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Evaluation of a web-based platform for osteoarthritis treatment – study protocol for a randomized clinical study

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ABSTRACT

Introduction

Despite favorable results from structured face-to-face treatment of osteoarthritis (OA) in Sweden through the Better management of OsteoArthritis (BOA) initiative, only around 20% of people with OA receive proper treatment. In 2014, a digital treatment program named Joint Academy was introduced in Sweden, based on the same concept as the face-to-face program. In line with BOA, Joint Academy follows national and international guidelines and best practice for OA treatment. Results from observational studies suggest that this digital treatment is a valuable alternative to the traditional treatment approach. However, conclusions from such studies commonly suggest that more rigorous testing is necessary to ascertain the benefits of digital treatment delivery for people with OA.

Methods and analysis

A randomized clinical trial will be performed, comparing regular face-to-face care according to BOA with the digital version, Joint Academy. A total of 270 participants will be recruited at primary care centers and randomized to either standard treatment, or the experimental group. Both groups will receive educational sessions and exercises but there will be a difference in the way the programs are delivered. The two treatment groups will be compared with respect to the number of repetitions of the 30-second chair stand test using Student's t-test and a mixed model repeated measures ANOVA.

Ethics and dissemination

Ethical approval has been attained from the Regional Board of Ethics in Lund, Sweden (Dnr 2017/719). Results will be published in peer-reviewed journals.

Trial registration number: NCT03328741 (Clinicaltrials.gov)

Strengths and limitations of this study

- **This study will evaluate the usefulness of web-based treatment for osteoarthritis, a common chronic disease**
- **The sample size ensures sufficient power for group comparisons**
- **The trial has a pragmatic design, to compare two existing treatment programs without any alterations to fit trial methodology**
- **The nature of the two treatment modalities makes blinding of patients and physiotherapists impossible**

INTRODUCTION

To facilitate the implementation of evidence-based guidelines for osteoarthritis (OA) treatment[1-4], the Swedish National quality register *BOA* (*Better management of patients with OsteoArthritis*) was established, with an OA self-management program including education and supervised exercise (the BOA program). The purpose of the BOA program is to provide patients with structured and relevant OA information and the opportunity to do leg-strengthening exercises[3]. The BOA program is clinic-based and provided at more than 500 primary care centers. The program varies slightly between regions, but in general it consists of three educational sessions and for most patients six weeks of individually adapted neuromuscular exercises. The program has been shown to be feasible in clinical practice; the intervention was rated as good or very good by 94% of the patients[5]. After three months, 62% reported daily use of what they had learned and 91% reported weekly use. Preliminary results also suggest significant improvements in pain, quality of life and self-efficacy for participants of the BOA program, in comparison to patients on a waiting list for surgery[6]. However, despite the systematic and thorough work put into BOA and the appurtenant program, only around 20% of the Swedish OA population in need of treatment receive such therapy[7].

In 2014 *Joint Academy* (JA), a web-based digital platform for individuals with clinically verified OA[8], was created based on the face-to-face BOA program. In an observational pilot study, 53 patients with OA were enrolled into JA and results showed that the mean pain level continuously decreased during the 30-week study period. In addition, the patients highly recommended JA to other OA patients[7]. In a recent publication these results were confirmed in a study cohort of 350 patients[9]. Although inferences of causality cannot be made due to the lack of a control group, these results suggest that JA has the potential to successfully deliver treatment to patients with OA. Digital treatment may be a cost-effective alternative to face-to-face meetings with clinicians when delivering treatment that promotes changes in lifestyle,

since follow-up and guidance for the patient are easily accessible through computers/laptops or wearable devices. In addition, traditional health care cannot be required to offer necessary *chronic treatment to chronic diseases* but must rely on patients' self-management. Digital support may prove valuable in this regard. Currently there is evidence of the effectiveness and/or efficacy of digital interventions for increasing physical activity, reducing the risk of diabetes and weight loss, or alleviating chronic joint pain[10-12]. However, previous research within the area of chronic joint pain has concluded that studies with more rigorous design are needed, especially for enabling comparison to standard care[13]. Hence, it is still unknown whether a web-based program may benefit people with OA, and if so, to what extent compared with current standard treatment. The aim of the study is to investigate whether JA is more effective than (superior to) the BOA program, primarily with reference to decreasing joint pain, for individuals with knee OA. Thus, the proposed randomized clinical trial will provide new knowledge regarding whether an individualized around-the-clock treatment delivered online is superior and more cost-effective than regular OA care.

METHODS AND ANALYSIS

In this two-armed randomized controlled superiority trial (RCT), 270 patients with knee OA will be recruited, 135 allocated to each arm. The primary evaluation of outcomes (see *Outcome measures* below for details) will be performed at 12 months. Ten primary care centers around Sweden that are experienced in OA and use the face-to-face BOA program will participate, and include approximately 30 patients each (one group of each treatment including 15 patients). After providing consent to participate in the study, all participants will be registered in the study database. All outcome variables will be patient-reported and monitored at baseline, and at 3, 6 and 12 months after start, for both groups.

The allocation of patients will be performed using permuted blocks with a random block size (4 and 6) and stratification for gender and center. The randomization sequences will be based on computer-generated random numbers, and concealed treatment allocation will be achieved using sequentially numbered opaque envelopes that are only opened once the patient's consent to participate has been received. A statistician will generate the random numbers and instructions of use, while the physiotherapist at each clinic will be responsible for preparation and distribution of envelopes. The treatment allocation will be concealed from the statistician performing the data analysis, but unfortunately the design of the study and the nature of the two treatment modalities prevent blinding of patients and physiotherapists. Participants randomized to JA will receive a link to the web application by email, after which these participants can start the program. Participants randomized to the BOA program will be invited to their primary care center to participate, according to regional standard protocol. Figure 1 contains a flow chart of the overall study design.

- *Figure 1 here* -

Patient selection – population and sample

For patient recruitment, primary care centers around Sweden that are experienced in OA and use the face-to-face treatment will be enrolled and recruit patients. All patients seeking care for OA and fulfilling the inclusion criteria will be asked to participate in the study to minimize selection bias.

A pre-randomization screening will be performed in which patients will report their knee pain (Numerical Rating Scale (NRS) 0-10) as well as perform a 30-second chair stand test (30 CST). The data collected at screening will be used to validate the baseline assessments (which

will be performed after randomization) to avoid the risk of misclassification bias, as well as minimize the risk of floor and ceiling effects.

Additionally, patients with clinically verified knee OA will be enrolled, according to the inclusion and exclusion criteria outlined below:

Inclusion criteria:

I: A clinical diagnosis of knee OA according to the American College of Rheumatology (ACR) diagnostic criteria as well as national and international guidelines[14,15]: knee pain and three of the following: > 50 years of age, morning stiffness >30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth;

II: Reported knee pain ≥4 and ≤8 on the NRS[16], and ≥6 to ≤16 in number of repetitions during a 30 CST[9], at pre-randomization screening.

