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Exploring the Effect of Space and Place on Response to Exercise Therapy for Knee and Hip; a protocol for a double-blind randomised controlled clinical trial. The CONEX trial

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ABSTRACT

Introduction

´Context effects' are described as effects of a given treatment, not directly caused by the treatment itself, but rather caused by the context in which treatment is delivered. Exercise is a recommended core treatment in clinical guidelines for musculoskeletal disorders. Although overall moderately effective, variation is seen in size of response to exercise across RCT studies. Part of this variation may be related to the fact, that exercise interventions are performed in different physical environments, which may affect participants differently. The study aims to investigate the effect of exercising in a contextually enhanced physical environment for 8 weeks for people with knee or hip pain.

Methods and analysis

The study is a double-blind randomised controlled trial. Eligible participants are 35 years or older with persisting knee and/or hip pain for 3 months. Participants are randomised to one of three groups; 1) exercise in contextually enhanced environment 2) exercise in standard environment 3) waiting list. The contextually enhanced environment is located in a newly built facility, has large windows providing abundant daylight, overlooking a recreational park. The standard environment is in a basement, has artificial lighting and is marked of use, i.e. resembling many clinical environments. Primary outcome is participant's global perceived effect rated on a 7-point Likert scale after 8 weeks exercise. Patient-reported and objective secondary outcomes are included.

Ethics and dissemination

Context effects may potentially add to the effect of and compliance with exercise therapy and consequently benefit people with chronic diseases, where exercise is recommended as treatment.

Trial registration: NCT02043613

Strengths and limitations of the study

The randomised controlled trial aims to investigate the effect of the physical environment on the effect of exercise therapy and focuses on the significance of the context in which treatment is delivered.

The physical environment is a single component of the multifactorial concept of contextual effect and isolating only one component may be difficult as interaction between several components may occur.

INTRODUCTION

The physical environment affects the persons in it and may potentially be of significance for health and treatment effects. Studies on the role of physical environments conducted in hospital settings have reported that factors such as noise, daylight deprivation and light intensity may increase stress and pain level, reduce patient satisfaction and affect length of hospital stay[1-5]. Many rehabilitation and hospital exercise facilities are today located in large rooms in basements or other windowless rooms with poor acoustics, not designed for optimal exercise therapy delivery. These physical environments may affect patients negatively and potentially result in a poorer result from the exercise or rehabilitation, if patients are feeling unwelcomed or are not motivated to comply with the exercise in the given environment. Theoretically, enhanced physical environments may create positive atmosphere, enhance communication during exercise and potentially improve exercise performance, compliance and perceived wellbeing. Exercise is recommended as a life-long treatment for chronic diseases such as cardiovascular diseases, diabetes and musculoskeletal disorders, including hip and knee osteoarthritis (OA) and joint pain. Despite high-level evidence that exercise provides on average moderate pain relief and functional improvement in patients with osteoarthritis, large variation in effect is observed across studies and treatment effects may vary from small to large[6, 7]. In addition to differences in characteristics of the exercise programs studied, this may also relate to the fact that exercise interventions have been performed in different physical environments and that these environments may influence patients differently [8]. It is plausible, but currently unknown, whether the physical environment can be modified in ways, that enhances the effect of exercise therapy. To our knowledge, this is the first trial to actively investigate if modification of the physical environment can be used in a positive way to enhance the effect from exercise therapy.

This study applies the term 'context effect' as a framework for elucidating how treatment effect is potentially caused by a complexity of factors in addition to the actual treatment effect. Context effects are defined as the effects of a given treatment, not directly caused by the treatment itself, but rather caused by the context or environment in which the treatment is given[8-11]. Context effects may be considered as a parallel to placebo effects, which has been one of the most debated topics in modern medicine[12-15]. Several authors have objected to the term placebo, as they argue, that the definition is self-contradictory and inadequate[9, 16-19]. Placebo is in its classical term defined as giving an inert substance or treatment[10, 18]. However, if placebos are inert, they cannot have an effect, and if they have an effect, they cannot be inert[9, 10, 16, 18]. Other terms have been suggested, such as; non-specific effect, non-characteristic effect, incidental effects, meaning response, placebo components and context effects, as applied in this study[9, 20-24]. A clear distinction should be made between placebo effects and context effects. Placebo is associated with giving pills, injections or having surgery and often entails a form of deliberate deception, whereas context effects rather classify factors creating or enhancing a treatment effect[8-11]. Factors contributing to context effects can be divided into different categories, such as; characteristics of the patient and the practitioner, type of treatment, nature of disease and the physical environment[8, 11]. This study will focus on the physical environment where exercise therapy is delivered, as it can be modified in a standardised and reproducible way to potentially enhance adherence and enhance the positive effects of exercise therapy.

The study aim is to investigate the effect of exercising in a contextually enhanced physical environment for 8 weeks for people with knee or hip pain. We hypothesize that, participants exercising according to a standardised program in a contextually enhanced physical environment will report greater improvement from exercise compared to participants following the same

exercising program in a standard physical environment as measured by patients' Global Perceived Effect (GPE). Further, we expect that the two exercise groups will be superior to a passive waiting list.

METHODS AND ANALYSIS

Study design

This study is designed as a 3-armed randomised controlled clinical trial. Participants are randomised to three intervention groups; exercise in a context enhanced physical environment (EX+ROOM), exercise in a standard physical environment (EX) or waiting list (WL). Participants, investigators and exercise instructors are blinded to treatment allocation. Primary endpoint is patient's global perceived effect assessed after 8 weeks exercise on a 7-point Likert scale. The Regional Scientific Ethical Committee for Southern Denmark has approved the study (study ID: S-20130130). It is consistent with the Helsinki Declaration and registered with www.clinicaltrials.gov (ID: NCT02043613). Results from this study will be reported according to the CONSORT statement[25].

Participants

Eligible participants are 35 years or older, self-reporting persisting knee and/or hip pain within the last 3 months and are willing and able to attend exercise therapy twice weekly at the University of Southern Denmark, Odense M. Exclusion criteria are: 1) Co-morbidities or contraindication prohibiting participation in exercise therapy; 2) Inability to answer questionnaires or to speak, read or understand Danish; 3) Already participating in exercise therapy, defined as an exercise program supervised by a physiotherapist, or systematic training with duration of 6 weeks or more started within 3 months to inclusion, aimed specifically at relieving knee or hip joint problems; 4) Having had surgery to the hip/knee within the last 3 months or waiting for joint surgery in the coming 6

months. Participants are recruited via different pathways; posters and informational leaflets at general practitioners offices, the orthopaedic department at Odense University Hospital or participant initiated contact through posters and articles in local newspapers, social media and word of mouth (figure 1).

Insert Figure 1 around here

Intervention

Participants are randomly assigned to one of three groups.

Group EX+ROOM: exercise in contextually enhanced physical environment

This exercise room is placed on the second floor in a newly build facility. It has a view to a newly reconstructed outdoor sport and recreational park. It has not prior been used in studies investigating exercise as a treatment option.

Group EX: exercise in a standard physical environment

This group will exercise in a room, which has been used in other exercise studies. The room is marked by years of use. It is placed in the basement and accessed through a series of staircases and hall-ways through the basement. This facility resembles many existing exercise facilities at hospitals and rehabilitation clinics and is considered a standard exercise environment.

Contextual factors

The physical environments are described and classified by a variety of contextual factors (**table 1**).

Acoustic properties such as speech interpretability, reverberation and background noise are measured by use of standard acoustic methods[26]. Better acoustic properties, such as shorter reverberation time and higher speech interpretability, may reduce stress and improve communication. In hospital environments high noise levels are associated with worse patient outcomes such as psychological stress and satisfaction with care[27]. Background noise (dB(A)) is measured in empty rooms. Reverberation is measured as T20, the time interval for a 20 dB decay within a room. Reverberation is a measure of how long it takes for sound to decay in a room and a long reverberation time affects speech comprehension negatively[26]. Reverberation and speech interpretability are descriptive of how well speech is perceived in a room. Speech interpretability is measured as speech clarity and transmission. Speech clarity is measured as a Clarity Index within the initial 50ms (C50), it compares early sound reflection with later sound reflection. Early sound reflections are positive for speech interpretability and later sound reflection will be perceived as noise. A high C50 indicates good speech interpretability. Speech Transmission index (STI) is a measure of sound quality in transmission from sound source to receiver. Reverberation and speech interpretability are derived from tape recordings of loud clear noises emitted in the exercise rooms. Acoustic measures are obtained from two positions in the room with small, medium and large distance to the sound source. Light intensity is assessed using an adapted method from Walch et al, 2005. Light intensity is measured using a LUX meter (Amprobe, LM-100, light meter, Everett, WA, USA) on two representative positions in the exercise rooms and additionally directly at windows, if present in the room. Three consecutive measures are obtained from each position and averaged. Light measurements are taken as close to the exercise time as possible. Daylight and brighter rooms are associated with lower pain perception and lower postoperative analgesic intake in hospital environments[28, 29]. Air quality is described by CO_2 concentration, temperature and air humidity in the exercise rooms during exercise. Air quality is assessed with an air quality data logger, set to

collect data on 30 sec. intervals (Trotec, BZ-30, data logger, Heinsberg, Germany). Furthermore, carefully selected pictures of nature scenes are hung in the contextually enhanced physical environment. Viewing nature pictures or visual stimuli of nature elements have been known to reduce stress in office setting and influence recovery time and decrease pain in patients following surgery[1, 5, 30-33].

Table 1: Descriptive environmental factors

Dimension	**Factor**	**Contextually enhanced physical environment**	**Standard physical environment**
Indoor environment	Light - Strength (Lux) - Source - Window/no window	@ Daylight + artificial light Windows, Floor to ceiling	@ Artificial light. No windows
	Air quality - CO_2 (ppm) - Temperature (˚C) - Humidity (%)	@ @ @	@ @ @
	Sound/noise - Background noise (dB(A)) - Speech clarity (C50, STI) - Reverberation (T20)	@ @ @	@ @ @
Décor	Wall decorations View	Picture of nature scenes View of nature and outdoor exercise environment	No decorations No view

Table 1: Parameters assessed in the different physical environments @ = assessed/measured and will be reported. Ppm: parts per million, C50, clarity index with first 50 ms of sound, STI: speech interpretability index, T20: reverberation time for sound decay of 20 dB.

Exercise

The exercise program for participants in the EX+ROOM and EX group is based on the standardised NEuroMuscular EXercise (NEMEX) program. It is described in detail elsewhere[34] and has previously been investigated for feasibility in patients with severe knee or hip OA[34]. The NEMEX program is based on biomechanical and neuromuscular principles, which aim to improve sensorimotor control and achieve functional stability[34]. The NEMEX program has previously been shown to be effective to relieve pain and improve function in populations with knee or hip pain such as anterior cruciate ligament injuries[35-38], meniscectomized participants[39, 40] patients with hip or knee OA undergoing total joint arthroplasty[34, 41]. Exercise is performed as group exercise and all exercise sessions are supervised. All instructors will be certified in the NEMEX program. To ensure consistency between instructors, they will participate in a two-day course, Good Life with osteoarthritis in Denmark, focusing on lower-limb osteoarthritis management and neuromuscular exercise. After completing the course all instructors will go through the exercise program with the primary investigator to ensure consistency in instructing and supervising exercise as well as going through how volume, load and progression of exercise and pre- and post-exercise pain should be documented in participants' exercise dairies. The EX+ROOM and EX group will exercise on the same weekdays, twice a week for one hour duration. An instructor will first supervise the EX+ROOM group and then the EX group. Consequently, all of the instructors will have supervised the NEMEX program in both physical environments and for the same amount of time, i.e. if an instructor supervises the EX+ROOM group then they supervise the EX group as well. This is done to ensure consistency in delivery instructions and supervision of exercise across study participants

and to ensure that any effect that a given instructors may have on the exercise and participants should be similar between physical environments.

Group WL: waiting list/control group

Participants randomised to waiting list are placed on a passive waiting list for a period of 8 weeks, and thereafter offered 8 weeks of structured resistance exercise. These participants act as an observational group and represent the natural course of disease in participants with knee and/or hip pain. After the 8 weeks when follow-up data for the current study has been collected, the participants are offered resistance exercise rather than neuromuscular exercise for logistic reasons, such as avoiding taking up place in the designated exercise rooms used in the study and consequently affecting the time to completion of the study.

Primary outcome

Participants' Global Perceived Effect (GPE) assessed at 8 weeks will be the primary endpoint of the trial. Participants are asked to respond to the following question; *"Compared to before you entered the study, how are your knee/hip problems now?"* on a 7-point Likert scale. The GPE scale ranges from 'markedly worse' through 'no change' to 'markedly improved'. GPE is a reliable method for measuring the effect of clinical interventions[42, 43]. It has prior been used in studies investigating contextual effect of treatment[44]. The validity of GPE scales has been questioned. However, a study on the correlation between transition ratings and pre and post score of quality of life questionnaires showed a correlation of 0.8 between the change score of the questionnaire and the transition ratings suggesting that transition scales, such as global perceived effects, are valid for detecting changes and can be used in clinical trials as primary outcome measures[43].

