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Protocol for a systematic review of reporting standards of anaesthetic interventions in randomised controlled trials

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Keywords:	ANAESTHETICS, SURGERY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Abstract

Introduction There is significant variation in how anaesthesia is defined and reported in clinical research. This lack of standardisation complicates the interpretation of published evidence and planning of future clinical trials. This systematic review will assess the reporting of anaesthesia as an intervention in randomised controlled trials (RCTs) against the Consolidated Standards of Reporting Trials for Non-Pharmacological Treatments (CONSORT-NPT) framework.

Methods and Analysis Online archives of the top 6 journals ranked by impact factor for anaesthesia and the top 3 general medicine and general surgery journals will be systematically hand searched over a 42 month time period to identify RCTs describing the use of anaesthetic interventions for any invasive procedure. All modes of anaesthesia and anaesthesia techniques will be included. All study data, including the type of anaesthetic intervention described, will be extracted in keeping with the CONSORT-NPT checklist. Descriptive statistics will be used to summarise general study details including types/modes of anaesthetic interventions, and reporting standards of the trials.

Ethics and dissemination No ethical approval is required. The results will be used to inform a funding application to formally standardise general, local, regional anaesthesia and sedation for use in clinical research. The systematic review will be disseminated via peer-reviewed manuscript and conferences.

International Prospective Register for Systematic Reviews (PROSPERO) registration number CRD42019141670

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Article Summary

Strength and Limitations

- This will be the first systematic review to summarise the reporting of anaesthesia, to include general, local, regional anaesthesia and sedation as an intervention in RCTs against the CONSORT-NPT checklist.
- The findings from this systematic review will guide future research to improve the standardisation and reporting of anaesthetic interventions in clinical research.
- Only RCTs comparing anaesthetic interventions (e.g. where anaesthesia is the main focus) will be included.

Key Words

Anaesthetics
Surgery
Protocols and Guidelines

Word Count

1,673

Update

This is an original review.

Introduction

The choice of anaesthetic technique for different types of surgery and invasive procedures, and their suitability for individual patients, relies largely upon evidence from high quality randomised controlled trials (RCTs) and clinician expertise. Despite the widespread use of anaesthesia, there is significant variation in how it is defined and reported in clinical research and consensus definitions are lacking.[1] For example, there is significant overlap between definitions of deep sedation and general anaesthesia (GA).[1] The American Society of Anaesthesiologists (ASA) define GA as a "drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation"[2] and sedation is defined by the Royal College of Anaesthetists (RCoA) as "a continuum of depressed conscious state with unpredictable inter-individual dose responses to the drugs used, which may result in unconsciousness".[3] This may explain why standardised scales to routinely measure, record and standardise depth of sedation are lacking.

Clinician autonomy is acknowledged as a necessity in anaesthesia and is a fundamental reason for variation in practice. There is emerging evidence that the choice of mode of anaesthesia (GA, LA, regional or sedation) is multifactorial, formulated around clinicians' expertise, preference, habit, policies, practicalities and may also be influenced by other healthcare professionals and patients.[4] Whilst the autonomous nature of anaesthesia is partly unavoidable, the lack of standardisation and consistency in how anaesthetic techniques are defined, administered and reported complicates the interpretation of published evidence and planning of future RCTs.[1,5]

The Consolidated Standards of Reporting Trials (CONSORT) makes recommendations for improving the quality of reporting in clinical trials, and is endorsed by many journals.[6] Although published in 1996, several reviews have established that reporting standards of RCTs relating to anaesthetic interventions remain poor and concluded that clinicians and researchers would benefit from more uniform reporting.[5789] The more recent CONSORT extension for Non-Pharmacological Treatments (CONSORT-NPT) recognises the complexity of non-pharmacologic interventions (which includes anaesthesia), that comprise multiple interacting components.[10,11] Specific additions include the need to fully describe interventions, and standardise and monitor their delivery (i.e. intervention fidelity) during RCTs, to facilitate reproducibility and ensure that effective interventions can be successfully implemented in clinical practice.[10]

Study Aim

Anaesthesia provides an example of a complex intervention that the CONSORT-NPT extension targets for improved reporting in RCTs. To date, no study has assessed the quality of reporting of

anaesthesia in relation to CONSORT-NPT. The aim of this study, therefore, is to systematically review the reporting of anaesthesia as an intervention in RCTs.

