PCRC Proposal Cover Sheet

Title: Frequency of Succinylcholine Use in Various Anesthetizing/Sedating Locations

Principal Investigator: Thomas Tam Klumpner, M.D.

Co-Investigators: Sachin Kheterpal, M.D., Marilyn Green Larach, M.D., F.A.A.P.

Approved by Mentor: Sachin Kheterpal, M.D.

Type of Study: retrospective

Hypothesis: Succinylcholine use, without concomitant volatile anesthetic use, occurs frequently enough in various anesthetizing/sedating locations to justify dantrolene availability for the treatment of succinylcholine-triggered malignant hyperthermia

Number of Patients/Participants: n/a

Power Analysis: n/a

Proposed statistical test/analysis: descriptive only

Resources (Brief summary of resources for data collection, personnel, financial): This is a volunteer effort that is not supported by external grant funding.

*This research project is part of a broader systematic review of the MHAUS recommendation concerning the availability of dantrolene for the treatment of malignant hyperthermia in anesthetizing and sedating locations. The P.I. of the entire project is Marilyn Green Larach, M.D., F.A.A.P., Director Emeritus of The North American Malignant Hyperthermia Registry of MHAUS. All co-authors are in alphabetical order. (If the PCRC proposal is approved, then Drs. Klumpner and Kheterpal will be added to the co-authorship list.) They include: Kumar G Belani, MBBS, MS, F.A.A.P., Barbara W. Brandom, M.D., John Capacchione, M.D.,, Andrew Herlich, D.M.D., M.D., F.A.A.P., Tae W. Kim, M.D., M.E.H.P., Janine Limoncelli, M.D., Darlene Mashman, M.D., Sheila Riazi, M.Sc., M.D., FRCPC, Erica L. Sivak, M.D.

Introduction

Malignant hyperthermia (**MH**) events are uncommon but potentially lethal adverse responses to the administration of either volatile anesthetic agents and/or succinylcholine. Dantrolene, a hydantoin analogue, is a specific and effective antidote for MH.[i] In Canada, intravenous dantrolene was approved for the treatment of malignant hyperthermia by the Canadian Health Agency in 1974.[ii] In the U.S.A., intravenous administration of dantrolene was approved for the treatment of human malignant hyperthermia events in 1979.[iii]

Current Malignant Hyperthermia Association of the United States (**MHAUS**) guidelines state that within 10 minutes of a decision to treat for MH, dantrolene must be available for all anesthetizing locations where MH trigger agents are used.[iv] Recently, this guideline has been questioned by The Society for Ambulatory Anesthesia for those anesthetizing locations that do not use volatile anesthetic agents and stock succinylcholine solely for emergency use.[v] However, state regulations in Florida, Massachusetts and Tennessee mandate availability of both succinylcholine for airway rescue and dantrolene to treat possible succinylcholine-induced MH.[vi]

We, therefore, performed a systematic review of evidence to: (1) evaluate current MHAUS recommendations for dantrolene availability for the treatment of malignant hyperthermia events in anesthetizing and sedating locations; and (2) formulate new recommendations if indicated.

However, a systematic review using the PubMed, Embase, and Cochrane databases of the English language literature (>20,000 records) reveals little relevant information and no multi-center studies to answer the following questions:

1. The frequency of succinylcholine administration, with and without concomitant volatile anesthetic administration, in hospital-based operating suites e.g. main operating rooms, labor and delivery.[1]

2. The frequency of succinylcholine administration, with and without concomitant volatile anesthetic administration, in off-site procedural suits e.g. radiology, electroconvulsive treatment.[1]

3. The frequency of succinylcholine administration, with and without concomitant volatile anesthetic administration, in ambulatory surgery centers.

4. The frequency with which succinylcholine is administered for rescue of difficulty with mask ventilation?

Search of the multicenter perioperative outcomes group database to analyze the frequency of succinylcholine use with and without concomitant volatile anesthetics will permit us to analyze data to answer these the four questions above. Once the frequency of succinylcholine administration is known,

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[1] There is one paper that gives statistics on the number of cases in which succinylcholine was used at a single hospital center for a 69 month period ending in 2011. However, the specific anesthetizing/sedating locations are not specified. (Dexter et al., Estimate of the relative risk of succinylcholine for triggering malignant hyperthermia. Anesth Analg 2013;116:118-22).

then MHAUS can perform cost-benefit analyses concerning the stocking of dantrolene and revise their recommendations if necessary.

Methods

For this study, we will collaborate with the Multicenter Perioperative Outcomes Group (MPOG), which is an international consortium of medical centers combining large sets of observational electronic medical record data. By accessing the large collection of data assembled by MPOG, we believe we can arrive at a good approximation of the utilization rate of succinylcholine in various anesthetizing locations. The **primary goal** of this query will be to determine the utilization rate of succinylcholine, with and without volatile anesthetic administration in acute care hospital primary anesthetizing locations. Secondarily, this query will also determine the utilization rate of succinylcholine, with and without volatile anesthetic administration across other various anesthetizing locations. Only MPOG cases with location data recorded will be included in the analysis. Administration of succinylcholine will be defined as the percentage of eligible anesthetics where the dose of succinylcholine administered was greater than zero. Administration of volatile anesthetic will be defined as any documented end tidal concentration of isoflurane, sevoflurane or desflurane greater than zero at any point during the anesthetic. We will define anesthetizing location subgroups *a priori*, based on the location where the anesthetic was performed. These subgroups will be determined by the location data available within MPOG and will be mapped by the study authors from the MPOG field "MPOG_Procedure_Room_Type_Concept_ID." (See Location Mapping section below).

Another secondary analysis will be performed to grossly approximate the utilization rate of succinylcholine for rescue of difficulty with mask ventilation. Only cases of eligible patients with a scaled difficulty consistent with difficult mask ventilation (grade III or IV) charted will be included. The number of cases where difficulty with mask ventilation was charted and succinylcholine subsequently administered (within 30 minutes of documenting difficulty with mask ventilation) will be compared to the number of cases where difficulty with mask ventilation was charted and succinylcholine was not subsequently documented within this time frame. The analysis will be performed on all MPOG anesthetics where graded difficulty of mask ventilation is available. The frequency of succinylcholine use for rescue of difficulty with mask ventilation will also be determined for each of the previously defined location subgroups. A subgroup analysis will also be performed to examine the usage rate of succinylcholine for rescue of grade IV mask ventilation alone in each of the previously defined location subgroups. A final subgroup analysis will examine the incidence of succinylcholine rescue of difficulty with mask ventilation (grade III or IV mask ventilation and grade IV mask ventilation alone) in patients that are 0 to <10 years old, and those that are 10 years of age or older categorized by mapped location.

The MPOG database will be queried for all **eligible patients**: patients of all ages who received an anesthetic from **January 1, 2005** through **December 31, 2016**. Access to the North American Malignant Hyperthermia Registry of MHAUS database has been conducted under the following approved protocol: PRO17030102 University of Pittsburgh IRB 2017 Clinical Correlates of Malignant Hyperthermia Susceptibility, P.I. Richard Henker, PHD, RN, CRNA, FAAN).

For reporting observational data from the MPOG database, relevant portions from the STROBE checklist (attached) will be used.

Study type

This is a systematic literature review with a supplemental retrospective observational component using data from The North American Malignant Hyperthermia Registry of MHAUS, the American Society of Anesthesiologists Closed Claim Study, and MPOG. It is anticipated that the quality of the studies found in the literature review will not support a meta-analysis. The entire project is registered in PROSPERO: CRB42017064696. We are conducting this study in accordance with PRISMA guidelines and their checklist.

Primary outcome

Utilization rate of succinylcholine, with and without volatile anesthetic administration in acute care hospital primary anesthetizing locations among MPOG cases with a clearly defined location.

Secondary outcome(s), where applicable

Among MPOG cases with clearly defined location data, determine the utilization rate of succinylcholine in anesthetics in various anesthetizing locations, defined in the Location Mapping section below.

Utilization rate of succinylcholine in anesthetics with evidence of difficulty with mask ventilation (scaled difficulty of grade III or IV) among MPOG anesthetics, categorized by mapped location, where a scaled difficulty in mask ventilation is reported. A subgroup analysis will be performed to examine the usage rate of succinylcholine for rescue of grade IV mask ventilation alone across the different mapped locations. A final subgroup analysis will examine the incidence of succinylcholine rescue of difficulty with mask ventilation (grade III or IV mask ventilation and grade IV mask ventilation alone) in patients that are 0 to <10 years old, and those that are 10 years of age or older categorized by mapped location.

Patient inclusion criteria

All patients with an MPOG anesthetic record with an anesthesia start time within the study period.

Patient exclusion criteria

Any patient with an MPOG anesthetic record with an anesthesia start time outside of the study period. Patients without clearly defined location data will be **excluded** from the analysis relating to location specific utilization of succinylcholine. Patients without a clearly defined scaled difficulty with mask ventilation will be **excluded** from subgroup analysis related to gross approximation of the rate of succinylcholine use for rescue of difficulty with mask ventilation. Patients without a clearly defined age will be **excluded** from the age subgroup analysis.

Data source

MPOG database

North American Malignant Hyperthermia Registry of MHAUS database.

American Society of Anesthesiologists Closed Claim Study database (no relevant information found)

For the systematic literature review:

We searched the databases of PubMed, EMBASE, and the Cochrane Library for human studies including qualitative studies and case reports that were either in English or had an English abstract and had a publication date from 1969-2017 using the following key words with combinations.

Airway rescue: ambulatory surgery anesthetics, drugs, medications, succinylcholine

Adverse events: surgery, medications, succinylcholine

Ambulatory surgery: adverse events, anesthetics, medications, sedation, succinylcholine

Cesarean section: dantrolene (initial dose/administration time), general anesthesia, succinylcholine

Dental or oral: adverse events dental or oral surgical anesthetic, drugs, medications, succinylcholine, surgical sedation

Electroconvulsive treatment: adverse events, anesthetic treatment, sedation, succinylcholine

Emergency department: adverse events, drugs, medications, sedation, tracheal intubation

Intensive care: drugs, medications, succinylcholine, tracheal intubations

Malignant hyperthermia: anesthetic triggers, epidemiology, mortality rate, morbidity rate, succinylcholine

Maternal: anesthetic, dantrolene, morbidity, mortality, treatment

Radiologic procedure: adverse events, anesthetic adverse events, malignant hyperthermia, sedation

Inclusion criteria for articles were: human patients, malignant hyperthermia triggered by the administration of either volatile anesthetic agents or succinylcholine and whose severity was graded as "somewhat greater than likely", "very likely" or "almost certain" on the MH clinical grading scale[vii] or the event in the study or case report was described as "fulminant" by the clinician. MH morbidity and mortality rates were derived from U.S.A. and Canadian populations only and were limited to rates calculated for the acute hospitalization (including referral hospitalization) up to discharge from the initial MH event.

Exclusion criteria for articles were: non-human patients/subjects, malignant hyperthermia events whose severity was graded as "almost never" or "unlikely" by the MH clinical grading scale or not "fulminant" as reported by the clinician, malignant hyperthermia not triggered by the administration of either volatile anesthetic agents or succinylcholine (e.g. "awake" MH or "stress-induced" MH), MH morbidity and

mortality rates for countries outside of the U.S.A. and Canada and morbidity and mortality rates for patients/subjects after acute/referral hospitalization discharge.

These literature searches were repeated just before the final analyses and further studies were retrieved for inclusion. A total of 41 studies were included for qualitative analysis. In addition, the databases of the American Society of Anesthesiologists Closed Claim Study, The North American Malignant Hyperthermia Registry of MHAUS (PRO17030102 University of Pittsburgh IRB 2017 Clinical Correlates of Malignant Hyperthermia Susceptibility, P.I. Richard Henker, PHD, RN, CRNA, FAAN), and the Multicenter Perioperative Outcomes Group were searched for relevant data. The author for each query prepared a PRISMA flow diagram to depict the identification, screening, eligibility, and inclusion process for his/her literature search[viii].

Statistical analysis

Analysis will be conducted using SAS v. 9.4 (SAS Institute, Cary, NC). Among cases with a documented location, the frequency of succinylcholine use will be calculated across all acute care hospital primary anesthetizing locations and separately for each location subgroup (see Location Mapping section below). Among cases with documented scaled difficulty with mask ventilation (grade III or IV), the overall frequency of succinylcholine use will be calculated. A subgroup analysis among those with documented grade IV mask ventilation will compare succinylcholine use across mapped locations. Finally, among patients with a documented age <18 y and documented grade IV mask ventilation, we will compare the frequency of patients aged 0-9 versus aged 10-17 receiving succinylcholine. Descriptive statistics will be reported for patient and case demographic variables using frequencies and percentages for categorical variables and means/standard deviations or medians/interquartile ranges for continuous variables based on normality; confidence intervals around the estimates will also be calculated. A two-sided Pearson's chi-square tests will compare proportions across the two pediatric age groups; a p-value of 0.05 will be considered statistically significant.

Power analysis

Since this is a descriptive analysis, no formal power analysis is needed.

Variables to be collected

Source	Data Column	Data type	Source table, column, and concept
MPOG Patient Demographics	AIMS_Patient_Age_Years	Numeric	Standardized Views.Patient Demographics. AIMS_Patient_Age_Years
	AIMS_Patient_Age_Months		Standardized Views.Patient Demographics. AIMS_Patient_Age_Months
	AIMS_Patient_Age_Weeks		Standardized Views.Patient Demographics. AIMS_Patient_Age_Weeks
	AIMS_Sex		Standardized Views.Patient Demographics.AIMS_Sex

MPOG General Case Information	MPOG_Admission_Type_Concept_ID	Character	MPOG_Admission_Type_Concept_ID
	MPOG_Admission_Type_Desc	Character	Standardized Views.General Case Information. MPOG_Admission_Type_Desc
	MPOG_Procedure_Room_Type_Concept_ID	Character	Standardized Views.General Case Information. MPOG_Procedure_Room_Type_Concept_ID
	MPOG_Procedure_Room_Type_Desc	Character	Standardized Views.General Case Information. MPOG_Procedure_Room_Type_Desc
	AIMS_Procedure_Room_Name	Character	Standardized Views.General Case Information. AIMS_Procedure_Room_Name
	AIMS_Scheduled_Procedure_Text	Character	Standardized Views.General Case Information. AIMS_Scheduled_Procedure_Text
	AIMS_Actual_Procedure_Text	Character	Standardized Views.General Case Information. AIMS_Actual_Procedure_Text
	Anesthesia_Start_DT	DateTime	Standardized Views.Case Times.Anesthesia_Start_DT
Intraoperative Medications	Succinylcholine – dose administered in mg	Numeric	Concept ID 10413
	Airway - Mask Ventilation Difficulty Scaled	Text/Categorical	Concept ID 50113
Physiologic Observations	Sevoflurane Exp %		Concept ID 3270
	Sevoflurane Insp %		Concept ID 3275
	Sevoflurane (mmHg)		Concept ID 3503
	Sevoflurane actual consumption (ml)		Concept ID 3008
	Isoflurane Exp %		Concept ID 3260
	Isoflurane Insp %		Concept ID 3265
	Isoflurane actual consumption (ml)		Concept ID 3006
	Desflurane Exp %		Concept ID 3280
	Desflurane Insp %		Concept ID 3285
	Desflurane actual consumption (ml)		Concept ID 3007

Location Mapping

The following “Procedure Room Types” within MPOG will be mapped to these location subgroups:

Acute care hospital anesthetizing location - "Acute care hospital - mixed use operating room", "Acute care hospital - outpatient operating room", "Acute care hospital - minor procedure room"

Acute care hospital remote anesthetizing location – "Acute care hospital - remote interventional radiology procedure room", "Acute care hospital - remote diagnostic radiology procedure room", "Acute care hospital - remote minor procedure room"

Attached ambulatory surgery center - "Attached ambulatory surgery center - outpatient operating room", "Attached ambulatory surgery center - minor procedure room", "Attached ambulatory surgery center - remote minor procedure room"

Free-standing ambulatory surgery center - "Freestanding ambulatory surgery center - outpatient operating room", "Freestanding ambulatory surgery center - minor procedure room", "Freestanding ambulatory surgery center - remote minor procedure room"

Pediatric acute care hospital anesthetizing location - "Pediatric acute care hospital - mixed use operating room", "Pediatric acute care hospital - minor procedure room"

Pediatric acute care hospital remote anesthetizing location – "Pediatric acute care hospital - remote interventional radiology procedure room", "Pediatric acute care hospital - remote diagnostic radiology procedure room", "Pediatric acute care hospital - remote minor procedure room"

Obstetrics Operating Room - "Obstetrics - operating room"

Management of missing data

MPOG anesthetic records with inadequate location information, will not be included in the analysis. MPOG anesthetic records with inadequate scaled mask ventilation difficulty data will not be included in the analysis pertaining to use of succinylcholine for rescue of difficulty with mask ventilation.

References

[i] Snyder HR, Davis CS, Bickerton RK, Halliday RP. 1-[(5-Arylfurfuylidene)amino]hydantoins. A new class of muscle relaxants. J Med Chem1967;10:807-809, Kolb ME, Home ML, Martz R. Dantrolene in human malignant hyperthermia. Anesthesiology 1982;56;254-62

[ii] Personal communication from S.Riazi, M.D., on August 8, 2017.

[iii] FDA Drug Bull 1979 Nov;9(5):27.

[iv] Malignant Hyperthermia Association of the United States. URL: https://www.mhaus.org/ Accessed: June 25, 2017.

[v] Joshi GP, Desai MS, Gayer S, Vila H on behalf of the Society for Ambulatory Anesthesia (SAMBA). Succinylcholine for emergency airway rescue in class B ambulatory facilities: the society for ambulatory anesthesia position statement. Anesth Analg 2017; 124:1447-1449

[vi] Florida (64B5=Board of Dentistry, 64B8= Board of Medicine, 64B15=Board of Osteopathic Medicine, Massachusetts 234 CMR 6.04. 6.04: Facility Permit D-A: Facility Requirements for the Administration of General Anesthesia and Deep Sedation, Tennessee Comp. R. & Regs. 0880-02-.21, 1050-02-.21, (Office Based Surgery) 1200-08-10-.06 (Basic Services)

[vii] Larach MG et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 1994; 80:771-779

[viii] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). URL: http://www.prisma-statement.org/ Accessed April 23, 2017.

STROBE Statement

Checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

Bias		9	Describe any efforts to address potential sources of bias
Study size		10	Explain how the study size was arrived at
Quantitative variables		11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods		12	(*a*) Describe all statistical methods, including those used to control for confounding
			(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
			(*e*) Describe any sensitivity analyses
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for	

		and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow	

		diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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