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Community-based exercise and physical activity programmes led by exercise professionals for osteoarthritis (Protocol)

Walsh N, Jordan JL, Babatunde OO, Powell J, Healey EL

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[Intervention Protocol]

Community-based exercise and physical activity programmes led by exercise professionals for osteoarthritis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the benefits and harms of community-based exercise and physical activity programmes led by non-healthcare exercise professionals for osteoarthritis, compared to those delivered by healthcare professionals, self-directed interventions, home-based programmes or continued general practitioner (GP) care.

BACKGROUND

Osteoarthritis (OA) is predicted to become the 4th leading cause of worldwide disability by 2020 as the population ages, and people become heavier and less active (Woolf 2003). The World Health Organisation estimates that approximately 10% of the population over 60 years old may experience pain and functional limitation associated with OA (Cooper 2013) . At an individual level almost three quarters of people with OA live in constant pain. One third either have to give up work or reduce their working hours; and one third report emotional distress. Forty per cent of people with OA report that their current treatment is either not very effective or totally ineffective (Arthritis Care 2012). This is a social and economic burden that is poorly managed and is unsustainable within the present healthcare system.

Evidence-based guidelines recommend exercise and physical activity as a core modality for OA to reduce pain and increase function (NICE 2014; Fernandes 2013). A variety of definitions exist for exercise and physical activity. For the purpose of this review we will use the definition provided by the UK Department of Health: "all forms of activity, such as everyday walking or cycling to get from A to B, active play, work-related activity, active recreation (such as working out in a gym), dancing, gardening or playing active games, as well as organised and competitive sport" (Department of Health 2011).

Healthcare professionals are ideally placed and appropriately skilled to provide this advice, but timely access to health services is a growing problem in the face of increasing referrals and limited resources (Salisbury 2013). As such, a strategic health care and public health approach to long-term management of OA is required to ensure people receive timely access to effective interventions and activities. Current lack of access may contribute to the problem of almost half of people with OA reporting they do

no exercise or physical activity to help their condition (Arthritis Care 2012).

Cochrane reviews evaluating the effectiveness of land- and water-based exercise interventions for OA conclude that short-term improvements in pain and function are gained (Bartels 2007; Fransen 2014; Fransen 2015), particularly in the knee joint (Fransen 2015). The evidence for the effects on the hip joint are less conclusive, notably for functional improvements (Fransen 2014). Evidence synthesis also suggests that in the short term, supervised regimens effect greater benefit although home-based interventions tend to result in greater adherence in the long-term (Ashworth 2005), although these outcomes are based on other chronic diseases as no studies in OA met the inclusion criteria. The most effective means of enhancing adherence to exercise remains unclear; nor is there a validated tool to reliably measure adherence (Jordan 2010). No evidence synthesis exists regarding the effectiveness of exercise or physical activity led by community-based, non-healthcare professionals.

In recent years, community-based exercise and physical activity delivered by non-healthcare professionals has gained prevalence, as demands on primary and secondary care services are heightened. In particular, cardiac rehabilitation schemes that facilitate the transition from hospital-based services to community and self-management approaches have achieved success using appropriately trained and accredited leisure-based exercise facilitators (Anderson 2016) - a model which may be suitable for other pathologies. Currently, therapeutic exercise provision for OA is generally managed within the health service. Exercise Referral Schemes (ERS) located within leisure centres are available, but rarely evaluated to determine short or long-term efficacy (Sowden 2008). A recent review of ERS for all pathologies (these included obesity, cardiovascular disease, diabetes and mental health) and where referral came from a healthcare professional, suggested inconclusive evidence regarding clinical and cost-effectiveness in the short-term and no evidence to support long-term changes to physical activity (Pavey 2011).

Although outcomes of community-based trials in OA are available, the effects of this type of intervention remain uncertain, and an accumulation of the evidence would inform future service planning and provision.

Description of the condition

OA is the most common form of arthritis, normally affecting people over the age of 45 (NICE 2014). Pathological changes can occur in any joint, but the knees, hips, hands and spine are predominantly affected, resulting in pain, reduced mobility and loss of function (Arthritis Research UK 2013). Pathophysiological characteristics of OA include localised cartilage loss, periarticular remodelling of bone and local signs of connective tissue inflammation. Local muscle weakness and atrophy are also frequently observed (Felson 2013; NICE 2014).

