Reply to: comparative effectiveness medicines research cannot assess efficacy

We appreciate the insightful comments from Drs. Dal-Ré and Carcas in their letter to the editor [1] regarding our paper ''Publication of comparative effectiveness research (CER) has not increased in high-impact medical journals, 2004−2013'' [2].

The authors were correct that the patient-reported outcomes column in Table 1 of our original brief report missed two head-to-head studies. We have made this correction in an updated version of Table 1 in this letter. As requested by Drs. Dal-Ré and Carcas, we have also included a bibliography of the 468 articles used in the 20% random sample of published studies on pharmacologic interventions in the five highest impact medical journals from 2004 through 2013.

In their letter, Drs. Dal-Ré and Carcas state concerns about our definition of CER, notably that we included efficacy studies in this definition. Definitions of CER vary across governmental, nonprofit, and academic entities, making it difficult to pinpoint which study types fall under this label. The US Institute of Medicine's (IOM) core CER definition is one of the most cited, describing CER as ''the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care'' [3,4]. This core definition does not exclude head-to-head efficacy studies or studies assessing comparative harms of pharmacologic interventions, despite the fact that these are not considered effectiveness studies. Therefore, we included comparative efficacy and safety studies in our CER definition. Additionally, we included efficacy and safety studies to allow comparison with a similar systematic review describing publications of head-to-head studies with pharmacologic interventions in the top five medical journals from June 2008 through September 2009 [5]. To align with the CER definition in this review, we required at least one intervention to have established effectiveness.

Although we had a specific rationale for including efficacy studies in our broad definition of CER, we acknowledge that ''effectiveness'' is part of the term CER and generally refers to results from studies conducted in real-world settings that indicate treatment benefits. Later in their report, the IOM indicates that CER includes the direct comparison of effective interventions in patients who are ''typical of those found in clinical care'' [3] (i.e., real-world patient populations). To align with this definition, our Table 1 included a row indicating that there were 20 studies with head-to-head designs that assessed effectiveness of interventions in real-world settings (observational studies and pragmatic trials). Based on this value, we infer that approximately 4.3% of studies on pharmacologic interventions published in high-impact medical journals between 2004 and 2013 were real-world, comparative studies. Fig. 1 shows trends of these studies over time.

Studies comparing benefits and harms of pharmacologic interventions, both in ideal and real-world settings, provide critical evidence for health care decisions in a society with competing priorities. By including comparative efficacy and safety studies in our CER definition, we showed that there has been limited change in publication of any comparative research, not just for comparative real-world studies.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2017.09.009.

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Table 1
Study characteristics of 20% sample of articles with pharmacologic intervention studies published in five high-impact medical journals from 2004 through 2013

Characteristic	CER, *n* (%)		PROs, *n* (%)	
	Yes (*n* = 142)	No (*n* = 326)	Yes (*n* = 154)	No (*n* = 314)
Journal				
NEJM	51 (35.9)	126 (38.7)	71 (46.1)	106 (33.8)
Lancet	47 (33.1)	86 (26.4)	33 (21.4)	100 (31.8)
JAMA	26 (18.3)	54 (16.6)	30 (19.5)	50 (15.9)
BMJ	11 (7.7)	36 (11.0)	7 (4.5)	40 (12.7)
Annals	7 (4.9)	24 (7.4)	13 (8.4)	18 (5.7)
Size				
<250	26 (18.3)	89 (27.3)	59 (38.3)	56 (17.8)
251–2,500	74 (52.1)	140 (42.9)	76 (49.4)	138 (44.0)
>2,500	42 (29.6)	97 (29.8)	19 (12.3)	120 (38.2)
Randomization				
Nonrandomized	21 (14.8)	65 (19.9)	4 (2.6)	82 (26.1)
Randomized	121 (85.2)	261 (80.1)	150 (97.4)	232 (73.9)
Study purpose				
Effectiveness	20 (14.1)	43 (13.2)	9 (5.8)	54 (17.2)
Efficacy	49 (34.5)	173 (53.1)	90 (58.4)	132 (42.0)
Efficacy/safety	64 (45.1)	76 (23.3)	52 (33.8)	88 (28.0)
Safety	9 (6.3)	34 (10.4)	3 (2.0)	40 (12.7)
Comparison type[a]				
Placebo	—	—	93 (60.4)	119 (37.9)
No treatment	—	—	10 (6.5)	52 (16.5)
Head to head[b]	—	—	41 (26.6)	101 (32.2)
Additive[c]	—	—	22 (14.3)	26 (8.3)
Treatment varying	—	—	18 (11.7)	37 (11.7)
Other	—	—	2 (1.3)	11 (3.5)
Treatment indication[d]				
Cardiovascular/renal	33 (23.2)	68 (20.9)	20 (13.0)	81 (25.8)
Endocrine	10 (7.0)	19 (5.8)	11 (7.1)	18 (5.7)
Gastrointestinal	5 (3.5)	8 (2.5)	1 (0.7)	12 (3.8)
Hematology/oncology	21 (14.8)	50 (15.3)	25 (16.2)	46 (14.7)
Infectious disease	35 (24.7)	91 (27.9)	35 (22.7)	91 (29.0)
Neurologic	4 (2.8)	14 (4.3)	10 (6.5)	8 (2.6)
Psychiatric	6 (4.2)	10 (3.1)	11 (7.1)	5 (1.6)
Reproductive	5 (3.5)	6 (1.8)	6 (3.9)	5 (1.6)
Respiratory	5 (3.5)	18 (5.5)	9 (5.8)	14 (4.5)
Rheumatologic/ orthopedic	12 (8.5)	13 (4.0)	9 (5.8)	16 (5.1)
Other	6 (4.2)	29 (8.9)	17 (11.0)	18 (5.7)
Patient-reported outcome (PRO)				
No PRO	101 (71.1)	213 (65.3)	—	—
≥1 PRO	41 (28.9)	113 (34.7)	—	—

