Statistical Analysis Plan (SAP)

The effect of targeted exercise on knee muscle function in patients with persistent hamstring deficiency following ACL reconstruction – a randomized controlled trial (RATE)

Version 2, September 8, 2020

Trial registration: ClinicalTrials.gov number NCT02939677

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CONTENT

Section 1: Administrative Information

Protocol version:
This is the statistical analysis plan (SAP) for the abovementioned project, in adherence to the previously published Protocol Article, by the same authors (1). For further information:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5787267/

SAP revisions:
Statistical analysis plan (SAP) sections and items described by Gamble et al. (2), concerning Recommended items to Address in a Clinical Trial SAP. Previous version of SAP has been published on Clinicaltrials.gov on January 7th, 2020. Current SAP revisions has been performed due to trial deviations related with COVID-19 and due to insufficient reporting of SAP details in the previously published issue. Trial data collection has currently not been completed and randomized allocation is still concealed (Sep 2020).

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Section 2: Introduction

Background and rationale

Anterior cruciate ligament (ACL) reconstruction is a common arthroscopic procedure, with approximately 300,000 reconstructions performed annually in the United States (3). ACL reconstruction aims to restore functional stability of the knee and can be performed using a variety of different surgical techniques and graft sites (4). The hamstring tendon is one of the most used graft donor sites for ACL reconstruction (3, 5). Although current ACL reconstruction procedures intend to restore internal knee biomechanics, function of the ACL-reconstructed knee remains different from that of healthy knees (5, 6) and is associated with early development of osteoarthritis (7-9). Therefore, information about factors associated with increased risk of osteoarthritis, such as lower-limb muscle strength deficits, should be part of the risk management with ACL reconstruction (7).

Post-surgery, ACLR with the HS graft present a risk that concerns reduced hamstring muscle strength and persistent muscular deficiency has been seen for more than one and two years after reconstruction (10, 11). Moreover, recent studies showed that only 42% of recreational athletes return to pre-injury level of sport activity (RTS) following ACLR (11) and up to 50% of patients develop knee osteoarthritis within 10 years of ACLR (12).

Therefore, regaining adequate strength of the quadriceps and hamstrings muscles after ACLR is considered important. But according to international standards and consensus, ACL postoperative rehabilitation is generally limited to the first 9–12 months post-surgery and the effect on muscle strength deficits after early (first 12 months post-surgery) rehabilitation phase has previously been studied (13, 14). To date, no high level evidence exist to support interventions that can eliminate long-term and persistent risks factors of reduced muscle strength, after HS graft ACLR. Thus, long-term rehabilitation protocols of ACL-reconstructed patients, examining interventions to resolve these muscle strength deficits, especially when using hamstring auto-grafts, are strongly advised (15).

Objectives

The objective of this study is to investigate the effect of targeted exercise on knee- muscle strength and joint function in ACL-reconstructed patients with persistent hamstring muscle deficiency 12–24 months post-surgery compared with low-intensity home-based exercise.

Section 3: Study Methods

Trial design

The study is designed as a prospective, superiority, parallel group randomized controlled trial (RCT) with balanced and blinded randomization (1:1) and blinded outcome assessment (level of evidence: II). The trial adheres to the CONSORT Statement (Consolidated Standards of Reporting Trials) http://www.consort-statement.org/.
Trial registration: NCT02939677

Randomization

The randomization sequence was computer generated using Stata 13.0 (Stata Corp, College Station, TX, USA) statistical software with a 1:1 allocation ratio using sequentially numbered opaque, sealed envelopes. The allocation sequence and preparation of the concealed envelopes was completed by a central study coordinator not involved in the conduct of the trial. The primary investigator was blinded to allocation and did not participate in testing, randomization, or completion of intervention. The statistical analysis will be performed on allocation codes only and thus the data analysts will be blinded in relation to intervention allocation. Blinding to treatment allocation of participants, and healthcare providers was not possible due to the nature of the interventions.