Currently there is no cure for OA, but management guidelines suggest exercise and physical activity as a core modality to manage symptoms and reduce the impact of the disease (NICE 2014; Fernandes 2013).

Description of the intervention

Pain, functional disability and reduced muscle strength are correlated in OA, and as such the benefits of exercise and physical activity interventions are recognised (Bijlsma 2011; Jan 2008). Strengthening, mobilising and aerobic interventions are all recommended and induce benefits (Ashworth 2005; Bartels 2007; Fransen 2015; NICE 2014), but evidence regarding frequency and intensity is not conclusive. However, previous data suggest that despite the strength of the recommendation for exercise, only 20% of patients with OA reportedly receive physiotherapy and advice on exercise (Arthritis Research Campaign 2002). Many people may not be exercising at all, but equally others are likely to be seeking advice from other 'exercise professionals' based in the community providing a variety of exercise and physical interventions for people with OA. An evidence synthesis regarding the effectiveness of these types of interventions is currently unavailable.

How the intervention might work

Exercise and physical activity can increase health status, modify disease activity, reduce disability, improve function and enhance sense of well-being in patients with lower limb OA (Bennell 2005; Pelland 2004). From a biomedical perspective the disease process in OA may be a result of, or contribute to, muscle weakness and sensorimotor dysfunction resulting in further biomechanical stress around the joints (Hurley 1999). Exercise can strengthen muscle and therefore positively influence associated pain and reduced function (Bennell 2005). Furthermore, clinical symptoms of OA can impact upon psychosocial factors such as health beliefs, self-efficacy and coping strategies; evidence suggests that exercise can have a positive effect on these traits through provision of an active coping strategy (Hurley 2013). Traditionally, physical interventions for OA are delivered within a healthcare environment by physiotherapists following referral from primary or secondary care (NICE 2014). However, in other chronic conditions such as cardiac and respiratory disease, provision of community-based exercise in leisure centres or exercise facilities, delivered by 'exercise professionals' is becoming increasingly prevalent (Pavey 2011). In some locations (e.g. UK, Australia, Scandinavia) individuals can receive subsidised exercise if referred from a healthcare professional (Anderson 2016; Pavey 2011). In other areas where referral schemes are not supported, access to publicly-available exercise provision, in leisure centres for example, is ubiquitous. We

are currently unaware of the potential benefit or harm of community-based, non-healthcare led exercise and physical activity interventions for people with OA.

Why it is important to do this review

Timely access to healthcare interventions is becoming a growing issue in the face of an ageing population, increasing referrals and limited resources (Salisbury 2013). Individuals with OA are advised to exercise and remain physically active, but physiotherapy is only provided to the minority (Arthritis Research Campaign 2002). Alternative exercise providers may therefore have a role in managing the vast population of people with OA who seek advice on either self-managing their condition or continuing with exercise and physical activity interventions post-discharge from healthcare services (Pavey 2011). Although highly skilled and competent, these providers do not have traditional professional qualifications commensurate with healthcare provision (Department of Health 2001). Therefore it is imperative that the effectiveness of interventions delivered by such providers is established. If clinical effectiveness is determined, greater consideration can be given to models of care and appropriate providers of interventions throughout the patient pathway.
This review will be conducted according to the guidelines recommended by the Cochrane Musculoskeletal Group Editorial Board (Ghogomu 2014).

OBJECTIVES

To assess the benefits and harms of community-based exercise and physical activity programmes led by non-healthcare exercise professionals for osteoarthritis, compared to those delivered by healthcare professionals, self-directed interventions, home-based programmes or continued general practitioner (GP) care.

METHODS

Criteria for considering studies for this review

Types of studies

We will include (cluster) randomised controlled trials (RCTs) and controlled clinical trials (CCTs) that use quasi-randomised methods of allocation, including cross-over designs. We will include studies reported as full-text, those published as abstract only, and unpublished data. There will be no language restriction.