II: Able to handle a software program via phone, tablet, or computer.

III: Able to read and write the Swedish language.

Exclusion criteria:

I: Neurological disease, inflammatory joint disease, or cancer.

II: Cognitive disorder, e.g. dementia.

III: Exercise is contra-indicated for the patient

Estimated sample size and power

The two treatment groups will be compared with respect to the number of repetitions during the 30 CST (see *Outcome measures* below). The null hypothesis is that the effects of the experimental treatment (web-based JA) and the standard treatment (the BOA program) are identical, i.e. the mean number of repetitions in the standard treatment group is not significantly different from the mean number of repetitions in the experimental treatment group. The alternative hypothesis is that the experimental treatment is superior. The null

hypothesis will be tested with a one-sided significance level of 0.025, equivalent to a two-sided significance level of 0.05, using Student's t-test, assuming that the number of repetitions is a continuous variable having a Gaussian distribution. If the underlying assumptions for the Student's t-test are unfulfilled, the Satterthwaite's t-test will be used instead[17].

The sample size has been calculated for a number of different scenarios with treatment effects of 1.0, 2.0 and 3.0 repetitions, statistical power of 0.80, and standard deviations of 4.0 to 5.0 repetitions using Stata v.15. Calculations are based on the previously reported mean number of repetitions and standard deviation in a Swedish sample, as well as the major clinically important improvement (MCII) in persons with OA[9,18]. Hence, according to Table 1 below, 162 patients are required to be 80% sure that the experimental treatment is superior to the standard treatment, if the standard deviation of 30 CST repetitions is 4.5 and the MCII is 2.0. To compensate for 40% withdrawals, in line with withdrawals reported in the BOA program[3], the number of randomized patients has been adjusted to 270. A sample size reassessment will be performed after six months in order to verify the assumptions made or to adjust the sample size if the assumptions are not fulfilled. This sample size reassessment will be blinded. No interim analysis will be performed.

Table 1. Sample size calculation based on difference between treatments and standard deviation of 30 CST repetitions, with 80% statistical power and 5% statistical significance. Calculated using Student's t-test.

Difference	***Standard deviation***		
	4.0	***4.5***	***5.0***
1.0	506	638	788
2.0	128	162	200
3.0	58	74	90

Outcome measures

Table 2 below provides an overview of measurements, according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

Table 2. Standard protocol items: Recommendations for Interventional Trials (SPIRIT) schedule.

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		
TIMEPOINT	***-t_1***	***0 Baseline***	***t_1 3 months***	***t_2 6 months***	***t_3 12 months***
ENROLMENT:					
Eligibility screen	X				
Individual informed consent	X				
Allocation		X			
INTERVENTIONS:					
[Standard treatment]		X	X		
[Experimental treatment]		X	X		
ASSESSMENTS:					
Demographics		X	X	X	X
Physical functioning[1]		X	X	X	X
Knee pain[2]		X	X	X	X
HRQoL[3]		X	X	X	X
Self-reported function[4]		X	X	X	X
Physical activity[5]		X	X	X	X
PASS[6]			X	X	X
Absenteeism[7]					X
Presenteeism[8]		X	X	X	X
Health care costs[9]					X

[1]30 sec chair stand test.[2]Numeric rating scale (NRS) 0-10. [3]HRQoL=Health-related quality of life measured using the EQ5D-5L. [4]KOOS-PS. [5]The Swedish Board of Health and Welfare indicator questions. [6]Patient acceptable symptom state. [7]Productivity loss measured using data from the Social Insurance Agency's Register. [8] Productivity loss while working, measured using the Work Productivity and Activity Impairment Questionnaire (WPAI). [9]Estimated using data from the Swedish patient register, medication register, and data from each participant's primary care provider.

The primary outcome will be the mean group difference in number of repetitions of the 30 CST (continuous variable) from baseline to 12 months follow-up[19]. In the 30 CST, the participant rises from a chair repeatedly for 30 seconds. Instructions will be given to both groups using an instructional video, and the number of repetitions will be recorded by the participant.

Secondary outcomes

Knee pain will be measured using the numeric rating scale (NRS), a valid, reliable and appropriate scale for pain intensity measurement[20]. The NRS is an 11-point Likert scale (0-10) (continuous variable) and the participants will be asked to indicate the average pain in the specified knee over the last week. Higher scores indicate more severe pain[21]. Health-related quality of life (HRQoL) will be measured using a descriptive EQ-5D-5L instrument[22]. The EQ-5D-5L instrument contains five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient will be asked to indicate his/her health state in each dimension. In addition, an index score based on the five dimensions and general population value surveys is calculated using an EQ-5D index calculator. The EQ-5D index calculator combines the individual levels from the five dimensions into one of 3125 health states, and converts the state into a single index value using a country-specific value set.

Self-reported function (continuous variable) will be measured using KOOS-PS[23]. The instrument contains seven items covering daily activities: rising from bed, putting on socks, rising from sitting, bending to the floor, twisting/pivoting on the painful knee, kneeling and squatting. A total score will be calculated and converted using a nomogram of a 0-100 score.

Physical activity/exercise (continuous variable) will be measured using the Swedish Board of Health and Welfare indicator questions[24]. The instrument contains two questions; patient-defined minutes of physical activity and minutes of exercise, both per week. The amount of activity minutes/week is calculated by adding up the number of minutes (number of minutes of exercise is multiplied by 2 before summing up).

To assess the patient acceptable symptom state (PASS), two questions, previously described by Ingelsrud et al[25] will be used; participants will report whether current symptoms are acceptable, and if not, if they feel the treatment has failed.

Quality-adjusted life years (QALYs) will be calculated by multiplying a health state utility (measured by the EQ-5D-5L index score) by the time spent in that health state[26]. This measurement will be used in conducting a cost-utility analysis alongside the trial.

Productivity loss refers to monetary value of the time lost due to the disease or its treatment. It includes two main parts: absenteeism (time missed from work), and presenteeism (decreased productivity while working). In the current study absenteeism ≥ 14 days will be measured using data from the Swedish Social Insurance Agency's Register. To measure absenteeism of less than 14 days and presenteeism, a validated questionnaire entitled "the Work Productivity and Activity Impairment Questionnaire (WPAI)"[27] will be used. Productivity losses will be translated into monetary values using the human capital approach (HCA) based on the average salary in Sweden. Subsequently, to estimate health care cost per patient related to their OA, data from the inpatient register, medication registry, and each patient's primary health care provider will be accessed. Data on the number and type of visits, prescribed medication, and type of health care provider will be utilized for analysis.

