The clinical efficacy of transcutaneous electrical nerve stimulation (TENS) for acute and chronic pain: a protocol for a meta-analysis of randomised controlled trials (RCTs)

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ABSTRACT

Introduction The aim of this systematic review with meta-analysis is to evaluate the clinical efficacy of transcutaneous electrical nerve stimulation (TENS) for any type of acute and chronic pain in adults.

Methods and analysis We intend to search electronic databases (Cochrane Library, MEDLINE, Embase, CINAHL, PsycINFO, LILACS, PEDRO, Web of Science, AMED and SPORTDiscus) from inception to the present day to identify all randomised controlled trials (RCT) on the use of TENS in adults for any type of pain including acute pain, chronic pain and cancer-related pain. We will screen the RCTs against eligibility criteria for inclusion in our review. Two reviewers will independently undertake RCT selection, data extraction and risk of bias assessment. Primary outcomes will be: (i) participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data; and (ii) participant-reported pain intensity expressed as mean (continuous) data. We will conduct meta-analyses to determine risk ratio for dichotomous data, and mean difference (MD) or standardised MD for continuous data for TENS versus placebo TENS, no treatment or waiting list control, standard of care, and other treatments. Subgroup analyses will include different pain conditions (eg, acute vs chronic), TENS intensity, during versus after TENS, TENS treatments and TENS administered as a single dose versus repetitive dose.

Ethics and dissemination This systematic review will not use data from individual participants, and the results will be disseminated in a peer-reviewed publication and presented at a conference.

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INTRODUCTION

Pain is a major healthcare issue. Estimates of the prevalence of acute pain in adults suggest that it may be as high as 70.7% in accident and emergency departments and 50% in hospital inpatients, with up to 35% of patients reporting severe pain.3 Estimates of the worldwide prevalence of chronic pain in the general adult population suggest it may affect up to 45% of people, with up to 15% reporting severe disabling pain.2,4 Pain is financially expensive in terms of medical consultations, treatments and time lost from work, and socially expensive in terms of suffering and impaired quality of life.7,8 Gaskin and Richard7 estimated that annual costs related to healthcare and loss of worker productivity in the USA was between US$560 and US$635 billion. This was greater than heart disease (US$309 billion), cancer (US$243 billion), and diabetes (US$188 billion). In Europe, Breivik et al6 estimated the national healthcare and socioeconomic costs of chronic pain to be 3%–10% of gross domestic product.
Approximately 40% of people living with chronic pain report inadequate pain management and over 60% report that medication does not adequately control pain. Desirable pain-management strategies adopt a biopsychosocial approach using pharmacological and non-pharmacological interventions tailored to the individual. The goal of treatment is to relieve pain and improve physiological functioning associated with activities of daily living, role functioning associated with jobs and hobbies, and emotional, cognitive and social functioning associated with quality of life. Early pain management is critical to reduce the likelihood of acute pain developing into chronic pain. Transcutaneous electrical nerve stimulation (TENS) has been used across the world for the management of acute and chronic pain irrespective of cause, including pain related to cancer and its treatment.

Description of the intervention
TENS is the delivery of pulsed electrical currents across the intact surface of the skin to stimulate peripheral nerves, principally for pain relief. TENS may be self-administered by the patient, ideally following instruction from a healthcare practitioner using a portable, battery-powered TENS device to produce electrical currents that are delivered to the body using self-adhesive electrodes attached to the surface of the skin. TENS is available without a prescription, is inexpensive and has a good safety profile compared with medication. Contraindications include patients who also have cardiac pacemakers and implantable cardioverter defibrillators. Precautions include pregnancy, epilepsy, active malignancy, deep-vein thrombosis and frail or damaged skin. Two techniques are commonly used: conventional TENS administered to produce a strong non-painful TENS sensation that are delivered to the body using self-adhesive electrodes attached to the surface of the skin. TENS is available without a prescription, is inexpensive and has a good safety profile compared with medication. Contraindications include patients who also have cardiac pacemakers and implantable cardioverter defibrillators. Precautions include pregnancy, epilepsy, active malignancy, deep-vein thrombosis and frail or damaged skin.

