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Process evaluations of complex interventions tested in randomised controlled trials in musculoskeletal disorders: a systematic review protocol

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Abstract

Introduction

The effectiveness of complex interventions for the management of musculoskeletal disorders has been estimated in many randomised controlled trials (RCTs). These trials inform which interventions are the most effective, however they do not always inform how an intervention achieved its clinical outcomes, nor how and what elements of an intervention were delivered to patients. Such information is useful to translate findings into clinical practice. Few process evaluation studies have been conducted alongside RCTs, and a variety of methods have been used. To gain a better understanding of current practices of process evaluation in RCTs in musculoskeletal disorders, this systematic review is designed to answer the following research question: How process evaluations of complex interventions tested in randomised controlled trials in musculoskeletal disorders are being conducted?

Methods and analysis

We will systematically search seven electronic databases (MEDLINE, SCOPUS, CINAHL, PsycINFO, EMBASE, Web of Science, and Cochrane database) from the date of inception to August 2018 for studies on process evaluation of RCTs on non-surgical and non-pharmacological for the management of musculoskeletal disorders. We will include qualitative or quantitative studies conducted alongside a RCT, reported with the RCT or as a separate study that assessed interventions for musculoskeletal disorders. Two reviewers will screen abstracts and apply pre-specified inclusion criteria to identify relevant studies, extract the data, and assess the risk of bias within included studies. We will follow recommendations from the "Cochrane Qualitative and Implementation Methods Group Guidance Series" when assessing methodological strengths and limitations of included studies. We will use a narrative synthesis to describe findings.

Ethics and dissemination

Ethical approval is not required as this review will not collect original data. Findings from this systematic review will be presented at a scientific conference and published in a peer-reviewed journal.

PROSPERO registration: CRD42018109600

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Introduction

Musculoskeletal disorders are the second largest cause of disability.[1] Common musculoskeletal disorders include: low back pain (the most frequent disorder),[1] shoulder pain and neck pain (the second and third most prevalent musculoskeletal disorders),[2] and osteoarthritis (the most common joint disorder).[1] The burden of musculoskeletal disorders is high. For example, in New Zealand, between 2005 and 2013, the direct cost of physiotherapy interventions for shoulder injuries was $134 million ($14 million/year).[3] The total direct costs of osteoarthritis were greater than 500 million in 2005.[4] Together, high direct costs and waiting lists highlight the need for effective and affordable interventions to minimize the growing burden (social and economic) of musculoskeletal pain.

To improve healthcare services, it is crucial to identify which interventions are the most effective.[5-7] Randomized clinical trials (RCTs) estimate the effectiveness of different interventions[5 8-11] and can be referred to as an "*outcome evaluation*" trial.[12] Some RCTs may also include an economic analysis that is run in parallel.[13-16] This type of trial is referred to as "*economic evaluation*" trial.[12] While extremely important to improve healthcare, "*outcome and economic evaluation*" trials do not inform how interventions achieved its clinical outcomes.[12]

Complex interventions (e.g. exercise therapy, education, behaviour change)[13 17 18] are defined as interventions with multiple factors which interact with each other. [19 20] Such interaction might impact on clinical outcomes.[19 20] When assessing the effect of a complex intervention, researchers might need to take into account for example: the interacting elements within the experimental and control interventions, variability of outcomes, behaviour of professionals delivering as well as behaviour of patients receiving the intervention, and how much flexibility is permitted for adapting an intervention being tested.[20 21] There is no clear threshold for classifying an intervention as simple or complex, but only few interventions can be considered simple. [19 20] Understanding how an intervention achieves its clinical outcomes is particularly relevant when assessing effectiveness of complex interventions.[20]

Process evaluation studies inform how a complex intervention achieves its clinical outcomes.[12] These studies provide information about how and what elements of an intervention were delivered to patients,[8 11 12 22] and why an intervention work (or fail to do so) the way they do.[23] Process evaluation studies may inform about what and how interventions are implemented (i.e. implementation), how intervention generates change in clinical outcomes (i.e. mechanism of impact), and how context affect clinical outcomes (i.e. context).[8 11 24] Such information is useful to translate findings into clinical practice. [12 25]

Process evaluation methods are still being developed,[12] and methods are relatively scarce in musculoskeletal research.[26] The Medical Research Council (UK) has published its first guideline for process evaluation of clinical trials in 2015.[12] The number of process evaluation studies conducted alongside RCTs is small, and the approaches used to assess implementation of interventions are varied. Previous reviews have focused on process evaluation of trials in fields other than musculoskeletal disorders, for example: complex interventions for patients with chronic diseases,[25] interventions for patients with neurological disorders,[27] another review assessed what is being measured in process evaluations for worksite health promotion programs.[28]

We planned this review to identify approaches used for assessing process evaluations of trials focusing on complex interventions (non-surgical and non-pharmacological) for the management of musculoskeletal disorders. The systematic review was designed to answer the following overarching research question: How process evaluations of complex interventions tested in randomised controlled trials in musculoskeletal disorders are being conducted?

The specific research questions were:

(1) Is a theory adopted by research teams when conducting process evaluations? If so, which theory is used (e.g. theory-based evaluation, realistic evaluation)?

(2) Which study designs were used during the process evaluation (e.g. qualitative, quantitative, or mixed-method)?

(3) When is process evaluation being performed (i.e. Phase II - feasibility and piloting; III - evaluation; or IV - implementation)?

(4) How are results of the trial being integrated with findings from the respective process evaluation study?

(5) Is the process evaluation independent or does it become independent at some stage in the trial?

(6) What are the barriers and facilitators faced by the authors while conducting process evaluations?

(7) What are the strengths and limitations of the process evaluation methods reported by the study authors?

Methods

We used PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) for planning this and reporting this protocol.[29] The review has been prospectively registered in PROSPERO registry (CRD42018109600). We planned the assessment of process evaluation of randomized clinical trials based on Cochrane Qualitative and Implementation Methods Group guidance papers.[30-35]

Searches

We will search seven databases including MEDLINE, SCOPUS, CINAHL, PsycINFO, Embase, Web of Science, and Cochrane database in order to identify relevant studies evaluating process evaluation on complex interventions for the management of musculoskeletal disorders tested in RCTs. To identify any unpublished literature, we will additionally search four clinical trial registries (Cochrane Central Registry of Controlled Trials, ClinicalTrials.gov, EU clinical trials register, and Australian New Zealand Clinical Trial Registry). If we identify any project that is likely to meet the inclusion criteria, we will contact the authors for the results related to the process evaluation.

We will combine “process evaluation”, “program evaluation”, “fidelity” or other search terms that mean process evaluation with “musculoskeletal disorders” and its related terms. We will exclude all the surgical or study protocols by using NOT “surgery” and “protocol” respectively or its substitute words.

Pilot search

Prior to conducting the full search on electronic databases, we conducted a pilot search using MEDLINE, SCOPUS, CINAHL, PsycINFO, Embase, Web of Science databases. This was done for scoping purposes, and the pilot search yielded a total of 1695 studies. The terms used during the pilot search are reported on Table 1. Following this, we have consulted with a health sciences librarian and we are currently optimizing the search strategy. The search strategy will be adapted to reflect different characteristics from each database.

Table 1. Pilot search strategy.

Database	Search term 1	Search term 2	Filter	Number of articles retrieved
Medline	MesH: Program evaluation [mh] OR Process assessment (healthcare) [mh] OR Outcome assessment (healthcare) [mh] OR Title/Abstract/Keywords: "Process Evaluation" OR "Programme Evaluation" OR "Program Evaluation" OR "Process assessment" OR Fidelity.	MeSH: Musculoskeletal Diseases [∗diagnosis; *rehabilitation; ∗therapy]; OR Osteoarthritis [diagnosis; *rehabilitation; therapy]; OR Shoulder Pain [diagnosis; *rehabilitation; therapy] OR Back pain [diagnosis; *rehabilitation; therapy] OR Neck pain [diagnosis; *rehabilitation; therapy] OR musculoskeletal pain [diagnosis; *rehabilitation; therapy] OR Arthritis [diagnosis; *rehabilitation; therapy].	Age >18 years Humans Study design: clinical trial (All phases); OR randomized controlled trials; Clinical trials OR qualitative studies.	218
Scopus	Search in title, abstract, keywords: "Program evaluation" OR "Process Evaluation" OR "Programme Evaluation" OR "Process assessment" OR Fidelity.	Search in title, abstract, keywords: Musculoskeletal OR Osteoarthritis OR "Shoulder Pain" OR "Back pain" OR "Neck pain" OR "Knee pain" OR Arthritis.	NOT: (surger*(title, abstract, keywords) OR protocol (title)) Limits: Document type, article; Keyword, Human and humans; Source type, Journals.	756
CINAHL	MeSH: Program evaluation [mh] OR Process assessment (healthcare) [mh] OR Outcome assessment [mh] OR	MeSH: (MH "Musculoskeletal Diseases") OR (MH "Musculoskeletal Abnormalities") OR (MH "Diagnosis,	Limiters: All adults AND humans AND [therapy(best balance between sensitivity and	341

	Title/abstract: “Process Evaluation” OR “Programme Evaluation” OR “Program Evaluation” OR “Process assessment” OR Fidelity.	musculoskeletal”) OR (MH “Osteoarthritis”) OR (MH "Osteoarthritis, Spine") OR (MH "Osteoarthritis, Wrist") OR (MH "Osteoarthritis, Knee") OR (MH "Osteoarthritis, Hip") OR (MH "Osteoarthritis, Cervical") OR (MH "Low Back Pain") OR (MH "Back Pain") OR (MH "Neck Pain") OR (MH "Chronic Pain") OR (MH "Shoulder Pain") OR (MH "Nociceptive Pain") OR (MH "Patellofemoral Pain Syndrome") Keywords: Musculoskeletal	specificity) OR qualitative(best balance between sensitivity and specificity)]	
PsycINFO	Subject heading search: Program evaluation Title, abstract, Keyword: “Program evaluation” OR fidelity OR “process assessment” OR “process evaluation” OR “process assessment” OR programme evaluation	Subject heading: Musculoskeletal disorders OR back pain OR pain OR chronic pain OR arthritis Title, abstract, keywords: neck pain OR musculoskeletal pain OR osteoarthritis OR shoulder pain OR “knee pain”	Limits: (("therapy (maximizes sensitivity)" or "qualitative (maximizes sensitivity)") and adulthood <18+ years> and human)	85
Embase	Emtree search: program evaluation. Keyword: process evaluation, process assessment, fidelity, programme evaluation, Title and abstract: “process evaluation”, “process assessment”, fidelity, “programme evaluation”, “program evaluation”.	Emtree search [Diagnosis, Rehabilitation, Therapy]: arthritis OR musculoskeletal pain OR Musculoskeletal disease OR neck pain OR backache OR shoulder pain OR osteoarthritis	Limits: humans AND adults. Additional limits: qualitative study to maximize specificity OR clinical trials (all phases) OR RCTs OR controlled clinical trials.	25
Web of Science	“Program evaluation” OR “Process Evaluation” OR “Programme Evaluation” OR “Process assessment” OR Fidelity	Musculoskeletal OR Osteoarthritis OR “Shoulder Pain” OR “Back pain” OR “Neck pain” OR “Knee pain” OR musculoskeletal OR Arthritis		270
Total				1695

Eligibility criteria

Types of study to be included

We will include all the qualitative or quantitative studies conducted alongside a RCT, reported with the RCT or as a separate report that assessed process evaluation of RCTs on complex interventions (non-surgical and non-pharmacological interventions) for musculoskeletal disorders. We defined process evaluation study as any study aiming to understand the functioning of an intervention, by examining implementation, mechanisms of impact, and/or its contextual factors.[12]

To be included, studies need to indicate in the title or the aim of the study that they are assessing components of process evaluation (e.g. implementation, mechanisms of impact or context). We will include articles that: (1) explicitly indicate that the study was a process evaluation study in the title or the aim of the study; or (2) intend to evaluate process evaluation (e.g. fidelity, dose delivered, dose received, reach, recruitment, context, barriers, implementation), without explicitly stating that it is a process evaluation study (e.g. qualitative study alongside an RCT).

Condition or domain being studied

We will include process evaluation of RCTs investigating complex interventions for the management of musculoskeletal disorders. For the purpose of this review, we defined musculoskeletal disorders as health problems of the locomotor apparatus (including muscle, tendon, skeleton, and ligaments) including for example: low back pain, neck pain, shoulder pain, elbow pain, hip pain, knee pain, soft tissue injuries. We will exclude systemic conditions (e.g. gout, rheumatoid arthritis, Raynaud disease, scleroderma, dermatomyositis), osteoporosis, tumours, infections of bones and joints, fibromyalgia, diabetic neuropathy, fractures, ankylosing spondylitis, and spinal cord injuries.

Participants/population

Studies should include participants with musculoskeletal disorders who received complex interventions (non-surgical and non-pharmacological) as part of a RCT, or clinicians delivering

interventions as a part of a clinical trial. To be included in the review, studies must have recruited and analysed humans with adult age (i.e. > 18 years old).

Intervention

Complex interventions of musculoskeletal disorders in a RCT, including but not limited to exercise therapy, physical activity, self-management advice, education, and psychosocial interventions. We will not include studies related to surgical and pharmacological interventions.

Comparator(s)/control

Not applicable.

Context

We will include studies that assessed effectiveness of interventions in primary care (e.g. private practice, home-based and community-based interventions).

Primary outcome(s)

These are in line with our study questions and are as follows:

a) Theory adapted to conduct the process evaluation (if any);
b) Study designs used for process evaluation;
c) Phase of the trial when the process evaluation was performed;
d) Approach used to integrate process evaluation with the main results of the RCT;
e) Barriers and facilitators faced by authors while conducting process evaluation of RCTs;
f) Strengths and limitations of the process evaluation methods as reported by the study authors.

Secondary outcome(s)

None.

Data extraction (selection and coding)

Study selection:

Prior to screening, we will remove duplicate articles. Then, two reviewers will independently screen all titles and abstracts following the eligibility criteria, and using a standard form (Additional File 1). After the first screening, two reviewers will meet to assess the agreement on inclusion or exclusion of the studies based on title and abstract reading. Then, both the reviewers will independently screen full text articles for all the articles that meet the inclusion criteria based on title and abstract or the inclusion based on just title and abstract is unsure. During title, abstract, and full-text screening, disagreements will be resolved by consensus. If consensus is not reached, then a third reviewer will be consulted.

Data extraction:

The research team will develop a form for extracting data from included studies. The data extraction form will be designed based on the "Medical research council of UK (MRC) recommendation for process evaluations" and the "Cochrane Qualitative and Implementation Methods Group Guidance Series".[30-35]

Data extraction forms will be piloted by two reviewers using articles that were included after full-text screening. Following recommendations from The University of York Centre for Research and Dissemination (CDR), data extraction forms will be piloted on a random sample of 10 included studies. This will ensure that resources are not wasted, and that all relevant information is being extracted from included studies. Once the research team agrees that the form is comprehensive and coherent, two reviewers will independently extract data from studies that were included after full text screening. Disagreements will be resolved by consensus. If consensus is not reached, then a third reviewer will be consulted.

We will extract data regarding:

a) Basic information about the study: publication year, authors, title, study type, aims;
b) Context and participants: study setting, population, participant characteristics, intervention delivered;
c) Methods used: design, methods used for sample recruitment, data collection and analysis, theoretical model used to interpret data and contextualize findings;

d) Process evaluation: rationale for study design adopted, dose delivered, participants' attitudes and beliefs, approach used to assess participants' adherence and fidelity to intervention protocol, approach used to assess clinicians' adherence and fidelity to intervention protocol, description of clinicians, training of clinicians, implementation monitoring, theory supporting process evaluation, process evaluation findings, association between process evaluation and outcome evaluation findings.

Risk of bias assessment

We will follow recommendations from the "Cochrane Qualitative and Implementation Methods Group Guidance Series" for assessing methodological strengths and limitations of included studies. The following domains will be included in the assessment:

a) Clear aims and research question;
b) Congruence between the research aims/question and research design/method(s);
c) Rigor of case and/or participant identification, sampling, and data collection to address the question;
d) Appropriate application of the method; richness/conceptual depth of findings, exploration of deviant cases and alternative explanations, and reflexivity of the researchers;
e) We will use the Critical Appraisal Skills Programme (CASP) tool for assessing methodological strengths and limitations of included studies.[36] This is the most used tool by systematic reviews focusing on qualitative evidence synthesis.[35] As per recommendations from the "Cochrane Qualitative and Implementation Methods Group Guidance Series", we may add other tools if we deem that a specific type of study might be in disadvantage if we use only CASP;
f) We will classify and group interventions using the 10-dimension Complexity Assessment Tool for Systematic Reviews (iCAT-SR).[37]

Strategy for data synthesis

We will use a narrative synthesis to describe:

a) The theory (if any) adopted by research teams when conducting process evaluations;
b) The study designs used during the process evaluation alongside RCTs;
c) The phase in which process evaluation was performed;
d) The way results of the trial are being integrated with findings from the respective process evaluation;

e) The barriers and facilitators faced by the authors while conducting process evaluations;

f) Strengths and limitations of the process evaluation methods as reported by the study authors.

We will use narrative summaries of individual studies and shared themes to synthesize the findings.

Analysis of subgroups or subsets

Depending on the number of articles included, we will conduct subgroup data analysis based on: context (e.g. indigenous, non-indigenous participants; non-developed and developed countries, healthcare systems) or the category of interventions (as categorized by iCAT-SR) for describing barriers and facilitators, fidelity and adherence to implementation of the planned intervention.[30 37]

Discussion

Process evaluation studies can help to improve translation from research into clinical practice. The information gathered by process evaluation studies is valuable for healthcare professionals, policy makers, and researchers. Such evidence can inform whether findings from a small trial should be scaled up or whether findings from a trial need to be modified and adapted into another context.

This review will contribute to the field, by identifying methods used for assessing process evaluation of clinical trials assessing the effectiveness of interventions for musculoskeletal disorders. There are no definitive methods or guidelines for conducting process evaluation studies.[12 32] This is caused in part by the fact that the term "process evaluation" includes different domains: *implementation* of interventions, the *mechanisms of action* of an intervention and the impact that *context factors* (i.e. how context influences clinical outcomes or is influenced by an intervention). To address each of these three domains, different research methods are required. Findings from this review will identify current practices adopted by musculoskeletal researchers when conducting, analysing and reporting process

evaluations studies. Our findings will identify gaps in the literature and inform future research conducted in the area of musculoskeletal disorders and rehabilitation.

Conclusions

To our knowledge, this will be the first systematic review to assess how process evaluations are currently being conducted in randomized controlled trials of non-surgical and non-pharmacological interventions in the management of musculoskeletal disorders. This review will describe current practices on process evaluation of clinical trials and inform future research that is conducted in this area. Recently, there has been an increased encouragement to conduct process evaluation studies to better inform implementation of findings from clinical trials into clinical practice and policy-making. It is reasonable to expect this review will yield a diversity of methods used by different researcher groups. Hence, the importance of this review is to identify best practices for future process evaluation studies tested in randomised controlled trials in musculoskeletal disorders.

Patient and public involvement

Patients and/or the public were not involved with the development of this research project.

Ethics and dissemination

This review will not collect original data, hence ethical approval is not required. Findings from this systematic review will be presented at scientific conferences and be published in a peer-reviewed journal.

Author contributions

DCR is the leading researcher, and was responsible for conceiving this study, designing the protocol, preparing the search strategy and co-authoring the first draft of this manuscript. SS contributed to the design of the review protocol, preparing the search strategy and co-authoring the first draft of this manuscript. JHA, SL, and TB has contributed to the design of

the review protocol, and to the manuscript. SM contributed to the design of the review protocol and to the manuscript. DCR (principal investigator), JHA (mentor) and SL (mentor) secured the Sir Charles Hercus Health Research Fellowship of the Health Research Council of New Zealand [Grant number: 18/111]. All authors have contributed to the drafting of this protocol, and accepted the final version of the manuscript for submission.

Competing interests

None declared.

Patient consent

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Dissemination and protocol amendments

The systematic review will be submitted for publication to a peer-reviewed journal and findings will be presented at a relevant conference and research seminars. We will follow the recommendations from the International Committee of Medical Journal Editors (ICMJE) for authorship eligibility.

Any important protocol amendments will be registered at PROSPERO and described in the systematic review report.

Data sharing statement

This is a protocol and all data is available on the protocol reporting.

Funding statement

The research was conducted during tenure of The Sir Charles Hercus Health Research Fellowship of the Health Research Council of New Zealand [Grant number: 18/111]. The Health Research Council – New Zealand had no role in the design of the review and will not have any role in its execution, data analysis and interpretation, or on the submission of the review for publication.

Competing interests statement

None declared.

Article summary

Strengths and limitations of this study

- The main limitation is likely to be the number of studies included. To minimize this, we piloted and reported an electronic search strategy to ensure this systematic review is feasible.
- A strength of this review is its relevance to clinical practitioners, researchers and policy-makers. We will identify the methods used by process evaluation studies in randomized controlled trials of complex interventions in the management of musculoskeletal disorders.
- Another strength of this protocol is its scientific robustness. When designing this protocol we followed the Cochrane Qualitative and Implementation Methods Group Guidance Series.

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Article: Process evaluations of complex interventions tested in randomised controlled trials in musculoskeletal disorders: a systematic review protocol

Authors: Daniel Cury Ribeiro, J Haxby Abbott, Saurab Sharma, Sarah E Lamb

Submitted to BMJ Open

Screening form

Article number			
Authors			
Year			
Journal			
Title			
Abstract			
1. Is the study population one with musculoskeletal disorders?			
2. Is it a clinical trial, qualitative study, or a process evaluation study?			
3. Did it assess process evaluation (e.g. adherence, fidelity, barriers, dosage)?			

4. Did it use a complex intervention (not surgical or pharmacological)?			
5. Are research participants adults?			
6. Is the article published in English?			
Include? Y/ N/ Unclear			
Reason for exclusion?			
Comments/clarification?			
Screener 1's Judgement			
Screener 2's judgement			
Final decision - Include?			

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	15
	#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	16
Sources	#5a	Indicate sources of financial or other support for the review	NA

Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	16
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9
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	7
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	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Study records - 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)	11
Study records - 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	11
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	11 - 12
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
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	12 - 13

		level, or both; state how this information will be used in data synthesis	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	NA
	#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 I2, Kendall's τ)	NA
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

BMJ Open

Process evaluations of complex interventions tested in randomised controlled trials in musculoskeletal disorders: a systematic review protocol

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Process evaluations of complex interventions tested in randomised controlled trials in musculoskeletal disorders: a systematic review protocol

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Abstract

Introduction

The effectiveness of complex interventions for the management of musculoskeletal disorders has been estimated in many randomised clinical trials (RCTs). These trials inform which interventions are the most effective, however they do not always inform how an intervention achieved its clinical outcomes, nor how and what elements of an intervention were delivered to patients. Such information is useful to translate findings into clinical practice. Few process evaluation studies have been conducted alongside RCTs, and a variety of methods have been used. To gain a better understanding of current practices of process evaluation in RCTs in musculoskeletal disorders, this systematic review is designed to answer the following research question: How are process evaluations of complex interventions tested in RCTs in musculoskeletal disorders being conducted?

Methods and analysis

We will systematically search seven electronic databases (MEDLINE, SCOPUS, CINAHL, PsycINFO, EMBASE, Web of Science, and Cochrane database) from the date of inception to August 2018 for studies on process evaluation of RCTs on non-surgical and non-pharmacological management of musculoskeletal disorders. We will include qualitative or quantitative studies conducted alongside a RCT, reported with the RCT or as a separate study that assessed interventions for musculoskeletal disorders. Two reviewers will screen abstracts and apply pre-specified inclusion criteria to identify relevant studies, extract the data, and assess the risk of bias within included studies. We will follow recommendations from the "Cochrane Qualitative and Implementation Methods Group Guidance Series" when assessing methodological strengths and limitations of included studies. We will use a narrative synthesis to describe findings.

Ethics and dissemination

Ethical approval is not required as this review will not collect original data. Findings from this systematic review will be presented at a scientific conference and published in a peer-reviewed journal.

PROSPERO registration: CRD42018109600

Word count: 2353

Article summary

Strengths and limitations of this study

- A strength of this study is the comprehensive search of published and unpublished literature in different databases and trial registries.
- Another strength of this protocol is its scientific robustness. When designing this protocol we followed the Cochrane Qualitative and Implementation Methods Group Guidance Series.
- A limitation of this review is that we may not identify other *process* or *outcome* evaluation studies that have assessed aspects of process evaluation but did not explicitly reported it in the title or abstract.

Introduction

Musculoskeletal disorders are the second largest cause of disability.[1] Common musculoskeletal disorders include: low back pain (the most frequent disorder),[1] shoulder pain and neck pain (the second and third most prevalent musculoskeletal disorders),[2] and osteoarthritis (the most common joint disorder).[1] The individual, societal and economic burden of musculoskeletal disorders is high. For example, in New Zealand, between 2005 and 2013, the direct cost of physiotherapy interventions for shoulder injuries alone was $134 million ($14 million/year).[3] The total direct costs of osteoarthritis were greater than 500 million in 2005.[4] Together, high direct costs and waiting lists highlight the need for effective and affordable interventions to minimize the growing burden (social and economic) of musculoskeletal pain.

To improve healthcare services, it is crucial to identify which interventions are the most effective.[5-7] Randomised clinical trials (RCTs) estimate the effectiveness of different interventions[5 8-11] and can be referred to as an "*outcome evaluation*" trial.[12] Some RCTs may also include an economic analysis that is run in parallel.[13-16] This type of trial is referred to as "*economic evaluation*" trial.[12] While extremely important to improve healthcare, "*outcome and economic evaluation*" trials do not inform how interventions achieved its clinical outcomes.[12]

Complex interventions are defined as interventions with multiple components that may interact with each other, influencing clinical outcomes. [17 18] The interaction between these components of an intervention can impact on clinical outcomes.[17 18] Examples of complex interventions include exercise therapy, education, behaviour change.[13 19 20] Complex interventions represent a challenge to researchers when planning a trial.[21] These challenges are caused by difficulties with standardising the way an intervention is delivered,[22] the possible influence of local context on clinical outcomes,[23] logistic challenges at organisational level, and complex interactions between components of the intervention and the clinical outcome. [21 22 24]

When assessing the effect of a complex intervention, researchers might need to take into account: the interacting elements within the experimental and control interventions, variability of outcomes, behaviour of professionals delivering as well as behaviour of patients receiving the intervention, and how much flexibility is permitted for adapting an intervention being tested.[18 21] There is no clear threshold for classifying an intervention as simple or complex, but only few interventions can be considered simple. [17 18] Understanding how an intervention achieves its clinical outcomes is particularly relevant when assessing effectiveness of complex interventions.[18]

Process evaluation studies inform how a complex intervention achieves its clinical outcomes.[12] These studies provide information about how and what elements of an intervention were delivered to patients,[8 11 12 25] and why an intervention work (or fail to do so) the way they do.[26] Process evaluation studies may inform about what and how interventions are implemented (i.e. implementation), how intervention generates change in clinical outcomes (i.e. mechanism of impact), and how context affect clinical outcomes (i.e. context).[8 11 27] Such information is useful to translate findings into clinical practice. [12 28]

Process evaluation methods are still being developed,[12] and methods are relatively scarce in musculoskeletal research.[29] The Medical Research Council (UK) published its first guideline for process evaluation of clinical trials in 2015.[12] The number of process evaluation studies conducted alongside RCTs is small, and the approaches used to assess implementation of interventions are varied. Previous reviews have focused on process evaluation of trials in fields other than musculoskeletal disorders, for example: complex interventions for patients with chronic diseases,[28] interventions for patients with neurological disorders,[30] another review assessed what is being measured in process evaluations for worksite health promotion programs.[31]

We planned this review to identify approaches used for assessing process evaluations of trials focusing on complex interventions (non-surgical and non-pharmacological) for the management of musculoskeletal disorders. The systematic review was designed to answer the following overarching research question: How are process evaluations of complex interventions tested in RCTs in musculoskeletal disorders being conducted?

The specific research questions were:

(1) Is a theory adopted by research teams when conducting process evaluations? If so, which theory is used (e.g. theory-based evaluation, realistic evaluation)?

(2) Which study designs were used during the process evaluation (e.g. qualitative, quantitative, or mixed-method)?

(3) When is process evaluation being performed (i.e. Phase II - feasibility and piloting; III - evaluation; or IV - implementation)?

(4) How are results of the trial being integrated with findings from the respective process evaluation study?

(5) Is the process evaluation independent or does it become independent at some stage in the trial?

(6) What are the barriers and facilitators faced by the authors while conducting process evaluations?

(7) What are the strengths and limitations of the process evaluation methods reported by the study authors?

Methods

We used PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) for planning this and reporting this protocol.[32] The review has been prospectively registered in PROSPERO registry (CRD42018109600). We planned the assessment of process evaluation of RCTs based on Cochrane Qualitative and Implementation Methods Group guidance papers.[33-38]

Searches

We will search seven databases including MEDLINE, SCOPUS, CINAHL, PsycINFO, Embase, Web of Science, and Cochrane database in order to identify relevant studies evaluating process evaluation on complex interventions for the management of musculoskeletal disorders tested in RCTs. To identify any unpublished literature, we will additionally search four clinical trial registries (Cochrane Central Registry of Controlled Trials, ClinicalTrials.gov,

EU clinical trials register, and Australian New Zealand Clinical Trial Registry). If we identify any project that is likely to meet the inclusion criteria, we will contact the authors for the results related to the process evaluation.

We will combine "process evaluation", "program evaluation", "fidelity" or other search terms that mean process evaluation with "musculoskeletal disorders" and its related terms. We will exclude all the surgical or study protocols by using NOT "surgery" and "protocol" respectively or its substitute words.

Pilot search

Prior to conducting the full search on electronic databases, we conducted a pilot search using MEDLINE, SCOPUS, CINAHL, PsycINFO, Embase, Web of Science databases. This was done for scoping purposes, and the pilot search yielded a total of 1695 studies. The terms used during the pilot search are reported on Table 1. Following this, we consulted with a health sciences librarian for optimizing the search strategy. The search strategy will be adapted for each database.

Table 1. Pilot search strategy.

Database	Search term 1	Search term 2	Filter	Number of articles retrieved
Medline	MesH: Program evaluation [mh] OR Process assessment (healthcare) [mh] OR Outcome assessment (healthcare) [mh] OR Title/Abstract/Keywords: "Process Evaluation" OR "Programme Evaluation" OR "Program Evaluation" OR "Process assessment" OR Fidelity.	MeSH: Musculoskeletal Diseases [∗diagnosis; *rehabilitation; ∗therapy]; OR Osteoarthritis [diagnosis; *rehabilitation; therapy]; OR Shoulder Pain [diagnosis; *rehabilitation; therapy] OR Back pain [diagnosis; *rehabilitation; therapy] OR Neck pain [diagnosis; *rehabilitation; therapy] OR musculoskeletal pain [diagnosis; *rehabilitation; therapy] OR Arthritis [diagnosis; *rehabilitation; therapy].	Age >18 years Humans Study design: clinical trial (All phases); OR randomized controlled trials; Clinical trials OR qualitative studies.	218
Scopus	Search in title, abstract, keywords:	Search in title, abstract, keywords:	NOT:	756

	"Program evaluation" OR "Process Evaluation" OR "Programme Evaluation" OR "Process assessment" OR Fidelity.	Musculoskeletal OR Osteoarthritis OR "Shoulder Pain" OR "Back pain" OR "Neck pain" OR "Knee pain" OR Arthritis.	(surger*(title, abstract, keywords) OR protocol (title)) Limits: Document type, article; Keyword, Human and humans; Source type, Journals.	
CINAHL	MeSH: Program evaluation [mh] OR Process assessment (healthcare) [mh] OR Outcome assessment [mh] OR Title/abstract: "Process Evaluation" OR "Programme Evaluation" OR "Program Evaluation" OR "Process assessment" OR Fidelity.	MeSH: (MH "Musculoskeletal Diseases") OR (MH "Musculoskeletal Abnormalities") OR (MH "Diagnosis, musculoskeletal") OR (MH "Osteoarthritis") OR (MH "Osteoarthritis, Spine") OR (MH "Osteoarthritis, Wrist") OR (MH "Osteoarthritis, Knee") OR (MH "Osteoarthritis, Hip") OR (MH "Osteoarthritis, Cervical") OR (MH "Low Back Pain") OR (MH "Back Pain") OR (MH "Neck Pain") OR (MH "Chronic Pain") OR (MH "Shoulder Pain") OR (MH "Nociceptive Pain") OR (MH "Patellofemoral Pain Syndrome") Keywords: Musculoskeletal	Limiters: All adults AND humans AND [therapy(best balance between sensitivity and specificity) OR qualitative(best balance between sensitivity and specificity)]	341
PsycINFO	Subject heading search: Program evaluation Title, abstract, Keyword: "Program evaluation" OR fidelity OR "process assessment" OR "process evaluation" OR "process assessment" OR programme evaluation	Subject heading: Musculoskeletal disorders OR back pain OR pain OR chronic pain OR arthritis Title, abstract, keywords: neck pain OR musculoskeletal pain OR osteoarthritis OR shoulder pain OR "knee pain"	Limits: (("therapy (maximizes sensitivity)" or "qualitative (maximizes sensitivity)") and adulthood <18+ years> and human)	85
Embase	Emtree search: program evaluation. Keyword: process evaluation, process assessment, fidelity, programme evaluation, Title and abstract:	Emtree search [Diagnosis, Rehabilitation, Therapy]: arthritis OR musculoskeletal pain OR Musculoskeletal disease OR neck pain OR backache OR shoulder pain OR osteoarthritis	Limits: humans AND adults. Additional limits: qualitative study to maximize specificity OR clinical trials (all phases) OR RCTs	25

	"process evaluation", "process assessment", fidelity, "programme evaluation", "program evaluation".		OR controlled clinical trials.	
Web of Science	"Program evaluation" OR "Process Evaluation" OR "Programme Evaluation" OR "Process assessment" OR Fidelity	Musculoskeletal OR Osteoarthritis OR "Shoulder Pain" OR "Back pain" OR "Neck pain" OR "Knee pain" OR musculoskeletal OR Arthritis		270
Total				1695

Eligibility criteria

Types of study to be included

We will include all the qualitative or quantitative studies conducted alongside a RCT, reported with the RCT or as a separate report that assessed process evaluation of RCTs on complex interventions (non-surgical and non-pharmacological interventions) for musculoskeletal disorders. We defined process evaluation study as any study aiming to understand the functioning of an intervention, by examining implementation, mechanisms of impact, and/or its contextual factors.[12]

To be included, studies need to indicate in the title or the aim of the study that they are assessing components of process evaluation (e.g. implementation, mechanisms of impact or context). We will include articles that: (1) explicitly indicate that the study was a process evaluation study in the title or the aim of the study; or (2) intend to evaluate process evaluation (e.g. fidelity, dose delivered, dose received, reach, recruitment, context, barriers, implementation), without explicitly stating that it is a process evaluation study (e.g. qualitative study alongside an RCT).

Condition or domain being studied

We will include process evaluation of RCTs investigating complex interventions for the management of musculoskeletal disorders. For the purpose of this review, we defined musculoskeletal disorders as health problems of the locomotor apparatus (including muscle, tendon, skeleton, and ligaments) including for example: low back pain, neck pain, shoulder

pain, elbow pain, hip pain, knee pain, soft tissue injuries. We will exclude systemic conditions (e.g. gout, rheumatoid arthritis, Raynaud disease, scleroderma, dermatomyositis), osteoporosis, tumours, infections of bones and joints, fibromyalgia, diabetic neuropathy, fractures, ankylosing spondylitis, and spinal cord injuries.

Participants/population

Studies should include participants with musculoskeletal disorders who received complex interventions (non-surgical and non-pharmacological) as part of a RCT, or clinicians delivering interventions as a part of a clinical trial. To be included in the review, studies must have recruited adult humans (i.e. > 18 years old).

Intervention

Complex interventions of musculoskeletal disorders in a RCT, including but not limited to exercise therapy, physical activity, self-management advice, education, and psychosocial interventions. We will not include studies assessing surgical or pharmacological interventions.

Comparator(s)/control

We will include studies that compared complex intervention with an appropriate control group (e.g. waiting list, placebo group, other active interventions). We will exclude studies that compared surgical or pharmacological intervention to a non-surgical or non-pharmacological intervention.

Context

We will include studies that assessed effectiveness of interventions in primary care (e.g. private practice, home-based and community-based interventions).

Primary outcome(s)

These are in line with our study questions and are as follows:

a) Theory adapted to conduct the process evaluation (if any);

b) Study designs used for process evaluation;
c) Phase of the trial when the process evaluation was performed;
d) Approach used to integrate process evaluation with the main results of the RCT;
e) Barriers and facilitators faced by authors while conducting process evaluation of RCTs;
f) Strengths and limitations of the process evaluation methods as reported by the study authors.

Secondary outcome(s)

None.

Data extraction (selection and coding)

Study selection:

Prior to screening, we will remove duplicate articles. Then, two reviewers will independently screen all titles and abstracts following the eligibility criteria, and using a standard form (Additional File 1). After the first screening, two reviewers will meet to assess the agreement on inclusion or exclusion of the studies based on title and abstract reading. Then, both the reviewers will independently screen full text articles for all the articles that meet the inclusion criteria based on title and abstract or the inclusion based on just title and abstract is unsure. During title, abstract, and full-text screening, disagreements will be resolved by consensus. If consensus is not reached, then a third reviewer will be consulted.

Data extraction:

The research team will develop a form for extracting data from included studies. The data extraction form will be designed based on the "Medical research council of UK (MRC) recommendation for process evaluations" and the "Cochrane Qualitative and Implementation Methods Group Guidance Series".[33-38]

Data extraction forms will be piloted by two reviewers using articles that were included after full-text screening. Following recommendations from The University of York Centre for Research and Dissemination (CRD), data extraction forms will be piloted on a random sample of 10 included studies. This will ensure that resources are not wasted, and that all relevant information is being extracted from included studies. Once the research team agrees that the

form is comprehensive and coherent, two reviewers will independently extract data from studies that were included after full text screening. Disagreements will be resolved by consensus. If consensus is not reached, then a third reviewer will be consulted.

We will extract data regarding:

a) Basic information about the study: publication year, authors, title, study type, aims;
b) Context and participants: study setting, population, participant characteristics, intervention delivered;
c) Methods used: design, methods used for sample recruitment, data collection and analysis, theoretical model used to interpret data and contextualize findings;
d) Process evaluation: rationale for study design adopted, dose delivered, participants' attitudes and beliefs, approach used to assess participants' adherence and fidelity to intervention protocol, approach used to assess clinicians' adherence and fidelity to intervention protocol, description of clinicians, training of clinicians, implementation monitoring, theory supporting process evaluation, process evaluation findings, association between process evaluation and outcome evaluation findings.

Risk of bias assessment

We will assess risk of bias of the RCT report if process evaluation is reported within the outcome evaluation (i.e. RCT study). In that case, we will use the Cochrane Collaboration's tool for assessing risk of bias [reference].

When process evaluation is reported as an independent study, we will follow recommendations from the "Cochrane Qualitative and Implementation Methods Group Guidance Series" for assessing methodological strengths and limitations of included studies. In those cases, we will assess the risk of bias of the process evaluation study alone. The following domains will be included in the assessment:

a) Clear aims and research question;
b) Congruence between the research aims/question and research design/method(s);
c) Rigor of case and/or participant identification, sampling, and data collection to address the question;

d) Appropriate application of the method; richness/conceptual depth of findings, exploration of deviant cases and alternative explanations, and reflexivity of the researchers;
e) We will use the Critical Appraisal Skills Programme (CASP) tool for assessing methodological strengths and limitations of included studies.[39] This is the most used tool by systematic reviews focusing on qualitative evidence synthesis.[38] As per recommendations from the "Cochrane Qualitative and Implementation Methods Group Guidance Series", we may add other tools if we deem that a specific type of study might be in disadvantage if we use only CASP;
f) We will classify and group interventions using the 10-dimension Complexity Assessment Tool for Systematic Reviews (iCAT-SR).[40]

Strategy for data synthesis

We will use a narrative synthesis to describe:

a) The theory (if any) adopted by research teams when conducting process evaluations;
b) The study designs used during the process evaluation alongside RCTs;
c) The phase in which process evaluation was performed;
d) The way results of the trial are being integrated with findings from the respective process evaluation;
e) The barriers and facilitators faced by the authors while conducting process evaluations;
f) Strengths and limitations of the process evaluation methods as reported by the study authors.

We will use narrative summaries of individual studies and shared themes to synthesize the findings.

Analysis of subgroups or subsets

Depending on the number of articles included, we will conduct subgroup data analysis based on: context (e.g. indigenous, non-indigenous participants; non-developed and developed countries, healthcare systems) or the category of interventions (as categorized by iCAT-SR) for describing barriers and facilitators, fidelity and adherence to implementation of the planned intervention.[33 40]

Discussion

Process evaluation studies can help to improve translation of research into clinical practice. The information gathered by process evaluation studies is valuable for healthcare professionals, policy makers, and researchers. Such evidence can inform whether findings from a small trial should be scaled up or whether findings from a trial need to be modified and adapted into another context.

This review will contribute to the field, by identifying methods used for assessing process evaluation of clinical trials assessing the effectiveness of interventions for musculoskeletal disorders. There are no definitive methods or guidelines for conducting process evaluation studies.[12 35] This is caused in part by the fact that the term "process evaluation" includes different domains: *implementation* of interventions, the *mechanisms of action* of an intervention and the impact that *context factors* (i.e. how context influences clinical outcomes or is influenced by an intervention). To address each of these three domains, different research methods are required. Findings from this review will identify current practices adopted by musculoskeletal researchers when conducting, analysing and reporting process evaluations studies. Our findings will identify gaps in the literature and inform future research conducted in the area of musculoskeletal disorders and rehabilitation.

This protocol has limitations. We will only include studies that explicitly state process evaluation of an intervention was assessed, or that include outcome measures that allow researchers assessing process evaluation of an intervention (e.g. fidelity, or adherence of an intervention). It would not be feasible to screen full-text of all published trials within musculoskeletal disorders. We may not identify other *process* or *outcome* evaluation studies that have assessed process evaluation but did not explicitly reported it in the title or abstract. The advantage of our approach is to identify current practices using studies within the broad area of musculoskeletal disorders.

Conclusions

To our knowledge, this will be the first systematic review to assess how process evaluations are currently being conducted in RCTs of non-surgical and non-pharmacological interventions in the management of musculoskeletal disorders. This review will describe current practices on process evaluation of clinical trials and inform future research that is conducted in this area. Recently, there has been an increased encouragement to conduct process evaluation studies to better inform implementation of findings from clinical trials into clinical practice and policy-making. It is reasonable to expect this review will yield a diversity of methods used by different researcher groups. Hence, the importance of this review is to identify best practices for future process evaluation studies tested in RCTs in musculoskeletal disorders.

Patient and public involvement

Patients and/or the public were not involved with the development of this research project.

Ethics and dissemination

This review will not collect original data, hence ethical approval is not required. Findings from this systematic review will be presented at scientific conferences and be published in a peer-reviewed journal.

Author contributions

DCR is the leading researcher, and was responsible for conceiving this study, designing the protocol, preparing the search strategy and co-authoring the first draft of this manuscript. SS contributed to the design of the review protocol, preparing the search strategy and co-authoring the first draft of this manuscript. JHA and SL contributed to the design of the review protocol, and to the manuscript. DCR (principal investigator), JHA (mentor) and SL (mentor) secured the Sir Charles Hercus Health Research Fellowship of the Health Research Council of New Zealand [Grant number: 18/111]. All authors have contributed to the drafting of this protocol, and accepted the final version of the manuscript for submission.

Competing interests

None declared.

Patient consent

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Dissemination and protocol amendments

The systematic review will be submitted for publication to a peer-reviewed journal and findings will be presented at a relevant conference and research seminars. We will follow the recommendations from the International Committee of Medical Journal Editors (ICMJE) for authorship eligibility.

Any important protocol amendments will be registered at PROSPERO and described in the systematic review report.

Data sharing statement

This is a protocol and all data is available on the protocol reporting.

Funding statement

The research was conducted during tenure of The Sir Charles Hercus Health Research Fellowship of the Health Research Council of New Zealand [Grant number: 18/111]. The Health Research Council – New Zealand had no role in the design of the review and will not

have any role in its execution, data analysis and interpretation, or on the submission of the review for publication.

Competing interests statement

None declared.

References

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Article: Process evaluations of complex interventions tested in randomised controlled trials in musculoskeletal disorders: a systematic review protocol

Authors: Daniel Cury Ribeiro, J Haxby Abbott, Saurab Sharma, Sarah E Lamb

Submitted to BMJ Open

Screening form

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Title			
Abstract			
1. Is the study population one with musculoskeletal disorders?			
2. Is it a clinical trial, qualitative study, or a process evaluation study?			
3. Did it assess process evaluation (e.g. adherence, fidelity, barriers, dosage)?			

4. Did it use a complex intervention (not surgical or pharmacological)?			
5. Are research participants adults?			
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	15
	#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	16
Sources	#5a	Indicate sources of financial or other support for the review	NA

Sponsor	#5b	Provide name for the review funder and / or sponsor	16
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	16
Rationale	#6	Describe the rationale for the review in the context of what is already known	5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9
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	7
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	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Study records - 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)	11
Study records - 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	11
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	11 - 12
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12
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	12 - 13

		level, or both; state how this information will be used in data synthesis	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	NA
	#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 I2, Kendall's τ)	NA
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA