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Does exercise dose matter in patients with long-term osteoarthritis of the knee? A study protocol of a randomized controlled trial in Sweden and Norway – the SWENOR study (NCT02024126)

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Complete List of Authors:	Torstensen, Tom Arild; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy Grooten, Wilhelmus; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Østerås, Håvard; Norwegian University of Science and Technology, Department of Neuromedicine and Movement Science Heijne, Annette; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Harms-Ringdahl, Karin; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Äng, Björn; Dalarna University, School of Education, Health and Social Sciences; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy
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Does exercise dose matter in patients with long-term osteoarthritis of the knee? A study protocol of a randomized controlled trial in Sweden and Norway – the SWENOR study (NCT02024126)

Torstensen TA (1), Grooten WJA (1,2), Østerås H (3), Heijne A (1,2), Harms-Ringdahl K (1,2), Äng BO (1,4,).

1) Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Huddinge, Sweden
2) Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy, Karolinska University Hospital, Stockholm, Sweden
3) Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway
4) School of Education, Health and Social Sciences, Dalarna University, Falun, Sweden

Corresponding author:
Tom Arild Torstensen
Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy
Karolinska Institutet

Alfred Nobels Allé 23 23100
141 83 Huddinge, Sweden

Tel: +46 707344102
E-mail: tom.torstensen@ki.se

ABSTRACT

Introduction: Osteoarthritis (OA) of the knee is characterized by knee pain, disability, and degenerative changes, and places a burden on societies all over the world. Medical exercise therapy (MET) is an often-used modality, but there is little evidence of what type of exercise dose is effective, indicating a need for controlled studies of the effect of different dosages. The aim of this study protocol was therefore to describe our planned study that is designed to evaluate the effects of high-dose versus low-dose MET in patients with knee OA.

Methods and analysis: This is a multicenter prospective randomized two arm trial with blinded evaluation. We are planning to include 200 patients aged 45-85 years with an X-ray verified diagnosis of knee OA . Those eligible for participation will be randomly allocated to either high-dose (n=100) or low-dose MET (n=100). All patients receive three supervised treatments each week for 12 weeks, giving a total of 36 MET sessions. The high-dose group receives a greater number of exercises, sets, and repetitions than the low-dose group, revealing an exercise dose of 80-90 min versus 20-30 min, respectively. Background and outcome variables are recorded at inclusion, and outcome measures are collected after every 6th treatment, at end of treatment, and at six- and 12-month follow-ups. Primary outcome is self-rated knee function and pain using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and different visual analogue scales (VAS). The primary endpoint is at end of treatment – three months, and secondary endpoints are at 6 and 12 months after end of treatment.

Ethics and dissemination: This project has been approved by the Regional Research Ethics Committees in Stockholm, Sweden, and in Norway. Our results will be submitted to peer-reviewed journals and presented at national and international conferences.

Trial Registration number: (ClinicalTrials.gov NCT02024126)

Strengths and limitations of this study

- To the best of our knowledge, this is the first multicenter study prospectively comparing the effectiveness of two clearly defined doses of exercise therapy in patients with knee osteoarthritis.
- The proposed project includes a relatively large sample where primary outcomes are evaluated both during the 12-week intervention period, at the end of treatment, and at six and twelve months, respectively.
- The project uses both subjective and objective data, and includes analyses of cost-effectiveness and early predictors for a follow-up clinical outcome.
- Even though the different components of the exercise programmes are well described, one limitation could be possible confounders related to the exercise dose given.

MAIN TEXT

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and is a major worldwide health problem causing illness and disability [1, 2]. Internationally, the burden to society, cost of the interventions and persistent clinical course of knee OA, is substantial [3]. The knee joint is most frequently affected, which commonly results in chronic joint pain, knee stiffness, decreased functioning, reduced quality of life, and sick leave [4]. The associated costs of

osteoarthritis are estimated to range between 1-2.5% of the gross national product as calculated in six industrialized countries (Sweden, Australia, Canada, France, UK, and US) [5].

The prevalence of knee OA has increased during the last 20 years [1], and is expected to continue to increase [6]. Murphy et al. [7] reported that almost half of US adults will have symptomatic knee OA by the age of 85, with the highest risk being among obese individuals. There is a sex difference, where the prevalence is estimated to be 40% in women and 30% in men in people aged 65-75 years [8]. Although knee OA is known to be more common in older age groups, the increasing global prevalence of obesity is anticipated to elevate the prevalence of knee OA in younger people [9]. Currently, knee OA in younger people is most often secondary to congenital disorders or sporting injuries and other traumas to the knee [10, 11].

Traditionally, knee OA has been defined as a pathological condition characterized by focal areas of loss of articular cartilage within the synovial joints, associated with hypertrophy of the bone (osteophytes and sub-chondral bone sclerosis) and thickening of the capsule [12]. The mechanisms of knee OA-related pain are, however, complex [13], particularly in chronic pain conditions where pain experience is nowadays believed to be more a result of changes in the nervous system than in tissue structures [14], which somehow reflects a paradigm shift in the understanding of the pathology of pain related to knee OA. Because of the plasticity of the nervous system, pain lowers the threshold level of the nociceptive receptor system [15], making it more sensitive to stimuli during normal movements like walking and bending – so-called mechanical or loading allodynia. These changes occur in the peripheral

receptor system located in the knee and in the receptor system in the spinal cord resulting in changes in the nervous system, i.e. peripheral and central sensitization [16]. The fact that the problem lies more in the nervous system than in the knee makes it easier to understand why there are poor correlations between structural degenerative changes of the knee, pain, and functioning [17, 18].

The level of pain caused by these sensitization processes is also affected by psychological factors such as anxiety and depression, which cause increased nociceptive input that increases the pain experience [19, 20]. When pain becomes more persistent and does not resolve, the person can develop negative attitudes and beliefs [20-22] that are closely linked to catastrophizing and anxiety. This results in further sensitization with long-term pain [19, 23, 24]. Shifting our understanding of pain-related knee OA from exclusively involving changes in tissue structures to involving changes in the nervous system is an important paradigm shift for not only a better understanding of what knee OA is, but also for improved optimal treatment designs including exercise therapy which is a frequently used modality in treating knee OA.

In a systematic review, it was concluded that there exists high-level evidence that land-based therapeutic exercise provides short-term effects of pain relief and function, and that there is a moderate level of quality evidence regarding improvement in physical function among patients with knee OA [25]. Despite this, several questions remain unanswered, particularly regarding dose, intensity, and duration of the exercise therapy applied [26]. These unanswered questions may be one of the reasons why we see a large variation in treatment effects observed across studies making it difficult to conclude what is the optimal

dose when delivering exercise therapy [25, 26]. The exercises vary from neuromuscular exercise [27], knee joint stabilization exercises [28], strengthening exercises [29], and endurance exercises. The theoretical basis for these different exercise programmes is not always clear, especially when matching them to the cause of long-term knee pain; peripheral and central senistization. The knowledge that pain and swelling inhibits motor output, decreases range of motion, and changes coordination [30], and that a traditional strengthening exercise program can cause adverse effects [31], questions the use of strengthening exercises. There is increasing evidence [32] that exercise therapy should focus on treating the causality of pain-related knee OA such as peripheral and central sensitization [14] and pain-related bodily and psychological changes [19] from a biopsychosocial perspective [33, 34], rather than an impairment like muscle strength .

Medical Exercise Therapy

Medical Exercise Therapy (MET) was developed in Norway more that 50 years ago and is an established treatment in the Nordic countries, other parts of Europe, and North America [33, 35, 36]. MET focuses on applying the optimal dose of exercise; i.e combining global aerobic exercises with semiglobal and local joint exercises, where the goal is to apply 70 to 90 minutes of active dynamic exercise therapy [36-45]. The patient is to perform more than 1000 pain-free repetitions or close to pain-free repetitions per MET-session [36-45]. Even though the optimal dose goal of MET is high, the treatment usually starts with a low dose lasting 15 to 20 minutes mirroring the ability of the patient within a biopsychosocial context [34], starting with an acceptable baseline where the patient manages the exercise therapy [33, 36].

The theoretical basis for MET differs from most other forms of exercise therapy in that MET focuses on treating the pain experience and the bodily and psychological reactions to the pain experience [33] by applying an exercise dose lasting from 15 to 90 minutes [33]. The goal is to reach 70 to 90 minutes of graded exercise resulting in a decrease of pain and improvement of function. Possible physiological mechanisms for achieving this are believed to activate the descending pain inhibiting system [46, 47], achieving spinal and cortical control of nociceptive input and decreasing low inflammatory processes [48-50], which are believed to contribute to sensitization [51, 52]. The goal of MET is hence to modulate the pain experience and decrease sensitization like allodynia and hyperalgesia [32, 53], increase range of motion, and improve functioning [43], resulting in improved muscle strength [43]. Expressions such as “exercise for the modulation of pain”, “exercise therapy as anti-nocicpetive therapy”, “exercise as anti allodyni therapy”, or “exercise as anti-inflammatory therapy” [50] are used to better explain the goal of the exercise therapy when treating a painful condition. For this purpose, exercises are adapted so that they can be performed pain free or close to pain free. When a patient becomes pain free or close to pain free, the exercise dose is increased with an aim to achieve neural changes in the central nervous system and chemical changes in the muscle tissue, to achieve muscle strength, muscle volume, and/or muscle endurance [33].

The practical application of MET protocols also differs from most other forms of exercise therapies due to MET mixing global, semiglobal, and local exercises [33].

Global exercises are aerobic exercises activating large muscle groups of the body, semiglobal exercises are exercises focusing on one extremity with movements in multiple joints, and local exercises are exercises focusing on one isolated joint (e.g. knee joint) in an open chain situation (Figure 1).

[Figure 1 about here]

Sessions of global exercises are performed several times during one treatment occasion, where the goal is to substantially increase the heart rate activating the endocrine and pain modulating systems of the body, i.e. the descending pain inhibiting system, achieving cortical and spinal inhibition of nociceptive input. Semiglobal and local exercises are performed for the same purpose, however, they are performed in sets of three where each set consists of 30 repetitions. A local exercise can also be performed continuously for 3 to 5 minutes as one set, for example. The goals of local knee exercises are biological and psychosocial. Biological goals include increasing local circulation stimulating mechanoreceptors, activating muscles and collagen tissue in the knee resulting in pain modualtion having an anti-inflammatory effect. Psychosocial, where the local exercise is a form of exposure therapy where the patient is exercising the part of the body, in this case the knee, that is painful causing anxiety and fear of movement [54]. The goal of the local exercise is for the person to “regain the knee” as a part of the body resulting in a decrease of negative psychological factors.

Another element that differs between MET from many other exercise therapies is the focus for the grade and dose of exercises to be pain free or close to pain free [33, 36]. From an ethical point of view it may be questionable to push patients through painful exercises,

when simple doses and grades can make exercises basically pain free. Another theoretical and practical argument for such doses is that it seems to be easier to motivate patients to exercise when there is no or very little pain involved. By activating the pain-modulating systems of the body [55, 56], negative psychological reactions can be avoided that may inhibit the pain modulating systems [57, 58], and even decrease possible adverse effects from the exercises [31]. However, when a person experiences pain as "meaningful", as a type of reward, it seems to be possible to activate the pain modulating systems [59, 60]. Thus, when it is not possible to grade and dose the MET exercises at a pain-free or close to pain-free level, the patient may exercise with pain, but these painful exercises should be at an acceptable level and not increase any negative psychological reactions. As summerized by Lorås et al. [33], MET has been evaluated in several clinical trials, and has been shown to be effective, both in the short and long term, in patients with long-term low back pain with or without sciatica [35], subacromial pain [43-45], and long-term anterior knee pain [37, 38]. In these latter studies, an exercise dose lasting 70 to 90 minutes has been been more favourable when compared to an exercise dose lasting 20 to 30 minutes. High-dose MET was also found to be more effective when compared to a hospital-based traditional exercise program given after arthroscopic surgery after a degenerative meniscectomy [39, 40, 42]. One pilot study compared high-dose MET with arthroscopic surgery in patients with knee pain [41] and found it to be associated with lower rates of depression.

In a narrative review, Lorås et al., 2015 [33], included four RCTs on the effectiveness of high-dose MET, concluding that high-dose MET was positive and promising. However, to be able to draw any firm conclusions about the efficacy of MET for patients with knee OA, rigorous

trials are needed on the effect of MET in this major patient group [61]. Effect trials of cost-effectiveness are also needed as they are presently lacking in the scientific literature, and the present project has the potential to fill this knowledge gap. It is also important to point out that no exercise protocol is suited to all patients, and as knowledge of early predictors of poor treatment outcomes obtained from longitudinal data is sparse, the development of patient-customized treatments is hindered [62]. According to the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) [63], as well as a recent review [64], prediction studies are needed to be able to better individualize the treatment and match the most promising treatment option to a certain patient profile in order to maximize treatment outcomes and minimize costs. Therefore, we plan to conduct an RCT post-hoc prediction study to gain insights into which patient characteristics predict treatment outcome and which patients benefit more or less from exercise treatments.

AIM OF THE STUDY

The aim of this project is to prospectively evaluate short- and long-term effects of high-dose MET compared to low-dose of MET in patients with X-ray verified knee OA regarding pain, function, and cost-effectiveness. Another aim is to evaluate the effects on pain and function during the intervention period after every sixth treatment. A further aim is to conduct a post-hoc analysis on early prognostic factors that predict short- and long-term follow-up outcomes, by targeting patients' early status and patient adherence to the intervention. The long-term goal is to further develop and implement updated knowledge into knee OA rehabilitation to meet the challenge of tomorrow's patients with knee OA pain.

1. What is the effect of high-dose MET compared to a low-dose exercise therapy (low-dose MET) with respect to self-rated pain, functional limitations, health-related quality of life, depression, and anxiety?
2. What is the effect of high-dose MET compared to low-dose MET on objective measures such as physical functioning of a 20-metre walk, sit to stand, and single knee bends, and pain threshold as determined by a pain-matcher instrument?
3. What is the cost-effectiveness of MET in patients with knee OA with respect to costs against potential effects (incremental cost-effectiveness ratio, ICER), and cost per quality-adjusted life year (QALY)?
4. Which patient characteristics (demographic or disease-related) predict long-term treatment outcomes with a focus on pain, functional limitation, and health-related quality of life? What important interaction effects between patient characteristics and exercise dose may predict treatment outcomes?

MATERIAL AND METHODS

Study design

This project is a double blinded randomized two-arm multicentre trial of a 12-week exercise intervention with a 12-month follow-up. Measurements will be taken at baseline, and follow-ups at two, four, six, eight, ten, 12, 26, and 52 weeks. Primary endpoint is after end of treatment at the 12-week follow-up. Secondary endpoints are at 26 weeks and at 52 weeks follow-up. The study will conform to CONSORT guidelines for reporting parallel randomised trials [65], figure 2.

[Figure 2 about here]

Participants

We are planning to include 200 patients with a diagnosis of symptomatic and radiographic knee OA who will be recruited from primary and secondary health care settings in Luleå and Västervik in Sweden, and in Trondheim and Mosjøen in Norway, the SWENOR knee OA study.

Inclusion criteria:

Subjects aged 45-85 years, living in the defined geographic areas (Västervik and Luleå municipalities in Sweden, and Trondheim and Mosjøen in Norway), who have had a diagnosis of symptomatic and radiographic osteoarthritis grade I-III according to Kellgren and Lawrence [66, 67], with pain (at least of three months duration), and decreased functioning.

Exclusion criteria:

Physiotherapy or other conservative therapy during the previous three months or a history of major knee trauma. Inflammatory joint disease, hip symptoms more aggravating than the knee symptoms, about to have knee replacement surgery within six months, and co-morbidities not allowing exercise such as cardiovascular, respiratory, systemic, or metabolic conditions limiting exercise tolerance.

Procedure

Before intervention starts, regular visits will be made to each intervention place by the first author (TAT), informing and communicating the local research team about the aims and run

of the study. Detailed description of the different stages of the study from recruitment, treatment, and follow-up assessments after the end of the intervention period will be instructed and discussed. Physiotherapists in charge of the objective clinical testing, not otherwise involved in the treatment, will be educated theoretically and practically on how these tests should be performed. The physiotherapists delivering the exercise intervention will, in addition, have structured theoretical and practical sessions on how to apply and grade the exercise therapies. A handbook will be made describing in detail all aspects of the practical run of the study.

Recruitment will be achieved through referrals from medical doctors in primary and secondary health care clinics. Patients will receive oral and written information about the study, and after signing an informed consent form, patients will be assessed for eligibility by physiotherapists at each intervention centre. Participants initially fill out questionnaires for baseline data and perform the physical objective tests. Each patient is then randomized, as described below, to either high or low dose medical exercise therapy.

Data collection and management.

Data from the questionnaires will be depersonalised at each intervention centre by the local research assistant. In order to transfer data from Norway to Sweden, a data transfer agreement between Norges Teknisk-Naturvitenskapelige Universitet (NTNU)/Norwegian University of Science and Technology and Karolinska Institutet, NVS, has been set up.

Post-recruitment retention and compliance strategies

Our experiences of MET as an experimental intervention (HØ and TAT) [33, 37-43, 45, 68] leads to the following retention and compliance strategies to be applied in this study.

- An independent research assistant at each intervention centre will always be available to answer questions when the patient is filling out the questionnaires. This is important to avoid any unnecessary misunderstandings regarding the content of the questionnaire and making sure that the patient understands that all information will be made depersonalized.
- During the interventions, the treating physiotherapist is present the whole time in the exercise room answering questions from the patient and re-grading the exercises according to changes in patients' exercise status and knee-OA symptoms.
- At the end of the 12-week intervention period the patient is again informed about the six- and 12-month follow-ups.
- During the post-intervention follow-ups, the patient will be contacted three weeks prior to the assessment and informed when to come to the intervention site for the planned post treatment evaluation.

During the intervention period, pain and functioning are assessed after every sixth treatment, giving a total of six assessments. The purpose of such repeated measurements is to obtain a reasonable measurement accuracy of both functioning status and pain during this period. The primary end-point will be on completion of the intervention after 36 treatments, which will take an average of three months. This is to obtain evaluation of effects on organized exercise therapy related with its direct implementation, while further follow-ups evaluate its retention effects. At this point primary and secondary outcomes are assessed.

Randomization procedure

In this individual randomized trial, a stratified allocation by age and intervention centre is used, using a computerized program, where the goal is to get equal number of patients between the ages of 45 and 64 years and 65 and 85 years at each of the four intervention centres. The randomization key is concealed at each intervention place and kept under lock by a research assistant not involved with the assessment or interventions.