Methods

This systematic review protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA) guidelines.[12] This review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) number CRD42019141670, and the protocol will be updated with amendments if required.

Data sources and search strategy

We will employ a hand search methodology similar to that previously described by Blencowe et al in a systematic review of intervention design and delivery in surgery.[13]

Online archives of selected journals will be systematically hand searched to identify relevant articles. Articles published in the top six journals by impact factor as listed in the Scimago Journal and Country Rank for anaesthesia and the top 3 journals for general medicine and general surgery will be included (Table 1).[14,15,16] Thomson Reuters Journal Citation Reports: Web of Knowledge will be accessed to confirm impact factor by citation.

There will be no limit on country of study. Studies published from 1st January 2016 to 1st September 2019 written in English will be included. This time period was chosen following scoping work to ensure a sufficient number of RCTs will be included in the review.

Study selection

Full text RCTs describing the use of anaesthetic interventions within any invasive procedure in humans will be included. Studies where techniques comparing anaesthesia in cadavers, laboratory and animal studies will be excluded.

We define invasive procedures as 'purposeful/deliberate access to the body is gained via an incision, percutaneous puncture, where instrumentation is used in addition to the puncture needle, or instrumentation via a natural orifice. It begins when entry to the body is gained and ends when the instrument is removed, and/or the skin is closed. Invasive procedures are performed by trained healthcare professionals using instruments, which include, but are not limited to, endoscopes, catheters, scalpels, scissors, devices and tubes.'[17] All modes of anaesthesia and anaesthesia techniques will be included. This will include studies comparing different modes of anaesthesia (for example, general, local, regional anaesthesia or sedation), as well as studies comparing different

types/techniques of the same mode of anaesthesia (volatile versus intravenous general anaesthesia).

Case reports, non-randomised studies, retrospective and other non-comparative studies will be excluded. Abstracts and conference proceedings will be excluded due to high probability of incomplete data.

Study management

Electronic article information will be downloaded into EndNote software. Abstracts and titles will be screened independently by two researchers to identify articles that are potentially relevant, for which the full-text articles will be obtained. Full-text articles will be screened against the inclusion criteria by one researcher.

Data Extraction and assessment

Data will be extracted using a pre-specified form in keeping with the standard CONSORT checklist for reporting trials. Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Bristol, United Kingdom.[18,19] Data extraction will be completed by one researcher and verified by a second independent researcher. Disagreements will be resolved through discussion with the senior researcher/other members of the research team.

The country of study, number and type of included centres and the volume of invasive procedures undertaken in each setting will be recorded.

Descriptions of the following study demographics will be recorded: journal of publication, anaesthetic mode and subtype as stated in the paper, availability of study protocol and, if available, the format of the protocol (weblink, published article, or obtained through contacting authors directly).

The type of anaesthetic intervention described in each study will be recorded in keeping with the CONSORT-NPT checklist in as much detail as is published in either the included study or extracted study protocol.

The anaesthetic intervention will be recorded according to an initial draft typology of anaesthetic interventions developed by the authors. Reporting of anaesthetic technique will be categorised according to whether it was performed pre-procedurally, intra-procedurally or post-procedurally. This will be to allow as much information as is included in each study to be recorded and subsequently categorised. All studies providing information about any aspect of the anaesthetic

intervention will be classified as reporting a description, regardless of the included level of detail. Any citations to anaesthetic interventions within the studies will be recorded separately.

Any reference to standardisation with regard to any anaesthetic technique will be recorded, including how and why this was done, and to which standard. For the purpose of this review, standardisation will be defined as a process 'to establish a standard consisting of regulations for how something is to be done'.[20]

The invasive procedure for which the anaesthetic was being used will be recorded, but no details regarding how the invasive procedure was performed will be recorded.

Fidelity

Fidelity will be defined as 'how far those responsible for delivering an intervention actually adhere to the intervention as it is outlined by its designers' as previously described by Blencowe et al.[13] For each study, the reporting of fidelity to the anaesthetic intervention will be recorded as per the CONSORT-NPT guideline. Assessment of fidelity will be performed through details of any strategies implemented in the study to improve fidelity and details of how it was measured. This will include any crossover between trial arms of participants.

Assessment of risk of bias

The Cochrane Collaboration's revised risk of bias tool will be used to assess the internal validity of selected RCTs.[21] The tool includes an assessment of sequence generation and allocation concealment, blinding of participants and outcome assessment, incomplete outcome data and selective outcome reporting. Given that no meta-analysis will be performed for this review, the risk of bias assessment will be reported as an appendix within the main review.

Data analysis

A PRISMA flow chart of search and study selection with included and excluded studies will be presented. Reasons for exclusion of studies will be given. Extracted data will be presented in tables.

Descriptive statistics will be used to summarise general study details including types and modes of anaesthetic interventions and reporting standards of the trials. The reporting of anaesthetic interventions against the CONSORT-NPT checklist will be reported qualitatively and in tabulated form.

Formal statistical comparisons will not be undertaken in this review as the aim is to summarise reporting standards and not analyse specific trial results.

Patient and public involvement

There was no involvement of patients or the public in the design of this systematic review, and the research question was not formulated or developed with patient or public involvement. Additionally, no patients or public members will be required in order to complete the systematic review.

Dissemination

The systematic review will be published in a peer-reviewed journal and presented at appropriate anaesthesia conferences.

Author Contributions

LE contributed to conception and design of the study, has written and reviewed the manuscript before submission.

KC, NB, RM and RJH contributed to conception and design of the study and have reviewed the manuscript before submission.

MQ and SW have reviewed the manuscript before submission.

All authors have given final approval for publication and agree to be accountable for all aspects of the work.

Competing interests statement

The authors have no competing interests to declare.

Funding statement

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The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Data sharing statement

Given that this is a protocol, there are no data in this work.

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Table 1: *The top six Scimago Journal and Country Rank for 'Anesthesiology and Pain Medicine'[14] and the top three for 'Medicine'[15] and 'Surgery'[16] for all countries in 2018 by impact factor (excluded journals from this list include those specifically related to leukaemia, pain, neuromodulation, palliative and perioperative medicine).*

Anaesthesiology and Pain Medicine	1. Anaesthesiology
	2. British Journal of Anaesthesia
	3. Regional Anesthesia and Pain Medicine
	4. Anaesthesia
	5. European Journal of Anaesthesiology
	6. Anaesthesia and Analgesia
Medicine	1. New England Journal of Medicine
	2. The Lancet
	3. JAMA
Surgery	1. Annals of Surgery
	2. British Journal of Surgery
	3. JAMA Surgery

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia, Surgery, Research methods
Keywords:	ANAESTHETICS, SURGERY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Protocol for a systematic review of reporting standards of anaesthetic interventions in randomised controlled trials

Abstract

Introduction There is significant variation in how anaesthesia is defined and reported in clinical research. This lack of standardisation complicates the interpretation of published evidence and planning of future clinical trials. This systematic review will assess the reporting of anaesthesia as an intervention in randomised controlled trials (RCTs) against the Consolidated Standards of Reporting Trials for Non-Pharmacological Treatments (CONSORT-NPT) framework.

Methods and Analysis Online archives of the top 6 journals ranked by impact factor for anaesthesia and the top 3 general medicine and general surgery journals will be systematically hand searched over a 42 month time period to identify RCTs describing the use of anaesthetic interventions for any invasive procedure. All modes of anaesthesia and anaesthesia techniques will be included. All study data, including the type of anaesthetic intervention described, will be extracted in keeping with the CONSORT-NPT checklist. Descriptive statistics will be used to summarise general study details including types/modes of anaesthetic interventions, and reporting standards of the trials.

Ethics and dissemination No ethical approval is required. The results will be used to inform a funding application to formally standardise general, local, regional anaesthesia and sedation for use in clinical research. The systematic review will be disseminated via peer-reviewed manuscript and conferences.

International Prospective Register for Systematic Reviews (PROSPERO) registration number CRD42019141670

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Article Summary

Strength and Limitations

- This will be the first systematic review to summarise the reporting of anaesthesia, to include general, local, regional anaesthesia and sedation as an intervention in RCTs against the CONSORT-NPT checklist.
- The findings from this systematic review will guide future research to improve the standardisation and reporting of anaesthetic interventions in clinical research.
- Only RCTs comparing anaesthetic interventions (e.g. where anaesthesia is the main focus) will be included.

