**Version Control Table**

| Version | Author | Purpose/Change | Date |
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| V1-0 | Kay Cooper | Protocol approved by NIHR & RGU Ethics (SHSREC20/01) | 18.01.2020 |
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## 1. Title

Exercise therapy for the treatment of tendinopathies: A mixed methods evidence synthesis.

## 2. Summary of research

### Background

Tendinopathy is a common condition in athletic and non-athletic populations. Although it can theoretically affect any tendon in the body, it is most commonly reported in the Achilles, patellar, lateral elbow, rotator cuff and hip tendons. Exercise therapy is the core method of managing tendinopathy, as first or second-line intervention, and despite the plethora of literature on exercise for tendinopathy, uncertainties remain. Exercise has been studied on its own and in combination with other interventions including manual therapies, extracorporeal shockwave therapy, laser therapy, taping and splinting, and various types of injection. Exercise is generally classified by contraction mode (eccentric, concentric, isometric, stretch-shortening) or by intensity of load (e.g. heavy slow resistance exercise, heavily loaded eccentric exercise). A significant body of literature exists comparing one exercise type to another exercise type, to another conservative intervention, or to a control (e.g. “wait and see”). There is also literature concerning factors such as dosage, mode of delivery, and the patient experience. Previous systematic reviews have been conducted, but to date there is no evidence synthesis that combines the exercise related research findings across all tendinopathies and identifies commonalities and heterogenic treatment effects, whilst taking into account relevant variables and participant characteristics.

### Aim

The aim of this mixed methods evidence synthesis is to examine the evidence base on exercise therapy for tendinopathies in order to make recommendations for clinical practice and future research.

### Review Questions

1. What exercise interventions have been reported in the literature and for which tendinopathies?

2. What outcomes have been reported in studies investigating exercise interventions for tendinopathies?

3. Which exercise interventions are most effective across all tendinopathies?

4. Does type/location of tendinopathy or other specific covariates affect which are the most effective exercise therapies?

5. How feasible and acceptable are exercise interventions for tendinopathies?

### Methods

We propose a mixed-methods evidence synthesis comprising a scoping review (review questions 1 & 2), followed by two contingent systematic reviews (review questions 3-5). The scoping review will identify important subgroups who have participated in research, and outcome measures that have been reported. On conclusion of the scoping review, we will hold workshops with rehabilitation specialists and people with tendinopathy. Participants will identify any gaps in the proposed contingent syntheses and make suggestions for additional criteria/outcomes/covariates, which the review team will consider prior to registration of the protocols for the contingent reviews. The contingent reviews will include a quantitative review of effectiveness and a mixed-methods review of feasibility and acceptability of exercise interventions for tendinopathy. All reviews will follow internationally-recognised guidance, will be conducted in accordance with an *a priori registered/* published protocol, and will comply with PRISMA reporting guidelines, including a summary of

findings table created using the GRADE approach where indicated (Grading of Recommendations, Assessment, Development and Evaluation). The syntheses will result in: (i) a map of the existing evidence on exercise therapy for the treatment of tendinopathy (scoping review); (ii) identification of gaps in the existing evidence-base where primary research will be required; and (iii) direct implications for clinical practice. We will hold a second stakeholder workshop on conclusion of the contingent reviews. Stakeholders will help us to interpret the review findings from their perspectives, in order to inform the design of outputs for wide dissemination.

**Dissemination & Impact**

We will use a range of strategies and types of output to disseminate widely, using audience-specific detail, including publishing in academic journals, presenting at conferences, and using a range of media to coincide with publication of each review (e.g. press release, social media, YouTube videos, infographics). Impact from this mixed-methods evidence synthesis will include: (i) informing evidence-based guidelines for clinical practice; (ii) informing commissioners of health services; (iii) adoption of recommendations by clinicians to the benefit of patients and health services, and (iv) adoption of recommendations on remaining gaps in the evidence-base by research funders in order for funding to be appropriately allocated.

**Stakeholder Involvement**

In addition to the stakeholder workshops described above, rehabilitation specialists and people with tendinopathy will be part of the steering committee and will contribute throughout the life of the project. We consulted with both groups during the development of this proposal.

## 3. Background and rationale

**The problem**

Tendinopathy, commonly defined as “tendon degeneration characterised by a combination of pain, swelling, and impaired performance” can theoretically affect any of the 600+ muscle-tendon units in the body [1], however it is most commonly reported in the Achilles, patellar, lateral elbow, rotator cuff, and hip tendons. Exercise is the mainstay of conservative management of the condition and has focussed largely on eccentric strengthening techniques to date [2]. However, other exercise types, including isotonic and heavy slow resistance exercise have also been recommended for some tendinopathies (e.g. patellar [3]). Exercise may be used in isolation or as an adjunct to other interventions, such as extracorporeal shockwave [4] or laser therapy [5], or following regenerative or orthobiologic procedures such as prolotherapy, platelet-rich plasma or stem-cell treatments [6]. Due to the heterogeneity of tendinopathy (anatomical location, duration), the range of people it can affect (age, gender, activity level, other risk factors and comorbidities) and the variation in exercise approaches (type, dosage, setting) a broad and comprehensive evidence synthesis is essential to inform future clinical practice.

**Literature review**

A search of MEDLINE, AMED and CINAHL using the terms (MH tendinopathy OR TX tendin* OR TX tendon*) AND (MH exercise OR TX exercis*), limited to English language publications in scientific journals from 2009-2019 returned 1485 results, 183 of which were systematic reviews or meta-analyses. There is therefore a large body of evidence that can be synthesised to make recommendations for practice and research. This body of evidence covers a range of tendinopathies such as those affecting the shoulder [e.g.7] elbow [e.g.8], wrist and hand [e.g.9], and hip regions [e.g.10], and the hamstring [e.g.11], patellar [e.g.12] and Achilles [e.g.13] tendons.

Exercise has been studied individually or as part of a multi-component intervention, where it is often combined with modalities such as manual therapies [e.g.14], extracorporeal shockwave

therapy [e.g.15], laser therapy [e.g.16], taping and splinting [e.g.17] and various types of injection [e.g.18]. This approach reflects current expert opinion and evidence syntheses, which recommend exercise-based physiotherapy as the first-line management for tendinopathy with the addition of other interventions in recalcitrant cases [1,19].

