Supplementary files

Efficacy and safety of oral sprays used to manage dry mouth – Systematic review and network meta-analysis

Journal: Brazilian Dental Journal

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Table S4. PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis.

Table S1. Search strategies applied to the databases

Database	**Search strategy**	**Number of studies identified**
MEDLINE via PubMed	(("Xerostomia"[Mesh] OR Asialia OR Hyposialia OR "Mouth Dryness" OR "Dryness, Mouth" OR "Dry mouth" OR "Mouth, Dry" OR Hyposalivation) AND ("Oral Sprays"[Mesh] OR "Sprays, Oral" OR "Oral Spray" OR "Spray, Oral")) AND ((((((((((randomized controlled trial) OR (randomized controlled trial)) OR (randomized)) OR (placebo)) OR (drug therapy)) OR (randomly)) OR (trial)) OR (groups)) NOT (animals [MeSH] NOT humans [MeSH]))))	16
Cochrane CENTRAL	Xerostomia OR Asialia OR Hyposialia OR "Mouth Dryness" OR "Dryness, Mouth" OR "Dry mouth" OR "Mouth, Dry" OR Hyposalivation in Title Abstract Keyword AND "Oral Sprays" OR "Sprays, Oral" OR "Oral Spray" OR "Spray, Oral" in Title Abstract Keyword	31
Web of Science	"Xerostomia" OR asiatia OR hypossialia OR "Mouth Dryness" OR "Dryness, Mouth" OR "Dry mouth" OR "Mouth, Dry" OR hyposalivation (All Fields) and "Oral Sprays" OR "Sprays, Oral" OR "Oral Spray" OR "Spray, Oral" (All Fields) and "randomized controlled trial" OR "randomized controlled trial" OR randomized OR placebo OR drug AND therapy OR randomly OR trial OR groups (All Fields)	11
Scopus	(TITLE-ABS-KEY (xerostomia OR asialia OR "Mouth Dryness" OR "Dryness, Mouth" OR "Dry mouth" OR "Mouth, Dry" OR hyposalivation) AND TITLE-ABS-KEY ("Oral Sprays" OR "Sprays, Oral" OR "Oral Spray" OR "Spray, Oral") AND TITLE-ABS-KEY ("randomized controlled trial" OR	42

	randomized OR placebo OR "drug therapy" OR randomly OR trial OR groups))	
EMBASE	#1 ‘xerostomia’/exp #2 asialia OR hyposialia OR ‘mouth dryness’ OR ‘dryness, mouth’ OR ‘dry mouth’ OR ‘mouth, dry’ OR hyposalivation #3 #1 OR #2 #4 ‘oral spray’/exp #5 ‘sprays, oral’ OR ‘oral spray’ OR ‘ spray, oral’ #6 #4 OR #5	48
LILACS via BVS	("Xerostomia" OR asialia OR hyposialia OR "Mouth Dryness" OR "Dryness, Mouth" OR "Dry mouth" OR "Mouth, Dry" OR hyposalivation) AND ("Oral Sprays" OR "Sprays, Oral" OR "Oral Spray" OR "Spray, Oral")	1
Clinical Trials	Xerostomia | oral spray	23
WHO ICTRP	XEROSTOMIA AND ORAL SPRAYS	4
ReBEC	Xerostomia | oral spray	0
BDTD	(Todos os campos:XEROSTOMIA OR HIPOSSALIVAÇÃO E Todos os campos:SPRAY ORAL	2

