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The Proximal Hamstring Avulsion Clinical Trial (PHACT)- a randomised controlled non-inferiority trial of operative versus non-operative treatment of proximal hamstrings avulsions: study protocol

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The Proximal Hamstring Avulsion Clinical Trial (PHACT)- a randomised controlled non-inferiority trial of operative versus non-operative treatment of proximal hamstrings avulsions: study protocol

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Abstract

Introduction: The treatment of proximal hamstring avulsions is controversial. While several trials have investigated the outcome for patients treated surgically, there is today no prospective trial comparing operative treatment with non-operative treatment. This protocol describes the design for the Proximal Hamstring Avulsion Clinical Trial (PHACT) - the first randomized controlled trial of operative versus non-operative treatment for proximal hamstring avulsions.

Methods and analysis: PHACT is a multicentre randomised controlled trial conducted across Sweden, Norway and Finland. Eligible patients (60 participants/treatment arm) with a proximal hamstring avulsion of at least two of three tendons will be randomized to either operative or non-operative treatment. Participants allocated to surgery will undergo reinsertion of the tendons with suture anchors. The rehabilitation program will be the same for both treatment groups. When patient or surgeon equipoise for treatment alternatives cannot be reached and randomization therefore is not possible, patients will be invited to participate in a parallel observational non-randomized cohort. The primary outcome will be the patient reported outcome measure Perth Hamstring Assessment Tool at 24 months. Secondary outcomes include the Lower Extremity Functional Score, physical performance and muscle strength tests, patient satisfaction and MR imaging. Data analysis will be blinded and intention-to-treat analysis will be preformed.

Ethics and dissemination: Ethical approval has been granted by the Ethical Committee of Uppsala University (DNR: 2017-170) and by the Norwegian ethical board (REC: 2017/1911). The study will be conducted in agreement with the Helsinki declaration. The findings will be disseminated in peer-reviewed publications.

This study is registered at ClinicalTrials.gov
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Strength and limitations of this study

- This is the first randomized clinical trial on operative versus non-operative treatment of proximal hamstring avulsions.
- The multicentre design including patients from different healthcare regions across Sweden, Norway and Finland will support external validity and implementation.
- The treatment outcome will be assessed with a hamstring specific validated PROM and objective functional tests and imaging.
- Owing to the type of interventions, blinding of the patients and treatment providers is not possible.

Introduction

The treatment of proximal hamstring avulsions is controversial. The literature suggests that surgical treatment is the treatment of choice. For example, in a recent systematic review by Bodendorfer et al. [1] it is claimed that surgically treated patients have better results in psychometric scores, functional- and strength tests than non-surgically treated patients. However, existing literature may be biased. The studies conducted so far are mainly retrospective case series [1 2] and have only occasionally used validated outcome measures, such as Harris Hip Score [3] and Lower Extremity Functional Scale [3-5]. The Perth Hamstring Assessment Tool (PHAT) [6] is designed and validated for follow up of patients with hamstring avulsion [6], but was only recently developed.

Bodendorfer et al. [1] only found 28 non-surgical treated patients compared to 767 surgical treated patients to include in their review, suggesting a publication bias in the existing literature and providing limited power for comparisons between the surgically and non-surgically treated patients. In the light of the apparent lack of comparative studies one needs to be aware of surgical complication rates when suggesting operative treatment. With

a reported aggregated complication rate as high as 23% in the surgically treated group [1], surgery cannot be considered harmless.

The aim of this prospective, multicentre, randomized controlled trial is to provide reliable evidence on how to treat physically active patients, 30 to 70 years of age, with proximal hamstring avulsions. We will use PHAT [6] at 24 months post treatment allocation as our primary outcome measure.

Methods and analysis

Study design and setting

The Proximal Hamstring Avulsion Clinical Trial (PHACT) is a multicentre, prospective, preference-tolerant, randomised, controlled, non-inferiority trial with two treatment arms. The protocol was developed in accordance with Standard Protocol Items: Recommendations for Interventional Trials and Template for Intervention Description and Replication statements [7 8].

The study is conducted in cooperation with Swedish Orthopaedic Trauma Society and has eleven study sites at orthopaedic departments across Sweden, Norway and Finland. Inclusion started in September 2017 and recruitment is expected to finalise in 2021, which would allow for read-out of the primary endpoint in 2023.

Recruitment strategy

Patients with proximal hamstring avulsions that are diagnosed or referred to the orthopaedic department at one of the eleven hospitals will be screened for participation in the study. Eligible patients are invited to participate and provided with oral and written information. Thereafter patients are asked to sign a written informed consent statement before any study procedure occurs.