Abbreviations: CER, comparative effectiveness research; PRO, patient-reported outcome.
[a] Each study could have more than one comparison type. Percentages may add to >100%.
[b] Comparison of a pharmacologic intervention with any other non-placebo intervention.
[c] Comparisons between a pharmacologic intervention alone and with the addition of ≥1 interventions.
[d] Disease that is being treated by the main pharmacological intervention.

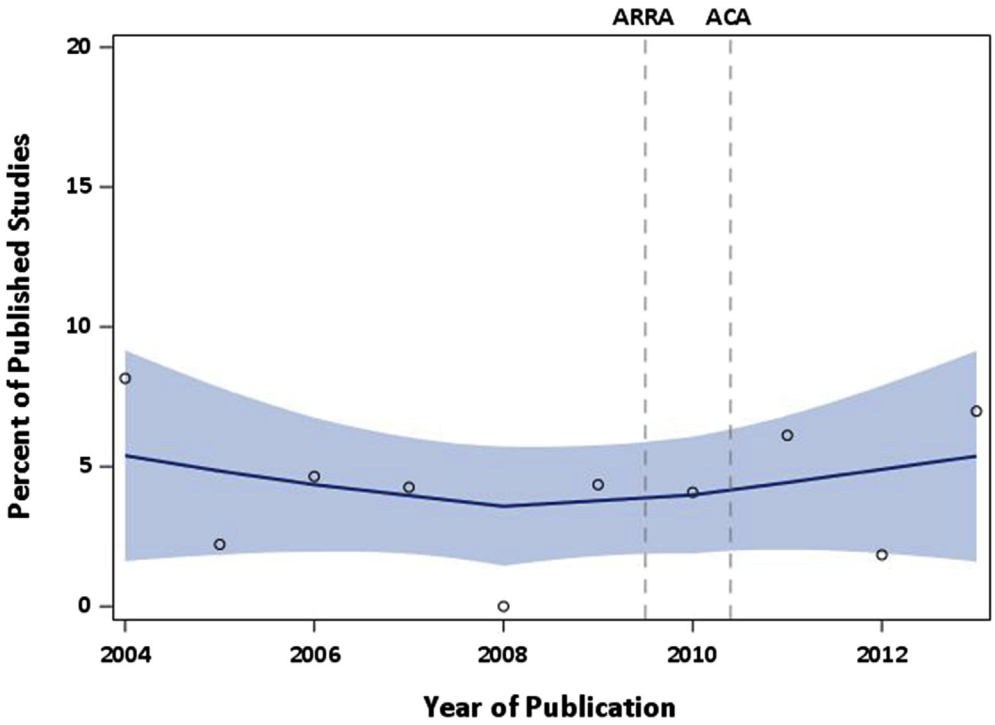

Fig. 1. Locally weighted scatterplot smoothing (LOESS) curve showing the proportion of all studies on pharmacologic interventions published in the five highest impact medical journals from 2003 to 2014 that used real-world comparisons. The circles represent the annual proportions of comparative, real-world effectiveness studies on pharmacologic interventions in the sample from high-impact medical journals. The dark blue line represents the variation in publication of comparative, real-world effectiveness studies over time estimated from the annual proportions using locally-weighted smoothing. ARRA, American Recovery and Reinvestment Act; ACA, Affordable Care Act. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)