Sample size

Sample size estimation was performed using maximal unilateral isometric knee-flexor strength of the operated leg (primary outcome) from a previously published pilot study on the present test protocol and reliability data from our laboratory (6). The statistical model contains one baseline and one follow-up assessment. Between-group difference in change score of 0.31 Nm bw^{-1} in knee-flexor strength in the ACL-reconstructed limb resulting in a less than 2.5% deficit of the healthy leg prior to intervention was considered of clinical relevance (6). To achieve a statistical power of 80% (β= 0.80), using a SD of 0.37 Nm bw^{-1} pre and post intervention, and allowing the detection of statistically significant differences at an $\alpha = 0.05$ level (two-tailed testing), a sample size of n = 23 was calculated for each group; the estimated recruitment of 50 participants (in total) allows for possible dropouts.

Framework

The study was designed as a prospective, superiority, parallel group randomized controlled trial (RCT) with balanced and blinded randomization (1:1). To minimize interpretation bias, we have a-priori decided how to interpret potential different result scenarios: (1) If knee-flexor strength improvement is superior (statistically significant and clinically relevant (≥0.31 Nm bw^{-1} in knee-flexor strength)) in SNG compared with CON, the combined intervention of strength and neuromuscular exercises will be considered the preferred treatment of choice; (2) If gains in knee-flexor strength are superior in CON compared with SNG, home-based exercises will be considered the preferred treatment of choice; and (3) if knee-flexor strength improvement does not differ between the two treatment groups, the intervention associated with the greatest functional improvement and pain relief, and the least adverse events, will be favored.

Statistical interim analysis and stopping guidance

No interim analyses or planned adjustment of the significance level due to interim analysis, were carried out in this study. Allocation was not disclosed to other study personnel including other site personnel, monitors, corporate sponsors, or project office staff. The primary investigator will maintain blinded as far as possible.

Timing of outcome assessments

Assessments were performed at baseline (prior to randomization), following the intervention (12 weeks post baseline) (the primary endpoint) and six months post intervention in accordance with previous protocol paper (1) (Fig. 2; Table 2: Outcome measurements)(1). Six months post intervention data will not be included in the current analyses.

Section 4: Statistical Principles

Confidence intervals and P values

The significance level (α) for statistically significant differences was set at an α = 0.05 level (two-tailed testing).

All statistical tests will use an α-level of 0.05 and data will be presented as means and 95% confidence interval unless otherwise stated. No adjustments for multiplicity are planned.

Adherence and protocol deviations

Minor trial deviations from the initial trial protocol (1) and clinical trial registration (NCT02939677) occurred primarily due to the ongoing COVID-19 virus and related shut-down of clinical testing and exercise intervention.

Randomization of included participants was raised and ended on 51 participants, due to underestimation of dropouts related with the COVID-19 situation during the final phase of data collection. Inclusion and dropouts during the trial will be presented in the final publication in accordance with previously published flowchart (1).

Further deviations to protocol:

- One-leg jump for distance was also performed at the 6 months follow-up.
- Collaborator/advisor Professor Uffe Jorgensen left the project due to retirement.
- Collaborator/advisor MD, Ph.D. Nis Nissen left the project due to departure (Deceased 03-06-2019). However, since he greatly contributed to the project Nis Nissen kept his affiliation and will appear as co-author on the primary publications.
- The “last-observation- carried-forward” method was replaced with Multiple imputation analysis.
- Tegner activity scale was applied together with the other patient reported outcomes (KOOS, IKDC) at baseline and 3 + 6 months follow-up.
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Analysis population

Analysis for participants demonstrating the a-priori-defined acceptable compliance to exercise (> 80 % completed exercise sessions). All analyses will follow the “intention-to-treat principle” (16). The multiple imputation analysis will be used for data imputation in cases of missing outcome measures.

Section 5: Trial population

Screening data

Reporting of screening data to describe representativeness of trial sample was collected. Data will be presented in the inclusion flowchart (17).

Eligibility

Summary of eligibility criteria:

Inclusion criteria

- ACL reconstruction using hamstring tendon auto-graft
- Age between 18 and 40 years
- BMI > 35
- A pathologically defined between-limb asymmetry ratio (> 10% leg-to-leg difference evaluated by hand-held dynamometry) for maximal isometric strength of the knee flexors at 12–24 months' follow-up

Exclusion Criteria:

- Other known joint pathology that will affect participation in the intervention.
- Not understanding written Danish language
- Other known medical conditions that will affect participation in the intervention

Recruitment

Information to be included in the CONSORT flow diagram.

- Assessment for eligibility
- Baseline assessment
- Randomization
- Allocation to intervention
- Twelve weeks Post intervention follow-up assessment

Withdrawal/follow-up

Participants had the possibility to withdraw from the study for any reason at any time. The primary investigator could also withdraw participants from the study to protect their safety and/or if they were unwilling or unable to comply with required study procedures. Throughout the intervention and follow-up period, participants were reminded, by email, about consecutive clinical visits. All withdrawals concerning study participation, will be reported in future publications, including incomplete outcome datasets, due to incomplete follow-up, participant discontinue or deviation from intervention.

Timing, Level, and reason of withdrawal from intervention will be presented in detail in the manuscript's results section and in the flowchart. Lost to follow-up data, reasons, and details of how lost to follow-up data will be presented in both in the manuscript and flowchart.

Baseline participant characteristics

List of baseline characteristics is outlined in Figure 1.

Section 6: Analysis

Outcome definitions

Assessments will be performed at baseline (prior to randomization), following the intervention (12 weeks post baseline) (the primary endpoint) and at 6 months follow-up (not reported in current SAP and primary analysis).

Primary outcome includes:

- Between-group change in maximal unilateral isometric knee-flexor strength (hamstring) recorded in the leg that has been operated on, using stabilized dynamometry at a 90° angle (0° = full anatomical extension) (Nm/kg).

Secondary outcomes include:

- Between-group changes in maximal unilateral isometric extensor strength (quadriceps) and hamstring-to quadricep muscle-strength ratio, using the same type of stabilized dynamometry as used for the primary outcome variable (Nm/kg).

Subscale scores (Pain, Symptoms, ADL, Sport & Recreation, and QoL) on the Knee injury and Osteoarthritis Outcome Score (KOOS)

Analysis methods

All outcome measures will be checked for Gaussian distribution by use of QQ-plots and parametric statistical and/or non-parametric analyses will be used when deemed appropriate. All statistical tests will use an α-level of 0.05 and data will be presented as means and 95% confidence interval unless otherwise stated.
Between-group mean differences in outcome measures and 95% confidence intervals will be evaluated using a mixed effect model regression analysis, for analyzing within- and between-subjects variance, both fixed and random variables.

Missing data

Multiple imputation analysis will be used for data imputation in cases of missing outcome measures.

Additional analyses

Additional analysis of muscle strength outcomes will be performed, with an additional analysis of Limb Symmetry Index (LSI). No further plans for additional analyses are made.

Harms

Adverse events were monitored with a non-leading questionnaire during the entire phase of intervention, as a part of participant's training diary. All events will be coded in accordance with the Medical Dictionary for Regulatory Activities, as currently required by all regulatory authorities, including the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products. There were no stopping criteria based on the collected data.

Statistical software

All statistical analyses will be performed using Stata 13 software (Stata- Corp, College Station, TX, USA).

References

1. Bregenhof B, Jorgensen U, Aagaard P, Nissen N, Creaby MW, Thorlund JB, et al. The effect of targeted exercise on knee-muscle function in patients with persistent hamstring deficiency following ACL reconstruction - study protocol for a randomized controlled trial. Trials. 2018;19(1):75.
2. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Dore C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43.
3. Chechik O, Amar E, Khashan M, Lador R, Eyal G, Gold A. An international survey on anterior cruciate ligament reconstruction practices. International orthopaedics. 2013;37(2):201-6.
4. Duchman KR, Lynch TS, Spindler KP. Graft Selection in Anterior Cruciate Ligament Surgery: Who gets What and Why? Clinics in sports medicine. 2017;36(1):25-33.
5. Shaerf DA, Pastides PS, Sarraf KM, Willis-Owen CA. Anterior cruciate ligament reconstruction best practice: A review of graft choice. World J Orthop. 2014;5(1):23-9.
6. Patel RR, Hurwitz DE, Bush-Joseph CA, Bach BR, Jr., Andriacchi TP. Comparison of clinical and dynamic knee function in patients with anterior cruciate ligament deficiency. The American journal of sports medicine. 2003;31(1):68-74.
7. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. The American journal of sports medicine. 2007;35(10):1756-69.
8. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J. A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: A controlled, prospective trial. American Journal of Sports Medicine. 2007;35(4):564-74.
9. Stergiou N, Ristanis S, Moraiti C, Georgoulis AD. Tibial rotation in anterior cruciate ligament (ACL)-deficient and ACL-reconstructed knees: a theoretical proposition for the development of osteoarthritis. Sports medicine (Auckland, NZ). 2007;37(7):601-13.
10. Holsgaard-Larsen A, Jensen C, Mortensen NH, Aagaard P. Concurrent assessments of lower limb loading patterns, mechanical muscle strength and functional performance in ACL-patients--a cross-sectional study. The Knee. 2014;21(1):66-73.
11. Freedman KB, D'Amato MJ, Nedeff DD, Kaz A, Bach Jr BR. Arthroscopic anterior cruciate ligament reconstruction: A metaanalysis comparing patellar tendon and hamstring tendon autografts. American Journal of Sports Medicine. 2003;31(1):2-11.
12. Oiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. The American journal of sports medicine. 2009;37(7):1434-43.
13. Kruse LM, Gray B, Wright RW. Rehabilitation after anterior cruciate ligament reconstruction: a systematic review. The Journal of bone and joint surgery American volume. 2012;94(19):1737-48.
14. Smekal D, Kalina R, Urban J. [Rehabilitation after arthroscopic anterior cruciate ligament reconstruction]. Acta Chir Orthop Traumatol Cech. 2006;73(6):421-8.
15. Bien DP, Dubuque TJ. Considerations for late stage acl rehabilitation and return to sport to limit re-injury risk and maximize athletic performance. Int J Sports Phys Ther. 2015;10(2):256-71.
16. Helms RW. Precise definitions of some terminology for longitudinal clinical trials: subjects, patient populations, analysis sets, intention to treat, and related terms. Pharm Stat. 2016;15(6):471-85.
17. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Ann Intern Med. 2017;167(1):40-7.

Table 1: Baseline characteristics of study participants

Baseline characteristics	SNG (n =) Mean (SD)	CON (n =) Mean (SD)
Age		
Weight		
Height		
Body mass index (kg/m²)		
Male: Female ratio, n (%)		
Time since ACLR (months)		
Meniscus injury		
Injured leg		
Time since ACLR (months)		
Primary outcome:		
Maximal isometric knee flexor strength (Nm/kg)		
Secondary outcome:		
KOOS–5 subscales score - Pain - Symptoms - ADL - Sport/Rec - QOL		
Maximal isometric knee-extensor strength (Nm/kg)		
Hamstring-to-quadriceps ratio		
Not pre-specified explorative outcomes:		
LSI (%)		

Data are shown as mean (SD +/-), except male: female ratio shown as n (percentage). KOOS ranging from 0 to 100 with higher score equal fewer problems. LSI: Limb symmetry index in percent.