How the intervention might work
In 1965, Melzack and Wall proposed that TENS could stimulate low-threshold cutaneous afferents to inhibit onward transmission of nociceptive information in the central nervous system and thus, alleviate pain (ie, segmental modulation). In addition, TENS could stimulate small-diameter afferents to activate descending pain inhibitory pathways or block afferent activity in peripheral neurons, creating a ‘busyline’ effect.

Previous reviews
There is a plethora of systematic reviews on TENS for specific conditions and most are inconclusive (for review see ). An overview of Cochrane reviews provides tentative evidence that TENS reduces pain intensity when administered as a stand-alone treatment for acute pain in adults. A meta-analysis found the superiority of TENS over placebo for reducing postoperative analgesic consumption when administered using a strong, subnoxious intensity and adequate frequency. A Cochrane review to assess the effects of TENS on pain during labour found limited evidence of effect but concluded women should have the choice of using TENS.

In 2008, a Cochrane review on TENS for chronic pain was inconclusive although this review has now been withdrawn. An overview of Cochrane reviews on TENS for chronic pain included a descriptive analysis of 9 reviews and 51 RCTs but did not pool data for meta-analyses. It was not possible to conclude whether TENS was beneficial or harmful. Most Cochrane reviews on specific chronic pain conditions are inconclusive (eg, osteoarthritis of the knee, neuropathic pain, chronic low back pain, cancer pain, and phantom pain and stump pain). Interestingly, non-Cochrane reviews with meta-analyses have found the superiority of TENS over placebo for chronic musculoskeletal pain and osteoarthritis of the knee.

Systematic reviews and meta-analyses are hindered by methodological weaknesses of included RCTs. Bennett et al harvested RCTs from Cochrane reviews on TENS for acute pain, chronic pain and cancer-related pain and found that inadequate method of randomisation, small sample sizes and issues associated with the implementation of a sham (placebo) control such as allocation concealment and blinding contributed to an overestimation of TENS effects. The design of an authentic placebo control is a challenge. Credible sham TENS devices have been used that are identical in appearance to real TENS devices and deliver no current or deliver stimulation at the start of treatment and fade to zero current output over a brief period of time (eg, within 45s). It is not possible to blind participants to TENS sensation. Nevertheless, uncertainty about allocation to active and inactive TENS can be achieved by informing participants that some types of electrical stimulation devices do not produce sensation during stimulation (ie, microcurrent therapy). Blinding can be monitored by asking participants whether they believed that ‘...the device was functioning properly?’ Bennett et al also found that aspects of fidelity may contribute to underestimation of TENS effects including inadequacy of TENS technique; inadequate dosing; and the effect of concurrent analgesia in placebo groups.

Why it is important to do this review
The debate about the clinical efficacy of TENS for the relief of pain in adults has been ongoing since TENS was introduced in the early 1970s. The majority of systematic reviews published to date have been inconclusive, despite
a vast number of published RCTs. This has resulted in contradictory recommendations from clinical guideline panels. For example, the National Institute of Health and Care Excellence recommends that TENS should be offered as an adjunct to core treatment for osteoarthritis but not for non-specific chronic low back pain.

Previous systematic reviews tend to focus on pain associated with specific medical conditions, in line with classical pathology-based categorisation of pain as a secondary outcome of the disease. This markedly reduces sample sizes of pooled data and the statistical power of the meta-analysis. In general, the findings of systematic reviews of the efficacy of TENS for specific medical conditions are inconclusive due to insufficient data. Methodological factors influencing estimates of efficacy include analyses used to measure treatment outcome, trial duration, withdrawals and statistical imputation following withdrawal. Based on the work of Moore et al, the Pain, Palliative and Supportive Care group from Cochrane Collaboration suggest that trials with fewer than 200 participants in RCTs or fewer than 500 participants in meta-analyses are at a high risk of bias seriously undermining confidence in findings. To date, only two meta-analyses on TENS have come close to this threshold of acceptability and both found superiority over placebo (for acute postoperative pain and chronic musculoskeletal pain). Pooling data on pain intensity from RCTs irrespective of diagnostic condition would markedly improve the statistical power associated with meta-analyses of TENS. However, the inclusion of a wide variety of types of pain has the potential for increasing heterogeneity. The recent overview of Cochrane reviews on TENS for chronic pain published by the Cochrane Collaboration did not pool data and was inconclusive.