Exercise interventions can largely be classified by contraction mode as isotonic-eccentric [3], isotonic-concentric [20], isometric [3] stretch-shortening [21] or by intensity of load compared to maximum; e.g. heavy slow resistance or heavily loaded eccentric exercise [22]; or combinations of two or more of these types. However, other types of exercise, including aquatic therapy and whole-body vibration, have also been reported. In intervention studies, the success of exercise therapy is measured against alternative exercise types, or to splinting or bracing, electro/physical modalities (e.g. ultrasound, extracorporeal shockwave, laser, ice), manual therapies (massage, manual therapy), injection therapies (corticosteroid, prolotherapy) or, less commonly, to a control situation (wait and see).

There is currently no consensus on outcome measures for tendinopathy research. Consequently, a range of measures has been reported in the literature. Studies commonly evaluate the effectiveness of exercise therapy on pain (upon activity or over a specified timeframe [23]) and on function, by way of physical performance tests (e.g. standing heel-rise test for Achilles [24]) and patient-reported outcome measures [25]. These outcomes can be generic (e.g. quality of life) or specific to the body part (e,g, DASH/Quick DASH for shoulder), with some tendinopathy-specific measures being utilised (e.g. VISA-A for achilles; WORC for rotator cuff [25]). Other outcome measures include patient satisfaction, global rating of change, physical activity (particularly in lower limb tendinopathies, and work participation or presenteeism [25].

While most of the literature appears to focus on the effectiveness of exercise in relation to another intervention, or to a control, there is a body of literature concerning dosage [e.g. 26], and contextual factors that may influence effectiveness or interventions, such as supervised versus unsupervised exercise [27]. It is therefore clear that a broad evidence synthesis will be possible, and that a diverse range of factors must be accounted for in the design of the synthesis.

Previous systematic reviews have either compared exercise with other intervention types [29], or compared specific exercise modes such as eccentric, isotonic, or heavy slow resistance [e.g. 3]. Dosage has been considered for Achilles', patellar and rotator cuff tendinopathies [26,28,30], and contextual factors such as supervised or unsupervised exercise have been considered in the case of the upper limb [28]. The novel approach for this proposed evidence synthesis project is to combine the exercise related research across all tendinopathies and identify commonalities and heterogenic treatment effects, whilst also taking into account relevant variables and participant characteristics. It is anticipated that this more extensive modelling approach will greatly enhance existing knowledge regarding the most effective type and content of exercise treatments across multiple tendinopathy outcomes.

To avoid duplication of existing work, in addition to the search reported above which identified some systematic review protocols, we also searched for reviews in-progress using PROSPERO, Epistemonikos, PEDro, and the Cochrane Database of Systematic Reviews (using tendinopathy and exercise as keywords). Although a number of in-progress reviews were identified (73 registered with PROSPERO), none are similar in scope to the evidence synthesis being proposed here. Many are investigating exercise *per se* and not the relative effects of different types and dosages, and several are limited in scope to conducting one comparison or to investigating a limited number of outcomes. The majority are also concerned with one specific tendinopathy. Since the proposed synthesis will encompass all tendinopathies and all exercise interventions, and will consider a number of important exercise, measurement and participant characteristics, it will add to the body of knowledge and complement findings of existing and in-progress syntheses.

## 3a. Evidence explaining why this research is needed now

This evidence synthesis is required to aid clinical decision-making, to provide key commissioning data, and to identify gaps where future high-quality research is indicated. The Global Burden of Disease 2010 study highlighted that “other musculoskeletal” conditions, including disorders of the synovium and tendon, are common, accounting for 28.3 million years lived with disability, making them one of the world’s top 10 contributors to global disability burden [31]. Tendinopathy is common not only in athletic populations but also in the general population. For example, a study of prevalence and incidence of lower extremity tendinopathy in a Dutch general population reported rates of 11.83 and 10.52 per 1000 person-years, respectively [32]. Tendinopathies can affect children, adolescents, and adults of all ages, and many tendinopathies have a chronic or recurrent course [1]. Costs to the individual, the NHS and economy (due to absenteeism and loss of productivity) are therefore substantial, and identifying effective interventions is a priority.

Around one in five General Practitioner (GP) appointments in the UK are for musculoskeletal conditions, including tendinopathy. By identifying effective interventions across the range of tendinopathies, GP’s and other first-contact practitioners (e.g. physiotherapists), managing the condition can be confident in delivering effective evidence-based practice. With an ageing population, increasing pressure and demands on primary care, the current staffing crisis within the NHS and the recent role development of musculoskeletal physiotherapists as first contact practitioners in General Practice [33], the need for clear guidance for evidence-based practice has never been more important.

This evidence synthesis will provide evidence of the effectiveness of exercise as a single or multi-component and first or second-line intervention for any tendinopathy. We will establish the effectiveness of different types and formats of exercise for tendinopathy *per se* and by anatomical location and other important subgroups such as age, gender, athleticism, chronicity and comorbidity. The synthesis will result in: (i) a map of the existing evidence on exercise therapy for the treatment of tendinopathy; (ii) identification of gaps in the existing evidence-base where primary research will be required; and (iii) direct implications for clinical practice and commissioners of services.

## 4. Aims and objectives

The aim of this mixed methods evidence synthesis is to examine the evidence base on exercise therapy for tendinopathies in order to make recommendations for clinical practice and future research. The specific review questions to be addressed are:

1. What exercise interventions have been reported in the literature and for which tendinopathies?

2. What outcomes have been reported in studies investigating exercise interventions for tendinopathies?

3. Which exercise interventions are most effective across all tendinopathies?

4. Does type/location of tendinopathy or other specific covariates affect which are the most effective exercise therapies?

5. How feasible and acceptable are exercise interventions for tendinopathies?

## 5. Research Plan / Methods

### I: Health technology being assessed

The health technology being assessed is exercise therapy (any type or format) for the treatment of any tendinopathy. We will therefore assess any type of exercise therapy, including but not limited

to: eccentric, concentric, heavy slow resistance, stretching, cardiovascular, whole-body or combinations of two or more of these exercise types. The exercise therapy may be used as a first or second-line intervention for tendinopathy, and may be delivered in isolation or with adjunct therapies, as described above; we will assess all such scenarios. Exercise therapy may be delivered in a range of settings (e.g. primary care, secondary care, community, people's homes) by a range of health or exercise professionals (e.g. physiotherapists, strength & conditioning coaches, personal trainers) or support workers. We will assess exercise therapy in a supervised or unsupervised (self-management) manner; in any setting, using any mode of delivery by any professional or support worker, including self-management. We will compare different exercise types to each other, to other conservative interventions, and to control settings where this is possible.