Key Words

Anaesthetics
Surgery
Protocols and Guidelines

Word Count

1,795

Update

This is an original review.

Introduction

The choice of anaesthetic technique for different types of surgery and invasive procedures, and their suitability for individual patients, relies largely upon evidence from high quality randomised controlled trials (RCTs) and clinician expertise. Despite the widespread use of anaesthesia, there is significant variation in how it is defined and reported in clinical research and consensus definitions are lacking.[1] For example, there is significant overlap between definitions of deep sedation and general anaesthesia (GA).[1] The American Society of Anaesthesiologists (ASA) define GA as a "drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation"[2] and sedation is defined by the Royal College of Anaesthetists (RCoA) as "a continuum of depressed conscious state with unpredictable inter-individual dose responses to the drugs used, which may result in unconsciousness".[3] This may explain why standardised scales to routinely measure, record and standardise depth of sedation are lacking.

Clinician autonomy is acknowledged as a necessity in anaesthesia and is a fundamental reason for variation in practice. There is emerging evidence that the choice of mode of anaesthesia (GA, local anaesthesia (LA), regional or sedation) is multifactorial, formulated around clinicians' expertise, preference, habit, policies, practicalities and may also be influenced by other healthcare professionals and patients.[4] Whilst the autonomous nature of anaesthesia is partly unavoidable, the lack of standardisation and consistency in how anaesthetic techniques are defined, administered and reported complicates the interpretation of published evidence and planning of future RCTs.[1,5]

The Consolidated Standards of Reporting Trials (CONSORT) makes recommendations for improving the quality of reporting in clinical trials, and is endorsed by many journals.[6] Although published in 1996, several reviews have established that reporting standards of RCTs relating to anaesthetic interventions remain poor and concluded that clinicians and researchers would benefit from more uniform reporting.[5,7,8,9] The more recent CONSORT extension for Non-Pharmacological Treatments (CONSORT-NPT) recognises the complexity of non-pharmacologic interventions (which includes anaesthesia), that comprise multiple interacting components.[10,11] Specific additions include the need to fully describe interventions, and standardise and monitor their delivery (i.e. intervention fidelity) during RCTs, to facilitate reproducibility and ensure that effective interventions can be successfully implemented in clinical practice.[10]

Study Aim

Anaesthesia provides an example of a complex intervention that the CONSORT-NPT extension targets for improved reporting in RCTs. To date, no study has assessed the quality of reporting of

anaesthesia in relation to CONSORT-NPT. The aim of this study, therefore, is to systematically review and summarise the reporting of anaesthesia as an intervention in RCTs.

Methods

This systematic review protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA) guidelines.[12] This review protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) number CRD42019141670, and the protocol will be updated with amendments if required.

Data sources and search strategy

We will employ a hand search methodology similar to that previously described by Blencowe et al in a systematic review of intervention design and delivery in surgery.[13]

Online archives of selected journals will be systematically hand searched to identify relevant articles. Articles published in the top journals by impact factor as listed in the Scimago Journal and Country Rank for anaesthesia (n=6), general medicine (n=3) and general surgery (n=3) will be included (Table 1).[14,15,16] Thomson Reuters Journal Citation Reports: Web of Knowledge will be accessed to confirm impact factor by citation. A hand-searching methodology will be used whereby contents pafes of relevant journals will be screend to identify eligible articles, rather than undertaking a formal search of using MeSH terms and text words.

There will be no limit on country of study. Studies published from 1st January 2016 to 1st September 2019 written in English will be included. This time period was chosen following scoping work to ensure a sufficient number of RCTs will be included in the review.

Study selection inclusion and exclusion criteria

Full text RCTs describing the use of anaesthetic interventions within any invasive procedure in humans will be included. Studies where techniques comparing anaesthesia in cadavers, laboratory and animal studies will be excluded.

