when a drug is approved under an NOC/c, Health Canada and the manufacturer should jointly take responsibility for ensuring that clinicians are aware of the preliminary nature of the evidence for the product and the details of the confirmatory studies that are required. This could be accomplished through a detailed posting on the Health Canada Web site as well as sending "Dear Doctor" letters and requiring specific information about the nature of the uncertainty of the evidence in any promotional material. When the confirmatory studies are completed and accepted by Health Canada, Health Canada and the relevant company should use similar communication strategies to convey this information, along with the availability of the publication(s), to health care practitioners. These communication methods would need to be evaluated to be sure that they are achieving their objective.

References

1. Notice of compliance with conditions (NOC/c) [guidance document]. Ottawa: Health Canada; 2002.
2. Notice of compliance with conditions (NOC/c) [guidance document]. Ottawa: Health Products and Food Branch, Health Canada; 2011.
3. Lexchin J. Notice of compliance with conditions: a policy in limbo. *Healthc Policy* 2007;2:114-22.
4. Frequently asked questions: Summary Basis of Decision (SBD) Project — phase II. Ottawa: Health Canada; 2012. Available: www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/sbd_qa_smd_fq-eng.php (accessed 2014 Dec. 13).
5. Law MR. The characteristics and fulfillment of conditional prescription drug approvals in Canada. *Health Policy* 2014;116:154-61.
6. Hoekman J, Klamer TT, Mantel-Teeuwisse AK, et al. Characteristics and follow-up of postmarketing studies of conditionally authorized medicines in the EU. *Br J Clin Pharmacol* 2016;82:213-26.

Affiliation: School of Health Policy and Management, York University, Toronto, Ont.

Contributors: Joel Lexchin gathered and analyzed all the data for this study and wrote the manuscript. He approved the final version to be published and agreed to act as guarantor of the work.

Acknowledgement: The author thanks Catherine Oliver for the duplicate data extraction.

Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/5/2/E295/suppl/DC1