The mechanism of action of TENS primarily involves neuromodulation of central nociceptive transmission irrespective of medical diagnosis. Therefore, TENS is used for symptomatic relief of pain rather than treatment (cure) of pathology. The relationship between pain experience, response to treatment and pathology is variable within and between individuals with similar conditions. The pain experience is complex and influenced by contextual, social, psychological and biological factors. Traditionally, pain is evaluated from a pathology-based perspective and dichotomised into acute and chronic. Even when pain is attributed to a medical condition, the specifics of pathology driving an individual’s pain may be elusive. Sometimes pain does not fit into a classical pathology-based category, as recognised by the WHO who introduced a new phenomenological definition for chronic primary pain in the International Statistical Classification of Diseases and Related Health Problems (11th Revision, ICD-11). Moreover, pathophysiological processes do not dichotomise at specific time points, leading Loeser to suggest that the dichotomy of pain into acute and chronic should be abolished.

There has been no convincing evidence that TENS outcome is affected by the nature of pathology, the type of pain or medical diagnoses. Thus, it seems logical to undertake a meta-analysis of the clinical efficacy of TENS by evaluating pain outcomes from a phenomenological perspective, irrespective of medical condition. This would increase statistical power and confidence in findings, and provide clinicians, policy-makers and patients with a source of information on the effects of TENS for any type of pain. We appreciate that there may be substantial differences in the context in which different types of pain are experienced (eg, acute vs chronic, negligible consequence vs life-threatening and so on) and that this has the potential to generate clinical and statistical heterogeneity. Thus, concerns over an increase in clinical heterogeneity associated with combining different clinical conditions will be offset by conducting subgroup analyses of specific medical conditions based on ICD-11 categories if sufficient data are available.

**Aim**

The aim of this systematic review with meta-analysis is to evaluate the clinical efficacy and safety of TENS for any type of acute and chronic pain in adults. The review protocol has been adapted from a Cochrane review on TENS for fibromyalgia previously published by the investigators.

**METHODS**

The protocol is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines. The completed checklist can be found in the online supplementary material (Table S1).

**Patient and public involvement**

There is no direct patient or public involvement in this study. Patients were not involved in the development of the research question and outcome measures or the design of the systematic review. Patients will not be involved with the conduct of the systematic review.

**Criteria for considering studies for this review**

**Types of studies**

We plan to include RCTs of TENS treatment for acute or chronic pain of any origin. We will exclude studies that were non-randomised, case reports and clinical observations. We plan to include parallel group and crossover trial designs. We plan to include single treatment interventions without follow-up. However, we will conduct a subgroup analysis of RCTs that delivered at least 2 weeks of treatment and had a duration of at least 8 weeks as these are considered as best practice. We require a full journal publication of a full trial report. We will not include, online clinical trial results, summaries of otherwise unpublished clinical trials, abstracts or letters.

**Types of participants**

We will include RCTs of adult participants aged ≥18 years with any type of clinical pain.
Types of TENS interventions

We will include all RCTs that administered TENS as non-invasive electrical stimulation of the skin with the intention of stimulating peripheral nerves to alleviate pain using a standard TENS device.\textsuperscript{11}

Non-invasive

We will only include RCTs that administered TENS across the intact surface of the skin using surface electrodes. We will exclude invasive nerve stimulation techniques such as percutaneous electrical nerve stimulation and electroacupuncture.

Type of TENS device

We will only include RCTs that administered TENS using a standard TENS device,\textsuperscript{11} regardless of the device manufacturer, that delivered biphasic or monophasic pulsed electrical currents. We will exclude RCTs that administered “TENS-like” currents that are not typical output specifications of a standard TENS device.\textsuperscript{11} We will exclude neuromuscular electrical stimulation (NMES) devices, interferential current devices and microcurrent devices.\textsuperscript{11} We will exclude TENS delivered using single probe electrodes (ie, TENS pens) or using matrix electrodes and electrode arrays.