In terms of the secondary outcomes, mean knee pain will be tested confirmatory only if the primary outcome is statistically significant. The other secondary outcomes are considered

supportive, explanatory, or exploratory. Multiplicity issues will therefore not complicate the evaluation.

Standard treatment - the BOA program

Individuals randomized to the BOA program will be offered three educational sessions at their respective clinic, according to the standardized minimal intervention in BOA. The first session consists of providing information regarding the nature of OA, evidence-based risk factors, general symptoms, and available treatment. The second session focuses on the benefits and mechanisms behind the effects of exercise, daily life activities, how to cope with OA, and practical information on how to self-manage the disease. In the final session, an OA-communicator, an individual with OA, presents their experience with living with the disease, and how to manage on a more personal level. Each session is two hours long and is carried out during day time/office hours. After attending the sessions, the participant will meet with a physiotherapist and discuss whether he or she wants an individually adapted exercise plan, or no exercise. If the exercise plan is chosen, the individual is offered to join physiotherapist-supervised group exercises performed twelve times (twice per week for six weeks) during day time, or receive an instruction leaflet for home exercises (unpublished data from BOA suggest that 12.5% choose not to participate in supervised exercise).

Although all centers offering the BOA program in Sweden follow the original concept outlined by BOA[3], there may be regional differences between centers in terms of the total amount of exercise sessions, and whether they are offered before or after the three theoretical sessions.

In total (including start-up visits, screening, education and training as well as end sessions), the number of personal visits for each patient will range between 6-22 (regional variation taken into account).

After the program patients receive a leaflet describing their exercises, and are advised to continue exercising at home, according to the routine at the center they attended.

The questionnaires are distributed at baseline, 3 months (3 month-evaluation includes an individual physiotherapy visit at the clinic) and at 6 and 12 months. At 6 and 12 months, questionnaires are delivered by mail.

Experimental treatment - Joint Academy

Individuals in the JA group will undergo an interactive six-week program to treat their OA pain, followed by the Sustain program to enable maintained individual compliance with the necessary life style changes. The six-week program includes individualized physical activity, education about lifestyle changes, and one-on-one asynchronous coaching from a physical therapist via online chat (i.e. without the participant having to visit a specific location). The six-week and the Sustain program together run for a total of one year.

In the six-week program neuromuscular exercises are introduced to improve lower extremity physical function. The participant is instructed to perform two of these exercises every day of the week and each exercise has 1-5 levels of intensity. The level of intensity is based on an algorithm that adjusts for individual progress and the patient's perceived ability to perform the exercise without exacerbating pain. Thus, JA individualizes a schedule for each participant. Furthermore, participants watch short and engaging video sessions explaining how to live with OA; these videos provide education regarding lifestyle changes. After each session, participants are given a quiz to confirm that they understand the content. The educational component of JA is developed to improve the patient's understanding of the exercises. Thereafter, participants are assigned a professional physiotherapist who guides each patient via the interactive interface within the platform. All physiotherapists are extensively educated in the platform and have considerable experience in treating people with OA.

In the Sustain program, exercises will be delivered a patient-specified number of times per week. Similar to the six-week program, a physiotherapist is constantly available via the chat function.

For evaluation, participants will complete the web-based questionnaire (containing the measurements described previously) at baseline, after six weeks (according to standard protocol in JA), and at 3, 6 and 12 months. Additionally, participants will report their knee pain using an NRS scale weekly during the study period.

Patient and public involvement

The BOA program was developed on a foundation of current research and conclusions drawn from focus groups consisting of patients and representatives of the Swedish Rheumatism Association. The digital version (JA) is, as previously described, based on the same concept. Furthermore, beta-versions of the web-based platform has been improved by analyzing questionnaires and opinions from patients recruited via the Swedish Rheumatism Association. These patients were able to test JA and were thoroughly interviewed about their opinions. In addition, the outcomes in the proposed study are in agreement with the International Consortium for Health Outcomes Measurement (ICHOM) Standard set for knee and hip OA, defined through close involvement of patients. There was no patient involvement in regards to other aspects of the study design. Results will be disseminated to those participants expressing their interest during, before or after the study.

Statistical analysis plan

The statistical analysis will be performed in compliance with ICH-GCP guidelines and the report will be developed in line with the CONSORT statement. P-values and 95% confidence intervals for the change in number of 30 CST repetitions from baseline to 12 months between

the two treatment groups will be calculated using a mixed model repeated measures (MMRM) ANOVA. In this statistical model *patient* will be defined as a random factor. The follow-up time and treatment group will be fixed factors, and treatment-time interactions will be included. The results will be adjusted for the endpoint's baseline imbalance, and the model will include stratification for gender and center as the randomization procedure includes stratification by these factors. An unstructured variance-covariance matrix will be considered first. If this cannot be estimated, compound symmetry will be assumed instead.

As the MMRM can handle imbalanced data, there will be no imputation of missing data. Both the intention-to-treat and the per-protocol population will be analyzed, but the intention-to-treat analysis will be considered the main analysis.

A P-value for superiority will be presented, and if this is small enough (i.e. <0.05) to convincingly reject the null hypothesis of no difference in the intention-to-treat population for the primary outcome, the trial will be considered to show superiority for the treatment with the superior outcome. Additional exploratory and hypothesis-generating analyses will be performed to identify gender differences in the treatment effect, and these analyses will be performed both by stratifying by gender and by including terms for estimating interaction effects with gender. After collecting the required data, a cost-utility analysis from a societal perspective will be conducted. The uncertainty in cost-utility analysis will be handled using a bootstrap approach. All statistical calculations will be performed using Stata v15 (StataCorp. 2017. College Station, TX: StataCorp LLC).

ETHICS AND DISSEMINATION

The trial will be performed in compliance with the Helsinki Declaration, and has been approved by the Regional Board of Ethics, Lund University, Sweden (Dnr 2017/719). Potential participants must provide written informed consent before entering the study. The

results of the main trial and each of the secondary outcomes will be submitted for publication in peer-reviewed journals.

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AUTHORS' CONTRIBUTIONS

HN, JR, AAK and LD designed the study. HN wrote the first draft of the manuscript, and together with JR, AAK and LD revised the manuscript and produced the final draft. All authors have read and approved the final version of the manuscript.

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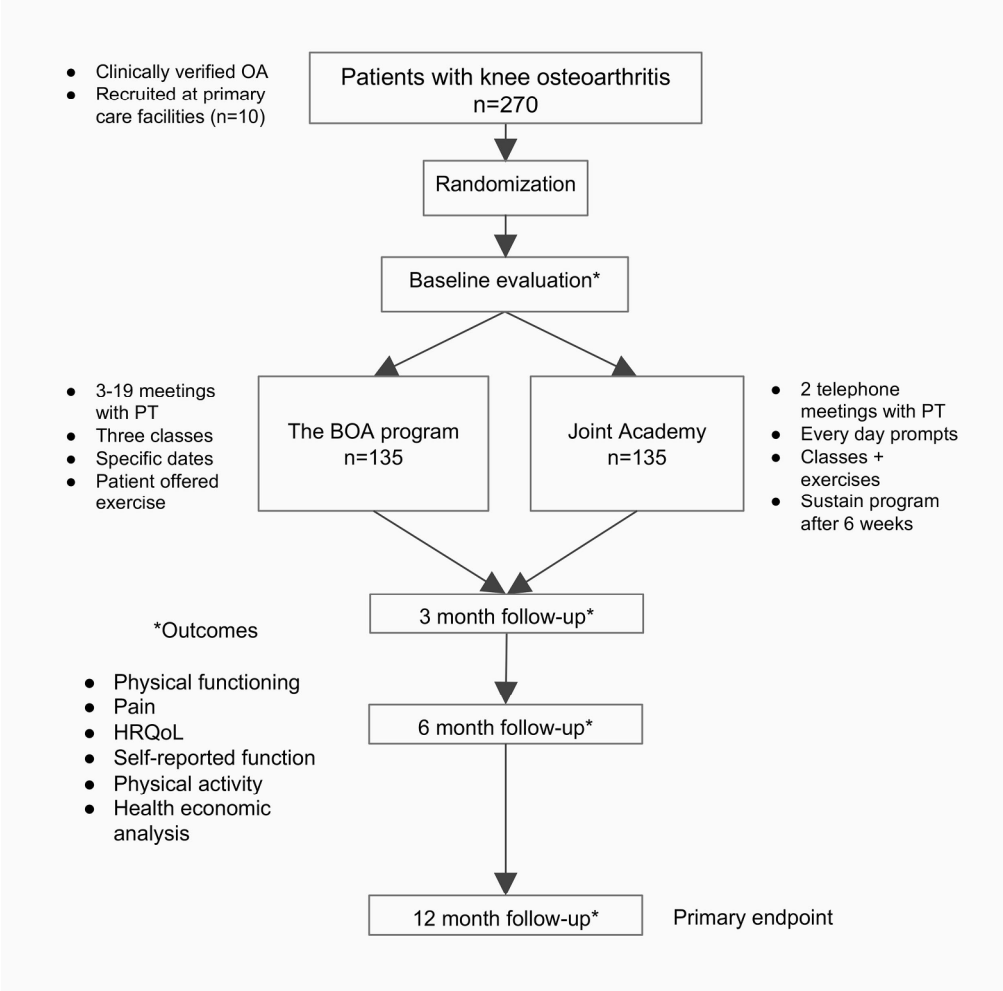
COMPETING INTERESTS STATEMENT

HN is hired as a part-time consultant for Arthro Inc., the corporation behind JA, and LED is the unemployed CMO of Arthro Inc. JR and AAK have no competing interests to report.

FIGURE LEGENDS

Figure 1. Flowchart of the study design. OA=osteoarthritis. PT=physiotherapist. HRQoL=Health-related quality of life.



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ABSTRACT

Introduction

Despite favorable results from structured face-to-face treatment of osteoarthritis (OA) in Sweden through the Better management of OsteoArthritis (BOA) initiative, only around 20% of people with knee or hip OA receive the primary treatment recommended by international guidelines (i.e. information, exercise, weight management). In 2014, a digital treatment program named Joint Academy was introduced in Sweden, based on the same concept as the face-to-face BOA program. In line with BOA, Joint Academy follows national and international guidelines and best practice for OA treatment. Results from observational studies suggest that this digital treatment is a valuable alternative to the traditional treatment approach and can positively impact patients function and pain. However, conclusions from such studies commonly suggest that more rigorous testing is necessary to ascertain the benefits of digital treatment delivery for people with OA.

Methods and analysis

A randomized clinical trial will be performed, comparing regular face-to-face care according to BOA with the digital version, Joint Academy. A total of 270 participants with clinically diagnosed knee OA will be recruited at primary care centers and randomized to either standard treatment (BOA) for 3 months, or the experimental group (6-week online intervention program). Both groups will receive educational sessions and exercises yet with a difference in program deliverance. The objective of the trial is to evaluate the effectiveness of the online treatment program, in comparison with BOA. The two treatment groups will be compared with respect to the number of repetitions of the 30-second chair stand test at 3, 6 and 12 months, using a mixed model repeated measures ANOVA.

Ethics and dissemination

Ethical approval has been attained from the Regional Board of Ethics in Lund, Sweden (Dnr 2017/719). Results will be published in peer-reviewed journals.

Trial registration number: NCT03328741 (Clinicaltrials.gov)

Strengths and limitations of this study

- **This study will help in clarifying the potential effect and cost effectiveness of an online osteoarthritis treatment, facilitating implementation decisions for health care providers**
- **The sample size ensures sufficient power for group comparisons**
- **The trial has a pragmatic design, to compare two existing treatment programs without any alterations to fit trial methodology**
- **The nature of the two treatment modalities makes blinding difficult, although patients are blinded regarding what treatment is hypothesized to be superior**

INTRODUCTION

To facilitate the implementation of evidence-based guidelines for osteoarthritis (OA) treatment[1-4], the Swedish National quality register *BOA* (*Better management of patients with OsteoArthritis*) was established, with an OA self-management program including education and supervised exercise (the BOA program). The purpose of the BOA program is to provide patients with structured and relevant OA information and the opportunity to perform joint-strengthening exercises. The BOA program is clinic-based and provided at about 500 primary care centers[3]. The program varies slightly between regions, but in general it consists of three educational sessions and for most patients six weeks of individually adapted neuromuscular exercises. The program has been shown to be feasible in clinical practice; the intervention was rated as good or very good by 94% of the patients. After three months, 62% reported daily use of what they had learned and 91% reported weekly use[5]. Preliminary results also suggest significant improvements in pain, quality of life and self-efficacy for participants of the BOA program, in comparison to patients on a waiting list for surgery[6]. However, despite the systematic and thorough work put into BOA and the BOA program, only around 20% of the Swedish OA population seeking primary care for OA enter the self-management program[7].

