

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	History and Publication Trends in the Diffusion and Early Uptake of Indirect Comparison Meta-Analytic Methods to Study Drugs: Animated Co-Authorship Networks over Time
AUTHORS	Ban, Joann; Tadrous, Mina; Lu, Amy; Cicinelli, Erin; Cadarette, Suzanne

VERSION 1 – REVIEW

REVIEWER	Richard Jackson Liverpool Cancer Trials Unit, University of Liverpool
REVIEW RETURNED	02-Oct-2017

GENERAL COMMENTS	I think this is an interesting piece of research addressing the growth of an important component of statistical methodology.
-------------------------	--

REVIEWER	Chris Wichman, PhD University of Nebraska Medical Center, Omaha, Nebraska, United States
REVIEW RETURNED	24-Oct-2017

GENERAL COMMENTS	<p>Page 8 Line 21: Authors reference excluding articles that "did not clearly describe techniques used to perform indirect comparisons". Was there any effort made to contact these authors for clarification on methods?</p> <p>Page 10 Line 23: Searched Cochrane Database of Systematic Reviews - I may be mistaken, but Cochrane requires the use of their RevMan5 to be published, so I am not surprised <1% showed up as unique. Why were Google Scholar, JSTOR, PubMed not searched as well? Why only English language?</p> <p>Page 10 Line 48: Interquartile range is reported as a single number (5); what is the interval (4, 9)? (5, 10)? (3,8)?</p> <p>Page 10 Lines 50-52: Percentages add to more than 100 with no statement as to the proportion using more than 1 keyword to describe the technique.</p> <p>Page 11 Line 32: Authors use the word multiple when they really mean two.</p> <p>Page 12 Lines 25-28: Awkwardly worded sentence; not sure what the point is if you are not going to account for the remaining 5%.</p> <p>Page 17 Lines 47 - 54: Three of the five innovation attributes from Rogers' Diffusion model are never discussed, yet this diffusion model plays a central role in the abstract and purpose of the paper. The three missing elements are: simplicity, trialability, and observability.</p> <p>General comments: The authors put forth that this is an important methodology that is starting to take off in its use. The authors have</p>
-------------------------	--

	numerous references that point to the potential problems / reservations of using this methodology, yet only reference them once and do not discuss the limitations / concerns others have raised about the method. For example references 3, 9, 13, 14.
REVIEWER	David Bosanquet Royal Gwent Hospital, Newport, United Kingdom
REVIEW RETURNED	22-Dec-2017
GENERAL COMMENTS	<p>This paper analyses the diffusion of network meta-analysis for drug trials using a co-authorship network analysis. It is an interesting method to explore how a type of analysis is taken up by the medical research community. Overall it is very well written and thorough. My issue is mainly around clarity of the communication of what the study is. I needed to re-read a number of sections, and review a number of the references, to get a clear insight into what the study was about. This is picked up on the specific comments below.</p> <p>Secondly, it is difficult to comment on the overall value and use of such research. I'd expect all novel analytical methods to start slowly and then gradually increase, with some authors being directly 'linked' to the original developers of the technique, and others not. It would be difficult to conclude that those not directly linked to other authors are in some way producing 'inferior' papers. The graphical modelling produced by these data is visually appealing – but what does it tell the wider research community?</p> <p>I also have issues around the correlation with government guidelines-see below.</p> <p>Specific comments:</p> <p>Title: In this specific context, 'Diffusion' is not a widely understood term and I certainly have not heard of this process previously. The work is also not a classical style 'systematic review' (although it does contain this component). It has taken me some time to get my head around this title. Can it be made clearer? My brief attempt would be: "Publication trends and geographical diffusion of Network Meta-analysis in Drug Trials; systematic review and co-authorship network analysis" although this still doesn't address all above issues.</p> <p>Introduction: The background of indirect-comparison meta-analysis is described nicely. What is lacking is the definition of 'Diffusion', and why examining this is of use. Also – how have you placed an 'emphasis on how the social system may have influenced the diffusion of these methods over time'? This aspect appears nowhere in the methods nor results. This needs clarifying in abstract also. I don't buy the comments made in the discussion about the increase in these analyses being driven by government (see below).</p> <p>Methods: part of making the flow of the review easier to follow would be to clearly divide (with subheadings – journal style permitting) the paper into a 'systematic review' section (of minimal interest to the author), and the 'co-authorship network analysis' (of more interest to the author who has not seen such analysis before).</p> <p>Results: subheadings useful as above.</p> <p>What do Figures 3a and b add? This is not a paper on the value of each database in finding references? I would suggest remove, or if thought of value, add to appendix.</p> <p>Page 11 makes mention of a 'highly disconnected co-authorship network'. Based on what criteria? Has there been similar style studies with a much less disconnected network? What figure would you expect?</p> <p>Page 11 also mentions 'double the number of industry-sponsored papers published' with an n=3. Is this correct? Doesn't appear that</p>