Blinding procedures

Participants are not informed about the hypothesis of the study, thus being blinded regarding the experimental intervention. In addition, the physiotherapists performing the objective testing are blinded to allocation groups. Research assistants are also blinded to groups when entering data to data-sheets, i.e. they do not know which patient has received high-dose or low-dose MET. The group key will be opened after the analyses have been finalised and the results have been written up in a manuscript (using intervention A and B until results have been written).

Interventions

All participants receive an MET intervention, where they are treated in groups of four or five in sessions lasting 20 to 90 minutes. During the sessions, they are supervised by an experienced physiotherapist in an outpatient clinic. All participants are treated three times a week for 12 weeks, totalling in 36 treatments. Each patient in the group has an individualized exercise program tailored for their specific clinical symptoms and functional level. As the treatment proceeds, exercises are adapted and new exercises are considered according to changes in symptoms and functioning [33]. Specially designed exercise

equipment consisting of different forms of pulleys, exercise benches, dumbbells, and barbells, is used to grade and dose the exercises to be pain free or close to pain free, with the purpose of mitigating peripheral and central sensitization while exercising [33]. The difference between groups regarding exercise dose is outlined below in Table 1.

Table 1: *Differences between the high-dose and low-dose MET* regarding *number of exercises-, sets-, and repetitions. Difference in time, performing global exercises and total time duration for each treatment.*

	Number of exercises	***Number of sets***	***Number of repetitions***	***Time performing global exercise***	***Time duration of treatment***
High dose MET	*9*	*3*	*30*	*20 min+10 min +10 min*	*70-90 min*
Low dose MET	*5*	*2*	*10*	*10 min*	*20-30 min*

The grading of the exercises, including baseline settings, is based on the initial clinical assessment by the treating physiotherapist. From the patients' past and present histories and physical clinical assessments, information is gained about possible sensitization (local versus central sensitization), the ability to bear weights, range of motion of the knee, and tolerance for weight bearing within the available range of motion. From this information it is possible to have a clinical judgement about initial exercise grade, choosing a weight resistance that matches the desired number of repetitions and sets. It is hence possible for the patient to perform the exercise comfortably within the preferred active range of active motion (AROM). For example, if a part of the AROM in the knee joint is painful, the patient

starts to exercise within the pain-free or close to pain-free AROM. As the treatment proceeds, the AROM is adjusted, making the patient exercising in a larger and more functional AROM. If it is not possible to grade the exercise pain free or close to pain free, the patient is allowed to exercise with pain. When exercising with pain it is important that the pain experience does not cause any anxiety or fear. The pain has to be experienced as meaningful for improvement [59]. If the exercise therapy results in an acute increase in pain, the pain should have decreased to baseline before the next treatment session commences. The group of 4-5 patients also contains patients with other diagnoses, who are not participating in this study, making the delivery of the MET intervention pragmatically similar to a real life situation. To be able to monitor the exercise dose, the treating physiotherapists follow a structured progression plan of the exercises, and fill in a treatment log for each patient at each treatment. The log contains information about number of exercises, length of each global exercise, number of repetitions, and sets and weight resistance applied for semiglobal and local exercises. Figure 3 show the two different exercise interventions compared in this planned randomized trial, high dose MET versus low dose MET.

[Figure 3 about here]

To be able to reach a high number of repetitions despite ongoing pain, the principle of de-loading is applied, facilitating a high number of repetitions that are nearly or entirely pain free, see figure 1. For the high-dose MET, the deloaded knee extension is performed twice during a treatment, each time for a five-minute duration. Later, as the patient improves and

can tolerate increased loading, the exercises are adapted to be more functional, using closed chain exercises without deloading the body weight

Baseline data

The following data will be obtained by questionnaire; gender, age, height, weight, physical activity and exercise levels, living arrangement, education level, employment status, possible medication, co-morbidities, smoking habits, sleeping habits, pain and function of the knee, catastrophizing thoughts, fear avoidance beliefs, level of anxiety and depression, life satisfaction and quality of life, and beliefs about exercise. A schematic presentation of the outcome measures recorded at baseline and at the follow-ups is presented in Table 2. Each assessment, which involves filling out questionnaires, will take approximately one hour. The objective testing of the knee and the testing with the PainMatcher apparatus will occur the following day, and take approximately 30 minutes.

Table 2 . *Study measures to be collected*

	Instrument for data collection	Collection points
PRIMARY OUTCOME MEASURE		
KOOS average score of five of the KOOS subscale scores	KOOS subscales; 1) pain, 2) other symptoms, 3) ADL, 4) Sport/Rec, and 5) QOL	0, 2, 4, 6, 8, 10, 12, 26 and 52 wks
Knee pain to day/average last week		
Knee pain	100 mm VAS	0, 2, 4, 6, 8, 10, 12, 26 and 52 wks
Knee pain not loading (sitting, lying)	100 mm VAS	
Knee pain at weight bearing	100 mm VAS	
Knee pain at night	100 mm VAS	
SECONDARY OUTCOME MEASURES		
Quality of life (qol)		
Health related qol	EQ-5D-5L	0, 12, 26 and 52 wks
	SF-36	0, 12, 26 and 52 wks
Psychological outcomes		
Anxiety and Depression	HAD	0, 12, 26 and 52 wks
Catastrophizing	CSQ	0, 12, 26 and 52 wks
Fear Avoidance Beliefs	TSK	0, 12, 26 and 52 wks
Life Satisfaction	LISAT	0, 12, 26 and 52 wks
Beliefs of exercise		
Believes and attitudes to exercise	Self-efficacy for exercise (SEE)	0, 12, 26 and 52 wks
	Outc.expec. for exercise (OEE)	0, 12, 26 and 52 wks
Pain threshold and tolerance	Pain Matcher	0, 12 wks
Objective functional performance		
Functional performance	20 m walk test	0, 12 wks
	Chair stand test	0, 12 wks
	Unilateral knee bending	0, 12 wks
OTHER MEASURES		
Compliance with exercise	Treatment records, log-book	Continuously
Adverse events	Treatment records, log-book	Continuously
Satisfaction	A five-point Likert sacle	52 wks

Primary outcome measures

In accordance with international consensus regarding the core set of outcome measures for clinical trials in OA [69], self-rated functioning and pain scoring (The Knee Injury and Osteoarthritis Outcome Score, KOOS) [70-73] are used as primary outcome measures. KOOS consists of 5 subscales; Pain, other Symptoms, Functioning in daily living (ADL), Functioning in sport and recreation (Sport/Rec), and knee-related Quality of life (QOL). Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. For the purpose of an RCT, KOOS subscale scores can be aggregated and averaged as the primary outcome. We are planning to use KOOS at several time-points; at baseline, and during the intervention period until the final follow-up at 52 weeks, Table 2.

Other primary outcome measures are eight different pain measurements using a 100 mm visual analogue scale (VAS) [74], with terminal descriptors of “no pain” and “worst pain” asking about how painful a knee is, 1) today and 2) on average during the last week, related to the following four different life situations; 1) how painful is your knee, 2) how painful is your knee when loading your knee (e.g. walking, standing, 3) how painful is your knee when not loading your knee (e.g. sitting, lying), 4) how painful is your knee at night when you are sleeping (e.g. knee pain that disturbs your sleep).

Secondary outcome measures

Data on health related to quality of life are collected using the EQ 5-D questionnaire [75] and The SF-36 questionnaire [76]. These questionnaires will also be used to perform a health economic evaluation of the exercise interventions. Psychological factors such as anxiety, depression, catastrophizing, and fear-avoidance beliefs are believed to both predict outcome of an intervention [77] as well as influence the level of pain in patients with knee OA experience [78]. In this study, anxiety and depression are rated using the Hospital Anxiety and Depression Scale (HAD) [79], catastrophizing is rated using the Pain Catastrophizing Scale (PCS) [80], and fear avoidance beliefs [81] are rated using the Tampa Scale of Kinesiophobia (TSK) [82], see Table 2. Life satisfaction is assessed using the Life Satisfaction (LISAT) questionnaire by Fugl-Meyer [83]. Beliefs and attitudes towards exercise are rated using the Self-Efficacy for Exercise Scale (SEE) [84], and the patient's expectations of performing physical activity are rated using the Outcome Expectations for Exercise Scale (OEE) [85] . A PainMatcher apparatus [86] (Cefar Medical AB, Lund, Sweden) is used to record sensory level, pain level, and pain tolerance level. Pressing the thumb and first finger against a button on each side of the hand held PainMatcher apparatus; an electrode under each button activates an electrical current. As long as the pressure is kept against the buttons, the electrical current will slowly increase where the first sensation of the current is a measurement of sensory threshold. As the pressure is maintained, the electrical current slowly increases, and the sensation will turn into a pain sensation (pain threshold). Keeping the pressure on the buttons, the painful electrical current increases, and pain tolerance is recorded, i.e. the measure of how much painful electrical current the patient can endure.

Objective tests include the 20-meter walk test [87], first at a self-selected pace and then at maximum pace, 30-second maximum number of chair to standing test [88], and 30-second maximum number of repeated unilateral knee bends [87, 89]. Other measurements, logged by the supervising therapist, are recordings of compliance of the exercise treatments during the 12-week intervention also including a recording of exercise dose (weights, sets, repetitions, and treatment time) at each treatment occasion. Over the whole project period, from inclusion to end of the 52-week follow-up, any adverse effects are to be noted and reported.

Statistical analysis

In the statistical analyses of both primary and secondary outcomes, the principle of intention to treat will be used, comparing high-dose MET with low-dose MET. Within-group and inter-group statistical testing will be carried out using mixed model analyses where an alpha level of 0.05 will be used where appropriate. Significance of main or interaction effects will be explored using follow-up post hoc tests.

Analysis of cost-effectiveness will be performed using the incremental cost-effectiveness ratio (ICER), in order to provide a single measure for weighing costs against benefits of health care interventions. Cost per quality-adjusted life year (QALYs [90]), using data from EQ-5D and SF-36, will be added. In the predictive analyses, multivariable logistic regressions (e.g. GEE) will be used to estimate the association between potential predictors and outcomes. A purposeful selection procedure is planned resulting in a final model that

contains only significant independent variables, identified confounders and interactions. All final models will be examined for goodness-of-fit and accuracy according to established methods.

Sample size

The power calculation was based on proportions that can document a minimal clinical important change (MCIC). The primary outcome the Osteoarthritis Outcome Score (KOOS) is a numerical scale ranging from 0 (maximal problem) to 100 (no problem). A change of 10 points is evaluated as a clinical interesting change [71]. The hypothesis is that 40% of the patients receiving high-dose MET and 20% of the patients receiving low-dose MET will obtain a 10-point improvement after end of treatment at the three-month follow-up. The power calculation showed that 82 patients are needed in each arm to reach 80% between-group power. With a hypothetical drop out of the study of 20% the total sample is 82x2x1.2=197 patients. We plan to include 200 patients giving each exercise intervention group a total of 100 participants.

ETHICS AND DISSEMINATION

The guidelines from the Helsinki declaration will be followed and the protocol has been reviewed by the Regional Ethics Review Board in Stockholm. Some relevant ethical considerations related to this study are mentioned below:

The infliction of pain

An often overlooked ethical issue is the infliction of pain when instructing patients to exercise [31]. Knee OA is commonly a painful condition and it is questionable if it is ethical to

push patients through the painful exercise regimens included in the approach that today is recommended for treating knee OA. A worst-case scenario for this type of treatment is pushing the patient into endurance behaviour which in itself may result in long-term pain [91]. However, in this study, the focus on grading the exercises pain free or close to pain free resolves, to some extent, this problem.

The problem of large exercise dosage

Asking patients to exercise for 70 to 90 minutes three times a week for 12 weeks may be ethically questionable. However, such doses of exercise therapy have been shown to be effective in patients with depression [41], and there is an argument today that both exercise dose and exercise intensity should be increased for patients suffering from heart disease or a metabolic syndrome, respectively [92]. The high compliance with a relatively extensive exercise programme is possible because patients with chronic (or progressed) conditions commonly prioritize rehabilitation to maintain (or improve) good functioning. Thus, it is a need to investigate if a similar high dose of exercise therapy is effective for patients with knee OA. It is also of high relevance to study whether a less time-consuming exercise programme, such as the low-dose MET in the present study, results in similar effects including effects on costs.

DISCUSSION

In an extensive review by Pedersen and Saltin [93], it was concluded that there is evidence for prescribing exercise as a therapy for 26 different chronic diseases. In addition, there is increasing evidence that a higher dose of exercise is more effective than a lower dose in patients with long-term subacromial pain [44] and long-term anterior knee pain [37, 38],

patients suffering from depression [94], and patients suffering from a metabolic syndrome [95]. A high dose of exercise has a greater effect on heart function [96] and a greater positive impact on mood states and quality of life [97] in patients suffering from heart failure.

In terms of knee OA, however, the evidence level of exercise dose is poor [93, 98]. [25, 26]. Juhl and colleagues [99] argue that an optimal exercise program for knee OA should focus on improving quadriceps strength and aerobic capacity, as well as improving performance in the lower extremities. Exercise programmes should be supervised and carried out three times a week. They also argue that there is a great need to further investigate the effects of differing exercise doses and that the interventions in such studies are described in detail with regard to intensity, length of program, total number of supervised sessions, duration of individual supervised sessions, and number of sessions per week.

To our knowledge, this study is the first to compare, in a controlled manner, if a higher dose of exercise therapy is superior in terms of improvements in function and pain to a lower dose of exercise therapy in patients with knee OA.

CONTRIBUTOR SHIP STATEMENT.

Torstensen TA, Grooten WJA, Østerås H, Heijne A,-Harms-Ringdahl K and Äng B, have all actively been participating planning and designing the study as well as the writing of this manuscript describing the research protocol of the study.

COMPETING INTERESTS

I have read and understood the BMJ Group policy on declaration of interests and declare the following interests:

Name: Tom Arild Torstensen, Date: 2017-06-30

Declaration of interests: Teaches courses and seminars in medical exercise therapy

Name: Grooten WJA, Date: 2017-06-30

Declaration of interests: None

Name: Østerås H, Date: 2017-06-30

Declaration of interests: None

Name: Heijne A, Date: 2017-06-30

Declaration of interests: None

Name: Harms-Ringdahl K, Date: 2017-06-30

Declaration of interests: None

Name: Äng BO, Date: 2017-06-30

Declaration of interests: None

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FIGURE CAPTIONS

Figure 1: The principle of de-loading: The theoretical basis for the principle of de-loading is that the weight from the pulley de-loads the weight of the lower leg with a decrease of the compressive forces between bony and cartilaginous structures. The de-loading also results in decreased pull and loading of muscles, tendons and other soft tissue, decreasing sensitization like mechanical/loading allodynia making it possible to exercise pain free or close to pain free.

Figure 2. Flow chart of the design and run of the study. HDMET= High-dose MET and LDMET= Low-dose MET.

Figure 3: Show the two different exercise interventions compared in this randomized trial, high dose MET (HDMET) versus low dose MET (LDMET).

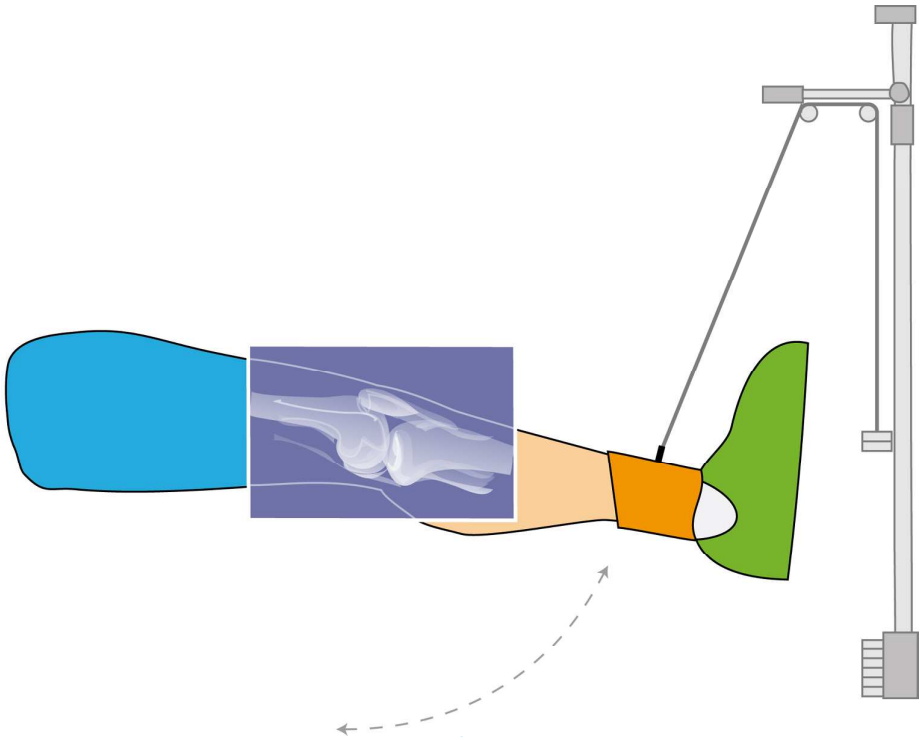


Figure 1: The principle of de-loading: *The theoretical basis for the principle of de-loading is that the weight from the pulley de-loads the weight of the lower leg with a decrease of the compressive forces between bony and cartilaginous structures. The de-loading also results in decreased pull and loading of muscles, tendons and other soft tissue, decreasing sensitization like mechanical/loading allodynia making it possible to exercise pain free or close to pain free.*