Patients

Patients must fulfil all the inclusion criteria and must not have any exclusion criteria to be eligible for randomization.

- Age at injury between 30 and 70 years

- Physical examination supports the diagnosis; e.g. a positive hip extension test, palpable defect and/or local tenderness and hematoma
- MRI shows a complete acute avulsion of at least two of three tendons from the footprint at the ischial tuberosity
- Patient has a moderate to high activity level
- Patient has linguistic and mental ability to understand the rehabilitation program explained in Swedish, Norwegian, Finnish or English
- Time from injury to inclusion in study is less than 4 weeks

Exclusion criteria

- Diabetes with secondary complications
- Previous major lower extremity injury or disease with sequelae
- Moderate or severe liver, pulmonary, kidney, psychiatric or heart disease that significantly increases the risk of complications after operative treatment
- Severe obesity (BMI>35)
- Alcohol or substance abuse
- High energy injury or combinations of injuries affecting the lower extremity

Intervention

We will randomly assign patients to either operative treatment (n=60) with suture anchor reinsertion of the tendons to the footprint at the ischial tuberosity or to non-operative treatment (n=60). Both groups will follow the same standardized rehabilitation protocol.

To minimize bias by indication, we will offer the patients that are eligible but where patient or doctor equipoise to treatment cannot be reached to participate in a parallel follow up cohort with identical treatment options and follow-up. In the parallel cohort, the patients/surgeons preferred treatment is provided.

Surgical procedure

Patients allocated to the operative group will undergo surgery at the earliest convenient time but no later than 6 weeks after the injury. The surgeon may choose whether to make a longitudinal or transversal skin incision. The proximal ends of the avulsed tendons are

identified and after dissection they are reattached to the ischial tuberosity using at least two suture anchors.

Rehabilitation

The rehabilitation protocol is based on a previously published rehabilitation protocol[9] and will be the same for both treatment allocations. In brief: No brace is used. Full weight bearing is allowed. The patients are instructed to keep their stride length short, and to avoid sitting and any motion that stretches the hamstring for the first three weeks. Patients are instructed to perform isometric exercises of the quadriceps and gluteal muscles to avoid muscle atrophy. After two weeks, isometric contractions of the hamstring muscles are allowed and progressed with cautious dynamic exercises during week four. Specific hamstring strengthening exercises are begun after five weeks.

Study outcomes

Primary outcome

The primary outcome measure will be the patient reported PHAT score[6] at 24 months. PHAT is a condition specific questionnaire with maximum score 100, with a higher score corresponding to higher function. The questionnaire uses a visual analogue scale for pain scores during different activities, as well as categorical scores for activity levels and tenderness, and has been shown to be sensitive to clinical changes [10].

Secondary outcomes

Additional patient reported outcomes

The Lower Extremity Functional Scale (LEFS) [11] will be used to assess patient reported outcome. LEFS is a reliable, valid and responsive tool for assessing functional status in several populations with lower extremity musculoskeletal conditions [11] [12]. Information regarding physical activity level will be collected using the short form of International Physical Activity Questionnaire, IPAQ-SF[13] [14]. Furthermore, data on general satisfaction, return to work and return to sports will be collected.

Functional tests and muscle strength tests

The functional performance will be assessed through the timed step test [15], which is a test previously validated for knee arthroplasty patients and the single leg hop test, which is a performance-based test validated in anterior cruciate ligament trials [16]. Measurement of

maximum kinetic force (Newton, N) will be conducted using a handheld isometric dynamometer (microFET 2; Hoggan health industries)[17]. Study sites equipped with a computer based isokinetic dynamometer, BiodexTM[18 19], will assess peak torque (N) and total workload (Joule, J) of the hamstrings. All strength and functional performance tests will be reported with ratio of injured/uninjured leg, with the uninjured leg serving as reference for each subject.

Imaging outcomes

Magnetic Resonance Imaging, MRI, will be used at 24 months to evaluate the entire thigh muscle volume and to assess muscle and tendon quality. We will use the uninjured side as reference for each subject.

Data collection procedure

Follow-up visits are planned at 3, 6, 12 and 24 months. A study nurse will provide a set of questionnaires for the patients to fill out. The nurse will also scan the patients' charts for adverse events or complications. A physiotherapist that is blinded to the intervention will perform the strength and functional test at 6, 12 and 24 months. At the 24-month follow-up, MRI of both thighs will be performed.