	<p>rapid, nor a true doubling?</p> <p>Discussion: as mentioned above, it is not right to mention a (particularly vague) correlation between more network meta-analyses and it being 'likely the result of an increase in demand by government for more comparative effectiveness research'. This unreferenced claim is such a vague claim of a correlation, and causation is clearly one step too far unless more data can be found. Further claims to back up this correlation (end page 14) refer to published guidelines from 2008-2014. How were these identified? Was there a systematic search for this? This is a weak/non-existent correlation and shouldn't be used to suggest that it were these guidelines which grew the publications of network meta-analyses.</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer Comments

Reviewer 1

1. I think this is an interesting piece of research addressing the growth of an important component of statistical methodology.
 - We thank the reviewer for taking the time to read our paper and providing us with a positive comment.

Reviewer 2

1. **Page 8 Line 21: Authors reference excluding articles that “did not clearly describe techniques used to perform indirect comparisons”. Was there any effort made to contact these authors for clarification on methods?**
 - Authors were not contacted to clarify methods, which we now acknowledge as a limitation on pages 16-17:
 - *“Articles that did not clearly describe the techniques used to perform these methods were also excluded, since we could not assume that these methods were used. While we acknowledge that this may have resulted in the exclusion of some applications, we included articles that clearly described these methods in the title, abstract, introduction, or methods sections to allow for as much inclusion as possible. Consequently, we believe that our systematic search is both comprehensive and robust, as this is the largest and only search completed to date that examines the diffusion of indirect comparison meta-analytic methods in the study of drugs.”*
2. **Page 10 Line 23: Searched Cochrane Database of Systematic Reviews – I may be mistaken, but Cochrane requires the use of their RevMan5 to be published, so I am not surprised <1% showed up as unique. Why were Google Scholar, JSTOR, PubMed not searched as well? Why only English language?**
 - Thank you for this insightful comment. We acknowledge that Cochrane requires use of RevMan5 to publish and that this may in part explain why <1% of the eligible articles identified in our study were unique.
 - Although Google Scholar, JSTOR, and PubMed were not searched, and may have led to missed articles; MEDLINE® and EMBASE® are the largest databases for biomedical journal articles; covering approximately 4,000 journals. Consequently, these databases were most

likely to yield the highest proportion of relevant articles to our study. We also used a robust search strategy to try to capture as many articles as possible.

- We limited our study to English language papers for feasibility, since English is our primary language.
- We now acknowledge these limitations in our search strategy in the discussion section of our paper on page 16.
 - *“First, our analysis limited the co-authorship of empirical applications to English language papers identified in select bibliographic databases: the Cochrane Database of Systematic Reviews®, EMBASE®, MEDLINE®, Scopus®, and Web of Science®. The limitation of our search to these databases may have resulted in missed articles that were published in other languages, or identifiable in other bibliographic databases, such as Google Scholar®, JSTOR®, Pubmed®, and RevMan5®.”*

3. Page 10 Line 48: Interquartile range is responded as a single number (5); what is the interval (4, 9)? (5, 10)? (3, 8)?

- Thank you for this observation. We have corrected this number with the appropriate interquartile range on page 10.
 - *“...interquartile range of 5-10...”*

4. Page 10 Lines 50-52: Percentages add to more than 100 with no statement as to the proportion using more than 1 keyword to describe the technique.

- We now clarify these proportions in the text on pages 10-11.
 - *“The sum of these percentages is greater than 100% due to an overlap in the terminology used. More specifically, 18% (n=65) of all eligible empirical applications used two or more terms to describe the methods used.”*

5. Page 11 Line 32: Authors use the word multiple when they really mean two.

- We thank the reviewer for this observation. We have changed the word ‘multiple’ to ‘two’ to reflect the two countries referenced (United States and Belgium). Please refer to the highlighted text on Page 11.

6. Page 12 Lines 25-28: Awkwardly worded sentence; not sure what the point is if you are not going to account for the remaining 5%.