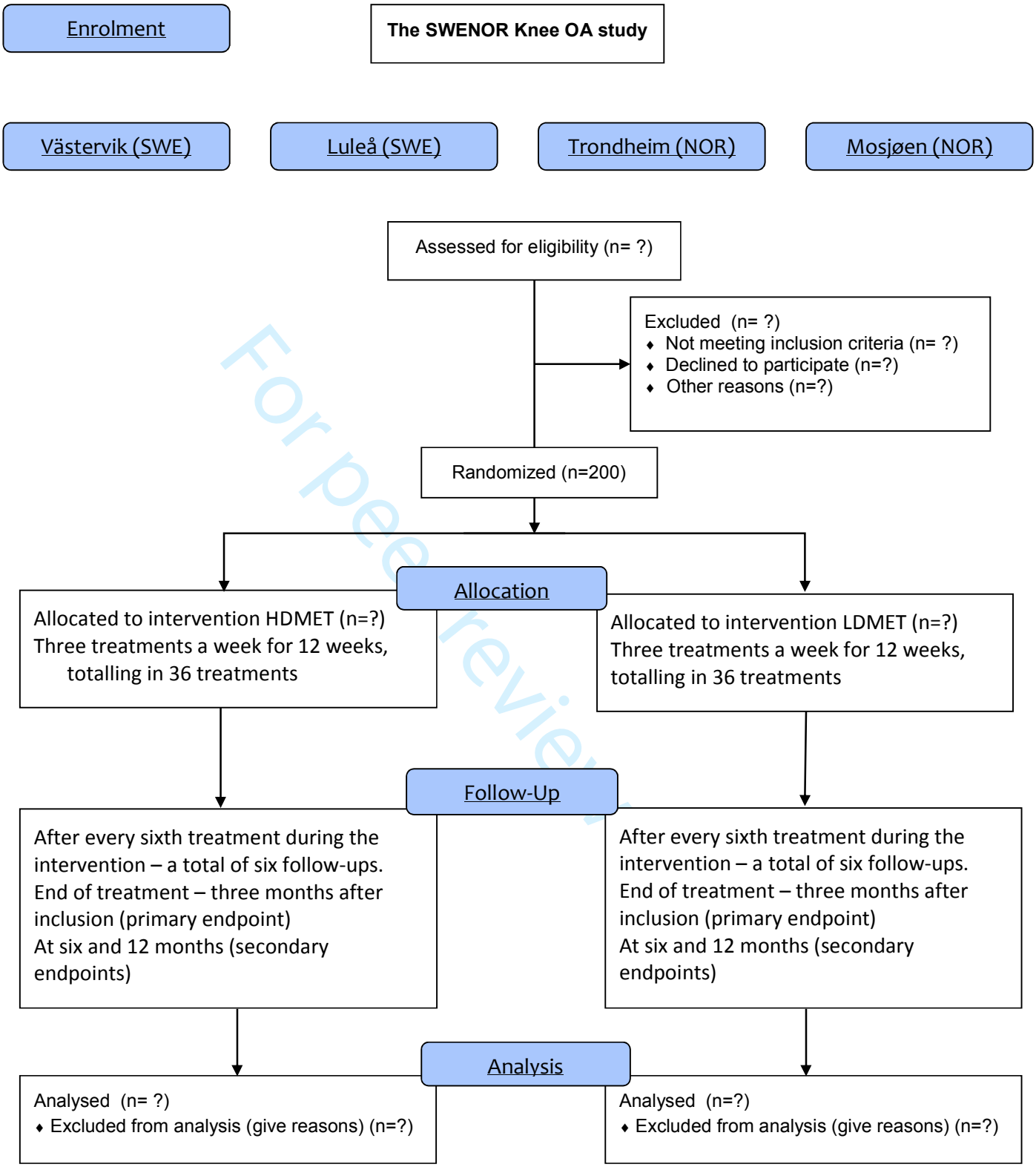


Figure 2. *Flow chart of the design and run of the study. HDMET= High-dose MET and LDMET= Low-dose MET.*

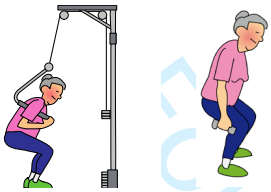
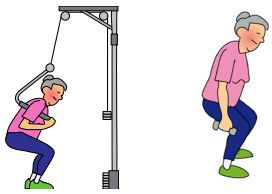
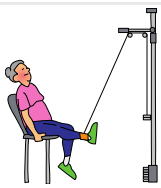
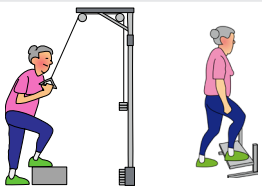
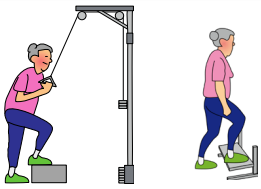
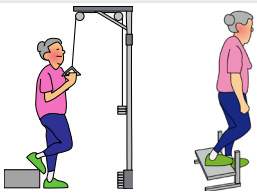
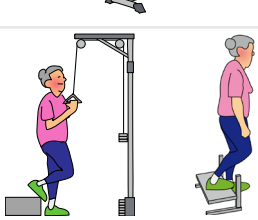
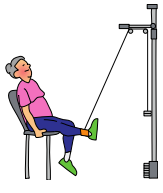
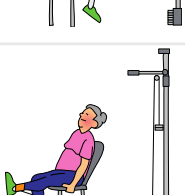
EXERCISE	HIGH DOSE MET (70-90 MIN)	DOSE	LOW DOSE MET (20-30 MIN)	DOSE
1		GLOBAL 20 min		GLOBAL 10 min
2		SEMI GLOBAL CLOSED CHAIN 3x30 reps		SEMI GLOBAL CLOSED CHAIN 2x10 reps
3		LOCAL OPEN CHAIN 5 min		SEMI GLOBAL CLOSED CHAIN 2x10 reps
4		SEMI GLOBAL CLOSED CHAIN 3x30 reps		SEMI GLOBAL CLOSED CHAIN 2x10 reps
5		GLOBAL 10 min		SEMI GLOBAL OPEN CHAIN 2x10 reps
6		SEMI GLOBAL CLOSED CHAIN 3x30 reps		
7		LOCAL OPEN CHAIN 5 min		
8		LOCAL OPEN CHAIN 3x30 reps		
9		GLOBAL 10 min		

Figure3. Show the two different exercise interventions compared in this randomized trial, high dose MET (HDMET) verus low dose MET (LDMET).

BMJ Open

Does exercise dose affect benefits in patients with long-term osteoarthritis of the knee? A study protocol of a randomized controlled trial in Sweden and Norway – the SWENOR study

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Complete List of Authors:	Torstensen, Tom Arild; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy Grooten, Wilhelmus; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Østerås, Håvard; Norwegian University of Science and Technology, Department of Neuromedicine and Movement Science Heijne, Annette; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Harms-Ringdahl, Karin; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Äng, Björn; Dalarna University, School of Education, Health and Social Sciences; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy
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Does exercise dose affect benefits in patients with long-term osteoarthritis of the knee? A study protocol of a randomized controlled trial in Sweden and Norway – the SWENOR study

Torstensen TA (1), Grooten WJA (1,2), Østerås H (3), Heijne A (1,2), Harms-Ringdahl K (1,2), Äng BO (1,4,5).

1) Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Huddinge, Sweden
2) Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy, Karolinska University Hospital, Stockholm, Sweden
3) Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway
4) School of Education, Health and Social Sciences, Dalarna University, Falun, Sweden
5) Center for Clinical Research Dalarna, Falun, Sweden

Corresponding author:
Tom Arild Torstensen
Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet

Alfred Nobels Allé 23 23100
141 83 Huddinge, Sweden

Tel: +46 707344102
E-mail: tom.torstensen@ki.se

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ABSTRACT

Introduction: Osteoarthritis (OA) of the knee is characterized by knee pain, disability, and degenerative changes, and places a burden on societies all over the world. Exercise therapy is an often-used modality, but there is little evidence of what type of exercise dose is the most effective, indicating a need for controlled studies of the effect of different dosages. Thus, the aim of this study described in this protocol is to evaluate the effects of high-dose versus low-dose medical exercise therapy (MET) in patients with knee OA.

Methods and analysis: This is a multicentre prospective randomized two-arm trial with blinded assessment and data analysis. We are planning to include 200 patients aged 45-85 years with a diagnosis of symptomatic (pain and decreased functioning) and X-ray verified diagnosis of knee OA. Those eligible for participation will be randomly allocated to either high-dose (n=100) or low-dose (n=100) MET. All patients receive three supervised treatments each week for twelve weeks, giving a total of 36 MET sessions. The high-dose group exercises for 80-90 min compared to 20-30 min in the low-dose group. The high-dose group not only exercises for a longer time, but also receives a greater number of exercises with more repetitions and sets. Background and outcome variables are recorded at inclusion, and outcome measures are collected after every sixth treatment, at end of treatment, and at six- and twelve-month follow-ups. Primary outcome is self-rated knee functioning and pain using the Knee Injury and Osteoarthritis Outcome Score (KOOS). The primary endpoint is at the end of treatment after three months, and secondary endpoints are at six and twelve months after end of treatment.

Ethics and dissemination: This project has been approved by the Regional Research Ethics Committees in Stockholm, Sweden, and in Norway. Our results will be submitted to peer-reviewed journals and presented at national and international conferences.

Trial Registration number: (ClinicalTrials.gov NCT02024126)

Strengths and limitations of this study

- To the best of our knowledge, this is the first multicentre study, with a bio-psycho-social view of pain, prospectively, comparing the effectiveness of two defined doses of pain-free or close to pain-free exercise therapies in patients with symptomatic knee osteoarthritis.
- The proposed project includes a relatively large sample where outcomes are evaluated both during the twelve-week intervention period, at the end of treatment, and at six and twelve months, respectively.
- The project uses both subjective and objective data, and includes analyses of cost-effectiveness and early predictors for a follow-up clinical outcome.
- Even though the different components of the exercise programmes are well described, one limitation could be possible confounders related to the exercise dose given.

MAIN TEXT

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and is a major worldwide health problem causing illness and disability [1, 2]. The burden to society caused by knee OA is substantial [3]. The knee joint is most frequently affected, which commonly results in chronic joint pain, knee stiffness, decreased functioning, reduced quality of life, and sick leave [4]. The associated costs of osteoarthritis are estimated to range between 1-2.5% of the gross national product as calculated in six industrialized countries (Sweden, Australia, Canada, France, UK, and US) [5].

The prevalence of knee OA has increased during the last 20 years [1] and is expected to continue to increase [6]. Murphy et al. [7] reported that almost half of US adults will have symptomatic knee OA by the age of 85, with the highest risk being among obese individuals. There is a sex difference, where the prevalence is estimated to be 40% in women and 30% in men in people aged 65-75 years [8]. Although knee OA is known to be more common in older age groups, the increasing global prevalence of obesity is anticipated to elevate the prevalence of knee OA in younger people [9]. Currently, knee OA in younger people is most often secondary to congenital disorders or sporting injuries and other traumas to the knee [10, 11].

Traditionally, knee OA has been defined as a pathological condition characterized by focal areas of loss of articular cartilage within the synovial joints, associated with hypertrophy of the bone (osteophytes and sub-chondral bone sclerosis) and thickening of the capsule [12]. The mechanisms of knee OA-related pain are, however, complex [13] particularly in chronic pain conditions where pain experience is nowadays believed to be more a result of changes in the nervous system than in tissue structures [14], which somehow reflects a paradigm shift in the understanding of the pathology of pain related to knee OA. Because of the plasticity of the nervous system, pain lowers the threshold level of the nociceptive receptor system [15], making it more sensitive to stimuli during normal movements like walking and bending – so-called mechanical or loading allodynia. These changes occur in the peripheral receptor system located in the knee and in the receptor system in the spinal cord resulting in changes in the nervous system, i.e. peripheral and central sensitization [16]. The rationale for this theory is that the problem lies more in the nervous system than in the knee and may

partly explain why there are poor correlations between structural degenerative changes of the knee, and pain, and functioning [17, 18].

The level of pain caused by these sensitization processes is also affected by psychological factors such as anxiety and depression, which cause increased nociceptive input that increases the pain experience [19, 20]. When pain becomes more persistent and does not resolve, the person can develop negative attitudes and beliefs [20-22] that are closely linked to catastrophizing and anxiety. This may result in further sensitization with long-term pain [19, 23, 24]. Shifting our understanding of pain-related knee OA from exclusively involving changes in tissue structures to involving changes in the nervous system is - we believe - an important paradigm shift for not only a better understanding of what knee OA is, but also for improved optimal treatment designs including exercise therapy which is a frequently used modality in treating knee OA.

In a systematic review, it was concluded that there exists high-level evidence that land-based therapeutic exercise provides short-term effects on pain relief, and that there is a moderate quality evidence regarding improvement in physical functioning among patients with knee OA [25]. Despite this, several questions remain unanswered, particularly regarding dose, intensity, and duration of the exercise therapy applied [26]. These unanswered questions may be one of the reasons why we see a large variation in treatment effects observed across studies making it difficult to conclude what is the optimal dose when delivering exercise therapy [25, 26]. The exercises vary from neuromuscular exercise [27], knee joint stabilization exercises [28], strengthening exercises [29], and endurance exercises [30]. These forms of exercise therapy do not necessarily take into consideration the theories

of local and central sensitization, thus opening up for new exercise therapies, where the goal is modulation of pain decreasing local and central sensitizations. The knowledge that pain and swelling inhibits motor output, decreases range of motion, and changes coordination [31] and that a traditional strengthening exercise program can cause adverse effects [32], questions the use of strengthening exercises. In their review [32], Liu et al. concluded that out of 121 trials, 53 had no comments about adverse events, 25 reported no adverse events, and 43 trials reported adverse events. The majority of the adverse events from the strength training were muscle strain and joint pain and more adverse events were reported when performing high intensity strength training. There was also a higher degree of these complications in trials recruiting elderly participants with health conditions and functional limitations. Liu et al. [32] also argue that adverse events may be underreported due to the lack of consensus on their definition. Another factor for underreporting could be a general attitude that increased pain due to strength training is expected and normal, and that patients should endure that. In a recent systematic review of randomized trials on the role of muscle strengthening exercise therapy in knee OA [33], the authors conclude that strength training provides superior outcomes in knee extensor strength but not in terms of pain and disability. In this context there is increasing evidence [34] that exercise therapy should focus more on treating the causality of pain-related knee OA such as peripheral and central sensitization [14] and pain-related bodily and psychological changes [19] from a biopsychosocial perspective [35, 36] rather than an impairment like muscle strength. This view is supported by research showing that pain-related fear is more disabling than pain itself [37]. To break the vicious circle of long-term knee pain, we believe it is important to see beyond the knee [14], beyond an impairment such as muscle strength [33], using a biopsychosocial sensitization model of pain [36].

Medical Exercise Therapy

Medical Exercise Therapy (MET) was developed in Norway more that 50 years ago and is an established treatment in the Nordic countries, other parts of Europe, and North America [36, 38, 39]. MET focuses on applying the optimal dose of exercise; i.e combining global aerobic exercises with semiglobal and local joint exercises, where the goal is to apply 70 to 90 minutes of active dynamic exercise therapy [38, 40-48] . Using the principle of self-paced exercises [49] the patient is to perform more than 1000 pain-free or close to pain-free repetitions per MET-session [38, 40-48] . Even though the optimal dose goal of MET is high, the treatment usually starts with a low dose lasting 15 to 20 minutes mirroring the ability of the patient within a biopsychosocial context [35, 36], starting with an acceptable baseline where the patient manages the exercise therapy [36, 38].

The theoretical basis for MET differs from most other forms of exercise therapy in that MET focuses on decreasing the pain experience and the bodily and psychological reactions to the pain experience [36] by applying an exercise time lasting from 15 to 90 minutes [36]. The goal is to reach 70 to 90 minutes of graded exercise that, over the course of the intervention period, results in a decerase in pain and improvement in functioning. Possible physiological mechanisms for achieving this are an activation of the descending pain inhibiting system [50, 51], achieving spinal and cortical inhibition of nociceptive input and decreasing low inflammatory processes [52-54], inflammatory processes which are believed to contribute to sensitization [55, 56]. The goal of MET is hence to modulate the pain experience and decrease sensitization like allodynia and hyperalgesia [34, 57], increase range of motion, and improve functioning [46], resulting in improved muscle strength [46].

The practical application of MET protocols also differs from most other forms of exercise therapies due to MET mixing global, semiglobal, and local exercises. Global exercises are exercises that activate the whole body exercising the trunk aswell as upper and lower extremities, a semiglobal exercise activates muscles, joints and other structures in an extremity and a local exercise activates one joint and the muscles acting on it. Sessions of global exercises are performed several times during one treatment occasion, where the goal is to substantially increase the heart rate activating the endocrine and pain modulating systems of the body, i.e. the descending pain inhibiting system, achieving cortical and spinal inhibition of nociceptive input. Semiglobal and local exercises are performed for the same purpose, however, they are performed in sets of three where each set consists of 30 repetitions. A local exercise can also be performed continuously for 3 to 5 minutes as one set, for example deloaded knee extension, see Figure 1.

[Figure 1 about here].

The principle of deloading also makes MET different from most other forms of exercise therapies. To achieve deloading, the weight stack from different pulley apparatus is used to deload a part of the body or the whole body, resulting in less joint forces in the knee joint, making it easier to perform a high volume of repetitions pain-free or close to pain-free. Deloaded squatting is performed using a deloading frame attached to a latissimus pulley (lat.pulley), exercise number, two high dose MET, see Figure two. Deloaded step up and step down exercises are performed using a handle attached to the lat.pulley, exercises number four and six high dose MET, see Figure two. Compared to walking and running, stationary cycling is also viewed as a form of deloading where the compressive forces in the knee are lower compared to weight bearing activities, exercise one, five and nine high dose MET, see Figure two.

The theoretical basis for the principle of the de-loading is that the weight from the pulley deloads the weight of the lower leg with a decrease in the compressive forces between bony and cartilaginous structures. The deloading also results in decreased pull and loading of muscles, tendons, and other soft tissue, decreasing sensitization including mechanical/loading allodynia, making it possible to exercise pain-free or close to pain-free. The goals of local knee exercises are both biological and psychological. Biologically, the exercises aim to increase the local circulation, stimulating mechanoreceptors activating the muscles and collagen tissue in the knee, which could result in pain modulation and an anti-inflammatory effect. Psychologically, the patient is instructed to exercise the part of the body, in this case the knee, that is painful and a reason for anxiety and fear of movement. The goal of the local exercise is therefore for the person to "regain the knee" as a part of the body resulting in a decrease of negative psychological factors.

[Figure 2 about here].

MET has been evaluated in several clinical trials, and has been shown to be effective, both in the short and long term, in patients with long-term low back pain with or without sciatica [39], subacromial pain [46-48], and long-term anterior knee pain [40, 41]. In these latter studies, an exercise dose lasting 70 to 90 minutes has been more favourable than an exercise dose lasting 20 to 30 minutes. In a narrative review, Lorås et al., 2015 [36], included four RCTs on the effectiveness of high-dose MET, concluding that high-dose MET was positive and promising. However, to be able to draw any firm conclusions about the efficacy of MET for patients with knee OA, rigorous trials are needed on the effect of MET in this major patient group [58]. Effect trials of cost-effectiveness are also needed as they are presently lacking in the scientific literature, and the present project has the potential to fill

this knowledge gap. It is also important to point out that no exercise protocol is suited to all patients, and as knowledge of early predictors of poor treatment outcomes obtained from longitudinal data is sparse, the development of patient-customized treatments is hindered [59]. According to the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) as well as a recent review [60], prediction studies are needed to be able to better individualize the treatment and match the most promising treatment option to a certain patient profile in order to maximize treatment outcomes and minimize costs. Therefore, we plan to conduct an RCT post-hoc prediction study to gain insights into which patient characteristics predict treatment outcome and which patients benefit more or less from exercise treatments.

In this trial, the rationale for comparing high dose MET (70-90 minutes) versus low dose MET (20-30 minutes) is that high dose MET should be more effective through an increased activation of the pain modulation systems like the descending pain inhibiting system [51]. The evidence is that exercise-induced hypoalgesia is obtained through higher and more intensive exercise doses of 70% of HRR activating the pain modulating systems and decreasing the sensation of pain [61]. However, it has also been shown that an exercise intensity of 50% of HRR is capable of producing an analgesic effect in healthy adults [62], similar exercise intensities used in both high and low dose MET. This could have important implications for the use of exercise in the management of pain, particularly in deconditioned individuals (e.g., older adults with OA of the knee). In 2008 it was shown for the first time that an endurance activity lasting two hours resulted in the production of endogenous neuropeptides (endorphins), creating chemical reactions in brain areas involved in cognitive function and pain modulation, primarily in the prefrontal cortices, insula, and the limbic

system [63]. The rationale is that high dose MET exercising for 70 to 90 minutes should result in an increased production of endogenous neuropeptides in the spinal cord, the brain stem, and in the brain, compared to a lower dose MET exercising 20-30 minutes. The hypothesis is that this should result in less pain and improved functioning in favour of the high dose MET therapy.

AIM OF THE STUDY

The aim of this project is to prospectively evaluate short- and long-term effects of high-dose MET compared to low-dose MET in patients with X-ray verified knee OA regarding pain, functioning, and cost-effectiveness. A further aim is to conduct a post-hoc analysis on early prognostic factors that predict short- and long-term follow-up outcomes, by targeting patients' early status and patient adherence to the intervention. The long-term goal is to further develop and implement updated knowledge into knee OA rehabilitation to meet the challenge of tomorrow's patients with knee OA pain.

1. What is the effect of high-dose MET compared to a low-dose exercise therapy (low-dose MET) with respect to self-rated pain, functional limitations, health-related quality of life, depression, and anxiety?
2. What is the effect of high-dose MET compared to low-dose MET on objective performance measures such as physical functioning of a 20-metre walk, sit to stand, and single knee bends, and pain threshold as determined by a pain-matcher instrument?
3. What is the cost-effectiveness of MET in patients with knee OA with respect to costs against potential effects (incremental cost-effectiveness ratio, ICER), and cost per quality-adjusted life year (QALY)?

4. Which patient characteristics (demographic or disease-related) predict long-term treatment outcomes with a focus on pain, functional limitation, and health-related quality of life? What important interaction effects between patient characteristics and exercise dose may predict treatment outcomes?

MATERIAL AND METHODS

Study design

This is a phase three superiority trial of high dose MET versus low dose MET. The trial is blinded regarding outcome assessment and analyses. It is a two-arm multicentre trial of a twelve-week exercise intervention with a twelve-month follow-up. Measurements will be taken at baseline and during the treatment at two weeks (six treatments), four weeks (12 treatments), six weeks (18 treatments), eight weeks (24 treatments), ten weeks (30 treatments), twelve weeks (36 treatments), which is end of treatment, and at follow-up at 26, and 52 weeks after end of treatment. Primary endpoint is at end of treatment. Secondary endpoints are at the 26 and 52 weeks follow-up. The study will conform to CONSORT guidelines for reporting parallel, randomised trials [64], see Figure 2.

[Figure 3 about here]

Participants

We are planning to include 200 patients with a diagnosis of symptomatic and radiographic knee OA who will be recruited from primary and secondary health care settings in Luleå and Västervik in Sweden, and in Trondheim and Mosjøen in Norway, named the SWENOR knee OA study.

Inclusion criteria:

Subjects aged 45-85 years, living in the defined geographic areas (Västervik and Luleå municipalities in Sweden, and Trondheim and Mosjøen in Norway), who have had a diagnosis of symptomatic and radiographic verified osteoarthritis grade I-III according to Kellgren and Lawrence [65, 66], with at least three months pain duration, and decreased functioning. The patient is willing to participate in a twelve-week intervention period with three sessions each week

Exclusion criteria:

Physiotherapy or other conservative therapy during the previous three months or a history of major knee trauma such as knee fractures or ligament ruptures. Inflammatory joint disease, hip symptoms more aggravating than the knee symptoms, scheduled to have knee replacement surgery within six months, and co-morbidities not allowing exercise such as cardiovascular, respiratory, systemic, or metabolic conditions limiting exercise tolerance.

Procedure

Before intervention starts, regular visits will be made to each intervention place by the first author (TAT), informing and communicating with the local research team about the aims and run of the study. Detailed description of the different stages of the study from recruitment, treatment, and follow-up assessments after the end of the intervention period will be instructed and discussed. Physiotherapists in charge of the objective clinical testing (two in Västervik, one in Luleå, two in Trondheim and two in Mosjøen), otherwise not involved in the treatment, will be educated theoretically and practically on how these tests should be performed. The physiotherapists delivering the exercise intervention (two in Västervik, one in Luleå, two in Trondheim and two in Mosjøen) will, in addition, have structured theoretical

and practical sessions on how to apply and grade the exercise therapies. A study nurse at each intervention place is in charge of randomization, questionnaires, and the scheduling of patients for treatments and assessments. Each of the four intervention centres has a local administration officer.

A data security monitoring plan is conducted by the current investigator monitoring the present pragmatic trial. Tom Arild Torstensen (TAT) will visit the four centres from the planning phase of the trial, during the treatment phase, and during the follow up phase in order to monitor that the protocol is followed. Adverse and SAEs are reported to the ethics committee.

Recruitment will be achieved through referrals from medical doctors in primary and secondary health care clinics. The local investigator at each study centre will contact medical doctors (MDs) and send written information about the study. The first screening is performed by a MD and a second screening is performed by one of the treating physiotherapists. Both the MD and the physiotherapist guarantee the radiographic inclusion criteria.

Patients will receive oral and written information about the study, and after signing an informed consent form, they will be assessed for eligibility by physiotherapists at each intervention centre. Participants initially fill out questionnaires for baseline data and perform the physical performance tests. Each patient is then randomized, as described below, to either high or low dose medical exercise therapy.

Data collection and management.

Data from the questionnaires will be depersonalised at each intervention centre by the local research assistant. In order to transfer data from Norway to Sweden, a data transfer agreement (DTA) between Norges Teknisk-Naturvitenskapelige Universitet (NTNU)/Norwegian University of Science and Technology and Karolinska Institutet, (KI/NVS), has been set up. The questionnaires from the Swedish centres are posted to Karolinska Institutet where data is registered on digital sheets. In Norway, questionnaires from Mosjøen are posted to Trondheim where all questionnaires from the two Norwegian centres are registered on sheets and delivered to Karolinska Institutet according to DTA; Tom Arild Torstensen, Björn Äng, and Wilhelmus Grooten are in charge of the data synthesis and analysis

Post-recruitment retention and compliance strategies

Our experiences of MET as an experimental intervention (HØ and TAT) [38, 40-48] leads to the following retention and compliance strategies to be applied in this study.

- An independent study nurse at each intervention centre will always be available to answer questions when patients are filling out the questionnaires
- This is important to avoid any unnecessary misunderstandings regarding the content of the questionnaire and to make sure that patients understand that all information will be depersonalized.
- During the interventions, the treating physiotherapist is present the whole time in the exercise room answering questions from patients and re-grading the exercises according to changes in patients' exercise status and knee-OA symptoms. Participants are not informed about the hypothesis of the study.

- At inclusion and at the end of the 12-week intervention period the patient is informed by the local administration nurse about the six- and 12-month follow-ups.
- During the post-intervention follow-ups, the patient will be contacted three weeks prior to the assessment and informed when to come to the intervention site for the planned post treatment evaluation.

During the intervention period, KOOS and the eight different VAS scales are assessed after every sixth treatment meaning after two-, four,- six,- eight-, ten,- and 12 weeks giving a total of six assessments. The purpose of such repeated measurements is to obtain a reasonable measurement accuracy of both functioning status and pain during the twelve-week intervention period. The primary end-point will be on completion of the intervention after 36 treatments, which will take an average of twelve weeks. This is to obtain evaluation of effects on organized exercise therapy related with its direct implementation, while further follow-ups evaluate its retention effects. At this point primary and secondary outcomes are assessed.

Randomization procedure

In this individual randomized trial, a stratified allocation by age and intervention centre is used, using a computerized program, where the goal is to get an equal number of patients between the ages of 45 and 64 years and 65 and 85 years at each of the four intervention centres. The randomization key is concealed at each intervention place and kept under lock by a research assistant not involved with the assessment or interventions.

Blinding procedures

The physiotherapists conducting the physical performance tests are blinded to an allocation group and the study participants are instructed by the treating physiotherapists not to reveal details of their intervention during testing. The principal investigators (BÄ), the assistant principal investigator (TAT), and the research assistants are also blinded to groups when entering data to data-sheets, i.e. they do not know which patient has received high-dose or low-dose MET. The group key will be opened after the analyses have been finalised and the results have been written up in a manuscript (using intervention A and B until results have been written).

Interventions

All participants receive an MET intervention, where they are treated in groups of four or five in sessions lasting 20 to 90 minutes. During the sessions, they are supervised by an experienced physiotherapist in an outpatient clinic. All participants are treated three times a week for twelve weeks, giving a total of 36 treatments. Each patient in the group has an individualized exercise program tailored to their specific clinical symptoms and functional level. As the treatment proceeds, exercises are adapted according to changes in symptoms and functioning. The pain experience when exercising should not exceed a three on a zero to ten scale, where zero is no pain and ten is the worst imaginable pain [34]. Specially designed exercise equipment consisting of different forms of pulleys, exercise benches, dumbbells, and barbells is used to grade and dose the exercises to be pain free or close to pain free, with the purpose of mitigating peripheral and central sensitization while exercising [36]. The difference between groups regarding exercise dose is outlined below in Table 1.

Table 1: *Differences between the high-dose and low-dose MET* regarding *number of exercises, sets, and repetitions. Difference in time, performing global exercises and total time duration for each treatment.*

	Number of exercises	***Number of sets***	***Number of repetitions***	***Time performing global exercise***	***Time duration of treatment***
High dose MET	*9*	*3*	*30*	*20 min+10 min +10 min*	*70-90 min*
Low dose MET	*5*	*2*	*10*	*10 min*	*20-30 min*

The grading of the exercises, including baseline settings, is based on the initial clinical assessment by the treating physiotherapist. From the patients' past and present histories and physical clinical assessment, information is gained about the level of pain and possible sensitization (local versus central sensitization), range of motion, and tolerance for weight bearing within the available range of motion of the knee. This information is used for baseline setting of the exercises where the physiotherapist chooses a starting position, a rage of motion, and a weight resistance believed to match the patient´s ability to perform three sets of 30 repetitions (high dose MET) and two sets of ten repetitions (low dose MET), pain-free or close to pain-free. Then there is a test of each exercise where the physiotherapist asks the patient to do as many repetitions as the patient can manage. When the patient reaches ten repetitions the test is stopped and the patient has to evaluate if the weight/loading (L), starting position (SP), or range of motion (ROM) is appropriate to reach a total of 40 repetitions. Any of the above mentioned variables (L, SP, ROM), can be changed to reach 40 repetitions, making it possible to perform 30 repetitions in sets of three with a 30- to 60-second pause between each. The same test procedure is used for the low dose

group where the goal is a test of 15 repetitions making it possible to do two sets of 10 repetitions. At baseline setting, there is a continuous evaluation in the exercise room where the physiotherapist and the patient is working towards optimal exercise dose for each exercise, as is usually done in clinical practice [36]

It should also be possible for the patient to perform the exercise comfortably within the preferred active range of active motion (AROM). For example, if a part of the AROM in the knee joint is painful, the patient starts to exercise within the pain-free or close to pain-free AROM. As the treatment proceeds, the AROM is adjusted, making the patient exercising in a larger and more functional AROM. If it is not possible to grade the exercise pain-free or close to pain-free, the patient is allowed to exercise with pain. When exercising with pain it is important that the pain experience dose not cause any anxiety or fear. The pain has to be experienced as meaningful for improvement [67]. If the exercise therapy results in an acute increase in pain, the pain should have returned to baseline before the next treatment session commences. If pain does not go back to the prior level, exercises are reassessed, with the most comfortable exercise performed several times, preferably deloaded knee extension and stationary. The group of four to five patients also contains patients with other diagnoses, who are not participating in this study, making the delivery of the MET intervention pragmatically similar to a real life situation. To be able to monitor the exercise dose, the treating physiotherapists follow a structured progression plan of the exercises, and fill in a treatment log for each patient at each treatment, see appendix number one – progression plan for high dose MET, and appendix number two – progression plan for low dose MET. The log contains information about the number of exercises, duration of each global exercise, number of repetitions, and sets and weight resistance applied for semiglobal

and local exercises. Figure two shows the main exercises from the two different exercise interventions compared in this planned randomized trial: high dose MET versus low dose MET.

[Figure 2 about here]

To be able to reach a high number of repetitions despite on-going pain, the principle of de-loading is applied, facilitating a high number of repetitions that are nearly or entirely pain free, see figure 1. For the high-dose MET, the deloaded knee extension is performed twice during a treatment, each time for a five-minute duration. This exercise and the cycling in the middle of each treatment session is a form of restitution, making it easier to both perform the deloaded closed chain exercises and endure the high dose MET. Later, as the patient improves and can tolerate increased loading, the exercises are adapted to be more functional, using closed chain exercises without deloading the body weight.

To further increase the exercise dose for the high dose MET group patients perform one home exercise - the seated deloaded knee extension with a yellow tube theraband. The exercise is similar to exercise number three, see Figure two. They perform this home exercise once every day, where the dose is three lots of three minutes with a 30- to 60-second pause between each set. The treating physiotherapists make sure that the patients are compliant in doing their home exercises. Patients in the low dose MET receive no home exercises.

Baseline data

The following data will be obtained by questionnaire; gender, age, height, weight, physical activity and exercise levels, living arrangement, education level, employment status,

Table 2. *Study measures to be collected*

Baseline measures and outcomes	Description and instrument	Data source	Collection points
Patient´s characteristics	Date of birth, gender, BMI (height, weight) social and living status, leisure activities, level of physical activity, smoking, medicine, sleep, co-morbidities, anxiety and depression, catastrophizing, life satisfaction, kinesiophobia	SAQ	t0
Primary outcome measure	**Clinical Outcomes**		
Pain	KOOS: subscale pain	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Other symptoms	KOOS: subscale other symptoms	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Function	KOOS: subscale physical functioning	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Sport, recreation	KOOS: subscale sport and recreation	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Secondary outcome measures	**Clinical Outcomes**		
	VAS (100mm scale): pain	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100mm scale): knee pain not loading	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100 mm scale): pain at weight bearing	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100 mm scale): knee pain at night	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	Physical functioning		
	20 m walk test	PT	t0, t12
	Chair stand test	PT	t0, t12
	Unilateral knee bending	PT	t0, t12
	Pain threshold and tolerance		
	Pain Matcher Pain matcher apparatus		t0, t12
	Quality of life		
	(EQ-5D-5L)	SAQ	t0, t12, t26, t52
	(SF-36)	SAQ	t0, t12, t26, t52
	Life satisfaction		
	Life Satisfaction Questionnaire (LISAT)	SAQ	t0, t12, t26, t52
	Psychological outcomes		
	Anxiety and depression (HAD),	SAQ	t0, t12, t26, t52
	Catastrophizing (Pain Catastrophizing Scale)	SAQ	t0, t12, t26, t52
	Kinesiophobia (TSK)	SAQ	t0, t12, t26, t52
	Beliefs and attitude towards exercise		
	Self-efficacy for exercise (SEE)	SAQ	t0, t12, t26, t52
	Outcome Expectancy for Exercise Scale (OEE	SAQ	t0, t12, t26, t52

Data source: Self-administered questionnaire (SAQ), physical testing (PT). Collection points: t0=inclusion, t1-t12= measurement every second week during the 12 week intervention period, t1=2 weeks, t2= 4 weeks, t3= 6 weeks, t4= 8 weeks, t5= 10 weeks, t6= 12 weeks (end of inclusion), t26= 6 months follow up, t52= 12 months follow up. Questionnaires: The Knee Injury and Osteoarthritis Scale (KOOS), Life Satisfaction Questionnaire (LISAT), Hospital Anxiety and Depression Scale (HAD), Pain Catastrophizing Scale (PCS), Tampa Scale of Kinesiophobia (TSK), Self-efficacy for exercise (SEE) and Outcome Expectancy for Exercise Scale (OEE)

possible medication, co-morbidities, smoking habits, sleeping habits, pain and function of the knee, catastrophizing thoughts, fear avoidance beliefs, level of anxiety and depression, life satisfaction and quality of life, and beliefs about exercise. A schematic presentation of the outcome measures recorded at baseline and at the follow-ups is presented in Table 2. Each assessment, which involves filling out questionnaires, will take approximately one hour. The objective testing of the knee and the testing with the PainMatcher apparatus takes approximately 30 minutes and will occur the following day.

Primary outcome measures

In accordance with international consensus regarding the core set of outcome measures for clinical trials in OA [68], self-rated functioning and pain scoring (The Knee Injury and Osteoarthritis Outcome Score, KOOS) [69-72] is used as primary outcome measures. KOOS consists of 5 subscales; Pain, other Symptoms, Functioning in daily living (ADL), Functioning in sport and recreation (Sport/Rec), and knee-related Quality of life (QOL). Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. For the purpose of an RCT, KOOS subscale scores can be aggregated and averaged as the primary outcome. We are planning to use KOOS at several time-points; at baseline, and during the intervention period until the final follow-up at 52 weeks, see Table 2.

Secondary outcome measures

As a secondary outcome measure, there are eight different pain measurements using a 100 mm visual analogue scale (VAS) [73], with terminal descriptors of “no pain” and “worst pain”

asking about how painful the knee is, 1) today and 2) on average during the last week, related to the following four different life situations; 1) how painful is your knee, 2) how painful is your knee when loading your knee (e.g. walking or standing), 3) how painful is your knee when not loading your knee (e.g. sitting, lying), 4) how painful is your knee at night when you are sleeping (e.g. knee pain that disturbs your sleep).