TENS technique

We will include RCTs that used a standard TENS device irrespective of the term to describe the type of TENS technique (eg, conventional TENS, acupuncture-like TENS, high-frequency-low-intensity, low-frequency-high intensity and so on). We will exclude RCTs that did not use pulsed electrical currents. We will only include RCTs that administered TENS on areas of the body that were sensate, and where electrodes were located at (a) the site of pain or (b) over nerve bundles proximal (or near) to the site of pain. We will include TENS delivered at acupuncture points only if the point was lying over nerve bundles proximal (or near) to the site of pain. We will include all RCTs irrespective of the current amplitude of TENS and/or participant-reported TENS intensity. We consider participant-reported strong but comfortable TENS sensations as optimal and will conduct a subgroup analysis to compare TENS at intensities described as ‘strong’ (optimal) versus those described as ‘mild’, ‘faint’ or ‘barely perceptible’ (suboptimal). We will include RCTs that delivered TENS at intensities reported to generate muscle twitches providing TENS was administered using a standard TENS device with the primary goal to alleviate pain. We will only include RCTs that delivered pulse frequencies of TENS that were <250 pulses per second and pulse durations <1 ms. We will include any type of pulse pattern.

Dosage and regimen

We will include RCTs that administered TENS for any duration or regularity of treatment. We will include TENS that was administered by a therapist and/or self-administered by study participants.

Evaluation of TENS treatment effects

We will include TENS administered as a sole treatment or in combination with usual care and/or other treatments. We will exclude RCTs where it was not possible to isolate the effects of TENS from other treatments. We will include RCTs that evaluate TENS versus

- Placebo TENS (eg, sham (no current) TENS device).
- No treatment or waiting list control.
- Standard of care.
- Another treatment, both pharmacological and non-pharmacological.

We will include two TENS interventions from the same RCT. To avoid ‘double-counting’ and unit-of-analysis errors, we will not enter several interventions versus one comparison group in common (eg, placebo TENS) into the same meta-analysis. We will follow recommendations from Cochrane to combine TENS intervention groups to create a single pairwise comparison unless one or more of the TENS interventions do not meet our criteria for optimal TENS technique as described in the section TENS technique. In such situations, we will select one TENS intervention that meets the criteria for optimal technique.

Criteria and credibility of placebo TENS

The credibility and blinding of placebo TENS is an issue in TENS studies as it is not possible to blind participants to TENS sensation, although it is possible to generate uncertainty about allocation to active and inactive TENS.\textsuperscript{39} We define a sham TENS device as a device similar in appearance to the real TENS device used in the study but where the current output was modified so that there is no electrical current, or a barely perceptible electrical current and/or electrical current that ceases within 1 min.\textsuperscript{16,38} We will identify RCTs that attempt to assess the credibility of placebo TENS and will conduct a subgroup analysis of RCTs that judge the intervention to be a credible placebo TENS.

Search methods for identification of studies

The systematic review process will be guided by the Cochrane Collaboration of Systematic Reviews\textsuperscript{47} and the PRISMA statement.\textsuperscript{48}

We will conduct a literature search to identify RCTs published from the date of inception of the database (online supplementary material - Appendix 1) and screen them against our eligibility criteria for inclusion in our review. The purpose of the search is to provide comprehensive coverage of a wide variety of pain conditions (eg, ICD-11 categories) at various stages and settings (eg, acute, chronic, palliative, community, primary, secondary and tertiary). Also, we will conduct a literature search to identify systematic reviews published from inception and will harvest RCTs to gain insights into the consistency of RCTs included across systematic reviews of similar conditions, including our own (online supplementary material Appendix 2). There is no intention to evaluate or quality assess previously published systematic reviews.
Electronic searches
We will search the following electronic databases using a combination of controlled vocabulary, that is, medical subject headings (MeSH) and free-text terms to identify published RCTs and systematic reviews from inception to the date of the search.
- Cochrane Library (CENTRAL).
- MEDLINE (via PubMed).
- Embase (via OVID).
- CINAHL (via EBSCO).
- PsycINFO (via EBSCO).
- LILACS (via Birme).
- PEDRO.
- Web of Science.
- AMED (via OVID).
- SPORTDiscus (via EBSCO).

We will tailor searches to the individual databases by adapting the MEDLINE search strategy for the other databases listed. There will be no language restrictions and we will identify all relevant RCTs irrespective of language and will translate articles where required.