Sample size

Taking into account the cost and risks associated with surgery, and the fact that the literature clearly recommends surgery, a non-inferiority design was considered appropriate. Thus, the study aims to demonstrate that non-operative treatment is no worse than operative treatment by more than the non-inferiority margin.

Based on the existing literature the standard deviation of PHAT measurements is approximately 16-21 [6 20]. A reasonable non-inferiority margin is half of the standard deviation and this effect size is lower than the minimal detectable change of the PHAT [6]. To achieve 85% power, with α=0.5, for demonstrating non-inferiority using a non-inferiority margin of 10, 50 patients in each arm are required. Heterogeneity of treatment effects is likely in surgical interventions and is best handled by increasing power. Some crossover and loss to follow-up will occur. For these reasons, we will continue inclusion until at least 60 patients in each group has initiated treatment.

Randomisation procedure

The REDCap (REDCap Software TM) randomization tool will be used to facilitate randomisation [21]. Allocation tables with a random block size (2-6), stratified by study site, were created by a statistician and uploaded blinded into the REDCap project. The randomisation is permanent and not editable within the participant record and, like all other activity within REDCap, is tracked and not modifiable in the audit log.

Blinding

To minimize ascertainment bias this trial is single-blinded, where the physiotherapist conducting strength and functional tests at 6, 12 and 24 months will be blinded to the intervention, by informing the patients not to tell and asking them to wear clothes concealing the surgery scar. The statistician analysing the data will also be blinded to treatment arms.

Data management

All study data will be collected and managed in a digital case report form, CRF, using REDCap electronic data capture tools hosted at Karolinska Institutet. REDCap is a secure, web-based application supporting data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. [21]

Data will be kept securely in order to protect confidentiality before, during and after the trial. A codebook matching the personal identification number and the trial identification number is kept at each study site and the trial identification number is noted in the patient's electronic chart. The study nurses and investigators can log on and enter data directly into the database. Patients will complete surveys at each visit. Any paper forms used are stored for cross checking at each study site.

Statistical analysis plan

The flow of patients through the trial is displayed in a CONSORT diagram (Figure 1). The number of patients screened for trial entry; those who are ineligible and the reasons why; number of eligible patients not providing consent; and the number of eligible patients

subsequently randomised will be presented. The characteristics of the screened population, the ineligible participants, and eligible participants who consent and do not consent will be summarised. Information regarding the number of surgeons and centres, as well as number of patients treated by each surgeon will be provided. Data on patient eligibility and reasons for withdrawal from treatment or the trial will be summarised. Baseline patient characteristics will be summarized using descriptive statistics; counts for categorical variables and mean/median and inter-quartile range for continuous variables.

Primary analyses will be by intention-to-treat. However, since ITT analyses can be anti-conservative for non-inferiority trials, we will also conduct per-protocol and as-treated analyses. Cases will only be considered treatment cross-overs if the randomly assigned treatment is changed by patient preferences. Non-operative treated patients that are treated operatively due to late complaints (>3 mo. after inclusion) will not be considered cross-overs.

All analyses will be conducted blinded for treatment allocation. All statistical tests will be two-sided with an α of 0.05. Differences between groups in continuous skewed main outcome variables will be analysed by the Mann-Whitney U-test, and by the t-test when variables are from a symmetrical distribution. Results will be presented with 95% confidence intervals. Two-way-tables with the chi-square test will be used for dichotomous variables. No adjustment of p-values for multiple comparisons (secondary analyses) will be undertaken.

In secondary analyses, multivariate regression models will be used to analyse the primary outcome (PHAT score at 24 months follow-up). The main variables of interest included are; the intervention, age, sex, study site and the degree of tendon retraction. We will also jointly analyse all timepoints in a linear mixed model (to adjust for within-patient correlations). Patients will be treated as a random effects, and time points, randomization arm, age at baseline, sex, and degree of tendon retraction will be included as fixed effects. As further secondary analyses, the randomized and observational cohorts will be analysed together using propensity scores adjustment (the randomized patients will get propensity score 0.5). The propensity score will be based on age, sex, study site, IPAQ and the degree of tendon retraction.

We will test for heterogeneity of treatment effects by testing for significant interactions in the following subgroups: Tendon retraction > 2 cm vs ≤ 2 cm and age > 50 years vs ≤ 50 years.

Missing data can occur in two different ways in the study: (1) Questions in the PHAT questionnaire can be left unanswered; and (2) patients can miss specific follow-up visits or drop out of the study altogether. Missing PHAT score questions will be imputed based on the answered questions. Missed follow-up visit at 24 months will be handled using a multiple imputed model for the primary analysis. The multiple imputation protocol will be based on a longitudinal model for predicting PHAT at 24 months based on the PHAT score recorded at previous time points together with patient age, sex, and degree of tendon retraction. The mixed effects model handles data missing at random seamlessly and no imputation will be needed for that specific analysis. We will test the robustness of the results to data not missing at random by assuming a missingness model where missingness is associated with PHAT score.