Secondary outcomes

All outcomes and time points for data collection are listed in **table 2**.

Table 2: Summary of collected data and time points

Variable	Baseline	4 weeks	8 weeks
Baseline data			
Height (cm)	@	n.a.	@
Weight (kg)	@	n.a.	@
Age (yrs.)	@	n.a.	n.a.
Gender (f/m)	@	n.a.	n.a.
Marital status	@	n.a.	n.a.
Educational level	@	n.a.	n.a.
Employment status	@	n.a.	n.a.
Alcohol consumption	@	n.a.	n.a.
Smoking	@	n.a.	n.a.
Physical activity level at work and leisure	@	n.a.	n.a.
Primary outcome			
Global Perceived Effect (7 point Likert scale).	n.a.	@	@
Secondary outcomes			
Patient reported outcomes			
Knee/Hip Injury and Osteoarthritis Outcome Score	@	@	@
Short-form 36 Health Survey	@	@	@
Modified Arthritis Self-Efficacy Scale	@	@	@
Patient Acceptable Symptom State (y/n)	n.a.	n.a.	@
Patient satisfaction (5 point Likert scales).	n.a.	n.a.	@
Stress (100 mm VAS)	@	n.a.	@

Objective physical function tests			
Aerobic capacity (ml O_2/min/kg)	@	n.a.	@
Isometric strength hip abduction (Nm)	@	n.a.	@
Isometric strength knee extension (Nm)	@	n.a.	@
Single-limb mini squat	@	n.a.	@
Knee bends/30 sec. (no.)	@	n.a.	@
Chair stands/30 sec. (no.)	@	n.a.	@
Walking test, 40 m fast paced. (sec)	@	n.a.	@
One-leg hop of distance (cm)	@	n.a.	@

Table 2: Summary of primary and secondary outcomes and respective time collection points, @ = assessed/measured, n.a. = not assessed VAS: visual analogue scale.

Patient reported outcomes

Participants answer the Danish versions of the Knee injury and Osteoarthritis Outcome Score (KOOS) or The Hip disability and Osteoarthritis Outcome Score (HOOS) depending on either knee or hip problems being primary complaint. The KOOS and the HOOS are joint-specific questionnaires, developed to assess participants' opinion about their knee or hip problems[45, 46]. KOOS/HOOS consists of 5 subscales; pain, symptoms, activities of daily life function, sport and recreational function and joint related quality of life [47]. Each subscale consists of a set of items specific to the subscale and each item is assed via a Likert scale with 5 possible answer options ranging from 0 (no problems) to 4 (extreme problems). The Likert score is transformed to a 0-100 scale with zero representing extreme knee problems and 100 representing no knee problems[45]. KOOS and HOOS have good psychometric properties for patient groups with knee injury, knee replacement, hip dysfunction and hip replacement[46-50].

The Medical Outcome Study 36-item short form general health survey (SF-36) is a generic patient-reported health status measure[51-53]. It consists of 36 items organised under 8 subscales; 1) physical functioning, 2) role limitations because of physical health, 3) bodily pain, 4) social functioning, 5) general mental health, 6) role limitations because of emotional problems, 7) vitality, and 8) general health perception[53]. Low scores indicate limitations in activities and a perception of poor health, high score indicate no limitations and good health [53]. Validity and reliability of the SF-36 is adequate and the questionnaire is widely used[51, 52].

A modified measure of self-efficacy is included to evaluate patients' perception of functionality or limitations to their functionality caused by their knee of hip problem. Self-efficacy is defined by Bandura as "belief in one's capability to organise and execute the course of action required to produce given attainments[54]. Self-efficacy is assessed with a modified version of the Arthritis Self-Efficacy Scale (ASES)[55] previously used in a similar patient group[56]. The modified version of ASES consists of 11 single items from the two subscales pain and other symptoms. Participants rate their ability to cope with pain and symptoms related to their joint problem, on a10-100 scale, with 10 indicating very uncertain and 100 indicating very certain with 10 point increments[57].

Patient reported outcomes are collected using an online survey. At baseline and 8 weeks follow-up participants answer the survey on a computer in the examination room without the investigator present. At 4-week follow-up an email is sent to participants, who answer at home. To ensure high data completion an email reminder is sent, if no reply is received within 3-5 days. Further, participants are called by phone if there is no reply to the reminder e-mail.

A series of single item questions are included. Patient Acceptable Symptom State is assessed by asked a single yes/no question; "Considering your knee function, do you feel that your current state as satisfactory? With knee function you should *take into account all the activities you have during your daily life, your level of pain and other symptoms and your quality of life"*[58]. If participants rate

their current symptom state as unacceptable, a follow-up question is asked as to if they consider the treatment to have failed. Further, participants are asked to answer five global perceived effects questions specific for each of the five subscales of either KOOS or HOOS, rating either improvement or deterioration and finally an indication of whether these changes are perceived as important of unimportant by the participants. These single items are included in order to assess minimal clinical important changes for the five subscales of the KOOS and HOOS. Stress is estimated as 'general stress level' measured on a 100 mm visual analogue scale ranging from no stress to stress as severe as could be[59].

Functional performance

Patients' aerobic capacity is estimated during a submaximal work rate bicycle test[60]. Patients pedal until reaching a steady state, with a stabile pulse rate ranging between 120 to 170 beats per minute, normally within 6-7 minutes[60]. Participants' aerobic capacity is estimated from work rate and stabile pulse rate by use of Åstrand's Nomogram[60].

Maximal isometric knee extension and hip abduction strength will be tested using dynamometry (JTECH medical, Commander Echo, Salt Lake City, Utah, USA). A suction cup is mounted on a door behind the examination couch. A strain gauge, measuring pull in newton, is placed in between the suction cup and a fixation belt strapped around the participant's ankle above the lateral malleoli. For knee extension, participants sit on an examination couch with a hip angle of 90° and a knee angle of 90°. Participants are asked to press against their foot the belt in a forward motion. The distance from the knee joint axis to the middle of the fixation belt is measured. Consequently, isometric muscle strength is measured as torque. For hip abduction, participants lie on the couch with their leg strait and are asked to press their lateral malleoli against the belt. The distance from the trochanter major on the femoral bone to the middle of the fixation belt is measured. One practice

trial is allowed and thereafter three maximal contractions are performed separated by a 60 sec. pause. Isometric muscle strength is normalised to body weight to increase comparability. The methods for assessing isometric muscle strength have been adapted from Thorborg et al. who reported good inter-tester reliability with an interclass correlation coefficient ranging from 0.76 – 0.95 and standard error of measurement between 5.0% to 10.4% for hip and knee strength assessments[61].

Physical function is assessed by 5 performance tests; 1) single limb mini squats[62], 2) number of knee bendings on one leg during 30 sec standing[63, 64], 3) number of chair stands during 30 sec[65, 66], 4) 40 m fast-paced walking test[65] and 5) one leg hop for distance[63]. All performance tests have been found valid to assess lower extremity function in different patient groups with knee or hip problems[63, 66-68]. As large variation regarding age and function within participants of this trial is expected, and therefore a test battery with a wide range of difficulty of the performance tests is chosen to ensure that all participants would be challenged. A floor effect may be evident in the one leg hop for distance test as some participants may not be able to hop at all. No ceiling effects are expected for any of the functional performance measures.

Explanatory outcomes and nested qualitative study

To investigate how the physical environment and other potential context factors, such as participant and practitioner interaction and behaviour, may interact and mediate the treatment effects, explanatory outcomes are included. Explanatory outcomes have been selected to explain the process by which context effects work and possibly elucidate which elements within the physical environment that enhance treatment effects and how these elements affect the patients and practitioners. A qualitative study will be embedded within the randomised controlled trial design. The aim of the qualitative study is to investigate, how the participants experience the two different

physical environments. Observation is performed in both rooms during exercise sessions to describe and identify behaviour of practitioners and participants specific to the different physical environments. Focus group interviews will be conducted with participants to investigate their experiences with the exercise environments and to invite participants to articulate and elaborate on their thoughts on how the physical environment has affected them. Three focus group interviews will be conducted with a total of 10 to 20 participants from the contextually enhanced physical environment and 3 focus group interviews with similar number of participants from the standard physical environment, i.e. 6 focus groups in total. Participants invited to the focus groups will be those randomized to exercise in the RCT design (group EX+ROOM and group EX). The interviews will be transcribed and analysed using thematic coding comparing within and across the different physical environments. Additionally, in-depth individual interviews will be performed with 6 participants. To ensure the blinding of participants throughout the study all interviews will be conducted after the intervention and after follow-up testing has been completed.

Additionally, a patient reported outcome 'participant satisfaction' is reported as participants' satisfaction with the exercise intervention in itself as well as satisfaction with specific contextual factors within the physical environment. Eleven single items scoring the different factors of the physical environment such as lighting, cleanliness, access, decoration etc. are administered to participants in intervention groups EX+ROOM and EX. The items are adapted from Tsai et al.[69]. Satisfaction is scored on a 5-point Likert scale ranging from 1 to 5 (1=strongly dissatisfied, 2=dissatisfied, 3=fair, 4=satisfied, and 5=strongly satisfied).

Compliance and adverse events

In the two exercise groups, compliance is considered good at 75% or if 12 of 16 possible exercise sessions are attended. Participants in the WL group are asked at 8 weeks follow-up, whether they

have started any exercise courses with the last 8 weeks. If answering yes, they are asked to describe the change. This is done in order to account for compliance to the waiting list design. Self-reported adverse events occurring in-between exercise sessions are recorded at 4 and 8 weeks in the online survey. Adverse events are defined as any events that the participants found restricting them physically, mentally or socially. Participants also indicate whether of they have been in contact with either their general practitioner or the hospital in relation to their adverse event. Any adverse events occurring during the exercise sessions are recorded by the supervising instructors.

Randomisation

Randomisation is performed immediately after baseline assessment and is administered by a research coordinator, not otherwise involved in the study. Patients are consecutively assigned and given a numbered, sealed, opaque envelope entailing treatment allocation. The randomisation sequence is computer-generated and prepared by a statistician with no clinical involvement in conducting the trial. To avoid imbalances in treatment allocation among people with knee and hip pain, two block randomisation lists were computer-generated (with a 2:2:1 allocation). The block size is kept secret to maintain blinding; each block consisted of either 5 or 10 patients. The randomisation lists and envelopes are kept in a secure location at the university.

Blinding procedure

Participants are blinded to the study aim in order to avoid excess focus on the physical environment, which potentially could exaggerate context effects from the physical environment. Participants are therefore informed that they are participating in a study evaluating the effects from exercise compared to being on a waiting list and are not made aware that the true aim of the study is to investigate the possible additional effect from an enhanced physical environment on exercise. The

instructors supervising the exercise sessions are neither informed about the true aim of the study. However, they are aware that exercise sessions are performed in different rooms as they supervise sessions in both rooms. The instructors have been informed that the different exercise rooms are used for practical and logistic reasons. The primary investigator conducting baseline and follow-up testing is also blinded to treatment allocation and participants are instructed to not to speak about the intervention with the investigator, thereby keeping blinding intact.

Sample size estimation and power considerations

This study is designed as a superiority trial with three groups (EX+ROOM, EX and WL). Since this is the first study to investigate the additional effect of an enhanced physical environment on the effect of exercise therapy as treatment for knee or hip pain, there are no previous data to base our sample size estimation on. Thus the power calculation is based on factors such as feasibility, i.e. how many participants will be realistic to include with the recruitment period and pragmatic issues such as availability and capacity of the different exercise rooms. Taking these aspects into consideration 100 participants will be included into the trial. To be able to account for the natural disease progression or regression towards the mean the waiting list (WL) is included in the design. A randomisation with a 2:2:1 allocation is chosen and thus 40 participants are randomised to EX+ROOM and EX groups, respectively, and 20 participants are randomised to the WL group. We anticipate that individuals in the WL group will experience limited effect. With 40 subjects in each of the two exercise groups (EX+ROOM and EX), we are able to detect a difference of 0.75 on the GPE scale ranging from -3 to 3 with a standard deviation of 1.2, a p-value of 0.05 and a power of 80%.

Statistical evaluation

All three intervention groups (EX+ROOM, EX and WL) will be examined for comparability at baseline with respect to demographic factors using ANalysis Of VAriance (ANOVA) and Chi-squared test as appropriate.

The primary analysis on the GPE data will be conducted with a Student's unpaired t-test comparing the EX+ROOM intervention group with EX intervention group at the 8-week follow-up. The Bonnet-Price median test will be conducted if assumption of normality in the GPE data is not supported. The WL intervention group is considered a reference group describing the natural progression of disease for the included study population and is not included in the primary analysis. However, to check the general assumption, that exercise is more effective than no intervention, an unpaired t-test is conducted to compare the exercise groups with the waiting list.

The secondary outcomes, the KOOS/HOOS, SF-36, ASES and physical function outcomes are analysed as repeated measures (i.e. change from baseline over 4 and 8 weeks follow-up for patient reported outcomes and baseline to 8 week follow-up for physical function tests) applying a mixed linear effects model with 'participant' as random effect and sex, age and joint as fixed effects. As for the primary outcome, only the EX+ROOM and EX groups are compared. Additionally, to test an *a priori* hypothesis of a graded relationship between groups EX+ROOM > EX > WL a linear test for trend will be conducted as an explanatory analysis on all outcomes. Here, a χ^2 test for trend is applied for dichotomous outcomes and a linear test for trend is applied for continuous outcomes. Pairwise comparison of groups will be conducted if the trend test was significant, to describe the association between group and outcome, i.e. EX+ROOM vs EX and EX vs WL. For dichotomised outcomes a χ^2 test is applied, and for continuous ANOVA is applied.

Intention-to-treat analysis is performed and last observation is carried forward for missing data at follow-up for the secondary outcomes. The primary outcome is a transition score, which is not assessed as baseline. For any participants lost to follow-up GPE data will be missing. Further, a per-

protocol analysis is conducted including only those with good compliance with the exercise intervention (participated in at least 12 of 16 sessions) in the EX+ROOM and EX groups, respectively.

A detailed statistical analysis plan will be drafted and made publicly available before breaking randomisation code and conducting data analysis. To further minimise the risk for bias introduced during analysis and interpretation, data analysis will be performed by a third party not otherwise related to the study. Intervention groups will be allocated with arbitrary names. Interpretation will be performed by the primary investigator in collaboration with the research team prior to revealing treatment allocation, thereby interpreting the results blindly[70]. Consequently, two interpretation scenarios will be drafted on the basis of the primary outcome data, i.e. comparing treatment A with treatment B. One assuming that group A will be the EX+ROOM group and another assuming that A will be the EX group.

ETHICS AND DISSEMINATION

Context effects may constitute an important part of the effects of exercise therapy. Investigating context effects will provide knowledge on how the physical environment may be exploited to enhance the effects of exercise therapy in addition to the effect of the specific exercise. Exercise is an effective and widely used core treatment strategy for chronic diseases, such as musculoskeletal disorders, cardio vascular disease and diabetes. Adding to the effect of exercise through context effects from a contextually enhanced physical environment in exercise facilities may be highly beneficial for patients across a number of diseases.

Previous research in context effects from physical environments has been conducted in hospital settings[27]. A comprehensive review from 2008 showed that certain elements within a hospital

context such as noise and lighting level have impact on number of medical errors as well as increased pain and stress levels for patients and staff[27]. Research in other health care settings has been sparse. During an initial literature review only one study was identified investigating physical therapy and its relation to the physical environment. The literature review comprised groups of search terms for context effects, exercise/physical therapy and terms for physical environments. Articles were search for in Medline, Scopus and single specific journals such as Health Environment Research and Design journal. When reviewed, this single study used observation, surveys and interviews to learn more about the design of a hospital roof-top garden rather than investigating if the physical environment had an additional effect on the physical therapy[71]. Further, the therapy of the study was described as activities including gardening, golf putting and events such as concerts or barbeques, not regular exercise. Consequently, this is to our knowledge the first study investigating if there is an effect from an enhanced physical environment in addition to exercise when compared to exercise performed in a standard setting.

The three-armed RCT design of the present study has several advantages. It has been widely discussed whether the placebo effect can be explained by spontaneous remission or regression towards the mean[15, 72-74]. To rule out either of these as explanatory factors of a possible effect, the waiting list group is included into the design as an untreated reference group. The waiting list group illustrates the natural course of disease for the study population during the study period. Consequently, if a difference is seen between the two exercise rooms, the waiting list group enables an assessment of whether the difference is caused by spontaneous remission by comparing the exercise groups to the waiting list. To optimise the number of study participants, a 2:2:1 allocation with half the number of participants allocated to the waiting list is chosen. The three-armed design

also allows for a test for trend across groups. This form of analysis has been previously applied in a study investigating context effects originating from patient and practitioner interaction[44].

Context effects are a multifactorial concept and several factors, other than the physical environment, may contribute to the context effect of a given treatment. Literature reviews on context effect have additionally suggested factors, such as characteristics of patients/participants, practitioner/instructors or treatment and nature of disease as potentially contributing to the total context effect and theoretically, components may interact and possibly have synergistic effects[8, 9, 16, 24, 75]. Especially the interaction between patient and practitioner has been suggested as a significant contributor to context effects[44, 76-85]. In a recent study, Kaptchuk et al. found, that patients with irritable bowel syndrome, who were treated by a warmer and friendlier practitioner, had significantly better results from sham-acupuncture, than patients treated by a practitioner, who limited eye-contact and avoided conversation[44]. Similarly, Suarez-Almazor et al. found that knee osteoarthritis patients treated with sham-acupuncture by a practitioner, who expressed high expectations to the treatment, had better outcomes than those treated by a practitioner with a neutral position towards treatment effects[83]. Although the interaction between patient and practitioner is suggested as the most robust component of context effect, behaviour, communication and interaction between patient and practitioner is difficult to change and may be hard to reproduce. An advantage in exploiting the potential context effect from the physical environment is that, the components of the environment can be thoroughly described and more easily implemented or changed in existing exercise environments.

There are some limitations to the study design that must be acknowledged. The multifactorial concept of context effects questions whether the physical environment can be isolated and studied

alone. Several actions are taken to isolate the physical environment as the only difference between groups in this trial. The exercise program is standardised and delivered in a group fashion by the same instructors and all instructors have supervised in both physical environments. Consequently, treatment characteristics are similar between the intervention groups. Participants' characteristics, known and unknown, should be equally distributed between groups as a result of the randomisation process. Any specific characteristics that may origin from the instructor or from instructor-participant interaction should also be comparable between groups, as instructors supervise in both rooms.

Additionally, the nested qualitative study is aimed to investigate how the physical environment may affect behaviour of the participants or instructors or the interaction between them. The study will elucidate these issues and help explain the process of how a standard and enhanced physical environment affects participants and instructors.

The primary ethical concern in this study is that the true aim of the study is withheld from participants. Withholding the aim disables participants to consider the implications of the research and to assess whether or not they want to contribute to investigating this aim. However, blinding the true aim is imperative to the study design as an effect from the physical environment may be over- or underestimated, if participants are explicitly made aware of the actual aim of the study. Participants are therefore told that the study is designed to investigate the effect of neuromuscular exercise as an early treatment strategy for musculoskeletal pain. Similarly the supervising instructors are also blinded to the true aim of the study. Instructors are aware that the exercise is performed in different environments, but are told this due to logistic reasons. The ethics committee has been explicitly made aware that study participants and instructors are not made aware of the true study aim and despite this sanctioned the study without any reservations or conditions.

This study is designed to investigate the significance of the physical environment for the effects of exercise therapy and rehabilitation. The design of the study is novel and the results will provide knowledge on the significance of creating an optimal context for exercise therapy. Further studies investigating context effects of treatment are warranted to further enhance treatment effects.

List of abbreviations used

CONEX: CONtext effect in EXercise.

RCT: Randomised Controlled Trial

OA: OsteoArthritis

GPE: participant's Global Perceived Effects.

EX+ROOM: EXercise in a context enhanced physical environment

EX: EXercise in a standard physical environment.

WL: waiting list

T20: Time for 20dB decay

C50: Clarity index, for initial 50 ms.

STI: Speech Interpretability Index

NEMEX: NEuroMuscular EXercise.

KOOS: the Knee Osteoarthritis and injury Outcome Score

HOOS: the Hip disability and Osteoarthritis Outcome Score

SF-36: Short-Form (36 item) Health Survey

ASES: Arthritis Self-Efficacy Scale

MVC: Maximal Voluntary Contraction.

ANOVA: ANalysis Of VAriation

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Peter Møller Juhl, MSc EE, PhD, Associate Professor for assisting in measuring acoustic properties, and Anne Marie Rosager for invaluable help during the randomisation process. The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

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Competing interests

The listed author(s) have no competing interests to declare.

Author's contributions

LFS, JBT, RU, PD and ER were involved in the design of the study. All authors contributed to drafting the manuscript or revising it. All authors read, commented and approved the manuscripts for publication.

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Figure legend

Figure 1: Flow chart, overview of the recruitment flow in the CONEX trial.

References

1. Ulrich R. View through a window may influence recovery from surgery. Science 1984;**224**(4647):420-21.
2. Ulrich R, Simons RF, Losito BD, et al. Stress recovery during exposure to natural and urban environments. Journal of enviromental psychology 1991;**11**:201-30.
3. Parish JT, Berry LL, Lam SY. The effect of the servicescape on service workers. J Serv Res-Us 2008;**10**(3):220-38.
4. Malenbaum S, Keefe FJ, Williams AC, et al. Pain in its environmental context: implications for designing environments to enhance pain control. Pain 2008;**134**(3):241-4.
5. Kweon BS, Ulrich RS, Walker VD, et al. Anger and stress - The role of landscape posters in an office setting. Environment and Behavior 2008;**40**(3):355-81.
6. Fransen M, McConnell S, Bell M. Therapeutic exercise for people with osteoarthritis of the hip or knee. A systematic review. The Journal of Rheumatology 2002;**29**(8):1738-46.
7. Fransen M, McConnell S. Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. J Rheumatol 2009;**36**(6):1109-17.
8. Di Blasi Z, Harkness E, Ernst E, et al. Influence of context effects on health outcomes: a systematic review. The Lancet 2001;**357**(9258):757-62.
9. Miller FG, Kaptchuk TJ. The power of context: reconceptualizing the placebo effect. J R Soc Med 2008;**101**(5):222-5.

10. Koshi EB, Short CA. Placebo theory and its implications for research and clinical practice: A review of the recent littrature. Pain practice : the official journal of World Institute of Pain 2007;**7**(1):4-20.

11. Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Ann Intern Med 2002;**136**(11):817-25.

12. Beecher HK. The Powerful Placebo. Jama-J Am Med Assoc 1955;**159**(17):1602-06.

13. Miller FG, Rosenstein DL. The nature and power of the placebo effect. J Clin Epidemiol 2006;**59**(4):331-5.

14. Hrobjartsson A. The uncontrollable placebo effect. Eur J Clin Pharmacol 1996;**50**(5):345-8.

15. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. The New England journal of medicine 2001;**344**(21):1594-602.

16. Barrett B, Muller D, Rakel D, et al. Placebo, meaning, and health. Perspect Biol Med 2006;**49**(2):178-98.

17. Breidert M, Hofbauer K. Placebo: Misunderstandings and prejudices. Deutsches Arzteblatt international 2009;**106**(46):751-55.

18. Margo CE. The placebo effect. Surv Ophthalmol 1999;**44**(1):31-44.

19. Grunbaum A. The Placebo Concept. Behav Res Ther 1981;**19**(2):157-67.

20. Doherty M, Dieppe P. The "placebo" response in osteoarthritis and its implications for clinical practice. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2009;**17**(10):1255-62.

21. Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. BMJ 2005;**330**(7501):1202-5.

22. Dellmann T, Lushington K. How can complementary medicine practitioners enhance non-specific effects? journal of the Australian Traditional-Medicine Society 2008;**14**(1):13-17.

23. Dieppe P, Doherty M. Contextualizing osteoarthritis care and the reasons for the gap between evidence and practice. Clin Geriatr Med 2010;**26**(3):419-31.

24. Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. Ann Intern Med 2002;**136**(6):471-6.

25. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med 2010;**8**.

26. Kuttruff H. *Room acoustics*. London: Spon Press, 2000.

27. Ulrich RS, Zimring C, Zhu XM, et al. A Review of the Research Literature on Evidence-Based Healthcare Design. Herd-Health Env Res 2008;**1**(3):61-125.

28. Shepley MM, Gerbi RP, Watson AE, et al. The Impact of Daylight and Views on ICU Patients and Staff. Health Environments Research & Design Journal (HERD) 2012;**5**(2):46-60.

29. Walch JM, Rabin BS, Day R, et al. The effect of sunlight on postoperative analgesic medication use: A prospective study of patients undergoing spinal surgery. Psychosom Med 2005;**67**(1):156-63.

30. Ulrich RS. Human Responses to Vegetation and Landscapes. Landscape Urban Plann 1986;**13**(1):29-44.

31. Ulrich RS. Natural Versus Urban Scenes - Some Psychophysiological Effects. Environment and Behavior 1981;**13**(5):523-56.

32. Tse MMY, NG JKF, Chung JWY, et al. The effect of visual stimuli on pain threshold and tolerance. J Clin Nurs 2002;**11**:462-69.

33. Diette GB, Lechtzin N, Haponik E, et al. Distraction therapy with nature sights and sounds reduces pain during flexible bronchoscopy: a complementary approach to routine analgesia. Chest 2003;**123**(3):941-8.

34. Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patients with severe hip or knee OA: the individualized goal-based NEMEX-TJR training program. BMC Musculoskelet Disord 2010;**11**:126.

35. Zätterström R, Friden T, Linstrand A, et al. Early rehabilitation of acute anterior cruciate ligament injury - a randomized clinical trial. Scand J Med Sci Sports 1998(8):154-59.