Types of participants

We will include adults with a clinical or radiographic diagnosis of lower limb osteoarthritis (OA) in accordance with internationally-recognised diagnostic criteria (Altman 1986).
These criteria are as follows:
OA should be diagnosed clinically without investigation if a person:

- is 45 or over; and
- has activity-related joint pain; and
- has no morning joint-related stiffness, or morning stiffness that lasts no longer than 30 minutes.

Studies that diagnose according to radiographic evidence are also eligible for inclusion (Altman 1986). The evidence suggesting radiographic OA are as follows:

- non-uniform joint space loss;
- osteophyte formation;
- cyst formation;
- subchondral sclerosis.

We will exclude participants that do not meet the diagnostic criteria.

Types of interventions

We will include trials comparing an exercise or physical activity programme, delivered to groups or individuals in the community and facilitated or supervised by a professional exercise provider (exercise professional).
The definitions of each of these criteria are detailed below.

Professional exercise provider

Graduate in exercise-related discipline (e.g. sports science, sports rehabilitation). Trained exercise instructor (e.g. Register of Exercise Professionals (UK), European Register of Exercise Professionals (EU), Canadian Fitness Professionals, American Council on Exercise (US), Fitness Professionals Association (Russia)). Specialist trained instructor (e.g. Tai Chi, Pilates).
To meet the definition of 'professional exercise provider', the person must not be a healthcare professional or a lay leader. Healthcare professionals are defined as those with a recognised professional qualification in medical or allied health professions (e.g. physiotherapy, physical therapy, occupational therapy, nursing, medicine, chiropractic, osteopathy).

Programmes

Physical activity or exercise-based programmes can include:

- Exercise on prescription schemes;
- Exercise classes (any strength, aerobic, flexibility, co-ordination regimens);

- Gym sessions;
- Water-based activities;
- Walking programmes;
- Cycling programmes;
- Tai chi/Pilates;
- Dancing;
- Gardening.

No restrictions will be applied on the duration or intensity of interventions.

For reporting clarity, the Cochrane Musculoskeletal Group (CMSG) classification criteria will be applied to interventions:

a. Static weight bearing (SWB); including single leg standing.

b. Dynamic weight bearing exercise low force (DWBLF); including walking and Tai chi.

c. Dynamic weight bearing exercise high force (DWBHF); including jogging, jumping, running, dancing and whole body vibration platforms.

d. Non-weight bearing exercise low force (NWBLF); e.g. low load, high repetition strength training.

e. Non-weight bearing exercise high force (NWBHF); e.g. progressive resisted strength training.

f. Combination (COMB); more than one of the above exercise interventions.

Intervention settings

- Adult education centre;
- Community-based facility;
- Leisure centre/gymnasium;
- Village hall;
- University/college campus;
- Outside spaces;
- Home-based programmes that are supervised by an exercise professional rather than self-directed domestic interventions.

To be included, the interventions must not be based in primary or secondary health care.

Primary care is defined as health care provided in the community by a healthcare practitioner or clinic. Secondary care is defined as a specialist healthcare provider (e.g. hospital) where interventions are provided following referral from another source (normally primary care).

Comparator interventions will include:

1. No intervention;
2. 'Sham' intervention;
3. Continued general practitioner (GP) care;
4. Self-managed physical activity (i.e. self-initiated and managed outside of any formal or organised group activity);
5. Lay-led interventions;
6. Health professional led interventions;
7. Healthcare-based classes or exercise sessions;
8. Physiotherapy;
9. Nurse-led interventions;
10. Self-management or education sessions.

Interventions that compare other interventions such as bracing or medication will not be included, as the use of alternative deliverers of exercise is of interest rather than other non-pharmacological interventions.

Co-interventions that include education and self-management delivered by non-healthcare professionals will be eligible if they are applied equally across all groups. Education and self-management interventions can also be included as comparator interventions.

Important anticipated comparisons will include but will not be limited to:

1. Interventions delivered by exercise professionals compared to healthcare professionals;
2. Interventions delivered by exercise professionals compared to self-management;
3. Interventions delivered by exercise professionals compared to no intervention.

