Major Mistakes or Errors in the use of Trial Sequential Analysis in Systematic Reviews or Meta-analyses – the METSA Systematic Review

Supplemental material

Christian Gunge Riberholt (0000-0002-6170-186)[1,2,3], Markus Harboe Olsen (0000-0003-0981-0723)[1,3], Joachim Birch Milan (0000-0001-7093-5432)[1], Sigurlaug Hanna Hafliðadóttir (0000-0002-7570-565X)[4], Jeppe Houmann Svanholm (0000-0002-1131-2216)[5], Elisabeth Buck Pedersen (0009-0000-2333-7405)[2], Charles Cin Han Lew (0000-0001-6410-3859)[6,7], Mark Aninakwah Asante (0009-0002-8034-4139)[1], Johanne Marie Pereira Ribeiro[8], Vibeke Wagner (0000-0002-1712-1648)[2,9], Buddheera W.M.B Kumburegama[1], Zheng-Yii Lee (0000-0003-4505-7476)[10,11], Julie Perrine Schaug (0000-0002-1283-4024)[8], Christina Madsen (0009-0002-9764-7144)[8], Christian Gluud (0000-0002-8861-0799)[1,12]

1. Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital − Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark. christian.riberholt@regionh.dk, markus.harboe.olsen@regionh.dk, joachimbirchmilan@hotmail.com, mark.asante@ctu.dk and christian.gluud@ctu.dk
2. Department of Brain and Spinal Cord Injury, Neuroscience Centre, Copenhagen University Hospital − Rigshospitalet, Valdemarsvej 23, 2600 Glostrup, Denmark. vibeke.wagner@regionh.dk, elisabeth2830@gmail.com
3. Department of Neuroanaesthesiology, Neuroscience Centre, Copenhagen University Hospital − Rigshospitalet, Blegdamsvej 9, 2100, Copenhagen, Denmark.
4. Bjarg Rehabilitation Center, Bugðusíðu 1, 603 Akureyri, Iceland. sigurlaughanna@gmail.com
5. Department of Gastrointestinal Surgery, Aalborg University Hospital South, Hobrovej 18-22, 9000 Aalborg, Denmark. jepardy.svanholm@gmail.com.
6. Department of Dietetics and Nutrition, Ng Teng Fong General Hospital, Singapore
7. Faculty of Health and Social Sciences, Singapore Institute of Technology, Singapore
8. Psychiatric Research Unit, Psychiatry Region Zealand, Region Zealand, Fælledvej 6, 4200 Slagelse, Denmark jscha@regionsjaelland.dk, chmads@regionsjaelland.dk
9. Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
10. Department of Anaesthesiology, Faculty of Medicine, University of Malaya, Malaysia
11. Department of Cardiac Anesthesiology & Intensive Care Medicine, Charité Berlin, Germany
12. Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark

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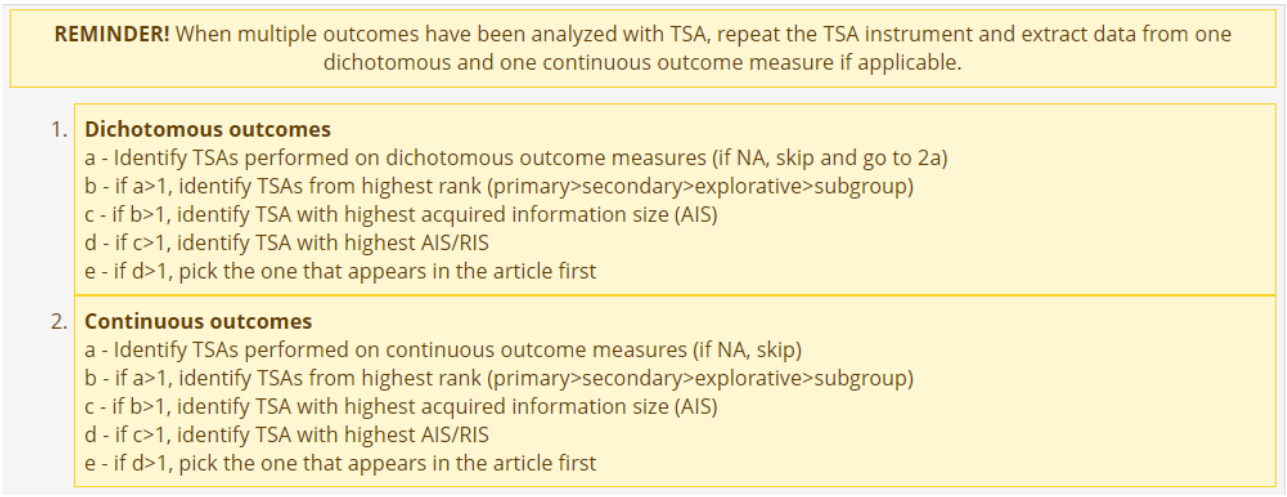
Supplemental Material A. Amendments to the protocol

We have added a decision algorithm to select the trial sequential analyses of interest when more than two are performed in a systematic review. For each type of outcome (dichotomous and continuous), primary outcomes were prioritised over secondary and others. If more than one primary outcome were defined, the outcome with the largest acquired information size (largest number of participants and outcomes) was chosen. If this was equal, the outcome with the highest percentage of acquired information size over the required information size was chosen. If this was equal, we chose the outcome that was first presented in the study. This was decided in the METSA group on the 5th of January 2022 after data was extracted from the first 12 studies.

Figure. Algorithm from the data extraction form in REDCap



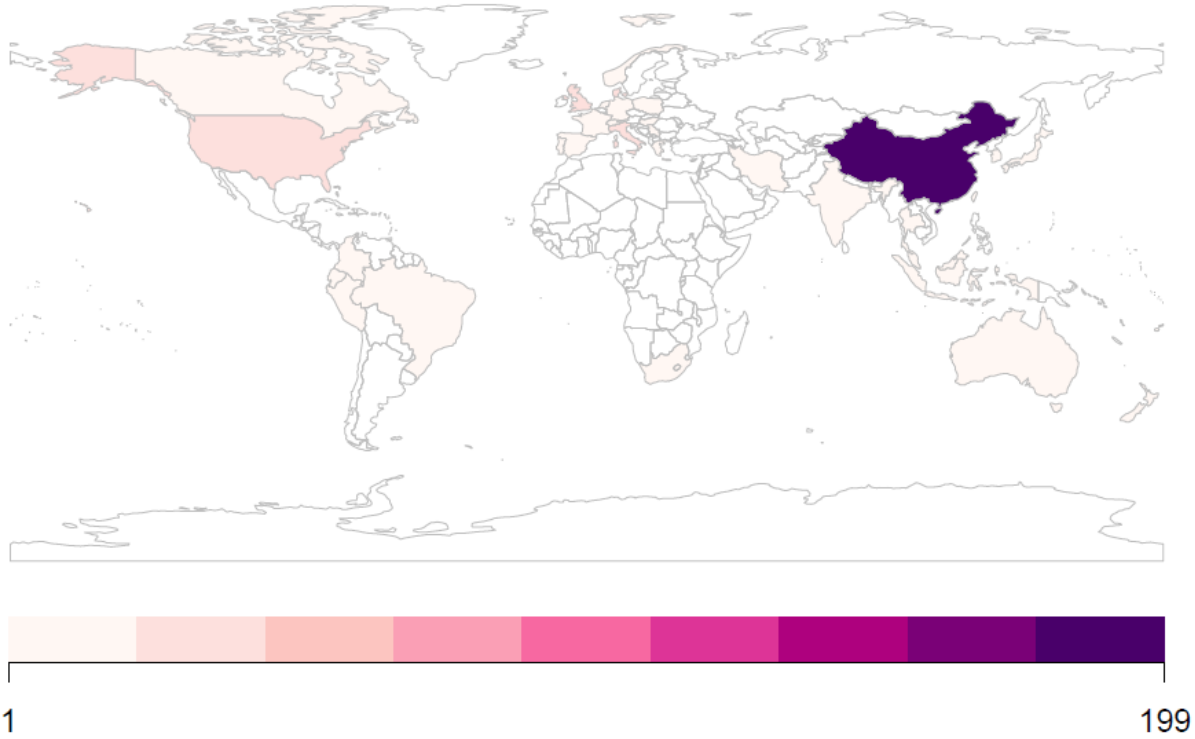
Throughout the extraction process, minor changes were made to the REDCap database to comply with the choices made by the study authors. The largest update was made on the 22nd of June 2022 after extracting data on 260 (48%) of 543 studies. We updated the extraction checklist to contain more generic choices (checkboxes). The extractions and experiences from the choices made in the first 48% of extractions were used as prerequisites for these changes (e.g. choices of outcomes). The updates did not directly affect the ability to answer a certain question but were made to optimise the data extraction and analysis. After all studies were extracted, we adapted the first 48% of the studies to resemble the newly formed extraction checklist.

In the protocol, we initially intended to find all mistakes and errors. As we cannot distinguish between the two, we have decided to change this to “mistakes or errors”. This has been changed in the title and throughout the text.

We have abandoned statistical analysis in the paper. We did mention in the protocol that we would compare systematic reviews with no major mistakes to those with any major mistake. We believe that the current presentation is more in line with the results and still illustrates the challenges with transparency.

Supplemental Figure 1. Distribution of studies across the world, on medical fields and intervention types

Figure 1A. World map



36 out of 195 countries are represented.

	Systematic review	Meta-analysis	Overall
	(N=270)	(N=274)	(N=544)
country			
Australia	5 (1.9%)	1 (0.4%)	6 (1.1%)
Bahrain	6 (2.2%)	2 (0.7%)	8 (1.5%)
Brazil	7 (2.6%)	6 (2.2%)	13 (2.4%)
Canada	6 (2.2%)	6 (2.2%)	12 (2.2%)
China	64 (23.7%)	135 (49.3%)	199 (36.6%)
Colombia	1 (0.4%)	0 (0%)	1 (0.2%)
Denmark	33 (12.2%)	2 (0.7%)	35 (6.4%)
Fiji	1 (0.4%)	0 (0%)	1 (0.2%)
France	1 (0.4%)	3 (1.1%)	4 (0.7%)
Germany	3 (1.1%)	5 (1.8%)	8 (1.5%)
Greece	1 (0.4%)	5 (1.8%)	6 (1.1%)
Hungary	2 (0.7%)	3 (1.1%)	5 (0.9%)
India	11 (4.1%)	7 (2.6%)	18 (3.3%)
Italy	17 (6.3%)	16 (5.8%)	33 (6.1%)
Japan	13 (4.8%)	8 (2.9%)	21 (3.9%)
Malaysia	12 (4.4%)	6 (2.2%)	18 (3.3%)
Netherlands	8 (3.0%)	5 (1.8%)	13 (2.4%)
Norway	1 (0.4%)	0 (0%)	1 (0.2%)
Peru	1 (0.4%)	0 (0%)	1 (0.2%)
Poland	1 (0.4%)	0 (0%)	1 (0.2%)
Portugal	1 (0.4%)	2 (0.7%)	3 (0.6%)
Serbia	1 (0.4%)	0 (0%)	1 (0.2%)
Singapore	1 (0.4%)	0 (0%)	1 (0.2%)
South Africa	2 (0.7%)	0 (0%)	2 (0.4%)
South Korea	1 (0.4%)	3 (1.1%)	4 (0.7%)
Spain	1 (0.4%)	5 (1.8%)	6 (1.1%)
Switzerland	14 (5.2%)	5 (1.8%)	19 (3.5%)
Taiwan	11 (4.1%)	8 (2.9%)	19 (3.5%)
Thailand	1 (0.4%)	0 (0%)	1 (0.2%)
United Kingdom	29 (10.7%)	16 (5.8%)	45 (8.3%)
United States	14 (5.2%)	20 (7.3%)	34 (6.3%)
Ecuador	0 (0%)	1 (0.4%)	1 (0.2%)
Indonesia	0 (0%)	1 (0.4%)	1 (0.2%)
Iran	0 (0%)	1 (0.4%)	1 (0.2%)
New Zealand	0 (0%)	1 (0.4%)	1 (0.2%)
Qatar	0 (0%)	1 (0.4%)	1 (0.2%)

36 out of 195 countries are represented. The map shows through colour coding the number of studies included. The table shows the exact numbers from each country based on systematics reviews, meta-analysis and overall.

Figure 1B. Number of studies with Trial Sequential Analysis included within different medical specialities.

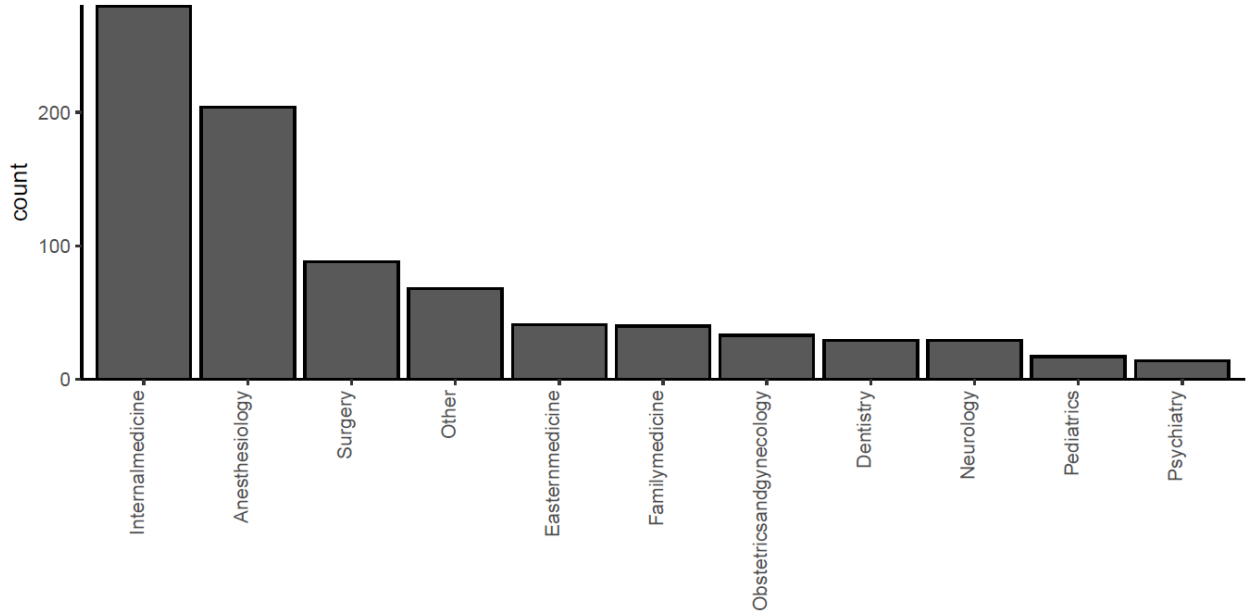
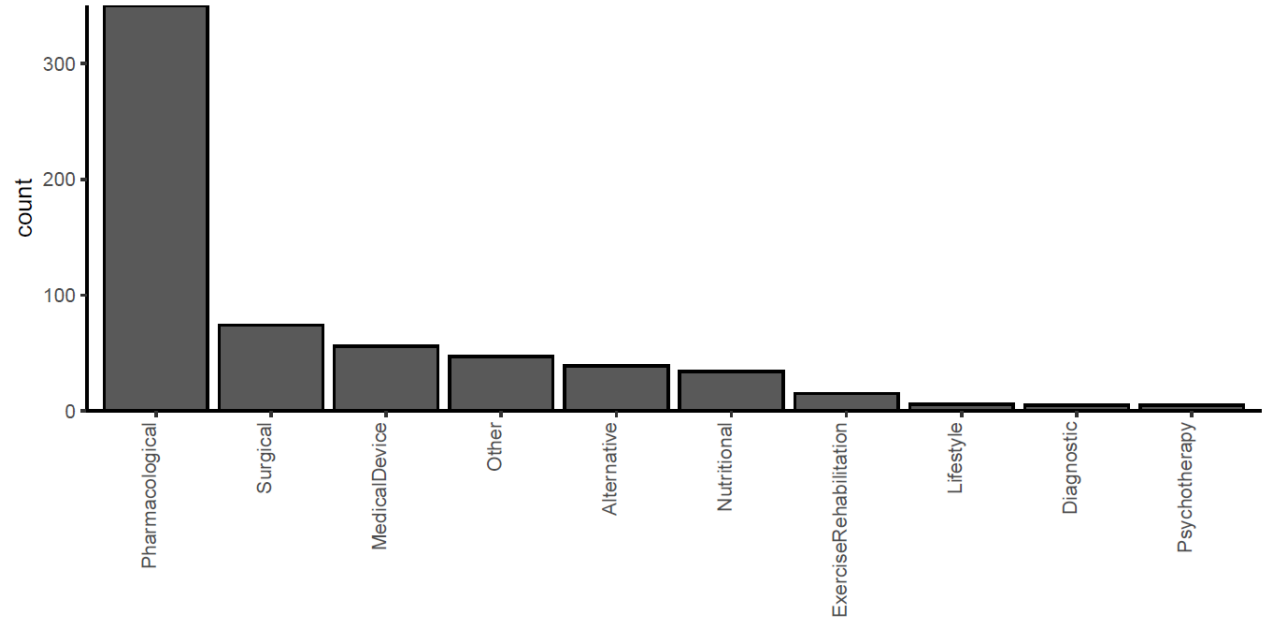


Figure 1C. Number of studies with Trial Sequential Analysis included within different types of interventions.



Supplemental Table 1. PRISMA and PRISMA-S Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 7 to8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 10
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplemental Table 2 and page 10
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 10
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 10 to 11
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 10 to 11
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 10 to 11
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 11
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 11
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 11

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 12
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1 Page 13ff
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplemental Table 3
Study characteristics	17	Cite each included study and present its characteristics.	NA
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 13ff
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 13ff
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 19
	23b	Discuss any limitations of the evidence included in the review.	Page 23f

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Page 23f
	23d	Discuss implications of the results for practice, policy, and future research.	Page 23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 9
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 9
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplemental Material A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 26
Competing interests	26	Declare any competing interests of review authors.	Page 25
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 25 Supplemental

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

For more information, visit: http://www.prisma-statement.org/

PRISMA-S Checklist

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	P9
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	P9
Study registries	3	List any study registries searched.	NA
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	NA
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	P10
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	NA
Other methods	7	Describe any additional information sources or search methods used.	NA
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Supplement
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	P9
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	NA
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	NA
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	P10
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	P10
PEER REVIEW			
Peer review	14	Describe any search peer review process.	P27
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	Figure 1 Supplement
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	P10

Supplemental Table 2. Search strategy

Search strategies for
'Trial Sequential Analysis'
(C Gunge Riberholt)

Searches performed 9 July 2021

Total number of records identified:	**2109 records**
Number of duplicates excluded:	**12 records**
Number of records in final list:	**2097 records**
Number of new records sent to authors:	**825 records**

Cochrane Database of Systematic Reviews (2021; Issue 7) in the Cochrane Library (253 Cochrane Reviews, 95 Cochrane Protocols)
#1 ("trial sequential" and (analys* or (monitoring next boundar*))) or (cumulative next meta-analys*)

MEDLINE Ovid (2004 to July 2021) (1761 hits)
1. ((trial sequential and (analys* or monitoring boundar*)) or cumulative meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2. limit 1 to yr="2004 -Current"

Supplemental Table 3. Studies excluded in full text with reason

Study		Reason for exclusion
1	Osterlind J, Gerhardsson J, Myrberg T. Critical care transition programs on readmission or death: a systematic review and meta-analysis. *Acta Anaesthesiol Scand* 2020; **64**:870–83. doi:10.1111/aas.13591	Less than two randomised clinical trials in the forest plot and TSA
2	Song G, Zhang J, Wang X, *et al.* Usefulness of speckle-tracking echocardiography for early detection in children with Duchenne muscular dystrophy: a meta-analysis and trial sequential analysis. *Cardiovasc Ultrasound* 2020;**18**:26. doi:10.1186/s12947-020-00209-y	Less than two randomised clinical trials in the forest plot and TSA
3	XX Y, MQ L, YF Z, *et al.* Associations of KCNQ1 Polymorphisms with the Risk of Type 2 Diabetes Mellitus: an Updated Meta-Analysis with Trial Sequential Analysis. *J Diabetes Res* 2020;**2020**:7145139. doi:10.1155/2020/7145139	Less than two randomised clinical trials in the forest plot and TSA
4	Chen W, Li H, Chen Y, *et al.* Bone-Patellar Tendon-Bone Autografts Versus Hamstring Autografts Using the Same Suspensory Fixations in ACL Reconstruction: a Systematic Review and Meta-analysis. *Orthop J Sport Med* 2019;**7**:2325967119885314. doi:10.1177/2325967119885314	Both observational and RCT in TSA
5	Huang G, Jiang H, Lin Y, *et al.* Prognostic value of plasma fibrinogen in hepatocellular carcinoma: a meta-analysis. *Cancer Manag Res* 2018;**10**:5027–41. doi:10.2147/CMAR.S175780	Less than two randomised clinical trials in the forest plot and TSA
6	Li Y, Du M, Wang S, *et al.* Clinicopathological Implication of Long Non-Coding RNAs SOX2 Overlapping Transcript and Its Potential Target Gene Network in Various Cancers. *Front Genet* 2019;**10**:1375. doi:10.3389/fgene.2019.01375	Less than two randomised clinical trials in the forest plot and TSA
7	Zhu M, Qiu S, Zhang X, *et al.* The associations between CYP24A1 polymorphisms and cancer susceptibility: a meta-analysis and trial sequential analysis. *Pathol Res Pract* 2018;**214**:53–63. doi:10.1016/j.prp.2017.11.014	Less than two randomised clinical trials in the forest plot and TSA
8	Wang X, Huang Y, Li L, *et al.* Assessment of performance of the Gail model for predicting breast cancer risk: a systematic review and meta-analysis with trial sequential analysis. *Breast cancer Res* 2018;**20**:18. doi:10.1186/s13058-018-0947-5	Less than two randomised clinical trials in the forest plot and TSA
9	Jiang W, Shi L, Liu H, *et al.* Systematic review and meta-analysis of the genetic association between protamine polymorphism and male infertility. *Andrologia* 2018;**50**:e12990. doi:10.1111/and.12990	Less than two randomised clinical trials in the forest plot and TSA
10	Cao Z, Wei L, Zhu W, *et al.* Meta-analysis of CDKN2A methylation to find its role in prostate cancer development and progression, and also to find the effect of CDKN2A expression on disease-free survival (PRISMA). *Medicine (Baltimore)* 2018;**97**:e0182. doi:10.1097/MD.0000000000010182	Less than two randomised clinical trials in the forest plot and TSA
11	AK K, SL N, Nizamuddin J, *et al.* Clinical Study Designs and Sources of Error in Medical Research. *J Cardiothorac Vasc Anesth* 2018;**32**:2789–801. doi:10.1053/j.jvca.2018.02.009	Wrong study design
12	Chen L, Wang Y, Zhang T, *et al.* Utility of posaconazole therapeutic drug monitoring and assessment of plasma concentration threshold for effective prophylaxis of invasive fungal infections: a meta-analysis with trial sequential analysis. *BMC Infect Dis* 2018;**18**:155. doi:10.1186/s12879-018-3055-3	Less than two randomised clinical trials in the forest plot and TSA
13	Qiao W, Liu H, Liu R, *et al.* Prognostic and clinical significance of histone deacetylase 1 expression in breast cancer: a meta-analysis. *Clin Chim acta* 2018;**483**:209–15. doi:10.1016/j.cca.2018.05.005	Less than two randomised clinical trials in the forest plot and TSA

14	JS K, Qiu S, Cheng Y, *et al.* Associations between three common single nucleotide polymorphisms (rs266729, rs2241766, and rs1501299) of ADIPOQ and cardiovascular disease: a meta-analysis. *Lipids Health Dis* 2018;**17**:126. doi:10.1186/s12944-018-0767-8	Less than two randomised clinical trials in the forest plot and TSA
15	He H, WT C, YH Z, *et al.* Lack of associations between the FTO polymorphisms and gestational diabetes: a meta-analysis and trial sequential analysis. *Gene* 2018;**677**:169–75. doi:10.1016/j.gene.2018.07.064	Less than two randomised clinical trials in the forest plot and TSA
16	Zhang J, Zhang H, Xiu Y, *et al.* Prognostic Significance of P16INK4a Expression in Penile Squamous Cell Carcinoma: a Meta-Analysis with Trial Sequential Analysis. *Biomed Res Int* 2018;**2018**:8345893. doi:10.1155/2018/8345893	Less than two randomised clinical trials in the forest plot and TSA
17	Naing C, NH H, W ST, *et al.* Association of tumour necrosis factor-alpha (TNF-alpha) gene polymorphisms (-308 G>A and -238 G>A) and the risk of severe dengue: a meta-analysis and trial sequential analysis. *Plos ONE [electronic Resour* 2018;**13**:e0205413. doi:10.1371/journal.pone.0205413	Less than two randomised clinical trials in the forest plot and TSA
18	Meng J, Wang S, Zhang M, *et al.* TP73 G4C14-A4T14 polymorphism and cancer susceptibility: evidence from 36 case-control studies. *Biosci Rep* 2018;**38**. doi:10.1042/BSR20181452	Less than two randomised clinical trials in the forest plot and TSA
19	Qi M, Xiong X. Promoter hypermethylation of RARbeta2, DAPK, hMLH1, p14, and p15 is associated with progression of breast cancer: a PRISMA-compliant meta-analysis. *Medicine (Baltimore)* 2018;**97**:e13666. doi:10.1097/MD.0000000000013666	Less than two randomised clinical trials in the forest plot and TSA
20	Jiang Y, Li W, Lu J, *et al.* Association between PRKAA1 rs13361707 T>C polymorphism and gastric cancer risk: evidence based on a meta-analysis. *Medicine (Baltimore)* 2018;**97**:e0302. doi:10.1097/MD.0000000000010302	Less than two randomised clinical trials in the forest plot and TSA
21	Yan L, Gu Y, Luan T, *et al.* Associations between serum vitamin D and the risk of female reproductive tumors: a meta-analysis with trial sequential analysis. *Medicine (Baltimore)* 2018;**97**:e0360. doi:10.1097/MD.0000000000010360	Less than two randomised clinical trials in the forest plot and TSA
22	Yuan Y, Wang X, Ren L, *et al.* Associations between interleukin-10 gene polymorphisms and systemic lupus erythematosus risk: a meta-analysis with trial sequential analysis. *Clin Exp Rheumatol* 2019;**37**:242–53.NS -	Less than two randomised clinical trials in the forest plot and TSA
23	Singh V, SK B, DVS S, *et al.* SNPs in ERCC1, ERCC2, and XRCC1 genes of the DNA repair pathway and risk of male infertility in the Asian populations: association study, meta-analysis, and trial sequential analysis. *J Assist Reprod Genet* 2019;**36**:79–90. doi:10.1007/s10815-018-1339-6	Less than two randomised clinical trials in the forest plot and TSA
24	MX L, BB L, Li F, *et al.* Roles of Cyclooxygenase-2 gene -765G>C (rs20417) and -1195G>A (rs689466) polymorphisms in gastric cancer: a systematic review and meta-analysis. *Gene* 2019;**685**:125–35. doi:10.1016/j.gene.2018.10.077	Less than two randomised clinical trials in the forest plot and TSA
25	RK M, MA K, Hussain A, *et al.* A trial sequential meta-analysis of TNF-alpha -308G>A (rs800629) gene polymorphism and susceptibility to colorectal cancer. *Biosci Rep* 2019;**39**. doi:10.1042/BSR20181052	Less than two randomised clinical trials in the forest plot and TSA
26	Hoshijima H, Mihara T, Denawa Y, *et al.* Airtraq R is superior to the Macintosh laryngoscope for tracheal intubation: systematic review with trial sequential analysis. *Am J Emerg Med* 2019;**37**:1367–8. doi:10.1016/j.ajem.2018.12.018	Less than two randomised clinical trials in the forest plot and TSA
27	Li Y, Liu B, Jing X, *et al.* Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis. *Cardiovasc Diabetol* 2019;**18**:3. doi:10.1186/s12933-019-0807-3	Less than two randomised clinical trials in the forest plot and TSA
28	ML G, HS M, AD M, *et al.* Restrictive Versus Liberal Fluid Regimens in Patients Undergoing Pancreaticoduodenectomy: a Systematic Review and	Both observational and RCT in TSA

	Meta-Analysis. *J Gastrointest Surg* 2019;**23**:1250–65. doi:10.1007/s11605-018-04089-6	
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31	Chen Y, Hu Y, Song Z. The association between interleukin-6 gene -174G/C single nucleotide polymorphism and sepsis: an updated meta-analysis with trial sequential analysis. *BMC Med Genet* 2019;**20**:35. doi:10.1186/s12881-019-0766-2	Less than two randomised clinical trials in the forest plot and TSA
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37	Zhu M, Tan Z, Luo Z, *et al.* Association of the vitamin D metabolism gene GC and CYP27B1 polymorphisms with cancer susceptibility: a meta-analysis and trial sequential analysis. *Biosci Rep* 2019;**39**. doi:10.1042/BSR20190368	Less than two randomised clinical trials in the forest plot and TSA
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44	Baloyiannis I, Perivoliotis K, Ntellas P, *et al.* Comparing the safety, efficacy, and oncological outcomes of laparoscopic and open colectomy in transverse colon cancer: a meta-analysis. *Int J Colorectal Dis* 2020;**35**:373–86. doi:10.1007/s00384-020-03516-y	Less than two randomised clinical trials in the forest plot and TSA
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	perioperative medicine. *Br J Anaesth* 2021;**126**:903–11. doi:10.1016/j.bja.2021.01.004	
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60	Perivoliotis K, Baloyiannis I, Sarakatsianou C, *et al.* Comparing the efficacy and safety of laparoscopic and robotic adrenalectomy: a meta-analysis and trial sequential analysis. *Langenbecks Arch Surg* 2020;**405**:125–35. doi:10.1007/s00423-020-01860-9	Less than two randomised clinical trials in the forest plot and TSA
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66	Chen G, Hu C, Song Y, *et al.* Relationship Between the ApaI (rs7975232), BsmI (rs1544410), FokI (rs2228570), and TaqI (rs731236) Variants in the Vitamin D Receptor Gene and Urolithiasis Susceptibility: an Updated Meta-Analysis and Trial Sequential Analysis. *Front Genet* 2020;**11**:234. doi:10.3389/fgene.2020.00234	Less than two randomised clinical trials in the forest plot and TSA
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69	Bassi F, Cicciu M, R DL, *et al.* Piezoelectric bone surgery compared with conventional rotary instruments in oral surgery and implantology: summary and consensus statements of the International Piezoelectric Surgery Academy Consensus Conference 2019. *Int J oral Implantol* 2020;**13**:235–9.NS -	Wrong study design
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75	Pergialiotis V, Fanaki M, Bellos I, *et al.* Evaluation of umbilical cord entanglement as a predictive factor of adverse pregnancy outcomes: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2019;**243**:150–7. doi:10.1016/j.ejogrb.2019.10.038	Less than two randomised clinical trials in the forest plot and TSA
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77	Zhong D, Wu C, Bai J, *et al.* Comparative diagnostic efficacy of serum Krebs von den Lungen-6 and surfactant D for connective tissue disease-associated interstitial lung diseases: a meta-analysis. *Medicine (Baltimore)* 2020;**99**:e19695. doi:10.1097/MD.0000000000019695	Less than two randomised clinical trials in the forest plot and TSA
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79	Wu Z, Zhang S, Xu J, *et al.* Norepinephrine vs Vasopressin: which Vasopressor Should Be Discontinued First in Septic Shock? A Meta-Analysis. *Shock* 2020;**53**:50–7. doi:10.1097/SHK.0000000000001345	Less than two randomised clinical trials in the forest plot and TSA
80	Liu B, Li Y, Liu Y, *et al.* Association of epicardial adipose tissue with non-alcoholic fatty liver disease: a meta-analysis. *Hepatol Int* 2019;**13**:757–65. doi:10.1007/s12072-019-09972-1	Less than two randomised clinical trials in the forest plot and TSA
81	Pergialiotis V, Bellos I, Hatziagelaki E, *et al.* Progestogens for the prevention of preterm birth and risk of developing gestational diabetes mellitus: a meta-analysis. *Am J Obstet Gynecol* 2019;**221**:429-436.e5. doi:10.1016/j.ajog.2019.05.033	Less than two randomised clinical trials in the forest plot and TSA
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86	Zhao B, Hu L, Dong Y, *et al.* The Effect of Magnesium Intake on Stroke Incidence: a Systematic Review and Meta-Analysis With Trial Sequential Analysis. *Front Neurol [electronic Resour* 2019;. **10**:852. doi:10.3389/fneur.2019.00852	Less than two randomised clinical trials in the forest plot and TSA
87	Wang Y, Huang S, Wu X, *et al.* Correlation between MCP-1-2518A/G polymorphism and the risk of Alzheimer's disease. *J Neural Transm* 2018;**125**:1781–6. doi:10.1007/s00702-018-1936-7	Less than two randomised clinical trials in the forest plot and TSA
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93	Han S, Huang T, Li W, *et al.* Association Between Hypoxia-Inducible Factor-2alpha (HIF-2alpha) Expression and Colorectal Cancer and Its Prognostic Role: a Systematic Analysis. *Cell Physiol Biochem* 2018;**48**:516–27. doi:10.1159/000491806	Less than two randomised clinical trials in the forest plot and TSA
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95	Li Q, Ma C, Zhang Z, *et al.* Association between cyclooxygenase-2 (COX-2) 8473 T > C polymorphism and cancer risk: a meta-analysis and trial sequential analysis. *BMC Cancer* 2018;**18**:847. doi:10.1186/s12885-018-4753-3	Less than two randomised clinical trials in the forest plot and TSA
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100	YS R, LF L, Peng T, *et al.* The effect of milrinone on mortality in adult patients who underwent CABG surgery: a systematic review of randomized clinical trials with a meta-analysis and trial sequential analysis. *BMC Cardiovasc Disord* 2020;**20**:328. doi:10.1186/s12872-020-01598-8	Only forest plot, not Trial Sequential Analysis
101	Capion T, Lilja-Cyron A, Juhler M, *et al.* Prompt closure versus gradual weaning of external ventricular drainage for hydrocephalus in adult patients with aneurysmal subarachnoid haemorrhage: a systematic review. *BMJ Open* 2020;**10**:e040722. doi:10.1136/bmjopen-2020-040722	Less than two randomised clinical trials in the forest plot and TSA
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104	Hu Y, Xu K, Jiang L, *et al.* Associations between Three CTLA-4 Polymorphisms and Hashimoto's Thyroiditis Risk: an Updated Meta-Analysis with Trial Sequential Analysis. *Genet Test Mol Biomarkers* 2018;**22**:224–36. doi:10.1089/gtmb.2017.0243	Less than two randomised clinical trials in the forest plot and TSA
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109	H-L C, M-L Z, Qin G. Prevention strategy for father-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. *J Matern neonatal Med* 2018;**31**:3275–82. doi:10.1080/14767058.2017.1368482	Less than two randomised clinical trials in the forest plot and TSA
110	Yang F, Wei K, Qin Z, *et al.* Association between TNF-a-308G/A polymorphism and esophageal cancer risk: an updated meta-analysis and trial sequential analysis. *J Cancer* 2019;**10**:1086–96. doi:10.7150/jca.29390	Less than two randomised clinical trials in the forest plot and TSA
111	Han S, Huang T, Hou F, *et al.* The prognostic value of hypoxia-inducible factor-1alpha in advanced cancer survivors: a meta-analysis with trial sequential analysis. *Ther Adv Med Oncol* 2019;**11**:1758835919875851. doi:10.1177/1758835919875851	Less than two randomised clinical trials in the forest plot and TSA
112	Xiong Y, Zhang Q, Ye J, *et al.* Associations between three XRCC1 polymorphisms and hepatocellular carcinoma risk: a meta-analysis of case-control studies. *Plos ONE [electronic Resour* 2018;**13**:e0206853. doi:10.1371/journal.pone.0206853	Less than two randomised clinical trials in the forest plot and TSA

113	Casans-Frances R, AT R-A, MA G-R, *et al.* The importance of trial sequential analysis in the evaluation of the results of a meta-analysis. *Minerva Anestesiol* 2019;**85**:342–3. doi:10.23736/S0375-9393.19.13599-7	Wrong study design
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116	Kumar A, Shariff M. Trial sequential analysis of studies comparing the frequency of target-vessel revascularization with drug-coated balloons as compared with second-generation drug-eluting stents in coronary in-stent restenosis: have we generated enough evidence in the fiel. *Indian Heart J* 2019;**71**:288–90. doi:10.1016/j.ihj.2019.06.001	Only Trial Sequential Analysis, no forest plot
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119	Alfirevic Z, Gates S. Trial sequential analysis: useful or useless? *BJOG* 2020;**127**:1227–8. doi:10.1111/1471-0528.16282	Wrong study design
120	Shah A, AF S. Trial sequential analysis: adding a new dimension to meta-analysis. *Anaesthesia* 2020;**75**:15–20. doi:10.1111/anae.14705	Wrong study design
121	HH K, HP G. Optimal Interpretation of Trial Sequential Analysis in Understanding the Effect of Dexmedetomidine on Acute Kidney Injury After Cardiac Surgery. *J Cardiothorac Vasc Anesth* 2020;**34**:2548. doi:10.1053/j.jvca.2020.04.016	Wrong study design
122	KR K, Taljaard M. Enough is enough: does trial sequential analysis tell us when we don't need to do any more studies? *Anaesthesia* 2021;**76**:594–7. doi:10.1111/anae.15242	Wrong study design
123	Lu S, Wang Y, Hu J, *et al.* The IL-6 rs1800795 and rs1800796 polymorphisms are associated with coronary artery disease risk. *J Cell Mol Med* 2020;**24**:6191–207. doi:10.1111/jcmm.15246	Less than two randomised clinical trials in the forest plot and TSA
124	Amar A, Afzal A, SA H, *et al.* Association of vitamin D receptor gene polymorphisms and risk of urolithiasis: results of a genetic epidemiology study and comprehensive meta-analysis. *Urolithiasis* 2020;**48**:385–401. doi:10.1007/s00240-019-01157-7	Less than two randomised clinical trials in the forest plot and TSA
125	Mahto H, Pati A, SK S, *et al.* Association of MBL-2 gene polymorphisms with systemic lupus erythematosus: an updated meta-analysis and trial sequential analysis. *Lupus* 2020;**29**:1227–37. doi:10.1177/0961203320939156	Less than two randomised clinical trials in the forest plot and TSA
126	Song G, Qiao W, Liu K, *et al.* Epicardial adipose tissue in patients with chronic kidney disease: a meta-analysis study and trial sequential analysis. *Int Urol Nephrol* 2020;**52**:2345–55. doi:10.1007/s11255-020-02575-y	Less than two randomised clinical trials in the forest plot and TSA
127	Ang E, KT N, ZX L, *et al.* Effect of regional anaesthesia only versus general anaesthesia on cancer recurrence rate: a systematic review and meta-analysis with trial sequential analysis. *J Clin Anesth* 2020;**67**:110023. doi:10.1016/j.jclinane.2020.110023	Less than two randomised clinical trials in the forest plot and TSA

128	Liu J, Song G, Zhao G, *et al.* Gene polymorphism associated with TGF-beta1 and susceptibility to preeclampsia: a meta-analysis and trial sequential analysis. *J Obstet Gynaecol Res* 2021;**47**:2031–41. doi:10.1111/jog.14751	Less than two randomised clinical trials in the forest plot and TSA
129	Jiang C, Li L, Wu M, *et al.* Association of KCNJ10 variants and the susceptibility to clinical epilepsy. *Clin Neurol Neurosurg* 2021;**200**:106340. doi:10.1016/j.clineuro.2020.106340	Less than two randomised clinical trials in the forest plot and TSA
130	Wang C, Zhou X, Liu H, *et al.* Three polymorphisms of renin-angiotensin system and preeclampsia risk. *J Assist Reprod Genet* 2020;**37**:3121–42. doi:10.1007/s10815-020-01971-8	Less than two randomised clinical trials in the forest plot and TSA
131	Kumar A, Doshi R, Shariff M. Role of antibiotic envelopes in preventing cardiac implantable electronic device infection: a meta-analysis of 14 859 procedures. *J arrhythmia* 2020;**36**:176–9. doi:10.1002/joa3.12262	Less than two randomised clinical trials in the forest plot and TSA
132	Yuan M, Yu C, Yu K. Association of human XPA rs1800975 polymorphism and cancer susceptibility: an integrative analysis of 71 case-control studies. *Cancer Cell Int* 2020;**20**:164. doi:10.1186/s12935-020-01244-5	Less than two randomised clinical trials in the forest plot and TSA
133	Huang J, Gao H, HZ T. SOX1 Promoter Hypermethylation as a Potential Biomarker for High-Grade Squamous Intraepithelial Neoplasia Lesion and Cervical Carcinoma: a Meta-Analysis With Trial Sequential Analysis. *Front Genet* 2020;**11**:633. doi:10.3389/fgene.2020.00633	Less than two randomised clinical trials in the forest plot and TSA
134	Caputo R, Asprea M, Giovannetti L, *et al.* Nephrotoxicity of three formulations of amphotericin B: trial sequential analysis. *Arch Med Sci* 2020;**16**:1493–5. doi:10.5114/aoms.2020.93338	Only Trial Sequential Analysis, no forest plot
135	LS S, LM L, LH Z, *et al.* Ablation strategies for arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis. *J Geriatr Cardiol* 2020;**17**:694–703. doi:10.11909/j.issn.1671-5411.2020.11.001	Less than two randomised clinical trials in the forest plot and TSA
136	JM A, Bakare L, AM C, *et al.* Cefazolin Versus Anti-Staphylococcal Penicillins for the Treatment of Patients with Methicillin-Susceptible Staphylococcus aureus Infection: a Meta-Analysis with Trial Sequential Analysis. *Infect Dis Ther* 2019;**8**:671–86. doi:10.1007/s40121-019-00259-4	Less than two randomised clinical trials in the forest plot and TSA
137	Zhang Y, Chen L, Chen H. A meta-analysis of the correlation between non-steroidal anti-inflammatory drugs and recurrent colorectal adenomatous polyps. *Am J Transl Res* 2021;**13**:2432–8.NS -	Only forest plot, no Trial Sequential Analysis
138	Liu X, Zhao Y, Li Y, *et al.* Association between HOTAIR genetic polymorphisms and cancer susceptibility: a meta-analysis involving 122,832 subjects. *Genomics* 2020;**112**:3036–55. doi:10.1016/j.ygeno.2020.05.018	Less than two randomised clinical trials in the forest plot and TSA
139	Liu J, MQ L, DF C, *et al.* The Association between Interleukin-6 Gene Polymorphisms and Risk of Systemic Lupus Erythematosus: a Meta-analysis with Trial Sequential Analysis. *Immunol Invest* 2021;**50**:259–72. doi:10.1080/08820139.2020.1769646	Less than two randomised clinical trials in the forest plot and TSA
140	Corrao S, Natoli G, Argano C. Nonalcoholic fatty liver disease is associated with intrahepatic cholangiocarcinoma and not with extrahepatic form: definitive evidence from meta-analysis and trial sequential analysis. *Eur J Gastroenterol Hepatol* 2021;**33**:62–8. doi:10.1097/MEG.0000000000001684	Less than two randomised clinical trials in the forest plot and TSA
141	YH H, WH F, DJ T, *et al.* The Decisive Case-Control Study Elaborates the Null Association between ESR1 XbaI and Osteoarthritis in Asians: a Case-Control Study and Meta-Analysis. *Genes (Basel)* 2021;**12**. doi:10.3390/genes12030404	Less than two randomised clinical trials in the forest plot and TSA
142	Zhang J, Li X, Cai Z, *et al.* Association between testosterone with type 2 diabetes in adult males, a meta-analysis and trial sequential analysis. *Aging male* 2020;**23**:607–18. doi:10.1080/13685538.2018.1557139	Less than two randomised clinical trials in the forest plot and TSA

143	Osman M, MB M, Regner S, *et al.* Induced Hypothermia in Patients with Cardiac Arrest and a Non-shockable Rhythm: meta-analysis and Trial Sequential Analysis. *Neurocrit Care* 2021;**34**:279–86. doi:10.1007/s12028-020-01034-x	Less than two randomised clinical trials in the forest plot and TSA
144	PB W, XM W, Qian R, *et al.* Association between IL12B polymorphisms and inflammatory bowel disease in Caucasian population: a meta-analysis. *Cytokine* 2020;**136**:155296. doi:10.1016/j.cyto.2020.155296	Less than two randomised clinical trials in the forest plot and TSA
145	JSK C. Aspirin-omitted dual antithrombotics vs. triple antithrombotics: a trial sequential analysis. *Eur Hear J Cardiovasc Pharmacother* 2021;**7**:e32–4. doi:10.1093/ehjcvp/pvaa061	Wrong study design
146	Yan F, Jiang Q, He M, *et al.* PARP inhibitor treatment of advanced breast cancer beyond the BRCA-mutated type: a meta-analysis. *Future Oncol* 2021;**17**:2381–93. doi:10.2217/fon-2020-1175	Only forest plot, no Trial Sequential Analysis
147	WC H, YY C, YH L, *et al.* Composite Cardiovascular Outcomes in Patients With Primary Aldosteronism Undergoing Medical Versus Surgical Treatment: a Meta-Analysis. *Front Endocrinol (Lausanne)* 2021;**12**:644260. doi:10.3389/fendo.2021.644260	Less than two randomised clinical trials in the forest plot and TSA
148	Liu J, Song G, Zhao G, *et al.* Association between TNF-alpha polymorphisms and gestational diabetes mellitus: a meta-analysis and trial sequential analysis. *Gynecol Endocrinol* 2021;**37**:506–10. doi:10.1080/09513590.2020.1804549	Less than two randomised clinical trials in the forest plot and TSA
149	Yu L, Shao M, Zhou T, *et al.* Association of CTLA-4 (+49 A/G) polymorphism with susceptibility to autoimmune diseases: a meta-analysis with trial sequential analysis. *Int Immunopharmacol* 2021;**96**:107617. doi:10.1016/j.intimp.2021.107617	Less than two randomised clinical trials in the forest plot and TSA
150	JSK C, Harky A. Trial sequential analysis in forest plots: a clinically oriented approach with real-world example. *J Thorac Cardiovasc Surg* 2021;**162**:167–73. doi:10.1016/j.jtcvs.2020.06.063	Only Trial Sequential Analysis, no forest plot
151	Pergialiotis V, Kotrogianni P, Koutaki D, *et al.* Umbilical cord coiling index for the prediction of adverse pregnancy outcomes: a meta-analysis and sequential analysis. *J Matern neonatal Med* 2019;:1–8. doi:10.1080/14767058.2019.1594187	Less than two randomised clinical trials in the forest plot and TSA
152	Shariff M, Kumar A, Adalja D, *et al.* Inferior vena cava filters reduce symptomatic but not fatal pulmonary emboli after major trauma: a meta-analysis with trial sequential analysis. *Eur J trauma Emerg surgery 2020 MAR 27* Published Online First: 2020. doi:10.1007/s00068-020-01350-z	Both observational and RCT in TSA
153	JSK C. The results are in: cardiovascular benefits of glucagon-like peptide-1 receptor agonists - a trial sequential analysis. *Eur J Prev Cardiol 2020 apr 17* Published Online First: 2020. doi:10.1177/2047487320918722	Only Trial Sequential Analysis, no forest plot
154	YP L, Fan S, Liang Z, *et al.* Phosphodiesterase Type 5 Inhibitors and Risk of Skin Cancers in Men: a Meta-Analysis and Trial Sequential Analysis Involving 7,479,852 Subjects. *world J mens Heal 2020 aug 28* Published Online First: 2020. doi:10.5534/wjmh.200082	Less than two randomised clinical trials in the forest plot and TSA
155	A DC, Pasin L, Boscolo A, *et al.* Trial Sequential Analysis: plain and Simple. *Korean J Anesthesiol 2020 dec 18* Published Online First: 2020. doi:10.4097/kja.20637	Wrong study design
156	YY H, GB J, YF S, *et al.* Association between the pri-miR-26a-1 rs7372209 C>T polymorphism and cancer susceptibility: multivariate analysis and trial sequential analysis. *Aging (Albany NY)* 2020;**12**:19060–72. doi:10.18632/aging.103696	Less than two randomised clinical trials in the forest plot and TSA

157	JSK C, Singh S, Eriksen P, *et al.* Transcatheter Aortic Valve Implantation in Bicuspid Aortic Valve with Aortic Stenosis: a Meta-Analysis and Trial Sequential Analysis. *Brazilian J Cardiovasc surgery 2020 dec 23* Published Online First: 2020. doi:10.21470/1678-9741-2020-0146	Less than two randomised clinical trials in the forest plot and TSA
158	MJ O, Seron P, Buitrago-Garcia D, *et al.* Cardiac rehabilitation effectiveness for coronary artery disease by clinical era: trial sequential analysis. *Eur J Prev Cardiol 2020 dec 01* Published Online First: 2020. doi:10.1093/eurjpc/zwaa110	Only Trial Sequential Analysis, no forest plot
159	Wang J, Liu H, Wang Y, *et al.* The Polymorphisms of Interleukin-12B Gene and Susceptibility to Inflammatory Bowel Diseases: a Meta-analysis and Trial Sequential Analysis. *Immunol Invest* 2021;:1–20. doi:10.1080/08820139.2020.1863981	Less than two randomised clinical trials in the forest plot and TSA
160	Gao S, Xu T, Mao C, *et al.* Lack of Associations between Endoplasmic Reticulum Aminopeptidase 2 Gene Polymorphisms and Ankylosing Spondylitis: a Meta-analysis with Trial Sequential Analysis. *Immunol Invest* 2021;:1–12. doi:10.1080/08820139.2020.1869253	Less than two randomised clinical trials in the forest plot and TSA
161	PB W, Zhang Y, Nie G, *et al.* Association between genetic variants in ZNF365 and inflammatory bowel disease risk in Caucasians: a meta-analysis and trial sequential analysis. *Expert Rev Clin Immunol* 2021;:1–7. doi:10.1080/1744666X.2021.1939012	Less than two randomised clinical trials in the forest plot and TSA
162	Iaculli F, Rengo C, Lodato V, *et al.* Fracture resistance of endodontically-treated maxillary premolars restored with different type of posts and direct composite reconstructions: a systematic review and meta-analysis of in vitro studies. *Dent Mater 2021 jun 17* Published Online First: 2021. doi:10.1016/j.dental.2021.06.007	Less than two randomised clinical trials in the forest plot and TSA
163	Iddawela S, SL M, SA Z, *et al.* Pedicled or skeletonized bilateral internal mammary artery harvesting - a meta- analysis and trial sequential analysis. *Expert Rev Cardiovasc Ther* 2021;:1–8. doi:10.1080/14779072.2021.1939684	Less than two randomised clinical trials in the forest plot and TSA
164	CC Y, Wang J. E-cadherin (CDH1) gene -160C/A polymorphism and the risk of colorectal cancer: a meta-analysis involving 17,291 subjects. *J Gene Med* 2021;:e3370. doi:10.1002/jgm.3370	Less than two randomised clinical trials in the forest plot and TSA
165	Song G, Qiao W, Wang X, *et al.* Association of lung ultrasound score with mortality and severity of COVID-19: a Meta-analysis and Trial Sequential Analysis. *Int J Infect Dis* Published Online First: 2021. doi:10.1016/j.ijid.2021.06.026	Less than two randomised clinical trials in the forest plot and TSA
166	HT W, TB H, ML L, *et al.* Magnesium sulphate treatment decreases the risk of cerebral palsy after preterm birth. *Ugeskr Laeger* 2020;**182**.NS -	Language not in English
167	JSK C, DHH L. Does lysing make life better? A trial sequential analysis. *J Neurol* 2020;**267**:1842–5. doi:10.1007/s00415-020-09801-8	Wrong study design
168	LP F, HL C. Early amniotomy for induction of labor: a trial sequential analysis. *Am J Obstet Gynecol* 2020;**222**:99–100. doi:10.1016/j.ajog.2019.09.028	Wrong study design
169	Trial Sequential Analysis of Drug-Eluting Stents Versus Bare-Metal Stents in Saphenous Vein Graft Intervention. *Am J Cardiol* 2019;**124**:823–4. doi:10.1016/j.amjcard.2019.05.043	Only Trial Sequential Analysis, no forest plot
170	HT W, Brok J, TB H, *et al.* Antenatal magnesium sulphate for the prevention of cerebral palsy in infants born preterm: a double-blind, randomised, placebo-controlled, multi-centre trial. *BJOG* 2020;**127**:1217–25. doi:10.1111/1471-0528.16239	Wrong study design
171	Heneghan C, JK A. Sodium valproate: who knew what and when? Cumulative meta-analysis gives extra insights. *BMJ evidence-based Med* 2019;**24**:127–9. doi:10.1136/bmjebm-2018-111068	Wrong study design

172	KT N, ZX L, Ang E, *et al.* Association of obstructive sleep apnea and postoperative cardiac complications: a systematic review and meta-analysis with trial sequential analysis. *J Clin Anesth* 2020;**62**:109731. doi:10.1016/j.jclinane.2020.109731	Less than two randomised clinical trials in the forest plot and TSA
173	MS L, HZ L, GJ H, *et al.* Trial sequential analysis suggested the potential overestimated effect of carbonic anhydrase inhibitor for respiratory failure and metabolic alkalosis. *Crit Care* 2019;**23**:138. doi:10.1186/s13054-019-2384-y	Wrong study design
174	YJ W. Does oral Nonsteroidal Anti-inflammatory Drugs (NSAIDs) premedication in patients with irreversible pulpitis increase the success rate of inferior alveolar nerve block? *Evid Based Dent* 2019;**20**:20–1. doi:10.1038/s41432-019-0014-9	Wrong study design
175	Han S, Huang T, Wu X, *et al.* Prognostic value of ALDH1 and Nestin in advanced cancer: a systematic meta-analysis with trial sequential analysis. *Ther Adv Med Oncol* 2019;**11**:1758835919830831. doi:10.1177/1758835919830831	Less than two randomised clinical trials in the forest plot and TSA
176	Gartlehner G, Nussbaumer-Streit B, Wagner G, *et al.* Increased risks for random errors are common in outcomes graded as high certainty of evidence. *J Clin Epidemiol* 2019;**106**:50–9. doi:10.1016/j.jclinepi.2018.10.009	Wrong study design
177	HA V, Pedersen J, Faltinsen E, *et al.* Training, executive, attention and motor skills (TEAMS) training versus standard treatment for preschool children with attention deficit hyperactivity disorder: a randomised clinical trial. *BMC Res Notes* 2018;**11**:366. doi:10.1186/s13104-018-3478-3	Wrong study design
178	Cortegiani A, Giarratano A. Untargeted antifungal treatment in nonneutropenic critically Ill patients: should further studies be performed based on trial sequential analysis results? *Antimicrob Agents Chemother* 2018;**62**. doi:10.1128/AAC.00810-18	Wrong study design
179	PM S, Borle A, JK M, *et al.* Evaluation of transversus abdominis plane block for renal transplant recipients - A meta-analysis and trial sequential analysis of published studies. *Saudi J Anaesth* 2018;**12**:261–71. doi:10.4103/sja.SJA_598_17	Less than two randomised clinical trials in the forest plot and TSA
180	Yan Y, AP D, Chen W, *et al.* Cumulative meta-analysis and trial sequential analysis of correlation between hOGG1 Ser326Cys polymorphism and the risk of head and neck squamous cell carcinoma. *Oncotarget* 2018;**9**:13077–87. doi:10.18632/oncotarget.24055	Less than two randomised clinical trials in the forest plot and TSA
181	RK M, SA D, Jawed A, *et al.* Impact of LMP7 (rs2071543) gene polymorphism in increasing cancer risk: evidence from a meta-analysis and trial sequential analysis. *Oncotarget* 2018;**9**:6572–85. doi:10.18632/oncotarget.23547	Less than two randomised clinical trials in the forest plot and TSA
182	Sridharan K, Sivaramakrishnan G. Botulinum Toxin for Refractory Trigeminal Neuralgia: a Trial Sequential Analysis of Randomized Clinical Trials. *J Neurosci Rural Pract* 2018;**9**:3–4. doi:10.4103/jnrp.jnrp_447_17	Only Trial Sequential Analysis, no forest plot
183	Dong F, BH Z, SL Z, *et al.* Association Between SLC30A8 rs13266634 Polymorphism and Risk of T2DM and IGR in Chinese Population: a Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)* 2018;**9**:564. doi:10.3389/fendo.2018.00564	Less than two randomised clinical trials in the forest plot and TSA
184	Khan S, SA D, RK M, *et al.* Angiotensin-Converting Enzyme Gene I/D Polymorphism Is Associated With Systemic Lupus Erythematosus Susceptibility: an Updated Meta-Analysis and Trial Sequential Analysis. *Front Physiol* 2018;**9**:1793. doi:10.3389/fphys.2018.01793	Less than two randomised clinical trials in the forest plot and TSA
185	Zhuang Q, Chen Z, Shen J, *et al.* RASSF1A promoter methylation correlates development, progression, and poor cancer-specific survival of renal cell	Less than two randomised clinical trials in the forest plot and TSA

	carcinoma: trial sequential analysis. *Onco Targets Ther* 2019;**12**:119–34. doi:10.2147/OTT.S183142	
186	Han S, Huang T, Wu X, *et al.* Prognostic Value of CD133 and SOX2 in Advanced Cancer. *J Oncol print* 2019;**2019**:3905817. doi:10.1155/2019/3905817	Less than two randomised clinical trials in the forest plot and TSA
187	Han S, Huang T, Li W, *et al.* Prognostic Value of CD44 and Its Isoforms in Advanced Cancer: a Systematic Meta-Analysis With Trial Sequential Analysis. *Front Oncol* 2019;**9**:39. doi:10.3389/fonc.2019.00039	Less than two randomised clinical trials in the forest plot and TSA
188	PH C, HJ J, LJ O-Y, *et al.* Does hydroxychloroquine reduce mortality in patients with COVID-19? A meta-analysis with trial sequential analysis. *Int J Clin Pract* 2021;**75**:e14448. doi:10.1111/ijcp.14448	Wrong study design
189	Safi S, NJ S, SK K, *et al.* Beta-blockers in patients without heart failure after myocardial infarction. *Cochrane Database Syst Rev* Published Online First: 2021. doi:10.1002/14651858.CD012565.pub2	Only forest plot, no Trial Sequential Analysis
190	Wang Y, Tian G, Chen S, *et al.* Myosteatosis reduces overall survival in patients with digestive system malignancies: a meta-analysis with trial sequential analysis. *Nutr Res* 2021;**94**:25–33. doi:10.1016/j.nutres.2021.08.003	Less than two randomised clinical trials in the forest plot and TSA
191	YW H, JW L, TL C. Volumetric Bone Mineral Density Measured by HR-pQCT in Patients with Psoriasis or Psoriatic Arthritis: a Systematic Review and Meta-Analysis with Trial Sequential Analysis. *Healthcare* 2021;**9**. doi:10.3390/healthcare9081056	Less than two randomised clinical trials in the forest plot and TSA
192	Yi H, Wang Y. A meta-analysis of exosome in the treatment of spinal cord injury. *Open Med* 2021;**16**:1043–60. doi:10.1515/med-2021-0304	Wrong study design
193	Guo J, Wang Y, Chen J, *et al.* Systematic review and trial sequential analysis of high-intensity focused ultrasound combined with chemotherapy versus chemotherapy in the treatment of unresectable pancreatic ductal adenocarcinoma. *Int J Hyperth* 2021;**38**:1375–83. doi:10.1080/02656736.2021.1962550	Less than two randomised clinical trials in the forest plot and TSA
194	A DC, Tassone M, Geraldini F, *et al.* Explanation of trial sequential analysis: using a post-hoc analysis of forest plots published in Korean Journal of Anesthesiology. *Korean J Anesthesiol* 2021;**74**:383–93. doi:10.4097/kja.21218	No TSA or forest plot

TSA: Trial Sequential Analysis

Supplemental Table 4. Included studies

Abushanab, D., & Al-Badriyeh, D. (2021). Efficacy and Safety of Ibuprofen Plus Paracetamol in a Fixed-Dose Combination for Acute Postoperative Pain in Adults: Meta-Analysis and a Trial Sequential Analysis. *CNS Drugs*, *35*(1), 105–120. https://doi.org/10.1007/s40263-020-00777-7
Aiolfi, A., Cavalli, M., Micheletto, G., Bruni, P. G., Lombardo, F., Morlacchi, A., Bonitta, G., Campanelli, G., & Bona, D. (2020). Open mesh vs. suture umbilical hernia repair: systematic review and updated trial sequential meta-analysis of randomized controlled trials. *Hernia*, *24*(4), 707–715. https://doi.org/10.1007/s10029-020-02146-1
Aiolfi, A., Cavalli, M., Del Ferraro, S., Manfredini, L., Lombardo, F., Bonitta, G., Bruni, P. G., Panizzo, V., Campanelli, G., & Bona, D. (2021). Total extraperitoneal (TEP) versus laparoscopic transabdominal preperitoneal (TAPP) hernioplasty: systematic review and trial sequential analysis of randomized controlled trials. *Hernia*, *25*(5), 1147–1157. https://doi.org/10.1007/s10029-021-02407-7
Albrecht, E., Grape, S., Frauenknecht, J., Kilchoer, L., & Kirkham, K. R. (2020). Low- versus high-dose intraoperative opioids: A systematic review with meta-analyses and trial sequential analyses. *Acta Anaesthesiologica Scandinavica*, *64*(1), 6–22. https://doi.org/10.1111/aas.13470
Albrecht, E., Wegrzyn, J., Dabetic, A., & El-Boghdadly, K. (2021). The analgesic efficacy of iPACK after knee surgery: A systematic review and meta-analysis with trial sequential analysis. *Journal of Clinical Anesthesia*, *72*(PG-110305), 110305. https://doi.org/10.1016/j.jclinane.2021.110305
Alhajj, M. N., Qi, C. H., Sayed, M. E., Johari, Y., & Ariffin, Z. (2022). Fracture Resistance of Titanium and Fiber Dental Posts: A Systematic Review and Meta-Analysis. *Journal of Prosthodontics*, *31*(5), 374–384. https://doi.org/10.1111/jopr.13428
Al-Rudayni, A. H. M., Gopinath, D., Maharajan, M. K., Veettil, S. K., & Menon, R. K. (2021). Efficacy of photobiomodulation in the treatment of cancer chemotherapy-induced oral mucositis: A meta-analysis with trial sequential analysis. *International Journal of Environmental Research and Public Health*, *18*(14). https://doi.org/10.3390/ijerph18147418
Al-Rudayni, A. H. M., Gopinath, D., Maharajan, M. K., Veettil, S. K., & Menon, R. K. (2021). Efficacy of oral cryotherapy in the prevention of oral mucositis associated with cancer chemotherapy: Systematic review with meta-analysis and trial sequential analysis. *Current Oncology*, *28*(4), 2852–2867. https://doi.org/10.3390/curroncol28040250
Andersen, I. B., Andreassen, M., & Krogh, J. (2021). The effect of dopamine agonists on metabolic variables in adults with type 2 diabetes: A systematic review with meta analysis and trial sequential analysis of randomized clinical trials. *Diabetes, Obesity and Metabolism*, *23*(1), 58–67. https://doi.org/10.1111/dom.14183
Ando, T., Holmes, A. A., Pahuja, M., Javed, A., Briasoulis, A., Telila, T., Takagi, H., Schreiber, T., Afonso, L., Grines, C. L., & Bangalore, S. (2018). Meta-Analysis Comparing Patent Foramen Ovale Closure Versus Medical Therapy to Prevent Recurrent Cryptogenic Stroke. *American Journal of Cardiology*, *121*(5), 649–655. https://doi.org/10.1016/j.amjcard.2017.11.037

Antoniou, G. A., & Antoniou, S. A. (2021). Editor's Choice – Percutaneous Access Does Not Confer Superior Clinical Outcomes Over Cutdown Access for Endovascular Aneurysm Repair: Meta-Analysis and Trial Sequential Analysis of Randomised Controlled Trials. *European Journal of Vascular and Endovascular Surgery*, *61*(3), 383–394. https://doi.org/10.1016/j.ejvs.2020.11.008

Antoniou, G. A., Onwuka, C. C., Antoniou, S. A., & Russell, D. (2019). Meta-analysis and trial sequential analysis of prophylactic negative pressure therapy for groin wounds in vascular surgery. *Journal of Vascular Surgery*, *70*(5), 1700-1710.e6. https://doi.org/10.1016/j.jvs.2019.01.083

Antoniou, S. A., García-Alamino, J. M., Hajibandeh, S., Hajibandeh, S., Weitzendorfer, M., Muysoms, F. E., Granderath, F. A., Chalkiadakis, G. E., Emmanuel, K., Antoniou, G. A., Gioumidou, M., Iliopoulou-Kosmadaki, S., Mathioudaki, M., & Souliotis, K. (2018). Single-incision surgery trocar-site hernia: an updated systematic review meta-analysis with trial sequential analysis by the Minimally Invasive Surgery Synthesis of Interventions Outcomes Network (MISSION). *Surgical Endoscopy*, *32*(1), 14–23. https://doi.org/10.1007/s00464-017-5717-4

Arulkumaran, N., Khpal, M., Tam, K., Baheerathan, A., Corredor, C., & Singer, M. (2020). Effect of Antibiotic Discontinuation Strategies on Mortality and Infectious Complications in Critically Ill Septic Patients: A Meta-Analysis and Trial Sequential Analysis. *Critical Care Medicine*, *48*(5), 757–764. https://doi.org/10.1097/CCM.0000000000004267

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Supplemental Table 5. Data on study type and overall proportions

	Systematic review	Meta-analysis	Overall
Number of TSA extracted	312	312	624
Dichotomous outcomes	218 (69.9%)	221 (70.8%)	439 (70.4%)
Continuous outcomes	94 (30.1%)	91 (29.2%)	185 (29.6%)
Extracted TSA was done on			
Primary outcome	281 (90.1%)	287 (92.0%)	568 (91.0%)
Secondary outcome	30 (9.6%)	25 (8.0%)	55 (8.8%)
Exploratory outcome	1 (0.3%)	0	1 (0.2%)
Model used			
Random-effects model	224 (71.8%)	203 (65.1%)	427 (68.4%)
Fixed-effect model	53 (17.1%)	76 (24.4%)	129 (20.7%)
Fixed- and random-effects models	34 (10.9%)	30 (9.6%)	64 (10.3%)
Other[a]	0	1 (0.3%)	1 (0.2%)
Not mentioned	1 (0.3%)	2 (0.6%)	3 (0.5%)
Number of trials included in TSA[b]			
Mean (SD)	11.0 (9.3)	10.4 (8.6)	10.7 (8.9)
Median (IQR)	8 (5 to 14)	8 (5 to 13)	8 (5 to 13)
Acquired information size			
Mean (SD)	9,420 (73,100)	4,310 (10,500)	6,870 (52,300)
Median (IQR)	1,160 (551 to 3,300)	1,290 (597 to 3,410)	1,220 (594 to 3,310)
No extractable information	22 (7.1%)	22 (7.1%)	44 (7.1%)
TSA results			
Beneficial	117 (37.7%)	128 (41.0%)	245 (39.3%)
Harmful	19 (6.1%)	12 (3.8%)	31 (5.0%)
Futility	45 (14.5%)	44 (14.1%)	89 (14.3%)
Insignificant	92 (29.5%)	111 (35.6%)	203 (32.5%)
Uninterpretable	39 (12.5%)	17 (5.4%)	56 (9.0%)
Alpha level chosen			
< 0.025	11 (3.5%)	4 (1.3%)	15 (2.4%)
0.025 to 0.033	26 (8.4%)	5 (1.6%)	31 (5.0%)
0.033 to 0.05	14 (4.5%)	1 (0.3%)	15 (2.4%)
0.05	236 (75.6%)	273 (87.5%)	509 (81.6%)
0.1	0	1 (0.3%)	1 (0.2%)
Not reported	25 (8.0%)	28 (9.0%)	53 (8.5%)
Power chosen (*1-beta*)			
< 0.8	1 (0.3%)	0 (0%)	1 (0.2%)
0.85	0 (0%)	1 (0.3%)	1 (0.2%)
0.9	194 (62.2%)	245 (75.0%)	428 (68.6%)
> 0.9	1 (0.3%)	2 (0.6%)	3 (0.5%)
Not reported	116 (37.2%)	75 (24.0%)	191 (30.6%)
Heterogeneity			
D^2	125 (40.1%)	85 (27.2%)	209 (33.7%)
I^2	16 (5.1%)	27 (8.7%)	43 (6.9%)
No heterogeneity corrected in TSA	15 (4.8%)	19 (6.1%)	34 (5.4%)
Not described / not clear	115 (36.9%)	128 (41.0%)	243 (38.9%)
Not described, but I^2=0%	41 (13.1%)	53 (17.0%)	94 (15.1%)
How was the required information size presented?			
DARIS	108 (34.6%)	93 (29.8%)	201 (32.2%)

RIS (unadjusted)	48 (15.4%)	46 (14.7%)	94 (15.1%)
RIS not presented	18 (5.8%)	9 (2.9%)	27 (4.3%)
Unclear[c]	138 (44.2%)	164 (52.6%)	302 (48.4%)
TSA-adjusted CI included			
No	226 (72.4%)	274 (87.8%)	500 (80.1%)
Yes	61 (19.6%)	24 (7.7%)	85 (13.6%)
Yes, but mislabelled	18 (5.8%)	13 (4.2%)	31 (5.0%)
Not reported[d]	7 (2.3%)	1 (0.3%)	8 (1.3%)
Percentage AIS over RIS			
Mean (SD)	137 (285)	136 (228)	136 (258)
Median (IQR)	79.5 (32.8 to 137.0)	75.2 (37.5 to 136.0)	76.8 (35.2 to 137.0)
Not reported	40 (12.8%)	37 (11.9%)	77 (12.3%)
Transparency			
Excellent	55 (17.6%)	15 (4.8%)	70 (11.2%)
Good	74 (23.7%)	71 (22.8%)	145 (23.2%)
Poor	72 (23.1%)	102 (32.7%)	174 (27.9%)
Very poor	111 (35.6%)	124 (39.7%)	235 (37.7%)

AIS: acquired information size; D2: diversity; DARIS: diversity adjusted required information size; I2: inconsistency; Meta-analysis: a non-systematic approach which lacks a pre-published protocol at the time of data extraction; OR: odds ratio; Pc: proportion of events in the control group; Peto OR: Peto odds ratio; RD: risk difference; RIS: required information size; RR: risk ratio; RRR: relative risk reduction; Systematic review: a detailed, organised, and transparent method of gathering, appraising and synthesising data to answer a well-defined question, including a pre-published protocol before starting data extraction; TSA: Trial Sequential Analysis; TSA adjusted CI: Trial Sequential Analysis adjusted confidence interval;

a. One study used empirical Bayes binary random effect;

b. Missing value in 5 systematic reviews;

c. Unclear if RIS was adjusted or unadjusted;

d. Missing either AIS, RIS, or both.

Supplemental Material B. Subgroup comparing Cochrane reviews to non-Cochrane reviews

The 27 Cochrane reviews performed better on most parameters. We extracted 32 Trial Sequential Analysis of which 23 (62%) were on dichotomous outcomes and nine (28%) on continuous outcomes. The AMSTAR 2 evaluation showed that 20/27 (74%) were evaluated as high confidence, 2/27 (7%) as moderate confidence, 1/27 (4%) as low confidence, and 4/27 (15%) critically low confidence (**Supplemental Table 5**).

Eighteen of 23 (78%) dichotomous outcomes were primary outcomes and included a median of 4 (IQR 2 to 13) trials, with a median acquired information size of 643 (IQR 213 to 1,320) (**Supplemental Table 6**). Six of nine (66%) of the continuous outcomes were categorised as primary outcomes with a median number of trials of 9 (IQR 4 to 16), and a median acquired information size of 627 (IQR 313 to 1,310) (**Supplemental Table 7**). The DARIS was presented in 18 (78.3%) of the dichotomous and 7 (77.8%) of the continuous outcomes.

