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[Intervention Protocol]

Exercise and physical therapy for systemic sclerosis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the efficacy and safety of exercise and physical therapies in people with systemic sclerosis.

BACKGROUND

Description of the condition

Systemic sclerosis (SSc), or scleroderma, is an autoimmune rheumatic disease, characterised by inflammation, widespread microvascular injury, and excessive collagen deposition in the skin and internal organs, resulting in generalised fibrosis in the skin and visceral organs (Bairkdar 2021). SSc has a broad spectrum of clinical manifestations, varying from Raynauds phenomenon and fatigue to more serious complications, such as pulmonary arterial hypertension and lung fibrosis. The two main subtypes of SSc, limited and diffuse, typically have different courses and prognoses. Throughout the literature, SSc has been described as a rare disease, with occurrence rates differing greatly between geographic region, criteria of diagnosis, population size, and study design. The prevalence has been reported to be increasing in different countries to over 20 per million, possibly due to improved diagnosis (Nikpour 2010). Prevalence ranges from 3.1 to 144.5 per 100,000 individuals, with a pooled prevalence of 17.6 (95% confidence interval (CI) 15.1 to 20.5) per 100,000. The overall pooled incidence rate of SSc is 1.4 (95% CI 1.1 to 1.9) per 100,000 person-years, with considerable variance between studies (Bairkdar 2021). The pooled incidence and prevalence in women is five times higher than in men, and is more frequent in the working-age population (Bairkdar 2021).

Clinical manifestations of SSc include excessive fibrosis of the skin due to collagen deposits, which are confined to the face, neck, and the area distal to elbows and knees, which can extend to upper arms, thighs, and trunk; microvascular injury, skin ulcerations, and visceral involvement, which can include the lungs, heart, kidneys, and gastrointestinal tract (Decuman 2012; Nikpour 2010). SSc has pervasive effects on people living with the disease, such as disabling pain, mental deterioration, and debilitating fatigue (Nakayama 2016).

Both limited and diffuse forms can limit or compromise work capacity, due to the skin and musculoskeletal compromise with skin retraction, stiffness, pain, dysfunction in joints, bursas, and tendons, and movement restriction. This may have a negative influence on the level of activity and participation, decrease life expectancy, decrease productivity, and increase cost (Decuman 2012). People with SSc are significantly less physically active than those without SSc (1704 minutes/week versus 2614 minutes/week), and nearly three quarters of people with SSc without pulmonary involvement are insufficiently active, compared with only 27% aged-matched controls (De Oliveira 2007). Joint stiffness and contractures, shortness of breath, fatigue, and pain have been identified as barriers for people with SSc to engage in exercise (Harb 2021).

Description of the intervention

Exercise is regarded as a non-pharmaceutical intervention for people with SSc (Willems 2015). For this review, we will focus on studies that examine all types of structured exercise and physical therapies for the management of SSc. Evidence suggests that exercise and physical therapy interventions are essential to maintain range of motion and prevent functional limitation.

According to the American College of Sports Medicine (ACSM), exercise is defined as a type of physical activity consisting of planned, structured, and repetitive bodily movement, done to improve or maintain (or both) one or more components of physical fitness (Caspersen 1985; Koeneman 2011; Pescatello 2014). This definition contrasts with physical activity, which is described as an unstructured activity incorporated into daily life, and can include household activities, and walking or strolling for entertainment, social goals, or transport (Caspersen 1985; Koeneman 2011).

The three main types of exercise include aerobic, resistance, and range of movement (Caspersen 1985; Koeneman 2011; Pescatello 2014). Aerobic exercise is aimed at improving the efficiency of the cardiovascular system, and represents a broad range of physical activities, such as walking, jogging, cycling, and dancing. Resistance training is a type of physical exercise that uses resistance to induce muscular contraction, which builds the strength, anaerobic endurance, and size of skeletal muscles. It can be structured or unstructured, for example sitting to standing, walking upstairs, or picking up groceries. Range of motion exercise refers to activity aimed at improving the range of movement of a specific joint, for example yoga, tai chi, or stretching.