We define invasive procedures as 'purposeful/deliberate access to the body is gained via an incision, percutaneous puncture, where instrumentation is used in addition to the puncture needle, or instrumentation via a natural orifice. It begins when entry to the body is gained and ends when the instrument is removed, and/or the skin is closed. Invasive procedures are performed by trained healthcare professionals using instruments, which include, but are not limited to, endoscopes, catheters, scalpels, scissors, devices and tubes.'[17] All modes of anaesthesia and anaesthesia

techniques will be included. This will include studies comparing different modes of anaesthesia (for example, general, local, regional anaesthesia or sedation), as well as studies comparing different types/techniques of the same mode of anaesthesia (volatile versus intravenous general anaesthesia).

Case reports, non-randomised studies, retrospective and other non-comparative studies will be excluded. Abstracts and conference proceedings will be excluded due to high probability of incomplete data. The hand-search strategy is shown in Appendix 1.

Study management

Electronic article information will be downloaded into EndNote software. Abstracts and titles will be screened independently by two researchers to identify articles that are potentially relevant, for which the full-text articles will be obtained. Full-text articles will be screened against the inclusion criteria by one researcher.

Data Extraction and assessment

Data will be extracted using a pre-specified form in keeping with the standard CONSORT checklist for reporting trials. Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Bristol, United Kingdom.[18,19] Data extraction will be completed by one researcher and verified by a second independent researcher. Disagreements will be resolved through discussion with the senior researcher/other members of the research team.

The country of study, number and type of included centres and the volume of invasive procedures undertaken in each setting will be recorded.

Descriptions of the following study demographics will be recorded: journal of publication, anaesthetic mode and subtype as stated in the paper, availability of study protocol and, if available, the format of the protocol (weblink, published article, or obtained through contacting authors directly).

The type of anaesthetic intervention described in each study will be recorded in keeping with the CONSORT-NPT checklist in as much detail as is published in either the included study or extracted study protocol.

The anaesthetic intervention will be recorded according to an initial draft typology of anaesthetic interventions developed by the authors. Reporting of anaesthetic technique will be categorised according to whether it was performed pre-procedurally, intra-procedurally or post-procedurally. This will be to allow as much information as is included in each study to be recorded and

subsequently categorised. All studies providing information about any aspect of the anaesthetic intervention will be classified as reporting a description, regardless of the included level of detail. Any citations to anaesthetic interventions within the studies will be recorded separately.

Any reference to standardisation with regard to any anaesthetic technique will be recorded, including how and why this was done, and to which standard. For the purpose of this review, standardisation will be defined as a process 'to establish a standard consisting of regulations for how something is to be done'.[20]

The invasive procedure for which the anaesthetic was being used will be recorded, but no details regarding how the invasive procedure was performed will be recorded.

Fidelity

Fidelity will be defined as 'how far those responsible for delivering an intervention actually adhere to the intervention as it is outlined by its designers' as previously described by Blencowe et al.[13] For each study, the reporting of fidelity to the anaesthetic intervention will be recorded as per the CONSORT-NPT guideline. Assessment of fidelity will be performed through details of any strategies implemented in the study to improve fidelity and details of how it was measured. This will include any crossover between trial arms of participants.

Assessment of risk of bias

The Cochrane Collaboration's revised risk of bias tool will be used to assess the internal validity of selected RCTs.[21] The tool includes an assessment of sequence generation and allocation concealment, blinding of participants and outcome assessment, incomplete outcome data and selective outcome reporting. Given that no meta-analysis will be performed for this review, the risk of bias assessment will be reported as an appendix within the main review.

Data analysis

A PRISMA flow chart of search and study selection with included and excluded studies will be presented. Reasons for exclusion of studies will be given. Extracted data will be presented in tables.

Descriptive statistics will be used to summarise general study details including types and modes of anaesthetic interventions and reporting standards of the trials. The reporting of anaesthetic interventions against the CONSORT-NPT checklist will be reported qualitatively and in tabulated form. The reporting of anaesthetic interventions for the anaesthesia and non-anaesthesia journals

will be reported both in combination and separately, to examine reporting standards between these journal types.

Formal statistical comparisons will not be undertaken in this review as the aim is to summarise reporting standards and not analyse specific trial results. This is in keeping with published systematic reviews that have summarised reporting standards in other research fields[22,23].

Patient and public involvement

There was no involvement of patients or the public in the design of this systematic review, and the research question was not formulated or developed with patient or public involvement. Additionally, no patients or public members will be required in order to complete the systematic review.

Ethics and Dissemination

No ethical approval is required as this is a secondary research study. The results will be used to inform a funding application to develop methods to standardise the description of anaesthesia interventions for use in clinical research. The systematic review will be disseminated via peer-reviewed manuscript and conferences.

Author Contributions

LE contributed to conception and design of the study, has written and reviewed the manuscript before submission.

KC, NB, RM and RH contributed to conception and design of the study and have reviewed the manuscript before submission.

MQ and SW have reviewed the manuscript before submission.

All authors have given final approval for publication and agree to be accountable for all aspects of the work.

Competing interests statement

The authors have no competing interests to declare.

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The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Data sharing statement

Given that this is a protocol, there are no data in this work.

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Table 1: *The top six Scimago Journal and Country Rank for 'Anesthesiology and Pain Medicine' and the top three for 'Medicine' and 'Surgery' for all countries in 2018 by impact factor (excluded journals from this list include those specifically related to leukaemia, pain, neuromodulation, palliative and perioperative medicine).*

Anaesthesiology and Pain Medicine	1. Anaesthesiology
	2. British Journal of Anaesthesia
	3. Regional Anesthesia and Pain Medicine
	4. Anaesthesia
	5. European Journal of Anaesthesiology
	6. Anaesthesia and Analgesia
Medicine	1. New England Journal of Medicine
	2. The Lancet
	3. JAMA
Surgery	1. Annals of Surgery
	2. British Journal of Surgery
	3. JAMA Surgery

Appendix 1: Example of Full Journal hand-search Strategy

Inclusion Criteria:

- Region of Study: no limit on country of study
- Time period of study: published from 1st January 2016 to 1st September 2019
- Language exclusions: English language only
- Study type: full text randomized-controlled trials
- Journals: the top six Scimago Journal and Country Rank for 'Anesthesiology and Pain Medicine'[14] and the top three for 'Medicine'[15] and 'Surgery'[16] for all countries in 2018 by impact factor (excluded journals from this list include those specifically related to leukaemia, pain, neuromodulation, palliative and perioperative medicine); see Table 1 of protocol
- Intervention studied: all modes of anaesthesia and anaesthesia techniques where used as an interventions within any invasive procedure in humans
- Invasive procedures defined as 'purposeful/deliberate access to the body is gained via an incision, percutaneous puncture, where instrumentation is used in addition to the puncture needle, or instrumentation via a natural orifice. It begins when entry to the body is gained and ends when the instrument is removed, and/or the skin is closed. Invasive procedures are performed by trained healthcare professionals using instruments, which include, but are not limited to, endoscopes, catheters, scalpels, scissors, devices and tubes.'[17]
- Studies comparing different modes of anaesthesia (for example, general, local, regional anaesthesia or sedation), as well as studies comparing different types/techniques of the same mode of anaesthesia (volatile versus intravenous general anaesthesia).

Exclusion criteria:

- RCTs comparing anaesthesia in cadavers, laboratory and animal studies
- Case reports, non-randomised studies, retrospective and other non-comparative studies
- Abstracts and conference proceedings

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page/Line numbers of your manuscript where the relevant information can be found
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title, page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Prospero registration number page 2, end of Abstract
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 3, Section named: Authors
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8, Section named: Author Contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 8, Section named: Funding Statement
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 8, Section named: Funding Statement
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 8, Section named: Funding Statement
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 1, Introduction and Study Aim
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4, Section named: Study Aim
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting,	Page 5, Section named: Data Sources and Search Strategy and Section

		time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	named: Study Selection inclusion and exclusion criteria
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 5, Section named: Data Sources and Search Strategy
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix 1: Search Strategy
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6, Section named: Study Management
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 5, Section named: Study Selection inclusion and exclusion criteria
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 6, Section named: Data Extraction and assessment
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 6, Section named: Data Extraction and assessment
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 6, Section named: Data Extraction and assessment
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 7, Section named: Assessment of Risk of Bias
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 7, Section named: Data Analysis
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	N/A
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 7, Section named: Data Analysis
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication	N/A

		bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7, Section named: Assessment of Risk of Bias

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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