**II: Study design**

We propose a mixed-methods evidence synthesis consisting of an initial scoping review (to address review questions 1 & 2) followed by two contingent systematic reviews incorporating the quantitative and qualitative evidence (to address review questions 3-5). This approach, informed by the approach taken by Pollock et al [34] in their mixed methods synthesis on stakeholder involvement in systematic reviews, is appropriate for addressing clearly defined objectives and assimilating evidence according to relevance, rather than grouping by research design alone [35]. The approach has been implemented successfully by the project team in a recent comprehensive evidence synthesis project on falls prevention in hospital in-patients and is based on first conducting an initial scoping review [36] to provide a systematic map [35] of the literature. Systematic maps can have several purposes; in this study, the map will: (i) describe the nature of the research field; and (ii) inform the conduct of subsequent (contingent) syntheses (Figure 1).

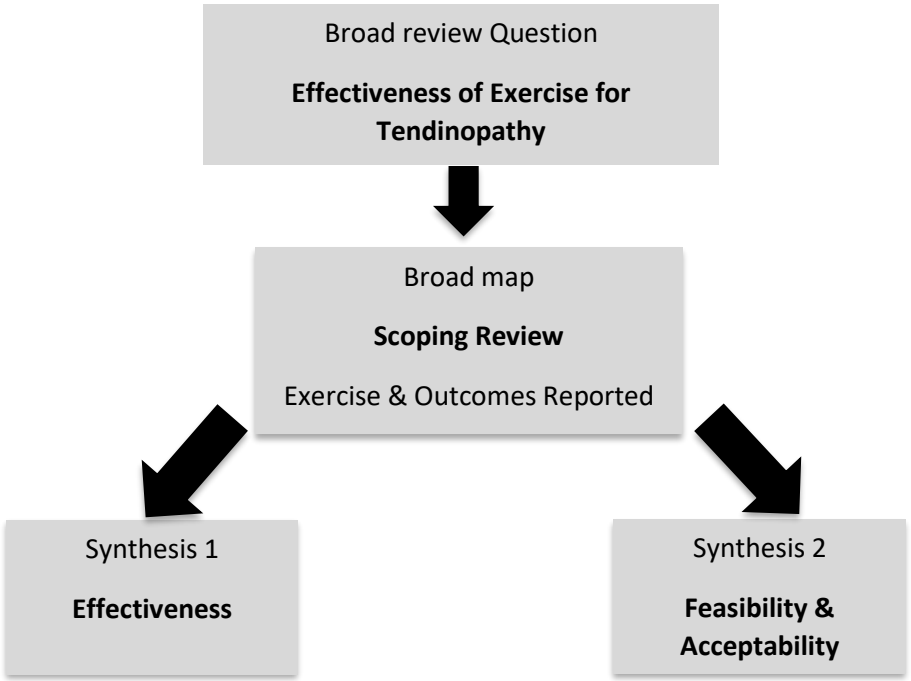


**Figure 1: Systematic map leading to several syntheses.** Adapted from Gough et al [35]

The scoping review will identify all quantitative and qualitative primary studies on exercise for any tendinopathy, as well as any previous systematic reviews, to ensure that no duplication of previous recent high-quality syntheses are proposed. The proposed contingent reviews include: (i) a synthesis of direct and indirect comparisons of exercise interventions across tendinopathies, which

also considers important subgroups and covariates; and (ii) a mixed-methods review, incorporating a range of study designs, including cross-sectional and qualitative, to address the question of feasibility and acceptability. However, the final contingent reviews will be informed by the literature identified by the scoping review (i.e. by what is appropriate and relevant to synthesise) and refined by our stakeholder group.

**III: Methods: Scoping review**

Scoping reviews are a relatively recent addition to the field of evidence synthesis [36] and have gained popularity in recent years. Arksey & O'Malley's 2005 framework [37], considered by many to be seminal work in the field, prompted further methodological developments with the Joanna Briggs Institute (JBI) producing formal guidance in 2015 [38]. The scoping review conducted for this evidence synthesis project will adhere to these guidelines. The scoping review will be reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews). [39]. To aid transparency of the methods and facilitate publication of the review, an *a priori* protocol will be fully developed and published on OSF (open science framework www.osf.io) prior to commencing the scoping review, since PROSPERO does not register scoping review protocols. In addition, it will be submitted to the peer-reviewed journal JBI Evidence Synthesis.

***Search strategy***

A 3-step search strategy will be developed by the review team. It will incorporate the following. (1): a limited search of MEDLINE and CINAHL using initial keywords (MH tendinopathy OR TX tendin* OR TX tendon*) AND (MH exercise OR TX exercis*) followed by analysis of the text words in the title/abstract and those used to describe articles in order to develop a full search strategy. (2): The full search strategy will be adapted to each database and applied systematically to: MEDLINE, CINAHL, AMED, EMBase, SPORTDiscus, Cochrane library (Controlled trials, Systematic reviews), JBI Database of Systematic Reviews and Implementation Reports, PEDRo, and Epistemonikos. The following trial registries will also be searched: ClinicalTrials.gov, ISRCTN, The Research Registry, EU-CTR (European Union Clinical trials Registry), ANZCTR (Australia and New Zealand Clinical trials Registry). We will also search for unpublished studies via: Open Grey, MedNar, The New York Academy Grey Literature Report, Ethos, CORE, and Google Scholar. (3): For each article located in steps 1 and 2 we will conduct a search of cited and citing articles using Scopus and hand-searching where necessary. We will not place a language limit on searching; rather, we will include any literature where a translation is accessible via the international collaborations of the project team members. Searching will start from 1998 as:

(i) the heavy load eccentric calf-training protocol for Achilles tendinosis by Alfredsson et al [40] was published in 1998 and may be considered seminal work in the field of tendinopathy;
(ii) there was a proliferation of research on exercise interventions for tendinopathies post-1998; and
(iii) the relevance of including findings from studies conducted more than 20-years ago may be questioned due to advances in research methodologies.

Searching will be undertaken mainly using the EBSCoHost platform via the Robert Gordon University (RGU) library, which facilitates saving searches and exporting to reference management software (Proquest®Refworks). Additional databases will be accessed using the Ovid platform via the NHS Knowledge Network.

The search undertaken during the scoping review will identify literature relevant to the contingent reviews. Each article will be indexed appropriately during the scoping review process to allow relevant studies to be extracted for consideration in each of the contingent reviews. In order for the reviews to be as current and comprehensive as possible, searches will be updated at the start and towards the end of each contingent review. Any additional studies that meet the inclusion criteria will be included.

### *Inclusion criteria*

In keeping with scoping review guidance, a modified PICO (PCoCo) will be used to frame the scoping review [38].

***Population:*** We will include people of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location. The term “tendinopathy” has been in widespread use for some time. Some literature may use “tendinitis” or “tendinosis” to describe participants’ tendon pathology as the precise aetiology of tendinopathy remains undetermined [1]. Therefore, we will include all the above terms, as long as the population has a tendon complaint presenting with one or more of pain, swelling and impaired function or performance. Diagnostic criteria vary across tendinopathy studies with there being a need to vary inclusion criteria by tendon site, especially for the shoulder and hip areas where there is a continuum of rotator cuff or gluteal tendinopathy extending through to full tear. Studies that include participants with tendinopathy in the absence of a tear, or a small tear will be included. Large, full-thickness or massive tears will be excluded, as will groups where the tear size cannot be determined [41].

We will accept trial authors’ diagnoses where a clearly verifiable group of clinical features is reported including; pathognomonic location of pain; a symptom altering response to applied load and/or stretch, with there being a specific test for most tendinopathies; strategies to rule out differential diagnoses; and ultrasound or magnetic resonance imaging confirmation of structural change. Trials with mixed groups will have data included where there is clear reporting of the tendinopathic group, or they make up > 90% of the investigated cohort [42].

Our definition of tendinopathy therefore includes tendinopathies such as PTTD (posterior tibial tendon dysfunction), tibialis posterior tendinopathy, peroneal tendinopathy, and GTPS (greater trochanteric pain syndrome). However, it excludes plantar heel pain as this condition may respond differently to exercise therapy and could potentially confound the review findings.

***Concept:*** The concept is exercise therapy for the treatment of tendinopathy, therefore the definitions described under “Health technology being assessed” above will be employed.

***Context:*** The context will include primary care, secondary care or community locations in any developed nation (defined as the top 59 countries in the human development index [43], in order for the findings to be relevant to the UK health service.

***Types of studies:*** We will include a broad range of study designs in order to produce a comprehensive map and to inform the contingent reviews. We will include: systematic reviews (to avoid duplicating existing syntheses); quantitative studies including randomised controlled trials and quasi-experimental studies (i.e. studies with a control group; for effectiveness data); mixed-method, descriptive (cross-sectional survey) and qualitative studies (for data on feasibility and acceptability of interventions).

### *Study selection*

Proquest® Refworks will be used to manage references and remove duplicates, before importing to systematic review software (Covidence; Melbourne, Australia) to facilitate screening. Covidence allows members of the review team to conduct screening independently, provides an audit trail of the review process, and allows the creation of bespoke settings (e.g. which members of the study team are eligible to screen and to resolve conflicts). Two levels of screening will be conducted. First all titles/abstracts will be reviewed, independently, by two members of the research team. Conflicts will be resolved by discussion or by input from a third member of the team (experienced reviewer). Full-text copies of all studies included at title/abstract screening stage will be retrieved and these will also be screened independently by two members of the research team with conflicts resolved in the same way.

### *Data extraction*

The results will be charted to provide a summary of the results that address objectives 1 & 2 (what exercise interventions have been reported; what outcomes have been reported). A draft charting form will be developed at the protocol stage, and may be refined during the review after trialling it on two or three studies to ensure all relevant results can be extracted [38]. The chart will be created using Microsoft Excel® and will include dimensions such as: authors, year of publication, country of origin, study type, purpose, population & sample size, methods, details of exercise therapy and outcome measures used. Details of the exercise therapy will include setting, mode of delivery, type, dosage, and adjunct therapies (if appropriate). Details of the population will include dimensions such as age, gender, body mass index, athleticism, health behaviours (e.g. smoking), co-morbidities (e.g. diabetes) and medication, where reported. The population details will assist in deciding on relevant subgroups to investigate in the contingent reviews. Once the charting form has been piloted and refined as appropriate, data extraction will be conducted by one reviewer, with independent data extraction by a second reviewer for at least 10% of studies. In keeping with guidance on conducting scoping reviews [38], critical appraisal will not be conducted.

### *Outcome of scoping review*

The results will be presented as a series of figures and tables, i.e. a map of the exercise therapies and outcome measures reported in the literature. The scoping review will itself be disseminated in the form of a journal article, infographic, lay summary (public), and scientific summary (professionals). It will also form the basis for making decisions about the contingent syntheses.

## IV: Stakeholder workshop

We will hold stakeholder workshops in Aberdeen and London in month 8 in order to inform interpretation of the review findings and the contingent review stage of the project. Our stakeholders will include: (i) up to 20 rehabilitation specialists (up to 10 in each location) with experience of prescribing exercise therapy for tendinopathy and; (ii) up to 20 people (up to 10 in each location) with experience of receiving exercise therapy for tendinopathy. Tendinopathy affects the athletic and general population and as such, rehabilitation specialists include physiotherapists working in NHS and private settings, and sports and exercise professionals includes coaches, strength and conditioning professionals, personal trainers and fitness professionals. Recruitment of stakeholders will be as follows:

### *Aberdeen*

NHS physiotherapists will be recruited by e-mail invitation via the three lead physiotherapists in the Grampian region of Scotland. Several NHS physiotherapists took part in a stakeholder workshop to inform this proposal and have already expressed an interest in taking part in the proposed workshop. Private physiotherapists will be recruited by e-mailing practices within the same region, as well as snowball sampling via word of mouth from private practices that the authors have pre-established links with. Physiotherapists working with elite athletes will be recruited via the sportscotland institute of sport. Gatekeepers known to the research team will be approached for the recruitment of other rehabilitation specialists (coaches, strength and conditioning professionals, personal trainers and fitness professionals).