Exercise interventions are usually described using intensities, which determine the effort required by the person performing the exercise. Intensity may either be high (70% to < 90% of maximum heart rate (HRmax); or a rating of perceived exertion (RPE) value of 5/10 to 7/10); moderate (55% to < 70% HRmax, or an RPE value of 3/10 to 4/10); or light (40% to < 55% HRmax, or an RPE value of 1/10 to 2/10). An exercise intervention may be supervised by allied health practitioners, medical health practitioners, or other exercise professionals. It can be individually supervised, supervised in a group setting, or completely unsupervised, and performed independently. Unsupervised exercise is usually reported as home-based exercise, but can also include someone exercising in a park or in a gym without supervision. The exercise environment may be water-based (indoors or outdoors), or land-based (indoors or outdoors); in a gym or clinic, outdoors at a park, or along a walking or bike track, or in one's home.

Physical therapy is a branch of rehabilitation that uses specifically designed equipment, manual and physical therapies, and exercises to help people regain or improve their physical abilities. Physical therapy is multimodal; rehabilitation techniques used in SSc include massage, hydrotherapy, electrical stimulation therapy, exercise movement techniques, or physiotherapy techniques, among others (Poole 2010). Many of these interventions have been evaluated in randomised controlled trials with contrasting results.

How the intervention might work

Regular exercise training may lead to anti-inflammatory benefits in chronic diseases with systemic low-grade inflammation (i.e. type 2 diabetes) by reducing inflammatory markers. Given the potential role of inflammation in the aetiology and clinical symptoms of SSc, if exercise training can alleviate the inflammatory process, it could be a helpful intervention in managing some concerning symptoms of SSc, including pain (Perandini 2012). Structured exercise seems to be a safe and effective management strategy for people with SSc (Liem 2019). Improvements have been seen in cardiovascular fitness (Mitropoulos 2018; Mitropoulos 2019; Pinto 2011), quality of life (Liem 2019), muscle strength and function (Pinto 2011), and fatigue (Alexanderson 2014).

Rehabilitation for people with SSc, including physical therapies, improves functional status, the ability to perform physical activities, and hand mobility, two to twelve weeks after therapy; however, loss of improvements in hand mobility at 24 weeks suggests that the continuation of therapy is important to preserve the benefits of physical therapy (Peddi 2014).

Why it is important to do this review

Few reviews have evaluated the effectiveness of exercise alone and physical therapy alone to prevent limitations in musculoskeletal systems and skin, and to maintain and improve function and pain in people with SSc. Furthermore, the most recent systematic review on exercise in SSc was published in 2019, and included studies that were mostly considered to be low quality, leading to uncertain results (Liem 2019).

The aim of this review is to update the evidence on physical therapy and exercise in SSc. We will capture any updated evidence on the safety and effectiveness of all physical therapy and exercise programs reported in the literature. We will conduct this review according to the guidelines recommended by the Cochrane Musculoskeletal Group Editorial Board (Ghogomu 2014).

OBJECTIVES

To evaluate the efficacy and safety of exercise and physical therapies in people with systemic sclerosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCT) and trials using quasi-randomised methods of participant allocation that evaluate exercise or physical therapies (or both) in systemic sclerosis (SSc). We will include parallel and cross-over trials, and cluster-RCTs. We will include published and unpublished studies, provided they are reported in full-text or abstract format.

We will exclude cross-over trials without pre-cross-over data, due to the carry-over effect of exercise and physical therapy interventions and the impossibility of a wash-out period.

Types of participants

We will include trials with adult participants (18 years and older), who have been diagnosed with SSc according to the American College of Rheumatology and the European League Against Rheumatism criteria, and who have systemic disease involving at least two body sites or organ systems (van den Hoogen 2013). We will include trials that define systemic sclerosis according to incomplete or partial diagnostic criteria, and provide notes to identify possible weaknesses in selection. We will include intervention trials without regard to the race, gender, or disease duration of participants.

We will exclude trials that include participants with SSc and another diagnosed condition, if the effects of the intervention cannot be determined separately for the participants with SSc. We will also exclude trials that only report results for the number of body parts improving, instead of the number of participants reporting improvement (e.g. number of hands), or studies in which the control group is the other extremity (e.g. left versus right hand).

Types of interventions

We will include trials that compare any modality or programme of exercise, any modality or programme of physical therapy, or any combination of both exercise and physical therapy (Table 1). We will compare any trial that evaluates the efficacy and safety of an exercise, physical therapy programme, or both, with sham procedures or usual care in participants with SSc. We will include studies in which exercise or physical therapies are used adjunctive to other therapies, such as pharmacological management or dietary modification, if we can determine the separate effect of the exercise or physical therapy intervention.

We will include physical therapy techniques applied either individually or in combination with other treatment modalities. Physical therapy sessions can be individualised according to the person's needs, can take place at home or in an outpatient clinic, can be self-administered or delivered by a trained physical therapist or health care professional, in individual or group sessions. Physical therapy may include massage, hydrotherapy, electrical stimulation therapy, exercise movement techniques, or physiotherapy techniques, among others.

Exercise interventions may be completed at any intensity, in any environment, and can include an individual type of exercise or a combination of various types (Table 1). Exercise interventions must be structured and recurring; prescriptions should include specific dosage information (i.e. frequency, intensity, timing, type). Aerobic exercises may include, but are not limited to, walking (treadmill or free), cycling (stationary or free), swimming, or aerobics classes. Range of movement exercises may include Pilates; yoga; tai chi; active, ballistic, or static stretching. Other forms of exercises, such as sports and games; and recreational activities, such as dancing, lawn bowls, and Wii fit may also be included, as long as they are structured. Exercise environments may include water- or land-based exercise, home-based or community-led, supervised or unsupervised.

Control groups may receive usual care (no exercise or waiting-list control); an active control, during which participants receive an alternative intervention, such as education about exercise or counselling about exercise; or a placebo control.

Types of outcome measures

Major outcomes

1. Mean or mean change in hand mobility, measured with either: the Hand Mobility in Scleroderma (HAMIS) test (Sandqvist 2000), the Duruoz Hand Index (self-report of hand abilities by people with SSc (Brower 2004)), the Delta finger-to-palm (delta FTP) for finger motion (Torok 2010), or the hand functional disability (measured with Cochin hand functional disability scale (Poiraudeau 2001))
2. Mean or mean change in skin thickness, measured by the modified Rodnan skin score (Khanna 2017)
3. Mean or mean change in function, measured with the Health Assessment Questionnaire (HAQ (Bruce 2005))
4. Mean or mean change in pain, measured by a visual analogue scale (VAS) or the numeric rating scale (NRS)

5. Mean or mean change in health-related quality of life (HRQoL), assessed with the Mental Component Score (MCS) of the Short Form-36 (SF-36 (Danieli 2005))
6. Withdrawals due to adverse events
7. Total adverse events

Minor outcomes

1. Mean or mean change in fatigue, assessed by the Fatigue Severity Scale (FSS), or the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F (FACIT 2022; Lai 2011))
2. Mean or mean change in aerobic fitness, assessed by the predicted or absolute value of maximum rate of oxygen consumption (VO_2max)
3. Six-minute walk distance (6MWD)
4. Mean or mean change in grip strength, measured with a dynamometer
5. Withdrawals due to lack of efficacy

When a study reports more than one outcome measure for the same outcome, we will prioritise according to the order in which they appear in this list. If a study has measured an outcome using a tool not listed above, we will report the outcome and specify the tool used.

We will group analyses based on duration of treatment into three groups: short duration (one month or less), intermediate duration (one to three months), or long duration (longer than three months). If data for more than one time point are provided, we will use the longest time point reported (primary time point).

We will not exclude studies on the basis of outcome reporting.

Search methods for identification of studies

Electronic searches

We will search these databases from their inception to the present. We will impose no restriction on language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE EBSCO
- Embase Ovid
- CINAHL EBSCO
- Web of Science (Clarivate)
- Physiotherapy Evidence Database (Neuroscience Research Australia (NeuRA))
- Center for International Rehabilitation Research Information and Exchange database (RehabDATA)
- National Rehabilitation Information Center (ProQuest)

We will also conduct a search for ongoing trials and protocols on:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/en/).

See Appendix 1 for the MEDLINE search strategy.

Searching other resources

We will not contact organisations to obtain additional references. We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and report the date this was done in the review. We will handsearch the reference lists of any included trials, to identify any additional studies.

Data collection and analysis

Selection of studies

Two review authors (SF, MC) will independently screen titles and abstracts for the inclusion of all of the potentially-relevant studies we identify as a result of the search, and code them as 'retrieve' (eligible, potentially eligible, or unclear), or 'do not retrieve'. We will retrieve the full-text study reports or publications, and two review authors (SF, MC) will independently screen the full text, to identify studies for inclusion, and identify and record reasons for excluding the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third person (GE). We will identify and exclude duplicates and collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete the characteristics of excluded studies table, and a PRISMA flow diagram (Page 2021).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. One review author (SF) will extract study characteristics from included studies. A second review author (MC) will spot-check study characteristics for accuracy against the trial report. We will extract the following study characteristics:

1. Methods: study design, total duration of study, details of any run-in period, number of study centres and location, study setting, withdrawals, and date of study
2. Participants: N, mean age, age range, sex, disease duration, severity of condition, diagnostic criteria, important systemic sclerosis baseline data, inclusion and exclusion criteria (Page 2021).
3. Interventions: intervention, comparison, concomitant medications, and excluded medications
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported
5. Characteristics of the design of the trial, as outlined in the Assessment of risk of bias in included studies section
6. Notes: funding for trial, and notable declarations of interest of trial authors

Two review authors (SF, MC) will independently extract outcome data from included studies. We will extract the number of events and number of participants per treatment group for dichotomous outcomes, and means and standard deviations and number of participants per treatment group for continuous outcomes. We will note in the characteristics of included studies table if outcome data were not reported in a usable way, and when data were transformed or estimated from a graph. We will resolve disagreements by consensus, or by involving a third person (GE). One review author

(SF) will transfer data into the Review Manager 5 file (Review Manager 2020). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

For efficacy outcomes, we will extract data from the end of the intervention time point. We will extract adverse event outcomes at the last time point (i.e. proportion who had an event by the end of the trial).

We will use Plot Digitiser to extract data from graphs or figures (Huwaldt 2015). We will also extract these data in duplicate.

We will extract the final values if both final values and change from baseline values are reported for the same outcome. If unadjusted and adjusted values for the same outcome are reported, we will extract unadjusted values for data collection. We will extract intention-to-treat samples for all outcomes. If data for more than one time point are provided, we will use the longest time point for the meta-analysis.

Assessment of risk of bias in included studies

Two review authors (SF, MC) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions, chapter 8* (Higgins 2017). We will resolve any disagreements by discussion, or by involving another author (GE). We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias: potential threats to validity, such as unit of analysis issues, inappropriate or unequal application of co-intervention across treatment groups

We will grade each potential source of bias as high, low, or unclear risk, and provide a quote from the study report, together with a justification for our judgment, in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for hand mobility may be different from a self-reported pain scale). We will also consider the impact of missing data by key outcomes.

Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will present the figures generated by the risk of bias (RoB 1) tool to provide summary assessments of the risk of bias.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol, and report any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RR) or Peto odds ratios (OR) when the outcome is a rare event (approximately less than 10%), and use 95% confidence intervals (CIs). We will analyse continuous data as mean difference (MD) or standardised mean difference (SMD), depending on whether the same scale is used to measure an outcome, and 95% CIs. We will enter data presented as a scale with a consistent direction of effect across studies.

When different scales are used to measure the same conceptual outcome (e.g. disability), we will calculate SMDs, with corresponding 95% CIs. We will back-translate SMDs to a typical scale (e.g. 0 to 10 for pain) by multiplying the SMD by a typical among-person standard deviation (e.g. the standard deviation of the control group at baseline from the most representative trial (Schünemann 2020b)).

For dichotomous outcomes, we will calculate the number needed to treat for an additional beneficial outcome (NNTB), or the number needed to treat for an additional harmful outcome (NNTH) from the control group event rate and the relative risk, using the Visual Rx NNT calculator (Cates 2008). We will calculate the NNTB or NNTH for continuous measures using the Wells calculator (available at the CMSG Editorial office, musculoskeletal.cochrane.org/). We will use the minimal clinically important difference (MCID) in the calculation of NNTB or NNTH; we will assume an MCID of 1.5 points on a 10-point scale for pain, and 10 points on a 100-point scale for function or disability for input into the calculator (Tubach 2012). For measures with no previously reported clinically important threshold, we will use the standardised mean difference interpretation, where values > 0.8 will be considered clinically significant (large effect).

For dichotomous outcomes, we will calculate the absolute percent change from the difference in the risks between the intervention and control group using GRADEpro GDT, expressed as a percentage (GRADEpro GDT).

In the Effects of interventions results section, and the What happens column of the summary of findings table, we will provide the absolute percent change and the NNTB or NNTH (we will provide the NNTB or NNTH only when the outcome shows a clinically significant difference).

Unit of analysis issues

When multiple trial arms are reported in a single trial, we will include only the relevant arms. If we combine two comparisons (e.g. exercise versus placebo and physcial therapy versus placebo) in the same meta-analysis, we will halve the control group to avoid double-counting. We will analyse non-standard designs (i.e. cluster-randomized trials and cross-over trials), using methods appropriate to the design, as suggested in sections 23.1.4, 23.1.5, 23.2.5 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Boutron 2020).

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only, or when data are not available for all participants). When this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results with a sensitivity analysis. We will clearly describe any assumptions and imputations to handle missing data, and explore the effect of imputation with sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we will calculate the withdrawal rate using the number of participants randomised to the group as the denominator.

For continuous outcomes (e.g. mean change in pain score), we will calculate the MD or SMD, based on the number of participants analysed at that time point. If the number of participants analysed is not presented for each time point, we will use the number of participants randomised to each group at baseline.

Where possible, we will compute missing standard deviations from other statistics, such as standard errors, CIs or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*. If we cannot calculate standard deviations, we will impute them (e.g. from other studies in the meta-analysis (Boutron 2020)).

Assessment of heterogeneity

We will assess clinical and methodological diversity of participants, interventions, outcomes, and study characteristics of the included studies to determine whether a meta-analysis is appropriate. We will conduct this by observing these data in the data extraction tables. We will assess statistical heterogeneity by visually inspecting the forest plots to assess for obvious differences in results between the studies, and using the I^2 and Chi^2 statistical tests.

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions, chapter 10* (Deeks 2020), we will interpret that an I^2 value of 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity. As noted in the *Cochrane Handbook for Systematic Reviews of Interventions, chapter 10*, we will keep in mind that the importance of I^2 depends on: (i) the magnitude and direction of effects, and (ii) the strength of evidence for heterogeneity (Deeks 2020).

When there is a P value ≤ 0.10, we will interpret that the Chi^2 test indicates evidence of statistical heterogeneity.

If we identify substantial heterogeneity (I^2= 50%), we will report it and investigate possible causes by following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions, chapter 10* (Deeks 2020).

Assessment of reporting biases

We will create and examine a funnel plot to explore possible small study biases only when 10 or more studies report on the same outcome measure and comparison. In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry, and relate this to the results of the review. If we are able to pool more than 10 trials, we will undertake formal statistical tests to investigate funnel plot asymmetry, and will follow the recommendations in section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2020).

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the WHO International Clinical Trials Registry Platform for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

We will undertake meta-analyses only when this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. We will use a random-effects model.

The primary analysis for our review for self-reported outcomes (e.g. pain, function, and health-related quality of life) will be restricted to trials at low risk of detection and selection bias.

The main planned comparisons include:

- Structured exercise versus sham control;
- Structured exercise versus no intervention or waiting-list control;
- Structured exercise versus active control;
- Physical therapy (any type) versus no intervention or wait-list control.

We will base our conclusions only on findings from the quantitative or narrative synthesis, according to the Synthesis Without Meta-analysis (SWiM) reporting guideline (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

- Disease duration (short ≤ 5 years versus long > 5 years)
- Type of systemic sclerosis (diffuse versus limited)
- Frequency of therapy (daily, weekly, monthly, etc)
- Intervention duration (1 month, 3 months, 6 months, etc)

We hypothesise that participants with a shorter disease duration may have a better response to these types of interventions and that participants with longer disease duration may have more skin or organ changes. Similarly, participants with diffuse disease may have a worse response than participants with limited disease. The efficacy of the exercise or physical therapy may also depend on how frequently the sessions are offered to the participants, or how long the intervention lasts. Evidence suggests that physical therapy offered for three months or longer leads to a greater benefit in functional ability (Peddi 2014).

We will restrict subgroup analyses to functional ability.

We will use the formal test for subgroup interactions in Review Manager 5, and will use caution in the interpretation of subgroup analyses (Review Manager 2020). We will compare the magnitude of the effects between the subgroups by assessing the overlap of the

CIs of the summary estimate (e.g. one intervention is clearly better than the other).

Sensitivity analysis

We plan to carry out the following sensitivity analyses using a fixed-effects model, to investigate the robustness of the treatment effect on functional ability.

- Impact of including studies with high or unclear risk of selection, detection, and attrition biases
- Impact of including studies with imputed data

Summary of findings and assessment of the certainty of the evidence

At least two review authors will assess the certainty of the evidence behind each estimate of treatment effect, using the GRADE approach. We will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020a; Schünemann 2020b). We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the evidence as it relates to the studies that contributed data to the meta-analyses for the prespecified outcomes, and report the certainty of the evidence as high, moderate, low, or very low.

We will use GRADEpro GDT software to prepare and display the summary of findings tables (GRADEpro GDT). We will justify all decisions to downgrade the certainty of the evidence for each outcome in footnotes, and we will provide comments to aid the reader's understanding of the review where necessary. We will provide the NNTB or NNTH, absolute and relative percent change in the What happens column of the summary of findings tables as described in the Measures of treatment effect section above, with the exception of the absolute difference for dichotomous outcomes, which is displayed by default in the GRADEpro GDT view.

We preselected the following important outcomes for the summary of findings tables: 1) hand mobility, 2) skin thickness, 3) functional ability, 4) pain, 5) health-related quality of life, 6) withdrawals due to adverse events, 7) total adverse events. We will use the longest time point (primary time point) reported for each outcome.

The comparisons in the summary of findings tables will be:

- Structured exercise versus sham control;
- Structured exercise versus no intervention or waiting-list control;
- Structured exercise versus active control;
- Physical therapy (any type) versus no intervention or waiting-list control.

Interpreting results and reaching conclusions

We will follow the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*, chapter 15 for interpreting results, and will distinguish a lack of evidence of effect from a lack of effect (Schünemann 2020b). We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. Our implications for research will suggest priorities for future research, and outline the remaining uncertainties in the area.

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ADDITIONAL TABLES

Table 1. Types of exercise and physical therapy

Physical therapy	Exercise interventions
Connective tissue massage	Hand exercises
McMennell joint manipulation	Mouth exercises
Manual lymphatic drainage (MLD)	Aerobic exercise
Kabat's method	Resistance exercise
Paraffin bath treatment	Range of motion exercise
Acupuncture	Kinesiotherapy
Laser therapy	Hydrokinesiology
Transcutaneous electric nerve stimulation (TENS)	Recreational exercise (i.e. lawn bowls)
Ultrasound therapy	

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp SCLERODERMA, SYSTEMIC/

2 (scleroderma* or (systemic* adj3 sclero*) or (CREST adj3 (syndrom* or disease*))).ti,ab.

3 or/1-2

4 randomized controlled trial.pt

5 controlled clinical trial.pt

6 clinical trial.ab

7 randomized.ab

8 placebo.ab

9 randomly.ab

10 trial.ab

11 groups.ab

12 or/4-11

13 exp animals/ not humans.sh

14 12 not 13

15 3 and 14

CONTRIBUTIONS OF AUTHORS

All authors contributed to each stage of the protocol, including conceiving the protocol, designing the protocol, planning the search strategy, designing data extraction methods, planning data management and analysis, writing, proof-reading, editing the protocol, and responding to critique from reviewers.

DECLARATIONS OF INTEREST

Stephanie Frade: nothing to declare

Melainie Cameron: nothing to declare

Gisela E: nothing to declare

Maria E: nothing to delcare

Maria A Lopez-Olivio: nothing to declare

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