BMJ open

Methods used to conduct and report Bayesian mixed treatment comparisons published in the medical literature: a systematic review

Diana M Sobieraj,[1] Joseph C Cappelleri,[2] William L Baker,[1] Olivia J Phung,[1] C Michael White,[1] Craig I Coleman[1]

To cite: Sobieraj DM, Cappelleri JC, Baker WL, *et al*. Methods used to conduct and report Bayesian mixed treatment comparisons published in the medical literature: a systematic review. *BMJ Open* 2013;**3**:e003111. doi:10.1136/bmjopen-2013-003111

▸ Prepublication history and additional material for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2013-003111).

Received 24 April 2013
Revised 12 June 2013
Accepted 17 June 2013

[1]University of Connecticut/ Hartford Hospital Evidence-based Practice Center, Hartford, Connecticut, USA
[2]Department of Biostatistics, Pfizer, Groton, Connecticut, USA

Correspondence to
Dr Craig I Coleman;
ccolema@harthosp.org

ABSTRACT

Objectives: To identify published closed-loop Bayesian mixed treatment comparisons (MTCs) and to summarise characteristics regarding their conduct and reporting.

Design: Systematic review.

Methods: We searched multiple bibliographic databases (January 2006–31 July 2011) for full-text, English language publications of Bayesian MTCs comparing the effectiveness or safety of ≥3 interventions based on randomised controlled trials and having at least one closed loop. Methodological and reporting characteristics of MTCs were extracted in duplicate and summarised descriptively.

Results: We identified 34 Bayesian MTCs spanning 13 clinical areas. Publication of MTCs increased over the 5-year period; with 76.5% published during or after 2009. MTCs included a mean (±SD) of 35.9±30.1 trials (n=33 459±71 233 participants) and 8.5±4.3 interventions (85.7% pharmacological). Non-informative and informative prior distributions were reported to be used in 44.1% and 8.8% of MTCs, respectively, with the remainder failing to specify the prior used. A random-effects model was used to analyse the networks of trials in 58.5% of MTCs, all using WinBUGS; however, code was infrequently provided (20.6%). More than two-thirds of MTCs (76.5%) also conducted traditional meta-analysis. Methods used to evaluate convergence, heterogeneity and inconsistency were infrequently reported, but from those providing detail, methods appeared varied. MTCs most often used a binary effect measure (85.3%) and ranking of interventions based on probability was common (61.8%), although rarely displayed in a figure (8.8% of MTCs). MTCs were published in 24 different journals with a mean impact factor of 9.20±8.71. While 70.8% of journals imposed limits on word counts and 45.8% limits on the number of tables/figures, online supplements/appendices were allowed in 79.2% of journals. Publication of closed-loop Bayesian MTCs is increasing in frequency, but details regarding their methodology are often poorly described. Efforts in clarifying the appropriate methods and reporting of Bayesian MTCs should be of priority.

ARTICLE SUMMARY

Article focus

- To identify published closed-loop Bayesian mixed treatment comparisons (MTCs) and to summarise characteristics regarding their conduct and reporting.

Key messages

- We identified 34 closed-loop Bayesian MTCs spanning 13 clinical areas, published in 24 different journals.
- Closed-loop Bayesian MTCs are increasing in frequency, but details regarding their methodology are often poorly described. Efforts in clarifying the appropriate methods and reporting of Bayesian MTCs should be of priority.

Strengths and limitations of this study

- Our systematic review adds to this existing literature by updating results and adding new information as prior reviews only included literature through 2007/2008. Unlike prior publications, our systematic review focused only on Bayesian MTCs of networks with at least one closed loop.
- Unlike prior reviews, we evaluated reporting of additional model characteristics in depth including testing for model fit, evaluation of convergence, adjustment for covariates or multiarm trials, the specific priors used and availability of the code and aggregated study-level data.
- An important limitation of our review is that we cannot say with certainty that a lack of reporting means a given method or analysis was not undertaken (ie, the testing for convergence or inconsistency need not be described in a paper for it to have been performed by the investigators) or that the reporting of a piece of data or statistical code was not considered.

INTRODUCTION

Clinicians and decision-makers often need to select from multiple available interventions when determining the optimal treatment for a disease. Ideally, high-quality randomised

controlled trials (RCTs) that estimate the effectiveness of all possible interventions directly against one another would be available to guide decision-making.[1–4] However, interventions are commonly compared with placebo or non-active control in RCTs rather than another active intervention. When direct comparative trials are completed, they typically include only two interventions from a larger group of possible treatments. As such, decision-makers are faced with a lack of adequate direct comparative data with which to make their judgements.

In the absence of head-to-head trials, indirect comparisons may provide valuable information. For example, if two different interventions have been evaluated against a common comparator, the comparative effects of the two interventions versus each other can be estimated indirectly.[1 2] Even in the presence of head-to-head data, indirect comparisons may add value by improving precision of treatment effect estimates.

Methodologies exist to indirectly compare interventions, as do modes to implement such methodologies.[1 5–8] In the simplest form, interventions that are evaluated against a common comparator in separate trials can be compared using an anchored-indirect treatment comparison approach.[5] As a generalisation of indirect comparisons, when more than two treatments are being compared indirectly, and at least one pair of treatments is being compared directly as well as indirectly (a closed loop is present), both direct and indirect types of data can be used to estimate effects in a mixed treatment comparison (MTC) meta-analysis using a Bayesian or frequentist framework.[1–8] Prior research has attempted to categorise the use of indirect comparisons in the medical literature, but either did not included Bayesian MTCs or collected limited data on this approach.[9 10] The Agency for Healthcare Research and Quality commissioned us to evaluate how MTCs in published systematic reviews are conducted and reported.[11] We present the findings of our systematic review identifying closed-loop MTCs using a Bayesian framework and descriptively summarise their methodological and reporting characteristics.