Data collection and analysis
Selection of studies
Two review authors will independently screen records to identify RCTs. We will remove duplicates and eliminate records that clearly do not satisfy the inclusion criteria. Full-text reports of potentially eligible RCTs will be obtained and screened for eligibility by two review authors. Also, two review authors will screen records to identify systematic reviews on TENS and will read full-text reports to create a list of RCTs included in each systematic review. Disagreements at any stage of the process will be resolved by consensus using a third review author as arbiter. We will not anonymise records of systematic reviews or RCTs in any way before assessment. We will create a PRISMA flowchart.47 48

Data extraction and management
Two review authors will independently extract data from included RCTs and will check for agreement before entering into a software. Disagreement will be resolved by consensus with a third author acting as arbiter. We will include information about study design, study participants, sample size and interventions used. We will use these data to populate a ‘Characteristics of included RCTs’ table (online supplementary material Appendix 3). We will contact authors via email to clarify issues relating to inclusion, risk of bias and missing data.

Types of outcome measures
We will include RCTs that measure pain using standard subjective scales (numerical rating scale or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We will include measures of pain at rest and pain on movement. We will extract pain measures assessed using condition-specific questionnaires (eg, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Fibromyalgia Impact Questionnaire (FIQ)). We plan to extract outcome measurement data before, during and after the intervention, where data are available. We plan to extract data on clinical status or health-related quality of life and treatment satisfaction. We will capture data for adverse effects of any type or severity as descriptions from participants and number of withdrawals and/or stopping of treatment. Serious adverse events are defined as untoward medical occurrence or effect resulting in death, threat to life, hospitalisation, significant disability or incapacity, congenital anomaly or birth defect.

Assessment of risk of bias in included studies
Two review authors will independently assess the risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.47 Risk of bias assessment consists of the assessment of selection bias, attrition bias, blinding and sample size (online supplementary material Appendix 4).

Measures of treatment effect
Pain outcomes tend to have a U-shaped distribution with some patients experiencing substantial reductions in pain and others experiencing minimal or no improvement.49 Thus, data expressed as averages may be misleading as a small average between-group effect size may represent a proportion of participants that actually responded very well to the intervention.50 We do not know whether outcomes are bi-modally distributed in trials of TENS but we expect most RCTs in this review to present effect sizes as the average between intervention groups. There is little consensus or evidence regarding what the threshold should be for a clinically important difference in pain intensity based on the between-group difference during or after the intervention. The Outcome Measures in Rheumatology (OMERACT 12)51 group states that the proportion of patients achieving one or more thresholds of improvement from baseline pain should be reported in addition to mean change. We will follow the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions when analysing response to treatment and consider reports of pain relief of ≥30% compared with baseline as responders.52

Primary outcomes
Proportion of participant-reported pain relief of ≥30% expressed as frequency (dichotomous) data
Our primary outcome is the responder rate. The proportion of participants reporting pain relief of ≥30% (ie, at least moderate pain relief) compared with baseline in each group will be classed as responders.49 53 We will calculate risk ratio and risk difference with 95% CIs. Comparisons between groups will then be finalised by calculating the number needed to treat to benefit (NNTB) as an absolute measure of treatment effect where possible.52
Participant-reported pain intensity expressed as mean (continuous) data

We intend to calculate the mean difference (MD) with 95% CI for continuous data collected on identical scales. We intend to calculate the standardized MD with 95% CI for continuous data collected on different scales. We intend to use a between-group difference of ≥10 mm on a 0–100 mm VAS for a minimally important outcome for pain intensity. We will interpret these findings with caution as it remains possible that estimates that fall close to this point may reflect a treatment that benefits an appreciable number of patients. In addition, we will calculate the difference between groups in the percentage change in pain intensity during treatment relative to baseline. This will enable us to classify according to IMMPACT criteria for clinically important change, as previously used in Cochrane reviews, where no important change <15%, minimally important change 15%–30%, moderately important change 30%–50% and substantially important change ≥50%.52

Secondary outcomes
- Proportion of participants reporting pain relief of ≥50% (ie, at least substantial pain relief).
- Participant-reported condition-specific pain-outcomes (eg, WOMAC and FIQ).
- Participant-reported clinical status or health-related quality of life, including activities of daily living and fatigue, using any validated tool (eg, Patient Global Impression of Change (PGIC), Short-Form Health Survey (SF-36), EuroQol instruments).
- Participant-reported treatment satisfaction.
- Participant-reported adverse events expressed as frequency (dichotomous) data and/or severity.