- We have reworded this sentence for clarity, and have accounted for the remaining 5% to ensure complete reporting of our results on page 12.
 - *“Overall, institutional credit was given to 358 unique institutions around the world: 77% of contributions came from academic institutions, 18% from industry, 1% from government, and 4% from other institutions, Table 3.”*

7. Page 17 Lines 47-54: Three of the five innovation attributes from Rogers’ Diffusion model are never discussed, yet this diffusion model plays a central role in the abstract and purpose of the paper. The three missing elements are: simplicity, trialability, and observability.

- We agree that simplicity, trialability, and observability are also key innovation attributes of Rogers’ Diffusion model. To facilitate better clarity, we have added a few lines elaborating on the use of these attributes in our paper, page 14.
 - *“Active workshops demonstrating the use of this methodological innovation likely provided a vehicle for peer observation to occur, so that the results and benefits of using this innovation were visible to potential adopters (observability). The provision*

of sample datasets and statistical code, as well as the integration of these methods into established software and software packages, may have also eased the use of these methods (simplicity), and allowed potential adopters the chance to try using these methods with direct guidance from the innovators and early adopters themselves (trialability)."

8. **General comments:** The authors put forth that this is an important methodology that is starting to take off in its use. The authors have numerous references that point to the potential problems / reservations of using this methodology, yet only reference them once and do not discuss the limitations / concerns others have raised about the method. For example, references 3, 9, 13, 14.
 - We have added clarity regarding some potential limitations of indirect comparison meta-analysis, many of which parallel those of traditional pairwise meta-analysis. Importantly, our study did not explore methodological quality. We add clarity to our discussion section on pages 17-18.
 - *"Finally, our work did not examine the quality of eligible empirical articles, or explore the correlation and impact of early diffusion on the quality of indirect comparison meta-analytic methods... Similar to traditional pairwise meta-analysis; limitations related to the quality of the search conducted, quality and heterogeneity of studies included, and publication bias; can all influence the quality of the study. Uniquely, indirect comparison meta-analytic methods have additional limitations that should be accounted for, such as issues with transitivity and inconsistency of networks, as well as the presentation of results [44]. A recent systematic review of network meta-analyses in clinical research demonstrated improvement in methodological and reporting quality over time [45]. However, we acknowledge that this is an important area of future research that should be explored."*

Reviewer 3:

1. This paper analyses the diffusion of network meta-analysis for drug trials using a co-authorship network analysis. It is an interesting method to explore how a type of analysis is taken up by the medical research community. Overall it is very well written and thorough. My issue is mainly around clarity of the communication of what the study is. I needed to re-read a number of sections, and review a number of the references, to get a clear insight into what the study was about. This is picked up on the specific comments below.

Secondly, it is difficult to comment on the overall value and use of such research. I'd expect all novel analytical methods to start slowly and then gradually increase, with some authors being directly 'linked' to the original developers of the technique, and others not. It would be difficult to conclude that those not directly linked to other authors are in some way producing 'inferior' papers. The graphical modelling produced by these data is visually appealing – but what does it tell the wider research community?

I also have issues around the correlation with government guidelines-see below.

- We thank the author for the general feedback and have worked to make changes to improve the readability of our paper. We have addressed these suggestions with the specific points below.
2. **Title:** In this specific context, 'Diffusion' is not a widely understood term and I certainly have not heard of this process previously. The work is also not a classical style 'systematic review' (although it does contain this component). It has taken me some time to get my head around this title. Can it be made clearer? My brief attempt would be: "Publication trends and geographical diffusion of Network Meta-analysis in Drug Trials;

systematic review and co-authorship network analysis” although this still doesn’t address all above issues.

- Thank you for your helpful comments to clarify our methods and messaging. We have modified our title (below), and added clarity regarding “diffusion” in our introduction section (page 6). Given that we applied Roger’s diffusion of innovation model, we keep the word “diffusion” throughout, yet also clarify that we are considering “early uptake” of the methods.
 - New Title: *“History and Publication Trends in the Diffusion and Early Uptake of Indirect Comparison Meta-Analytic Methods to Study Drugs: Animated Co-Authorship Networks over Time”*
 - Addition to the introduction, page 6: *“Rogers’ Diffusion of Innovations Model defines diffusion as the process by which an innovation is communicated across individuals within a social system, particularly during the initial stages of its use [16, 17]. Our study sought to characterize the early diffusion of indirect comparison meta-analytic methods used to study drugs [16]. We interpreted diffusion and uptake relative to the social system, by creating co-authorship networks to examine the speed of uptake (number of publications) and spread of these methods (collaboration between authors, authors’ countries, and across institutions) over time.”*
- 3. Introduction: The background of indirect-comparison meta-analysis is described nicely. What is lacking is the definition of ‘Diffusion’, and why examining this is of use. Also – how have you placed an ‘emphasis on how the social system may have influenced the diffusion of these methods over time’? This aspect appears nowhere in the methods nor results. This needs clarifying in abstract also. I don’t buy the comments made in the discussion about the increase in these analyses being driven by government (see below).**
- We have included a definition of ‘diffusion’ in the Introduction and clarified how the social system was emphasized in our analysis of the diffusion of indirect comparison meta-analytic methods (i.e., collaboration trends between authors and across institutions) in our response to Comment 2 above.
 - Please refer to our response to Comment 9 below, which addresses the issues surrounding these methods being driven by government.
- 4. Methods: part of making the flow of the review easier to follow would be to clearly divide (with subheadings – journal style permitting) the paper into a ‘systematic review’ section (of minimal interest to the author), and the ‘co-authorship network analysis’ (of more interest to the author who has not seen such analysis before).**
- and*
- 5. Results: subheadings useful as above.**
- We have added the subheadings, ‘Systematic Search’ and ‘Co-Authorship Network of Empirical Applications’, to the methods and results sections to better guide the reader, pages 7, 9-11.
- 6. What do Figures 3a and b add? This is not a paper on the value of each database in finding references? I would suggest remove, or if thought of value, add to appendix.**
- The inclusion of proportional Venn diagrams was meant to illustrate search strategy yield, with circle size proportional to the total number of eligible papers identified by each database. We have moved these figures to Appendix A Figures A and B, in the supplemental appendix.
- 7. Page 11 makes mention of a ‘highly disconnected co-authorship network’. Based on what criteria? Has there been similar style studies with a much less disconnected network? What figure would you expect?**
- Thank you for this comment. Connectedness in a co-authorship network is based on the total number of components. The more components found in a co-authorship network, the more disconnected authors are from each other as a result of isolated publishing. Most authors who do not belong to the largest component are members of smaller, disconnected components

containing only a small number of other authors. In our paper, 63% (n= 946) of authors did not belong to the largest component. In addition, 25% (n=90) of all eligible papers made up single-paper components as a result of isolated publishing. This is higher relative to similar style studies that have examined the diffusion of other methodological innovations, particularly the disease risk score and high-dimensional propensity score methods (see changes below for more details). We do, however, acknowledge that the term “highly disconnected” can be misinterpreted in the absence of particular context, given its descriptive measure. Consequently, we have clarified these point in the discussion section, pages 15-16.

- *“However, uptake of these methods has been diffuse and highly disconnected when compared to the diffusion and early uptake of other methodological innovations [16], since many authors are publishing in isolation of each other (i.e., smaller, single paper components). In a prior study that examined the diffusion and early uptake of two confounder summary scores (the disease risk score and high-dimensional propensity score), only 19% and 11% of all eligible applications made up single paper components in their respective co-authorship networks in comparison with 25% of all indirect comparison meta-analytic applications [16].”*

8. Page 11 also mentions ‘double the number of industry-sponsored papers published’ with an n=3. Is this correct? Doesn’t appear that rapid, nor a true doubling?

- Thank you for raising this point. Yes, n=3 is correct in terms of the number of industry-sponsored papers published by 2008. However, we acknowledge that this ‘doubling’ is not really a rapid increase in the number of industry-sponsored publications and have consequently removed this line from our paper.

9. Discussion: as mentioned above, it is not right to mention a (particularly vague) correlation between more network meta-analyses and it being ‘likely the result of an increase in demand by government for more comparative effectiveness research’. This unreferenced claim is such a vague claim of a correlation, and causation is clearly one step too far unless more data can be found. Further claims to back up this correlation (end page 14) refer to published guidelines from 2008-2014. How were these identified? Was there a systematic search for this? This is a weak/non-existent correlation and shouldn’t be used to suggest that it was these guidelines which grew the publications of network meta-analyses.

- Thank you for the insightful comment. Published guidelines referenced in our paper were identified from the Indirect Treatment Comparisons Good Research Practices report (Part 1); published by the International Society for Pharmacoeconomics and Outcomes Research Task Force; which cites increasing use and acceptance by regulatory agencies due to its value (refer to page 15). Nonetheless, we acknowledge that multiple factors should be considered when examining possible influencers of adoption rates of novel methods, and that the more rapid uptake of indirect comparison meta-analytic methods compared to other novel methods (i.e., disease risk score, high-dimensional propensity score) was likely influenced by multiple factors. We have therefore taken care to revise the discussion section to improve clarity and soften the language in our paper with respect to diffusion as it relates to government influences over time. Please see below for changes, and note the softening of language throughout the paper, which is highlighted in yellow.
 - Page 2: *“Application spread to other European countries in 2005, and may have been supported by regulatory requirements for drug approval.”*
 - Page 3: *“The increase in uptake of these methods may have been facilitated by...”*
 - Page 13: *“Early use of indirect comparison meta-analytic method applications predominated from the United Kingdom, and may have been...”*
 - Pages 14-15: *“For example, the Canadian Agency for Drugs and Technologies in Health (CADTH) has published guidance documents to facilitate best practices in the use of indirect comparison meta-analytic methods to assess clinical and economic value of drugs and other health technologies in Canada, including how to best incorporate these methods to inform clinical parameters in these types of evaluations [19, 42]... We believe that this observation may have been a response to requests by these agencies, as we noted collaboration with core innovators from academia, and an increase in the number of industry-sponsored applications published from 2009.”*

- Page 18: *“Although speculative, and while there are likely multiple reasons for the relatively rapid adoption of these methods, we believe that adoption by government agencies may have contributed to more rapid uptake, and is worth noting; though further research should be explored. We believe that the social system can play a major role...”*

VERSION 2 – REVIEW

REVIEWER	Chris Wichman Department of Biostatistics, College of Public Health, University of Nebraska Medical Center
REVIEW RETURNED	16-Mar-2018
GENERAL COMMENTS	All of my original concerns have been addressed in this revision. In Appendix F 1) pages 94 to 106; the word Industry is spelled incorrectly in the legend (the 't' is missing). 2) Also, the same plots only have three colors in the legend, yet more than three colors are utilized in each network plot...what do the other colors represent. 3) I really like how the network plots show the diffusion of network meta-analysis.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer Comments

Reviewer 2

All of my original concerns have been addressed in this revision. In Appendix F:

2. **Pages 94 to 106; the word Industry is spelled incorrectly in the legend (the ‘t’ is missing).**
 - We thank the reviewer for identifying this typo. We have corrected this typo on all of the plots identified in Appendix F.
3. **Also, the same plots only have three colors in the legend, yet more than three colors are utilized in each network plot ... what do the other colors represent?**
 - We have clarified the other colours utilized in each network plot. These colours are secondary and tertiary colours, which represent combinations of the primary colours used in the legend of each plot. Please refer to the legend for Appendix E and Appendix F for these edits, which are highlighted in yellow.
 - Appendix E: *“Authors publishing on papers with more than one country affiliation were coloured based on combinations of the primary colours and white, thereby yielding secondary and tertiary colours. For example, authors on papers with affiliations from Canada and the United States were coloured purple (a combination of red and blue), authors on papers with affiliations from the United States and the United Kingdom were coloured green (a combination of blue and yellow), and authors on papers with affiliations from Canada and the United Kingdom were coloured orange (a combination of red and yellow). Authors on papers affiliated with Canada, the United States, and the United Kingdom were coloured grey (a combination of red, blue, and yellow). The addition of other European countries (light yellow) and all other regions (white) into the mix, lightened these colour combinations. For example, authors on papers affiliated with Canada, the United States, and all other regions were coloured light purple (a combination of red, blue, and white).”*

- *Appendix F: "Authors publishing on papers with more than one affiliation type were coloured based on combinations of the primary colours and white, thereby yielding secondary and tertiary colours. For example, authors on papers with affiliated with academia and government were coloured orange (a combination of red and yellow), authors on papers affiliated with government and industry were coloured green (a combination of yellow and blue), authors on papers affiliated with academia and industry were coloured purple (a combination of red and blue), and authors on papers affiliated with academic, government, and industry were coloured grey (a combination of red, yellow, and blue). The addition of other affiliation types into the mix, which were represented by the colour white, lightened these colour combinations. For example, authors on papers affiliated with academia, government, and other were coloured light orange (a combination of red, yellow, and white)."*

4. I really like how the network plots show the diffusion of network meta-analysis.

- Thank you for providing us with positive feedback on our network plots.