METHODS

A systematic literature search was conducted in MEDLINE, the Centre for Reviews and Dissemination Databases (including the Database of Abstracts and Reviews of Effects, Health Technology Assessment and the National Institute for Health Research Economic Evaluation Database), The Cochrane Library and the American College of Physicians Journal Club from 1 January 2006 through 31 July 2011. The search strategy in online supplementary appendix S1 was used. Manual additions were permitted based on the citations identified by the literature search.

Two independent investigators assessed citations for inclusion in a parallel manner based on a priori defined criteria. Specifically, we included meta-analyses that compared the clinical effectiveness or safety of interventions (any pharmacological (including placebo and different doses), behavioural or procedural interventions) based on RCTs, utilised a Bayesian approach to conduct MTC, had at least one closed loop (see online supplementary appendix S2) and were published in full-text and in the English language. There has been inconsistency in what constitutes a MTC in the medical literature[12]; therefore, for the purposes of this systematic review a MTC was defined as the comparison of three or more interventions in which direct as well as indirect evidence was used. Methodological publications that presented MTCs for illustrative purposes and cost-effectiveness analyses were not considered in this systematic review, nor were individual patient data meta-analyses.

Two reviewers independently extracted data with disagreements resolved through discussion. For each included closed-loop Bayesian MTC, all published material including the manuscript, supplements, appendices or external websites which the reader of the article was referred to for additional information were used during data extraction. Therefore, the extraction of data was predicated on the reporting of the information by the authors within these sources. When extracting data, we recorded what the authors reported without ourselves judging whether the methods were appropriate or not. If there was insufficient data from all available sources, we indicated 'not reported' for that criterion on data extraction.

General characteristics of each MTC were extracted including author and funding information, if a methodologist was an author, the number and type of intervention comparisons made, number of printed pages and use of supplement or appendix, the number of trials and patients in the analyses, clinical area (eg, cardiology and endocrinology) and the network pattern. For the purpose of this project, we defined a methodologist as an individual having an affiliation with a department of statistics, biostatistics, epidemiology, clinical epidemiology or public health services, as determined by author information and affiliations listed in the publication.[13] The country in which a review was conducted was determined by the corresponding author's affiliation.

The network pattern[3 4 11 14] was determined by figures presented within the identified publication. If a figure was not available, we determined the pattern based on text descriptions of included trials.

We also extracted information regarding the methodology used to conduct the closed-loop Bayesian MTC including the models applied (eg, fixed vs random effects), description of model parameters (eg, choices of prior distributions), methods for assessment of model fit, potential bias, inconsistency and heterogeneity, use of covariate adjustment in models, whether the model accommodated multiarm trials, software utilised and availability of code.

Finally, we extracted data concerning the reporting of results including the type of endpoint (eg, binary vs continuous), effect size and measure of variance, use of

other methods to report results (eg, probability of treatment being best, claims of equivalence or non-inferiority) and the format/presentation of results (eg, text, tables and figures). Characteristics of the journals in which included MTCs were published were collected, including journal name, impact factor, allowance of supplements or appendices, and limitations on word, table and figure counts.

The characteristics of the closed-loop Bayesian MTCs and journals were summarised descriptively. Categorical data are presented using frequencies and continuous data as means±SDs.

RESULTS

A total of 626 citations were identified through the database searches with an additional five MTCs identified through manual review (figure 1). After full text review, 35 articles representing 34 unique closed-loop Bayesian MTCs were included.[15–49] The publication by Orme *et al*[25] analysed two distinct networks of RCTs.

The rate of publication of closed-loop Bayesian MTCs increased over the 5-year search period, with 26 (76.5%) of the MTCs published between 2009 and 2011 compared with only 8 (23.5%) published prior to 2009. On average, 6.1±4.8 authors were listed per publication and less than half of publications (47.1%) included a methodologist as an author (table 1). The most common country from which authors published MTCs was the UK (35.3%), followed by the USA (11.8%) and Greece (11.8%).

Funding sources for the MTCs included governmental/foundation (29.4%), industry (26.5%) and unfunded (17.6%) with 23.6% not making a statement regarding funding source(s). Only two publications