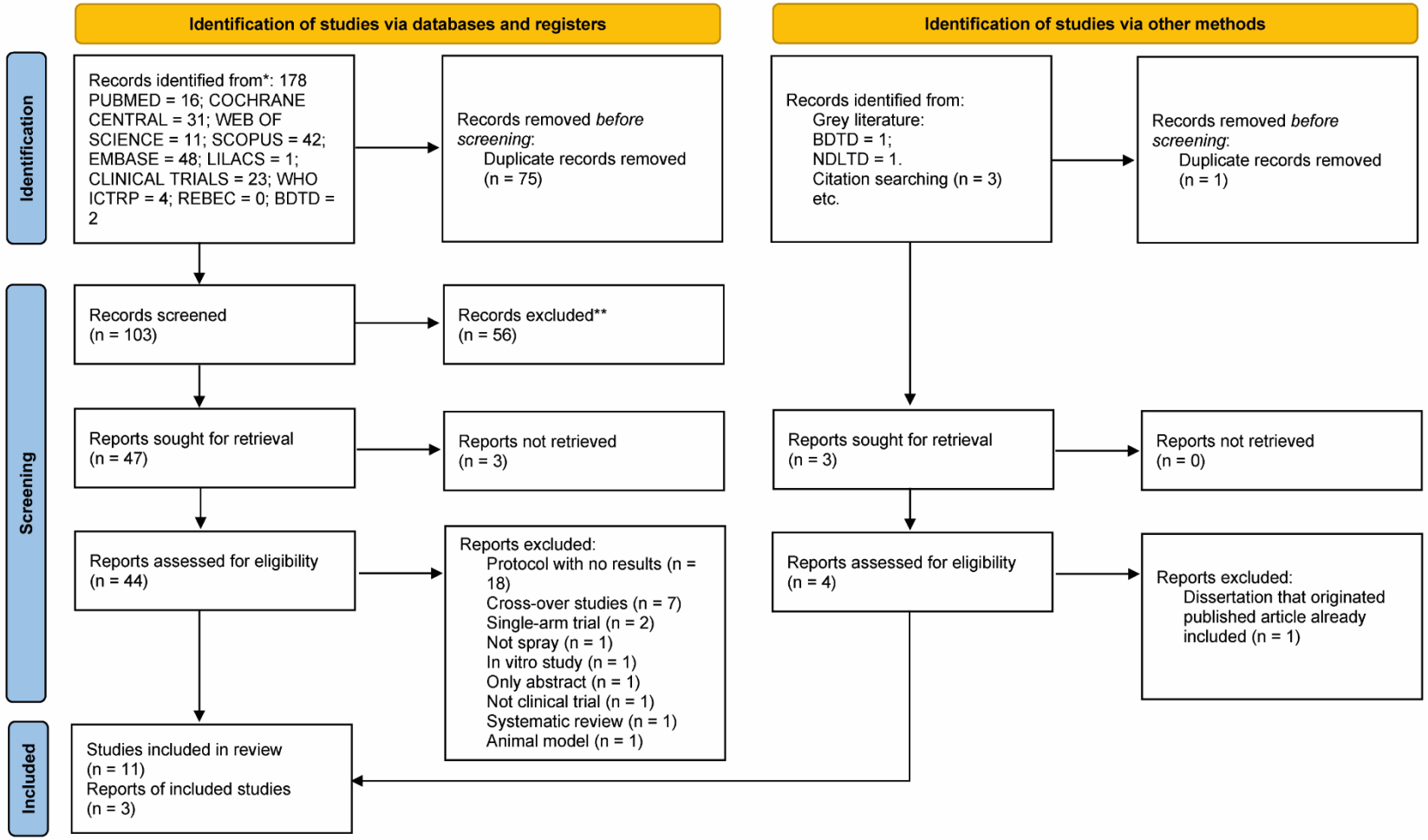
Table S2. Excluded records with reasons

Title	Reason
The Effectiveness of a Thyme and Honey Spray for the Management of Oral Mucositis and Xerostomia in Head and Neck Cancer Patients Undergoing Radiotherapy	Protocol
Clinical Evaluation of the Efficacy of "Hyaluronan" Formulation for Dry Mouth in Sleep Apnea Patients	Protocol
Clinical Evaluation of the Efficacy of "Hyaluronan" Formulation for Dry Mouth in Patients With Type 2 Diabetes	Protocol
Effectiveness of Malic Acid 1% in Patients With Xerostomia Induced by Drugs. Determination of Salivary Mucins and Buffering Capacity	Protocol
Development of a Milk Product Substitution for Patients Suffering From Xerostomia Caused by Psychotropic Drugs and Comparison of Its Efficiency With the Use of Aequasyal (Oxidized Glycerol Triester) Spray	Protocol
Phase 4 Study Evaluating Efficacy, Safety and Acceptability of Treatment With a New Salivary Equivalent Compared to Two Moisturizing Mouth Sprays on the Improvement of Dry Mouth Symptoms and Oral Comfort in Patients With Xerostomia.	Protocol
An Evaluation of the Efficacy of 3M Dry Mouth Moisturizing Spray on the Relief of Dry Mouth Symptoms	Protocol
A Clinical Study to Evaluate the Efficacy of an Experimental Oralbalance Gel, Oral Rinse and Spray Versus Water	Protocol
Use of Biotene Moisturizing Mouth Spray for Xerostomia Associated With Oral Oxybutynin Use	Protocol
Multicenter, Controlled Parallel Groups Trial to Evaluate the Efficacy, Safety and Acceptability of OGT Oromucosal Spray Versus a Saliva Substitute in the Treatment of Xerostomia in Geriatrics	Protocol

Early Phase Study Comparing the Effectiveness of a Dairy Product, Co-developed by Besancon University Hospital and the National School of Dairy Industry (ENIL), With the Reference Treatment Aequasyal® on Dry Mouth Symptoms in Patients Suffering From Xerostomia Caused by Psychotropic Medications.	Protocol
DRYLESS: Randomized Controlled Trial of EVADRY® vs Placebo in the Treatment of Xerostomia in Sjögren's Syndrome	Protocol
A Comparative Trial of Over-the-counter Dry Mouth Remedies for Dry Mouth After Radiation to the Head and Neck	Protocol
Comparison Study of BioXtra Spray and Mouth Rinse in Patient With Radiation-induced Xerostomia	Protocol
Experimental Study to Evaluate the Effectiveness of an Intervention Bundle on Thirst Intensity and Dry Mouth Among Patients of Selected Units	Protocol
Exploratory Study in the Relief of Drug-induced Xerostomia Associated With Hyposialia	Protocol
EVADRY® in the Treatment of Xerostomia in Sjögren's Syndrome	Protocol
The Effectiveness of a Thyme and Honey Spray for Oral Toxicities	Protocol
Evaluation of Two Mouth Sprays for Post-irradiation Xerostomia in Head and Neck Cancer Survivors: a Randomized, Double-blind Clinical Trial	Cross-over design
Duration of Effect of Biotene Spray in Patients With Symptomatic Dry Mouth	Cross-over design
Study of the Effect and Safety of Three New Oral Sprays and a Reference Marketed Oral Spray in the Relief of Drug-induced Xerostomia Associated With Hyposialia	Cross-over design
Clinical evaluation of the efficacy of an intra oral spray for patients with xerostomia	Cross-over design
Effectiveness of Three Different Oral Moisturizers in Palliative Care Patients	Cross-over design
Randomized trial of the efficacy and safety of a new oral spray for drug-induced xerostomia	Cross-over design
Efficacy and safety of a new oral saliva equivalent in the management of xerostomia: a national, multicenter, randomized study	Cross-over design
The Effect of ginger herbal spray on reducing xerostomia in patients with type II diabetes	Single arm trial
Clinical trial of a mucin-containing oral spray for treatment of xerostomia in hospice patients	Single arm trial
The effectiveness of thyme honey for the management of treatment-induced xerostomia in head and neck cancer patients: A feasibility randomized control trial	Not spray

Evaluation of a moisturising micro-gel spray for prevention of cell dryness in oral mucosal cells: an in vitro study and evaluation in a clinical setting.	In vitro study
Treatment of psma-255-actinium therapy induced xerostomia in patients with prostate cancer	Only abstract
Clinical evaluation of a moisturizing spray for xerostomia	Not randomized controlled trial
Effectiveness of an intervention bundle on thirst intensity and dry mouth among patients admitted in intensive care units	Systematic review
Ixeris dentata extract regulates salivary secretion through the activation of aquaporin-5 and prevents diabetes-induced xerostomia	Animal model

Figure S1. Study flow diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Table S3. Characteristics of studies, population, interventions and outcomes

First author, year	Journal	Protocol registration	Declared funding	Population	n	Sex (n male/n female)	Age	Treatment groups (n)	Outcomes
Sweeney, 1997 [18]	Palliative Medicine	-	Nycomed	Patients with advanced malignant disease in a hospice presenting dry mouth symptoms	35	10/25	49 (49-83)	Mucin-containing oral spray Saliva Orthana (15)	Xerostomia, salivary flow
								Spray without mucin (placebo) (16)	
Mouly, 2007a [19]	Drugs Aging	-	Laboratoires Carilene	Old institutionalized patients with xerostomia	41	13/28	84 ± 7	Oxygenated triester glycol oral spray	Xerostomia

								Aqueous electrolyte-containing solution (Salivese®)	
Mouly, 2007b [20]	Journal of Clinical Psychopharmacology	-	Laboratoires Carilene	Patients undergoing long-term psychotropic drug treatment	74	33/41	44 ± 15	Oxygenated triester glycol oral spray	Xerostomia
								Aqueous electrolyte-containing solution (Salivese®)	
Gómez-Moreno, 2013a [21]	Medicina Oral, Patologia Oral y Cirugia Bucal	-	FIS PI10/00932, Ministerio de Ciencia e	Patients with xerostomia induced by	45	20/25	54.3	1% malic acid spray (25)	Xerostomia, NSSF, SSF

			Innovación, Instituto de Salud Carlos III (Spain) and Proyecto OTRI CNT-2856 in cooperation with the University of Granada and Dentaid S.L. (Barcelona, Spain), sponsored by the Regional Government of Andalucía (Spain).	antihypertensive drugs					
							51.8	Placebo (20)	

Gómez-Moreno, 2013b [22]	Depression and Anxiety	NCT01652001	Proyecto de Investigación FIS PI10/00932 from the Ministerio de Ciencia e Innovación and Instituto de Salud Carlos III (Spain). Additionally, support was provided by Proyecto OTRI CNT-2856 in cooperation with the University of	Patients experiencing dry mouth induced by antidepressant drugs	70	10/25	51.2 ± 7.8	1% malic acid spray (35)	Xerostomia, NSSF, SSF

			Granada-Dentaid S.L. (Barcelona, Spain)						
						11/24	48.7 ± 8.3	Placebo (35)	
Gómez-Moreno, 2014 [23]	Gerodontology	NCT01652001	Proyecto de Investigación FIS PI10/00932, Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III (Spain) and Proyecto OTRI CNT-2856 in cooperation with the	Older people presenting dry mouth symptoms	41	7/14	77.8 ± 8.2	1% malic acid spray (21)	Xerostomia, NSSF, SSF

			University of Granada-Dentaid S.L. (Barcelona, Spain), within the framework of the Research Group Pharmacological Research in Dentistry CTS-654, sponsored by the Regional Government of Anda-lucía (Spain).						
						4/16	76.5 ± 7.8	Placebo (20)	

Niklander, 2018 [24]	Journal of Oral Science	-	Andres Bello University (grant: UNABDI-822-15/CB)	Patients with xerostomia 18 years or older	60	8/52	54.6 ± 14.9	1% malic acid spray (31)	Xerostomia, NSSF, SSF, QoL
							49.2 ± 14.9	Placebo (29)	
Bardellini, 2019 [25]	Medicina Oral, Patologia Oral y Cirugia Bucal	-	-	Patients with chronic graft-versus-host disease	28	22/6	45 ± 7.8	1% malic acid spray	Xerostomia, NSSF
							42 ± 7.3	Placebo	
Paterson, 2019 [26]	British Journal of Oral and Maxillofacial Surgery	NCT02687087	Lamellar Biomedical Limited	Patients treating head and neck cancer with radiotherapy	43	39/4	59 (41-78)	ViscoEase^{T} ^{M} oral spray	Xerostomia

								Placebo	
He, 2020 [27]	European Journal of Integrative Medicine	-	None	Patients that received general anesthesia for gynecological tracheal intubation	58	0/58	38.1 ± 11.1	*Phyllanthus emblica* spray	NSSF
							42.0 ± 9.3	Warm water spray (Placebo)	
Muhamed, 2022 [28]	Oral Diseases	NCT04756986	None	Patients with type 2 diabetes mellitus (DM) who experienced xerostomia	52	10/16	47.5 ± 4.3	1% malic acid spray (26)	Xerostomia, NSSF

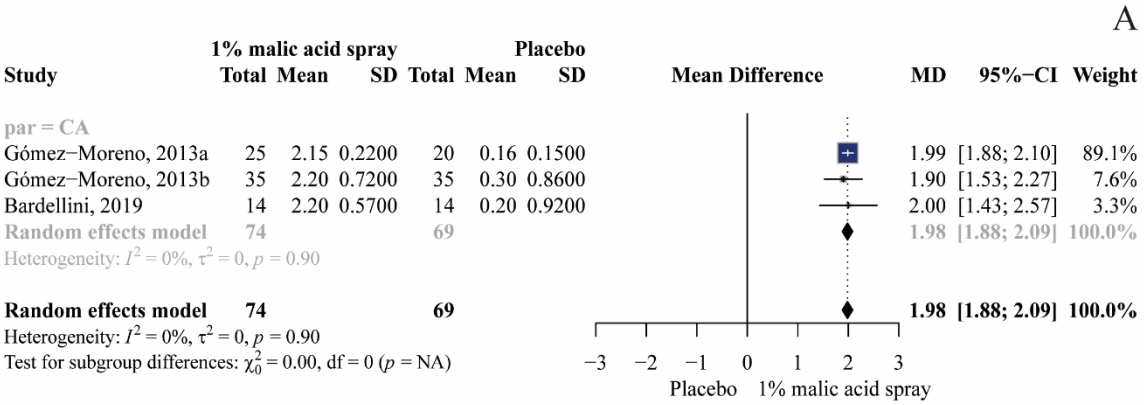
						11/15	46.2 ± 4.2	Placebo (26)	
Oztas, 2022 [29]	Journal of PeriAnesthesia Nursing	-	-	Patients undergoing major abdominal surgery due to gastrointestinal system malignancies	104	19/16	58.02 ± 12.63	Control group (water in a syringe)	Xerostomia
						15/19	61.44 ± 10.39	Intervention group 1 (cold water kept at +4°C in spray bottles, administered	

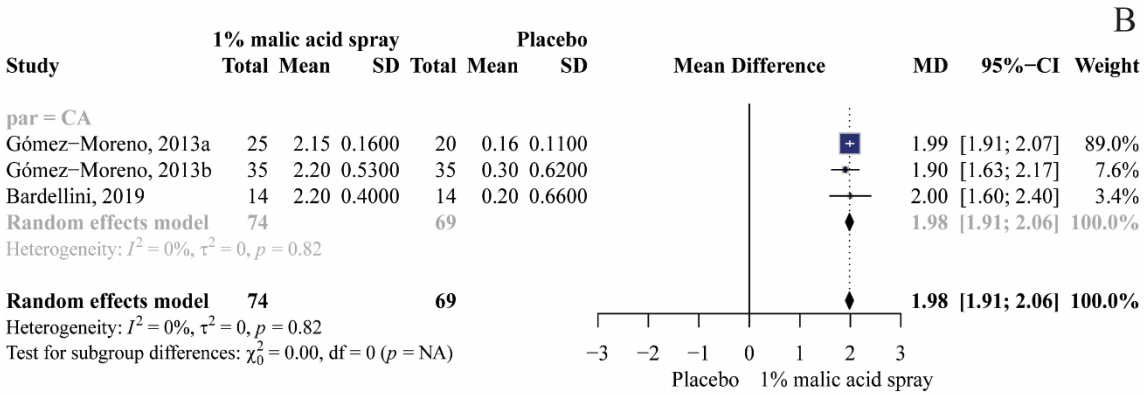
								orally twice hourly	
						19/16	63.48 ± 13.43	Intervention group 2	
Piboonratamakit, 2023 [30]	BMC Oral Health	Thai Clinical Trials Registry (TCTR20190817004)	CU Graduate School Thesis Grant and the Dental Research Fund at the Faculty of Dentistry, Chulalongkorn University. Mid-career research grant from the National	Patients with head and neck cancer who underwent radiotherapy	70	45/25	54.1 ± 13.9 (36-75)	10% trehalose-based oral spray	Xerostomia, NSSF, QoL

			Research Council of Thailand (NRCT), the Ratchadaphis eksomphot Endowment Fund, and the ASEAN Scholarship						
							58.3 ± 14.8 (22-85)	carboxymethyl cellulose (CMC) solution	
Porangaba, 2024 [31]	Current Oncology	REBEC: RBR-9sdf3k	None	Patients treating head and neck cancer with radiotherapy	40	34/6	60.09 ± 8.99 (40-72)	Bioxtra Spray (21)	Xerostomia, NSSF, QoL

							59.94 ± 11.80 (30-69)	Placebo (19)	

Figure S2. Sensitivity analysis of the r coefficient for SD of the change from baseline for xerostomia assessed by DMQ involving the comparison between 1% malic acid spray and placebo. A. r = 0; B. r = 0.5; C. r = 0.9





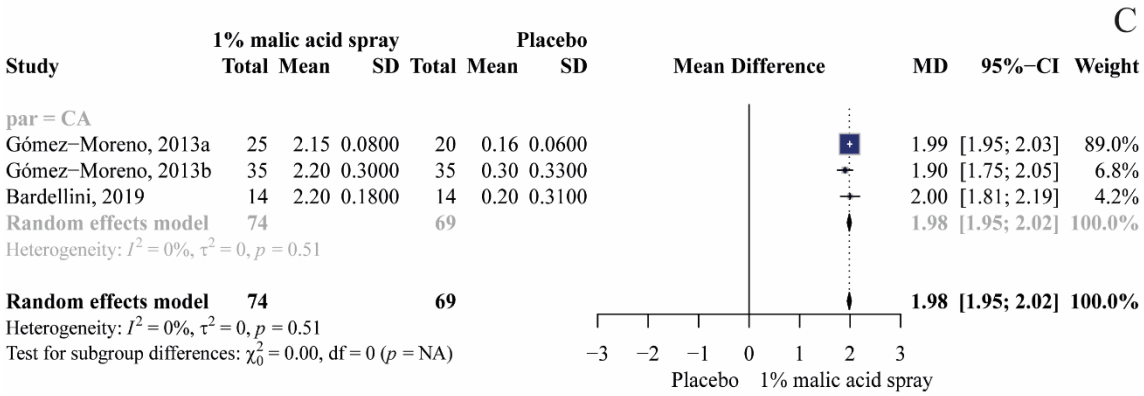
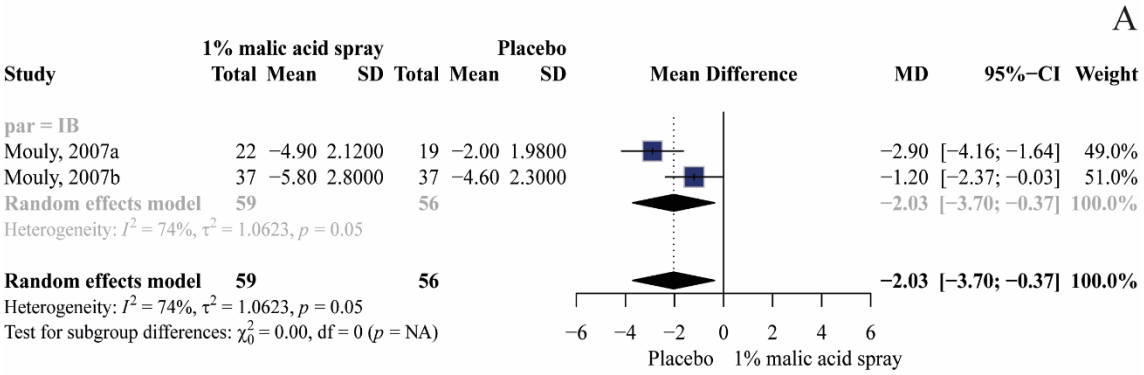
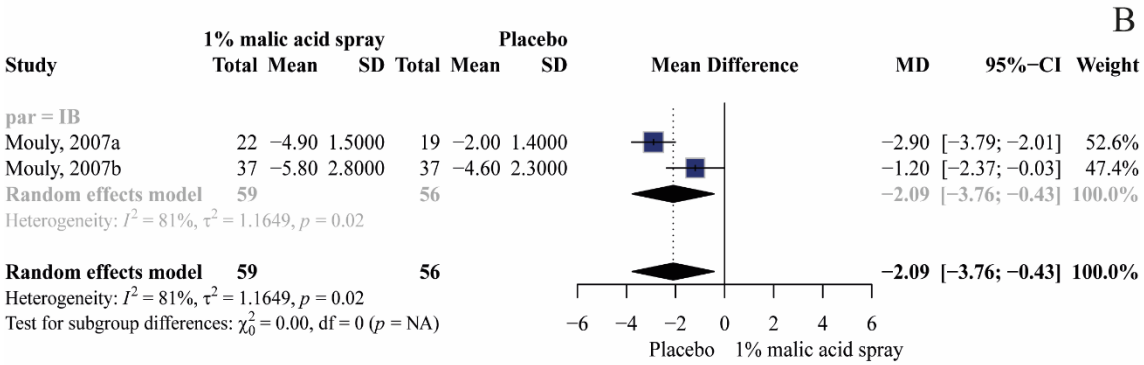


Figure S3. Sensitivity analysis of the r coefficient for SD of the change from baseline for xerostomia assessed by 10 cm VAS involving the comparison between OGT spray and Saliveze. A. r = 0; B. r = 0.5; C. r = 0.9





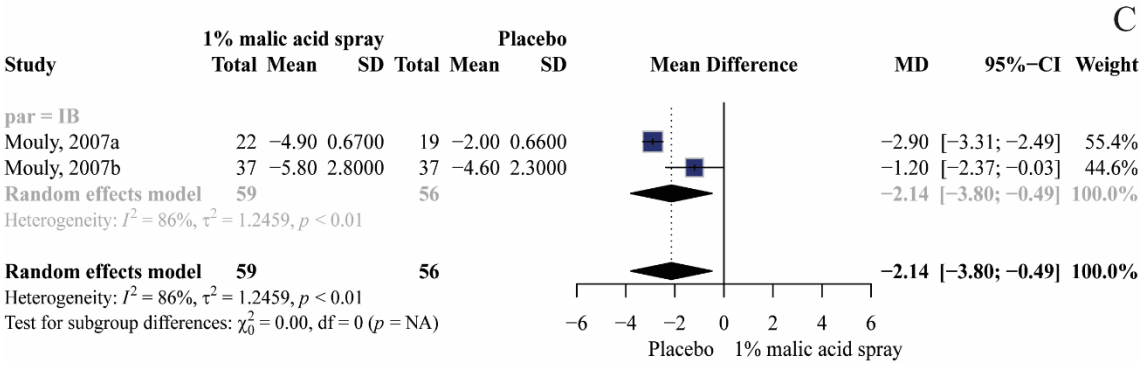
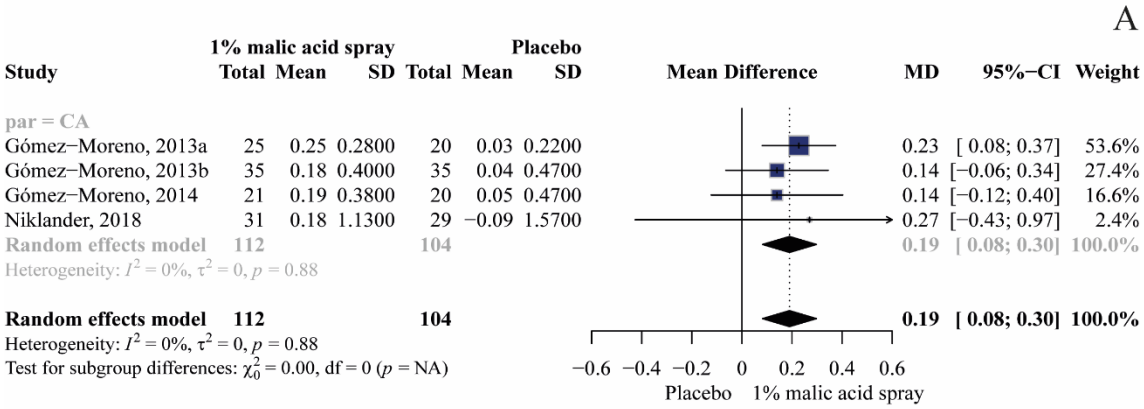
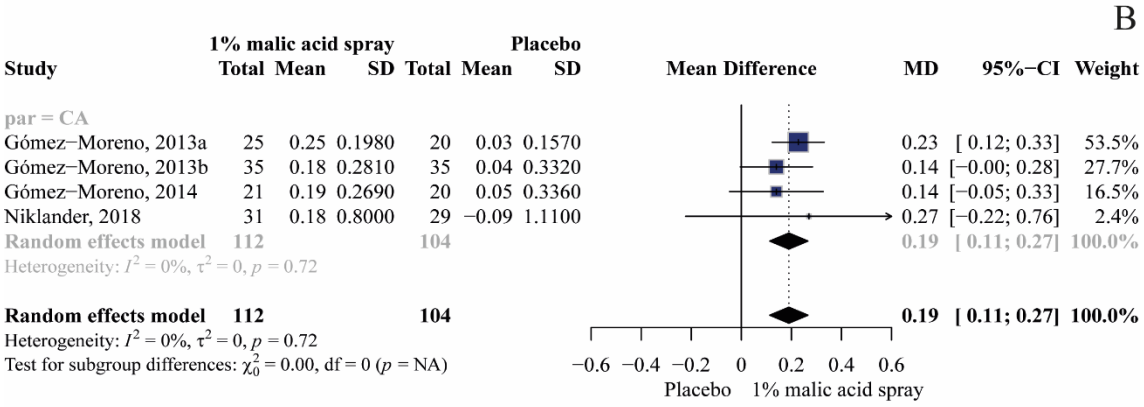


Figure S4. Sensitivity analysis of the r coefficient for SD of the change from baseline for stimulated salivary flow (SSF) involving the comparison between 1% malic acid spray and placebo. A. r = 0; B. r = 0.5; C. r = 0.9





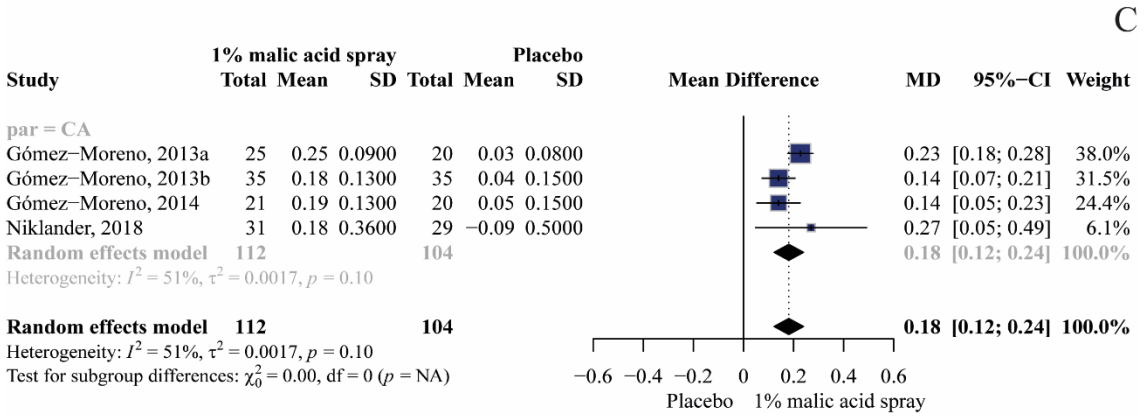


Figure S5. Network configuration

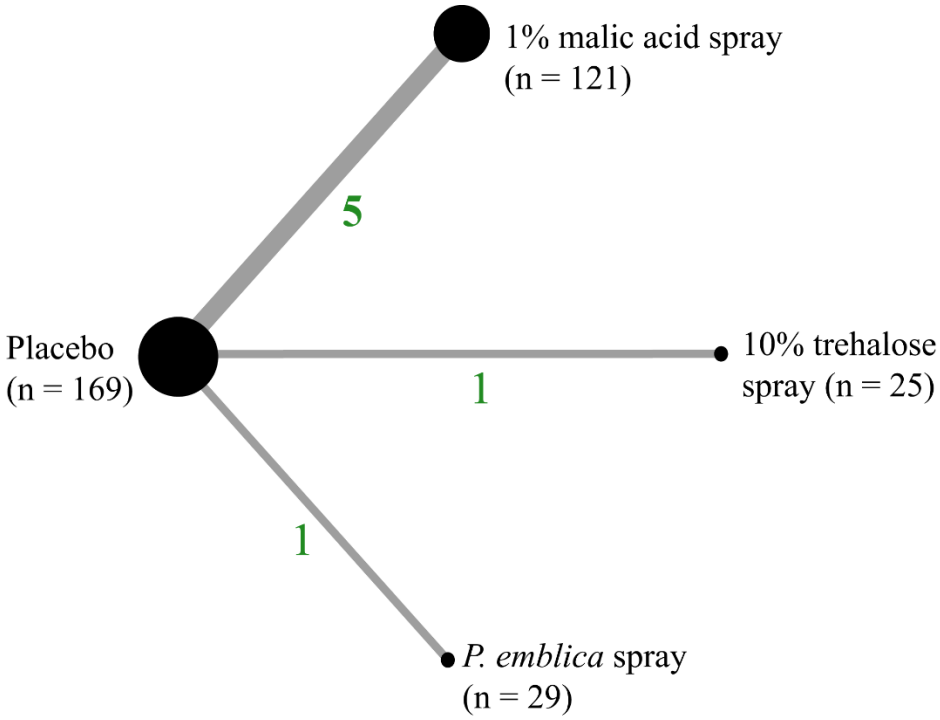


Figure S6. Sensitivity analysis of the r coefficient for SD of the change from baseline for ustimulated salivary flow (USF) involving the comparison between 1% malic acid spray, *P. emblica* spray, trehalose spray and placebo. A. r = 0; B. r = 0.5; C. r = 0.9

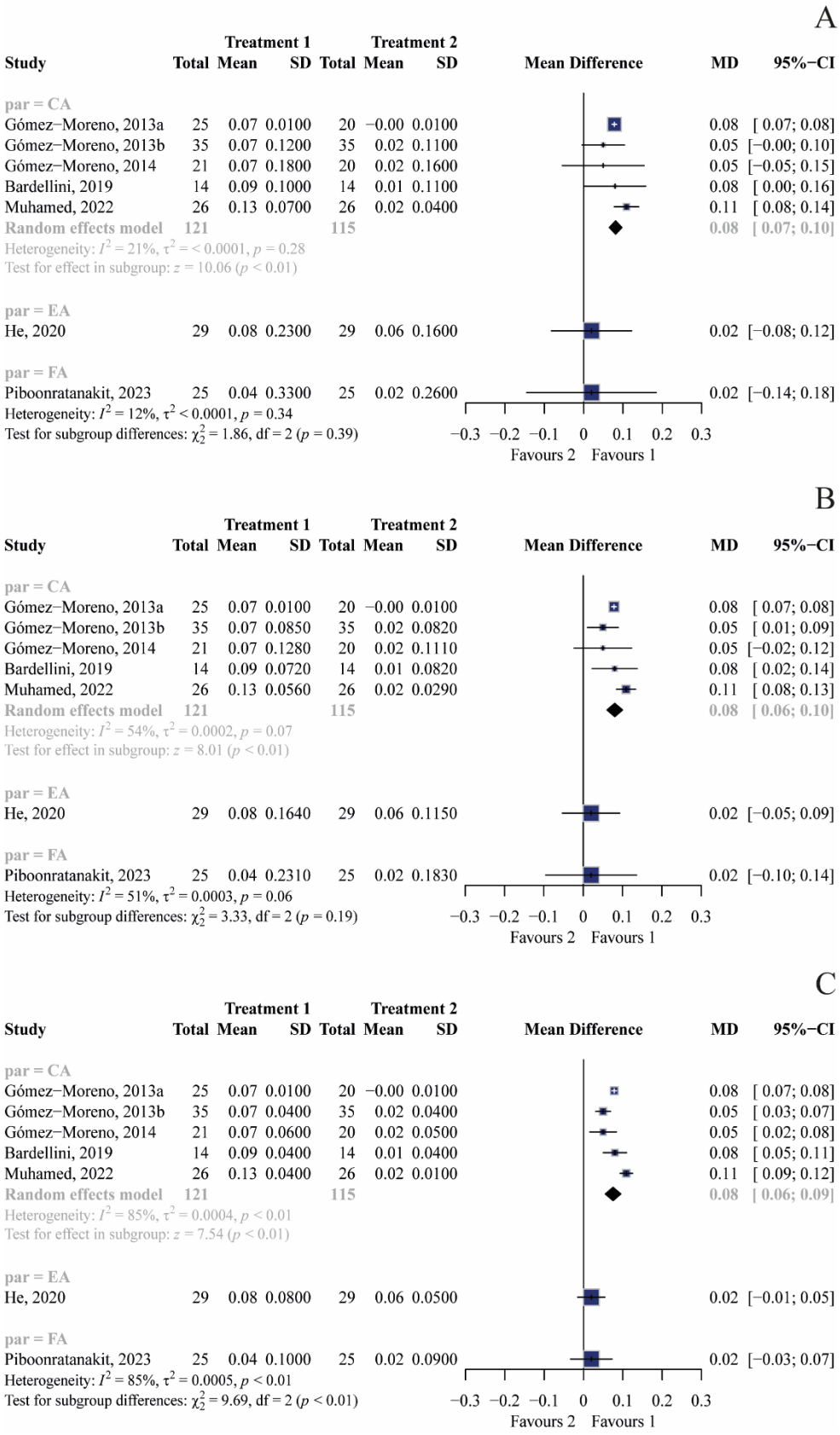
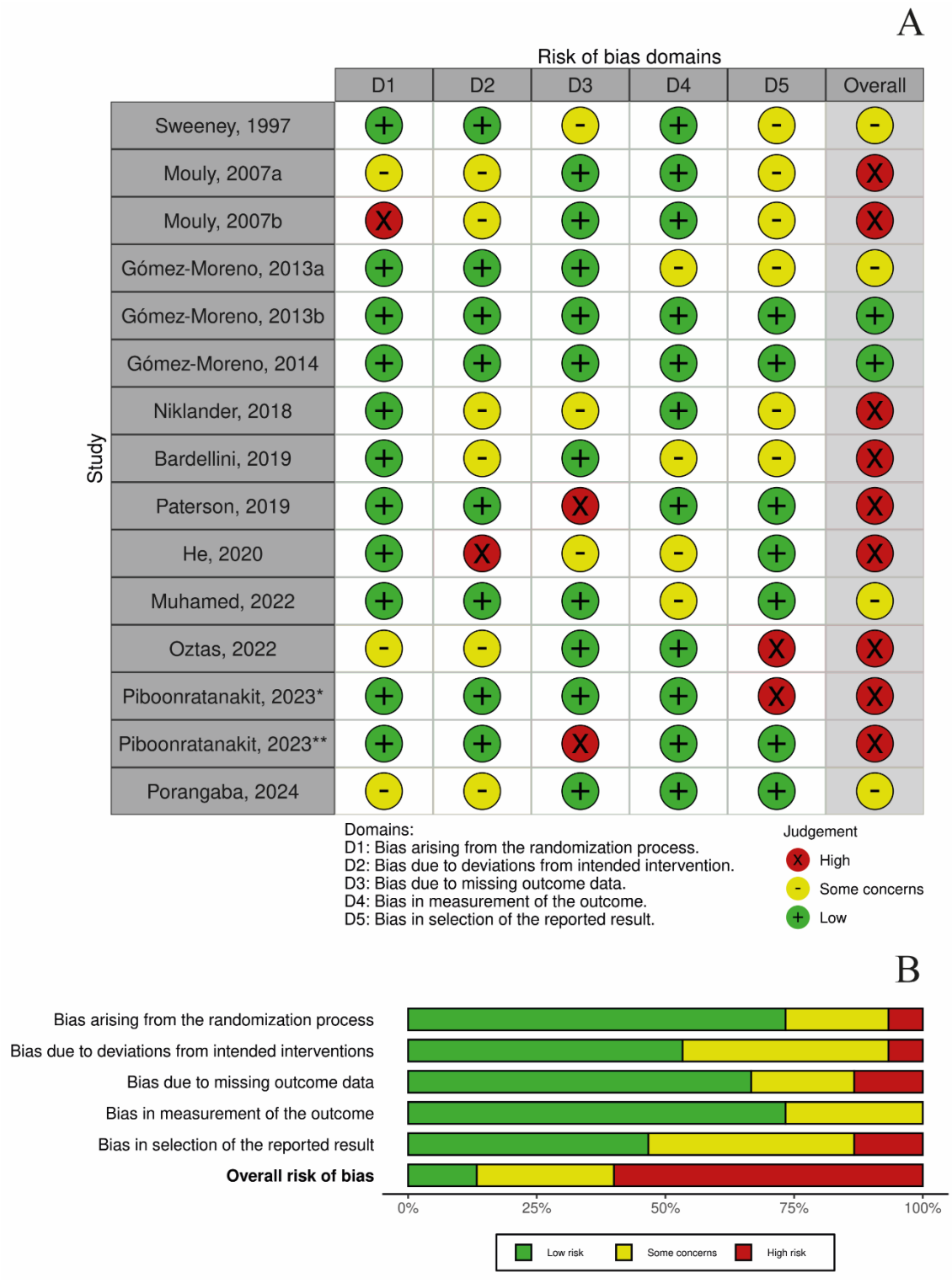


Figure S7. **A.** Risk of bias of each individual study; **B.** Percentage of risk of bias across studies



Piboonratanakit et al. (2023) presented high risk of bias in different domains according to different outcomes: * Result of VAS for dry mouth not reported; ** Missing outcome data for unstimulated salivary flow

Table S4. 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.*	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.	3
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).*	3, 4

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	T1, TS1
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).	4
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.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	5
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.	5
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.*	5
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.*	5
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.	5
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).	5, 6
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.	6, FS1
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	FS5
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.	8, FS5
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.	TS3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	9, FS7
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, 7, 8, 9, F1, F2, F3
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.	F1, F2, F3, F4
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.	6, 7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	9, FS7, T2, T3
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,*	FS2, FS3, FS4, FS6

		alternative choice of prior distributions for Bayesian analyses, and so forth).	
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).	9, 10, 12
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).*	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9, 10, 11, 12
FUNDING			Title page
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.	

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.