For dichotomous outcomes the relative risk was used in 20 of 23 (96%) analyses (**Supplemental Table 6**). In analyses of the continuous outcomes, the mean difference was used in 7 (78%) and the standardised mean difference in 2 (22%) (**Supplemental Table 7**). All Cochrane reviews reported the proportion of events in the control group, however, three (13%) of these did not provide the value for the proportion of events in the control group. The proportion from the current forest plot was used in 22 (81%) of analyses, and one from a previously published trial. The relative risk reduction was reported in 96% of analyses with 8 (34%) studies not reporting the rationale, three (13%) studies reporting that the value was predefined from a previous study, six studies (26%) used the current data from the forest plot, and five (22%) used clinical experience (**Supplemental Table 6**).

The alpha level was 5% in 11 (33%) analyses and lower for the remaining 21 (66%) Cochrane reviews. The power was set at 0.9 in 12 (38%) and not reported for 20 (62%) analyses. D^2 was used in 20/23 (91%) of the dichotomous outcomes and 9/9 (100%) of the continuous outcomes. Three did not report the use of heterogeneity adjustment (**Supplemental Table 6 and 7**).

Transparency of the Trial Sequential Analysis was considered excellent in 21/32 (66%), good in three (9%), poor in five (16%), and very poor in three (9%) (**Supplemental Table 6 and 7**).

Sixteen of 32 (50%) analyses had a Trial Sequential Analysis adjusted confidence interval. D^2 was used to calculate the required information size in 18/23 (78%) of dichotomous outcomes, while 7/9 (78%) of continuous outcomes used D^2. The remaining dichotomous outcomes did not present a required information size and two continuous outcomes used I^2. The median percentage acquired information size over the D^2-, I^2, or non-adjusted required information size was 12% (IQR 7% to 22%) for dichotomous outcomes and 61% (IQR 55% to 139%) for continuous outcomes (**Supplemental Table 6 and 7**).

Supplemental Table 6. Study characteristics for Cochrane reviews and non-Cochrane reviews

	Cochrane reviews	Non-Cochrane reviews
Publications	27	243
Publication year		
2018	14 (51.9%)	38 (15.8%)
2019	7 (25.9%)	48 (19.9%)
2020	2 (7.4%)	65 (27.0%)
2021	4 (14.8%)	92 (37.9%)
AMSTAR 2 evaluation		
High	20 (74.1%)	7 (2.9%)
Moderate	2 (7.4%)	16 (6.6%)
Low	1 (3.7%)	34 (14.0%)
Critically low	4 (14.8%)	186 (76.5%)
Number of TSA extracted	32	280
Dichotomous outcomes	23 (71.9%)	195 (69.6%)
Continuous outcomes	9 (28.1%)	85 (30.4%)
Planned details on TSA in protocol	21 (77.8%)	113 (46.9%)
Planned dichotomous outcomes	19 (70.4%)	83 (34.2%)
Planned continuous outcomes	13 (48.1%)	54 (22.2%)
Used GRADE	27 (100%)	167 (68.7%)
TSA affected GRADE evaluation	15 (55.6%)	51 (21.0%)

AMSTAR: Assessing the methodological quality of systematic reviews; GRADE: Grading of Recommendations Assessment, Development and Evaluation; Meta-analysis: a non-systematic approach which lacks a pre-published protocol at the time of data extraction; Systematic review: a detailed, organised, and transparent method of gathering, appraising and synthesising data to answer a well-defined question, including a pre-published protocol before starting data extraction; TSA: Trial Sequential Analysis;

Supplemental Table 7. Dichotomous outcomes for Cochrane reviews and non-Cochrane reviews

	Cochrane reviews	Non-Cochrane reviews
Number of TSA extracted	23	195
Extracted TSA was done on		
Primary outcome	18 (78.3%)	182 (93.3%)
Secondary outcome	5 (21.7%)	13 (6.7%)
Exploratory outcome	0	0
Model used		
Random-effects model	13 (56.6%)	128 (65.6%)
Fixed-effect model	2 (8.7%)	45 (23.1%)
Fixed- and random-effects models	8 (34.8%)	21 (10.8%)
Not mentioned	0	1 (0.5%)
Dichotomous effect estimates used		
RR	20 (87.0%)	154 (79.0%)
OR	2 (8.7%)	37 (19.0%)
Peto OR	1 (4.3%)	1 (0.5%)
RD	0	1 (0.5%)
Other[a]	0	2 (1.0%)
Number of trials included in TSA[b]		
Mean (SD)	9.0 (9.2)	11.3 (9.0)
Median (IQR)	4.0 (2.0 to 13.0)	9.00 (5.0 to 13.0)
Not reported	1 (4.3%)	3 (1.5%)
Acquired information size		
Mean (SD)	1,020 (1,130)	14,500 (92,500)
Median (IQR)	643 (213 to 1,320)	1,690 (771 to 5,680)
No extractable information	1 (4.3%)	15 (7.7%)
TSA results		
Beneficial	1 (4.3%)	66 (34.2%)
Harmful	1 (4.3%)	11 (5.6%)
Futility	1 (4.3%)	33 (16.9%)
Insignificant	12 (52.2%)	64 (3.8%)
Uninterpretable	8 (34.8%)	21 (10.8%)
Was the Pc presented?		
Yes, the value was reported	20 (87.0%)	90 (46.2%)
Yes, but no value was reported	3 (13.0%)	29 (14.9%)
No	0	76 (39.0%)
How was Pc selected?		
Previously published data[c]	1 (4.3%)	4 (2.1%)
From current forest plot	22 (95.7%)	90 (46.2%)
Not mentioned	0	14 (7.2%)
Other	0	0
Unclear	0	9 (4.6%)
Was the RRR presented?		
Yes	22 (95.7%)	147 (75.4%)
No	1 (4.3%)	48 (24.6%)
How was RRR selected?		
Previously published data[c]	3 (13.0%)	11 (5.7%)
From the current forest plot	6 (26.1%)	30 (15.5%)
From author's clinical experience	5 (21.7%)	23 (11.9%)

From other sources	4 (17.4%)	31 (16.1%)
Not mentioned	8 (34.8%)	65 (33.3%)
Level of RRR used in outcomes		
0 to 4.9%	0	1 (0.5%)
5 to 9.9%	1 (4.3%)	5 (2.6%)
10 to 14.9%	2 (8.7%)	28 (14.4%)
15 to 19.9%	3 (13.0%)	19 (9.7%)
20 to 24.9%	12 (52.2%)	50 (25.6%)
25 to 29.9%	0	11 (5.6%)
30 to 39.9%	0	12 (6.2%)
40 to 49.9%	0	5 (2.6%)
>50%	2 (8.7%)	10 (5.1%)
Alpha level chosen		
< 0.025	1 (4.3%)	3 (1.5%)
0.025 to 0.033	12 (52.2%)	9 (4.6%)
0.033 to 0.05	2 (8.7%)	11 (5.6%)
0.05	8 (34.8%)	156 (80.0%)
0.1	0	0
Not reported	0	16 (8.2%)
Power chosen (*1-beta*)		
0.9	9 (39.1%)	125 (64.1%)
Not reported	14 (60.9%)	68 (34.9%)
Heterogeneity		
D^2	20 (87.0%)	72 (36.9%)
I^2	0	11 (5.6%)
No heterogeneity corrected in TSA	0	8 (4.1%)
Not described / not clear	3 (13.0%)	68 (34.9%)
Not described, but I^2=0%	0	36 (18.5%)
How was the required information size presented?		
DARIS	18 (78.3%)	64 (32.8%)
RIS (unadjusted)	0	32 (16.4%)
RIS not presented	4 (17.4%)	10 (5.1%)
Unclear[d]	1 (4.3%)	89 (45.6%)
TSA-adjusted CI included		
Yes	11 (47.8%)	35 (17.9%)
Yes, but mislabelled	0	14 (7.2%)
No	7 (30.4%)	144 (73.8%)
Not reported	5 (21.7%)	2 (1.0%)
Percentage AIS over RIS		
Mean (SD)	19.6 (22.2)	134 (326)
Median (IQR)	12.3 (6.5 to 21.5)	70.3 (30.7 to 134)
Not reported[e]	4 (17.4%)	26 (13.5%)
Transparency		
Excellent	17 (73.9%)	28 (14.4%)
Good	1 (4.3%)	57 (29.2%)
Poor	3 (13.0%)	45 (23.1%)
Very poor	2 (8.7%)	65 (33.3%)

AIS: acquired information size; D2: diversity; DARIS: diversity adjusted required information size; I2: inconsistency; Meta-analysis: a non-systematic approach which lacks a pre-published protocol at the time of

data extraction; OR: odds ratio; Pc: proportion of events in the control group; Peto OR: Peto odds ratio; RD: risk difference; RIS: required information size; RR: risk ratio; RRR: relative risk reduction; Systematic review: a detailed, organised, and transparent method of gathering, appraising and synthesising data to answer a well-defined question, including a pre-published protocol before starting data extraction; TSA: Trial Sequential Analysis; TSA adjusted CI: Trial Sequential Analysis adjusted confidence interval;

a. Preferred alternative method was hazard ratio;

b. Missing value in 4 systematic reviews;

c. Previous systematic reviews, randomised clinical trials or observational studies;

d. Unclear if RIS was adjusted or unadjusted;

e. Missing either AIS, RIS, or both.

Supplemental Table 8. Continuous outcomes for Cochrane reviews and non-Cochrane reviews

	Cochrane reviews	Non-Cochrane reviews
Number of TSA extracted	9	85
Extracted TSA was done on		
Primary outcome	6 (66.7%)	75 (88.2%)
Secondary outcome	2 (22.2%)	10 (11.8%)
Exploratory outcome	1 (11.1%)	0
Model used		
Random-effects model	8 (88.9%)	75 (88.2%)
Fixed-effect model	0	6 (7.1%)
Fixed- and random-effects models	1 (11.1%)	4 (4.7%)
Continuous effect estimates used		
Mean difference	7 (77.8%)	77 (90.6%)
Standardised mean difference	2 (22.2%)	7 (8.2%)
Other[a]	0	1 (1.2%)
Number of trials included in TSA		
Mean (SD)	14.7 (17.1)	10.4 (8.8)
Median (IQR)	9.0 (4.0 to 16.0)	8.0 (5.8 to 12.3)
Acquired information size		
Mean (SD)	1,080 (1,220)	1,090 (1,280)
Median (IQR)	627 (313 to 1,310)	691 (405 to 1,140)
No extractable information	0	6 (7.1%)
TSA results		
Beneficial	3 (33.3%)	47 (55.3%)
Harmful	2 (22.2%)	5 (5.9%)
Futile	2 (22.2%)	9 (10.6%)
Insignificant	1 (11.1%)	15 (17.6%)
Uninterpretable	1 (11.1%)	9 (10.6%)
Was the minimally relevant difference presented		
Yes	7 (77.8%)	33 (38.8%)
No	2 (22.2%)	52 (61.2%)
Was variance presented		
Yes	6 (66.7%)	23 (27.1%)
No	3 (33.3%)	62 (72.9%)
Alpha level chosen		
< 0.025	4 (44.4%)	3 (3.5%)
0.025 to 0.033	1 (11.1%)	(4.7%)
0.033 to 0.05	1 (11.1%)	0
0.05	3 (33.3%)	69 (81.2%)
Not reported	0	9 (10.6%)
Power chosen (*1-beta*)		
0.9[b]	3 (33.3%)	57 (67.1%)
Not reported	6 (66.7%)	28 (32.9%)
Heterogeneity		
D^2	9 (100%)	24 (28.2%)
I^2	0	5 (5.9%)

No heterogeneity corrected in TSA	0	7 (8.2%)
Not described / not clear	0	44 (51.8%)
Not described, but I^2=0%	0	5 (5.9%)
How was the RIS presented?		
DARIS	7 (77.8%)	19 (22.4%)
RIS (unadjusted)	2 (22.2%)	46 (54.1%)
RIS not presented	0	4 (4.7%)
Unclear[c]	0	16 (18.8%)
TSA adjusted CI included		
Yes	4 (44.4%)	11 (12.9%)
Yes, but mislabelled	1 (11.1%)	3 (3.5%)
No	4 (44.4%)	71 (83.5%)
Percentage AIS over RIS		
Mean (SD)	118 (107)	174 (225)
Median (IQR)	61.1 [55.1,139]	105 [68.2,180]
Missing	0	10 (11.8%)
Transparency		
Excellent	4 (44.4%)	6 (7.1%)
Good	2 (22.2%)	14 (16.5%)
Poor	2 (22.2%)	22 (25.9%)
Very poor	1 (11.1%)	43 (50.6%)

AIS: acquired information size; D2: diversity; DARIS: diversity adjusted required information size; I2: inconsistency; Meta-analysis: a non-systematic approach which lacks a pre-published protocol at the time of data extraction; RIS: required information size; Systematic review: a detailed, organised, and transparent method of gathering, appraising and synthesising data to answer a well-defined question, including a pre-published protocol before starting data extraction; TSA: Trial Sequential Analysis; TSA adjusted CI: Trial Sequential Analysis adjusted confidence interval;

a. Hedges' g;

b. Studies only reported a power of 0.9;

c. Unclear if RIS was adjusted or unadjusted.

Supplemental Table 9. Agreement between two reviewers on selected extraction variables

Question	Kappa	95% confidence interval
How many RCTs were included in the article?	*0.92*	0.90 to 0.93
Were the downgrade methods for imprecision described?	*0.65*	0.54 to 0.77
What did the authors conclude about the intervention effect on the outcome(s) analysed with trial sequential analysis?	*0.68*	0.63 to 0.73
How much was imprecision downgraded?	*0.65*	0.54 to 0.77
Was the alpha-level defined?	*0.72*	0.66 to 0.78
Was the power defined?	*0.81*	0.75 to 0.86
Was heterogeneity correction used for trial sequential analysis?	*0.50*	0.46 to 0.53
Was proportion of events in the control group (Pc) defined?	*0.77*	0.69 to 0.84
Was the relative risk reduction (RRR) defined?	*0.85*	0.75 to 0.94
Was variance defined?	*0.75*	0.60 to 0.90
Was the minimally relevant difference defined?	*0.70*	0.55 to 0.85
Please rate the overall transparency of the trial sequential analysis	*0.50*	0.46 to 0.55

1. ID

Record ID

_____

Standard procedure for data extraction

General workflow Source files via Covidence: Major mistakes and Errors conducted using Trial Sequential Analysis in systematic reviews or meta-analyses (METSA) (covidence.org) Filter by #CovidenceID Add missing files to covidence (e.g. protocol or supplementary material) Go through REDcap instruments 1-5 in the pre-specified order

Handling missing data or incompatibility When a numerical value is required but none is available, input: "-99" When text is required but none is available, input: "NA" If question is missing appropriate answer, consult JBM

Misc. When citing paper, place citation in " " If in doubt about any of the above, consult CGR or JBM

Reviewer identification

- ◯ BK
- ◯ CGR
- ◯ CL
- ◯ CM
- ◯ EBP
- ◯ JBM
- ◯ JHPR
- ◯ JHS
- ◯ JPS
- ◯ MA
- ◯ MHO
- ◯ SHH
- ◯ VW
- ◯ ZYL
- ◯ Not assigned

REDcap extraction number

_____

CovidenceID #

_____

DOI-number of the systematic review

_____
(Copy/paste the record number)

Provide first author surname and publication year

_____
(e.g. Johnson 2021)

In which country did the corresponding author have it's address/primary affiliation?

- ◯ Afghanistan
- ◯ Albania
- ◯ Algeria
- ◯ Andorra
- ◯ Angola
- ◯ Antigua & Deps
- ◯ Argentina
- ◯ Armenia
- ◯ Australia
- ◯ Austria
- ◯ Azerbaijan
- ◯ Bahamas
- ◯ Bahrain
- ◯ Bangladesh
- ◯ Barbados
- ◯ Belarus
- ◯ Belgium
- ◯ Belize
- ◯ Benin
- ◯ Bhutan
- ◯ Bolivia
- ◯ Bosnia Herzegovina
- ◯ Botswana
- ◯ Brazil
- ◯ Brunei
- ◯ Bulgaria
- ◯ Burkina
- ◯ Burundi
- ◯ Cambodia
- ◯ Cameroon
- ◯ Canada
- ◯ Cape Verde
- ◯ Central African Rep
- ◯ Chad
- ◯ Chile
- ◯ China
- ◯ Colombia
- ◯ Comoros
- ◯ Congo
- ◯ Congo (Democratic Rep)
- ◯ Costa Rica
- ◯ Croatia
- ◯ Cuba
- ◯ Cyprus
- ◯ Czech Republic
- ◯ Denmark
- ◯ Djibouti
- ◯ Dominica
- ◯ Dominican Republic
- ◯ East Timor
- ◯ Ecuador
- ◯ Egypt
- ◯ El Salvador
- ◯ Equatorial Guinea
- ◯ Eritrea
- ◯ Estonia
- ◯ Ethiopia
- ◯ Fiji
- ◯ Finland
- ◯ France
- ◯ Gabon
- ◯ Gambia
- ◯ Georgia
- ◯ Germany
- ◯ Ghana
- ◯ Greece
- ◯ Grenada
- ◯ Guatemala
- ◯ Guinea

◯ Guinea-Bissau
◯ Guyana
◯ Haiti
◯ Honduras
◯ Hungary
◯ Iceland
◯ India
◯ Indonesia
◯ Iran
◯ Iraq
◯ Ireland {Republic}
◯ Israel
◯ Italy
◯ Ivory Coast
◯ Jamaica
◯ Japan
◯ Jordan
◯ Kazakhstan
◯ Kenya
◯ Kiribati
◯ Korea North
◯ Korea South
◯ Kosovo
◯ Kuwait
◯ Kyrgyzstan
◯ Laos
◯ Latvia
◯ Lebanon
◯ Lesotho
◯ Liberia
◯ Libya
◯ Liechtenstein
◯ Lithuania
◯ Luxembourg
◯ Macedonia
◯ Madagascar
◯ Malawi
◯ Malaysia
◯ Maldives
◯ Mali
◯ Malta
◯ Marshall Islands
◯ Mauritania
◯ Mauritius
◯ Mexico
◯ Micronesia
◯ Moldova
◯ Monaco
◯ Mongolia
◯ Montenegro
◯ Morocco
◯ Mozambique
◯ {Burma}
◯ Namibia
◯ Nauru
◯ Nepal
◯ Netherlands
◯ New Zealand
◯ Nicaragua
◯ Niger
◯ Nigeria
◯ Norway
◯ Oman
◯ Pakistan
◯ Palau
◯ Panama
◯ Papua New Guinea
◯ Paraguay
◯ Peru
◯ Philippines
◯ Poland

◯ Portugal
◯ Qatar
◯ Romania
◯ Russian Federation
◯ Rwanda
◯ St Kitts & Nevis
◯ St Lucia
◯ Saint Vincent & the Grenadines
◯ Samoa
◯ San Marino
◯ Sao Tome & Principe
◯ Saudi Arabia
◯ Senegal
◯ Serbia
◯ Seychelles
◯ Sierra Leone
◯ Singapore
◯ Slovakia
◯ Slovenia
◯ Solomon Islands
◯ Somalia
◯ South Africa
◯ South Sudan
◯ Spain
◯ Sri Lanka
◯ Sudan
◯ Suriname
◯ Swaziland
◯ Sweden
◯ Switzerland
◯ Syria
◯ Taiwan
◯ Tajikistan
◯ Tanzania
◯ Thailand
◯ Togo
◯ Tonga
◯ Trinidad & Tobago
◯ Tunisia
◯ Turkey
◯ Turkmenistan
◯ Tuvalu
◯ Uganda
◯ Ukraine
◯ United Arab Emirates
◯ United Kingdom
◯ United States
◯ Uruguay
◯ Uzbekistan
◯ Vanuatu
◯ Vatican City
◯ Venezuela
◯ Vietnam
◯ Yemen
◯ Zambia
◯ Zimbabwe

CTU affiliated?