Figure 1: Flow diagram

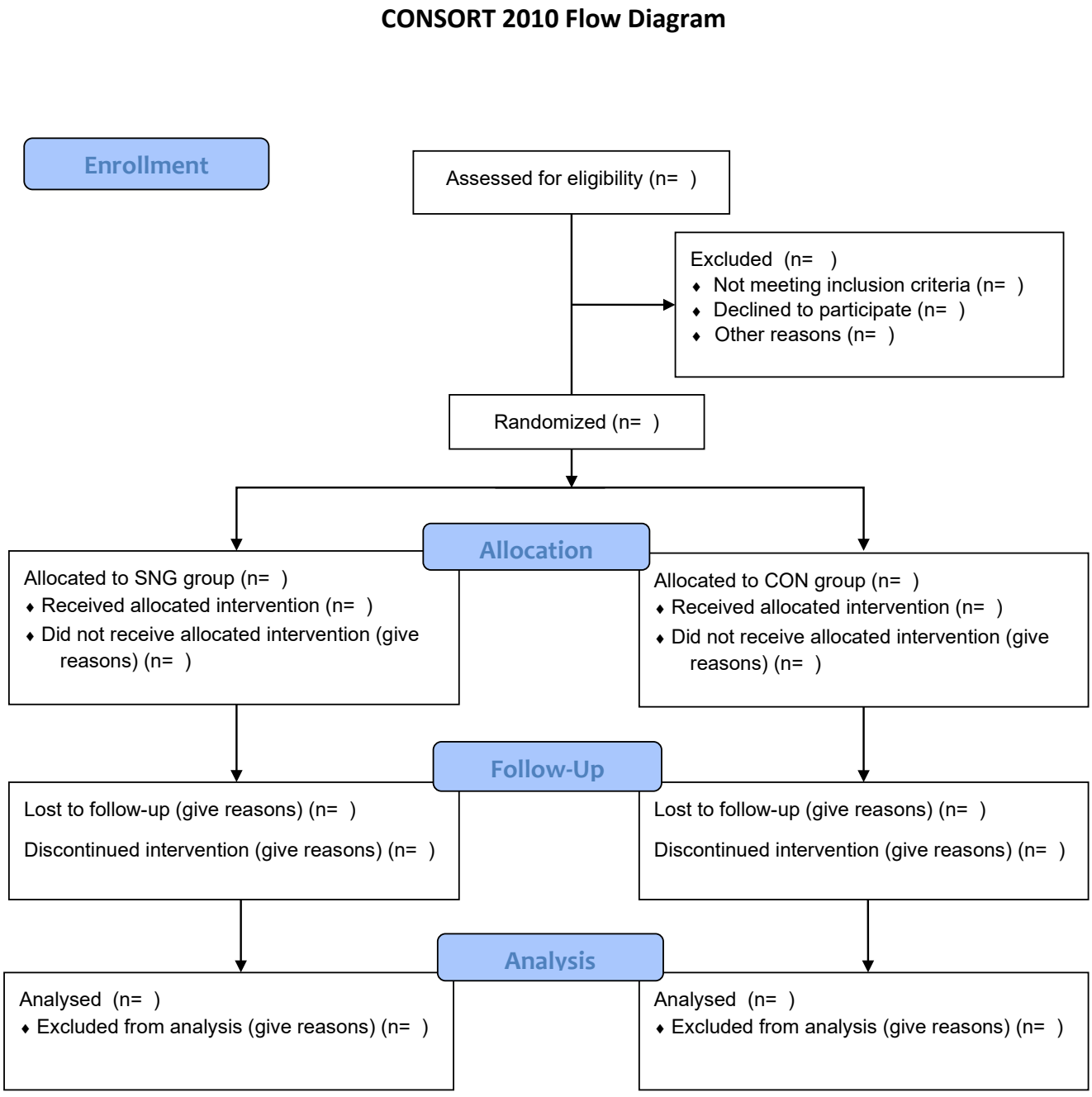

Table 2: Mean difference within groups and difference between groups at 12 weeks follow up [95% CI].

	SNG (mean [95 CI]) (change Within-group change from baseline)	CON (mean [95 CI]) (change Within-group change from baseline)	Between-group difference from baseline (mean [95% CI])	Effect size between groups (Hedge's g)
Primary outcome				
Maximal isometric knee flexor strength				
Secondary outcome				
KOOS–5 subscales score				
- Pain				
- Symptoms				
- ADL				
- Sport/Rec				
- QOL				
Maximal isometric knee extensor strength				
Hamstring-to-quadriceps ratio				
Not pre-specified explorative outcomes				
LSI				

Figure 2: The between-group changes for primary, secondary, and not pre-specified explorative outcomes. Values are presented as between group difference from baseline and 95% CIs (mean [95% CI]).