Comparative Effectiveness of Injection Therapies for Hemiplegic Shoulder Pain in Stroke: A Systematic Review and Network Meta-analysis

Supplemental Material:

Supplemental Method

Table S1-S3

Figure S1-S5

PRISMA-NMA checklist

Supplemental Method

Search strategy:

PubMed (updated on August 04, 2021)

1. stroke OR cerebrovascular disease OR cerebral infarction OR intracerebral hemorrhage OR hemiplegia OR hemiparesis: 635502
2. injection OR nerve block OR corticosteroid OR botulinum toxin OR hyaluronic acid: 1329359
3. shoulder OR upper limb: 275744

4. pain OR painful: 931877

5. #1 AND #2 AND #3 AND #4: 332

History and Search Details

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Search	Actions	Details	Query	Results	Time
#5	•••	>	Search: **#1 AND #2 AND #3 AND #4** Sort by: **Most Recent**	332	00:47:45
#4	•••	>	Search: **pain OR painful** Sort by: **Most Recent**	931,877	00:47:12
#3	•••	>	Search: **shoulder OR upper limb** Sort by: **Most Recent**	275,744	00:46:55
#2	•••	>	Search: **injection OR nerve block OR corticosteroid OR botulinum toxin OR hyaluronic acid** Sort by: **Most Recent**	1,329,359	00:46:36
#1	•••	>	Search: **stroke OR cerebrovascular disease OR cerebral infarction OR intracerebral hemorrhage OR hemiplegia OR hemiparesis** Sort by: **Most Recent**	635,502	00:46:16

EMBASE (updated on August 04, 2021)

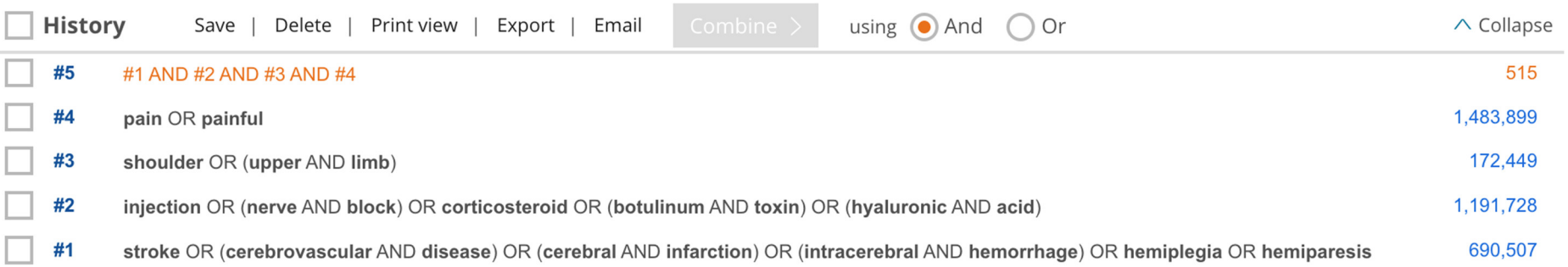
1. stroke OR (cerebrovascular AND disease) OR (cerebral AND infarction) OR (intracerebral AND hemorrhage) OR hemiplegia OR hemiparesis: 690507

2. injection OR (nerve AND block) OR corticosteroid OR (botulinum AND toxin) OR (hyaluronic AND acid): 1191728

3. shoulder OR (upper AND limb): 172449

4. pain OR painful: 1483899

5. #1 AND #2 AND #3 AND #4: 515



Scopus (updated on August 04, 2021)

1. (ALL (stroke) OR ALL (cerebrovascular AND disease) OR ALL (cerebral AND infarction) OR ALL (intracerebral AND hemorrhage) OR ALL (hemiplegia) OR ALL (hemiparesis)): 1574208

2. (ALL (injection) OR ALL (nerve AND block) OR ALL (corticosteroid) OR ALL (botulinum AND toxin) OR ALL (hyaluronic AND acid)): 3286987

3. (ALL (shoulder) OR ALL (upper AND limb)): 446363

4. (ALL (pain) OR ALL (painful)): 2294078

5. #1 AND #2 AND #3 AND #4: 4922

5	(((stroke) OR (cerebrovascular AND disease) OR (cerebral AND infarction) OR (intracerebral AND hemorrhage) OR (hemiplegia) OR (hemiparesis)) AND ((injection) OR (nerve AND block) OR (corticosteroid) OR (botulinum AND toxin) OR (hyaluronic AND acid)) AND ((shoulder) OR (upper AND limb)) AND ((pain) OR (painful))) Show less	4,922 results
4	(ALL (pain) OR ALL (painful))	2,294,078 results
3	(ALL (shoulder) OR ALL (upper AND limb))	446,363 results
2	(ALL (injection) OR ALL (nerve AND block) OR ALL (corticosteroid) OR ALL (botulinum AND toxin) OR ALL (hyaluronic AND acid)) Show less	3,286,987 results
1	(ALL (stroke) OR ALL (cerebrovascular AND disease) OR ALL (cerebral AND infarction) OR ALL (intracerebral AND hemorrhage) OR ALL (hemiplegia) OR ALL (hemiparesis)) Show less	1,574,208 results

Table S1 League table for the results of the meta-analysis according to the reduction of the visual analogue scale (VAS) of pain at the 4th week

IM BoNT	NA	NA	0.05 (-0.74, 0.84)	NA	1.44 (0.55, 2.32)
-0.39 (-3.75, 2.98)	**IB BoNT**	-0.12 (-0.44, 0.20)	NA	NA	NA
-0.50 (-2.58, 1.57)	-0.12 (-2.77, 2.54)	**Steroid**	-0.92 (-2.31, 0.47)	1.10 (-0.41, 2.61)	0.82 (0.31, 1.34)
-0.12 (-1.85, 1.62)	0.27 (-2.95, 3.49)	0.39 (-1.44, 2.21)	**SSNB**	NA	1.98 (1.31, 2.65)
-0.52 (-3.17, 2.12)	-0.13 (-3.61, 3.34)	-0.02 (-2.27, 2.23)	-0.40 (-2.93, 2.12)	**HA**	0.00 (-1.25, 1.25)
1.55 (0.09, 3.01)	1.17 (-1.91, 4.24)	1.05 (-0.51, 2.61)	1.44 (0.07, 2.80)	1.03 (-1.20, 3.26)	**Placebo**

All data are presented as weighted mean differences of VAS reduction with the 95% confidence interval. The left lower part is the findings of the network meta-analysis; the right upper part is the finding of the pairwise meta-analyses. BoNT, botulinum toxin; HA, hyaluronic acid; IB, intra-bursal; IM, intra-muscular; SSNB, suprascapular nerve block; NA: not applicable.

Table S2 League table for the results of the meta-analysis according to the reduction of the visual analogue scale (VAS) of pain between the 4th and 24th week

IM BoNT	NA	-1.70 (-3.45, 0.05)	-1.85 (-2.68, -1.02)	NA	0.87 (-0.11, 1.85)
-0.05 (-2.83, 2.73)	**IB BoNT**	-0.21 (-0.54, 0.12)	NA	NA	NA
-0.26 (-1.87, 1.36)	-0.21 (-2.48, 2.06)	**Steroid**	-1.85 (-4.00, 0.30)	1.20 (-0.26, 2.66)	1.96 (1.10, 2.81)
-0.85 (-2.41, 0.71)	-0.80 (-3.63, 2.03)	-0.59 (-2.29, 1.10)	**SSNB**	NA	1.75 (0.98, 2.51)
-0.12 (-2.36, 2.12)	-0.07 (-3.08, 2.94)	0.13 (-1.84, 2.11)	0.73 (-1.58, 3.03)	**HA**	0.50 (-0.65, 1.65)
1.57 (0.30, 2.84)	1.52 (-1.12, 4.17)	1.32 (-0.04, 2.67)	0.72 (-0.67, 2.11)	1.45 (-0.50, 3.39)	**Placebo**

All data are presented as weighted mean differences of VAS reduction with the 95% confidential intervals. The left lower part is the findings of the network meta-analysis; the right upper part is the finding of the pairwise meta-analyses. BoNT, botulinum toxin; HA, hyaluronic acid; IB, intra-bursal; IM, intra-muscular; SSNB, suprascapular nerve block; NA: not applicable.

Table S3 Network comparisons of the treatment effects before and after exclusion of the non-randomized controlled trials

Pair of Comparison		VAS reduction at the 4th week		VAS reduction between the 4th and 24th week	
Reference	**Comparator**	**All included studies**	**Only RCT**	**All included studies**	**Only RCT**
Placebo	IMBoNT	1.55 (0.09, 3.01)	1.46 (-0.03, 2.95)	1.57 (0.30, 2.84)	1.42 (0.15, 2.69)
	IBBoNT	1.17 (-1.91, 4.24)	NA	1.52 (-1.12, 4.17)	NA
	Steroid	1.05 (-0.51, 2.61)	0.96 (-0.64, 2.55)	1.32 (-0.04, 2.67)	1.19 (-0.16, 2.53)
	SSNB	1.44 (0.07, 2.80)	1.07 (-0.52, 2.65)	0.72 (-0.67, 2.11)	0.15 (-1.50, 1.80)
	HA	1.03 (-1.20, 3.26)	0.99 (-1.27, 3.25)	1.45 (-0.50, 3.39)	1.39 (-0.52, 3.29)
IMBoNT	IBBoNT	-0.39 (-3.75, 2.98)	NA	-0.05 (-2.83, 2.73)	NA
	Steroid	-0.50 (-2.58, 1.57)	-0.50 (-2.60, 1.60)	-0.26 (-1.87, 1.36)	-0.23 (-1.81, 1.35)
	SSNB	-0.12 (-1.85, 1.62)	-0.39 (-2.24, 1.46)	-0.85 (-2.41, 0.71)	-1.27 (-2.93, 0.39)
	HA	-0.52 (-3.17, 2.12)	-0.47 (-3.14, 2.21)	-0.12 (-2.36, 2.12)	-0.03 (-2.23, 2.16)
IBBoNT	Steroid	-0.12 (-2.77, 2.54)	NA	-0.21 (-2.48, 2.06)	NA
	SSNB	0.27 (-2.95, 3.49)	NA	-0.80 (-3.63, 2.03)	NA
	HA	-0.13 (-3.61, 3.34)	NA	-0.07 (-3.08, 2.94)	NA
Steroid	SSNB	0.39 (-1.44, 2.21)	0.11 (-1.83, 2.04)	-0.59 (-2.29, 1.10)	-1.04 (-2.84, 0.77)
	HA	-0.02 (-2.27, 2.23)	0.03 (-2.25, 2.31)	0.13 (-1.84, 2.11)	0.20 (-1.73, 2.13)
SSNB	HA	-0.40 (-2.93, 2.12)	-0.08 (-2.72, 2.57)	0.73 (-1.58, 3.03)	1.23 (-1.16, 3.63)

Values are given as mean with 95% confidence interval. BoNT, botulinum toxin; HA, hyaluronic acid; IB, intra-bursal; IM, intra-muscular;

RCT, randomized controlled trial; SSNB, suprascapular nerve block; VAS, visual analogue scale.

Figure S1 Risk of bias assessment of the included studies

Figure S2 Risk of bias graph of the included studies

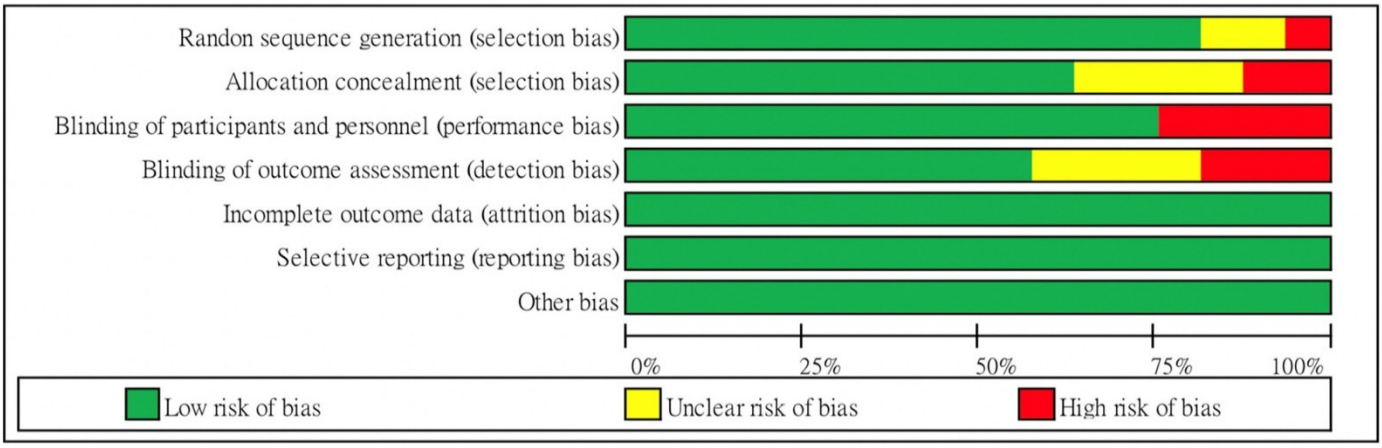


Figure S3 Loop inconsistency plots for different injection therapies in terms of VAS reduction (A) at the 4th week and (B) between the 4th and 24th weeks. The inconsistency factor (IF) is truncated by zero as the direction of the IF is not important. BoNT, botulinum toxin; HA, hyaluronic acid; IB, intra-bursal; IM, intra-muscular; SSNB, suprascapular nerve block; VAS, visual analogue scale.

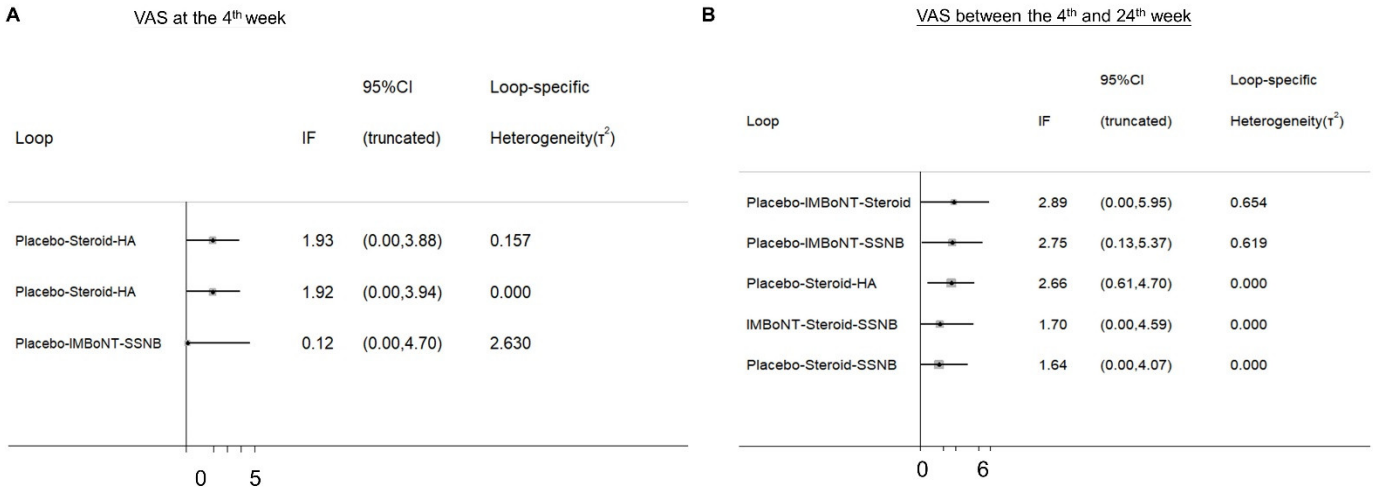


Figure S4 Forest plots of the network estimates derived from all the direct and indirect pairwise comparisons of the treatment effects in terms of VAS reduction **(A)** at the 4th week and **(B)** between the 4th and 24th weeks after interventions following exclusion of the non-randomized controlled trials. BoNT, botulinum toxin; HA, hyaluronic acid; IB, intra-bursal; IM, intra-muscular; SSNB, suprascapular nerve block; VAS, visual analogue scale.