In 2014 *Joint Academy* (JA), a web-based digital platform for individuals with clinically verified OA[8], was created based on the face-to-face BOA program. In an observational pilot study, 53 patients with OA were enrolled into JA and results showed that the mean pain level continuously decreased during the 30-week study period. In addition, the patients highly recommended JA to other OA patients[7]. In a recent publication these results were confirmed in a study cohort of 350 patients[9]. Although inferences of causality cannot be made due to the lack of a control group, these results suggest that JA has the potential to successfully deliver treatment to patients with OA. Digital treatment may be a cost-effective alternative to face-to-face meetings with clinicians when delivering treatment that promotes changes in lifestyle,

since follow-up and guidance for the patient are easily accessible through computers/laptops or wearable devices. In addition, traditional health care cannot be required to offer necessary *chronic treatment to chronic diseases* but must rely on patients' self-management. Digital support may prove valuable in this regard. Currently there is evidence of the effectiveness and/or efficacy of digital interventions for increasing physical activity, reducing the risk of diabetes and weight loss, or alleviating chronic joint pain[10-12]. However, previous research within the area of chronic joint pain has concluded that studies with more rigorous design are needed, especially for enabling comparison to standard care[13]. Hence, it is still unknown whether a web-based program may benefit people with OA, and if so, to what extent compared with current standard treatment. The objective of the trial is to evaluate the effectiveness of the online treatment program in comparison with BOA, primarily with reference to increased physical function, for individuals with knee OA. Thus, the proposed randomized clinical trial will provide new knowledge regarding whether an individualized around-the-clock treatment delivered online is superior and more cost-effective than regular OA care.

METHODS AND ANALYSIS

In this two-armed randomized controlled superiority trial (RCT), 270 patients with knee OA will be recruited, 135 allocated to each arm. Superiority is chosen over non-inferiority due to the lack of RCT's showing effects of the BOA program on pain and function, in comparison to a control group. The primary evaluation of outcomes (see *Outcome measures* below for details) will be performed at 12 months. Ten primary care centers around Sweden that are experienced in OA and use the face-to-face BOA program will participate and include a minimum of 26 patients each (13 patients per group). After providing consent to participate in

the study, all participants will be registered in the study database. All outcome variables will be patient-reported at baseline, and at 3, 6 and 12 months after start, for both groups.

The allocation of patients will be performed using permuted blocks with a random block size (4 and 6) and stratification for gender and center. The randomization sequences will be based on computer-generated random numbers, and concealed treatment allocation will be achieved using sequentially numbered opaque envelopes that are only opened once the patient's consent to participate has been received. A statistician will generate the random numbers and instructions of use, while the physiotherapist at each clinic will be responsible for preparation and distribution of envelopes. The treatment allocation will be concealed from the statistician performing the data analysis, but unfortunately the design of the study and the nature of the two treatment modalities prevent blinding of patients and physiotherapists. Participants randomized to JA will receive a link to the web application by email, after which these participants can start the program. Participants randomized to the BOA program will be invited to their primary care center to participate, according to regional standard protocol. Figure 1 contains a flow chart of the overall study design.

- *Figure 1 here* -

Patient selection – population and sample

For patient recruitment, primary care centers around Sweden that are experienced in OA and currently offering the face-to-face BOA treatment to 70-100 patients per year, will be enrolled and recruit patients. All patients being referred to the clinic or seeking care for OA, visiting the care center for a physiotherapist evaluation, and being eligible (fulfilling the inclusion criteria) will be invited to participate in the study to minimize selection bias. Anonymous data

on the number of patients declining participation along with stated reasons for declining will be collected at each clinic.

A pre-randomization screening will be performed in which patients will be asked to report their knee pain (Numerical Rating Scale (NRS) 0-10) as well as perform a 30-second chair stand test (30 CST) to minimize the risk of floor and ceiling effects. All inclusion- and exclusion criteria are listed below.

Inclusion criteria:

I: A clinical diagnosis of knee OA according to the American College of Rheumatology (ACR) diagnostic criteria as well as national and international guidelines[14,15]: knee pain and three of the following: > 50 years of age, morning stiffness >30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth;

II: Reported knee pain ≥4 and ≤8 on the NRS[16], and ≥6 to ≤16 in number of repetitions during a 30 CST[9], at pre-randomization screening.

II: Able to handle a software program via phone, tablet, or computer.

III: Able to read and write the Swedish language.

Exclusion criteria:

I: Neurological disease, inflammatory joint disease, or cancer.

II: Cognitive disorder, e.g. dementia.

III: Exercise is contra-indicated for the patient

Estimated sample size and power

The two treatment groups have been compared with respect to the number of repetitions during the 30 CST (see *Outcome measures* below). The null hypothesis was that there is no difference in the mean number of repetitions between the experimental treatment (web-based

JA) and the standard treatment (the BOA program). The alternative hypothesis was that the treatment effects differ. For sample size calculation, the null hypothesis has been tested with a one-sided significance level of 0.025, equivalent to a two-sided significance level of 0.05, using Student's t-test, assuming that the number of repetitions has a Gaussian distribution.

The sample size was calculated for a number of different scenarios with treatment effects of 1.0, 2.0 and 3.0 repetitions, statistical power of 0.80, and standard deviations of 4.0 to 5.0 repetitions using Stata v.15. Calculations are based on the previously reported mean number of repetitions and standard deviation in a Swedish sample, as well as the major clinically important improvement (MCII) in persons with OA[9,17]. Hence, according to Table 1 below, 162 patients are required to be 80% sure that the experimental treatment is superior to the standard treatment, if the standard deviation of 30 CST repetitions is 4.5 and the MCII is 2.0. To compensate for 40% withdrawals, in line with withdrawals reported in the BOA program[3], the number of randomized patients has been adjusted to 270. A sample size reassessment will be performed after six months of recruitment in order to verify the assumptions made or to adjust the sample size if the assumptions are not fulfilled. This sample size reassessment will be blinded. No interim analysis will be performed.

Table 1. Sample size calculation based on difference between treatments and standard deviation of 30 CST repetitions, with 80% statistical power and 5% statistical significance. Calculated using Student's t-test.

Difference	***Standard deviation***		
	4.0	***4.5***	***5.0***
1.0	506	638	788
2.0	128	162	200
3.0	58	74	90

Outcome measures

Table 2 below provides an overview of measurements, according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

Table 2. Standard protocol items: Recommendations for Interventional Trials (SPIRIT) schedule.