Adverse events and complications

At follow-up, questions with the aim of identifying adverse events and serious adverse events will be provided. Medical records will also be checked for adverse effects. Undesired events such as surgical site infections, neurological sequelae, thromboembolism, re-rupture or failure and hypertrophic scarring in surgical patients are defined as adverse effects. Serious adverse effects are defined as events resulting in death, hospitalization or threatening life, i.e. pulmonary embolism, sepsis or cardiovascular complications.

Patient involvement

Patients were not formally involved in designing the study protocol. In the process of designing the study protocol and selecting the primary outcome a few patients were interviewed in clinical practice. Patients have been invited to participate in monitor meeting with researchers from the participating sites present. The participants will receive a written summary of main findings when the study is finished.

Ethics and dissemination

Ethical approval has been granted by the Ethical Committee of Uppsala University (DNR: 2017-170) and the Norwegian Regional Ethical Committee (REC: 2017/1911). The study will be conducted in agreement with the Helsinki declaration.

As both treatment options are accepted in the catchment area for the study, the randomization procedure was deemed ethically acceptable. The results will provide evidence-based treatment algorithms for future patients.

The primary study results will be submitted for publication to an international, peer-reviewed journal, regardless of whether the results are positive, negative or inconclusive in relation to the study hypothesis.

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Authors' contributions: state how each author was involved in writing the protocol.

All authors have contributed to the design of this trial protocol. E Pihl, CJ Hedbeck and K B Jonsson have initiated the project. K B Jonsson is the primary investigator. The protocol was drafted by E Pihl and K B Jonsson and was refined by M Holen Kristofferssen, A-M Rosenlund, M Berglöf, E Ribom, K Eriksson, F Frihagen, G Snellman, J Schilcher, M Eklund, V M Mattila, M Skorpil, O Sköldenberg and CJ Hedbeck. Statistical advice was provided by Eklund. M Berglöf and E Ribom designed the protocol for physical functional tests and the rehabilitation program. M Skorpil, E Pihl and S Lazlo developed protocol for the imaging outcomes. S Lazlo was responsible for drafting the manuscript. All authors have read and approved the final manuscript.

The PHACT collaborative study group consists of all local investigators who are responsible for the execution of the trial and valid data gathering. They have all read and approved the final manuscript.

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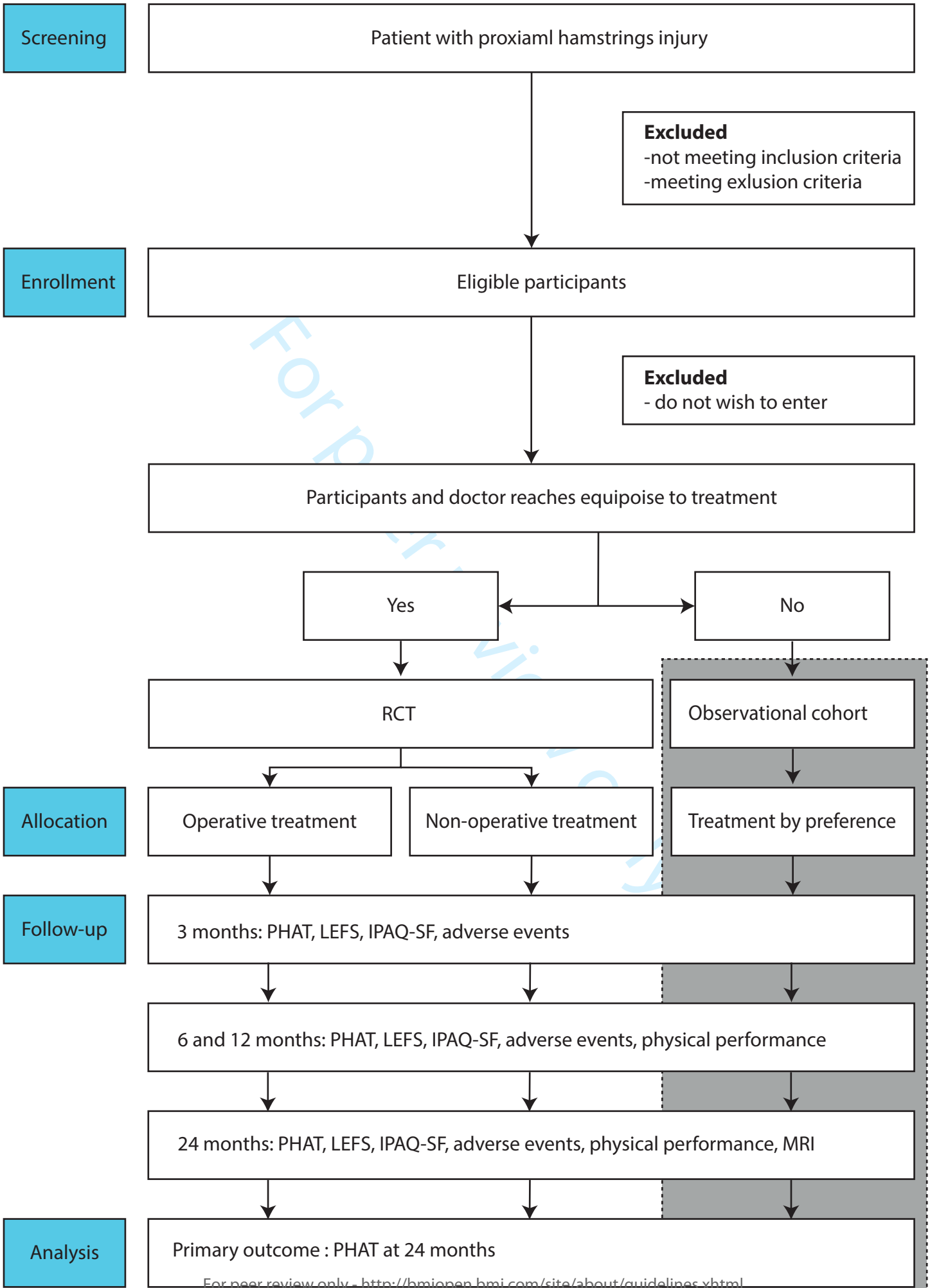
Competing interests statement.