People with experience of receiving exercise therapy for tendinopathy will be recruited via: (i) the NHS Grampian Public Involvement Network (e-mail and social media); (ii) RGU social media channels; (iii) using existing networks we will contact local professional and amateur sports clubs and teams such as Sport Aberdeen, RGU:SPORT, Aberdeen Football Club and Aberdeen Amateur Athletics club to request the circulation of information via gatekeepers and; (iv) Elite athletes will be recruited via the sportscotland institute of sport. Several people who have experienced exercise therapy for tendinopathy also took part in a workshop to inform this application. Many have likewise expressed an interest in taking part in the proposed workshop.

### *London*

Rehabilitation specialists will be recruited via relevant gatekeepers in the network of the MSc Sports and Exercise Medicine (SEM) at Queen Mary University (oldest SEM in the world) which includes: leading clinicians working in “Exercise as Medicine” for long-term conditions as well as with elite and recreational athletes and dancers. Specialists will also be recruited from private physiotherapy practices (methods as above) and from Bart’s and the London NHS trust.

People with experience of receiving exercise therapy for tendinopathy will be recruited from an existing PPI network and via the gatekeepers described above.

Prior to each workshop, we will send participants a summary and infographic of the scoping review findings to read. During the workshop, we will present the key findings and our plans for the contingent syntheses. We will invite discussion from participants on their interpretation of the review findings and on the following aspects of the contingent syntheses: inclusion/exclusion criteria; primary and secondary outcomes; subgroups and covariates. This will provide participants with an opportunity to identify any gaps or omissions in the planned syntheses and to make suggestions for additional criteria/outcomes/subgroups/covariates. The research team would consider these suggestions carefully and consult the literature prior to finalising the protocols for the contingent syntheses. The proposed approach is in keeping with guidance from the Cochrane Collaboration on involving stakeholders in systematic reviews [44].

## V: Methods - Contingent Review 1: Effectiveness Review

To answer review questions 3 & 4 we will conduct a synthesis of direct and indirect comparisons of exercise interventions across tendinopathies, which also considers important subgroups and covariates. As for the scoping review, an *a priori* protocol will be developed and registered with PROSPERO prior to commencing the review, which will be reported in accordance with PRISMA guidance [45].

### *Overall approach*

To address the extensive research base and overarching questions regarding exercise and tendinopathy, the systematic review will feature comprehensive meta-analyses comprising the most up to date network techniques. The approach adopted will maximise the available information, borrowing strength from individual studies and will provide more complete findings to inform treatment compared with previous reviews and standard pairwise meta-analyses.

### *Search strategy*

Literature will have been located using the search strategy described above (scoping review) and charted in such a way that potentially relevant studies are identified. However, because there will be an 8-month gap between searching and commencing the contingent reviews, the search strategy will be re-run. This will allow identification and inclusion of any studies published in the intervening period.

### *Inclusion criteria*

***Population:*** People of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location. Important subgroups and covariates that may explain heterogeneity in relative treatment effects (e.g. symptom severity, chronicity, age, sex, activity levels/training volume, body mass index, co-morbidities, health behaviours and medication use) will be identified *a priori* from the scoping review and incorporated within meta-analyses where appropriate.

***Intervention:*** Exercise therapy for the treatment of tendinopathy, as described above (“Health technology being assessed”). The scoping review will identify exercise therapies that have been reported in the literature including factors such as type, dosage, mode of delivery, whether first or second-line, and whether a single or multi-component intervention. The map produced by the

scoping review will allow the research team to identify distinct treatment types to perform network meta-analyses and control for potential confounders such as exercise volume and frequency.

***Comparator:*** We will compare one type of exercise to another, to another conservative intervention (single or combined), or to a control group that received no intervention (e.g. waiting list, wait-and-see). We may compare exercise with surgery; the scoping review will identify whether there is a body of evidence comparing exercise to surgery that would be relevant to synthesise. If so, then this will be included as an additional comparator.

***Outcomes:*** The scoping review will identify the outcomes that have been reported. However, primary outcomes are likely to include pain and patient-reported function using general or anatomical-location and/or tendinopathy-specific measures, and secondary outcomes may include: quality of life; muscle strength; range of motion; work-related outcomes (e.g. work ability, sick leave); patient satisfaction; return to activities (including sport); and adverse events.

***Types of Studies:*** Randomised controlled trials (RCT) and quasi-experimental studies (with a control group) will be included. We aim to include the best quality research in our analysis. Whilst this will generally be high quality RCTs, where these are not available, (e.g. specific tendinopathies that may not have been subjected to RCT evaluation and/or poor quality RCTs conducted) we will supplement the analysis with lower quality RCTs and quasi-experimental studies, controlling for their inclusion using statistical methods. *This is a pragmatic approach with the aim to include the best available evidence within a review.* We will adhere to the recommendations made in Chapter 24 Cochrane Reviewers' Handbook: Including non-randomized studies on intervention effects; and the nature of this study (i.e. starting with broad scoping review) will allow the review team to identify the available quasi-experimental studies that might be considered for inclusion, prior to finalising the protocol for the effectiveness review. Simulation models will be run based on the likely research base to inform what research and adjustment methods are to be used.

### *Study selection*

Potentially relevant studies will be identified from the scoping review map, and additional studies from the updated search. Studies will be double-screened by title/abstract and full-text for inclusion. Any conflicts will be resolved by a third reviewer (experienced systematic reviewer). The results of the search and screening will be presented in a PRISMA flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram [45].

### *Assessment of Methodological Quality*

Cochrane risk of bias (for RCT) and JBI (for quasi-experimental) tools will be used to assess risk of bias and methodological quality. Critical appraisal will be performed by two independent reviewers and conflicts resolved through discussion or with a third reviewer. Covidence will be used for risk of bias assessment and JBI SUMARI software (Joanna Briggs Institute, Adelaide, Australia) for critical appraisal of quasi-experimental studies. Data will not be excluded based on methodological quality; however, quality will be accounted for in subsequent sensitivity analyses and quantitative downweighting.

### *Data extraction*

Data will be extracted from studies included in the review using a data extraction form designed by the study team. Data extracted will include specific details on the populations, interventions, study methods and outcomes of significance to review questions 3 & 4. Data extraction will be carried out by one reviewer with verification by another reviewer to minimise bias and potential errors. Microsoft Excel® will be used at this stage of the review. Authors of included studies will be contacted in the event of missing information.

### *Data synthesis*

Continuous outcome measures will be used to quantify treatment effects by calculating standardised mean differences. Initially, meta-analyses of direct comparisons will be performed.

Model building will then combine both direct and indirect comparisons within a network framework to quantify the probability of each intervention (or combined interventions) being the most effective (first-best), the second best and so on. All meta-analyses will be performed within a Bayesian random effects framework to facilitate flexible modelling and probabilistic interpretations [46]. Heterogeneity in relative treatment effects will be explored with meta-regression and *a priori* trial-level covariates relating to person and trial characteristics. Associations caused by reporting multiple outcomes due to repeated observations across different follow-up times, and studies incorporating several related variables, will be accounted for by performing multivariate models or including additional hierarchical parameters where appropriate [47]. Model fit, model comparison and network consistency will be assessed using standard methods including residual deviance, deviance information criterion and comparison of direct and indirect evidence, respectively. Sensitivity analyses adjusting for bias based on quality of evidence scores and subsequent down weighting of lower quality evidence will also be included [47]. Models analysed will be conducted with Bayesian Markov chain Monte Carlo methods using the WinBUGS language and the R2WinBUGS package in the R programming environment. Analyses will be performed with non-informative priors and convergence assessed using standard diagnostics.

A network compatible Bayesian selection model will be used to explore the potential impact of publication bias whilst also accounting for consistency assumptions in the network [48]. Any data that cannot be included in the meta-analyses (e.g. due to heterogeneity or missing values) will be included in a narrative synthesis.

While SMDs are readily understandable by people who are comfortable reading meta-analysis reports, it may be that translation to differences on a well-known patient-reported outcome measure in the context of a known MCID (minimal clinically important difference) will be useful. Presentation of results will be guided by our PPI work, and we will consider a range of audience-specific presentation formats for pooled results (both continuous and dichotomous) and tailor these to the relevant audience.

Prior to conducting the network meta-analyses a priori methods regarding data extraction, model building and reporting will be developed and mapped to DECiMAL, NICE and PRISMA guidelines, respectively. These will be documented in the protocol registered on PROSPERO. Furthermore, methods developed to make decisions regarding model building and suitability of data will be informed by calculating model fit and comparison statistics; estimation of “effective sample size” (Thorlund and Mills 2012); and assessing evidence of consistency. Where data are for example removed to resolve issues such as inconsistency, this will be based on a thorough review of the entire evidence base and decisions reported in sufficient depth to facilitate transparency.

### *Assessing certainty in the findings*

A Summary of Findings table will be created using GRADEpro software (McMaster University, Ontario, Canada) and the GRADE approach for grading the quality of evidence. The Summary of Findings table will present the following information where appropriate: absolute risks for treatment and control, estimates of relative risk and a ranking of the quality of the evidence based on study limitations (risk of bias), indirectness, inconsistency, imprecision and publication bias, as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [49].

## VI: Methods - Contingent Review 2: Feasibility & Acceptability

### *Overall approach*

The mixed methods review will address review question 5: How feasible and acceptable are exercise interventions for tendinopathy? Mixed methods reviews (also known as mixed methods research syntheses, mixed studies reviews and mixed research syntheses) are a relatively emergent field in evidence synthesis. Mixed methods reviews integrate findings from quantitative and qualitative evidence [50], and are well suited to addressing issues such as feasibility and acceptability of interventions and patient values and preferences; information which is valuable for

the implementation of review findings for example by decision makers and guideline development groups. Mixed methods reviews have proliferated in recent years despite methodological guidance being largely theoretical until recently [51]. The Joanna Briggs Institute published their guidance for mixed methods systematic reviews in 2017 [52]. As the project team includes two JBI certified systematic review trainers and two additional JBI accredited reviewers, and the lead applicant has published two JBI mixed-methods reviews to date, this methodology will be employed for the feasibility and acceptability contingent synthesis. There are different methodological approaches within mixed methods reviews, the choice dependent on the review question. As the question here (feasibility and acceptability) can be answered by both quantitative (e.g. cross-sectional studies) and qualitative (e.g. phenomenological studies), a convergent integrated approach will be taken, whereby data will be transformed to allow quantitative and qualitative data to be combined [50]. An *a priori* protocol will be developed and registered with PROSPERO prior to commencing the review, which will be reported in keeping with PRISMA guidance [45].

### *Search strategy*

As described above for the effectiveness review, literature will have been located during the scoping review, and an updated search will be undertaken in order to incorporate recent additional studies.

### *Inclusion criteria*

***Population:*** People of any age or gender with a diagnosis of tendinopathy of any severity or duration and at any anatomical location.

***Phenomena of Interest:*** Feasibility of delivering and acceptability of participating in any exercise therapy for any tendinopathy. In this context, feasibility refers to whether the exercise intervention *"can"* be delivered and will therefore include, but not be limited to, information such as attendance (for formal exercise therapy sessions), intervention fidelity and adherence. Acceptability refers to the acceptability *to patients/clients* of receiving exercise therapy for tendinopathy. As such, it will include, but not be limited to, information such as perceptions, experiences, enjoyment, barriers and facilitators to exercise therapies.

***Context:*** In keeping with the scoping review, the context will include primary care, secondary care or community locations in any developed nation.

### *Types of studies*

Any quantitative, qualitative or mixed methods design that potentially contains data relevant to the review question will be considered for inclusion in the review. It is anticipated that relevant designs will include pilot and/or feasibility studies, cross-sectional studies, and qualitative studies (stand-alone, part of mixed methods studies or embedded in trials). Trials and quasi-experimental studies that include a process evaluation may also be eligible for inclusion. Therefore, studies may be included in both the effectiveness and the feasibility & acceptability review.

### *Study selection*

Potentially relevant studies will be identified from the scoping review map, and additional studies from the updated search. Studies will be double-screened by title/abstract by two independent reviewers. Potentially relevant studies will be retrieved in full, and their citation details imported into JBI SUMARI software. Two independent reviewers will then assess the full text in detail against the inclusion criteria. Reasons for exclusion of full text studies that do not meet the inclusion criteria will be recorded. Conflicts that arise between reviewers at each stage will be resolved by discussion, or by consulting a third reviewer. Search and screening results will be presented in a PRISMA flow diagram [45].

### *Assessment of Methodological Quality*

Quantitative studies (and quantitative components of mixed methods studies) will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from JBI SUMARI [https://joannabriggs.org/critical_appraisal_tools]. Likewise, qualitative studies and qualitative components of mixed methods studies will be assessed using the JBI critical appraisal tool for qualitative studies. Disagreements between reviewers will be resolved by discussion or by a third reviewer. The *a priori* mixed methods review protocol will detail whether or not studies are to be excluded based on their methodological quality score; inspecting the scoping review results in terms of the quantity and type of potentially relevant studies will inform this decision.

### *Data extraction*

Data will be extracted from studies included in the review by one reviewer and checked by a second reviewer to minimise errors. A data extraction tool will be developed by the review team. This will be included in the *a priori* protocol. It will be piloted on two or three studies and amended as necessary before being applied across all studies in the review. The data extracted will include specific details about the populations, methods, phenomena of interest, context and outcomes of relevance to the review (i.e. feasibility and acceptability). Quantitative data will be in the form of data based outcomes of descriptive and/or inferential statistical tests. Qualitative data will be in the form of themes or subthemes with corresponding illustrations (participant quotes or author's interpretations) and will be assigned a level of credibility. Levels of credibility can be Unequivocal (supported by an illustration (e.g. participant quote) that is not open to challenge); Credible (supported by an illustration that may be open to challenge); or Not supported (i.e. findings not supported by data). Any "Not supported" findings will be excluded from the synthesis. Authors of studies will be contacted to request missing or additional data as required.

### *Data transformation*

Quantitative data will be converted into "qualitized" data [50, 52] by transformation of data into textual descriptions or narrative interpretation of the quantitative results. In practice, this involves repeated detailed examination of the quantitative results by two independent reviewers in order to transform data into appropriate textual descriptions.

### *Data synthesis and integration*

As per JBI mixed methods guidance [52] the qualitized data will be assembled with the qualitative data using JBI SUMARI software. Assembled data will then be categorised and pooled together based on similarity in meaning, producing a set of integrated findings in the form of action statements. This involves developing categories for at least two similar findings, and then developing integrated findings based on similarity of meaning of the categories. Please see figure 2 for an overview of data synthesis and integration.

Due to the complexities associated with integrating quantitative and qualitative findings, it is currently not recommended to assess the certainty of the evidence using the GRADE approach [52]. However, work is ongoing in this area, and the lead applicant is a member of the UK GRADE network steering group. Therefore, should advances be made during the course of the review, they will be implemented accordingly.

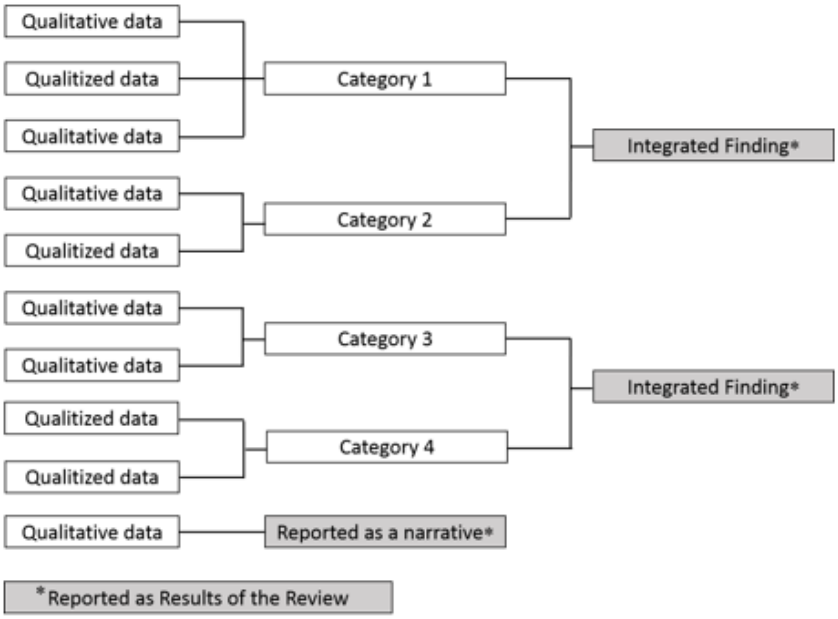


**Figure 2: Convergent integrated data synthesis and integration**

From: JBI Reviewer's Manual, Chapter 8, Mixed Methods [52], with permission

### *Outcome of contingent review 2*

The outcome of this stage will be knowledge of the feasibility of delivering exercise therapy for tendinopathy and their acceptability to people with tendinopathy. This knowledge will be crucial for contextualising the findings from the effectiveness review and informing decisions regarding implementation of these findings. It is also highly likely that gaps in the evidence base will be identified by this synthesis, thereby informing future research in this field.

### *Additional syntheses*

At this stage, based on initial literature searching, it is anticipated that the two contingent syntheses detailed above will comprehensively address all five review questions. However, the study design will remain flexible and be dependent on the findings of the scoping review. Therefore, it is possible that inclusion and exclusion criteria may be amended or refined.

### VII: Stakeholder Workshop 2

We will hold follow-up stakeholder workshops in Aberdeen and London to help us interpret the results from stakeholders' perspectives, and to inform the design of dissemination materials. We will in the first place invite participants from workshop 1; in the event of any drop-outs we will recruit additional participants as described for workshop 1.

## 6. Dissemination, Outputs and anticipated impact

Table 1 displays the intended outputs and timescales for delivery. A communication and dissemination strategy will be developed for the start of the project and will be reviewed at each stakeholder meeting; co-applicant Alexander will lead the strategy. We will use a range of output formats and a range of strategies to disseminate as widely as possible to clinicians, academics, decision-makers, and members of the public. The communications departments of RGU, Queen Margaret University London (QMUL), NHS Grampian and sportscotland will assist the research

team with press releases promoting the study findings and leading to further promotion on local radio, TV and social media.

. **Table 1: Project outputs**

| Output | Mechanism | Timescale |
|---|---|---|
| **Dissemination of findings** | Publication of each review in high impact peer reviewed journal, including use of blogs/slides/podcasts as available | Scoping review 2021<br>Effectiveness review late 2021/early 2022<br>Feasibility/acceptability review late 2021/early 2022 |
| | Present at Physiotherapy UK (scoping review) & International Scientific Tendinopathy Symposium (Effectiveness and Feasibility/Acceptability reviews) | November 2021<br>Autumn 2022 |
| | Press release – leading to radio & TV interviews<br><br>Social media including research team's personal and institutional Twitter accounts (e.g. Co-applicant Morrissey has 5,000 Twitter followers, many of whom are clinicians managing patients with tendinopathy) and @ahp2mintalks<br><br>YouTube videos<br><br>Podcasts (e.g. BJSM – attracts up to 10-20,000 listens per podcast)<br><br>Lay summaries and infographics disseminated via social media and networks that research team and stakeholders are associated with | Coincide with publication of each review |
| **Make recommendations** | Engage with professional bodies (e.g. CSP, BASEM) clinical & academic leads (research team's institutions), musculoskeletal lead for Scottish Government AHP Directorate, create bespoke summary for NHS England commissioners<br><br>Create resource for www.exercise.trekeducation.org | Following publication of final review |
| **Raise awareness** | ½-day workshop for clinicians (Aberdeen & London)<br>Public launch event (Aberdeen & London)<br>NB These will occur on same day to maximise impact, along with social media promotion<br><br>Engage with relevant patient groups | Following publication of final review |
| | Training & Education in best practice | In-service training NHS Grampian, Bart's and the London NHS trust, sportscotland institute of sport |

Key: BJSM=British Journal of Sports Medicine; CSP=Chartered Society of Physiotherapy; BASEM=British Association of Sport & Exercise Medicine; AHP=Allied Health Professions

PPI and rehabilitation specialist steering committee members will facilitate dissemination to relevant groups, and stakeholders who attended workshops 1 & 2 will be invited to assist also.

## 7. Project timetable

Table 2 details the key stages of the scoping review and 2 contingent syntheses (effectiveness review and feasibility & acceptability review) along with milestones and outputs. Dissemination will continue beyond the end of the funding period. We aim to commence the study on 1st March 2020, and therefore to complete by 31st August 2021.

## 8. Project management

The lead applicant (Cooper) will be responsible for overall management of the project. There will be a lead for each of the three reviews (Scoping: Alexander; Effectiveness: Swinton; Feasibility & acceptability: Cooper). Short weekly meetings of the team members actively conducting the reviews will take place to track progress and address any issues that may arise. Communication between the wider team will take place using Microsoft Teams (GDPR compliant) to enable discussion and document sharing, with the Zoom videoconferencing platform being used to facilitate virtual meetings with co-applicants Brandie and Morrissey. Quarterly Project Management Group meetings will track progress against the project timetable, review tasks conducted to date and plan forthcoming tasks and outputs. Cooper, with support from finance/administration will be responsible for tracking spending, ensuring that the project stays within budget. The research assistant will be line-managed by the lead applicant (Cooper), with support from co-applicant Alexander.

## 9. Ethics

NHS ethical approval is not required as the project is solely literature-based. Ethical approval is not required for involving patients and the public either (recommendation from NHS Grampian R&D Department); we will follow best practice and recommendations from INVOLVE. We are however seeking approval from the School of Health Sciences Research Ethics Committee for the project in general and specifically for the stakeholder workshops, in order to comply with good research practice.

## 10. Patient and public involvement

Our PPI strategy has been informed by published guidance from INVOLVE (https://www.invo.org.uk/) and the Cochrane Collaboration, and feedback from PPI participants from previous evidence synthesis projects conducted by the review team. We feel that the following activities represent meaningful PPI:

i) Involving patients and the public to date in developing this application;

ii) Inviting patients and the public to take part in the stakeholder workshop (month 8) to inform the dissemination strategy for the scoping review and the protocols for the contingent syntheses;

iii) Inviting patients and the public to take part in a second stakeholder workshop (month 17) to inform the dissemination and implementation strategy for the project as a whole, and;

iv) Recruiting three people who have experienced exercise therapy for tendinopathy to be active members of our steering committee.

**Table 2: Project Timetable**

| | Scoping | Effectiveness | Feasibility & Acceptability | Stakeholder Workshop | Committee Meeting | Outputs |
|---|---|---|---|---|---|---|
| **M1** | Finalise protocol<br>Register OSF<br>Submit JBI Evidence Synthesis<br>Detailed search strategy<br>Train RA | | | | PMG Meeting 1 | Scoping review protocol OSF & summitted JBI Evidence Synthesis |
| **M2** | Searching & selecting studies | | | | | |
| **M3** | Searching & selecting studies | | | | | |
| **M4** | Data extraction | | | | PMG Meeting 2 | |
| **M5** | Data extraction | | | | | |
| **M6** | Constructing evidence map | | | | | Evidence map |
| **M7** | Developing outputs | | | | PMG Meeting 3<br>SSC Meeting 1 | |
| **M8** | Developing outputs & contingent review protocols | | | Stakeholder workshop 1: Protocol review | | Scoping review manuscript + outputs |
| **M9** | | Update search<br>Study selection | Update search<br>Study Selection | | | Contingent review protocols |
| **M10** | | Critical appraisal | Critical appraisal | | PMG Meeting 4 | |
| **M11** | | Critical appraisal<br>Data extraction | Critical appraisal<br>Data extraction | | | |
| **M12** | | Data extraction | Data extraction | | | |
| **M13** | | Data synthesis | Data synthesis | | PMG Meeting 5 | |
| **M14** | | Data synthesis | Data synthesis | | | |
| **M15** | | Update search<br>Report writing | Update search<br>Report writing | | | |
| **M16** | | Report writing | Report writing | | PMG Meeting 6<br>SSC Meeting 2 | |
| **M17** | | Report writing | Report writing | Stakeholder workshop 2: Dissemination materials & strategy | | |
| **M18** | | Finalise all outputs; Submit manuscripts; Begin dissemination | Finalise all outputs; Submit manuscripts Begin dissemination | | | Final report + manuscript x 2 + outputs |

Key: M=Month; OSF=Open Science Framework; JBI=Joanna Briggs Institute; RA=Research Assistant; PMG=Project Management Group; SSC=Study Steering Committee

## 11. Success criteria and barriers to proposed work

We will implement the following measures of success:

- Recruitment of three PPI participants and three rehabilitation specialists Project Management Group (month 1)
- Scoping review protocol registration on OSF (prior to start date)
- Scoping review protocol acceptance for publication in JBI Evidence Synthesis (month 4)
- Scoping review completion (month 6)
- Recruitment of up to ten PPI participants and up to ten rehabilitation specialists to each stakeholder workshop (months 8 & 17)
- Scoping review manuscript submitted to peer review journal (month 8)
- Contingent review protocols registered on PROSPERO (month 9)
- Contingent reviews completion (month 16)
- Contingent reviews manuscript submission (month 18)

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