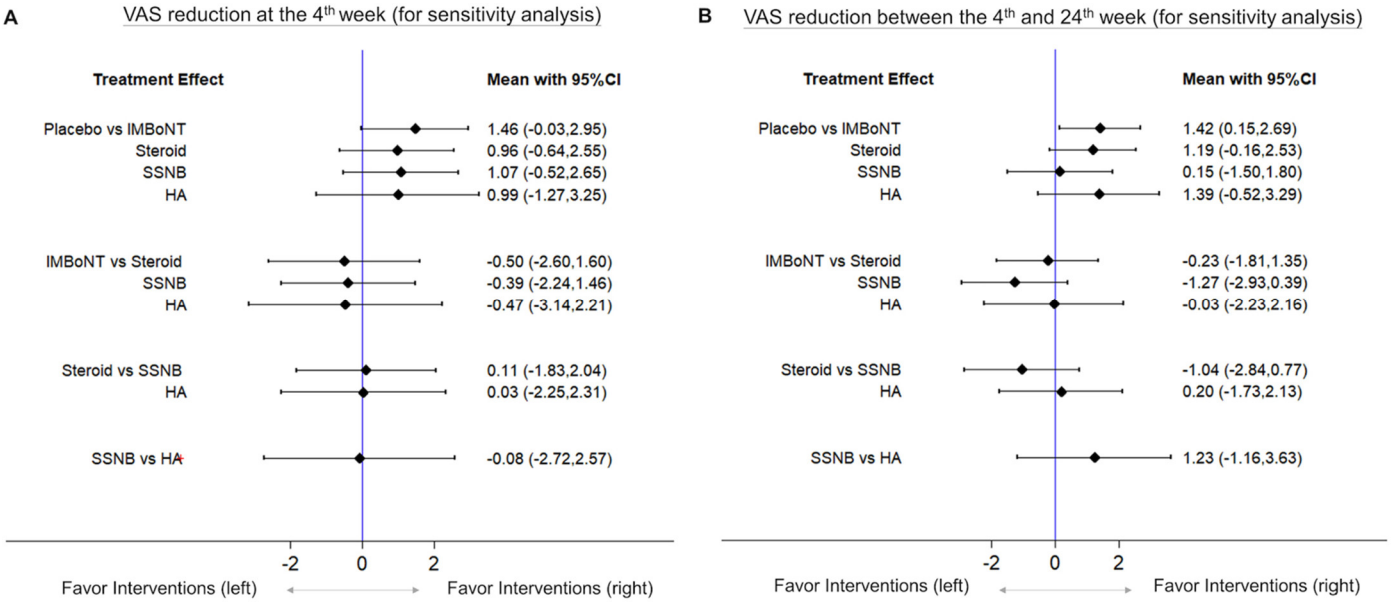
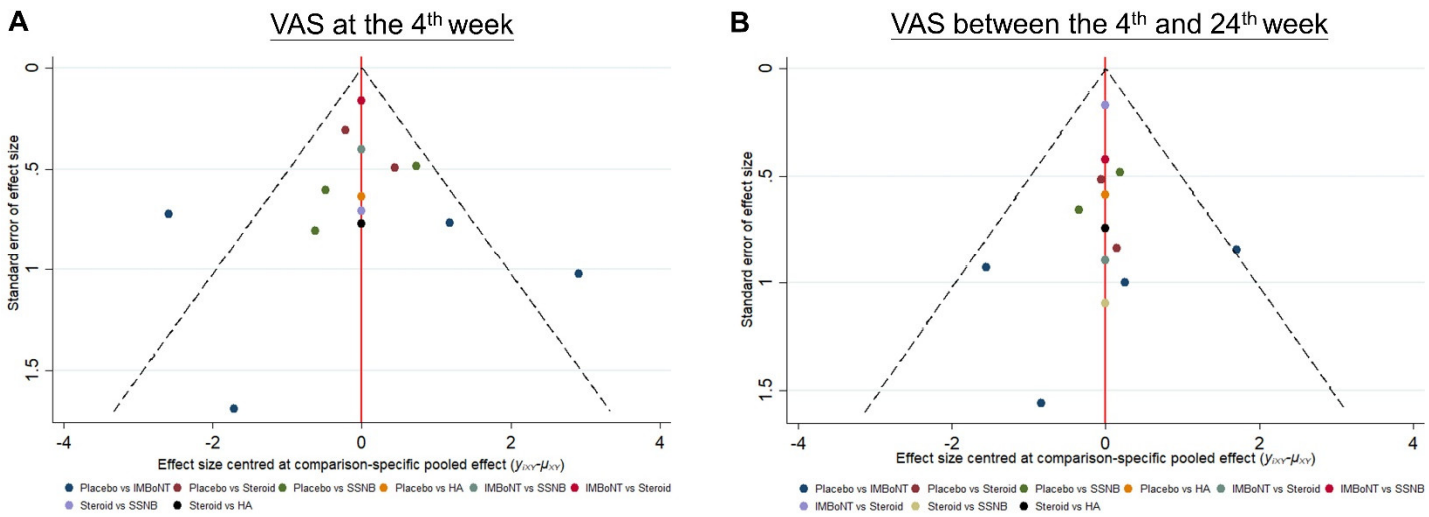


Figure S5 Funnel plots for the effect sizes between different injection therapies in terms of the VAS reduction (A) at the 4th week and (B) between the 4th and 24th weeks. BoNT, botulinum toxin; HA, hyaluronic acid; IB, intra-bursal; IM, intra-muscular; SSNB, suprascapular nerve block; VAS, visual analogue scale.



PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**1**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**1-2**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**2**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**2**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	**2-3**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify	**2**

		additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**2**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**2**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**3**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**3**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**4**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**3**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**3**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**3-4**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**3**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**4**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses;	**4**

		• Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**4**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**12**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**11, 14**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**9-10**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**11**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**6-8**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**11-14**
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**11**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**11, supplemental Table 1,2**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**14**

DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**15**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**16**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**17**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**17**

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.