We have no competing interest to declare.



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Abstract

Introduction: The treatment of proximal hamstring avulsions is controversial. While several trials have investigated the outcome for patients treated surgically, there is today no prospective trial comparing operative treatment with non-operative treatment. This protocol describes the design for the Proximal Hamstring Avulsion Clinical Trial (PHACT) - the first randomized controlled trial of operative versus non-operative treatment for proximal hamstring avulsions.

Methods and analysis: PHACT is a multicentre randomised controlled trial conducted across Sweden, Norway and Finland. Eligible patients (60 participants/treatment arm) with a proximal hamstring avulsion of at least two of three tendons will be randomized to either operative or non-operative treatment. Participants allocated to surgery will undergo reinsertion of the tendons with suture anchors. The rehabilitation program will be the same for both treatment groups. When patient or surgeon equipoise for treatment alternatives cannot be reached and randomization therefore is not possible, patients will be invited to participate in a parallel observational non-randomized cohort. The primary outcome will be the patient reported outcome measure Perth Hamstring Assessment Tool at 24 months. Secondary outcomes include the Lower Extremity Functional Score, physical performance and muscle strength tests, patient satisfaction and MR imaging. Data analysis will be blinded and intention-to-treat analysis will be preformed.

Ethics and dissemination: Ethical approval has been granted by the Ethical Committee of Uppsala University (DNR: 2017-170) and by the Norwegian ethical board (REC: 2017/1911). The study will be conducted in agreement with the Helsinki declaration. The findings will be disseminated in peer-reviewed publications.

This study is registered at ClinicalTrials.gov
Trial Registration Number: NCT03311997
Recrutiment Status: Recruiting
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Strength and limitations of this study

- This is the first randomized clinical trial on operative versus non-operative treatment of proximal hamstring avulsions.
- The multicentre design will support external validity and implementation.
- The treatment outcome will be assessed with a hamstring specific validated PROM, objective functional tests and imaging.
- Owing to the type of interventions, blinding of the patients and treatment providers is not possible.

Introduction

The treatment of proximal hamstring avulsions is controversial. The literature suggests that surgical treatment is the treatment of choice. For example, in a recent systematic review by Bodendorfer et al. [1] it is claimed that surgically treated patients have better results in psychometric scores, functional- and strength tests than non-surgically treated patients. However, existing literature may be biased. The studies conducted so far are mainly retrospective case series [1 2] and have only occasionally used validated outcome measures, such as Harris Hip Score [3] and Lower Extremity Functional Scale [3-5]. The Perth Hamstring Assessment Tool (PHAT) [6] is designed and validated for follow up of patients with hamstring avulsion [6], but was only recently developed.