36. Ageberg E, Zätterström R, Moritz U, et al. Influence of Supervised and Nonsupervised Training on Postural Control After an Acute anterior Cruciate Ligament Rupture: A Three-year Longitudinal Prospective Study. J Orthop Sports Phys Ther 2001;**31**(11):632-44.

37. Ageberg E. Consequences of a ligement injury on neuromuscular function and relevance to rehabilitation - using the anterior cruciate ligament injured knee as model. J Electromyogr Kinesiol 2002;**12**:205 - 12.

38. Zätterström R, Friden T, Lindstrand A, et al. Muscle training in chronic anterior cruciate ligament insufficiency--a comparative study. Scand J Rehabil Med 1992;**24**(2):91-7.

39. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. Arthritis Rheum 2005;**52**(11):3507-14.

40. Ericsson YB, Dahlberg LE, Roos EM. Effects of functional exercise training on performance and muscle strength after meniscectomy: a randomized trial. Scand J Med Sci Sports 2009;**19**(2):156-65.

41. Villadsen A, Overgaard S, Holsgaard-Larsen A, et al. Postoperative effects of neuromuscular exercise prior to hip or knee arthroplasty: a randomised controlled trial. Ann Rheum Dis 2013.

42. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. J Man Manip Ther 2009;**17**(3):163-70.

43. Guyatt GH, Norman GR, Juniper EF, et al. A critical look at transition ratings. J Clin Epidemiol 2002;**55**(9):900-8.

44. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008;**336**(7651):999-1003.

45. Roos E, Lohmander S. The knee injury and osteoarthritis outcome score (KOOS) - from joint injury to osteoarthritis. Health and Quality of Life Outcomes 2003.

46. Klassbo M, Larsson E, Mannevik E. Hip disability and osteoarthritis outcome score. An extension of the Western Ontario and McMaster Universities Osteoarthritis Index. Scand J Rheumatol 2003;**32**(1):46-51.

47. Roos E, Roos H, Lohmander S, et al. Knee injury and osteoarthritis outcome score (KOOS) - development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998;**78**(2):88-96.

48. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcomes 2003;**1**:17.

49. Roos EM, Roos HP, Ekdahl C, et al. Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. Scand J Med Sci Sports 1998;**8**(6):439-48.

50. Nilsdotter AK, Lohmander LS, Klassbo M, et al. Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement. BMC Musculoskelet Disord 2003;**4**:10.

51. Mchorney CA, Ware JE, Raczek AE. The Mos 36-Item Short-Form Health Survey (Sf-36) .2. Psychometric and Clinical-Tests of Validity in Measuring Physical and Mental-Health Constructs. Med Care 1993;**31**(3):247-63.

52. Mchorney CA, Ware JE, Lu JFR, et al. The Mos 36-Item Short-Form Health Survey (Sf-36) .3. Tests of Data Quality, Scaling Assumptions, and Reliability across Diverse Patient Groups. Med Care 1994;**32**(1):40-66.

53. Ware JE, Sherbourne CD. The Mos 36-Item Short-Form Health Survey (Sf-36) .1. Conceptual-Framework and Item Selection. Med Care 1992;**30**(6):473-83.

54. Bandura A. Self-Efficacy - toward a Unifying Theory of Behavioral Change. Psychol Rev 1977;**84**(2):191-215.

55. Lorig K, Chastain RL, Ung E, et al. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. Arthritis Rheum 1989;**32**(1):37-44.

56. Skou ST, Odgaard A, Rasmussen JO, et al. Group education and exercise is feasible in knee and hip osteoarthritis. Dan Med J 2012;**59**(12):A4554.

57. Brady TJ. Measures of self-efficacy: Arthritis Self-Efficacy Scale (ASES), Arthritis Self-Efficacy Scale-8 Item (ASES-8), Children's Arthritis Self-Efficacy Scale (CASE), Chronic Disease Self-Efficacy Scale (CDSES), Parent's Arthritis Self-Efficacy Scale (PASE), and Rheumatoid Arthritis Self-Efficacy Scale (RASE). Arthritis Care Res (Hoboken) 2011;**63 Suppl 11**:S473-85.

58. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;**64**(1):34-7.

59. Lesage FX, Berjot S. Validity of occupational stress assessment using a visual analogue scale. Occup Med (Lond) 2011;**61**(6):434-6.

60. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol 1954;**7**(2):218-21.

61. Thorborg K, Bandholm T, Holmich P. Hip- and knee-strength assessments using a hand-held dynamometer with external belt-fixation are inter-tester reliable. Knee Surg Sports Traumatol Arthrosc 2013;**21**(3):550-5.

62. Ageberg E, Bennell KL, Hunt MA, et al. Validity and inter-rater reliability of medio-lateral knee motion observed during a single-limb mini squat. BMC Musculoskelet Disord 2010;**11**.

63. Bremander AB, Dahl LL, Roos EM. Validity and reliability of functional performance tests in meniscectomized patients with or without knee osteoarthritis. Scand J Med Sci Sports 2007;**17**(2):120-7.

64. Thorlund JB, Aagaard P, Roos EM. Thigh muscle strength, functional capacity, and self-reported function in patients at high risk of knee osteoarthritis compared with controls. Arthritis Care Res (Hoboken) 2010;**62**(9):1244-51.

65. Dobson F, Hinman RS, Hall M, et al. Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. Osteoarthritis Cartilage 2012;**20**(12):1548-62.

66. Dobson F, Hinman RS, Roos EM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage 2013.

67. Wright AA, Cook CE, Baxter GD, et al. A comparison of 3 methodological approaches to defining major clinically important improvement of 4 performance measures in patients with hip osteoarthritis. J Orthop Sports Phys Ther 2011;**41**(5):319-27.

68. Gill S, McBurney H. Reliability of performance-based measures in people awaiting joint replacement surgery of the hip or knee. Physiother Res Int 2008;**13**(3):141-52.

69. Tsai CY, Wang MC, Liao WT, et al. Hospital outpatient perceptions of the physical environment of waiting areas: the role of patient characteristics on atmospherics in one academic medical center. BMC Health Serv Res 2007;**7**.

70. Jarvinen TLN, Sihvonen R, Bhandari M, et al. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. J Clin Epidemiol 2014;**67**(7):769-72.

71. Davis BE. Rooftop Hospital Gardens for Physical Therapy: A Post-Occupancy Evaluation. Health Environments Research & Design Journal (HERD) 2011;**4**(3):14-43.

72. Hrobjartsson A, Gotzsche PC. Placebo treatment versus no treatment. Cochrane database of systematic reviews 2003(1):CD003974.

73. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med 2004;**256**(2):91-100.

74. Thompson WG. Placebos: a review of the placebo response. The American journal of gastroenterology 2000;**95**(7):1637-43.

75. Di Blasi Z, Kleijnen J. Context effects. Powerful therapies or methodological bias? Eval Health Prof 2003;**26**(2):166-79.

76. Lang EV, Hatsiopoulou O, Koch T, et al. Can words hurt? Patient-provider interactions during invasive procedures. Pain 2005;**114**(1-2):303-09.

77. Benedetti F, Amanzio M. The placebo response: how words and rituals change the patient's brain. Patient Educ Couns 2011;**84**(3):413-9.

78. Bensing JM, Verheul W. The silent healer: the role of communication in placebo effects. Patient Educ Couns 2010;**80**(3):293-9.

79. Essers G, Kramer A, Andriesse B, et al. Context factors in general practitioner - patient encounters and their impact on assessing communication skills - an exploratory study. BMC Fam Pract 2013;**14**.

80. Griffin SJ, Kinmonth AL, Veltmn MWM, et al. Effect on health-related outcomes of interventions to alter the interaction between patients and practitioners: A systematic review of trials. Ann Fam Med 2004;**2**(6):595-608.

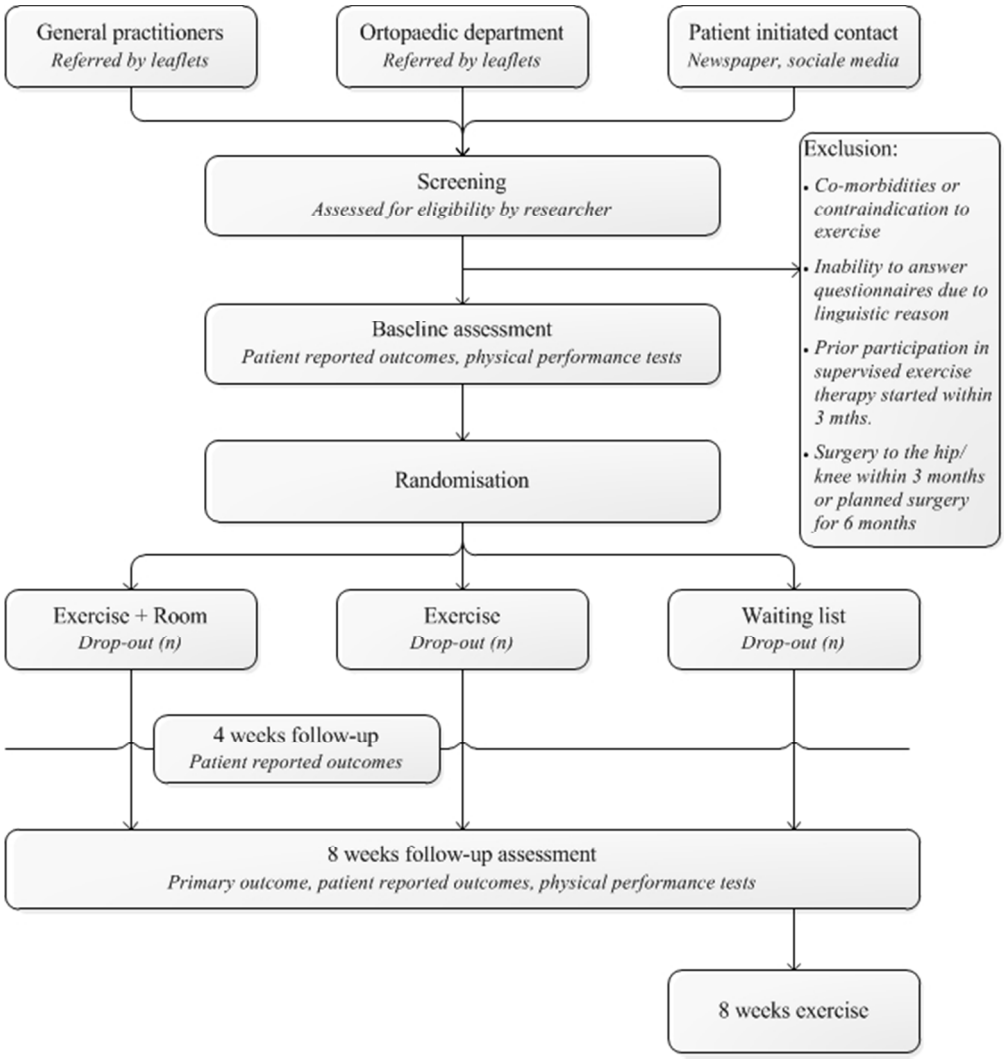
81. Lonsdale C, Hall AM, Williams GC, et al. Communication style and exercise compliance in physiotherapy (CONNECT): a cluster randomized controlled trial to test a theory-based intervention to increase chronic low back pain patients' adherence to physiotherapists' recommendations: study rationale, design, and methods. BMC Musculoskelet Disord 2012;**13**:104.

82. Neumann M, Edelhauser F, Kreps GL, et al. Can patient-provider interaction increase the effectiveness of medical treatment or even substitute it?--an exploration on why and how to study the specific effect of the provider. Patient Educ Couns 2010;**80**(3):307-14.

83. Suarez-Almazor ME, Looney C, Liu Y, et al. A randomized controlled trial of acupuncture for osteoarthritis of the knee: effects of patient-provider communication. Arthritis Care Res 2010;**62**(9):1229-36.

84. Teutsch C. Patient-doctor communication. Med Clin North Am 2003;**87**(5):1115-45.

85. Thomas K. General practice consultations_is there any point in being positive? Br Med J 1987;**294**(may):1200-02.



Flow chart, overview of the recruitment flow in the CONEX trial.
175x184mm (96 x 96 DPI)

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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	28
	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	28
	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)	22

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	5-7
	6b	Explanation for choice of comparators	8,12,23
Objectives	7	Specific objectives or hypotheses	6,7
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)	7
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	N/A
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)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15-18
	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	12-18
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)	Fig.1.

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	20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	19
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	19
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19-20
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	19-20
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	12-20
	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 protocols	15

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	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	22
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 about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22,28
	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	18-19
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	7,25
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	28
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	N/A
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	N/A
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	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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 "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Exploring the Effect of Space and Place on Response to Exercise Therapy for Knee and Hip Pain; a protocol for a double-blind randomised controlled clinical trial. The CONEX trial

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Exploring the Effect of Space and Place on Response to Exercise Therapy for Knee and Hip Pain; a protocol for a double-blind randomised controlled clinical trial. The CONEX trial

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ABSTRACT

Introduction

´Context effects' are described as effects of a given treatment, not directly caused by the treatment itself, but rather caused by the context in which treatment is delivered. Exercise is a recommended core treatment in clinical guidelines for musculoskeletal disorders. Although overall moderately effective, variation is seen in size of response to exercise across RCT studies. Part of this variation may be related to the fact, that exercise interventions are performed in different physical environments, which may affect participants differently. The study aims to investigate the effect of exercising in a contextually enhanced physical environment for 8 weeks for people with knee or hip pain.

Methods and analysis

The study is a double-blind randomised controlled trial. Eligible participants are 35 years or older with persisting knee and/or hip pain for 3 months. Participants are randomised to one of three groups; 1) exercise in contextually enhanced environment 2) exercise in standard environment 3) waiting list. The contextually enhanced environment is located in a newly built facility, has large windows providing abundant daylight, overlooking a recreational park. The standard environment is in a basement, has artificial lighting and is marked of use, i.e. resembling many clinical environments. Primary outcome is participant's global perceived effect rated on a 7-point Likert scale after 8 weeks exercise. Patient-reported and objective secondary outcomes are included.

Ethics and dissemination

The Regional Scientific Ethical Committee for Southern Denmark has approved the study. Study findings will be disseminated in peer-reviewed publications and presented at national and international conferences.

Trial registration: NCT02043613

Strengths and limitations of the study

The randomised controlled trial aims to investigate the effect of the physical environment on the effect of exercise therapy and focuses on the significance of the context in which treatment is delivered.

The physical environment is a single component of the multifactorial concept of contextual effect and isolating only one component may be difficult as interaction between several components may occur.

INTRODUCTION

The physical environment affects the persons in it and may potentially be of significance for health and treatment effects. Studies on the role of physical environments conducted in hospital settings have reported that factors such as noise, daylight deprivation and light intensity may increase stress and pain level, reduce patient satisfaction and affect length of hospital stay[1-5]. Many rehabilitation and hospital exercise facilities are today located in large rooms in basements or other windowless rooms with poor acoustics, not designed for optimal exercise therapy delivery. These physical environments may affect patients negatively and potentially result in a poorer result from the exercise or rehabilitation, if patients are feeling unwelcomed or are not motivated to comply with the exercise in the given environment. Theoretically, enhanced physical environments may create positive atmosphere, enhance communication during exercise and potentially improve exercise performance, compliance and perceived wellbeing. Exercise is recommended as a life-long treatment for chronic diseases such as cardiovascular diseases, diabetes and musculoskeletal disorders, including hip and knee osteoarthritis (OA) and joint pain. Despite high-level evidence that exercise provides on average moderate pain relief and functional improvement in patients with osteoarthritis, large variation in effect is observed across studies and treatment effects may vary from small to large[6, 7]. In addition to differences in characteristics of the exercise programs studied, this may also relate to the fact that exercise interventions have been performed in different physical environments and that these environments may influence patients differently [8]. It is plausible, but currently unknown, whether the physical environment can be modified in ways, that enhances the effect of exercise therapy. To our knowledge, this is the first trial to actively investigate if modification of the physical environment can be used in a positive way to enhance the effect from exercise therapy.

This study applies the term 'context effect' as a framework for elucidating how treatment effect is potentially caused by a complexity of factors in addition to the actual treatment effect. Context effects are defined as the effects of a given treatment, not directly caused by the treatment itself, but rather caused by the context or environment in which the treatment is given[8-11]. Context effects may be considered as a parallel to placebo effects, which has been one of the most debated topics in modern medicine[12-15]. Several authors have objected to the term placebo, as they argue, that the definition is self-contradictory and inadequate[9, 16-19]. Placebo is in its classical term defined as giving an inert substance or treatment[10, 18]. However, if placebos are inert, they cannot have an effect, and if they have an effect, they cannot be inert[9, 10, 16, 18]. Other terms have been suggested, such as; non-specific effect, non-characteristic effect, incidental effects, meaning response, placebo components and context effects, as applied in this study[9, 20-24]. A clear distinction should be made between placebo effects and context effects. Placebo is associated with giving pills, injections or having surgery and often entails a form of deliberate deception, whereas context effects rather classify factors creating or enhancing a treatment effect[8-11]. Factors contributing to context effects can be divided into different categories, such as; characteristics of the patient and the practitioner, type of treatment, nature of disease and the physical environment[8, 11]. This study will focus on the physical environment where exercise therapy is delivered, as it can be modified in a standardised and reproducible way to potentially enhance adherence and enhance the positive effects of exercise therapy.

The study aim is to investigate the effect of exercising in a contextually enhanced physical environment for 8 weeks for people with knee or hip pain. We hypothesize that, participants exercising according to a standardised program in a contextually enhanced physical environment will report greater improvement from exercise compared to participants following the same

exercising program in a standard physical environment as measured by patients' Global Perceived Effect (GPE). Further, we expect that the two exercise groups will be superior to a passive waiting list.

METHODS AND ANALYSIS

Study design

This study is designed as a 3-armed randomised controlled clinical trial. Participants are randomised to three intervention groups; exercise in a context enhanced physical environment (EX+ROOM), exercise in a standard physical environment (EX) or waiting list (WL). Participants, investigators and exercise instructors are blinded to treatment allocation. Primary endpoint is patient's global perceived effect assessed after 8 weeks exercise on a 7-point Likert scale. The Regional Scientific Ethical Committee for Southern Denmark has approved the study (study ID: S-20130130). It is consistent with the Helsinki Declaration and registered with www.clinicaltrials.gov (ID: NCT02043613). Results from this study will be reported according to the CONSORT statement[25].

Participants

Eligible participants are 35 years or older, self-reporting persisting knee and/or hip pain within the last 3 months and are willing and able to attend exercise therapy twice weekly at the University of Southern Denmark, Odense M. Exclusion criteria are: 1) Co-morbidities or contraindication prohibiting participation in exercise therapy; 2) Inability to answer questionnaires or to speak, read or understand Danish; 3) Already participating in exercise therapy, defined as an exercise program supervised by a physiotherapist, or systematic training with duration of 6 weeks or more started within 3 months to inclusion, aimed specifically at relieving knee or hip joint problems; 4) Having had surgery to the hip/knee within the last 3 months or waiting for joint surgery in the coming 6

months. Participants are recruited via different pathways; posters and informational leaflets at general practitioners offices, the orthopaedic department at Odense University Hospital or participant initiated contact through posters and articles in local newspapers, social media and word of mouth (figure 1). Participants are screened via telephone and if eligible, they are invited to a baseline visit and written information is sent to the participants. At the baseline visit the primary investigator gives oral information regarding the study and the participant signs the consent form if willing to participate. Baseline testing is performed directly hereafter.

Insert Figure 1 around here

Intervention

Participants are randomly assigned to one of three groups.

Group EX+ROOM: exercise in contextually enhanced physical environment

This exercise room is placed on the second floor in a newly build facility. It has a view to a newly reconstructed outdoor sport and recreational park. It has not prior been used in studies investigating exercise as a treatment option.

Group EX: exercise in a standard physical environment

This group will exercise in a room, which has been used in other exercise studies. The room is marked by years of use. It is placed in the basement and accessed through a series of staircases and hall-ways through the basement. This facility resembles many existing exercise facilities at hospitals and rehabilitation clinics and is considered a standard exercise environment.

Contextual factors

The physical environments are described and classified by a variety of contextual factors (**table 1**).

Acoustic properties such as speech interpretability, reverberation and background noise are measured by use of standard acoustic methods[26]. Better acoustic properties, such as shorter reverberation time and higher speech interpretability, may reduce stress and improve communication. In hospital environments high noise levels are associated with worse patient outcomes such as psychological stress and satisfaction with care[27]. Background noise (dB(A)) is measured in empty rooms. Reverberation is measured as T20, the time interval for a 20 dB decay within a room. Reverberation is a measure of how long it takes for sound to decay in a room and a long reverberation time affects speech comprehension negatively[26]. Reverberation and speech interpretability are descriptive of how well speech is perceived in a room. Speech interpretability is measured as speech clarity and transmission. Speech clarity is measured as a Clarity Index within the initial 50ms (C50), it compares early sound reflection with later sound reflection. Early sound reflections are positive for speech interpretability and later sound reflection will be perceived as noise. A high C50 indicates good speech interpretability. Speech Transmission index (STI) is a measure of sound quality in transmission from sound source to receiver. Reverberation and speech interpretability are derived from tape recordings of loud clear noises emitted in the exercise rooms. Acoustic measures are obtained from two positions in the room with small, medium and large distance to the sound source. Light intensity is assessed using an adapted method from Walch et al, 2005. Light intensity is measured using a LUX meter (Amprobe, LM-100, light meter, Everett, WA, USA) on two representative positions in the exercise rooms and additionally directly at windows, if present in the room. Three consecutive measures are obtained from each position and averaged. Light measurements are taken as close to the exercise time as possible. Daylight and brighter rooms

are associated with lower pain perception and lower postoperative analgesic intake in hospital environments[28, 29]. Air quality is described by CO_2 concentration, temperature and air humidity in the exercise rooms during exercise. Air quality is assessed with an air quality data logger, set to collect data on 30 sec. intervals (Trotec, BZ-30, data logger, Heinsberg, Germany). Furthermore, carefully selected pictures of nature scenes are hung in the contextually enhanced physical environment. Viewing nature pictures or visual stimuli of nature elements have been known to reduce stress in office setting and influence recovery time and decrease pain in patients following surgery[1, 5, 30-33].

Table 1: Descriptive environmental factors

Dimension	**Factor**	**Contextually enhanced physical environment**	**Standard physical environment**
Indoor environment	Light - Strength (Lux) - Source - Window/no window	@ Daylight + artificial light Windows, Floor to ceiling	@ Artificial light. No windows
	Air quality - CO_2 (ppm) - Temperature (˚C) - Humidity (%)	 @ @ @	 @ @ @
	Sound/noise - Background noise (dB(A)) - Speech clarity (C50, STI) - Reverberation (T20)	 @ @ @	 @ @ @
Décor	Wall decorations	Picture of nature scenes	No decorations

	View	View of nature and outdoor exercise environment	No view

Table 1: Parameters assessed in the different physical environments @ = assessed/measured and will be reported. Ppm: parts per million, C50, clarity index with first 50 ms of sound, STI: speech interpretability index, T20: reverberation time for sound decay of 20 dB.

Exercise

The exercise program for participants in the EX+ROOM and EX group is based on the standardised NEuroMuscular EXercise (NEMEX) program. It is described in detail elsewhere[34] and has previously been investigated for feasibility in patients with severe knee or hip OA[34]. The NEMEX program is based on biomechanical and neuromuscular principles, which aim to improve sensorimotor control and achieve functional stability[34]. The NEMEX program has previously been shown to be effective to relieve pain and improve function in populations with knee or hip pain such as anterior cruciate ligament injuries[35-38], meniscectomized participants[39, 40] patients with hip or knee OA undergoing total joint arthroplasty[34, 41]. Exercise is performed as group exercise and all exercise sessions are supervised. All instructors will be certified in the NEMEX program. To ensure consistency between instructors, they will participate in a two-day course, Good Life with osteoarthritis in Denmark, focusing on lower-limb osteoarthritis management and neuromuscular exercise. After completing the course all instructors will go through the exercise program with the primary investigator to ensure consistency in instructing and supervising exercise as well as going through how volume, load and progression of exercise and pre- and post-exercise pain should be documented in participants' exercise dairies. The EX+ROOM and EX group will exercise on the same weekdays, twice a week for one hour duration. An instructor will first supervise the EX+ROOM group and then the EX group. Consequently, all of the instructors will have supervised the NEMEX program in both physical environments and for the same amount of time, i.e. if an

instructor supervises the EX+ROOM group then they supervise the EX group as well. This is done to ensure consistency in delivery instructions and supervision of exercise across study participants and to ensure that any effect that a given instructors may have on the exercise and participants should be similar between physical environments.

Group WL: waiting list/control group

Participants randomised to waiting list are placed on a passive waiting list for a period of 8 weeks, and thereafter offered 8 weeks of structured resistance exercise. These participants act as an observational group and represent the natural course of disease in participants with knee and/or hip pain. After the 8 weeks when follow-up data for the current study has been collected, the participants are offered resistance exercise rather than neuromuscular exercise for logistic reasons, such as avoiding taking up place in the designated exercise rooms used in the study and consequently affecting the time to completion of the study.

Primary outcome

Participants' Global Perceived Effect (GPE) assessed at 8 weeks will be the primary endpoint of the trial. Participants are asked to respond to the following question; *"Compared to before you entered the study, how are your knee/hip problems now?"* on a 7-point Likert scale. The GPE scale ranges from 'markedly worse' through 'no change' to 'markedly improved'. GPE is a reliable method for measuring the effect of clinical interventions[42, 43]. It has prior been used in studies investigating contextual effect of treatment[44]. The validity of GPE scales has been questioned. However, a study on the correlation between transition ratings and pre and post score of quality of life questionnaires showed a correlation of 0.8 between the change score of the questionnaire and the transition ratings

suggesting that transition scales, such as global perceived effects, are valid for detecting changes and can be used in clinical trials as primary outcome measures[43].

Secondary outcomes

All outcomes and time points for data collection are listed in **table 2**.

Table 2: Summary of collected data and time points

Variable	Baseline	4 weeks	8 weeks
Baseline data			
Height (cm)	@	n.a.	@
Weight (kg)	@	n.a.	@
Age (yrs.)	@	n.a.	n.a.
Gender (f/m)	@	n.a.	n.a.
Marital status	@	n.a.	n.a.
Educational level	@	n.a.	n.a.
Employment status	@	n.a.	n.a.
Alcohol consumption	@	n.a.	n.a.
Smoking	@	n.a.	n.a.
Physical activity level at work and leisure	@	n.a.	n.a.
Primary outcome			
Global Perceived Effect (7 point Likert scale).	n.a.	@	@
Secondary outcomes			
Patient reported outcomes			
Knee/Hip Injury and Osteoarthritis Outcome Score	@	@	@
Short-form 36 Health Survey	@	@	@

Modified Arthritis Self-Efficacy Scale	@	@	@
Patient Acceptable Symptom State (y/n)	n.a.	n.a.	@
Patient satisfaction (5 point Likert scales).	n.a.	n.a.	@
Stress (100 mm VAS)	@	n.a.	@
Objective physical function tests			
Aerobic capacity (ml O_2/min/kg)	@	n.a.	@
Isometric strength hip abduction (Nm)	@	n.a.	@
Isometric strength knee extension (Nm)	@	n.a.	@
Single-limb mini squat	@	n.a.	@
Knee bends/30 sec. (no.)	@	n.a.	@
Chair stands/30 sec. (no.)	@	n.a.	@
Walking test, 40 m fast paced. (sec)	@	n.a.	@
One-leg hop of distance (cm)	@	n.a.	@

Table 2: Summary of primary and secondary outcomes and respective time collection points, @ = assessed/measured, n.a. = not assessed VAS: visual analogue scale.

Patient reported outcomes

Participants answer the Danish versions of the Knee injury and Osteoarthritis Outcome Score (KOOS) or The Hip disability and Osteoarthritis Outcome Score (HOOS) depending on either knee or hip problems being primary complaint. The KOOS and the HOOS are joint-specific questionnaires, developed to assess participants' opinion about their knee or hip problems[45, 46]. KOOS/HOOS consists of 5 subscales; pain, symptoms, activities of daily life function, sport and recreational function and joint related quality of life [47]. Each subscale consists of a set of items specific to the subscale and each item is assed via a Likert scale with 5 possible answer options ranging from 0 (no problems) to 4 (extreme problems). The Likert score is transformed to a 0-100 scale with zero representing extreme knee problems and 100 representing no knee problems[45].

KOOS and HOOS have good psychometric properties for patient groups with knee injury, knee replacement, hip dysfunction and hip replacement[46-50].

The Medical Outcome Study 36-item short form general health survey (SF-36) is a generic patient-reported health status measure[51-53]. It consists of 36 items organised under 8 subscales; 1) physical functioning, 2) role limitations because of physical health, 3) bodily pain, 4) social functioning, 5) general mental health, 6) role limitations because of emotional problems, 7) vitality, and 8) general health perception[53]. Low scores indicate limitations in activities and a perception of poor health, high score indicate no limitations and good health [53]. Validity and reliability of the SF-36 is adequate and the questionnaire is widely used[51, 52].

A modified measure of self-efficacy is included to evaluate patients' perception of functionality or limitations to their functionality caused by their knee of hip problem. Self-efficacy is defined by Bandura as "belief in one's capability to organise and execute the course of action required to produce given attainments[54]. Self-efficacy is assessed with a modified version of the Arthritis Self-Efficacy Scale (ASES)[55] previously used in a similar patient group[56]. The modified version of ASES consists of 11 single items from the two subscales pain and other symptoms. Participants rate their ability to cope with pain and symptoms related to their joint problem, on a10-100 scale, with 10 indicating very uncertain and 100 indicating very certain with 10 point increments[57].

A series of single item questions are included. Patient Acceptable Symptom State is assessed by asked a single yes/no question; "Considering your knee function, do you feel that your current state as satisfactory? With knee function you should *take into account all the activities you have during your daily life, your level of pain and other symptoms and your quality of life"*[58]. If participants rate their current symptom state as unacceptable, a follow-up question is asked as to if they consider the treatment to have failed. Further, participants are asked to answer five global perceived effects questions specific for each of the five subscales of either KOOS or HOOS, rating either

improvement or deterioration and finally an indication of whether these changes are perceived as important of unimportant by the participants. These single items are included in order to assess minimal clinical important changes for the five subscales of the KOOS and HOOS. Stress is estimated as 'general stress level' measured on a 100 mm visual analogue scale ranging from no stress to stress as severe as could be[59].

Patient reported outcomes are collected using an online survey. At baseline and 8 weeks follow-up participants answer the survey on a computer in the examination room without the investigator present. At 4-week follow-up an email is sent to participants, who answer at home. To ensure high data completion an email reminder is sent, if no reply is received within 3-5 days. Further, participants are called by phone if there is no reply to the reminder e-mail.

Functional performance

Patients' aerobic capacity is estimated during a submaximal work rate bicycle test[60]. Patients pedal until reaching a steady state, with a stabile pulse rate ranging between 120 to 170 beats per minute, normally within 6-7 minutes[60]. Participants' aerobic capacity is estimated from work rate and stabile pulse rate by use of Åstrand's Nomogram[60].

Maximal isometric knee extension and hip abduction strength will be tested using dynamometry (JTECH medical, Commander Echo, Salt Lake City, Utah, USA). A suction cup is mounted on a door behind the examination couch. A strain gauge, measuring pull in newton, is placed in between the suction cup and a fixation belt strapped around the participant's ankle above the lateral malleoli. For knee extension, participants sit on an examination couch with a hip angle of 90° and a knee angle of 90°. Participants are asked to press against their foot the belt in a forward motion. The distance from the knee joint axis to the middle of the fixation belt is measured. Consequently, isometric muscle strength is measured as torque. For hip abduction, participants lie on the couch

with their leg strait and are asked to press their lateral malleoli against the belt. The distance from the trochanter major on the femoral bone to the middle of the fixation belt is measured. One practice trial is allowed and thereafter three maximal contractions are performed separated by a 60 sec. pause. Isometric muscle strength is normalised to body weight to increase comparability. The methods for assessing isometric muscle strength have been adapted from Thorborg et al. who reported good inter-tester reliability with an interclass correlation coefficient ranging from 0.76 – 0.95 and standard error of measurement between 5.0% to 10.4% for hip and knee strength assessments[61].

Physical function is assessed by 5 performance tests; 1) single limb mini squats[62], 2) number of knee bendings on one leg during 30 sec standing[63, 64], 3) number of chair stands during 30 sec[65, 66], 4) 40 m fast-paced walking test[65] and 5) one leg hop for distance[63]. All performance tests have been found valid to assess lower extremity function in different patient groups with knee or hip problems[63, 66-68]. As large variation regarding age and function within participants of this trial is expected, and therefore a test battery with a wide range of difficulty of the performance tests is chosen to ensure that all participants would be challenged. A floor effect may be evident in the one leg hop for distance test as some participants may not be able to hop at all. No ceiling effects are expected for any of the functional performance measures.

Explanatory outcomes and nested qualitative study

To investigate how the physical environment and other potential context factors, such as participant and practitioner interaction and behaviour, may interact and mediate the treatment effects, explanatory outcomes are included. Explanatory outcomes have been selected to explain the process by which context effects work and possibly elucidate which elements within the physical environment that enhance treatment effects and how these elements affect the patients and

practitioners. A qualitative study will be embedded within the randomised controlled trial design. The aim of the qualitative study is to investigate, how the participants experience the two different physical environments. Observation is performed in both rooms during exercise sessions to describe and identify behaviour of practitioners and participants specific to the different physical environments. Focus group interviews will be conducted with participants to investigate their experiences with the exercise environments and to invite participants to articulate and elaborate on their thoughts on how the physical environment has affected them. Three focus group interviews will be conducted with a total of 10 to 20 participants from the contextually enhanced physical environment and 3 focus group interviews with similar number of participants from the standard physical environment, i.e. 6 focus groups in total. Participants invited to the focus groups will be those randomized to exercise in the RCT design (group EX+ROOM and group EX). The interviews will be transcribed and analysed using thematic coding comparing within and across the different physical environments. Additionally, in-depth individual interviews will be performed with 6 participants. To ensure the blinding of participants throughout the study all interviews will be conducted after the intervention and after follow-up testing has been completed.

Additionally, a patient reported outcome 'participant satisfaction' is reported as participants' satisfaction with the exercise intervention in itself as well as satisfaction with specific contextual factors within the physical environment. Eleven single items scoring the different factors of the physical environment such as lighting, cleanliness, access, decoration etc. are administered to participants in intervention groups EX+ROOM and EX. The items are adapted from Tsai et al.[69]. Satisfaction is scored on a 5-point Likert scale ranging from 1 to 5 (1=strongly dissatisfied, 2=dissatisfied, 3=fair, 4=satisfied, and 5=strongly satisfied).

Compliance and adverse events

In the two exercise groups, compliance is considered good at 75% or if 12 of 16 possible exercise sessions are attended. Participants in the WL group are asked at 8 weeks follow-up, whether they have started any exercise courses with the last 8 weeks. If answering yes, they are asked to describe the change. This is done in order to account for compliance to the waiting list design. Self-reported adverse events occurring in-between exercise sessions are recorded at 4 and 8 weeks in the online survey. Adverse events are defined as any events that the participants found restricting them physically, mentally or socially. Participants also indicate whether of they have been in contact with either their general practitioner or the hospital in relation to their adverse event. Any adverse events occurring during the exercise sessions are recorded by the supervising instructors.

Randomisation

Randomisation is performed immediately after baseline assessment and is administered by a research coordinator, not otherwise involved in the study. Patients are consecutively assigned and given a numbered, sealed, opaque envelope entailing treatment allocation. The randomisation sequence is computer-generated and prepared by a statistician with no clinical involvement in conducting the trial. To avoid imbalances in treatment allocation among people with knee and hip pain, two block randomisation lists were computer-generated (with a 2:2:1 allocation). The block size is kept secret to maintain blinding; each block consisted of either 5 or 10 patients. The randomisation lists and envelopes are kept in a secure location at the university.

Blinding procedure

Participants are blinded to the study aim in order to avoid excess focus on the physical environment, which potentially could exaggerate context effects from the physical environment. Participants are therefore informed that they are participating in a study evaluating the effects from exercise

compared to being on a waiting list and are not made aware that the true aim of the study is to investigate the possible additional effect from an enhanced physical environment on exercise. The instructors supervising the exercise sessions are neither informed about the true aim of the study. However, they are aware that exercise sessions are performed in different rooms as they supervise sessions in both rooms. The instructors have been informed that the different exercise rooms are used for practical and logistic reasons. The primary investigator conducting baseline and follow-up testing is also blinded to treatment allocation and participants are instructed to not to speak about the intervention with the investigator, thereby keeping blinding intact.

Sample size estimation and power considerations

This study is designed as a superiority trial with three groups (EX+ROOM, EX and WL). Since this is the first study to investigate the additional effect of an enhanced physical environment on the effect of exercise therapy as treatment for knee or hip pain, there are no previous data to base our sample size estimation on. Thus the power calculation is based on factors such as feasibility, i.e. how many participants will be realistic to include with the recruitment period and pragmatic issues such as availability and capacity of the different exercise rooms. Taking these aspects into consideration 100 participants will be included into the trial. To be able to account for the natural disease progression or regression towards the mean the waiting list (WL) is included in the design. A randomisation with a 2:2:1 allocation is chosen and thus 40 participants are randomised to EX+ROOM and EX groups, respectively, and 20 participants are randomised to the WL group. We anticipate that individuals in the WL group will experience limited effect. With 40 subjects in each of the two exercise groups (EX+ROOM and EX), we are able to detect a difference of 0.75 on the GPE scale ranging from -3 to 3 with a standard deviation of 1.2, a p-value of 0.05 and a power of 80%.

Statistical evaluation

All three intervention groups (EX+ROOM, EX and WL) will be examined for comparability at baseline with respect to demographic factors using ANalysis Of VAriance (ANOVA) and Chi-squared test as appropriate.

The primary analysis on the GPE data will be conducted with a Student's unpaired t-test comparing the EX+ROOM intervention group with EX intervention group at the 8-week follow-up. The Bonnet-Price median test will be conducted if assumption of normality in the GPE data is not supported. The WL intervention group is considered a reference group describing the natural progression of disease for the included study population and is not included in the primary analysis. However, to check the general assumption, that exercise is more effective than no intervention, an unpaired t-test is conducted to compare the exercise groups with the waiting list.

The secondary outcomes, the KOOS/HOOS, SF-36, ASES and physical function outcomes are analysed as repeated measures (i.e. change from baseline over 4 and 8 weeks follow-up for patient reported outcomes and baseline to 8 week follow-up for physical function tests) applying a mixed linear effects model with 'participant' as random effect and sex, age and joint as fixed effects. As for the primary outcome, only the EX+ROOM and EX groups are compared. Additionally, to test an *a priori* hypothesis of a graded relationship between groups EX+ROOM > EX > WL a linear test for trend will be conducted as an explanatory analysis on all outcomes. Here, a χ^2 test for trend is applied for dichotomous outcomes and a linear test for trend is applied for continuous outcomes. Pairwise comparison of groups will be conducted if the trend test was significant, to describe the association between group and outcome, i.e. EX+ROOM vs EX and EX vs WL. For dichotomised outcomes a χ^2 test is applied, and for continuous ANOVA is applied.

Intention-to-treat analysis is performed and last observation is carried forward for missing data at follow-up for the secondary outcomes. The primary outcome is a transition score, which is not assessed as baseline. For any participants lost to follow-up GPE data will be missing. Further, a per-protocol analysis is conducted including only those with good compliance with the exercise intervention (participated in at least 12 of 16 sessions) in the EX+ROOM and EX groups, respectively.

A detailed statistical analysis plan will be drafted and approved by all authors before being made publicly available prior to breaking randomisation code and conducting data analysis. To further minimise the risk for bias introduced during analysis and interpretation, data analysis will be performed by a third party not otherwise related to the study. Intervention groups will be allocated with arbitrary names. Interpretation will be performed by the primary investigator in collaboration with the research team prior to revealing treatment allocation, thereby interpreting the results blindly[70]. Consequently, two interpretation scenarios will be drafted on the basis of the primary outcome data, i.e. comparing treatment A with treatment B. One assuming that group A will be the EX+ROOM group and another assuming that A will be the EX group.

ETHICS AND DISSEMINATION

The findings of this study will be disseminated though peer-reviewed publications and through international conference presentations.

The primary ethical concern in this study is that the true aim of the study is withheld from participants. Withholding the aim disables participants to consider the implications of the research and to assess whether or not they want to contribute to investigating this aim. However, blinding the true aim is imperative to the study design as an effect from the physical environment may be over- or underestimated, if participants are explicitly made aware of the actual aim of the study.

Participants are therefore told that the study is designed to investigate the effect of neuromuscular exercise as an early treatment strategy for musculoskeletal pain. Similarly the supervising instructors are also blinded to the true aim of the study. Instructors are aware that the exercise is performed in different environments, but are told this due to logistic reasons. The ethics committee has been explicitly made aware that study participants and instructors are not made aware of the true study aim and despite this sanctioned the study without any reservations or conditions.

DISCUSSION

Context effects may constitute an important part of the effects of exercise therapy. Investigating context effects will provide knowledge on how the physical environment may be exploited to enhance the effects of exercise therapy in addition to the effect of the specific exercise. Exercise is an effective and widely used core treatment strategy for chronic diseases, such as musculoskeletal disorders, cardio vascular disease and diabetes. Adding to the effect of exercise through context effects from a contextually enhanced physical environment in exercise facilities may be highly beneficial for patients across a number of diseases.

Previous research in context effects from physical environments has been conducted in hospital settings[27]. A comprehensive review from 2008 showed that certain elements within a hospital context such as noise and lighting level have impact on number of medical errors as well as increased pain and stress levels for patients and staff[27]. Research in other health care settings has been sparse. During an initial literature review only one study was identified investigating physical therapy and its relation to the physical environment. The literature review comprised groups of search terms for context effects, exercise/physical therapy and terms for physical environments. Articles were search for in Medline, Scopus and single specific journals such as Health

Environment Research and Design journal. When reviewed, this single study used observation, surveys and interviews to learn more about the design of a hospital roof-top garden rather than investigating if the physical environment had an additional effect on the physical therapy[71]. Further, the therapy of the study was described as activities including gardening, golf putting and events such as concerts or barbeques, not regular exercise. Consequently, this is to our knowledge the first study investigating if there is an effect from an enhanced physical environment in addition to exercise when compared to exercise performed in a standard setting.

The three-armed RCT design of the present study has several advantages. It has been widely discussed whether the placebo effect can be explained by spontaneous remission or regression towards the mean[15, 72-74]. To rule out either of these as explanatory factors of a possible effect, the waiting list group is included into the design as an untreated reference group. The waiting list group illustrates the natural course of disease for the study population during the study period. Consequently, if a difference is seen between the two exercise rooms, the waiting list group enables an assessment of whether the difference is caused by spontaneous remission by comparing the exercise groups to the waiting list. To optimise the number of study participants, a 2:2:1 allocation with half the number of participants allocated to the waiting list is chosen. The three-armed design also allows for a test for trend across groups. This form of analysis has been previously applied in a study investigating context effects originating from patient and practitioner interaction[44].

Context effects are a multifactorial concept and several factors, other than the physical environment, may contribute to the context effect of a given treatment. Literature reviews on context effect have additionally suggested factors, such as characteristics of patients/participants, practitioner/instructors or treatment and nature of disease as potentially contributing to the total

context effect and theoretically, components may interact and possibly have synergistic effects[8, 9, 16, 24, 75]. Especially the interaction between patient and practitioner has been suggested as a significant contributor to context effects[44, 76-85]. In a recent study, Kaptchuk et al. found, that patients with irritable bowel syndrome, who were treated by a warmer and friendlier practitioner, had significantly better results from sham-acupuncture, than patients treated by a practitioner, who limited eye-contact and avoided conversation[44]. Similarly, Suarez-Almazor et al. found that knee osteoarthritis patients treated with sham-acupuncture by a practitioner, who expressed high expectations to the treatment, had better outcomes than those treated by a practitioner with a neutral position towards treatment effects[83]. Although the interaction between patient and practitioner is suggested as the most robust component of context effect, behaviour, communication and interaction between patient and practitioner is difficult to change and may be hard to reproduce. An advantage in exploiting the potential context effect from the physical environment is that, the components of the environment can be thoroughly described and more easily implemented or changed in existing exercise environments.

There are some limitations to the study design that must be acknowledged. The multifactorial concept of context effects questions whether the physical environment can be isolated and studied alone. Several actions are taken to isolate the physical environment as the only difference between groups in this trial. The exercise program is standardised and delivered in a group fashion by the same instructors and all instructors have supervised in both physical environments. Consequently, treatment characteristics are similar between the intervention groups. Participants' characteristics, known and unknown, should be equally distributed between groups as a result of the randomisation process. Any specific characteristics that may origin from the instructor or from instructor-

participant interaction should also be comparable between groups, as instructors supervise in both rooms.

Additionally, the nested qualitative study is aimed to investigate how the physical environment may affect behaviour of the participants or instructors or the interaction between them. The study will elucidate these issues and help explain the process of how a standard and enhanced physical environment affects participants and instructors.

This study is designed to investigate the significance of the physical environment for the effects of exercise therapy and rehabilitation. The design of the study is novel and the results will provide knowledge on the significance of creating an optimal context for exercise therapy. Further studies investigating context effects of treatment are warranted to further enhance treatment effects.

List of abbreviations used

CONEX: CONtext effect in EXercise.

RCT: Randomised Controlled Trial

OA: OsteoArthritis

GPE: participant's Global Perceived Effects.

EX+ROOM: EXercise in a context enhanced physical environment

EX: EXercise in a standard physical environment.

WL: waiting list

T20: Time for 20dB decay

C50: Clarity index, for initial 50 ms.

STI: Speech Interpretability Index

NEMEX: NEuroMuscular EXercise.

KOOS: the Knee Osteoarthritis and injury Outcome Score

HOOS: the Hip disability and Osteoarthritis Outcome Score

SF-36: Short-Form (36 item) Health Survey

ASES: Arthritis Self-Efficacy Scale

MVC: Maximal Voluntary Contraction.

ANOVA: ANalysis Of VAriation

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Peter Møller Juhl, MSc EE, PhD, Associate Professor for assisting in measuring acoustic properties, and Anne Marie Rosager for invaluable help during the randomisation process.

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Competing interests

The listed author(s) have no competing interests to declare.

Author's contributions

LFS, JBT, RU, PD and ER were all involved in the design of the study. All authors contributed to drafting the manuscript or revising it. All authors read, commented and approved the manuscripts for publication. LFS is the trial manager and responsible for the coordinating and conducting the study. LFS, JBT and ER comprise the steering committee for the study. LFS recruits, screens and conducts all baseline and follow-up testing. LFS monitors the data collection process during the trial, ensuring high completion rates for email based-surveys, objectively obtained outcomes and responses to reports of adverse events. Data analysis will be performed by a third party not related to the study.

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Figure legend

Figure 1: Flow chart, overview of the recruitment flow in the CONEX trial.

References

1. Ulrich R. View through a window may influence recovery from surgery. Science 1984;**224**(4647):420-21.
2. Ulrich R, Simons RF, Losito BD, et al. Stress recovery during exposure to natural and urban environments. Journal of enviromental psychology 1991;**11**:201-30.
3. Parish JT, Berry LL, Lam SY. The effect of the servicescape on service workers. J Serv Res-Us 2008;**10**(3):220-38.
4. Malenbaum S, Keefe FJ, Williams AC, et al. Pain in its environmental context: implications for designing environments to enhance pain control. Pain 2008;**134**(3):241-4.
5. Kweon BS, Ulrich RS, Walker VD, et al. Anger and stress - The role of landscape posters in an office setting. Environment and Behavior 2008;**40**(3):355-81.
6. Fransen M, McConnell S, Bell M. Therapeutic exercise for people with osteoarthritis of the hip or knee. A systematic review. The Journal of Rheumatology 2002;**29**(8):1738-46.

7. Fransen M, McConnell S. Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. J Rheumatol 2009;**36**(6):1109-17.

8. Di Blasi Z, Harkness E, Ernst E, et al. Influence of context effects on health outcomes: a systematic review. The Lancet 2001;**357**(9258):757-62.

9. Miller FG, Kaptchuk TJ. The power of context: reconceptualizing the placebo effect. J R Soc Med 2008;**101**(5):222-5.

10. Koshi EB, Short CA. Placebo theory and its implications for research and clinical practice: A review of the recent littrature. Pain practice : the official journal of World Institute of Pain 2007;**7**(1):4-20.

11. Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Ann Intern Med 2002;**136**(11):817-25.

12. Beecher HK. The Powerful Placebo. Jama-J Am Med Assoc 1955;**159**(17):1602-06.

13. Miller FG, Rosenstein DL. The nature and power of the placebo effect. J Clin Epidemiol 2006;**59**(4):331-5.

14. Hrobjartsson A. The uncontrollable placebo effect. Eur J Clin Pharmacol 1996;**50**(5):345-8.

15. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. The New England journal of medicine 2001;**344**(21):1594-602.

16. Barrett B, Muller D, Rakel D, et al. Placebo, meaning, and health. Perspect Biol Med 2006;**49**(2):178-98.

17. Breidert M, Hofbauer K. Placebo: Misunderstandings and prejudices. Deutsches Arzteblatt international 2009;**106**(46):751-55.

18. Margo CE. The placebo effect. Surv Ophthalmol 1999;**44**(1):31-44.

19. Grunbaum A. The Placebo Concept. Behav Res Ther 1981;**19**(2):157-67.

20. Doherty M, Dieppe P. The "placebo" response in osteoarthritis and its implications for clinical practice. Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society 2009;**17**(10):1255-62.

21. Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. BMJ 2005;**330**(7501):1202-5.

22. Dellmann T, Lushington K. How can complementary medicine practitioners enhance non-specific effects? journal of the Australian Traditional-Medicine Society 2008;**14**(1):13-17.

23. Dieppe P, Doherty M. Contextualizing osteoarthritis care and the reasons for the gap between evidence and practice. Clin Geriatr Med 2010;**26**(3):419-31.

24. Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. Ann Intern Med 2002;**136**(6):471-6.

25. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Med 2010;**8**.

26. Kuttruff H. *Room acoustics*. London: Spon Press, 2000.

27. Ulrich RS, Zimring C, Zhu XM, et al. A Review of the Research Literature on Evidence-Based Healthcare Design. Herd-Health Env Res 2008;**1**(3):61-125.

28. Shepley MM, Gerbi RP, Watson AE, et al. The Impact of Daylight and Views on ICU Patients and Staff. Health Environments Research & Design Journal (HERD) 2012;**5**(2):46-60.

29. Walch JM, Rabin BS, Day R, et al. The effect of sunlight on postoperative analgesic medication use: A prospective study of patients undergoing spinal surgery. Psychosom Med 2005;**67**(1):156-63.

30. Ulrich RS. Human Responses to Vegetation and Landscapes. Landscape Urban Plann 1986;**13**(1):29-44.

31. Ulrich RS. Natural Versus Urban Scenes - Some Psychophysiological Effects. Environment and Behavior 1981;**13**(5):523-56.

32. Tse MMY, NG JKF, Chung JWY, et al. The effect of visual stimuli on pain threshold and tolerance. J Clin Nurs 2002;**11**:462-69.

33. Diette GB, Lechtzin N, Haponik E, et al. Distraction therapy with nature sights and sounds reduces pain during flexible bronchoscopy: a complementary approach to routine analgesia. Chest 2003;**123**(3):941-8.

34. Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patients with severe hip or knee OA: the individualized goal-based NEMEX-TJR training program. BMC Musculoskelet Disord 2010;**11**:126.

35. Zätterström R, Friden T, Linstrand A, et al. Early rehabilitation of acute anterior cruciate ligament injury - a randomized clinical trial. Scand J Med Sci Sports 1998(8):154-59.

36. Ageberg E, Zätterström R, Moritz U, et al. Influence of Supervised and Nonsupervised Training on Postural Control After an Acute anterior Cruciate Ligament Rupture: A Three-year Longitudinal Prospective Study. J Orthop Sports Phys Ther 2001;**31**(11):632-44.

37. Ageberg E. Consequences of a ligement injury on neuromuscular function and relevance to rehabilitation - using the anterior cruciate ligament injured knee as model. J Electromyogr Kinesiol 2002;**12**:205 - 12.

38. Zätterström R, Friden T, Lindstrand A, et al. Muscle training in chronic anterior cruciate ligament insufficiency--a comparative study. Scand J Rehabil Med 1992;**24**(2):91-7.

39. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. Arthritis Rheum 2005;**52**(11):3507-14.

40. Ericsson YB, Dahlberg LE, Roos EM. Effects of functional exercise training on performance and muscle strength after meniscectomy: a randomized trial. Scand J Med Sci Sports 2009;**19**(2):156-65.

41. Villadsen A, Overgaard S, Holsgaard-Larsen A, et al. Postoperative effects of neuromuscular exercise prior to hip or knee arthroplasty: a randomised controlled trial. Ann Rheum Dis 2013.

42. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. J Man Manip Ther 2009;**17**(3):163-70.

43. Guyatt GH, Norman GR, Juniper EF, et al. A critical look at transition ratings. J Clin Epidemiol 2002;**55**(9):900-8.

44. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008;**336**(7651):999-1003.

45. Roos E, Lohmander S. The knee injury and osteoarthritis outcome score (KOOS) - from joint injury to osteoarthritis. Health and Quality of Life Outcomes 2003.

46. Klassbo M, Larsson E, Mannevik E. Hip disability and osteoarthritis outcome score. An extension of the Western Ontario and McMaster Universities Osteoarthritis Index. Scand J Rheumatol 2003;**32**(1):46-51.

47. Roos E, Roos H, Lohmander S, et al. Knee injury and osteoarthritis outcome score (KOOS) - development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998;**78**(2):88-96.

48. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcomes 2003;**1**:17.

49. Roos EM, Roos HP, Ekdahl C, et al. Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. Scand J Med Sci Sports 1998;**8**(6):439-48.

50. Nilsdotter AK, Lohmander LS, Klassbo M, et al. Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement. BMC Musculoskelet Disord 2003;**4**:10.

51. Mchorney CA, Ware JE, Raczek AE. The Mos 36-Item Short-Form Health Survey (Sf-36) .2. Psychometric and Clinical-Tests of Validity in Measuring Physical and Mental-Health Constructs. Med Care 1993;**31**(3):247-63.

52. Mchorney CA, Ware JE, Lu JFR, et al. The Mos 36-Item Short-Form Health Survey (Sf-36) .3. Tests of Data Quality, Scaling Assumptions, and Reliability across Diverse Patient Groups. Med Care 1994;**32**(1):40-66.

53. Ware JE, Sherbourne CD. The Mos 36-Item Short-Form Health Survey (Sf-36) .1. Conceptual-Framework and Item Selection. Med Care 1992;**30**(6):473-83.

54. Bandura A. Self-Efficacy - toward a Unifying Theory of Behavioral Change. Psychol Rev 1977;**84**(2):191-215.

55. Lorig K, Chastain RL, Ung E, et al. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. Arthritis Rheum 1989;**32**(1):37-44.

56. Skou ST, Odgaard A, Rasmussen JO, et al. Group education and exercise is feasible in knee and hip osteoarthritis. Dan Med J 2012;**59**(12):A4554.

57. Brady TJ. Measures of self-efficacy: Arthritis Self-Efficacy Scale (ASES), Arthritis Self-Efficacy Scale-8 Item (ASES-8), Children's Arthritis Self-Efficacy Scale (CASE), Chronic Disease Self-Efficacy Scale (CDSES), Parent's Arthritis Self-Efficacy Scale (PASE), and Rheumatoid Arthritis Self-Efficacy Scale (RASE). Arthritis Care Res (Hoboken) 2011;**63 Suppl 11**:S473-85.

58. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;**64**(1):34-7.

59. Lesage FX, Berjot S. Validity of occupational stress assessment using a visual analogue scale. Occup Med (Lond) 2011;**61**(6):434-6.

60. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol 1954;**7**(2):218-21.

61. Thorborg K, Bandholm T, Holmich P. Hip- and knee-strength assessments using a hand-held dynamometer with external belt-fixation are inter-tester reliable. Knee Surg Sports Traumatol Arthrosc 2013;**21**(3):550-5.

62. Ageberg E, Bennell KL, Hunt MA, et al. Validity and inter-rater reliability of medio-lateral knee motion observed during a single-limb mini squat. BMC Musculoskelet Disord 2010;**11**.

63. Bremander AB, Dahl LL, Roos EM. Validity and reliability of functional performance tests in meniscectomized patients with or without knee osteoarthritis. Scand J Med Sci Sports 2007;**17**(2):120-7.

64. Thorlund JB, Aagaard P, Roos EM. Thigh muscle strength, functional capacity, and self-reported function in patients at high risk of knee osteoarthritis compared with controls. Arthritis Care Res (Hoboken) 2010;**62**(9):1244-51.

65. Dobson F, Hinman RS, Hall M, et al. Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. Osteoarthritis Cartilage 2012;**20**(12):1548-62.

66. Dobson F, Hinman RS, Roos EM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage 2013.

67. Wright AA, Cook CE, Baxter GD, et al. A comparison of 3 methodological approaches to defining major clinically important improvement of 4 performance measures in patients with hip osteoarthritis. J Orthop Sports Phys Ther 2011;**41**(5):319-27.

68. Gill S, McBurney H. Reliability of performance-based measures in people awaiting joint replacement surgery of the hip or knee. Physiother Res Int 2008;**13**(3):141-52.

69. Tsai CY, Wang MC, Liao WT, et al. Hospital outpatient perceptions of the physical environment of waiting areas: the role of patient characteristics on atmospherics in one academic medical center. BMC Health Serv Res 2007;**7**.

70. Jarvinen TLN, Sihvonen R, Bhandari M, et al. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. J Clin Epidemiol 2014;**67**(7):769-72.

71. Davis BE. Rooftop Hospital Gardens for Physical Therapy: A Post-Occupancy Evaluation. Health Environments Research & Design Journal (HERD) 2011;**4**(3):14-43.

72. Hrobjartsson A, Gotzsche PC. Placebo treatment versus no treatment. Cochrane database of systematic reviews 2003(1):CD003974.

73. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med 2004;**256**(2):91-100.

74. Thompson WG. Placebos: a review of the placebo response. The American journal of gastroenterology 2000;**95**(7):1637-43.

75. Di Blasi Z, Kleijnen J. Context effects. Powerful therapies or methodological bias? Eval Health Prof 2003;**26**(2):166-79.

76. Lang EV, Hatsiopoulou O, Koch T, et al. Can words hurt? Patient-provider interactions during invasive procedures. Pain 2005;**114**(1-2):303-09.

77. Benedetti F, Amanzio M. The placebo response: how words and rituals change the patient's brain. Patient Educ Couns 2011;**84**(3):413-9.

78. Bensing JM, Verheul W. The silent healer: the role of communication in placebo effects. Patient Educ Couns 2010;**80**(3):293-9.

79. Essers G, Kramer A, Andriesse B, et al. Context factors in general practitioner - patient encounters and their impact on assessing communication skills - an exploratory study. BMC Fam Pract 2013;**14**.

80. Griffin SJ, Kinmonth AL, Veltmn MWM, et al. Effect on health-related outcomes of interventions to alter the interaction between patients and practitioners: A systematic review of trials. Ann Fam Med 2004;**2**(6):595-608.

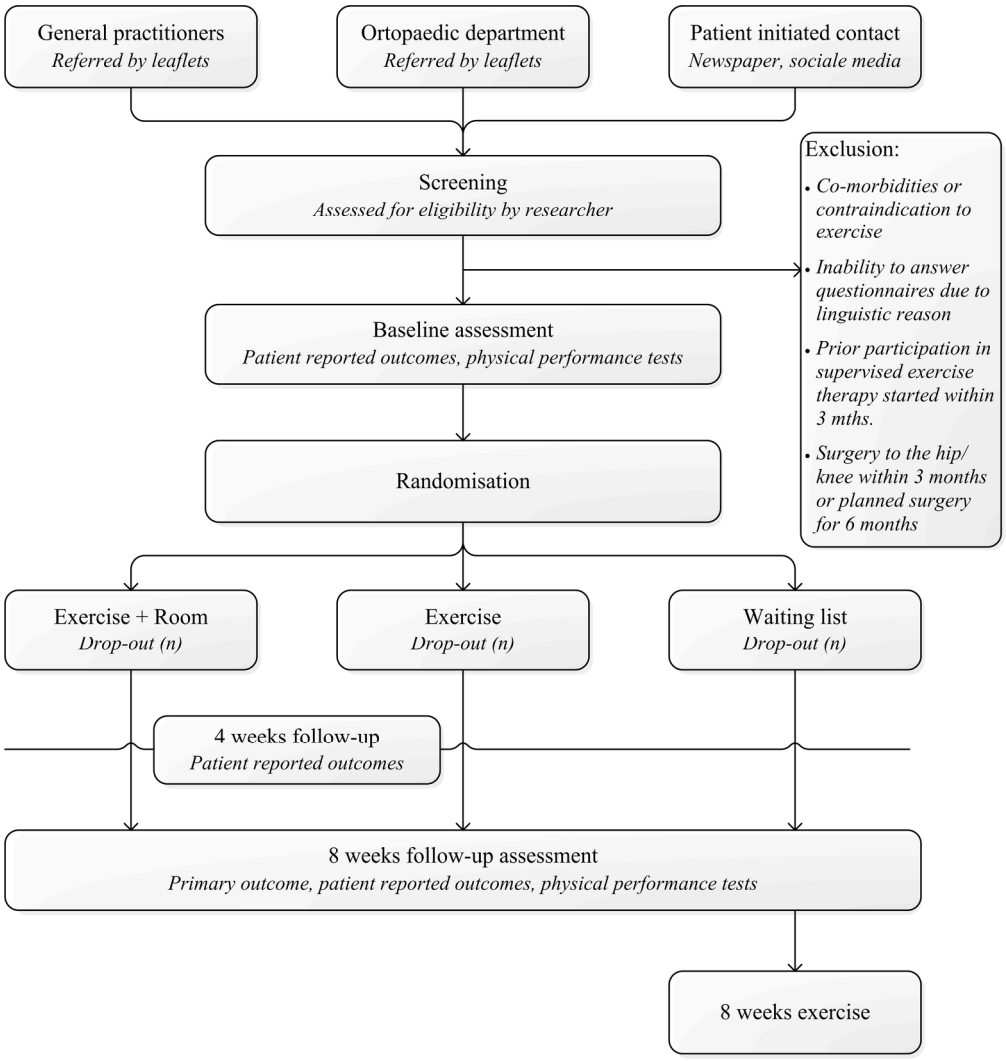
81. Lonsdale C, Hall AM, Williams GC, et al. Communication style and exercise compliance in physiotherapy (CONNECT): a cluster randomized controlled trial to test a theory-based intervention to increase chronic low back pain patients' adherence to physiotherapists' recommendations: study rationale, design, and methods. BMC Musculoskelet Disord 2012;**13**:104.

82. Neumann M, Edelhauser F, Kreps GL, et al. Can patient-provider interaction increase the effectiveness of medical treatment or even substitute it?--an exploration on why and how to study the specific effect of the provider. Patient Educ Couns 2010;**80**(3):307-14.

83. Suarez-Almazor ME, Looney C, Liu Y, et al. A randomized controlled trial of acupuncture for osteoarthritis of the knee: effects of patient-provider communication. Arthritis Care Res 2010;**62**(9):1229-36.

84. Teutsch C. Patient-doctor communication. Med Clin North Am 2003;**87**(5):1115-45.

85. Thomas K. General practice consultations_is there any point in being positive? Br Med J 1987;**294**(may):1200-02.



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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	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	28
	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	28
	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)	22, 28

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	5-7
	6b	Explanation for choice of comparators	8,12,23
Objectives	7	Specific objectives or hypotheses	6,7
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)	7
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	N/A
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)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	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)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15-18
	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	12-18
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)	Fig.1.

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	20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	19
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	19
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19-20
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	19-20
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	12-20
	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 protocols	15

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	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	20-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	22
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 about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16,22,28
	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	18-19
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	7,25
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)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	~~N/A~~ 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	N/A
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	28
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	N/A
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	N/A
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	~~N/A~~ 22
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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	N/A

*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 "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.