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		
TIMEPOINT	***-t_1***	***0 Baseline***	***t_1 3 months***	***t_2 6 months***	***t_3 12 months***
ENROLMENT:					
Eligibility screen	X				
Individual informed consent	X				
Allocation		X			
INTERVENTIONS:					
[Standard treatment]		X	X		
[Experimental treatment]		X	X		
ASSESSMENTS:					
Demographics		X	X	X	X
Physical functioning[1]		X	X	X	X
Knee pain[2]		X	X	X	X
HRQoL[3]		X	X	X	X
Self-reported function[4]		X	X	X	X
Physical activity[5]		X	X	X	X
PASS[6]			X	X	X
Absenteeism[7]					X
Presenteeism[8]		X	X	X	X
Health care costs[9]					X

[1]30 sec chair stand test.[2]Numeric rating scale (NRS) 0-10. [3]HRQoL=Health-related quality of life measured using the EQ5D-5L. [4]KOOS-PS. [5]The Swedish Board of Health and Welfare indicator questions. [6]Patient acceptable symptom state. [7]Productivity loss measured using data from the Social Insurance Agency's Register. [8] Productivity loss while working, measured using the Work Productivity and Activity Impairment Questionnaire (WPAI). [9]Estimated using data from the Swedish patient register, medication register, and data from each participant's primary care provider.

The primary outcome is the change in number of repetitions of the 30 CST (continuous variable) from baseline to 12 months follow-up[18]. In the 30 CST, the participant rises from a chair repeatedly for 30 seconds. Instructions will be given to both groups using an instructional video, and the number of repetitions will be recorded by the participant.

Secondary outcomes

Knee pain will be measured using the numeric rating scale (NRS), a valid, reliable and appropriate scale for pain intensity measurement[19]. The NRS is an 11-point Likert scale (0-10) (continuous variable) and the participants will be asked to indicate the average pain in the specified knee over the last week. Higher scores indicate more severe pain[20]. Health-related quality of life (HRQoL) will be measured using a descriptive EQ-5D-5L instrument[21]. The EQ-5D-5L instrument contains five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient will be asked to indicate his/her health state in each dimension. In addition, an index score based on the five dimensions and general population value surveys is calculated using an EQ-5D index calculator. The EQ-5D index calculator combines the individual levels from the five dimensions into one of 3125 health states, and converts the state into a single index value using a country-specific value set.

Self-reported function (continuous variable) will be measured using KOOS-PS[22]. The instrument contains seven items covering daily activities: rising from bed, putting on socks, rising from sitting, bending to the floor, twisting/pivoting on the painful knee, kneeling and squatting. A total score will be calculated and converted using a nomogram of a 0-100 score.

Physical activity/exercise (continuous variable) will be measured using the Swedish Board of Health and Welfare indicator questions[23]. The instrument contains two questions; patient-

defined minutes of physical activity and minutes of exercise, both per week. The amount of activity minutes/week is calculated by adding up the number of minutes (number of minutes of exercise is multiplied by 2 before summing up).

To assess the patient acceptable symptom state (PASS), two questions, previously described by Ingelsrud et al[24] will be used; participants will be asked to report whether current symptoms are acceptable, and if not, if they feel the treatment has failed.

Quality-adjusted life years (QALYs) will be calculated by multiplying a health state utility (measured by the EQ-5D-5L index score) by the time spent in that health state[25]. This measurement will be used in conducting a cost-utility analysis alongside the trial.

Productivity loss refers to monetary value of the time lost due to the disease or its treatment. It includes two main parts: absenteeism (time missed from work), and presenteeism (decreased productivity while working). In the current study absenteeism ≥ 14 days will be measured using data from the Swedish Social Insurance Agency's Register. To measure absenteeism of less than 14 days and presenteeism, a validated questionnaire entitled "the Work Productivity and Activity Impairment Questionnaire (WPAI)"[26] will be used. Productivity losses will be translated into monetary values using the human capital approach (HCA) based on the average salary in Sweden. Subsequently, to estimate health care cost per patient related to their OA, data from the inpatient register, medication registry, and each patient's primary health care provider will be accessed. Data on the number and type of visits, prescribed medication, and type of health care provider will be utilized for analysis.

In terms of the secondary outcomes, mean knee pain will be tested confirmatory only if the primary outcome is statistically significant. The other secondary outcomes are considered supportive, explanatory, or exploratory. Multiplicity issues will therefore not complicate the evaluation.

For a brief structured summary of the trial according to the WHO Trial Registration data set, please see the supplementary file (Supplementary file 1).

Questionnaires

For measurements in the BOA program, questionnaires are distributed at baseline, 3 months (3 month-evaluation includes an individual physiotherapy visit at the clinic) and at 6 and 12 months. At 6 and 12 months, questionnaires are delivered by mail. Participants entering the JA program will complete web-based questionnaires (containing the measurements described previously) at baseline, after six weeks (according to standard protocol in JA), and at 3, 6 and 12 months. Additionally, JA participants will be asked to report their knee pain using an NRS scale weekly during the study period.

Standard treatment - the BOA program

Individuals randomized to the BOA program will be offered three educational sessions at their respective clinic, according to the standardized minimal intervention in BOA. The first session consists of providing information regarding the nature of OA, evidence-based risk factors, general symptoms, and available treatment. The second session focuses on the benefits and mechanisms behind the effects of exercise, daily life activities, how to cope with OA, and practical information on how to self-manage the disease. In the final session, an OA-communicator, an individual with OA, presents their experience with living with the disease, and how to manage on a more personal level. Each session is two hours long and is carried out during day time/office hours. After attending the sessions, the participant will meet with a physiotherapist and discuss whether he or she wants an individually adapted exercise plan, or no exercise. If the exercise plan is chosen, the individual is offered to join physiotherapist-supervised group exercises performed twelve times (twice per week for six weeks) during day

time, or receive an instruction leaflet for home exercises (unpublished data from BOA suggest that 12.5% choose not to participate in supervised exercise).

Although all centers offering the BOA program in Sweden follow the original concept outlined by BOA[3], there may be regional differences between centers in terms of the total amount of exercise sessions, and whether they are offered before or after the three theoretical sessions.

In total (including start-up visits, screening, education and training as well as end sessions), the number of personal visits for each patient will range between 6-22 (regional variation taken into account).

After the program patients receive a leaflet describing their exercises, and are advised to continue exercising at home, according to the routine at the center they attended.

The physiotherapist will promote participant retention continuously through the program by discussing the importance of continued study participation with patients. Patient adherence is continuously documented by the physiotherapist in their medical record and after 3 months adherence is reported. No concomitant care is prohibited during trial participation.

Experimental treatment - Joint Academy

Individuals in the JA group will undergo an interactive six-week program to treat their OA pain, followed by the Sustain program to enable maintained individual adherence with the necessary life style changes. The six-week program includes individualized physical activity, education about lifestyle changes, and one-on-one asynchronous coaching from a physical therapist via online chat (i.e. without the participant having to visit a specific location). The six-week and the Sustain program together run for a total of one year.