Bodendorfer et al. [1] only found 28 non-surgical treated patients compared to 767 surgical treated patients to include in their review, suggesting a publication bias in the existing literature and providing limited power for comparisons between the surgically and non-surgically treated patients. In the light of the apparent lack of comparative studies one needs to be aware of surgical complication rates when suggesting operative treatment. With

a reported aggregated complication rate as high as 23% in the surgically treated group [1], surgery cannot be considered harmless.

The aim of this prospective, multicentre, randomized controlled trial is to provide reliable evidence on how to treat physically active patients, 30 to 70 years of age, with proximal hamstring avulsions. We will use PHAT [6] at 24 months post treatment allocation as our primary outcome measure.

Methods and analysis

Study design and setting

The Proximal Hamstring Avulsion Clinical Trial (PHACT) is a multicentre, prospective, preference-tolerant, randomised, controlled, non-inferiority trial with two treatment arms. The protocol was developed in accordance with Standard Protocol Items: Recommendations for Interventional Trials and Template for Intervention Description and Replication statements [7 8].

The study is conducted in cooperation with Swedish Orthopaedic Trauma Society and has eleven study sites at orthopaedic departments across Sweden, Norway and Finland. Inclusion started in September 2017 and recruitment is expected to finalise in 2021, which would allow for read-out of the primary endpoint in 2023.

Recruitment strategy

Patients with proximal hamstring avulsions that are diagnosed or referred to the orthopaedic department at one of the eleven hospitals will be screened for participation in the study. Eligible patients are invited to participate and provided with oral and written information. Thereafter patients are asked to sign a written informed consent statement before any study procedure occurs.

Patients

Patients must fulfil all the inclusion criteria and must not have any exclusion criteria to be eligible for randomization.

- Age at injury between 30 and 70 years

- Physical examination supports the diagnosis; e.g. a positive hip extension test, palpable defect and/or local tenderness and hematoma
- MRI shows a complete acute avulsion of at least two of three tendons from the footprint at the ischial tuberosity
- Patient has a moderate to high activity level
- Patient has linguistic and mental ability to understand the rehabilitation program explained in Swedish, Norwegian, Finnish or English
- Time from injury to inclusion in study is less than 4 weeks

Exclusion criteria

- Diabetes with secondary complications
- Previous major lower extremity injury or disease with sequelae
- Moderate or severe liver, pulmonary, kidney, psychiatric or heart disease that significantly increases the risk of complications after operative treatment
- Severe obesity (BMI>35)
- Alcohol or substance abuse
- High energy injury or combinations of injuries affecting the lower extremity

Intervention

We will randomly assign patients to either operative treatment (n=60) with suture anchor reinsertion of the tendons to the footprint at the ischial tuberosity or to non-operative treatment (n=60). Both groups will follow the same standardized rehabilitation protocol.

To minimize bias by indication, we will offer the patients that are eligible but where patient or doctor equipoise to treatment cannot be reached to participate in a parallel follow up cohort with identical treatment options and follow-up. In the parallel cohort, the patients/surgeons preferred treatment is provided.

Surgical procedure

Patients allocated to the operative group will undergo surgery at the earliest convenient time but no later than 6 weeks after the injury. The surgeon may choose whether to make a longitudinal or transversal skin incision. The proximal ends of the avulsed tendons are identified and after dissection they are reattached to the ischial tuberosity using at least two

suture anchors. Data on the surgical approach, the number of suture anchors and their manufacturer as well as the surgeon's intra-operative assessment of retraction and the number of tendons invovlved will be collected.

Rehabilitation

The rehabilitation protocol is based on a previously published rehabilitation protocol[9] and will be the same for both treatment allocations. In brief: No brace is used. Full weight bearing is allowed. The patients are instructed to keep their stride length short, and to avoid sitting and any motion that stretches the hamstring for the first three weeks. Patients are instructed to perform isometric exercises of the quadriceps and gluteal muscles to avoid muscle atrophy. After two weeks, isometric contractions of the hamstring muscles are allowed and progressed with cautious dynamic exercises during week four. Specific hamstring strengthening exercises are begun after five weeks.

Study outcomes

Primary outcome

The primary outcome measure will be the patient reported PHAT score[6] at 24 months. PHAT is a condition specific questionnaire with maximum score 100, with a higher score corresponding to higher function. The questionnaire uses a visual analogue scale for pain scores during different activities, as well as categorical scores for activity levels and tenderness, and has been shown to be sensitive to clinical changes [10].