Types of outcome measures

Major outcomes

1. Pain with a hierarchy of 11 levels
   - Pain overall
   - Pain on walking
   - KOOS/HOOS/WOMAC pain subscale
   - Pain on activities other than walking
   - KOOS/HOOS/WOMAC global scale
   - Lequesne osteoarthritis index global score
   - Other algofunctional scale
   - Patient's global assessment
   - Physician's global assessment
   - Other outcome
   - No continuous outcome reported

2. Physical function with a hierarchy of 8 levels
   - Global disability score
   - Walking disability
   - KOOS/HOOS/WOMAC disability subscore
   - Composite disability scores other than KOOS/HOOS/WOMAC
   - Disability other than walking
   - KOOS/HOOS/WOMAC global scale
   - Lequesne osteoarthritis index global score
   - Other algofunctional scale

3. Quality of life
   - Short Form (SF)-36, Mental Component Summary (MCS).
   - SF-12 MCS.
   - EuroQol.
   - Other measures

4. Number of participants experiencing any adverse or serious adverse event
5. Number of participants who withdrew for any reason
6. Number of participants experiencing any serious adverse events

Minor outcomes

1. Attrition rates (as a proxy for acceptability - limitations of this measure will be acknowledged)
2. Adherence (self-reported or direct measures)
3. Any data reporting cost-effectiveness, cost-benefit or cost-utility

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid), EMBASE (Ovid), AMED (Ovid), PsycINFO (Ovid), CINAHL (NICE Health Database Advanced Search), Science and Social Science Citation Index (Web of Science, ISI), SPORTDiscus (EBSCO), Ageline (EBSCO), Physiotherapy Effectiveness Database PEDRO (www.pedro.org.au/), OTSeeker (www.otseeker.com/), TRIP Database (www.tripdatabase.com/), Grey literature database (www.OpenGrey.eu) and clinical trial registries (ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/)).
We will search all databases from their inception to the present, and we will impose no restriction on language of publication.
See Appendix 1 for the MEDLINE search strategy.

Searching other resources

We will check reference lists of all primary studies and review articles for 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 within the review.

Data collection and analysis

Selection of studies

Review authors (OB, EH, JJ, NW) will independently screen for inclusion the titles and abstracts of all the studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (EH, NW) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (OB, JJ). 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 a PRISMA flow diagram (Moher 2009) and 'Characteristics of excluded studies' table.

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. Two review authors (of OB, EH, JJ, NW) will extract study characteristics from included studies. A third review author will resolve any discrepancies between the two authors. 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, gender, disease duration, severity of condition (based on self-report or diagnostic criteria), diagnostic criteria, disease duration; inclusion criteria, and exclusion criteria. When reported, other data such as educational attainment and socio-economic status or place of residence will be extracted.
3. Interventions: Description of the exercise intervention including type, supervision (group or individual), duration, intensity, provider (e.g. fitness instructor) and setting (e.g. leisure centre). Description of the comparator, including type, supervision, duration, intensity, provider and setting. Description of any co-interventions
4. Outcomes: major and minor outcomes specified and collected, and time points reported, including a description of the measurement tool used for continuous outcomes (scale of tool and direction of effect).
5. Characteristics of the design of the trial as outlined below 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 of the four review authors (OB, EH, JJ, NW) will independently extract outcome data from included studies. The number of events and number of participants per treatment group for dichotomous outcomes (e.g. adverse events) and means and standard deviations and number of participants per treatment group for continuous outcomes (e.g. pain) will be extracted. 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 (JJ, OB). Two review authors (OB, JJ) will transfer data into the Review Manager (RevMan

2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports.

Any studies that report health economic data will be reviewed and extracted by one author (JP). A second review author (NW) will spot-check study characteristics for accuracy against the trial report.

If both final values and change from baseline values are reported for the same outcome, we will extract change from baseline values. If both unadjusted and adjusted values for the same outcome are reported, we will extract adjusted values. If both ITT analysis and per-protocol analyses are reported, we will extract data based on ITT analysis preferentially. However, it is envisaged that most studies may not report ITT analysis, so per-protocol analysis data will also be extracted. The same procedure will apply to outcomes assessing benefits and outcomes assessing harms. For multiple time points reporting, we will extract data for all time points, but meta-analysis will only be undertaken at the 6-month follow-up point to reflect medium-term adherence. We anticipate that intervention effects are likely to be highest immediately post-intervention, but the longer-term benefits are of utmost importance as an indicator of continued and sustained exercise.

Assessment of risk of bias in included studies

Two of the four review authors (OB, EH, JJ, NW) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will resolve any disagreements by discussion or by involving another author (OB, JJ). 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. Blinding of self-report (subjective) and objective outcomes will be reported separately;
5. Incomplete outcome data;
6. Selective outcome reporting;
7. Other bias (conflicting interests). Possible sources of bias may include: inappropriate administration of an intervention (or co-intervention); baseline imbalance between the groups, treatment contamination, inappropriate analysis in cluster designs.

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 all-cause mortality may be different than for a patient-reported pain scale). As well, we will 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' tool to provide summary assessments of the risk of bias.

Risk of bias

Risk of bias will be assessed using the Cochrane 'Risk of bias' tool as described in the*Cochrane Handbook.*

Sequence generation: 'Low risk' of bias if a random component in the sequence generation process is described (for example, referring to a random number table). 'High risk' of bias when the authors describe a non-random component in the sequence generation process (e.g. sequence is generated by hospital or clinic record number). 'Unclear risk' of bias if not specified in the paper.

Allocation concealment: 'Low risk' of bias if the personnel allocated to enrol participants could not foresee assignment, by using an appropriate method used to conceal allocation (e.g. central allocation including telephone, web-based and pharmacy-controlled randomisation, sequentially-numbered, opaque, sealed envelopes. 'High risk' of bias if concealment allocation was not guaranteed. 'Unclear risk' of bias if not specified in the paper.

Blinding: We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. 'Low risk' of bias if the authors state explicitly that the primary outcome variables were assessed blindly. 'High risk' of bias if the outcomes were not assessed blindly and this was likely to affect results. 'Unclear risk' of bias if not specified in the paper.

Incomplete outcome data: 'Low risk' of bias if there are no missing data, or missing outcome data are balanced in numbers across intervention groups, with similar reasons for that missing data and unlikely to alter the results in the study. 'High risk' of bias if missing outcome data are likely to bias the results. 'Unclear risk' of bias if not specified in the paper.

Selective reporting: 'Low risk' of bias if there is no evidence that outcomes were selectively reported (for example, all relevant outcomes in the methods section are reported in the results section). 'High risk' of bias if some important outcomes are subsequently omitted from the results. 'Unclear risk' of bias if not specified in the paper.

Assesment 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 (e.g. adverse events) as risk ratios or Peto odds ratios when the outcome is a rare event (approximately less than 10%), and use 95% confidence intervals (CIs). Continuous data (e.g. quality of life, function) will be analysed as mean difference (MD) or standardised mean difference (SMD, depending on whether the same scale is used to measure an outcome, and 95% confidence intervals. 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. function), SMDs will be calculated instead, with corresponding 95% CI. SMDs will be back-translated 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) (as per Chapter 12 of the *Cochrane Handbook* (Schünemann 2011b).

In the 'Effects of intervention' results section and the 'Comments' column of the 'Summary of findings' table, we will provide the absolute per cent difference, the relative per cent change from baseline, and the number needed-to-treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) (the NNTB or NNTH will be provided only when the outcome shows a statistically significant difference).

For dichotomous outcomes, such as serious adverse events, the NNTH will be calculated from the control group event rate and the relative risk using the Visual Rx NNT calculator (Cates 2008).

The NNTB for continuous measures will be calculated using the Wells calculator (available at the CMSG editorial office http://musculoskeletal.cochrane.org/).

For dichotomous outcomes, the absolute risk difference will be calculated using the risk difference statistic in RevMan and the result expressed as a percentage. For continuous outcomes, the absolute benefit will be calculated as the improvement in the intervention group minus the improvement in the control group, in the original units.

The relative per cent change for dichotomous data will be calculated as the risk ratio - 1 and expressed as a percentage. For continuous outcomes, the relative difference in the change from baseline will be calculated as the absolute benefit divided by the baseline mean of the control group from the most representative study.

Unit of analysis issues

Where multiple trial arms are reported in a single trial, we will include only the relevant intervention arms. If two comparisons are combined in a three-arm trial , we will halve the control group to avoid double-counting. Such study characteristics (e.g. more than two intervention groups in single trials) will be detailed in the table 'Characteristics of included studies'.

Dealing with missing data

We will contact investigators or study sponsors in order 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). Where 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 by a sensitivity analysis. Any assumptions and imputations to handle missing data will be clearly described and the effect of imputation will be explored by sensitivity analyses.

For dichotomous outcomes (e.g. number of withdrawals due to adverse events), the withdrawal rate will be calculated using the number of patients randomised in 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 patients analysed at that time point. If the number of patients analysed is not presented for each time point, the number of randomised patients in each group at baseline will be used.

Where possible, missing standard deviations will be computed 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* (Higgins 2011b). If standard deviations cannot be calculated, they will be imputed (e.g. from other studies in the meta-analysis) (Higgins 2011b).

Assessment of heterogeneity

Clinical and methodological diversity will be assessed in terms of participants, interventions, outcomes and study characteristics for the included studies to determine whether a meta-analysis is appropriate. This will be determined by observing these data from the data extraction tables. Statistical heterogeneity will be assessed by visual inspection of the forest plot 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* (Deeks 2011), the interpretation of 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% represents 'considerable' heterogeneity. As noted in the *Handbook*, we will keep in mind that the importance of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity.

The Chi^2 test will be interpreted where a P value ≤ 0.10 will indicate evidence of statistical heterogeneity.

If we identify substantial heterogeneity we will report it and investigate possible causes by following the recommendations in section 9.6 of the *Handbook* (Deeks 2011).

A meta-regression analysis is not planned as it does not fit into the objectives of this review. In the event that a meta-analysis is not feasible, we will present a qualitative and narrative synthesis, based on the CMSG classification documented previously.

Assessment of reporting biases

We will create and examine a funnel plot to explore possible small study biases. In interpreting funnel plots, we will examine the different possible reasons for funnel plot asymmetry as outlined in section 10.4 of the *Handbook* 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 *Handbook* (Sterne 2011).

To assess outcome reporting bias, we will check trial protocols against published reports. For studies published after 1 July 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organisation (http://apps.who.int/trialssearch) for the a priori trial protocol. We will evaluate whether selective reporting of outcomes is present.

Data synthesis

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

We will present separate pair-wise analyses grouped by common comparator, for example, all water-based exercise delivered by exercise professionals versus all water-based exercise delivered by healthcare professionals.

Due to the nature of exercise as a highly-varied intervention and the complexity of models of care that may be associated with different delivery modes, substantial heterogeneity and subsequently difference in underlying treatment effects between trials is envisaged. Therefore, we will perform a random-effects meta-analysis for combining data to produce an overall summary of the average treatment effect across trials in RevMan. The random-effects summary will be treated as the average of the range of possible treatment effects. Also, to check the robustness of the treatment effects on pain and function, sensitivity analyses using a fixed-effect analysis will be performed and we will discuss clinical and practice implications of the difference in treatment effects between trials.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes at the stated primary end points:

- Pain
- Physical function
- Quality of life
- Number of participants experiencing any adverse event
- Number of participants who withdrew
- Number of participants experiencing any serious adverse events

Two review authors (EH, NW) will independently assess the quality of the evidence. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Chapter 11 the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a) using GRADEpro software (GRADEpro GDT 2015). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

The 'Summary of findings' table will be informed by the quality of evidence for treatment effects (as assessed by GRADE) and how the risks of bias in the primary studies contribute to each outcome. Hence, the 'Summary of findings' table will be created after data from all primary studies have been entered into RevMan (RevMan 2014), and after the 'Risk of bias' assessment has been conducted. This will reduce the risk of review bias and enhance the process of generating more accurate inferences about the review outcomes, the treatment effect and their confidence estimates for the review.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

- Site of joint pain (e.g. hip or knee);
- Group or individual format;
- Gender.

We will use the following outcomes in subgroup analyses:

- Pain;
- Function;
- Quality of life.

If data stratified by symptom duration are not available, but if there are sufficient continuous data from at least 10 studies, we will consider meta-regression to assess if symptom duration modifies the effect of the intervention on pain and function (using Stata statistical package STATA 2016).

We will consider presenting the estimate of treatment effects at two time points for the primary outcomes (pain, function and quality of life) as subgroups on a single forest plot.

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014) and will use caution in the interpretation of subgroup analyses as advised in section 9.6 of the *Handbook* (Deeks 2011). The magnitude of the effects will be compared between the subgroups by means of assessing the overlap of the CIs of the summary estimated. Non-overlap of the CIs indicates statistical significance.

Sensitivity analysis

The primary analysis for subjective self-reported outcomes (pain, function, quality of life) will be restricted to studies with low risk of selection and detection biases. We will conduct sensitivity analyses to investigate the effects of selection and detection biases

by including trials with low or unclear risk of these biases on the primary outcomes of pain and function. All studies can be included for adverse event outcomes.

Interpreting results and reaching conclusions

We will follow the guidelines in the *Cochrane Handbook* (Schünemann 2011b), for interpreting results and will be aware of distinguishing a lack of evidence of effect from a lack of effect. We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Exercise/
2. exp Exercise Therapy/
3. (strength$ or isometric$ or isotonic$ or isokinetic$).ti,ab.
4. (resistance adj3 train$).ti,ab.
5. ((physical$ or motion$) adj3 (fit$ or therap$)).ti,ab.
6. exp Physical Fitness/
7. (treadmill$ or cross-train$ or rowing).ti,ab.
8. sport$.ti,ab.
9. exercise$.ti,ab.
10. (tai adj1 (chi or ji)).ti,ab.
11. (dance or dancer$ or dances or dancing).ti,ab.
12. (aqua$ or water$).ti,ab.
13. hydr$.ti,ab.
14. exp Hydrotherapy/
15. (stretch$ or flexib$ or balanc$ or propriocept$).ti,ab.
16. (circuit$ adj1 train$).ti,ab.
17. exp "physical education and training"/
18. exp recreation/
19. exp Musculoskeletal Physiological Phenomena/
20. "physical activit$".ti,ab.
21. aerobic$.ti,ab.
22. (run or jog$ or running).ti,ab.
23. (walk or walks or walking).ti,ab.
24. gym$.ti,ab.
25. tai ji/ or yoga/
26. yoga.ti,ab.
27. tai-chi.ti,ab.
28. qigong.ti,ab.
29. pilates.ti,ab.
30. "leisure activit$".ti,ab.
31. "recreation$ activit$".ti,ab.
32. (zumba or salsa$).ti,ab.

33. (cycling or bicycle or bike).ti,ab.
34. swim$.ti,ab.
35. fitness.ti,ab.
36. (keep$ adj1 (active or fit)).ti,ab.
37. trainer$.mp.
38. instructor$.mp.
39. teacher$.mp.
40. program$.mp.
41. "personal training".mp.
42. (coaching or coach or coaches).mp.
43. (leisure adj2 centre$).mp.
44. (school$ or village$ or church$ or communit$).mp.
45. "adult education".mp.
46. or/1-45
47. exp Pain/
48. exp Knee/
49. exp Hand/
50. exp Hip/
51. or/48-50
52. 47 and 51
53. (pain$ adj2 joint$).ti,ab.
54. (pain$ adj2 musculoskeletal).ti,ab.
55. (degenerative adj2 (joint$ or arthr$)).ti,ab.
56. (pain$ adj2 (patell$ or knee$)).ti,ab.
57. (pain$ adj2 (thumb$ or hand$)).ti,ab.
58. (pain$ adj2 hip$).ti,ab.
59. exp osteoarthritis/
60. (osteoarthr$ or arthros?s).ti,ab.
61. or/52-60
62. randomized controlled trial.pt.
63. controlled clinical trial.pt.
64. placebo.ab.
65. randomly.ab.
66. clinical trials as topic.sh.
67. trial.ti.
68. randomi#ed.ab.
69. or/62-68
70. exp animals/ not humans.sh.
71. 69 not 70
72. 46 and 61 and 71

CONTRIBUTIONS OF AUTHORS

Task	Authors
Draft the protocol	Walsh, Healey, Babatunde, Powell, Jordan
Develop a search strategy	Jordan (with search terms from Walsh, Healey, Babatunde)

DECLARATIONS OF INTEREST

None known.

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