In the six-week program neuromuscular exercises are introduced to improve lower extremity physical function. The participant is instructed to perform two of these exercises every day of

the week and each exercise has 1-5 levels of intensity. The level of intensity is based on an algorithm that adjusts for individual progress and the patient's perceived ability to perform the exercise without exacerbating pain. Thus, JA individualizes a schedule for each participant. Furthermore, participants watch short and engaging video sessions explaining how to live with OA. These videos are based on the educational material within the BOA program (developed by trained health professionals) and provide education regarding lifestyle changes. After each session, participants are given a quiz to confirm that the take-home message has been received. The educational component of JA is developed to improve the patient's understanding of the exercises. Thereafter, participants are assigned a professional physiotherapist who guides each patient via the interactive interface within the platform. All physiotherapists are extensively educated in the platform and have considerable experience in treating people with OA. In the Sustain program, exercises will be delivered a patient-specified number of times per week. Similar to the six-week program, a physiotherapist is constantly available via the chat function. Push-notifications will be delivered every day of scheduled exercise, reminding participants to enter JA, exercise and report their experience of each activity. As in the first part of the program, difficulty level of exercises can be altered by either patient or physiotherapist. New educational sessions on subjects related to OA as well as previous ones will be steadily available. Should technical issues arise, the participant has constant access to the regular support channel offered at Joint Academy.

. As described previously, the physiotherapist promotes participant retention continuously through the program by discussing the importance of continued study participation with patients. Adding on, for patients treated online each physiotherapist is able to continuously follow and record the patient's adherence to the program in the JA Physiotherapist Dashboard. No concomitant care is prohibited during trial participation.

Patient and public involvement

The BOA program was developed on a foundation of current research and conclusions drawn from focus groups consisting of patients and representatives of the Swedish Rheumatism Association. The digital version (JA) is, as previously described, based on the same concept. Furthermore, beta-versions of the web-based platform has been improved by analyzing questionnaires and opinions from patients recruited via the Swedish Rheumatism Association. These patients were able to test JA and were interviewed in depth about their opinions. In addition, the outcomes in the proposed study are in agreement with the International Consortium for Health Outcomes Measurement (ICHOM) Standard set for knee and hip OA, defined through close involvement of patients. There was no patient involvement in regard to other aspects of the study design. Results will be disseminated to those participants expressing their interest during, before or after the study.

Statistical analysis plan

The statistical analysis will be performed in compliance with ICH-GCP guidelines and the report will be developed in line with the CONSORT statement. P-values and 95% confidence intervals for the change in number of 30 CST repetitions from baseline to 12 months between the two treatment groups will be calculated using a mixed model repeated measures (MMRM) ANOVA. In this statistical model *patient* will be included as a random factor and follow-up time and treatment group as fixed factors. Treatment-time interactions and covariates for the endpoint's baseline imbalance and randomization stratification factors (gender and center) will also be included. An unstructured variance-covariance matrix will be considered first. If this cannot be estimated, compound symmetry will be assumed instead.

As the MMRM can handle imbalanced data, there will be no imputation of missing data. Both the intention-to-treat and the per-protocol population will be analyzed, but the intention-to-treat analysis will be considered the main analysis.

A P-value will be presented, and if this is small enough (i.e. <0.05) to convincingly reject the null hypothesis of no difference in the intention-to-treat population for the primary outcome, the trial will be considered to show superiority for the treatment with the superior outcome. Additional exploratory and hypothesis-generating analyses will be performed to identify gender differences in the treatment effect, and these analyses will be performed both by stratifying by gender and by including terms for estimating interaction effects with gender. After collecting the required data, a cost-utility analysis from a societal perspective will be conducted. The uncertainty in cost-utility analysis will be handled using a bootstrap approach. All statistical calculations will be performed using Stata v15 (StataCorp. 2017. College Station, TX: StataCorp LLC).

ETHICS AND DISSEMINATION

The trial will be performed in compliance with the Helsinki Declaration, and has been approved by the Regional Board of Ethics (RBE), Lund University, Sweden (Dnr 2017/719). Important protocol modifications will be communicated to the RBE and participating clinics.

Potential participants must provide written informed consent to their physiotherapist before entering the study. All participant data at each clinic will be handled as patient-related data and therefore securely stored and administered according to Swedish Law. The JA database is equipped with modern authorization control as well as being fully encrypted. All patient-related data is de-identified (anonymous) and handled according to the standard of the SSL-certificate (Secure Sockets Layer). Two-factor authorization is utilized for user-logins.

Further, Joint Academy is in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and the GDPR, as well as being an IVO-approved (The Swedish Health and Social Care Inspectorate) health care provider. Only data of relevance to the study and its analyses (final trial dataset) will be shared with the Principal Investigator (HN), the Lead Statistician (JR) and the Health Economics Analyst (AAK). All participants are insured, through the Swedish Patient Injury Act or the specific health care provider. The results of the main trial and each of the secondary outcomes will be submitted for publication in peer-reviewed journals and will also be disseminated to participants expressing interest. Statistical analysis plan and informed consent form will be made available six months after study completion. Clinical study report and analytical code will be available after publication of results, upon reasonable request.

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AUTHORS' CONTRIBUTIONS

HN, JR, AAK and LD designed the study. HN wrote the first draft of the manuscript, and together with JR, AAK and LED revised the manuscript and produced the final draft. All authors have read and approved the final version of the manuscript. For this protocol and the final trial report, no ghost authors, guest authors or professional medical writers have or will be used, and author eligibility is and will be based upon the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals.

ROLES AND RESPONSIBILITIES

HN: Responsible for trial conduct and coordination.

JR: Statistical preparation and analysis of results.

AAK: Responsible for planning and conducting health economics analyses.

LED: Overseeing and assisting in trial conduct and coordination, overall guidance for HN.

Due to the short duration and minimal risks related to the described study, no data monitoring committee has been composed.

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form of technical assistance in matters regarding the online platform. The study sponsors and funders has had no role in study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication and does not own ultimate authority over any of these activities.

COMPETING INTERESTS STATEMENT

HN is hired as a part-time consultant for Arthro Inc., the corporation behind JA, and LED is the unemployed CMO of Arthro Inc. There are no other competing interests to report.

FIGURE LEGENDS

Figure 1. Flowchart of the study design. OA=osteoarthritis. PT=physiotherapist. HRQoL=Health-related quality of life.

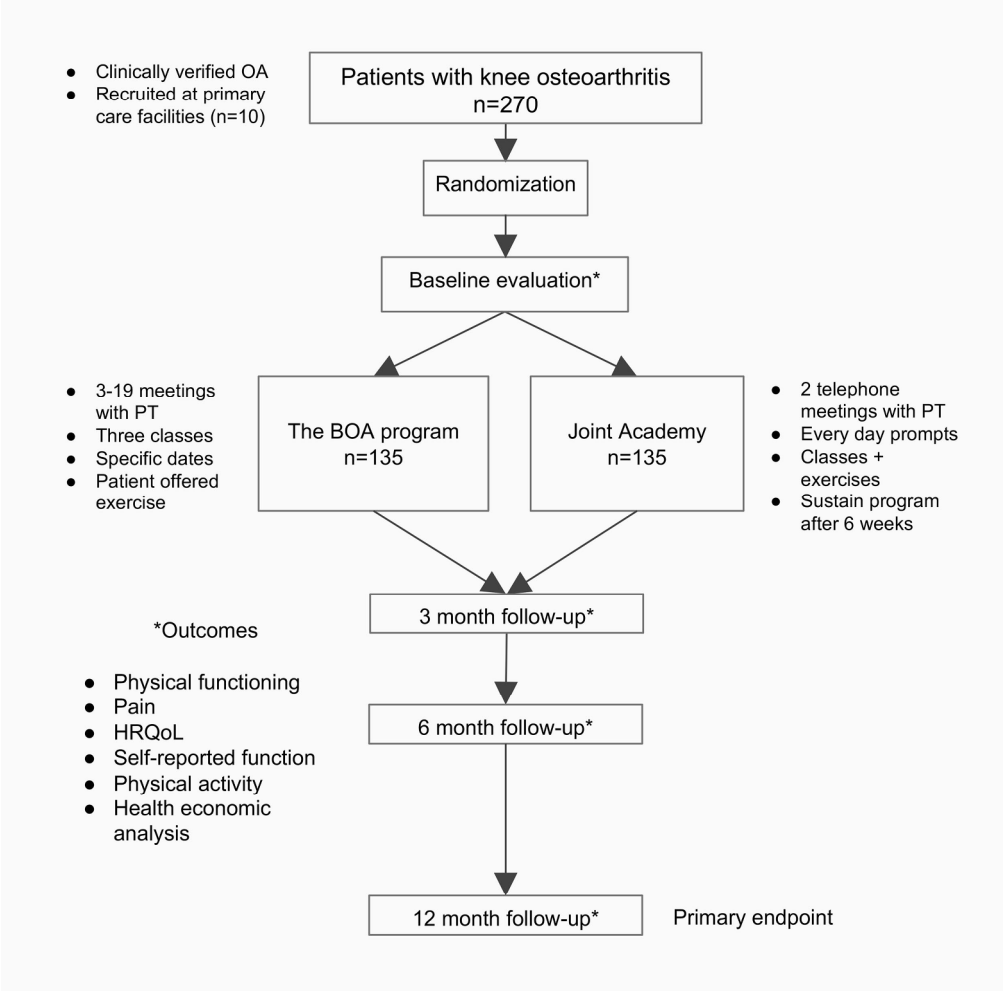

Figure 1. Flowchart of the study design. OA=osteoarthritis. PT=physiotherapist. HRQoL=Health-related quality of life.

209x208mm (300 x 300 DPI)

Data category	Information
Primary registry and trial identifying number	Clinicaltrials.gov: NCT03328741
Date of registration in primary registry	November 1st, 2017
Secondary identifying numbers	N/A
Source(s) of monetary or material support	Lund University, Sweden
Primary sponsor	Lund University, Sweden
Secondary sponsor(s)	The Swedish Rheumatism association, Stiftelsen för bistånd åt rörelsehindrade i Skåne and Sweden's innovation agency Vinnova
Contact for public queries	HN email address
Contact for scientific queries	HN email address
Public title	Evaluation of a Web-based Platform for Osteoarthritis Treatment
Scientific title	Evaluation of a Web-based Platform for Osteoarthritis Treatment
Countries of recruitment	Sweden. List of study sites can be obtained through HN email address
Health condition(s) or problem(s) studied	Osteoarthritis (OA) of the knee joint
Intervention(s)	Web-based structured treatment program, Joint Academy
	Face-to-face structured treatment, the BOA program
Key inclusion and exclusion criteria	I. A clinical diagnosis of knee OA according to American College of Rheumatology (ACR) diagnostic criteria as well as national and international guidelines: knee pain and 3 of the following: > 50 years of age, morning stiffness >30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth; II: Reported knee pain ≥4 and ≤8 on the NRS, and ≥6 to ≤16 in number of repetitions of the 30 second chair stand test, at pre-randomization screening. II. Able to handle a software program via smartphone, tablet or computer. III. Able to read and write the Swedish language.
	Exclusion: I. Neurological disease, inflammatory joint disease or cancer. II. Cognitive disorder, e.g. dementia. III. Exercise is contra-indicated for the patient.
Study type	Interventional
	Allocation: Randomized. Intervention model: Parallel assignment.
	Masking: Non-blinded.
Date of first enrolment	22nd of May, 2018
Target sample size	270
Recruitment status	Recruiting
Primary outcome(s)	Repetitions of the 30 second chair stand test

Key secondary outcomes	Knee joint pain, Health-related Quality of Life, Self-reported function, physical activity level, Patient Acceptable Symptom State, Absenteeism, Presenteeism and Health care costs.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ***Please see page 1***
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ***Please see page 1***
	2b	All items from the World Health Organization Trial Registration Data Set ***Please see Page 1***
Protocol version	3	Date and version identifier ***Please see Clinicaltrials.gov NCT03328741***
Funding	4	Sources and types of financial, material, and other support ***Please see Page 19***
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ***Please see Page 18***
	5b	Name and contact information for the trial sponsor ***Please see Page 1***
	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 ***Please see Page 19***

	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)
		Please see Page 19
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
	6b	Explanation for choice of comparators
		Please see Page 5-16
Objectives	7	Specific objectives or hypotheses
		Please see Page 6
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)
		Please see Page 6-7
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
		Please see Page 1 and 6
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)
		Please see Page 7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
		Please see Pages 15-18
	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)
		Please see Page 16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
		Please see Page 14 and 15
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
		Please see Page 9-12 and 15-16
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)
		Please see Page 10
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
		Please see Page 8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
		Please see Page 7
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
		Please see Page 7

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
		Please see Page 6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
		Please see Page 19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
		Please see Pages 2, 4 and 7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
		N/A

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
		Please see Page 1 and 9-13
	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
		Please see Page 7, 14 and 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
		Please see Page 18

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
		Please see Page 17
	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)
		Please see Page 17
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
		Please see Page 21
	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
		Please see Page 9
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
		N/A
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
		Please see Page 18

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)
		Please see Page 18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
		Please see Page 18
	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
		Please see Page 18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
		Please see Page 21
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
		Please see Page 18
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
		Please see Page 18
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
		Please see Page 18

	31b	Authorship eligibility guidelines and any intended use of professional writers ***Please see Page 20***
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code ***Please see Page 18***
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ***Please see Page 18***
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.