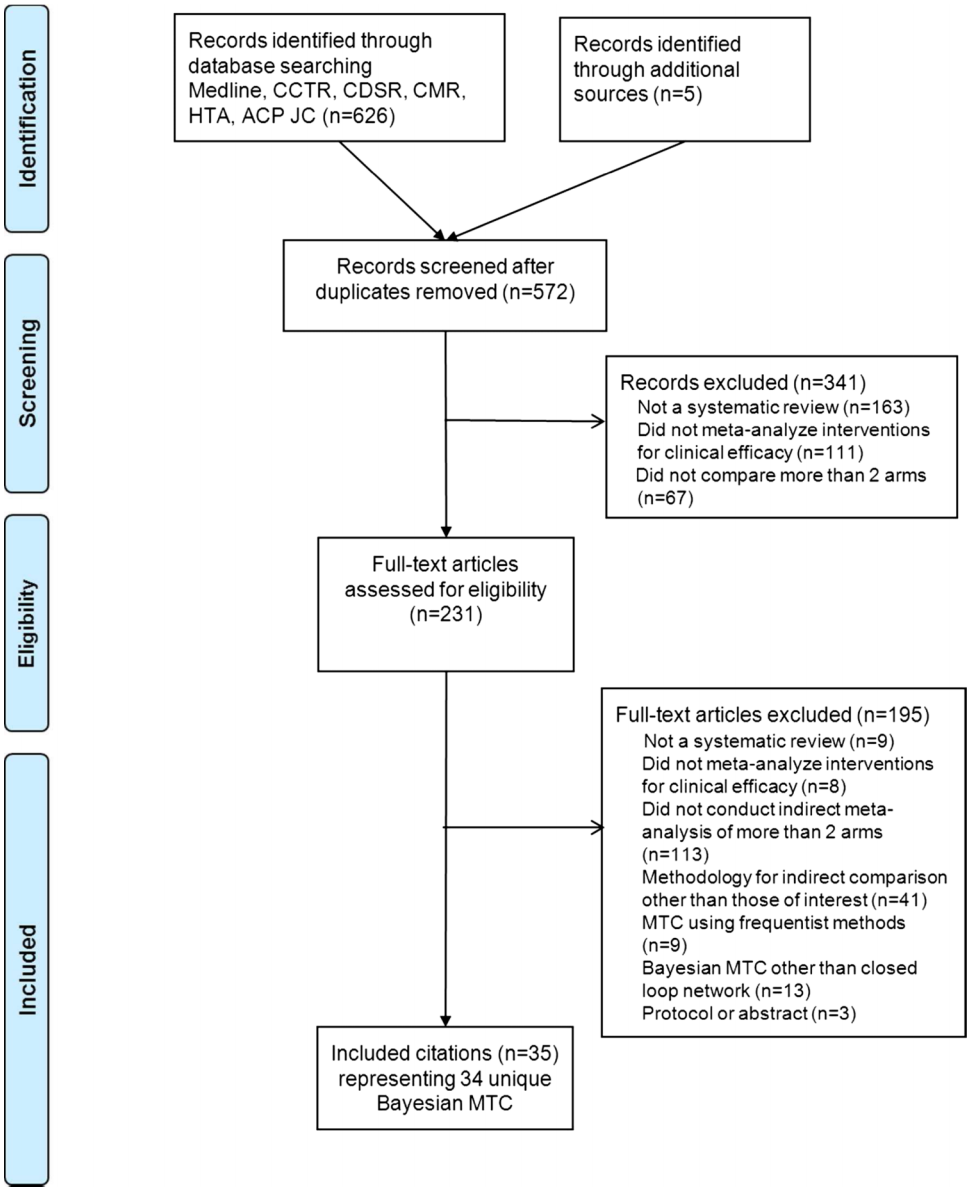

Figure 1 Flow diagram of citation inclusion and exclusion.

Table 1 General characteristics of Bayesian mixed treatment comparisons

Characteristic	n/N (%) or mean (SD)
Number of authors	6.1 (4.8)
Was a methodologist an author on the manuscript?	16/34 (47.1)
Country	
USA	4/34 (11.8)
UK	12/34 (35.3)
Canada	2/34 (5.9)
Brazil	1/34 (2.9)
China	2/34 (5.9)
Switzerland	3/34 (8.8)
The Netherlands	1/34 (2.9)
Italy	3/34 (8.8)
Belgium	1/34 (2.9)
Greece	4/34 (11.8)
Funding	
Industry	9/34 (26.5)
Government/foundation	10/34 (29.4)
Unfunded	6/34 (17.6)
Other	1/34 (2.9)
Not reported	8/34 (23.6)
Declared affiliation	2/34 (5.9)
Health Technology Assessment	1/2 (50.0)
Program	
The Cochrane Collaboration	1/2 (50.0)
Number of printed pages	16.6 (36.3)
Supplement or appendix published	20/34 (58.8)
Disease state evaluated	
Behavioural health	4/34 (11.8)
Cardiology	6/34 (17.6)
Infectious disease	2/34 (5.9)
Endocrine	2/34 (5.9)
Pulmonary	2/34 (5.9)
Pain	3/34 (8.8)
Dermatology	2/34 (5.9)
Ophthalmology	2/34 (5.9)
Rheumatology	2/34 (5.9)
Gastroenterology	3/34 (8.8)
Dental	1/34 (2.9)
Oncology	4/34 (11.8)
Substance abuse	1/34 (2.9)
Number of interventions compared*	8.5 (4.3)
Type of intervention*	
Pharmacological	30/35 (85.7)
Devices	3/35 (8.6)
Other	1/35 (2.9)
Device and pharmacological	1/35 (2.9)
Number of trials included in network*	35.9 (30.1)
Number of patients included in network*	33 459 (71 233)

*The trial by Orme *et al* included two individual networks and they are considered separately for this characteristic.

identified an organisational affiliation, one each with the Health Technology Assessment Program and The Cochrane Collaboration. The mean number of printed pages per publication was 16.6±36.3 (range 4–221) and over half published a supplement or appendix. From those that did not publish a supplement or appendix, one publication did not have the option to do so, given journal (or report) specifications.

There were 13 different categories of disease states evaluated among included MTCs. The mean number of interventions included within the analyses was 8.5±4.3, of which most were pharmacological (85.7%) in nature. The mean number of trials included in the MTCs was 35.9±30.1 and the mean number of patients included was 33 459±71 233 (range 594–324 168).

The most common model used in closed-loop Bayesian MTCs was a random-effects model (58.5%; table 2). Very few analyses reported information about whether there was adjustment for covariates (25.6%). Of the 28 MTCs that included trials with three or more arms, 10 (35.7%) reported use of an adjustment for multiarm trials. Less than half of all analyses reported testing model fit. Of the 15 analyses that reported testing model fit in some manner, the most common method was residual deviance (40%). More than two-thirds of the MTCs (76.5%) also included a traditional meta-analysis.

Closed-loop Bayesian MTCs used WinBUGS software, and two also specified the use of additional software including the BUGS XLA Wrapper and S-Plus. The statistical WinBUGS code was made available to the reader in only 20.6% of cases, most often in an online supplement/appendix (71.4%). Aggregated study-level patient data used in the MTC was frequently made available to the reader and of these 21 analyses (61.8%) it was most commonly published within the manuscript itself (85.7%). Evaluation of convergence was found in 35.3% of analyses, most commonly using the Gelman-Rubin statistic (58.3%).

Utilised priors were reported as either non-informative (vague or flat) or informative in 44.1% and 8.8% of analyses, respectively. The remaining analyses (47.1%) did not specify the nature of the prior distributions used. It was also uncommon for the actual prior distribution to be reported for the population treatment effect (d) and the between-study SD of population treatment differences across studies (σ); with only 32.4% and 29.4% of MTCs, respectively, reporting this information. Sensitivity analyses based on priors were conducted in 11.8% of MTCs.

Accompanying traditional meta-analyses were common (61.5%). The most common method used to assess heterogeneity was the I^2 statistic (81.3%) followed by the Cochrane Q-statistic (43.8%). Evaluation of heterogeneity within the MTC was less common, reported in only 32.4% of publications. Of these 11 analyses, τ^2 (among-study variance of true effects) was used in 54.5% of analyses followed by between-study SD (45.5%) and several other less frequent methods (some MTCs reported multiple means to test for heterogeneity and therefore are counted twice in the numerator).

Inconsistency between indirect and direct estimates was evaluated in 24 (70.6%) studies. One review

reported being unable to evaluate inconsistency due to lack of direct data while the remaining MTCs simply did not comment on inconsistency. The most common method used to evaluate inconsistency was comparing results of the MTC to those of a traditional meta-analysis conducted by the authors simultaneously or a previously published traditional meta-analysis.

Table 2 Methods characteristics in Bayesian MTCs

Characteristic	n/N (%)
Conducted traditional meta-analysis	26/34 (76.5)
Model	
Fixed effects	1/34 (2.9)
Random effects	20/34 (58.8)
Fixed and random effects	7/34 (20.6)
Not reported	6/34 (17.6)
Adjustment for covariates	9/34 (25.6)
Adjustment for multiple arms in MTCs including trials with three or more arms	10/28 (35.7)
Model fit tested	15/34 (44.1)
Residual deviance	6/15 (40.0)
Deviance information criterion	2/15 (13.3)
Residual deviance and deviance information criterion	3/15 (20.0)
Q–Q plots	1/15 (6.7)
Mean sum deviation	1/15 (6.7)
Method not reported	2/15 (13.3)
Code published	7/34 (20.6)
Online supplement	5/7 (71.4)
External website	2/7 (28.6)
Aggregate study-level data published	21/34 (61.8)
Manuscript	18/21 (85.7)
Online supplement	2/21 (9.5)
External website	1/21 (4.8)
Evaluation of convergence*	12/34 (35.3)
Gelman Rubin statistic	7/12 (58.3)
Kernel density plot	1/12 (8.3)
Visual plot inspection	1/12 (8.3)
Observation of chain mix	2/12 (16.7)
Method not reported	2/12 (16.7)
Priors	
Use of non-informative	15/34 (44.1)
Use of informative priors	3/34 (8.8)
Not specified	16/34 (47.1)
Prior distribution of d reported	11/34 (32.4)
Prior distribution for σ reported	10/34 (29.4)
Sensitivity analysis based on priors	4/34 (11.8)
Evaluation of heterogeneity in traditional meta-analysis*	16/26 (61.5)
I^2	13/16 (81.3)
Cochrane-Q statistic	7/16 (43.8)
PICO statement	1/16 (6.3)
Plot visualisation	2/16 (12.5)
L'Abbe plot	1/16 (6.3)
Evaluation of heterogeneity in network meta-analysis*	11/34 (32.4)
Precision (τ^2)	6/11 (54.5)
Between study SD	5/11 (45.5)
Heterogeneity p values	1/11 (9.1)
Evaluation of inconsistency*	24/34 (70.6)
Comparison to traditional or prior meta-analysis†	12/24 (50.0)
Inconsistency/incoherence factors	4/12 (33.3)
Posterior mean residual deviance	3/12 (25.0)
Method not reported	4/12 (33.3)
Trial sequential analysis	1/12 (8.3)
Overall inconsistency (σ^2w)	1/12 (8.3)

*Studies that used multiple methods to test heterogeneity were counted multiple times, in the respective categories.
†Authors either compared results of the MTC with a traditional meta-analysis that they conducted concurrently or with a traditional meta-analysis that was previously published.
MTC, mixed treatment comparison; PICO, patient, intervention, comparator, outcome.

Most analyses (85.3%) reported outcomes that were binary (table 3). Of these 29 analyses, ORs were the most commonly reported effect measure (62.1%), followed by relative risks (17.2%) and HRs (13.8%), among other less frequent measures. Of the 10 (29.4%) analyses that reported continuous outcomes, the weighted-mean difference was the most common effect measure (80%). All analyses reported variance with 95% credible intervals and one also reported SEs. Most analyses did not report if the posterior distribution was the mean or median value (85.3%). Presentation of results varied, although most analyses used multiple media including tables, figures and text.

Few analyses (8.8%) presented graphical representations of the posterior distributions of outcomes. Rank-ordering of interventions based on probability statements (including rankograms with the probability of a treatment being best, second best and so on) for a given outcome was reported in 21 (61.8%) of the MTCs. Only one MTC made claims of equivalence and two made claims of non-inferiority, of which two defined the minimally important difference required to make these statements.

Complete details of each journal in which at least one MTC was published can be found in tables 4 and 5. The 34 MTCs were published in 24 different journals, with a mean impact factor of 9.20±8.71. *BMJ* published the most MTCs (6 of the 34, 17.6%) followed by *Current Medical Research and Opinion* (4 of the 34, 11.8%). The majority of journals (70.8%) imposed word count limits and 45.8% imposed table/figure limitations; however, 79.2% of journals allowed online supplements or appendices.

DISCUSSION

Meta-analysis has been regarded as the most highly cited study design in health science.[50] However, a drawback of the traditional meta-analysis is its ability to compare only two interventions, without the ability to simultaneously evaluate other comparators. This is inconsistent with

Table 3 Outcomes and results reporting in Bayesian mixed treatment comparisons

Characteristic	n/N (%) or mean (SD)
Graphical representation of posterior distribution	3/34 (8.8)
Ranking of outcomes	21/34 (61.8)
Claims of equivalence	1/34 (2.9)
Claims of non-inferiority	2/34 (5.9)
Minimally important difference	8/47 (17.0)
Type of outcome	
Binary	23/34 (67.6)
Continuous	4/34 (11.8)
Binary and continuous	6/34 (17.6)
Categorical non-binary	1/34 (2.9)
Binary effect measure	29/34 (85.3)
Relative risk	5/29 (17.2)
OR	18/29 (62.1)
HR	4/29 (13.8)
Multiple effect measures	2/39 (6.9)
Continuous effect measure	10/34 (29.4)
Weighted mean difference	8/10 (80.0)
Multiple	2/10 (20.0)
Categorical non-binary effect measure	1/34 (2.9)
Relative risk	1/1 (100)
Presentation of results*	
Table	24/34 (70.6)
Text	32/34 (94.1)
Figure	21/34 (61.8
Posterior distribution	
Mean	1/34 (2.9)
Median	4/34 (11.8)
Not reported	29/34 (85.3)

*Studies were counted multiple times when more than one method was used.

clinical practice as in many instances there are a variety of interventions that exist and one must decide which is best. The use of statistical methods (including simple approaches as well as MTC meta-analysis) to compare greater than two interventions simultaneously is on the rise within the peer-reviewed literature. As recent as 2005, a search of the medical literature yielded four publications that utilised such methods; while in 2011, the number increased to 57.[12] The results of our systematic review also suggest that indirect comparisons, specifically closed-loop Bayesian MTC, have become more prevalent. A recent study found that a median of three studies (IQR 2–6) were included per meta-analysis, with close to 75% of meta-analyses including five or less trials.[51] Our results suggest that compared to traditional meta-analyses, closed-loop Bayesian MTCs are larger and more comprehensive. Moreover, identified MTCs were published in a wide variety of journals covering a range of disease states and thus likely to reach a large readership given their collective mean impact factor. However, we found a variety of reporting strategies or a lack of reporting of characteristics that are important to the conduct of closed-loop Bayesian MTC. This may be related to the limited guidance as to how to conduct and report an MTC, a topic which has been extensively reviewed and summarised elsewhere.[11]

Table 4 Aggregate journal characteristics

Characteristics	Yes n/N (%) or mean (SD)
Impact factor	9.20 (8.71)
Supplement or appendix allowed	19/24 (79.2)
Online	17/19 (89.5)
Not specified	2/19 (10.5)
Word count limit	17/24 (70.8)
Table count limit	11/24 (45.8)
Figure count limit	11/24 (45.8)

Prior research by Donegan *et al*[9] has attempted to categorise published indirect comparisons and evaluate their quality, although advanced methods including Bayesian (and frequentist) MTCs were not included. Of the 43 included comparisons, 23 used an anchored indirect approach while others used hypothesis testing, CI overlap and meta-regression methods to draw indirect comparisons. The authors concluded that quality of published indirect comparisons, in particular the assessment of model assumptions and the methods used to do so, were suboptimal. A set of quality criteria were proposed by the authors to be used in future indirect comparisons, specifically evaluating if the method of indirect comparison applied was appropriate, if methods to assess similarity, homogeneity and consistency were stated and if such methods were appropriate, and details of overall interpretation and reporting of results.

Song *et al*[10] also have systematically reviewed previously published indirect comparisons and, of the 88 identified, found only 18 using 'network or Bayesian approaches'. Their findings are similar to that of Donegan and colleagues, suggesting that the main methodological problems included unclear understanding of assumptions, incomplete inclusion of relevant studies, flawed or inappropriate methods, lack of similarity assessment and inappropriate combination of direct and indirect evidence.

Our systematic review adds to this existing literature by updating results and adding new information. First, the aforementioned prior reviews only included literature through 2007/2008, making ours the most up-to-date review available. Unlike prior publications, our systematic review focused only on Bayesian MTCs of networks with at least one closed loop, perhaps the most common method utilised of late to analyse complex networks of RCTs. While prior publications focused on the evaluation and reporting of assumptions made within the models, we evaluated additional model characteristics in depth including testing for model fit, evaluation of convergence, adjustment for covariates or multiarm trials, the specific priors used and availability of the code and

Table 5 Individual journal characteristics

Journals	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Alimentary Pharmacology and Therapeutics	Edwards[36]	3.861	Y, online	N	N	N
Annals of Internal Medicine	Gross *et al*[16]	16.792	Y, not specified	3500–4000	4 tables or figures	4 tables or figures
Archives of Internal Medicine	Sciarretta *et al*[20]; Cooper *et al*[47]	10.639	Y, online	3500	6–8 tables or figures	6–8 tables or figures
BMJ	Baldwin *et al*[49]; Hartling *et al*[17]; Stettler[43]; Trelle *et al*[21]; Wandel *et al*[30]; Lam and Owen[45]	13.471	Y, online	N	N	N
British Journal of Anaesthesia	Maund *et al*[18]†	4.224	Y, online	5000	N	N
British Journal of Ophthalmology	Van den Bruel *et al*[23]	2.934	Y, online	3000	5 tables or figures	5 tables or figures
Cancer Treatment Reviews	Golfinopoulus *et al*[38]	6.811	N	N	N	N
Clinical Therapeutics	Edwards[37]	2.551	Y, online	5500–6000	N	N
Cochrane Database of Systematic Reviews	Walsh *et al*[29]	6.186	N	N	N	N
Current Medical Research and Opinion	van de Kerkhof *et al*[22]; Orme *et al*[25]; Uthman and Abdulmalik[27]; Vissers *et al*[28]	2.609*	Y, online	11 200	N	N
Dermatology	Bansback *et al*[34]	2.714	Y, not specified	13 pages for text, tables, figures	Included in page count	Included in page count
Drug and Alcohol Dependence	Meader[40]	3.365	Y, online	6000	N	N
Gastroenterology	Woo *et al*[32]	12.023	Y, online	6000	Minimum of 4–6 figures or illustrations	Minimum of 4–6 figures or illustrations
Health technology assessment (Winchester, England)	Maund *et al* [18]†	4.197	N	N	N	N
The Journal of the American Medical Association	Phung *et al*[26]	30	Y, online	3500	4 tables or figures	4 tables or figures
Journal of Hospital Infection	Wang *et al*[31]	3.078	N	5000	N	N
Journal of Hypertension	Coleman *et al*[41]	3.98	Y, online	N	N	N
Journal of the National Cancer Institute	Mauri *et al*[42]; Kyrgiou *et al*[48]	14.697	Y, online	6000	8 table or figures	8 tables or figures
Lancet	Cipriani *et al*[35]	33.633	Y, online	4500	"Should include about 5 illustrations"	"Should include about 5 illustrations"
Lancet Infectious Disease	Manzoli *et al*[39]	16.144	Y, online	3000–5000	"Should include about 5 illustrations"	"Should include about 5 illustrations"
Lancet Oncology	Golfinopoulos *et al*[44]; Bangalore[15]	17.764	Y, online	3000–5000	"Should include about 5–6 illustrations"	"Should include about 5–6 illustrations"

Continued

Table 5 Continued

Journals	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Pharmacotherapy	Baker *et al*[33]	2.631	N	7000	N	N
Rheumatology	Nixon *et al*[46]	4.171	Y, online	3500	6 figures or tables	6 figures or tables
Value in Health	Dakin *et al*[24]	2.342	Y, online	N	N	N

*The impact factor was obtained from Web of Science in 2012, except when the symbol appears for that journal the impact factor was not available in Web of Science and was taken from the journal's website.
†Published as a manuscript and health technology assessment report, but counted as one unique publication.
N, no; Y, yes.

aggregated study-level data. Despite these differences, however, our findings are consistent with prior research and with the opinion of experts regarding the challenges and concerns around implementing and reporting these more complex statistical methods.[10 12 52] Perhaps clearer guidance as to how to conduct and report these types of meta-analyses will lead to a more optimal and consistent approach.

While we only characterised the methods and reporting of closed-loop Bayesian MTC in this report, our search strategy was designed to capture MTCs regardless of methodological approach (including frequentist MTC). Of note, only a handful (n=9) of frequentist MTCs were identified in our search, three of which specifically reference using the methods for MTC proposed by Lumley and colleagues, while the others more generically referenced mixed-model approaches.[49 53–60] This suggests that meta-analysts at present seem to favour a Bayesian approach to MTC, since investigators could have chosen to use either a Bayesian or frequentist method for any of the MTC identified in our search (given all analysed networks with at least one closed loop). Given the relative paucity of frequentist models, we do not describe the characteristics of their methods and reporting in this paper but they can be found elsewhere.[11]

An important limitation of our review is that we cannot say with certainty that a lack of reporting means a given method or analysis was not undertaken (ie, the testing for convergence or inconsistency need not be described in a paper for it to have been performed by the investigators) or that the reporting of a piece of data or statistical code was not considered. However, we evaluated word, table and figure limits imposed by journals in which these MTCs were published and our findings do not suggest journal space should be an obstacle to complete reporting. Another limitation is the definition used to describe a methodologist. While this definition has been used by previous researchers in a similar topic area,[13] to our knowledge it has not been validated and therefore may not accurately depict the true involvement of an individual who considered themselves a methodologist.

With the growing publication of Bayesian MTCs in the peer-reviewed literature and the recognised challenges of such methods, its appropriate use and interpretation becomes imperative. Efforts in clarifying the appropriate use and reporting of Bayesian MTC should be of priority.

Contributors DMS, JCC, CIC, WLB, OJP and CMW were responsible for study design. DMS, WLB and OJP were responsible for data collection. DMS, CIC and JCC were responsible for data analysis and interpretation. All authors contributed in drafting the manuscript, revising the manuscript and approved the final manuscript. CIC is responsible for the overall content as the corresponding author.

Funding This work was supported by the Agency for Healthcare Research and Quality contract number HHSA 290 2007 10067 I.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Individual study data that has been extracted can be found by accessing the full report on the AHRQ EHC website.

REFERENCES

1. Bucher HC, Guyatt GH, Griffith LE, *et al*. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683–91.
2. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stats Med* 2002;21:2313–24.
3. Jansen JP, Fleurence R, Devine B, *et al*. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011;14:417–28.
4. Hoaglin DC, Hawkins N, Jansen JP, *et al*. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health* 2011;14:429–37.
5. Sutton A, Ades AE, Cooper N, *et al*. Use of indirect and mixed treatment comparisons for technology assessments. *Pharmacoeconomics* 2008;26:753–67.
6. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105–24.
7. Caldwell DM, Ades AE, Higgins PT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331:897–900.
8. Health Information and Quality Authority. *Guidelines for evaluating the clinical effectiveness of health technologies in Ireland*. Dublin: Health Information and Quality Authority, 2011. http://www.hiqa.ie (accessed 28 Dec 2011).
9. Donegan S, Williamson P, Gamble C, *et al*. Indirect comparisons: a review of reporting and methodological quality. *PLoS ONE* 2010;5:e11054.
10. Song F, Loke YK, Walsh T, *et al*. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. *BMJ* 2009;338:b1147.
11. Coleman CI, Phung OJ, Cappelleri JC, *et al*. Use of mixed treatment comparisons in systematic reviews. Methods Research Report. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290 2007 10067I.) AHRQ Publication No. 12-EHC119-EF. Rockville, MD: Agency for Healthcare Research and Quality. August 2012.
12. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Method* 2012;3:80–97.
13. Sung L, Hayden J, Greenberg ML, *et al*. Seven items were identified for inclusion when reporting a Bayesian analysis of a clinical study. *J Clin Epidemiol* 2005;58:261–8.
14. Canadian Agency for Drugs and technologies in Health. *Guidelines for the economic evaluation of health technologies: Canada*. 3rd edn. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2006. http://www.cadth.ca (accessed 28 Dec 2011).
15. Bangalore S, Kumar S, Kjeldsen E, *et al*. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analysis of 324168 participants from randomized trials. *Lancet Oncol* 2011;12:65–82.
16. Gross JL, Kramer CK, Leitao CB, *et al*. Effect of antihyperglycemics agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. *Ann Intern Med* 2011;154:672–9.
17. Hartling L, Fernandes RM, Bialy L, *et al*. Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis. *BMJ* 2011;342:1714.
18. Maund E, McDaid C, Rice S, *et al*. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after major surgery: a systematic review. *Br J Anaesth* 2011;106:292–7.
19. McDaid C, Maund E, Rice S, *et al*. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for the reduction of morphine-related side effects after major surgery: a systematic review. *Health Technol Assess* 2010;14:1–153.
20. Sciarretta S, Palano F, Tocci G, *et al*. Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. *Arch Intern Med* 2011;171:384–94.
21. Trelle S, Reichenback S, Wandel S, *et al*. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
22. van de Kerkhof P, de Peuter R, Ryttov J, *et al*. Mixed treatment comparison of a two-compound formulation (TCF) product containing calcipotriol and betamethasone dipropionate with other topical treatments in psoriasis vulgaris. *Curr Med Res Opin* 2011;27:225–38.
23. Van den Bruel A, Gailly J, Devriese S, *et al*. The protective effect of ophthalmic viscoelastic devices on endothelial cell loss during cataract surgery: a meta-analysis using mixed treatment comparisons. *Br J Ophthalmol* 2011;95:5–10.
24. Dakin H, Fidler C, Harper C. Mixed treatment comparison meta-analysis evaluating the relative efficacy of nucleos(t)ides for treatment of nucleos(t)ide-naive patients with chronic hepatitis B. *Value Health* 2010;13:934–45.
25. Orme M, Collins S, Dakin H, *et al*. Mixed treatment comparison and meta-regression of the efficacy and safety of prostaglandin analogues and comparators for primary open-angle glaucoma and ocular hypertension. *Curr Med Res Opin* 2010;26:511–28.
26. Phung OJ, Scholle JM, Talwar M, *et al*. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* 2010;303:1410–18.
27. Uthman OA, Abdulmalik J. Comparative efficacy and acceptability of pharmacotherapeutic agents for anxiety disorders in children and adolescents: a mixed treatment comparison meta-analysis. *Curr Med Res Opin* 2010;26:53–9.
28. Vissers D, Stam W, Nolte T, *et al*. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. *Curr Med Res Opin* 2010;26:1037–45.
29. Walsh T, Worthington HV, Glenn A, *et al*. Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev* 2011;(1):CD007868.
30. Wandel S, Juni P, Tendal B, *et al*. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010;341:4675.
31. Wang H, Huang T, Jing J, *et al*. Effectiveness of different central venous catheters for catheter-related infections: a network meta-analysis. *J Hosp Infect* 2010;76:1–11.
32. Woo G, Tomlinson G, Nishikawa Y, *et al*. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. *Gastroenterology* 2010;139:1218–29.
33. Baker WL, Baker EL, Coleman CI. Pharmacologic treatments for chronic obstructive pulmonary disease: a mixed-treatment comparison meta-analysis. *Pharmacotherapy* 2009;29:891–905.
34. Bansback N, Sizto S, Sun H, *et al*. Efficacy of systemic treatments for moderate to severe plaque psoriasis: systematic review and meta-analysis. *Dermatology* 2009;219:209–18.
35. Cipriani A, Furukawa TA, Salanti G, *et al*. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009;373:746–58.
36. Edwards SJ, Lind T, Lundell L, *et al*. Systematic review: standard- and double-dose proton pump inhibitors for the healing of severe erosive oesophagitis—a mixed treatment comparison of randomized controlled trials. *Aliment Pharmacol Ther* 2009;30:547–56.
37. Edwards SJ, Smith CJ. Tolerability of atypical antipsychotics in the treatment of adults with schizophrenia or bipolar disorder: a mixed treatment comparison of randomized controlled trials. *Clin Ther* 2009;31(Pt 1):1345–59.
38. Golfinopoulos V, Pentheroudakis G, Salanti G, *et al*. Comparative survival with diverse chemotherapy regimens for cancer of unknown primary site: multiple-treatments meta-analysis. *Cancer Treat Rev* 2009;35:570–3.
39. Manzoli L, Georgia S, De Vito C, *et al*. Immunogenicity and adverse events of avian influenza A H5N1 vaccine in healthy adults: multiple-treatments meta-analysis. *Lancet Infect Dis* 2009;9:481–92.
40. Meader N. A comparison of methadone, buprenorphine and alpha2 adrenergic agonists for opiod detoxification: a mixed treatment comparison meta-analysis. *Drug Alcohol Depen* 2010;108:110–14.
41. Coleman CI, Baker WL, Kluger J, *et al*. Antihypertensive medication and their impact on cancer incidence: a mixed treatment comparison meta-analysis of randomized controlled trials. *J Hypertens* 2008;26:622–9.

42. Mauri D, Polyzos NP, Salanti G, *et al*. Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer. *J Natl Cancer Inst* 2008;100:1780–91.
43. Stettler C, Allemann S, Wandel S, *et al*. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ* 2008;337:a1331.
44. Golfinopoulos V, Salanti G, Pavlidis N, *et al*. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol* 2007;8:898–911.
45. Lam SK, Owen A. Combined resynchronisation and implantable defibrillator therapy in left ventricular dysfunction: Bayesian network meta-analysis of randomised controlled trials. *BMJ* 2007;335:925.
46. Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumour necrosis factor alpha and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. *Rheumatology* 2007;46:1140–7.
47. Cooper NJ, Sutton AJ, Lu G, *et al*. Mixed comparison of stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. *Arch Intern Med* 2006;166:1269–75.
48. Kyrgiou M, Salanti G, Pavlidis N, *et al*. Survival benefits with diverse chemotherapy regimens for ovarian cancer: meta-analysis of multiple treatments. *J Natl Cancer Inst* 2006;98:1655–63.
49. Baldwin D, Woods R, Lawson R, *et al*. Efficacy of drug treatments for generalized anxiety disorder: systematic review and meta-analysis. *BMJ* 2011;342:1199.
50. Patsopoulos NA, Analatos AA, Ioannidis JPA. Relative citation impact of various study designs in the health sciences. *JAMA* 2005;293:2362–6.
51. Davey J, Turner RM, Clarke MJ, *et al*. Characteristics of meta-analyses and their component studies in the Cochrane Database of Systematic Reviews: a cross-sectional, descriptive analysis. *BMC Med Res Methodol* 2011;11:160.
52. Li T, Puhan MA, Vedula SS, *et al*. Ad Hoc Network Meta-analysis Methods Meeting Working Group. Network meta-analysis-highly attractive but more methodological research is needed. *BMC Med* 2011;9:79.
53. Freemantle N, Lafuente-Lafuente C, Mitchell S, *et al*. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;13:329–45.
54. Anothaisintawee T, Attia J, Nickel JC, *et al*. Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. *JAMA* 2011;305:78–86.
55. Hansen RA, Gaynes BN, Gartlehner G, *et al*. Efficacy and tolerability of second-generation antidepressants in social anxiety disorder. *Int Clin Psychopharmacol* 2008;23:170–9.
56. Jalota L, Kalira V, George E, *et al*. Prevention of pain on injection of propofol: systematic review and meta-analysis. *BMJ* 2011;342:1110.
57. Trikalinos TA, Alsheikh-Ali AA, Tatsioni A, *et al*. Percutaneous coronary interventions for non-acute coronary artery disease: a quantitative 20-year synopsis and a network meta-analysis. *Lancet* 2009;373:911–18.
58. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007;369:201–7.
59. Singh JA, Wells GA, Christensen R, *et al*. Adverse effects of biologics: a network meta-analysis and Cochrane overview (review). *Cochrane Database Syst Rev* 2011;2:CD008794.
60. Roskell NS, Lip GYH, Noack H, *et al*. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparison versus dabigatran etexilate. *Thromb Haemost* 2010;104:1106–15.