Secondary outcomes

Additional patient reported outcomes

The Lower Extremity Functional Scale (LEFS) [11] will be used to assess patient reported outcome. LEFS is a reliable, valid and responsive tool for assessing functional status in several populations with lower extremity musculoskeletal conditions [11] [12]. Information regarding physical activity level will be collected using the short form of International Physical Activity Questionnaire, IPAQ-SF[13] [14]. Furthermore, data on general satisfaction, return to work and return to sports will be collected.

Functional tests and muscle strength tests

The functional performance will be assessed through the timed step test [15], which is a test previously validated for knee arthroplasty patients and the single leg hop test, which is a

performance-based test validated in anterior cruciate ligament trials [16]. Measurement of maximum kinetic force (Newton, N) will be conducted using a handheld isometric dynamometer (microFET 2; Hoggan health industries)[17]. Study sites equipped with a computer based isokinetic dynamometer, BiodexTM[18 19], will assess peak torque (N) and total workload (Joule, J) of the hamstrings. All strength and functional performance tests will be reported with ratio of injured/uninjured leg, with the uninjured leg serving as reference for each subject.

Imaging outcomes

Magnetic Resonance Imaging, MRI, will be used at 24 months to evaluate the entire thigh muscle volume and to assess muscle and tendon quality. We will use the uninjured side as reference for each subject.

Data collection procedure

At inclusion demographic data activity at injury and time from injury to treatment is collected. Follow-up visits are planned at 3, 6, 12 and 24 months. A study nurse will provide a set of questionnaires for the patients to fill out. The nurse will also scan the patients' charts for adverse events or complications. A physiotherapist that is blinded to the intervention will perform the strength and functional test at 6, 12 and 24 months. At the 24-month follow-up, MRI of both thighs will be performed.

Sample size

Taking into account the cost and risks associated with surgery, and the fact that the literature clearly recommends surgery, a non-inferiority design was considered appropriate. Thus, the study aims to demonstrate that non-operative treatment is no worse than operative treatment by more than the non-inferiority margin.

Based on the existing literature the standard deviation of PHAT measurements is approximately 16-21 [6 20]. A reasonable non-inferiority margin is half of the standard deviation and this effect size is lower than the minimal detectable change of the PHAT [6]. To achieve 85% power, with α=0.5, for demonstrating non-inferiority using a non-inferiority margin of 10, 50 patients in each arm are required. Heterogeneity of treatment effects is likely in surgical interventions and is best handled by increasing power. Some crossover and

loss to follow-up will occur. For these reasons, we will continue inclusion until at least 60 patients in each group has initiated treatment.

Randomisation procedure

The REDCap (REDCap Software TM) randomization tool will be used to facilitate randomisation [21]. Allocation tables with a random block size (2-6), stratified by study site, were created by a statistician and uploaded blinded into the REDCap project. The randomisation is permanent and not editable within the participant record and, like all other activity within REDCap, is tracked and not modifiable in the audit log.

Blinding

To minimize ascertainment bias this trial is single-blinded, where the physiotherapist conducting strength and functional tests at 6, 12 and 24 months will be blinded to the intervention, by informing the patients not to tell and asking them to wear clothes concealing the surgery scar. The statistician analysing the data will also be blinded to treatment arms.

Data management

All study data will be collected and managed in a digital case report form, CRF, using REDCap electronic data capture tools hosted at Karolinska Institutet. REDCap is a secure, web-based application supporting data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. [21]

Data will be kept securely in order to protect confidentiality before, during and after the trial. A codebook matching the personal identification number and the trial identification number is kept at each study site and the trial identification number is noted in the patient's electronic chart. The study nurses and investigators can log on and enter data directly into the database. Patients will complete surveys at each visit. Any paper forms used are stored for cross checking at each study site.

Statistical analysis plan

The flow of patients through the trial is displayed in a CONSORT diagram (Figure 1). The number of patients screened for trial entry; those who are ineligible and the reasons why; number of eligible patients not providing consent; and the number of eligible patients subsequently randomised will be presented. The characteristics of the screened population, the ineligible participants, and eligible participants who consent and do not consent will be summarised. Information regarding the number of surgeons and centres, as well as number of patients treated by each surgeon will be provided. Data on patient eligibility and reasons for withdrawal from treatment or the trial will be summarised. Baseline patient characteristics will be summarized using descriptive statistics; counts for categorical variables and mean/median and inter-quartile range for continuous variables.

Primary analyses will be by intention-to-treat. However, since ITT analyses can be anti-conservative for non-inferiority trials, we will also conduct per-protocol and as-treated analyses. Cases will only be considered treatment cross-overs if the randomly assigned treatment is changed by patient preferences. Non-operative treated patients that are treated operatively due to late complaints (>3 mo. after inclusion) will not be considered cross-overs.

All analyses will be conducted blinded for treatment allocation. All statistical tests will be two-sided with an α of 0.05. Differences between groups in continuous skewed main outcome variables will be analysed by the Mann-Whitney U-test, and by the t-test when variables are from a symmetrical distribution. Results will be presented with 95% confidence intervals. Two-way-tables with the chi-square test will be used for dichotomous variables. No adjustment of p-values for multiple comparisons (secondary analyses) will be undertaken.

In secondary analyses, multivariate regression models will be used to analyse the primary outcome (PHAT score at 24 months follow-up). The main variables of interest included are; the intervention, age, sex, study site and the degree of tendon retraction. We will also jointly analyse all timepoints in a linear mixed model (to adjust for within-patient correlations). Patients will be treated as a random effects, and time points, randomization arm, age at baseline, sex, and degree of tendon retraction will be included as fixed effects. As further secondary analyses, the randomized and observational cohorts will be analysed

together using propensity scores adjustment (the randomized patients will get propensity score 0.5). The propensity score will be based on age, sex, study site, IPAQ and the degree of tendon retraction.

We will test for heterogeneity of treatment effects by testing for significant interactions in the following subgroups: Tendon retraction > 2 cm vs ≤ 2 cm and age > 50 years vs ≤ 50 years.

Missing data can occur in two different ways in the study: (1) Questions in the PHAT questionnaire can be left unanswered; and (2) patients can miss specific follow-up visits or drop out of the study altogether. Missing PHAT score questions will be imputed based on the answered questions. Missed follow-up visit at 24 months will be handled using a multiple imputed model for the primary analysis. The multiple imputation protocol will be based on a longitudinal model for predicting PHAT at 24 months based on the PHAT score recorded at previous time points together with patient age, sex, and degree of tendon retraction. The mixed effects model handles data missing at random seamlessly and no imputation will be needed for that specific analysis. We will test the robustness of the results to data not missing at random by assuming a missingness model where missingness is associated with PHAT score.

Adverse events and complications

At follow-up, questions with the aim of identifying adverse events and serious adverse events will be provided. Medical records will also be checked for adverse effects. Undesired events such as surgical site infections, neurological sequelae, thromboembolism, re-rupture or failure and hypertrophic scarring in surgical patients are defined as adverse effects. Serious adverse effects are defined as events resulting in death, hospitalization or threatening life, i.e. pulmonary embolism, sepsis or cardiovascular complications.

Patient involvement

Patients were not formally involved in designing the study protocol. In the process of designing the study protocol and selecting the primary outcome a few patients were interviewed in clinical practice. Patients have been invited to participate in monitor meeting with researchers from the participating sites present. The participants will receive a written summary of main findings when the study is finished.

Ethics and dissemination

Ethical approval has been granted by the Ethical Committee of Uppsala University (DNR: 2017-170) and the Norwegian Regional Ethical Committee (REC: 2017/1911). The study will be conducted in agreement with the Helsinki declaration.

As both treatment options are accepted in the catchment area for the study, the randomization procedure was deemed ethically acceptable. The results will provide evidence-based treatment algorithms for future patients.

The primary study results will be submitted for publication to an international, peer-reviewed journal, regardless of whether the results are positive, negative or inconclusive in relation to the study hypothesis.

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Authors' contributions: state how each author was involved in writing the protocol.

All authors have contributed to the design of this trial protocol. E Pihl, CJ Hedbeck and K B Jonsson have initiated the project. K B Jonsson is the primary investigator. The protocol was drafted by E Pihl and K B Jonsson and was refined by M Holen Kristofferssen, A-M Rosenlund, M Berglöf, E Ribom, K Eriksson, F Frihagen, G Snellman, J Schilcher, M Eklund, V M Mattila, M Skorpil, O Sköldenberg and CJ Hedbeck. Statistical advice was provided by Eklund. M Berglöf and E Ribom designed the protocol for physical functional tests and the rehabilitation program. M Skorpil, E Pihl and S Laszlo developed protocol for the imaging outcomes. S Laszlo was responsible for drafting the manuscript. All authors have read and approved the final manuscript.

Collaborators

The PHACT collaborative study group consists of all local investigators who are responsible for the execution of the trial and valid data gathering. They have all read and approved the final manuscript.

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Competing interests statement.

We have no competing interest to declare.

Legends

Figure 1. Flow chart. This study illustrates the study design