Dichotomous and continuous data will be analysed using the same procedures described for primary outcomes. For health-related quality of life data, we intend to consider a difference >10% of the scale employed to be minimally important.54

Unit-of-analysis issues
We will include crossover designs but intend only to enter the first period data into the meta-analysis. If this was not reported, we will note this and not include the data. If data is reported appropriately then we intend to include the data using the generic inverse variance feature.

Dealing with missing data
An intention-to-treat (ITT) analysis will be used when the ITT population were randomised, received at least one dose of TENS, and provided at least one postbaseline outcome measurement. Missing participants will be assigned zero improvement wherever possible.

Assessment of heterogeneity
We will examine heterogeneity using visual inspection of forest plots, L’Abbé Plots,55 the F statistic and the χ² test, if appropriate.56 We will use the Cochrane Collaboration’s rough guide to interpretation as not important (0%–40%), moderate (30%–60%), substantial (50%–90%) and considerable (75%–100%). We will use a random-effects model as the studies are anticipated to be heterogeneous. This accounts for heterogeneity among study results beyond the variation associated with the fixed-effects model. Sources of heterogeneity will be investigated with subgroup analysis and/or a random-effects meta-regression analysis. We anticipate that causes of heterogeneity may be: clinical condition, acute versus chronic pain, and optimal versus suboptimal TENS. All analyses will be conducted contingent on data availability.57

Assessment of reporting biases
Publication bias will be assessed using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNTB of 10).58 The influence of small study samples will be assessed using the risk of bias criterion ‘study size’. We plan to visually inspect funnel plots to explore the likelihood of reporting biases if there are at least 10 RCTs in a meta-analysis and if RCTs differed in sample size. We will use Egger test to detect small study bias for RCTs using continuous outcomes.47

Data synthesis
We will pool data using Review Manager59 and will undertake meta-analyses of outcome data using a random-effects model. We will group data according to outcome and measurement time points as: (i) during stimulation or immediately after stimulation at each treatment session, or both; and (ii) postintervention follow-up at <2 weeks postintervention (short term), 2–7 weeks postintervention (mid-term), and ≥8 weeks postintervention (long term).

We plan to undertake a narrative synthesis if data are inadequate to support statistical pooling.

Quality of the evidence
We consider single RCTs too imprecise unless the sample size is >400 participants for continuous data and >300 events for dichotomous data. We will present the outcome of the ‘Risk of Bias’ assessments in the reporting. We consider pooled data to be imprecise unless the sample size for a treatment arm is >500 participants. We will present pooled effects for outcomes with Grades of Recommendation, Assessment, Development and Evaluation (GRADE) judgements in ‘Summary of findings’ tables. Two review authors will independently rate the quality of outcomes using the GRADE system (GRADEpro GDT 2015, online supplementary material Appendix 5).

Subgroup analysis
We plan to undertake subgroup analyses for acute versus chronic pain and for specific painful conditions. We also plan to conduct subgroup analyses to investigate the possible impact of TENS technique on analgesic efficacy as follows:

Johnson MI, et al. BMJ Open 2019;9:e029999. doi:10.1136/bmjopen-2019-029999
Optimal intensity described as ‘strong’ versus suboptimal intensity described as ‘barely perceptible’, ‘faint’, or ‘mild’.

Conventional TENS versus acupuncture-like TENS.

Assessment during TENS versus after TENS.

TENS administered as a sole treatment versus TENS administered in combination with other treatments.

TENS administered as a single dose versus repetitive dose.

Postsubgroup analysis, we contemplate conducting a network meta-analysis contingent on meeting transitivity assumption.

Sensitivity analysis
We plan to analyse the effect of excluding RCTs with a high risk of bias.

Ethics and dissemination
This systematic review will not use data from individual participants to protect privacy, and the results will be disseminated in a peer-reviewed publication and presented at a scientific conference.

Contributors
MIJ: conceived the study, MIJ and PGW: created the first draft of the protocol which was then revised by GJ and CAP. PGW: developed search strategy.

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Competing interests
MIJ’s institution has received research and consultancy funding for work that he has undertaken for GlaxoSmithKline.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
There are no data in this work. No data are available.

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Author note
Underlying materials related to this protocol and subsequent review can be accessed by contacting Professor Mark I. Johnson.

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