◯ Yes
◯ No

Which files were evaluated for this entry?	☐ Main paper ☐ Supplementary materials ☐ Prepublished protocol ☐ Pretrial registration (PROSPERO or elsewhere) ☐ Other (Include also material, that didn't contain relevant information, e.g., supplementary material when not relevant for TSA |||| To make a pdf searchable, use OCR like: https://online2pdf.com/convert-scanned-pdf-to-searchable-pdf#)
Please describe which files were evaluated	_____
Study details	
Choose the appropriate study type	◯ Systematic review (with pre-published/pre-registred protocol) ◯ Meta-analysis (without pre-published/pre-registred protocol) (Systematic reviews aim to minimize bias through the use of pre-specified research questions and methods that are documented in protocols)
Was the review an update of a previous systematic review?	◯ Yes ◯ No
When the review is an update of an existing review, please identify the protocol for updated review. If no protocol has been made specifically for the updated review, assess whether the updated review explicitly and firmly claims to adhere to methods defined in previous protocols/review versions. Otherwise, mark the updated review as having no predefined protocol.	
Please describe the review history (e.g. list previous versions, protocols, and describe if the update was performed by a different author group)	_____
Has the protocol been made public before data extraction began?	◯ Yes ◯ No ◯ Unclear
Was this a Cochrane Review?	◯ Yes ◯ No
Medical field and intervention type	
What was the overall research question?	_____

What is the medical field(s) of interest in the article?

- ☐ Allergy and immunology
- ☐ Alternative medicine
- ☐ Anesthesiology
- ☐ Cardiology
- ☐ Clinical biochemistry
- ☐ Dentistry
- ☐ Dermatology
- ☐ Diagnostic radiology
- ☐ Emergency medicine
- ☐ Endocrinology
- ☐ Family medicine
- ☐ Gastroenterology
- ☐ Gastroentestinal surgery
- ☐ Genetics
- ☐ Geriatric medicine
- ☐ Gynecology
- ☐ Hematology
- ☐ Hepatology
- ☐ Infectious diseases
- ☐ Intensive care
- ☐ Internal medicine
- ☐ Medical genetics
- ☐ Nephrology
- ☐ Neurology
- ☐ Neurosurgery
- ☐ Nuclear medicine
- ☐ Obstetrics
- ☐ Oncology
- ☐ Ophthalmology
- ☐ Orthopedic surgery
- ☐ Oto-rhino-laryngology (ear-nose-throat)
- ☐ Palliative care
- ☐ Pathology
- ☐ Pediatrics
- ☐ Pediatric psychiatry
- ☐ Physical medicine and rehabilitation
- ☐ Plastic surgery
- ☐ Preventive medicine
- ☐ Pulmonary diseases
- ☐ Psychiatry
- ☐ Thoracic surgery
- ☐ Urology
- ☐ Vascular surgery
- ☐ Other

Please describe the medical field of interest in the article

_____

What was the overall goal(s) with the intervention?

- ☐ Cure from disease
- ☐ Prevention of disease
- ☐ Prevention of complication to treatment (incl. perioperative care)
- ☐ Disease control
- ☐ Rehabilitation
- ☐ Palliation (pain management)
- ☐ Diagnostic
- ☐ Life support
- ☐ Other

Please describe the goal of the intervention	_____
Which intervention type(s) was examined in the article?	☐ Pharmacological ☐ Surgical ☐ Psychotherapy ☐ Diagnostic ☐ Medical device ☐ Nutritional ☐ Exercise/rehabilitation ☐ Lifestyle ☐ Alternative ☐ Other
Which intervention was examined in the article?	_____
To which specific diagnosis/health issue was the intervention applied?	_____

2. Quality assessment (AMSTAR 2)

Record ID

_____

Quality assessment of systematic reviews

AMSTAR 2 original guide for quality assessment of systematic reviews

[Attachment: "AMSTAR 2-Guidance-document.pdf"]

AMSTAR 2 original questionaire

[Attachment: "AMSTAR-2.pdf"]

Original publication AMSTAR 2

[Attachment: "Shea 2017.pdf"]

AMSTAR 2

If study design including statistical analysis plan was not defined prior to data extraction (e.g. in a pre-published protocol), skip ahead and rate as "Critically low"

- ☐ No protocol or protocol not publicly available prior to data extraction
- ☐ No critical flaws immediately identified

If study design including statistical analysis plan was not defined prior to data extraction (e.g. in a pre-published protocol), skip ahead and rate as "Critically low"

- ◯ Study design including statistical analysis plan not defined prior to data extraction
- ◯ No critical flaws immediately identified

1. Did the research questions and inclusion criteria for the review include the components of PICO?

- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome
- ☐ Timeframe for follow-up
- ☐ None of the above

2 = Yes | 1 = Partial yes |
0 = No

_____

Did the "PICO" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

2. Did the review explicitly state that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

The authors state that they had a written protocol or guide that included:

- ☐ Review question(s)
- ☐ A search strategy
- ☐ Inclusion/exclusion criteria
- ☐ A risk of bias assessment
- ☐ A meta-analysis/synthesis plan, if appropriate, and
- ☐ A plan for investigating causes of heterogeneity
- ☐ Justification for any deviations from the protocol (check also if NA)
- ☐ No

2 = Yes | 1 = Partial yes | 0 = No

_____

Did the "protocol" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

3. Did the review authors explain their selection of the study designs for inclusion in the review?

- ◯ Explanation for including only RCTs
- ◯ Explanation for including only NRSI
- ◯ Explanation for including both RCTs and NRSI
- ◯ None of the above

(Regarding missing explanation for including RCT's only: When many RCT's are available or the meta-analysis seek to find a "final conclusion" regarding intervention effects, it can be considered acceptable to not explain why only RCT's were included as this is standard practice. However, for more exploratory meta-analyses, non-RCT's should generally be included, and if they are not, the authors should explain why they weren't included. It is up to you to judge if the lack of explanation is acceptable or not.)

2 = Yes | 1 = Partial yes | 0 = No

_____

Did the "design" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

4. Did the review authors use a comprehensive literature search strategy?

- ☐ Searched at least 2 databases (relevant to research question)
- ☐ Provided keyword and/or search strategy (including timeframe)
- ☐ Justified publication restrictions (e.g. language)
- ☐ Searched the reference lists/bibliographies of included studies
- ☐ Searched trial/study registries
- ☐ Included/consulted content experts in the field
- ☐ Where relevant, searched for grey literature
- ☐ Conducted search within 24 months of completion of the review
- ☐ None of the above

2 = Yes | 1 = Partial yes | 0 = No

_____

Did the "search" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

5. Did the review authors perform study selection in duplicate?

- ◯ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ◯ Two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.
- ◯ No

2 = Yes | 1 = Partial yes | 0 = No

_____

Did the "selection" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

6. Did the review authors perform data extraction in duplicate?

- ◯ At least two reviewers achieved consensus on which data to extract from included studies
- ◯ Two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.
- ◯ No

2 = Yes | 1 = Partial yes | 0 = No

_____

Did the "extraction" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

7. Did the review authors provide a list of excluded studies and justify the exclusions?

☐ Provided a list of all potentially relevant studies that were read in full-text form but excluded from the review
☐ Justified the exclusion from the review of each potentially relevant study
☐ None of the above
(Applies only to studies excluded in full-text screening)

2 = Yes | 1 = Partial yes |
0 = No

_____

Did the "exclusion" question reveal any moderate or critical weaknesses?

◯ Yes, critical weakness
◯ Yes, moderate weakness
◯ No

Briefly describe the weakness

_____

8. Did the review authors describe the included studies in adequate detail (in relation to the PICO structure)?

☐ 1. Described populations
☐ 2. Described interventions
☐ 3. Described comparators
☐ 4. Described outcomes
☐ 5. Described research designs
☐ 6. Described populations in detail
☐ 7. Described interventions in detail (including doses where relevant)
☐ 8. Described comparators in detail (including doses where relevant)
☐ 9. Described study settings
☐ 10. Timeframe for follow-up
☐ No

2 = Yes | 1 = Partial yes |
0 = No

_____

Did the "details" question reveal any moderate or critical weaknesses?

◯ Yes, critical weakness
◯ Yes, moderate weakness
◯ No

Briefly describe the weakness

_____

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCT's

- ☐ Unconcealed allocation
- ☐ Lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)
- ☐ Allocation sequence that was not truly random
- ☐ Selection of the reported result from among multiple measurements or analyses of a specified outcome
- ☐ Includes only non-randomized studies of interventions (NRSI)
- ☐ None of the above

(Please read if in doubt: Chapter 8: Assessing risk of bias in a randomized trial)

2 = Yes | 1 = Partial yes | 0 = No

_____

Did the "RoB for RCT" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

NRSI's

- ☐ Assessed RoB from confounding
- ☐ Assessed RoB from selection bias
- ☐ Methods to ascertain exposures and outcomes
- ☐ Selection of the reported result from among multiple measurements or analyses of a specified outcome
- ☐ Includes only RCT's
- ☐ None of the above

2 = Yes | 1 = Partial yes | 0 = No

_____

Did the "RoB for NRSI" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

10. Did the review authors report on the sources of funding for the studies included in the review?

◯ Yes ◯ No

(Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies)

2 = Yes | 1 = Partial yes | 0 = No

_____

Did the "funding" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

11. Did the review authors use appropriate methods for statistical combination of results from RCT's?

- ☐ The authors justified combining the data in a meta-analysis
- ☐ They used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- ☐ They investigated the causes of any heterogeneity
- ☐ None of the above

2 = Yes | 1 = Partial yes |
0 = No

_____

Did the "meta analysis for RCT" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

11. Did the review authors use appropriate methods for statistical combination of results from NRSI's?

- ☐ The authors justified combining the data in a meta-analysis
- ☐ They used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
- ☐ Investigated the causes of any heterogeneity
- ☐ They statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
- ☐ None of the above
- ☐ The meta analysis did not include any NRSI's

2 = Yes | 1 = Partial yes |
0 = No

_____

Did the "meta analysis for NRSI" question reveal any moderate or critical weaknesses?

- ◯ Yes, critical weakness
- ◯ Yes, moderate weakness
- ◯ No

Briefly describe the weakness

_____

12. Did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

- ◯ Included only low risk of bias RCTs
- ◯ If the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.
- ◯ No

2 = Yes | 1 = Partial yes |
0 = No

_____

Did the "RoB impact" question reveal any moderate or critical weaknesses?	◯ Yes, critical weakness ◯ Yes, moderate weakness ◯ No
Briefly describe the weakness	_____
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	◯ Included only low risk of bias RCTs ◯ If RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results ◯ No
2 = Yes | 1 = Partial yes | 0 = No	_____
Did the "RoB interpretation" question reveal any moderate or critical weaknesses?	◯ Yes, critical weakness ◯ Yes, moderate weakness ◯ No
Briefly describe the weakness	_____
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	◯ There was no significant heterogeneity in the results ◯ If heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review ◯ No
2 = Yes | 1 = Partial yes | 0 = No	_____
Did the "heterogeneity" question reveal any moderate or critical weaknesses?	◯ Yes, critical weakness ◯ Yes, moderate weakness ◯ No
Briefly describe the weakness	_____
15. Did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	◯ Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias ◯ No
2 = Yes | 1 = Partial yes | 0 = No	_____
Did the "publication bias" question reveal any moderate or critical weaknesses?	◯ Yes, critical weakness ◯ Yes, moderate weakness ◯ No

Briefly describe the weakness

_____

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

◯ The authors reported no competing interests
◯ The authors described their funding sources and how they managed potential conflicts of interest
◯ No

2 = Yes | 1 = Partial yes |
0 = No

_____

Did the "conflict of interest" question reveal any moderate or critical weaknesses?

◯ Yes, critical weakness
◯ Yes, moderate weakness
◯ No

Briefly describe the weakness

_____

Were there any other flaws (critical or non-critical) noted during the AMSTAR 2 assessment?

◯ Yes
◯ No

Please decribe the flaws noted

_____

The table provides a rough overview based on the answers above - but AMSTAR 2 is NOT exhaustive and critical flaws that are not reported via the AMSTAR 2 assessment tool should still play a role in the overall assessment

Question

Yes (2), Partial yes (1), No (0)

Weakness: Critical (2), Moderate (1), No (0)

1. PICO

[amstar_pico_sum]

[amstar_pico_weak]

2. Protocol

[amstar_protocol_sum]

[amstar_protocol_weak]

3. Design

[amstar_design_sum]

[amstar_design_weak]

4. Search strategy

[amstar_search_sum]

[amstar_search_weak]

5. Study selection

[amstar_selection_sum]

[amstar_selection_weak]

6. Extraction

[amstar_extraction_sum]

[amstar_extraction_weak]

7. Exclusion

[amstar_exclusion_sum]

[amstar_exclusion_weak]

8. PICO details

[amstar_details_sum]

[amstar_details_weak]

9. RoB in RCT's

[amstar_rob_rct_sum]

[amstar_rob_rct_weak]

9. RoB in NRSI's

[amstar_rob_nrsi_sum]

[amstar_rob_nrsi_weak]

10. Study funding

[amstar_funding_sum]

[amstar_funding_weak]

11. Statistics RCT

[amstar_meta_rct_sum]

[amstar_meta_rct_weak]

11. Statistics NRSI

[amstar_meta_nrsi_sum]

[amstar_meta_nrsi_weak]

12. RoB impact

[amstar_meta_rob_sum]

[amstar_meta_rob_weak]

13. RoB interpretation

[amstar_res_rob_sum]

[amstar_res_rob_weak]

14. Heterogeneity

[amstar_hetero_sum]

[amstar_hetero_weak]

15. Publication bias

[amstar_pubbias_sum]

[amstar_pubbias_weak]

16. COI

[amstar_coi_sum]

[amstar_coi_weak]

What is the overall confidence in the study? See guide below	☐ High ☐ Moderate ☐ Low ☐ Critically low (Please see Shea et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358: j4008)

Guide to rating confidence level:

High
(No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

Moderate
(More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

Low
(One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

Critically low
(More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence

FILL AT CONSENSUS ONLY

How did you agree to rate the overall confidence level of the study?

- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Critically low

3. Study description (non-repeatable)

Record ID

_____

Instrument 3 contents

Study details
Outcomes TSA documentation
Study summary and conclusions
GRADE Misc. comments

To whom were the intervention group(s) compared (what is the type of comparator)?

- ☐ Standard care
- ☐ Other active intervention
- ☐ Placebo
- ☐ No treatment
- ☐ Other

Please describe the comparator

_____

Was the literature search date defined?

- ◯ Yes
- ◯ No

Date of literature search (final date)

_____
(If authors state month only, e.g, December 2019, choose the first day of the month, i.e., 01-12-2019)

Outcomes

Authors classify outcome measures inconsistently. In this database, outcomes are classified by the following definitions:

Primary or "main" outcome(s): The central research question(s) of the study and the reason that the study is done

Secondary or "additional" outcome(s): Research question(s) applied to all participants of the included studies. Provides additional information on the intervention effect.

Exploratory outcome(s): Research question(s) applied to all participants of the included studies. Primarily used for hypothesis generation.

Subgroup analysis: analyses of any of the outcomes described above, but in a subset of the sample population or the included trials. Can provide information on sources of heterogeneity (variations in demographics, intervention, etc.)
(Cochrane definition: https://handbook-5-1.cochrane.org/chapter_9/9_6_2_what_are_subgroup_analyses.htm)

How many primary outcomes were investigated in this study?

_____

List all primary outcomes in study

UDGÅR

_____
(Place each outcome on a separate line)

List all primary outcomes in the article _____

If more than 20 primary outcomes, use the field below

Please describe outcomes here IF more than 20 primary outcomes or the outcomes were otherwise incompatible with the table above	_____
How were the primary outcomes labelled by the authors?	◯ "Primary" ◯ "Main" ◯ Not labelled ◯ Other
Please describe how the primary outcomes were labelled by the authors	_____
How many secondary outcomes were investigated in this study?	_____

List all secondary outcomes in the article _____

If more than 20 secondary outcomes, use the field below

Please describe outcomes here IF more than 20 secondary outcomes or the outcomes were otherwise incompatible with the table above	_____
List all secondary outcomes in study UDGÅR	_____ (Place each outcome on a separate line)
How were the secondary outcomes labelled by the authors?	◯ "Secondary" ◯ "Additional" ◯ "Subgroup analysis" ◯ Not labelled ◯ Other
Please describe how the secondary outcomes were labelled by the authors	_____
How many exploratory outcomes were investigated in this study?	_____

List all exploratory outcomes in the article _____

If more than 20 secondary outcomes, use the field below

Please describe outcomes here IF more than 20 exploratory outcomes or the outcomes were otherwise incompatible with the table above	_____
List all exploratory outcomes in study UDGÅR	_____ (Place each outcome on a separate line)
How were the exploratory outcomes labelled by the authors?	◯ "Exploratory" ◯ "Additional" ◯ "Observational" ◯ "Subgroup analysis" ◯ Not labelled ◯ Other
Please describe how the exploratory outcomes were labelled by the authors	_____
Were any subgroup analysis performed?	◯ Yes ◯ No
To which outcome(s) were subgroup analyses applied?	

Primary _____ _____

Secondary _____

Exploratory _____

Please describe the subgroup analysis performed in the study UDGÅR	_____ (Describe to which outcome(s) the subgroup analysis was performed)
Please describe the subgroup analysis performed in the study	_____ (Describe how the subgroups were defined)

How were the subgroup analyses labelled by the authors?

◯ "Subgroup analysis"
◯ "Secondary"
◯ "Exploratory"
◯ "Additional"
◯ "Observational"
◯ Not labelled
◯ Other

Please describe how the subgroup analyses were labelled by the authors

_____

To which outcome(s) were TSA applied?

TSA applied with sufficient data TSA applied but insufficient data (AIS < 5% RIS/DARIS) Intention of TSA but no data available TSA not applied (justified) TSA not applied (not justified)

Primary _____ _____

_____

_____

—

_____

—

_____

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_____

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Secondary _____

_____

_____

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_____

—

_____

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_____

—

Exploratory _____

_____

_____

—

_____

—

_____

—

Subgroup analyses: define type of subgroup and to which outcome _____ _____ _____ _____ _____
Outcomes not listed above _____ _____ _____ _____ _____

UDGÅR Please list all outcomes and subgroup analyses to which the authors explicitly intended to apply TSA as described in the article

_____
(Disregarding insufficient information sizes, missing data)

Authors may choose to apply TSA but not share the graph and only report TSA CI's - look closely!

UDGÅR

Which outcomes and subgroup analyses did the authors explicitly intend to apply TSA to (as described in the article)?

Authors may choose to apply TSA but not share the graph and only report TSA CI's - look closely!

[outc_prim_1]

UDGÅR If applicable, please list outcomes where TSA was performed, but could not produce an output due to too small sample size (e.g., AIS < 2% RIS)

_____

UDGÅR If applicable, please list outcomes where TSA was intended, but could not be performed due to lack of data, i.e., no data available

_____

UDGÅR

On which outcomes were TSA performed, but could not produce an output due to too small sample size (e.g., AIS < 2% RIS)

_____

UDGÅR

To which outcomes where TSA was intended, but could not be performed due to lack of data, i.e., no data available

_____

[outc_prim_1]

TSA - Documentation

Has the authors stated which version of the Trial Sequential Analysis software they used?

◯ Yes
◯ No

Was the Trial Sequential Analysis software correctly referenced?	◯ Yes ◯ No ◯ Not referenced (Minimum requirement: exact software version e.g. 0.9.5.10 + source e.g. ctu.dk)
Reference	_____ (Please provide information. If "No" state which references were actually provided or "no references provided".)
Was the choice of statistical methods for Trial Sequential Analysis referenced?	◯ Yes ◯ No (Either the manual or relevant references should be cited)

Which reference(s) was used?	☐ Brok J et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many metaanalyses. J. Clin. Epidemiol.2008;61 (8), 763-769. ☐ Brok et al. Apparently conclusive meta-analyses may be inconclusive: trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol. 2009;38(1):287-298 ☐ Imberger G, Gluud C, Boylan J, Wetterslev J. Systematic Reviews of Anesthesiologic Interventions Reported as Statistically Significant: Problems with Power, Precision, and Type 1 Error Protection. Anesth Analg. 2015;121:1611-1622 ☐ Imberger G et al. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. British Medical Journal Open 2016; 6: e011890 ☐ Jakobsen JC et al. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol 2014;14:120. ☐ Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. Control Clin Trials. 1997;18:580-593. ☐ Thorlund K et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol 2009;38:276-86. ☐ Thorlund K et al. User manual for Trial Sequential Analysis (TSA). Available: www.ctu.dk/tsa/files/tsa_manual.pdf ☐ Wetterslev J et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J. Clin. Epidemiol. 2008;61 (1), 64-75. ☐ Wetterslev J et al. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol. 2009;9:86 ☐ Wetterslev J et al. Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 2017;17:39. ☐ Other
Other references	_____ (Please insert complete reference - If the reference is relevant inform Christian Riberholt by e-mail)
Did the authors provide a TSA-report (or other formative report)?	◯ Yes ◯ No (Check supplementary materials)
Study summary and conclusions	

How many RCT's were included in the article?	_____ (Please list the actual number of RCT included.)
How many RCT's were included in the largest meta analysis?	_____ (Largest by sample size. If the RCT has multiple groups and, therefore, is included in the meta-analysis more than once, count each data entry and make a note in the 'general comment field' below.)
How many non-randomized trials were included in the article?	_____
How many non-randomized trials were included in the largest meta analysis?	_____ (Largest by sample size)
Was the meta analysis presented in a forest plot?	◯ Yes ◯ No

The following questions ask for the FINAL conclusions of the study and not the "subconclusions" of the individual analyses, i.e., the results of individual TSA analyses or forest plots

What did the authors conclude about the intervention effect on the outcome(s) analyzed with TSA? Outcome(s) analyzed with TSA: [outc_tsa]	◯ Inconclusive ◯ Beneficial ◯ Harmful ◯ Futile ◯ Other/multiple (Reminder to read the entire conclusion - authors may conclude that data indicates effect, only to conclude that the data quality was too low and thus the final conclusion is "inconclusive")
Please describe the conclusion (or copy/paste)	_____
Were there any conclusions on the waste of research (relevant when limits for benefit, futility or harm are reached) ?	◯ Yes ◯ No (When trials have been made far past RIS/DARIS, the authors may conclude that excessive or unneccessary trials have been made.)
What did the authors conclude about the waste of research?	_____

GRADE

Was GRADE used for one or more outcomes to which TSA was applied? (including outcomes where TSA wasn't performed due to lack of data)	◯ Yes, one ◯ Yes, more than one ◯ No (GRADE = Grading of Recommendations, Assessment, Development and Evaluations)

How many outcomes were GRADE'd AND analyzed with TSA?

(including outcomes where TSA wasn't performed due to lack of data)

_____

UDGÅR

Describe to which outcome(s) GRADE was applied

_____
(Describe only outcomes to which TSA was applied. You noted, that the following outcomes were not analyzed: [outc_tsa_miss])

To which outcome(s) were GRADE applied?

Primary _____ _____
_____For outcomes not listed:_____
Secondary _____
_____For outcomes not listed:_____
Exploratory _____
_____For outcomes not listed:_____

Do you have any further comments on the application of GRADE?

_____

Did the Trial Sequential Analysis explicitly influence the GRADE assessment?

◯ Yes ◯ No

Describe how Trial Sequential Analysis influenced GRADE evaluation

_____

How was the outcome GRADE'd?

UDGÅR

◯ High
◯ Moderate
◯ Low
◯ Very low

How were the outcomes GRADE'd?

☐ High
☐ Moderate
☐ Low
☐ Very low

Were the downgrade methods for imprecision described?

◯ Yes
◯ No

Which parameters influenced the grading of imprecision in GRADE?

☐ Imprecision downgraded 2 levels if DARIS < 50%; 1 level if DARIS between 50-100%; 0 levels if DARIS is reached 100% or if the cumulative Z-curve crosses boundaries for futility, benefit or harm
☐ Imprecision downgraded but the cut-offs were different than (1) or not specified (describe below)
☐ Imprecision was evaluated using the Trial Sequential adjusted confidence interval
☐ Judgement of the width of conventional 95% CI's
☐ Other

Describe how	_____
How much was imprecision downgraded?	◯ 1 level ◯ 2 levels ◯ Imprecision was not explicitly downgraded ◯ Other
How much was imprecision downgraded?	☐ 1 level ☐ 2 levels ☐ Imprecision was not explicitly downgraded ☐ Other
Please describe how imprecision was downgraded	_____
Misc.	
General comments on study issues or other noteworthy details not described elsewhere:	_____ (Please fill in general comments that has not been elucidated in the questionaire)
Did the article mention/apply Bayesian approaches to statistical analysis? (search article for "bayes")	◯ Yes ◯ No (This question is used to screen for Bayesian content for a potential future project)

4. TSA Description (repeatable)

Record ID

_____

Instrument 4 contents

TSA - Outcome details TSA - Methods Dichotomous/continuous TSA - Graphical presentation and results Graphics Results

TSA - Outcome details

Please list all outcomes and subgroups analyzed with TSA (only in first instance of "Instrument 4 - TSA description)

_____

In the previous instrument, you listed the following:
[outc_tsa]

And noted that TSA wasn't performed on the following outcomes due to lack of data:
[outc_tsa_miss]

UDGÅR

How many outcomes were analyzed with TSA? UDGÅR

_____
(Those that were actually analyzed, i.e., not those with no data available - including subgroup analyses)

REMINDER! When multiple outcomes have been analyzed with TSA, repeat the TSA instrument and extract data from one dichotomous and one continuous outcome measure if applicable.

Dichotomous outcomes
a - Identify TSAs performed on dichotomous outcome measures (if NA, skip and go to 2a)
b - if a>1, identify TSAs from highest rank (primary>secondary>explorative>subgroup)
c - if b>1, identify TSA with highest acquired information size (AIS)
d - if c>1, identify TSA with highest AIS/RIS
e - if d>1, pick the one that appears in the article first Continuous outcomes
a - Identify TSAs performed on continuous outcome measures (if NA, skip)
b - if a>1, identify TSAs from highest rank (primary>secondary>explorative>subgroup)
c - if b>1, identify TSA with highest acquired information size (AIS)
d - if c>1, identify TSA with highest AIS/RIS
e - if d>1, pick the one that appears in the article first

What is the outcome to which TSA was applied?

UDGÅR

_____
(Please copy/paste from paper)

What is the outcome to which TSA was applied (pick only one!)

Primary _____ _____

Secondary _____

Exploratory _____

Subgroup analyses _____
If the outcome to which TSA was applied is not listed above, please describe here: _____

What is the data type for the outcome?	◯ Dichotomous ◯ Continuous
What is the type of outcome? UDGÅR - overflødigt	◯ Primary ◯ Secondary ◯ Exploratory ◯ Subgroup analysis
Was the outcome analyzed with TSA analyzed in a network meta analysis (NMA)?	◯ Yes ◯ No
Which analysis model was used for the outcome analyzed with TSA?	◯ Fixed-effect model ◯ Random-effects models ◯ Fixed- and random-effects models ◯ Other ◯ None
Please provide additional model details and/or describe other models	_____
Did the authors conclude that there was insufficient data, e.g., AIS < 5% RIS	◯ Yes ◯ No

TSA - Methods

This instrument asks for the details of the TSA analysis. Often, only one alpha-level will be chosen for all analyses (TSA, forest plots, etc.) but in the case that alpha-levels (or other details) differ, please note the value used for the TSA analysis and describe the difference in comments at the end of the instrument.

Values for each TSA should be presented in the figure, above the figure (figure head) or below the figure (legend), but will often be found in the description of statistical methods and/or results section.

Was the alpha-level defined?	◯ Yes ◯ Yes, conventional at 0.05 ◯ No (Provide values under comments)
Provide the alpha-level defined	_____ (Please provide as number, not percentage (e.g., 0.05 and not 5))
Describe the choice of alpha, if possible	_____ ((if alpha=0.05, note: "conventional"))
Was the alpha level explicitly corrected for multiplicity?	◯ Yes ◯ No
Which method was used to adjust alpha for multiplicity?	☐ Bonferroni ☐ Other
Please describe the method used for multiplicity correction	_____

Was the power defined?	◯ Yes ◯ Yes, conventional at 0.8 ◯ Yes, conventional at 0.9 ◯ No
Provide the power defined	_____ (Please provide as number, not percentage (e.g., 0.8 and not 80))
Describe the choice of power used in the Trial Sequential Analysis	_____ ((if power=0.8 or 0.9, note: "conventional"))
Was heterogeneity correction used for Trial Sequential Analysis?	◯ Inconsistency (I-square) ◯ Diversity (D-square) ◯ Not described, but no heterogeneity found in meta analysis (I^2=0%) ◯ Not described / not clear ◯ Other ◯ No (Model variance based = Diversity adjusted)
Describe the choice of heterogeneity used in the Trial Sequential Analysis	_____
Was the value for heterogeneity correction provided?	◯ Yes ◯ No
Please provide values for heterogeneity correction	_____
TSA methods - dichotomous outcome	
Which association measure was used for analysis in the dichotomous outcome?	☐ Relative risk (RR) ☐ Risk difference (RD) ☐ Odds Ratio (OR) ☐ Peto OR ☐ Other
Please provide information on association measures	_____
Was it relevant to correct for zero events in one group? (i.e. did one group have zero events?)	◯ Yes ◯ No ◯ Unclear (not described)

How did they correct for zero events?

- ☐ Constant
- ☐ Reciprocal
- ☐ Empirical
- ☐ Correction value = 1
- ☐ Correction value = 0.5
- ☐ Correction value = 0.01
- ☐ Correction value = 0.001
- ☐ Trials with no events were excluded
- ☐ No correction described
- ☐ Other methods

(Check all relevant boxes)

Please describe the method used for correction of zero events

_____

Was proportion of events in the control group (Pc) defined?

- ◯ Yes, with value
- ◯ Yes, but value not reported
- ◯ No

(Provide values under comments)

Where did the choice for the proportion of events in the control group (Pc) come from?

- ☐ From other published meta-analysis
- ☐ From one or more published randomised trials
- ☐ From one or more published observational studies
- ☐ From the observed data in their meta-analysis
- ☐ Unclear
- ☐ Other
- ☐ Not mentioned

Please describe the choice of Pc

_____

Please provide the value defined for Pc

_____

Was the relative risk reduction (RRR) defined?

- ◯ Yes
- ◯ No

Please provide the RRR defined

_____

(Input as decimal number, not percentage)

Was it described how the relative risk reduction (RRR) was defined?

- ☐ From a published meta-analysis
- ☐ From one or more published randomised trials
- ☐ From one or more observational studies
- ☐ From the observed data in their meta-analysis
- ☐ Clinical experience (pick this if authors have assessed the RRR as "realistic" or similar)
- ☐ Other
- ☐ No

Describe the choice of RRR used in the Trial Sequential Analysis

_____

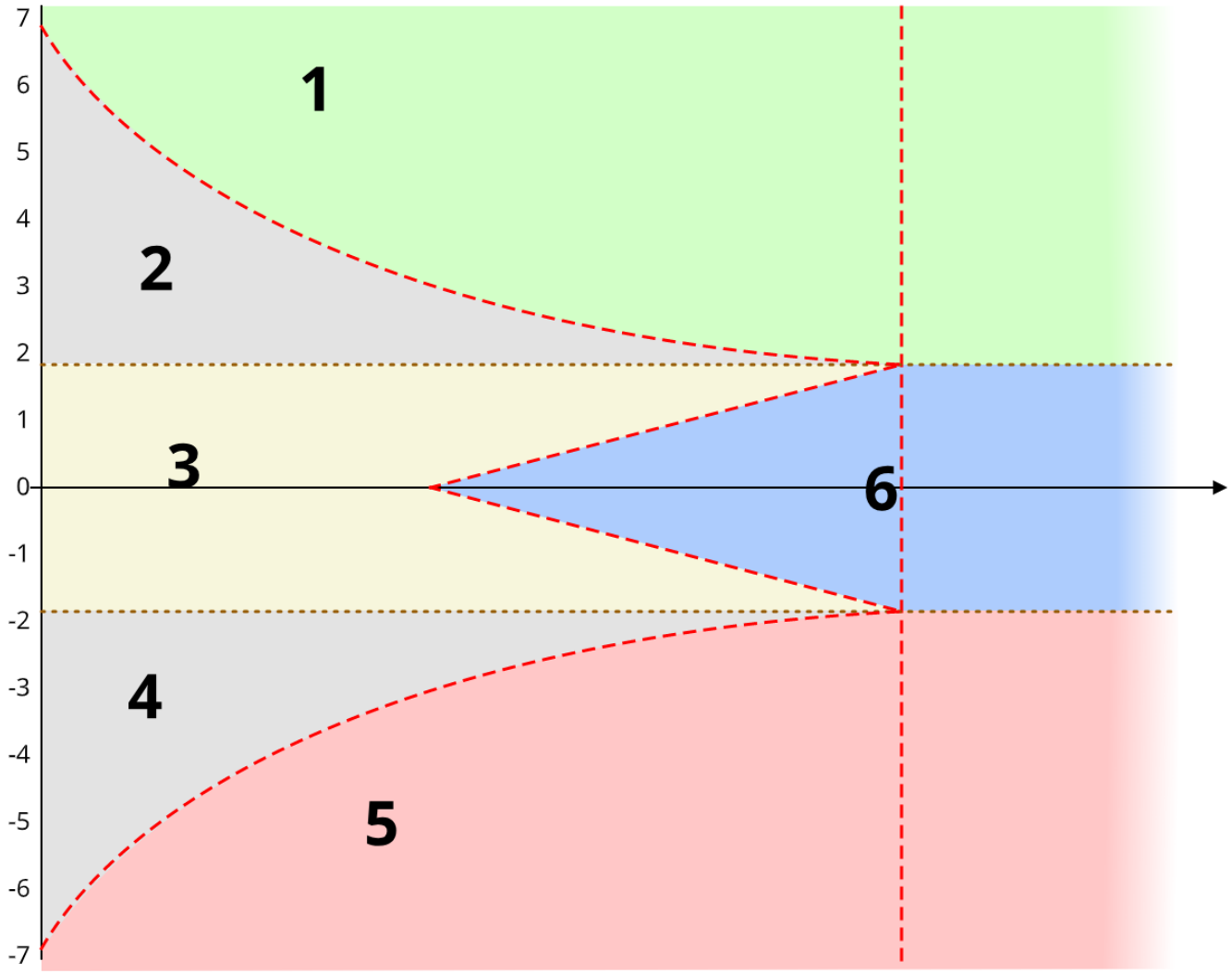
TSA methods - continuous outcome

Which association measure was used in the analysis for the continuous outcome?	☐ Mean difference (MD) ☐ Standardized mean difference (SMD) ☐ Other (Weighted mean difference (WMD) is the same as MD)
Please provide information on association measures	_____
Was variance defined?	◯ Yes ◯ No
Provide the variance defined	_____
Describe the choice of variance used in the Trial Sequential Analysis	_____
Was MIREDIF defined?	◯ Yes ◯ No ("MIREDIF" = Minimal relevant difference. Provide values under comments)
Provide the MIREDIF defined	_____
Describe the choice of MIREDIF used in the Trial Sequential Analysis	_____
TSA - Graphical presentation and results	
Graphics	
Was the Trial Sequential Analysis presented in a figure?	◯ Yes ◯ No
Were was the TSA graph presented?	◯ In article ◯ In supplementary materials ◯ Other
Please insert reference to the TSA figure, e.g., "Figure 4"	_____
Please describe where the TSA graph was presented	_____
Are the conventional 5% limits correctly outlined?	◯ Yes ◯ No ◯ Not outlined
Why was it not correct?	_____

Was the area of benefit above or below the x-axis?	◯ Above ◯ Below
Is the monitoring boundary of benefit correctly outlined?	◯ Yes ◯ No ◯ No, not outlined due to software limitation if first trial exceeds RIS/DARIS ◯ No, not outlined (but not relevant with only negative Z-scores)
Why was it not correct?	_____
Is the monitoring boundary of harm correctly outlined?	◯ Yes ◯ No ◯ No, not outlined due to software limitation if first trial exceeds RIS/DARIS ◯ No, not outlined (but not relevant with only positive Z-scores)
Why was it not correct?	_____
Is the area of futility (the inner wedge) correctly outlined?	◯ Yes ◯ No ◯ No, not outlined due to software limitation if first trial exceeds RIS/DARIS or cumulative sample size doesn't reach area of futility ◯ Inner wedge not applied
Why was it not correct?	_____
Is the line indicating required information size (RIS or DARIS) correctly outlined?	◯ Yes ◯ No ◯ No, not outlined due to software limitation if first trial exceeds RIS/DARIS
Why was it not correct?	_____
Is the cumulative Z-curve correctly outlined?	◯ Yes ◯ No ◯ No (trial spacing equal and not based on trial sizes) ◯ Not outlined
Why was it not correct?	_____
Was the graphical presentation of the TSA different or flawed in a way not already described?	◯ Yes ◯ No

Please describe flaws and/or differences	_____
Results	
How many trials were analyzed?	_____ (If discrepancy between figure and text/table/forest plot - report from figure! If trials are included more than once due to multiple groups, count each data entry and make a note in the 'Misc. comments on TSA' at the end.)
What was the acquired information size?	_____ (If NA, input '-99')
Was the AIS directly extracted from figure or figure legend or was it calculated by the extractor, e.g., from forest plots?	◯ Directly extracted (e.g., from figure, figure legend or text) ◯ Calculated (e.g., summing sample sizes from forest plot)
Did the authors present a required information size for the analysis?	☐ Yes, diversity-adjusted required information size (DARIS) ☐ Yes, non-adjusted required information size (RIS) ☐ Yes, but not clear if RIS or DARIS ☐ No
What was the estimated non-adjusted or diversity adjusted required information size (RIS or DARIS)?	_____
Was the non-adjusted or diversity adjusted required information size (RIS or DARIS) estimated from number of events or population size?	◯ Number of events ◯ Population size ◯ Not available

If futility wedge is missing, area 6 is limited to the area past RIS/DARIS



Please note in the table below were the individual trials of the Z-curve was placed in the TSA graphic (see area description in image above) - if TSA contains more than 84 studies, please leave a comment using the comment function and contact JBM

Trial number	TSA graph area (input integer: 1-6)	Trial number	TSA graph area (input integer: 1-6)	Trial number	TSA graph area (input integer: 1-6)
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	
19		20		21	
22		23		24	
25		26		27	
28		29		30	
31		32		33	
34		35		36	
37		38		39	
40		41		42	
43		44		45	
46		47		48	
49		50		51	
52		53		54	
55		56		57	
58		59		60	
61		62		63	
64		65		66	
67		68		69	
70		71		72	
73		74		75	

76 _____ 77 _____ 78 _____
79 _____ 80 _____ 81 _____
82 _____ 83 _____ 84 _____

Did the authors provide Trial Sequential adjusted confidence intervals?

◯ Yes
◯ Yes, but mislabelled
◯ No
(Should be labelled as Trial Sequential adjusted confidence interval or TSA CI (not 95%CI))

In what way did they mislabel the Trial Sequential adjusted confidence interval?

_____

What was the estimated effect size for the outcome analyzed with TSA?

Point estimate (e.g., mean dif, RR)

_____

Conventional CI, lower limit

_____

Conventional CI, upper limit

_____

TSA adjusted CI, lower limit

_____

TSA adjusted CI, upper limit

_____

How was the outcome GRADE'd?

◯ High
◯ Moderate
◯ Low
◯ Very low
◯ The outcome was not GRADE'd

How much was imprecision downgraded?

◯ 1 level
◯ 2 levels
◯ Imprecision was not explicitly downgraded
◯ Other

Misc. comments on TSA not considered elsewhere

_____

Please rate the overall transparency of the TSA analysis

You may consider the following variables:

Discrepancies between graph and text or between text segments Graphic quality of figure - including labels Specification of included trials Acquired information size Required information size (RIS or DARIS) Relative risk reduction or MIREDIF Heterogeneity Proportion of events in the control population (only dichotomous outcomes) Variance (only continuous outcomes) Chosen association measure

- ◯ Excellent / really good (all parameters transparently presented)
- ◯ Good (few parameters missing)
- ◯ Poor (several important parameters missing)
- ◯ Useless (graph unreadable and/or crucial parameters missing)

(Transparency almost equal to reproducibility)

Which parameters impaired the transparency of the TSA ?

- ☐ Discrepancies between graph and text or between text segments
- ☐ Graphic quality of figure - including labels
- ☐ Specification of included trials
- ☐ Acquired information size
- ☐ Required information size (RIS or DARIS)
- ☐ Relative risk reduction or MIREDIF
- ☐ Heterogeneity
- ☐ Proportion of events in the control population (only dichotomous outcomes)
- ☐ Variance (only continuous outcomes)
- ☐ Chosen association measure
- ☐ Other

Please describe which other parameters influenced your rating

_____

5. Protocol description (non-repeatable)

Record ID

_____

Instrument 5 contents

Protocol availability
Coherence check
Outcomes Planning of TSA Planning of dichotomous outcomes Planning of continuous outcomes Planning of GRADE

Protocol availability

Has a protocol been made public before data extraction began?

◯ Yes
◯ No
◯ Unclear

Do you have any comments?

_____

Where has the protocol been made publicly available?

☐ 1. Scientific journal
☐ 2. PROSPERO
☐ 3. Web-page
☐ 4. Other
(If available from multiple places (e.g. Scientific journal and Prospero) use highest ranked when moving forward)

Please insert link to the protocol in the box

_____
(Webpage; CRD-number; DOI; PubmedID etc.)

Date the protocol was first submitted

_____

Date the protocol was first published

_____

Was the protocol updated, i.e., are more than one version of the protocol available?

◯ Yes
◯ No

Please provide the dates at which the protocol versions were published (including the first)

Version DATE (Y-M-D)
First version _____
Second version _____
Third version _____
Fourth version _____
Fifth version _____

Was the complete search strategy publicly available before the literature search was completed?

◯ Yes
◯ No
◯ Not clear

Literature search completed:

[adddet_litdate]

Please describe how it was not clear if the search strategy was predefined

_____

Was the protocol publicly available before initiation of formal screening?

◯ Yes
◯ No
◯ Not clear

Please describe why it was not clear if protocol was defined prior to formal screening

_____

Was the protocol publicly available before completion of formal screening?

◯ Yes
◯ No
◯ Not clear

Please describe why it was not clear if protocol was defined prior to completion of formal screening

_____

Coherence check

Please extract information from the latest protocol version that was publicly available BEFORE DATA EXTRACTION

Outcomes

Were the outcomes in the article also defined in the protocol?

Yes No (or different)
Primary _____ _____
_____ _____
_____ _____

Secondary _____
_____
_____
_____

Exploratory _____
_____
_____
_____

If the outcomes in the article are not listed above, describe here _____ _____

Please describe if differences between article and protocol have been observed.	_____
Were any additional outcomes defined in the protocol?	◯ Yes ◯ No
In summary, which outcomes defined in the protocol are DIFFERENT from those analyzed in the paper?	☐ Primary was different ☐ Secondary was different ☐ Exploratory was different (CAREFULLY check each outcome. Check box if DIFFERENT)
How many primary outcomes are defined in the protocol?	_____
List all primary outcomes of the protocol	_____
Please comment on the differences between primary outcomes of protocol and the paper	_____
How many secondary outcomes are defined in the protocol?	_____
List all secondary outcomes of the protocol	_____
Please comment on the differences between secondary outcomes of protocol and the paper	_____
How many exploratory outcomes are defined in the protocol?	_____
List all exploratory outcomes of the protocol	_____
Please comment on the differences between exploratory outcomes of protocol and the paper	_____
Were any dichotomous outcomes defined?	◯ Yes ◯ No
Was TSA planned for the dichotomous outcomes?	◯ Yes ◯ No (Includes generic descriptions such as "TSA will be applied" without specification of outcome)
Were any continuous outcomes defined?	◯ Yes ◯ No

Was TSA planned for the continuous outcomes?	◯ Yes ◯ No (Includes generic descriptions such as "TSA will be applied" withouth specification of outcome)
Was supgroup analysis planned in the protocol?	◯ Yes ◯ No

Was the supgroup analysis that was planned in the protocol the same as was conducted in the study?

◯ Yes
◯ No

You wrote about the subgroup analysis performed in the study:
[outc_subtxt_2]

To the following outcomes:

Primary Secondary Exploratory
[outc_prim_sub_1]
[outc_prim_sub_2]
[outc_prim_sub_3]
[outc_prim_sub_4]
[outc_prim_sub_5]
[outc_prim_sub_6]
[outc_prim_sub_7]
[outc_prim_sub_8]
[outc_prim_sub_9]
[outc_prim_sub_10]
[outc_prim_sub_11]
[outc_prim_sub_12]
[outc_prim_sub_13]
[outc_prim_sub_14]
[outc_prim_sub_15]
[outc_prim_sub_16]
[outc_prim_sub_17]
[outc_prim_sub_18]
[outc_prim_sub_19]
[outc_prim_sub_20]

[outc_prim_sub_comment]

[outc_sec_sub_1]
[outc_sec_sub_2]
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[outc_sec_sub_comment]

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[outc_exp_sub_19]
[outc_exp_sub_20]

[outc_exp_sub_comment]

How many subgroup analyses were planned?	_____
Which subgroup analyses were planned?	_____
Please describe differences between planned and performed subgroup analyses	_____
Planning of Trial Sequential Analysis	
Did the protocol define that TSA would be applied?	◯ Yes ◯ No
Please copy/paste the description of the TSA plan	_____ (If TSA is not described in one continuous text, please define segments with " ")
Was the choice of statistical methods for Trial Sequential Analysis referenced?	◯ Yes ◯ No (Either the manual or relevant references should be cited)

Which reference(s) was used?

- ☐ Brok J et al. Trial sequential analysis reveals insufficient information size and potentially false positive results in many metaanalyses. J. Clin. Epidemiol. 2008;61 (8), 763-769.
- ☐ Brok et al. Apparently conclusive meta-analyses may be inconclusive: trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol. 2009;38(1):287-298
- ☐ Imberger G, Gluud C, Boylan J, Wetterslev J. Systematic Reviews of Anesthesiologic Interventions Reported as Statistically Significant: Problems with Power, Precision, and Type 1 Error Protection. Anesth Analg. 2015;121:1611-1622
- ☐ Imberger G et al. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. British Medical Journal Open 2016; 6: e011890
- ☐ Jakobsen JC et al. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol 2014;14:120.
- ☐ Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. Control Clin Trials. 1997;18:580-593.
- ☐ Thorlund K et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol 2009;38:276-86.
- ☐ Thorlund K et al. User manual for Trial Sequential Analysis (TSA). Available: www.ctu.dk/tsa/files/tsa_manual.pdf
- ☐ Wetterslev J et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J. Clin. Epidemiol. 2008;61 (1), 64-75.
- ☐ Wetterslev J et al. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol. 2009;9:86
- ☐ Wetterslev J et al. Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 2017;17:39.
- ☐ Other

Other references

_____

(Please insert complete reference - If the reference is relevant inform Christian (Christian who?) by e-mail)

Did the protocol define to which outcomes TSA would be applied?

- ◯ Yes
- ◯ No

Were those outcomes the same as were eventually analyzed with TSA in the study?

(disregard discrepancies caused by lack of data)

- ◯ Yes
- ◯ No

The study applied TSA to the following [tsaout_num][first-instance] outcome(s):

[tsaout_list][first-instance]

Please describe differences between TSA outcomes in protocol and study

_____

Which analysis model was planned for the outcome(s) analyzed with TSA?

- ◯ Fixed-effect model
- ◯ Random-effects models
- ◯ Fixed- and random-effects models
- ◯ Other
- ◯ The outcome to which TSA was applied was not defined in the protocol
- ◯ None

Please provide additional model details and/or describe other models if relevant

_____

Was the alpha-level defined for the outcome analyzed with TSA?

- ◯ Yes
- ◯ Yes, conventional alpha at 0.05
- ◯ No
- ◯ The outcome to which TSA was applied was not defined in the protocol

Provide the alpha-level defined

_____

(Please provide as number, not percentage (e.g., 0.05 and not 5))

Describe the choice of alpha (if possible)

_____

Was the alpha-level explicitly corrected for multiplicity?

- ◯ Yes
- ◯ No

Which method was chosen to adjust alpha for multiplicity?

- ☐ Bonferroni
- ☐ Other

Please describe the method chosen for multiplicity correction

_____

Was the power defined for the outcome analyzed with TSA?

- ◯ Yes
- ◯ Yes, conventional at 0.80
- ◯ Yes, conventional at 0.90
- ◯ No
- ◯ The outcome to which TSA was applied was not defined in the protocol

Provide the power defined	_____ (Please provide as number, not percentage (e.g., 0.8 and not 80))
Describe the choice of power used in the Trial Sequential Analysis	_____
Was heterogeneity correction planned for Trial Sequential Analysis and provided?	◯ Inconsistency (I-square) ◯ Diversity (D-square) ◯ Other ◯ No
Please provide details if relevant	_____
Did the authors plan to calculate TSA adjusted confidence intervals?	◯ Yes ◯ No
Planning of dichotomous outcomes	
Which association measure(s) was chosen for analysis of the dichotomous outcome(s)?	☐ Relative risk (RR) ☐ Risk difference (RD) ☐ Odds Ratio (OR) ☐ Peto OR ☐ Other ☐ Not described
Please provide information on association measures	_____
Was handling of the analysis in case of zero events proposed?	◯ Yes ◯ No
What was the planned strategy for handling zero events?	☐ Constant ☐ Reciprocal ☐ Emperical ☐ Correction value = 1 ☐ Correction value = 0.5 ☐ Correction value = 0.01 ☐ Correction value = 0.001 ☐ Trials with no events were excluded ☐ Other methods
Please provide details	_____
Did the protocol define the numerical value of Pc (Proportion of events in the control group)?	◯ Yes ◯ No
Please provide the value defined for Pc	_____

Did the protocol define where the proportion of events in the control group (Pc) would come from?	☐ From other published meta-analysis ☐ From one or more published randomised trials ☐ From one or more published observational studies ☐ From the observed data in their own meta-analysis ☐ Unclear ☐ Other ☐ No
Was the relative risk reduction (RRR) defined?	◯ Yes ◯ No
Please provide the RRR defined	_____
Was it described how the relative risk reduction (RRR) was/would be defined?	☐ From a published meta-analysis ☐ From one or more published randomised trials ☐ From one or more observational studies ☐ From the observed data in their meta-analysis ☐ Clinical experience ☐ Other ☐ No
Describe the choice of RRR	_____
Planning of continuous outcomes	
Which association measure was chosen for the analysis of the continuous outcome(s)?	☐ Mean difference (MD) ☐ Standardized mean difference (SMD) ☐ Other ☐ Not defined
Please provide information on association measures	_____
Was variance defined in the protocol for continuous outcomes?	◯ Yes, from published meta-analysis ◯ Yes, from one or more published randomised trials ◯ Yes, from one or more observational studies ◯ Yes, the squared standard deviation of the observed mean difference ◯ Other ◯ No (Provide values under comments)
Provide the variance(s) defined	_____
Describe the choice of variance	_____

Was the minimally relevant different (MIREDIF) defined for each relevant outcome?	◯ Yes, from published meta-analysis ◯ Yes, from one or more published randomised trials ◯ Yes, from one or more observational studies ◯ Yes, MIREDIF defined as observed SD/2 ◯ Other ◯ No (Provide values under comments)
Provide the MIREDIF(s) defined	_____
Describe the choice of MIREDIF	_____
Planning of GRADE	
Was GRADE assessment planned in the protocol	◯ Yes ◯ No
Did the protocol define which outcomes would undergo a GRADE assessment?	◯ Yes ◯ No
Was the outcome(s) planned for GRADE assessment the same as was assessed in the study? GRADE assessment(s) in study: [studcon_gradetxt]	◯ Yes ◯ No (Only for outcomes to which TSA were applied)
Please describe differences between GRADE plan in protocol and GRADE in study	_____
Was the downgrade methods for imprecision in GRADE described in the protocol?	◯ Yes ◯ No
Did the protocol describe how imprecision would be downgraded with the use of Trial Sequential Analysis?	☐ Yes, imprecision downgraded 2 levels if DARIS < 50%; 1 level if DARIS between 50-100%; 0 levels if DARIS is reached 100% or if the cumulative Z-curve crosses boundaries for futility, benefit or harm ☐ Yes, imprecision downgraded but the cut-offs were different than (1) or not specified (describe below) ☐ Yes, imprecision was evaluated using the Trial Sequential adjusted confidence interval ☐ Other ☐ No
Please describe the plan for downgrading imprecision with the use of TSA	_____
Please describe the plan for downgrading imprecision	_____

Do you have any additional comments?

_____