Data on health related to quality of life are collected using the EQ 5-D questionnaire [74] and the SF-36 questionnaire [75]. These questionnaires will also be used to perform a health economic evaluation of the exercise interventions. Psychological factors such as anxiety and depression, catastrophizing, and fear-avoidance beliefs are believed to both predict outcome of an intervention [76] as well as influence the level of pain in patients with knee OA experience [77]. In this study, anxiety and depression are rated using the Hospital Anxiety and Depression Scale (HAD) [78], catastrophizing is rated using the Pain Catastrophizing Scale (PCS) [79], and fear avoidance beliefs [80] are rated using the Tampa Scale of Kinesiophobia (TSK) [81], see Table 2. Life satisfaction is assessed using the Life Satisfaction (LISAT) questionnaire by Fugl-Meyer [82]. Beliefs and attitudes towards exercise are rated using the Self-Efficacy for Exercise Scale (SEE) [83], and the patient's expectations of performing physical activity are rated using the Outcome Expectations for Exercise Scale (OEE) [84]. PainMatcher apparatus [85] (Cefar Medical AB, Lund, Sweden) is used to record sensory level, pain level, and pain tolerance level. Pressing the thumb and first finger against a button on each side of the hand held PainMatcher apparatus; an electrode under each button activates an electrical current. As long as the pressure is kept against the buttons, the electrical current will slowly increase where the first sensation of the current is a measurement of sensory threshold. As the pressure is maintained, the electrical current slowly increases, and the sensation will turn into a pain sensation (pain threshold). Keeping

the pressure on the buttons, the painful electrical current increases, and pain tolerance is recorded, i.e. the measure of how much painful electrical current the patient can endure. Performance tests include the 20-meter walk test [86], first at a self-selected pace and then at maximum pace, 30-second maximum number of chair to standing test [87], and 30-second maximum number of repeated unilateral knee bends [86, 88]. Other measurements, logged by the supervising therapist, are recordings of compliance of the exercise treatments during the twelve-week intervention also including a recording of exercise dose (weights, sets, repetitions, and treatment time) at each treatment occasion. Over the whole project period, from inclusion to end of the 52-week follow-up, any adverse effects are to be noted and reported.

Statistical analysis

In the statistical analyses of both primary and secondary outcomes, the principle of intention to treat will be used, comparing high-dose MET with low-dose MET. Within-group and inter-group statistical testing will be carried out using general linear model where an alpha level of 0.05 will be used where appropriate. Significance of main or interaction effects will be explored using follow-up post hoc tests. Effect size Cohen´s d will aid clinical interpretation of the magnitude of treatment effect, where effect-size values below 0.2 will be considered small, 0.5 medium, and 0.8 large. The primary end-point is at the end of the twelve-week intervention period and potential baseline differences will be considered by adding additional baseline variables as covariates to the statistical models. Potential floor or ceiling effects will be computed and considered in our analyses. Because participants of both interventions of both intervention groups are treated together with other patients in MET groups, the treatment credibility and outcome expectations (OEE) will be evaluated as a

potential co-variate or confounder for treatment effects.

Analysis of cost-effectiveness will be performed using the incremental cost-effectiveness ratio (ICER), in order to provide a single measure for weighing costs against benefits of health care interventions. Cost per quality-adjusted life year (QALYs [89]), using data from EQ-5D and SF-36, will be added. In the predictive analyses, multivariable logistic regressions (e.g. GEE) will be used to estimate the association between potential predictors and outcomes. A purposeful selection procedure is planned resulting in a final model that contains only significant independent variables, identified confounders and interactions. All final models will be examined for goodness-of-fit and accuracy according to established methods.

Sample size

The power calculation was based on proportions that can document a minimal clinical important change (MCIC). The primary outcome the Osteoarthritis Outcome Score (KOOS) is a numerical scale ranging from 0 (makimal problem) to 100 (no problem). A change of ten points is evaluated as a clinically interesting change [70]. The hypothesis is that 40% of the patients receiving high-dose MET and 20% of the patients receiving low-dose MET will obtain a ten-point improvement after end of treatment at the three-month follow-up. The power calculation showed that 82 patients are needed in each arm to reach 80% between-group power. With a hypothetical drop out of the study of 20% the total sample is 82x2x1.2=197 patients. We plan to include 200 patients giving each exercise intervention group a total of 100 participants.

ETHICS AND DISSEMINATION

The guidelines from the Helsinki declaration will be followed and the protocol has been reviewed by the Regional Ethics Review Board in Stockholm. Some relevant ethical considerations related to this study are mentioned below:

The infliction of pain

An often overlooked ethical issue is the infliction of pain when instructing patients to exercise [32]. Knee OA is commonly a painful condition and it is questionable if it is ethical to push patients through the painful exercise regimens included in the approach that today is recommended for treating knee OA. A worst-case scenario for this type of treatment is pushing the patient into endurance behaviour that in itself may result in long-term pain [90]. However, in this study, the focus on grading the exercises pain free or close to pain free resolves, to some extent, this problem.

The problem of large exercise dosage

Asking patients to exercise for 70 to 90 minutes three times a week for twelve weeks may be ethically questionable. However, such doses of exercise therapy have been shown to be effective in patients with depression [91] and there is an argument today that both exercise dose and exercise intensity should be increased for patients suffering from heart disease or a metabolic syndrome, respectively [92]. The high compliance with a relatively extensive exercise programme is possible because patients with chronic (or progressed) conditions commonly prioritize rehabilitation to maintain (or improve) good functioning. Thus, it is a need to investigate if a similar high dose of exercise therapy is effective for patients with knee OA. It is also of high relevance to study whether a less time-consuming exercise

programme, such as the low-dose MET in the present study, results in similar effects including effects on costs.

DISCUSSION

We believe one important strength of this study is the use of self-paced exercises, grading the exercises pain-free or close to pain-free [49]. Research has shown that when patients are asked to self-select their exercise intensity, they choose an intensity that results in a positive affective response making them more motivated to do the exercise. This seems to be the case for both populations without pain [93] and patients suffering from a painful condition [94]. The use of a self-paced approach, exercising pain-free or close to pain-free may – we believe - decreases the probability of patients dropping out of the study due to adverse effects such as uncomfortable painful experiences [49, 94], which minimizes possible nocebo effects [20], and breaks the vicious circle of knee pain [36]

To decrease negative affective experiences from exercising, MET applys the principle of deloading, where the application of different types of exercise equipment deloads some of the body weight or the weight of the lower extremity. This is also the case for aquatic exercise therapy where the buoyancy of the water decreases compressive forces on the knee joint. However, aquatic exercises do not seem to be superior to land-based exercises [95], making a call for further research into dose-response effects from exercise therapy.

In an extensive review by Pedersen and Saltin [96], it was concluded that there is evidence for prescribing exercise as a therapy for 26 different chronic diseases. In addition, there is increasing evidence that a higher dose of exercise is more effective than a lower dose in

patients with long-term subacromial pain [47] and long-term anterior knee pain [40], patients suffering from depression [91], and patients suffering from a metabolic syndrome [92]. A high dose of exercise has a greater effect on heart function [97] and a greater positive impact on mood states and quality of life [98] in patients suffering from heart failure.

In terms of knee OA, however, the evidence level of exercise dose is poor [25, 26, 35, 96, 99, 100]. In a recent systematic review [26] only five studies that compared high-intensity versus low-intensity physical activity were included. Of these five studies, there is only one study [30] that is in any way similar to this planned study. The study [30] compared high-intensity versus low-intensity cycle ergometry in older adults with knee OA. Both groups cycled for 25 minutes three times a week for 10 weeks. The high dose high intensity group cycled with an intensity of 70% of HRR and the low dose low intensity group with an intensity of 40% of HRR. After the end of the intervention period both groups had improved significantly on all outcome measures but there were no differences between groups. Juhl and colleagues [100] argue that an optimal exercise program for knee OA should focus on improving quadriceps strength and aerobic capacity, as well as improving performance in the lower extremities. Exercise programmes should be supervised and carried out three times a week. They also argue that there is a great need to further investigate the effects of differing exercise doses and that the interventions in such studies are described in detail with regard to intensity, length of program, total number of supervised sessions, duration of individual supervised sessions, and number of sessions per week.

To our knowledge, this study is the first to investigate, in a controlled manner, if an exercise dose lasting 70-90 minutes is superior in terms of improvements in functioning and pain to a lower dose of exercise therapy lasting 20 to 30 minutes in patients with knee OA.

CONTRIBUTORSHIP STATEMENT

Torstensen TA, Grooten WJA, Østerås H, Heijne A,-Harms-Ringdahl K and Äng B, have all actively participated in the planning and design of the study as well as the writing of this manuscript describing the research protocol of the study. Principle investigator in Sweden is Björn Äng and in Norway Havard Østerås. Tom Arild Torstensen is the assistant principle investigator for the study.

COLLABORATORS

The authors would like to acknowledge the following colleagues:

Monitoring the study:

The following colleagues are monitoring the study at respective intervention centre; In Västervik, Nisse Wallberg PT, in Luleå Mikael Sjöström PT, in Trondheim Håvard Østerås M.Sc PT and in Mosjøen Morten A Romslo PT.

Assessment and treatment of patients:

in Mosjøen (Norway), Morten Andre Romslo PT (MSc) and Iselind Thoresen PT, in Trondheim (Norway) Lasse Haugerud PT and Håvard Østerås M.Sc PT, in Luleå (Sweden) Mikael Sjöström PT, and in Västervik (Sweden) Nisse Wallberg PT and Thomas Aupers PT.

Objective functional testing:

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Local study nurse handling questionnaires and in charge of the randomization procedure locally and informing patients about follow up assessments:

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COMPETING INTERESTS

I have read and understood the BMJ Group policy on declaration of interests and declare the following interests:

Name: Tom Arild Torstensen, Date: 2017-06-30

Declaration of interests: Teaches courses and seminars in medical exercise therapy

Name: Grooten WJA, Date: 2017-06-30

Declaration of interests: None

Name: Østerås H, Date: 2017-06-30

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Name: Heijne A, Date: 2017-06-30

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Name: Harms-Ringdahl K, Date: 2017-06-30

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Name: Äng BO, Date: 2017-06-30

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FIGURE CAPTIONS

Figure 1: The principle of deloading performing a local knee exercise.

Figure 2: The two different exercise interventions compared in this randomized trial, high dose MET (HDMET) and low dose MET (LDMET).

Figure 3. Flow chart of the design and run of the study. HDMET= High-dose MET and LDMET= Low-dose MET.

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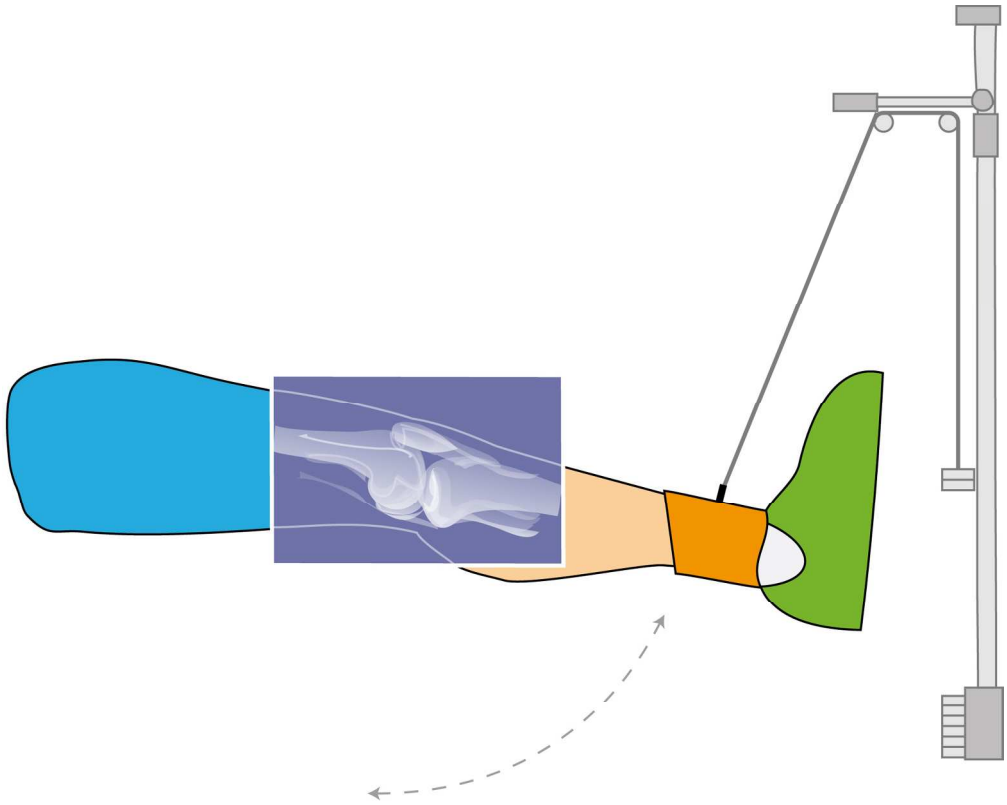

171x136mm (300 x 300 DPI)

EXERCISE	HIGH DOSE MET (70-90 MIN)	DOSE	LOW DOSE MET (20-30 MIN)	DOSE
1		GLOBAL 20 min		GLOBAL 10 min
2		SEMI GLOBAL CLOSED CHAIN 3x30 reps		SEMI GLOBAL CLOSED CHAIN 2x10 reps
3		LOCAL OPEN CHAIN 5 min		SEMI GLOBAL CLOSED CHAIN 2x10 reps
4		SEMI GLOBAL CLOSED CHAIN 3x30 reps		SEMI GLOBAL CLOSED CHAIN 2x10 reps
5		GLOBAL 10 min		SEMI GLOBAL OPEN CHAIN 2x10 reps
6		SEMI GLOBAL CLOSED CHAIN 3x30 reps		
7		LOCAL OPEN CHAIN 5 min		
8		LOCAL OPEN CHAIN 3x30 reps		
9		GLOBAL 10 min		

210x297mm (300 x 300 DPI)

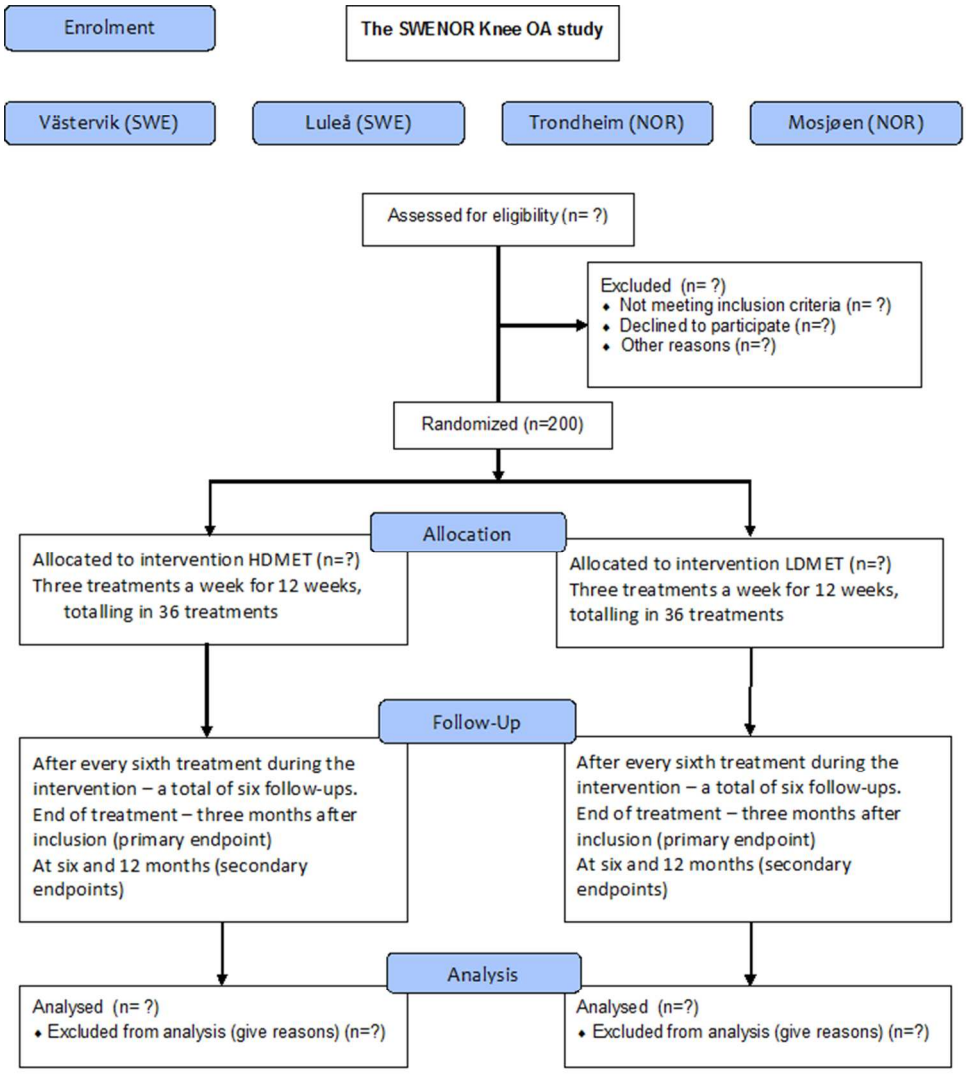

Figure 2. *Flow chart of the design and run of the study. HDMET= High-dose MET and LDMET= Low-dose MET.*

250x312mm (300 x 300 DPI)

HIGH DOSE MET 80-90 MINUTES | NAME:

Treatment / Exercises	1 date	2 date	3 date	4 date	5 date	6 date	7 date	8 date	9 date	10 date	11 date	12 date
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time
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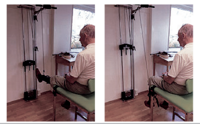	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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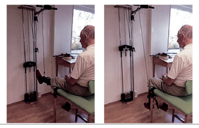	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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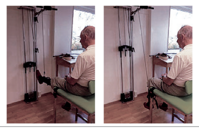
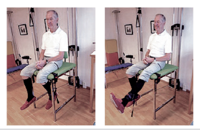
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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HIGH DOSE MET 80-90 MINUTES | NAME:

Treatment / Exercises	13 date	14 date	15 date	16 date	17 date	18 date	19 date	20 date	21 date	22 date	23 date	24 date
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time
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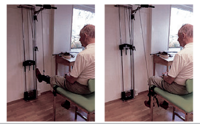	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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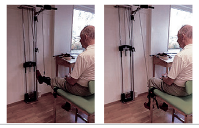	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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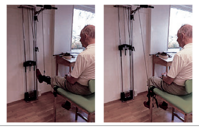
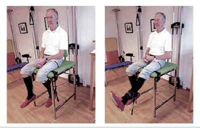
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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HIGH DOSE MET 80-90 MINUTES | NAME:

Treatment / Exercises	25 date	26 date	27 date	28 date	29 date	30 date	31 date	32 date	33 date	34 date	35 date	36 date
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time
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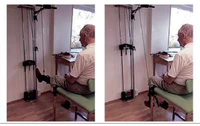	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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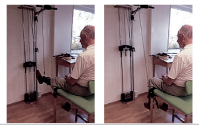	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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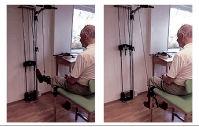
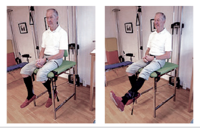
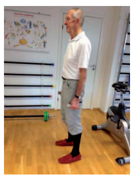
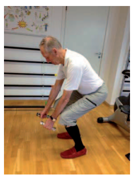
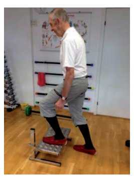
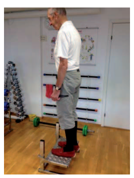
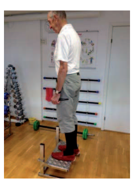
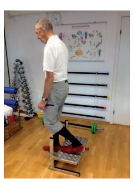
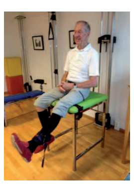
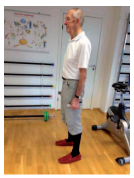
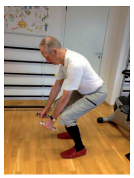
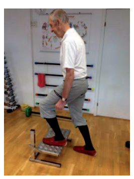
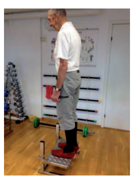
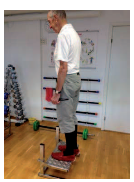
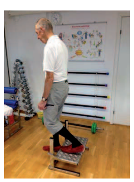
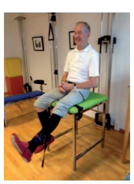
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time

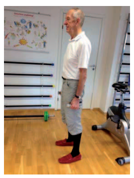
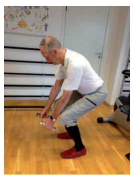
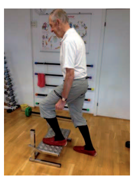
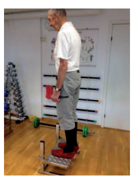
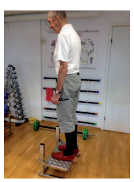
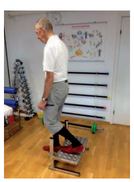
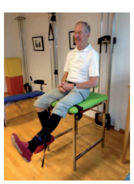
Low dose MET 30 minutes Name: ______________________

Treatment / Exercises	1	2	3	4	5	6	7	8	9	10	11	12
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time
 	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time
 	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time
 	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time
 	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time

Exercise program MET 30 minutter Name: ____________________

Treatment / Exercises	13	14	15	16	17	18	19	20	21	22	23	24
	Date	Date	Date	Date	Date	Date	Date	Date	Dato	Date	Date	Date
	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time
 	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time
 	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time
 	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time
 	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time

Exercise program MET 30 minutter Name: ______________________

Treatment / Exerises	25	26	27	28	29	30	31	32	33	34	35	36
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time
 	Weight Serie Rep Time	Weight Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time
 	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time
 	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time
 	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p1, line 8-10
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p2,line 27
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	p1, line 37
Funding	4	Sources and types of financial, material, and other support	p31,lines 2-5
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p1,line:13-23, p29,lne:5-10
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p31, lines 2-5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p14, lines 5-9,p15,lines 1-10

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p3-p10,
	6b	Explanation for choice of comparators	p10,lines 11-24 p11,linea1-4
Objectives	7	Specific objectives or hypotheses	p11,lines 7-24
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p12,line 6-14

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p12,lines17-20
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p13,lines1-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p17-20, figure 1,p 8 and fig 2 ,p 9, appendixes 1 and 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p19,lines 10-17,
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P27,lines 5-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p21-23, p 24, lines1-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	page 12, figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p25,lines 14-23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p14,lines 11-16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p16,lines 16-21
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p16,lines 16-21
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p13,line 24, p14, lines 1-3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p17,lines 1-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	p15, line 23 and p17, lines 3-4

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p15,lines 1-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocol	p15,lines1-10, and page 15,lines 13-15, and page 16, lines1-5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p15,lines 1-10

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p14,lines 5-9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p14,lines 8-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p2, lines 24-26, ' page 26,lines1-4
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p14,line 8-9

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p14,lines9-11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p14,lines20-23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p29,line1-2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p15,lines 6-8
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p2, lines 25-26
	31b	Authorship eligibility guidelines and any intended use of professional writers	not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	not applicable, only i in Swedish and Norwegian language
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons

BMJ Open

How does exercise dose affect patients with long-term osteoarthritis of the knee? A study protocol of a randomized controlled trial in Sweden and Norway – the SWENOR study

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Complete List of Authors:	Torstensen, Tom Arild; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy Grooten, Wilhelmus; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Østerås, Håvard; Norwegian University of Science and Technology, Department of Neuromedicine and Movement Science Heijne, Annette; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Harms-Ringdahl, Karin; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy ; Karolinska University Hospital, Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy Äng, Björn; Dalarna University, School of Education, Health and Social Sciences; Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Rheumatology, Sports and exercise medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, PAIN MANAGEMENT, Clinical trials < THERAPEUTICS, REHABILITATION MEDICINE

Words in text 5996
Words in abstract 299
Tables 2
Figures 3
Appendixes 2

How does exercise dose affect patients with long-term osteoarthritis of the knee? A study protocol of a randomized controlled trial in Sweden and Norway – the SWENOR study

Torstensen TA (1), Grooten WJA (1,2), Østerås H (3), Heijne A (1,2), Harms-Ringdahl K (1,2), Äng BO (1,4,5).

1) Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet, Huddinge, Sweden
2) Allied Health Professionals Function, Functional area Occupational Therapy and Physiotherapy, Karolinska University Hospital, Stockholm, Sweden
3) Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway
4) School of Education, Health and Social Sciences, Dalarna University, Falun, Sweden
5) Center for Clinical Research Dalarna, Falun, Sweden

Corresponding author:
Tom Arild Torstensen
Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Karolinska Institutet

Alfred Nobels Allé 23 23100
141 83 Huddinge, Sweden

Tel: +46 707344102
E-mail: tom.torstensen@ki.se

Version 3, review, 2018 -01-31

ABSTRACT

Introduction: Osteoarthritis (OA) of the knee is characterized by knee pain, disability, and degenerative changes, and places a burden on societies all over the world. Exercise therapy is an often-used modality, but there is little evidence of what type of exercise dose is the most effective, indicating a need for controlled studies of the effect of different dosages. Thus, the aim of this study described in this protocol is to evaluate the effects of high-dose versus low-dose medical exercise therapy (MET) in patients with knee OA.

Methods and analysis: This is a multicentre prospective randomized two-arm trial with blinded assessment and data analysis. We are planning to include 200 patients aged 45-85 years with a diagnosis of symptomatic (pain and decreased functioning) and X-ray verified diagnosis of knee OA. Those eligible for participation will be randomly allocated to either high-dose (n=100) or low-dose (n=100) MET. All patients receive three supervised treatments each week for twelve weeks, giving a total of 36 MET sessions. The high-dose group exercises for 80-90 min compared to 20-30 min in the low-dose group. The high-dose group not only exercises for a longer time, but also receives a greater number of exercises with more repetitions and sets. Background and outcome variables are recorded at inclusion, and outcome measures are collected after every sixth treatment, at end of treatment, and at six- and twelve-month follow-ups. Primary outcome is self-rated knee functioning and pain using the Knee Injury and Osteoarthritis Outcome Score (KOOS). The primary endpoint is at the end of treatment after three months, and secondary endpoints are at six and twelve months after end of treatment.

Ethics and dissemination: This project has been approved by the Regional Research Ethics Committees in Stockholm, Sweden, and in Norway. Our results will be submitted to peer-reviewed journals and presented at national and international conferences.

Trial Registration number: (ClinicalTrials.gov NCT02024126)

Strengths and limitations of this study

- To the best of our knowledge, this is the first multicentre study, with a bio-psycho-social view of pain, prospectively, comparing the effectiveness of two defined doses of pain-free or close to pain-free exercise therapies in patients with symptomatic knee osteoarthritis.
- The proposed project includes a relatively large sample where outcomes are evaluated both during the twelve-week intervention period, at the end of treatment, and at six and twelve months, respectively.
- The overall project uses both subjective and objective data, and includes analyses of cost- effectiveness and early predictors for a follow-up clinical outcome.
- Even though the different components of the exercise programmes are well described, one limitation could be possible confounders related to the exercise dose given.

MAIN TEXT

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis and is a major worldwide health problem causing illness and disability [1, 2]. The burden to society caused by knee OA is substantial [3]. The knee joint is most frequently affected, which commonly results in chronic joint pain, knee stiffness, decreased functioning, reduced quality of life, and sick leave [4]. The associated costs of osteoarthritis are estimated to range between 1-2.5% of the gross national product as calculated in six industrialized countries (Sweden, Australia, Canada, France, UK, and US) [5]

Traditionally, knee OA has been defined as a pathological condition characterized by focal areas of loss of articular cartilage within the synovial joints, associated with hypertrophy of the bone (osteophytes and sub-chondral bone sclerosis) and thickening of the capsule [6]. The mechanisms of knee OA-related pain are, however, complex [7] particularly in chronic pain conditions where pain experience is nowadays believed to be more a result of changes in the nervous system than in tissue structures [8], i.e. peripheral and central sensitization [9]. This may partly explain why there are poor correlations between structural degenerative changes of the knee, and pain, and functioning [10, 11].

In a systematic review, it was concluded that there exists high-level evidence that land-based therapeutic exercise provides short-term effects on pain relief, and that there is a moderate quality evidence regarding improvement in physical functioning among patients with knee OA [12]. Despite this, several questions remain unanswered, particularly regarding dose, intensity, and duration of the exercise therapy applied [13]. These unanswered questions may be one of the reasons why we see a large variation in treatment effects observed across studies making it difficult to conclude what is the optimal dose when delivering exercise therapy [12, 13]. The exercises vary from neuromuscular exercise [14], knee joint stabilization exercises [15], strengthening exercises [16], and endurance exercises [17]. These forms of exercise therapy do not necessarily take into consideration the theories of local and central sensitization, thus opening up for exercise therapies where the goal is modulation of pain decreasing local and central sensitizations. The knowledge that pain and swelling inhibits motor output, decreases range of motion, and changes coordination [18] and that a strengthening exercise program can cause adverse effects [19], questions the use of strengthening exercises. In their review [19], Liu et al. concluded that out of 121 trials, 53

had no comments about adverse events, 25 reported no adverse events, and 43 trials reported adverse events. The majority of the adverse events from the strength training were muscle strain and joint pain, while more adverse events were reported when performing high intensity strength training. In this context there is increasing evidence [20] that exercise therapy should focus more on treating pain-related knee OA such as peripheral and central sensitization [8] and pain-related bodily and psychological changes [21] from a biopsychosocial perspective [22, 23] rather than an impairment like muscle strength. This view is supported by research showing that pain-related fear is more disabling than pain itself [24]. To break the vicious circle of long-term knee pain, we believe it is important to see beyond the knee [8], beyond an impairment such as muscle strength [25], using a biopsychosocial sensitization model of pain [23].

Medical Exercise Therapy

Medical Exercise Therapy (MET) focuses on applying the optimal dose of exercise; i.e combining global aerobic exercises with semiglobal and local joint exercises, where the goal is to apply 70 to 90 minutes of active dynamic exercise therapy [26-35] . Using the principle of self-paced exercises [36] the patient is to perform more than a 1000 pain-free or close to pain-free repetitions per MET-session [26-35] . Even though the optimal dose goal of MET is high, the treatment usually starts with a low dose lasting 15 to 20 minutes mirroring the ability of the patient within a biopsychosocial context [22, 23], starting with an acceptable baseline where the patient manages the exercise therapy [23, 26].

A global exercise is an exercise that activate the whole body exercising the trunk aswell as upper and lower extremities, a semiglobal exercise activates muscles, joints and other

structures in an extremity and a local exercise activates one joint and the muscles acting on it. Sessions of global exercises are performed several times during one treatment occasion, where the goal is to substantially increase the heart rate activating the endocrine and pain modulating systems of the body, i.e. the descending pain inhibiting system, achieving cortical and spinal inhibition of nociceptive input. Semiglobal and local exercises are performed for the same purpose, however, they are performed in sets of three where each set consists of 30 repetitions. A local exercise can also be performed continuously for 3 to 5 minutes as one set, for example deloaded knee extension, see figure 1.

[Figure 1 about here].

To achieve a high volume of repetitions pain-free or close to pain-free the principle of deloading is applied where the weight stack from different pulley apparatus is used to deload a part of the body or the whole body, resulting in less joint forces in the knee joint, see Figure 1.

The theoretical basis for the principle of the de-loading is that the weight from the pulley deloads the weight of the lower leg with a decrease in the compressive forces between bony and cartilaginous structures. The deloading also results in decreased pull and loading of muscles, tendons, and other soft tissue, decreasing sensitization including mechanical/loading allodynia, making it possible to exercise pain-free or close to pain-free.

MET has been evaluated in several clinical trials, and has been shown to be effective, both in the short and long term, in patients with long-term low back pain with or without sciatica [37], subacromial pain [33-35], and long-term anterior knee pain [27, 28]. In these latter studies, an exercise dose lasting 70 to 90 minutes has been more favourable than an

exercise dose lasting 20 to 30 minutes. In a narrative review, Lorås et al., 2015 [23], included four RCTs on the effectiveness of high-dose MET, concluding that high-dose MET was positive and promising. However, to be able to draw any firm conclusions about the efficacy in patients with knee OA, rigorous trials are needed on the effect of MET in this major patient group [38]. Effect trials of cost-effectiveness are also needed as they are presently lacking in the scientific literature, and the present project has the potential to fill this knowledge gap. It is also important to point out that no exercise protocol is suited to all patients, and as knowledge of early predictors of poor treatment outcomes obtained from longitudinal data is sparse, the development of patient-customized treatments is hindered [39]. According to the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) as well as a recent review [40], prediction studies are needed to be able to better individualize the treatment and match the most promising treatment option to a certain patient profile in order to maximize treatment outcomes and minimize costs. Therefore, we plan to conduct an RCT post-hoc prediction study to gain insights into which patient characteristics predict treatment outcome and which patients benefit more or less from exercise treatments.

In this trial, the rationale for comparing high dose MET (70-90 minutes) versus low dose MET (20-30 minutes) is that high dose MET should be more effective through an increased activation of the pain modulation systems like the descending pain inhibiting system [41]. The evidence is that exercise-induced hypoalgesia is obtained through higher and more intensive exercise doses of 70% of HRR activating the pain modulating systems and decreasing the sensation of pain [42]. However, it has also been shown that an exercise intensity of 50% of HRR is capable of producing an analgesic effect in healthy adults [43], similar exercise intensities used in both high and low dose MET. This could have important

implications for the use of exercise in the management of pain, particularly in deconditioned individuals (e.g., older adults with OA of the knee). In 2008 it was shown for the first time that an endurance activity lasting two hours resulted in the production of endogenous neuropeptides (endorphins), creating chemical reactions in brain areas involved in cognitive function and pain modulation, primarily in the prefrontal cortices, insula, and the limbic system [44]. The rationale is that high dose MET exercising for 70 to 90 minutes may result in an increased production of endogenous neuropeptides in the spinal cord, the brain stem, and in the brain, compared to a lower dose MET exercising 20-30 minutes. The hypothesis is that this should result in less pain and improved functioning in favour of the high dose MET therapy.

AIM OF THE STUDY

The aim of this project is to prospectively evaluate short- and long-term effects of high-dose MET compared to low-dose MET in patients with X-ray verified knee OA regarding pain, functioning, and cost-effectiveness. A further aim is to conduct a post-hoc analysis on early prognostic factors that predict short- and long-term follow-up outcomes, by targeting patients' early status and patient adherence to the intervention. The long-term goal is to further develop and implement updated knowledge into knee OA rehabilitation to meet the challenge of tomorrow's patients with knee OA pain.

This study seeks to answer the following research questions:

1. What is the effect of high-dose MET compared to a low-dose exercise therapy (low-dose MET) with respect to self-rated pain, functional limitations, health-related quality of life, depression, and anxiety?

2. What is the effect of high-dose MET compared to low-dose MET on objective performance measures such as physical functioning of a 20-metre walk, sit to stand, and single knee bends, and pain threshold as determined by a pain-matcher instrument?
3. What is the cost-effectiveness of MET in patients with knee OA with respect to costs against potential effects (incremental cost-effectiveness ratio, ICER), and cost per quality-adjusted life year (QALY)?
4. Which patient characteristics (demographic or disease-related) predict long-term treatment outcomes with a focus on pain, functional limitation, and health-related quality of life? What important interaction effects between patient characteristics and exercise dose may predict treatment outcomes?

MATERIAL AND METHODS

Study design

This is a phase three superiority trial of high dose MET versus low dose MET. The trial is blinded regarding outcome assessment and analyses. It is a two-arm multicentre trial of a twelve-week exercise intervention with a twelve-month follow-up. Measurements will be taken at baseline and during the treatment at two weeks (six treatments), four weeks (12 treatments), six weeks (18 treatments), eight weeks (24 treatments), ten weeks (30 treatments), twelve weeks (36 treatments), which is end of treatment, and at follow-up at 26, and 52 weeks after end of treatment. Primary endpoint is at end of the treatment. Secondary endpoints are at the 26 and 52 weeks follow-up. The study will conform to CONSORT guidelines for reporting parallel, randomised trials [45], see Figure 2.

[Figure 2 about here]

Participants

We are planning to include 200 patients with a diagnosis of symptomatic and radiographic knee OA who will be recruited from primary and secondary health care settings in Luleå and Västervik in Sweden, and in Trondheim and Mosjøen in Norway, named the SWENOR knee OA study.

Inclusion criteria:

Subjects aged 45-85 years, living in the defined geographic areas (Västervik and Luleå municipalities in Sweden, and Trondheim and Mosjøen in Norway), who have had a diagnosis of symptomatic and radiographic verified osteoarthritis grade I-III according to Kellgren and Lawrence [46, 47], with at least three months pain duration, and decreased functioning. The patient is willing to participate in a twelve-week intervention period with three sessions each week

Exclusion criteria:

Physiotherapy or other conservative therapy during the previous three months or a history of major knee trauma such as knee fractures or ligament ruptures. Inflammatory joint disease, hip symptoms more aggravating than the knee symptoms, scheduled to have knee replacement surgery within six months, and co-morbidities not allowing exercise such as cardiovascular, respiratory, systemic, or metabolic conditions limiting exercise tolerance.

Procedure

Before intervention starts, regular visits will be made to each intervention place by the first author (TAT), informing and communicating with the local research team about the aims and run of the study. Detailed description of the different stages of the study from recruitment,

treatment, and follow-up assessments after the end of the intervention period will be instructed and discussed. Physiotherapists in charge of the objective clinical testing (two in Västervik, one in Luleå, two in Trondheim and two in Mosjøen), otherwise not involved in the treatment, will be educated theoretically and practically on how these tests should be performed. The physiotherapists delivering the exercise intervention (two in Västervik, one in Luleå, two in Trondheim and two in Mosjøen) will, in addition, have structured theoretical and practical sessions on how to apply and grade the exercise therapies. A study nurse at each intervention place is in charge of randomization, questionnaires, and the scheduling of patients for treatments and assessments. Each of the four intervention centres has a local administration officer.

A data security monitoring plan is conducted by the current investigator monitoring the present pragmatic trial. Tom Arild Torstensen (TAT) will visit the four centres from the planning phase of the trial, during the treatment phase, and during the follow up phase in order to monitor that the protocol is followed. Adverse and SAEs are reported to the ethics committee.

Recruitment will be achieved through referrals from medical doctors in primary and secondary health care clinics. The local investigator at each study centre will contact medical doctors (MDs) and send written information about the study. The first screening is performed by a MD and a second screening is performed by one of the treating physiotherapists. Both the MD and the physiotherapist guarantee the radiographic inclusion criteria.

Patients will receive oral and written information about the study, and after signing an informed consent form obtained by the local administration officer, they will be assessed for eligibility by physiotherapists at each intervention centre. Participants initially fill out questionnaires for baseline data and perform the physical performance tests. Each patient is then randomized, as described below, to either high or low dose medical exercise therapy.

Data collection and management.

Data from the questionnaires will be depersonalised at each intervention centre by the local research assistant. In order to transfer data from Norway to Sweden, a data transfer agreement (DTA) between Norges Teknisk-Naturvitenskapelige Universitet (NTNU)/Norwegian University of Science and Technology and Karolinska Institutet, (KI/NVS), has been set up. The questionnaires from the Swedish centres are posted to Karolinska Institutet where data is registered on digital sheets. In Norway, questionnaires from Mosjøen are posted to Trondheim where all questionnaires from the two Norwegian centres are registered on sheets and delivered to Karolinska Institutet according to DTA; Tom Arild Torstensen, Björn Äng, and Wilhelmus Grooten are in charge of the data synthesis and analysis

Post-recruitment retention and compliance strategies

Our experiences of MET as an experimental intervention (HØ and TAT) [26-35] leads to the following retention and compliance strategies to be applied in this study.

- An independent study nurse at each intervention centre will always be available to answer questions when patients are filling out the questionnaires

- This is important to avoid any unnecessary misunderstandings regarding the content of the questionnaire and to make sure that patients understand that all information will be depersonalized.
- During the interventions, the treating physiotherapist is present the whole time in the exercise room answering questions from patients and re-grading the exercises according to changes in patients' exercise status and knee-OA symptoms. Participants are not informed about the hypothesis of the study.
- At inclusion and at the end of the 12-week intervention period the patient is informed by the local administration nurse about the six- and 12-month follow-ups.
- During the post-intervention follow-ups, the patient will be contacted three weeks prior to the assessment and informed when to come to the intervention site for the planned post treatment evaluation.

During the intervention period, KOOS and the eight different VAS scales are assessed after every sixth treatment meaning after two-, four,- six,- eight-, ten,- and 12 weeks giving a total of six assessments. The purpose of such repeated measurements is to obtain a reasonable measurement accuracy of both functioning status and pain during the twelve-week intervention period. The primary end-point will be on completion of the intervention after 36 treatments, which will take an average of twelve weeks. This is to obtain evaluation of effects on organized exercise therapy related with its direct implementation, while further follow-ups evaluate its retention effects. At this point primary and secondary outcomes are assessed.

Randomization procedure

In this individual randomized trial, a stratified allocation by age and intervention centre is used, using a computerized program, where the goal is to get an equal number of patients between the ages of 45 and 64 years and 65 and 85 years at each of the four intervention centres. The randomization key is concealed at each intervention place and kept under lock by a research assistant not involved with the assessment or interventions.

Blinding procedures

The physiotherapists conducting the physical performance tests are blinded to an allocation group and the study participants are instructed by the treating physiotherapists not to reveal details of their intervention during testing. The principal investigators (BÄ), the assistant principal investigator (TAT), and the research assistants are also blinded to groups when entering data to data-sheets, i.e. they do not know which patient has received high-dose or low-dose MET. The group key will be opened after the analyses have been finalised and the results have been written up in a manuscript (using intervention A and B until results have been written).

Interventions

All participants receive an MET intervention, where they are treated in groups of four or five in sessions lasting 20 to 90 minutes. During the sessions, they are supervised by an experienced physiotherapist in an outpatient clinic. All participants are treated three times a week for twelve weeks, giving a total of 36 treatments. Each patient in the group has an individualized exercise program tailored to their specific clinical symptoms and functional level. As the treatment proceeds, exercises are adapted according to changes in symptoms

and functioning. The pain experience when exercising should not exceed a three on a zero to ten scale, where zero is no pain and ten is the worst imaginable pain [34]. Specially designed exercise equipment consisting of different forms of pulleys, exercise benches, dumbbells, and barbells is used to grade and dose the exercises to be pain free or close to pain free, with the purpose of mitigating peripheral and central sensitization while exercising [23]. The difference between groups regarding exercise dose is outlined below in Table 1.

Table 1: *Differences between the high-dose and low-dose MET* regarding *number of exercises, sets, and repetitions. Difference in time, performing global exercises and total time duration for each treatment.*

	Number of exercises	***Number of sets***	***Number of repetitions***	***Time performing global exercise***	***Time duration of treatment***
High dose MET	*9*	*3*	*30*	*20 min+10 min +10 min*	*70-90 min*
Low dose MET	*5*	*2*	*10*	*10 min*	*20-30 min*

The grading of the exercises, including baseline settings, is based on the initial clinical assessment by the treating physiotherapist. From the patients' past and present histories and physical clinical assessment, information is gained about the level of pain and possible sensitization (local versus central sensitization), range of motion, and tolerance for weight bearing within the available range of motion of the knee. This information is used for baseline setting of the exercises where the physiotherapist chooses a starting position, a rage of motion, and a weight resistance believed to match the patient´s ability to perform three sets of 30 repetitions (high dose MET) and two sets of ten repetitions (low dose MET),

pain-free or close to pain-free. Then there is a test of each exercise where the physiotherapist asks the patient to do as many repetitions as the patient can manage. When the patient reaches ten repetitions the test is stopped and the patient has to evaluate if the weight/loading (L), starting position (SP), or range of motion (ROM) is appropriate to reach a total of 40 repetitions. Any of the above mentioned variables (L, SP, ROM), can be changed to reach 40 repetitions, making it possible to perform 30 repetitions in sets of three with a 30- to 60-second pause between each. The same test procedure is used for the low dose group where the goal is a test of 15 repetitions making it possible to do two sets of 10 repetitions. At baseline setting, there is a continuous evaluation in the exercise room where the physiotherapist and the patient is working towards optimal exercise dose for each exercise, as is usually done in clinical practice [23]

It should also be possible for the patient to perform the exercise comfortably within the preferred active range of active motion (AROM). For example, if a part of the AROM in the knee joint is painful, the patient starts to exercise within the pain-free or close to pain-free AROM. As the treatment proceeds, the AROM is adjusted, making the patient exercising in a larger and more functional AROM. If it is not possible to grade the exercise pain-free or close to pain-free, the patient is allowed to exercise with pain. When exercising with pain it is important that the pain experience dose not cause any anxiety or fear. The pain has to be experienced as meaningful for improvement [48]. If the exercise therapy results in an acute increase in pain, the pain should have returned to baseline before the next treatment session commences. If pain does not go back to the prior level, exercises are reassessed, with the most comfortable exercise performed several times, preferably deloaded knee extension and stationary. The group of four to five patients also contains patients with other

diagnoses, who are not participating in this study, making the delivery of the MET intervention pragmatically similar to a real life situation. To be able to monitor the exercise dose, the treating physiotherapists follow a structured progression plan of the exercises, and fill in a treatment log for each patient at each treatment, see appendix number 1 – progression plan for high dose MET, and appendix number 2 – progression plan for low dose MET. The log contains information about the number of exercises, duration of each global exercise, number of repetitions, and sets and weight resistance applied for semiglobal and local exercises. Consent to publish the photographs in the appendices has been obtained from the person pictured. Figure 3 shows the main exercises from the two different exercise interventions compared in this planned randomized trial: high dose MET versus low dose MET. **[Figure 3 about here]**

To be able to reach a high number of repetitions despite on-going pain, the principle of de-loading is applied, facilitating a high number of repetitions that are nearly or entirely pain free, see figure 1. For the high-dose MET, the deloaded knee extension is performed twice during a treatment, each time for a five-minute duration. This exercise and the cycling in the middle of each treatment session is a form of restitution, making it easier to both perform the deloaded closed chain exercises and endure the high dose MET. Later, as the patient improves and can tolerate increased loading, the exercises are adapted to be more functional, using closed chain exercises without deloading the body weight.

To further increase the exercise dose for the high dose MET group patients perform one home exercise - the seated deloaded knee extension with a yellow tube theraband. The exercise is similar to exercise number three, see Figure 1. They perform this home exercise once every day, where the dose is three lots of three minutes with a 30- to 60-second pause

between each set. The treating physiotherapists make sure that the patients are compliant in doing their home exercises. Patients in the low dose MET receive no home exercises.

Baseline data

The following data will be obtained by questionnaire; gender, age, height, weight, physical activity and exercise levels, living arrangement, education level, employment status, possible medication, co-morbidities, smoking habits, sleeping habits, pain and function of the knee, catastrophizing thoughts, fear avoidance beliefs, level of anxiety and depression, life satisfaction and quality of life, and beliefs about exercise. A schematic presentation of the outcome measures recorded at baseline and at the follow-ups is presented in Table 2. Each assessment, which involves filling out questionnaires, will take approximately one hour. The objective testing of the knee and the testing with the PainMatcher apparatus takes approximately 30 minutes and will occur the following day.

Primary outcome measures

In accordance with international consensus regarding the core set of outcome measures for clinical trials in OA [49], self-rated functioning and pain scoring (The Knee Injury and Osteoarthritis Outcome Score, KOOS) [50-53] is used as primary outcome measures. KOOS consists of 5 subscales; Pain, other Symptoms, Functioning in daily living (ADL), Functioning in sport and recreation (Sport/Rec), and knee-related Quality of life (QOL). Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. For the purpose of an RCT, KOOS subscale scores can be aggregated and averaged as the primary outcome. We are planning to use KOOS at

Table 2. *Study measures to be collected*

Baseline measures and outcomes	Description and instrument	Data source	Collection points
Patient´s characteristics	Date of birth, gender, BMI (height, weight) social and living status, leisure activities, level of physical activity, smoking, medicine, sleep, co-morbidities, anxiety and depression, catastrophizing, life satisfaction, kinesiophobia	SAQ	t0
Primary outcome measure	**Clinical Outcomes**		
Pain	KOOS: subscale pain	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Other symptoms	KOOS: subscale other symptoms	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Function	KOOS: subscale physical functioning	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Sport, recreation	KOOS: subscale sport and recreation	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
Secondary outcome measures	**Clinical Outcomes**		
	VAS (100mm scale): pain	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100mm scale): knee pain not loading	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100 mm scale): pain at weight bearing	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	VAS (100 mm scale): knee pain at night	SAQ	t0, t2, t4, t6, t8, t10, t12, t26, t52
	Physical functioning		
	20 m walk test	PT	t0, t12
	Chair stand test	PT	t0, t12
	Unilateral knee bending	PT	t0, t12
	Pain threshold and tolerance		
	Pain Matcher	Pain matcher apparatus	t0, t12
	Quality of life		
	(EQ-5D-5L)	SAQ	t0, t12, t26, t52
	(SF-36)	SAQ	t0, t12, t26, t52
	Life satisfaction		
	Life Satisfaction Questionnaire (LISAT)	SAQ	t0, t12, t26, t52
	Psychological outcomes		
	Anxiety and depression (HAD),	SAQ	t0, t12, t26, t52
	Catastrophizing (Pain Catastrophizing Scale)	SAQ	t0, t12, t26, t52
	Kinesiophobia (TSK)	SAQ	t0, t12, t26, t52
	Beliefs and attitude towards exercise		
	Self-efficacy for exercise (SEE)	SAQ	t0, t12, t26, t52
	Outcome Expectancy for Exercise Scale (OEE	SAQ	t0, t12, t26, t52

Data source: Self-administered questionnaire (SAQ), physical testing (PT). Collection points: t0=inclusion, t1-t12= measurement every second week during the 12 week intervention period, t1=2 weeks, t2= 4 weeks, t3= 6 weeks, t4= 8 weeks, t5= 10 weeks, t6= 12 weeks (end of inclusion), t26= 6 months follow up, t52= 12 months follow up. Questionnaires: The Knee Injury and Osteoarthritis Scale (KOOS), Life Satisfaction Questionnaire (LISAT), Hospital Anxiety and Depression Scale (HAD), Pain Catastrophizing Scale (PCS), Tampa Scale of Kinesiophobia (TSK), Self-efficacy for exercise (SEE) and Outcome Expectancy for Exercise Scale (OEE)

several time-points; at baseline, and during the intervention period until the final follow-up at 52 weeks, see Table 2.

Secondary outcome measures

As a secondary outcome measure, there are eight different pain measurements using a 100 mm visual analogue scale (VAS) [54], with terminal descriptors of “no pain” and “worst pain” asking about how painful the knee is, 1) today and 2) on average during the last week, related to the following four different life situations; 1) how painful is your knee, 2) how painful is your knee when loading your knee (e.g. walking or standing), 3) how painful is your knee when not loading your knee (e.g. sitting, lying), 4) how painful is your knee at night when you are sleeping (e.g. knee pain that disturbs your sleep). Data on health related to quality of life are collected using the EQ 5-D questionnaire [55] and the SF-36 questionnaire [56]. These questionnaires will also be used to perform a health economic evaluation of the exercise interventions. Psychological factors such as anxiety and depression, catastrophizing, and fear-avoidance beliefs are believed to both predict outcome of an intervention [57] as well as influence the level of pain in patients with knee OA experience [58]. In this study, anxiety and depression are rated using the Hospital Anxiety and Depression Scale (HAD) [59], catastrophizing is rated using the Pain Catastrophizing Scale (PCS) [60], and fear avoidance beliefs [61] are rated using the Tampa Scale of Kinesiophobia (TSK) [62], see Table 2. Life satisfaction is assessed using the Life Satisfaction (LISAT) questionnaire by Fugl-Meyer [63]. Beliefs and attitudes towards exercise are rated using the Self-Efficacy for Exercise Scale (SEE) [64], and the patient’s expectations of performing physical activity are rated using the Outcome Expectations for Exercise Scale (OEE) [65]. PainMatcher apparatus [66] (Cefar Medical AB, Lund, Sweden) is used to record

sensory level, pain level, and pain tolerance level. Pressing the thumb and first finger against a button on each side of the hand held PainMatcher apparatus; an electrode under each button activates an electrical current. As long as the pressure is kept against the buttons, the electrical current will slowly increase where the first sensation of the current is a measurement of sensory threshold. As the pressure is maintained, the electrical current slowly increases, and the sensation will turn into a pain sensation (pain threshold). Keeping the pressure on the buttons, the painful electrical current increases, and pain tolerance is recorded, i.e. the measure of how much painful electrical current the patient can endure. Performance tests include the 20-meter walk test [67], first at a self-selected pace and then at maximum pace, 30-second maximum number of chair to standing test [68], and 30-second maximum number of repeated unilateral knee bends [67, 69]. Other measurements, logged by the supervising therapist, are recordings of compliance of the exercise treatments during the twelve-week intervention also including a recording of exercise dose (weights, sets, repetitions, and treatment time) at each treatment occasion. Over the whole project period, from inclusion to end of the 52-week follow-up, any adverse effects are to be noted and reported.

Statistical analysis

In the statistical analyses of both primary and secondary outcomes, the principle of intention to treat will be used, comparing high-dose MET with low-dose MET. Within-group and inter-group statistical testing will be carried out using general linear model where an alpha level of 0.05 will be used where appropriate. Significance of main or interaction effects will be explored using follow-up post hoc tests. Effect size Cohen´s d will aid clinical interpretation of the magnitude of treatment effect, where effect-size values below 0.2 will be considered

small, 0.5 medium, and 0.8 large. The primary end-point is at the end of the twelve-week intervention period and potential baseline differences will be considered by adding additional baseline variables as covariates to the statistical models. Potential floor or ceiling effects will be computed and considered in our analyses. Because participants of both interventions of both intervention groups are treated together with other patients in MET groups, the treatment credibility and outcome expectations (OEE) will be evaluated as a potential co-variate or confounder for treatment effects.

Analysis of cost-effectiveness will be performed using the incremental cost-effectiveness ratio (ICER), in order to provide a single measure for weighing costs against benefits of health care interventions. Cost per quality-adjusted life year (QALYs [70]), using data from EQ-5D and SF-36, will be added. In the predictive analyses, multivariable logistic regressions (e.g. GEE) will be used to estimate the association between potential predictors and outcomes. A purposeful selection procedure is planned resulting in a final model that contains only significant independent variables, identified confounders and interactions. All final models will be examined for goodness-of-fit and accuracy according to established methods.

Sample size

The power calculation was based on proportions that can document a minimal clinical important change (MCIC). The primary outcome the Osteoarthritis Outcome Score (KOOS) is a numerical scale ranging from 0 (makimal problem) to 100 (no problem). A change of ten points is evaluated as a clinically interesting change [51]. The hypothesis is that 40% of the patients receiving high-dose MET and 20% of the patients receiving low-dose MET will

obtain a ten-point improvement after end of treatment at the three-month follow-up. The power calculation showed that 82 patients are needed in each arm to reach 80% between-group power. With a hypothetical drop out of the study of 20% the total sample is 82x2x1.2=197 patients. We plan to include 200 patients giving each exercise intervention group a total of 100 participants.

ETHICS AND DISSEMINATION

The guidelines from the Helsinki declaration will be followed and the protocol has been approved by the Regional Ethics Review Board in Stockholm. Some relevant ethical considerations related to this study are mentioned below:

The infliction of pain

An often overlooked ethical issue is the infliction of pain when instructing patients to exercise [19]. Knee OA is commonly a painful condition and it is questionable if it is ethical to push patients through the painful exercise regimens included in the approach that today is recommended for treating knee OA. A worst-case scenario for this type of treatment is pushing the patient into endurance behaviour that in itself may result in long-term pain [71]. However, in this study, the focus on grading the exercises pain free or close to pain free resolves, to some extent, this problem.

The problem of large exercise dosage

Asking patients to exercise for 70 to 90 minutes three times a week for twelve weeks may be ethically questionable. However, such doses of exercise therapy have been shown to be effective in patients with depression [72] and there is an argument today that both exercise dose and exercise intensity should be increased for patients suffering from heart disease or

a metabolic syndrome, respectively [73]. The high compliance with a relatively extensive exercise programme is possible because patients with chronic (or progressed) conditions commonly prioritize rehabilitation to maintain (or improve) good functioning. Thus, it is a need to investigate if a similar high dose of exercise therapy is effective for patients with knee OA. It is also of high relevance to study whether a less time-consuming exercise programme, such as the low-dose MET in the present study, results in similar effects including effects on costs.

DISCUSSION

We believe one important strength of this study is the use of self-paced exercises, grading the exercises pain-free or close to pain-free [36]. Research has shown that when patients are asked to self-select their exercise intensity, they choose an intensity that results in a positive affective response making them more motivated to do the exercise. This seems to be the case for both populations without pain [74] and patients suffering from a painful condition [75]. The use of a self-paced approach, exercising pain-free or close to pain-free may – we believe - decreases the probability of patients dropping out of the study due to adverse effects such as uncomfortable painful experiences [36, 75], which minimizes possible nocebo effects [76], and breaks the vicious circle of knee pain [23]

To decrease negative affective experiences from exercising, MET applys the principle of deloading, where the application of different types of exercise equipment deloads some of the body weight or the weight of the lower extremity. This is also the case for aquatic exercise therapy where the buoyancy of the water decreases compressive forces on the knee joint. However, aquatic exercises do not seem to be superior to land-based exercises

[77], making a call for further research into dose-response effects from exercise therapy.

In an extensive review by Pedersen and Saltin [78], it was concluded that there is evidence for prescribing exercise as a therapy for 26 different chronic diseases. In addition, there is increasing evidence that a higher dose of exercise is more effective than a lower dose in patients with long-term subacromial pain [34] and long-term anterior knee pain [27], patients suffering from depression [72], and patients suffering from a metabolic syndrome [73]. A high dose of exercise has a greater effect on heart function [79] and a greater positive impact on mood states and quality of life [80] in patients suffering from heart failure.

In terms of knee OA, however, the evidence level of exercise dose is poor [12, 13, 22, 78, 81, 82]. In a recent systematic review [13] only five studies that compared high-intensity versus low-intensity physical activity were included. Of these five studies, there is only one study [17] that is in any way similar to this planned study. The study [17] compared high-intensity versus low-intensity cycle ergometry in older adults with knee OA. Both groups cycled for 25 minutes three times a week for 10 weeks. The high dose high intensity group cycled with an intensity of 70% of HRR and the low dose low intensity group with an intensity of 40% of HRR. After the end of the intervention period both groups had improved significantly on all outcome measures but there were no differences between groups. Juhl and colleagues [82] argue that an optimal exercise program for knee OA should focus on improving quadriceps strength and aerobic capacity, as well as improving performance in the lower extremities. Exercise programmes should be supervised and carried out three times a week. They also argue that there is a great need to further investigate the effects of differing exercise doses

and that the interventions in such studies are described in detail with regard to intensity, length of program, total number of supervised sessions, duration of individual supervised sessions, and number of sessions per week.

To our knowledge, this study is the first to investigate, in a controlled manner, if an exercise dose lasting 70-90 minutes is superior in terms of improvements in functioning and pain to a lower dose of exercise therapy lasting 20 to 30 minutes in patients with knee OA.

CONTRIBUTORSHIP STATEMENT

Torstensen TA, Grooten WJA, Østerås H, Heijne A,-Harms-Ringdahl K and Äng B, have all actively participated in the planning and design of the study as well as the writing of this manuscript describing the research protocol of the study. Principle investigator in Sweden is Björn Äng and in Norway Havard Østerås. Tom Arild Torstensen is the assistant principle investigator for the study.

COLLABORATORS

The authors would like to acknowledge the following colleagues:

Monitoring the study:

The following colleagues are monitoring the study at respective intervention centre; In Västervik, Nisse Wallberg PT, in Luleå Mikael Sjöström PT, in Trondheim Håvard Østerås M.Sc PT and in Mosjøen Morten A Romslo PT.

Assessment and treatment of patients:

in Mosjøen (Norway), Morten Andre Romslo PT (MSc) and Iselind Thoresen PT, in Trondheim (Norway) Lasse Haugerud PT and Håvard Østerås M.Sc PT, in Luleå (Sweden) Mikael Sjöström PT, and in Västervik (Sweden) Nisse Wallberg PT and Thomas Aupers PT.

Objective functional testing:

In Mosjøen (Norway) Stine Krogh Dagsvik PT and Marte Nystad Glad PT, in Trondheim (Norway) Maria Sommervold PT and Lisa Lid PT, in Luleå (Sweden) Peter Wallström PT and in Västervik (Sweden) Erik Sjöstedt PT and Fanny Ek Nordén PT.

Local study nurse handling questionnaires and in charge of the randomization procedure locally and informing patients about follow up assessments:

In Mosjøen (Norway) Elin Slänsby and Lena Aufles, in Trondheim (Norway) Beate Iversen, in Luleå (Sweden) Katarina Söderholm, and in Västervik (Sweden) Marita Johansson.

COMPETING INTERESTS

I have read and understood the BMJ Group policy on declaration of interests and declare the following interests:

Name: Tom Arild Torstensen, Date: 2017-06-30

Declaration of interests: Teaches courses and seminars in medical exercise therapy

Name: Grooten WJA, Date: 2017-06-30

Declaration of interests: None

Name: Østerås H, Date: 2017-06-30

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Name: Heijne A, Date: 2017-06-30

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Name: Harms-Ringdahl K, Date: 2017-06-30

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Name: Äng BO, Date: 2017-06-30

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FIGURE CAPTIONS

Figure 1: The principle of deloading performing a local knee exercise.

Figure 2: The two different exercise interventions compared in this randomized trial, high dose MET (HDMET) and low dose MET (LDMET).

Figure 3. Flow chart of the design and run of the study. HDMET= High-dose MET and LDMET= Low-dose MET.

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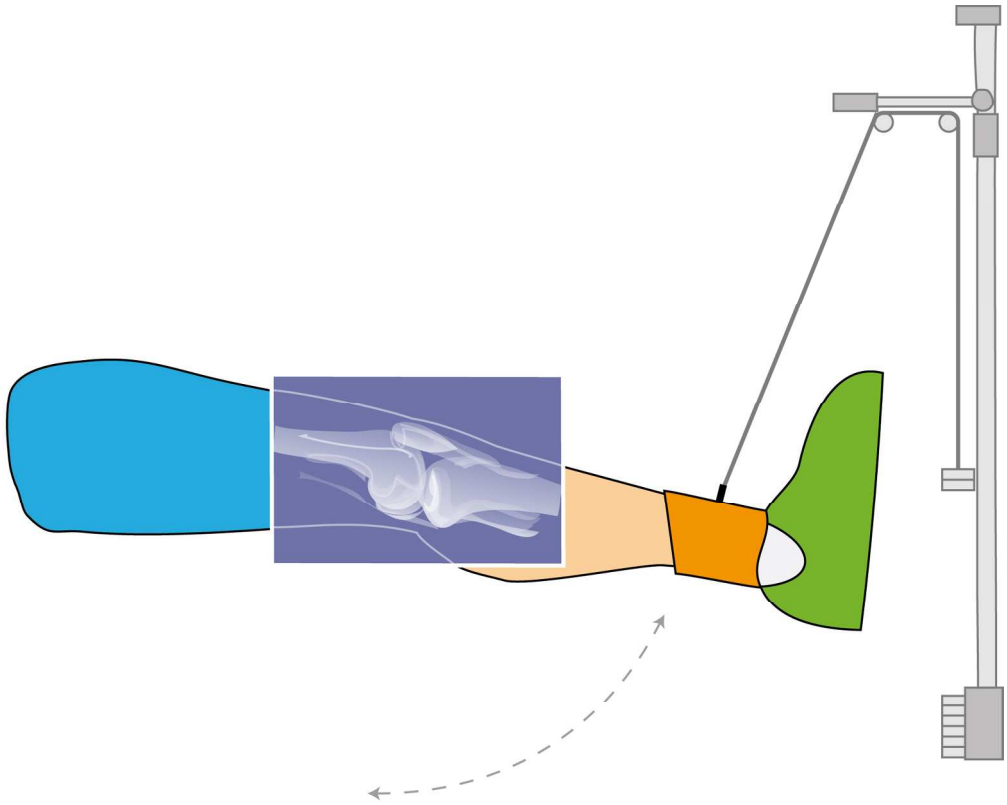

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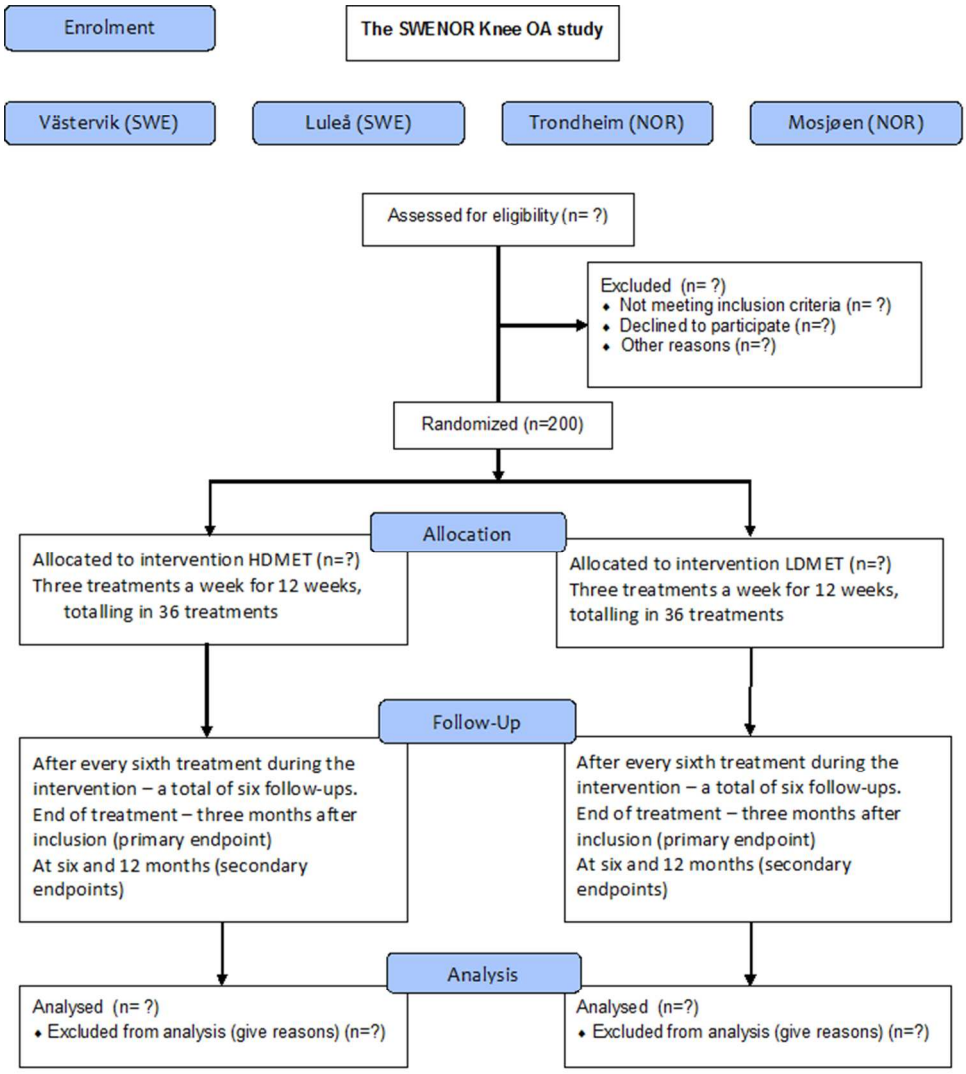

Figure 2. *Flow chart of the design and run of the study. HDMET= High-dose MET and LDMET= Low-dose MET.*

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EXERCISE	HIGH DOSE MET (70-90 MIN)	DOSE	LOW DOSE MET (20-30 MIN)	DOSE
1		GLOBAL 20 min		GLOBAL 10 min
2		SEMI GLOBAL CLOSED CHAIN 3x30 reps		SEMI GLOBAL CLOSED CHAIN 2x10 reps
3		LOCAL OPEN CHAIN 5 min		SEMI GLOBAL CLOSED CHAIN 2x10 reps
4		SEMI GLOBAL CLOSED CHAIN 3x30 reps		SEMI GLOBAL CLOSED CHAIN 2x10 reps
5		GLOBAL 10 min		SEMI GLOBAL OPEN CHAIN 2x10 reps
6		SEMI GLOBAL CLOSED CHAIN 3x30 reps		
7		LOCAL OPEN CHAIN 5 min		
8		LOCAL OPEN CHAIN 3x30 reps		
9		GLOBAL 10 min		

210x297mm (300 x 300 DPI)

HIGH DOSE MET 80-90 MINUTES | NAME:

Treatment / Exercises	1 date	2 date	3 date	4 date	5 date	6 date	7 date	8 date	9 date	10 date	11 date	12 date
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time
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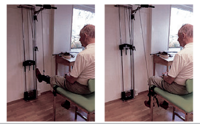	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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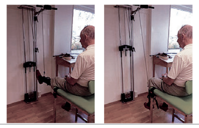	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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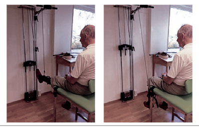
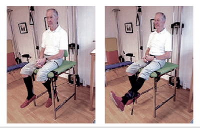
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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HIGH DOSE MET 80-90 MINUTES | NAME:

Treatment / Exercises	13 date	14 date	15 date	16 date	17 date	18 date	19 date	20 date	21 date	22 date	23 date	24 date
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time
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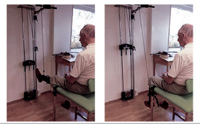	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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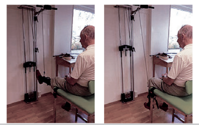	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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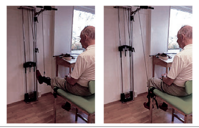
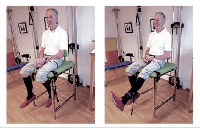
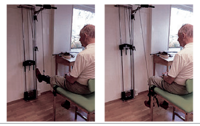
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time

HIGH DOSE MET 80-90 MINUTES | NAME:

Treatment / Exercises	25 date	26 date	27 date	28 date	29 date	30 date	31 date	32 date	33 date	34 date	35 date	36 date
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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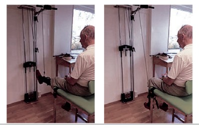	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
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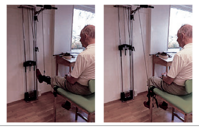
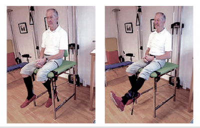
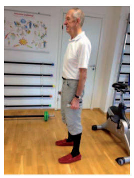
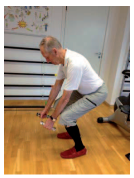
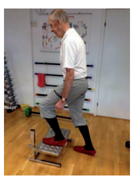
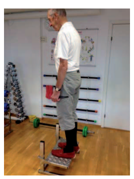
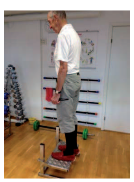
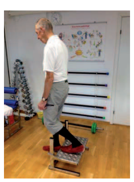
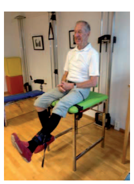
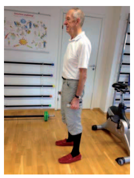
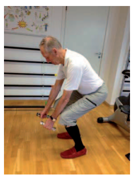
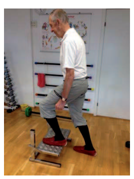
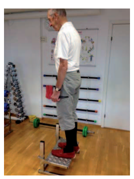
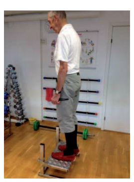
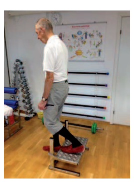
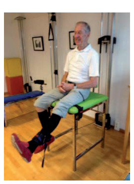
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time	Weight/Sets/Reps/Time
	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time	Borg scale/Time

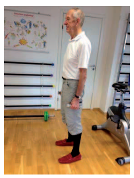
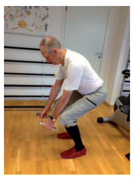
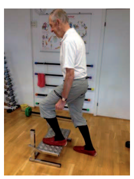
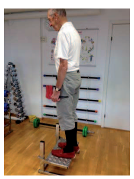
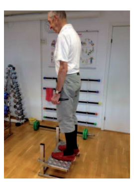
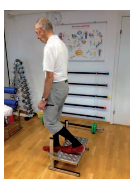
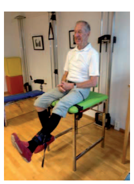
Low dose MET 30 minutes Name: ____________________

Treatment / Exercises	1	2	3	4	5	6	7	8	9	10	11	12
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time
 	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time
 	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time
 	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time
 	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time	Weight Sets Reps Time

Exercise program MET 30 minutter Name: ______________________

Treatment / Exercises	13 Date	14 Date	15 Date	16 Date	17 Date	18 Date	19 Date	20 Date	21 Dato	22 Date	23 Date	24 Date
	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time
 	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time
 	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time
 	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time
 	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time

Exercise program MET 30 minutter Name: ____________________

Treatment / Exerises	25	26	27	28	29	30	31	32	33	34	35	36
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date
	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time	Borg scale Time
 	Weight Serie Rep Time	Weight Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Serie Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time
 	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time
 	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time
 	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time	Weight Set Rep Time

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p1, line 8-10
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p2,line 27
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	p1, line 37
Funding	4	Sources and types of financial, material, and other support	p31,lines 2-5
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p1,line:13-23, p29,lne:5-10
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	p31, lines 2-5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	p14, lines 5-9,p15,lines 1-10

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p3-p10,
	6b	Explanation for choice of comparators	p10,lines 11-24 p11,linea1-4
Objectives	7	Specific objectives or hypotheses	p11,lines 7-24
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p12,line 6-14

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p12,lines17-20
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p13,lines1-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p17-20, figure 1,p 8 and fig 2 ,p 9, appendixes 1 and 2
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	p19,lines 10-17,
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P27,lines 5-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p21-23, p 24, lines1-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	page 12, figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p25,lines 14-23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p14,lines 11-16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p16,lines 16-21
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p16,lines 16-21
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p13,line 24, p14, lines 1-3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p17,lines 1-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	p15, line 23 and p17, lines 3-4

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p15,lines 1-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocol	p15,lines1-10, and page 15,lines 13-15, and page 16, lines1-5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p15,lines 1-10

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p14,lines 5-9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p14,lines 8-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p2, lines 24-26, ' page 26,lines1-4
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p14,line 8-9

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p14,lines9-11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	p14,lines20-23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p29,line1-2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p15,lines 6-8
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	p2, lines 25-26
	31b	Authorship eligibility guidelines and any intended use of professional writers	not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	not applicable, only i in Swedish and Norwegian language
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons