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ST. OLAVS HOSPITAL
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Exercise interventions in patients with postconcussion symptoms and posttraumatic headache. A randomized controlled trial.

Subsymptomtrening ved treningsintoleranse etter lette hodeskader. En randomisert studie av to ulike treningsintervensjoner

Short title: Exercise in PCS/PTH / PCS-treningsstudien

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Protocol version no 1- 10.10.22

1 PROTOCOL SUMMARY

1.1 Synopsis

Funding	The Liaison Committee for Education, Research and Innovation in Central Norway (researcher grant Toril Skandsen). St. Olavs Hospital
Phase and study type	Single center, randomized single blind controlled study.
Trial registration	Clinical Trials:
Centers	St. Olavs hospital, Clinic of Physical Medicine and Rehabilitation, Norwegian University of Science and Technology (NTNU), Dep. of Neuromedicine and Movement Science and Dep. of Public Health and Nursing.
Roles and responsibilities	Principal investigator: Toril Skandsen, MD, Professor, Clinic of Physical medicine and rehabilitation, St. Olavs Hospital and NTNU, Dep. of Neuromedicine and Movement Science. Cathrine Einarsen, MD, PhD, consultant Clinic of Physical medicine and rehabilitation, St. Olavs Hospital and NTNU. Co-researcher Janne Birgitte Bloch Børke, physiotherapist and research coordinator Camilla Indset Sørgjerd, physiotherapist, delivers the intervention
Study Period:	Estimated date of first patient enrolled: October 1st, 2022 Anticipated recruitment period: October 1st, 2022- June 19th 2024 Estimated date of last patient completed: September 30th, 2024
Treatment Duration:	Expected treatment duration pr. patient: 12 weeks
Follow-up:	Expected follow-up period pr. patient: 6 months from inclusion
Study aims	To compare results of two different deliveries of an exercise intervention in patients with PCS and PTH. To compare gain in symptoms and function obtained during the treatment period with that of a similar study at Oslo University Hospital.
Endpoints:	Primary outcomes: change in exercise tolerance (heart rate at test termination) Secondary outcomes: change in post-concussion symptom burden (RPQ). PSFS, QOLIBRI-OA, PHQ-9, GAD-7, HIT-6, FSS, IPAQ, participation in work or education. Number of days with moderate/severe headache.

Main Inclusion Criteria:	• Age 18-65 years. • Having sustained a minimal head injury (according to the Head Injury Severity Scale) or mild traumatic brain injury (MTBI) (according to the TBI definition and the WHO criteria for MTBI) within the last two years, at least 1 months ago. • At least one postconcussion symptoms of at least moderate degree occurring within the first week after the head injury. • Exercise intolerance defined by > 2 points increase in symptoms NRS and self-reported intolerance for exercise.
Main Exclusion Criteria	• More than 2years since injury • Symptoms better explained by other conditions. • Severe communication problems, typically due to poor knowledge of Norwegian. • Severe psychiatric, neurological, and somatic or substance abuse disorders that will complicate follow-up and outcome assessment.
Sample Size:	100 patients, 50 in each arm.

1.2 Schedule of Activities /SoA)

Procedure	**Screening**	**T0**	**W1**	**W2**	**W3**	**W6**	**W9**	**T2**	**T3**	**Notes**
Informed consent	X									
Inclusion and exclusion criteria	X									
Baseline interview PCS study	X									
Physical examination	X									
Register headache in app 2 weeks before T0.										
Medical checklist	X	(X)								
BP /HR orthostatic		X								
BCTT/BCCT		X						X		
SLC		X						X		
Study intervention		< ---------- X ---------- >								
Assess compliance			X	X	X	X	X	X		
Assess AE			X	X	X	X	X	X		
Study outcomes								X	X	
Blood test (optional)	X							X		
Autonomic testing/ pain thresholds (optional)	X							X		

2 INTRODUCTION

2.1 Study rationale

Prolonged postconcussion symptoms (PCS) and posttraumatic headache (PTH) are poorly understood, and these patients represent a large patient group who lack evidence-based health care service.
The current intervention study builds on our previous observational studies and treatment studies in this patient group as briefly explained:

The principal investigator (PI) of the current study, Toril Skandsen, MD, PhD, is also PI of a large cohort study of 378 patients with mild traumatic brain injury (MTBI): Trondheim mTBI Follow-up study[1]. Preliminary results from that study show that 10-15% experienced long lasting postconcussion symptoms, which was more than we expected, since half of the patients had not been hospitalised, rather been evaluated by general practitioners after their injury[1]. However, also among the clinical referrals, we can observe that many patients have suffered very mild injuries. Often the injury does not meet criteria for being a mild traumatic *brain* injury, but rather a minimal *head* injury (HI). Nevertheless, despite having a *milder* initial head trauma, seemingly, these patients suffer from a *higher symptom burden* than patients with more severe head traumas that we have followed for 12 months in the Trondheim mTBI Follow-up study. In 2019, we therefore initiated a study with both an observational part and an open, uncontrolled study of exercise, where all referred patients with MTBI or minimal head injury were invited (REK 2018/2159).

The current study will target patients with PCS or PTH; occurring after MTBI or minimal head injury where symptoms have lasted for more than one month. The study is a pragmatic randomized controlled study conducted at St. Olavs hospital, Clinic of Physical medicine and rehabilitation. We will apply a parallel group design, with one arm receiving the exercise intervention with face-to-face follow-up and exercise, and the other arm will be counselled by telephone after the baseline visit.

2.2 Background

2.2.1 Mild traumatic brain injury and minimal head injury

Mild traumatic brain injury (MTBI) is a prevalent health condition, and in our cohort study "Trondheim MTBI study"[1], we could calculate a yearly incidence of around 300 per 100 000 persons among people 16-60 years[2]. MTBI is mostly defined by a trauma towards the head that causes some acute signs of reduced cerebral functioning, such as a brief loss of consciousness or amnesia for the event. If such signs are not present in a patient who has had a trauma towards the head, the diagnosis is a minimal head injury according to existing classifications[3]. (APPENDIX 1)

2.2.2 Self-reported symptoms – the postconcussion syndrome

Patients with MTBI often report symptoms such as headache, dizziness, fatigue, and problems with sleep and attention[4]. Usually these symptoms resolve during the first few weeks, but some report long lasting symptoms[5]. This cluster of symptoms is referred to as " the postconcussive syndrome", (PCS)[6], and there are research criteria for the PCS in DSM-4 and ICD-10[7]. The prevalence of PCS differs between studies, but 10-20 % is an often-reported estimate, which also corresponds to findings in our cohort study "Trondheim MTBI study" (unpublished results). It is debated whether this cluster of symptoms should be regarded as a medical syndrome, and in this project, PCS rather denotes a high level of postconcussion symptoms. The exact etiological basis of PCS is unknown, but both structural brain abnormalities and personal factors are likely involved [6]. Patients with PCS suffer from a range of disturbing symptoms, often affecting their participation in working and social life.

2.2.3 Posttraumatic headache (PTH)

Headache is a dominating and very common symptom after MTBI[8], and the field of posttraumatic headache (PTH) represents another, rather separate, line of research and health care, driven by neurologists. PTH is classified among the secondary headaches in the International Classification of Headache Disorders[9], but with the large overlap in symptom profiles between PTH and primary headaches, especially Tension Type Headache (TTH) and migraine, the classification and definition of PTH is debated[10, 11]. The pathophysiological mechanisms in PTH are not well understood, but there are both similarities and differences[12] compared with mechanisms in migraine and other primary headaches.

2.2.4 Exercise as a treatment option of PCS and PTH

Few methods have been proven effective in preventing or treating PCS. Psychoeducation, cognitive behavioural therapy (CBT) and aerobic exercise are among the treatment options most studied, in addition to therapies targeting the specific symptoms, such as pain medication or vestibular rehabilitation[13]. PTH has been found to be remarkably persistent[8, 14], which calls for studies applying non-pharmacological approaches.

Physical activity with increase in heart rate is commonly experienced to be a trigger of symptom exacerbation. Typically, no systematic counselling on early return to physical activity is provided for patients with MTBI. On the contrary, they have often got advice about resting until they were free from symptoms at rest. This approach, however, is now challenged[15-17]. Recent studies indicate a benefit from exercise, with faster recovery[18], and complete rest should probably be discouraged after the first 24-72 hours[16, 19].

Aerobic exercise with intensity of 80-90% of symptom-threshold (the HR measured at the workload that induced a marked rise or change in perceived symptoms) has been most studied[20]. It has been recommended that a validated protocol, such as the Buffalo Concussion treadmill Test (BCTT) or the Buffalo Concussion Cycle Test (BCCT) is used to measure baseline values and progress during treatment[21, 22]. This exercise intervention has been most studied in the early phase of sports-related concussion[23], but some studies exist on PCS outside the sports context, and they provide evidence for prescribing light to moderate physical activity as treatment for PCS, although a review also emphasize that future research should investigate different options for delivery of the exercise intervention[24].

2.3 Benefit/Risk assessment

2.3.1 Risk assessment

The study targets persons who experience exercise intolerance, which has often led them to considerable inactivity. Both intervention groups will start exercising in this study, and some symptom exacerbation is likely to occur. For such events, procedures have been formulated (chap 7). From pilot studies at St. Olavs Hospital and Oslo University Hospital, as well as from the international literature, serious adverse events are not expected.

2.3.2 Benefit assessment

Based on clinical experience and results from the aforementioned pilot studies and literature, we expect that patients will be satisfied with the intervention, and that a majority will experience improved capacity and tolerance for exercise, which is highly rated among these patients. Potentially also, their symptom burden in general will be lower after the interventions.

2.3.3 Overall benefit: risk conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with sub-symptom threshold exercise are justified by the anticipated benefits that may be afforded to participants with PCS/PTH.

3 AIMS, OBJECTIVES AND ENDPOINTS

3.1 Study aim 1

To compare to methods of delivery of sub symptom-threshold exercise in patients with PCS and PTH.

Objective: to conduct an RCT where exercise with face-to face follow-up and regular testing is compared to exercise with follow-up over telephone.

3.2 Study aim 2

To compare gain in symptoms and function obtained during the treatment period with that of a similar study at Oslo University Hospital.

Objective: to pool some data and look for centre differences. Further, to evaluate the two centres study results and thereby provide input to future guidelines for rehabilitation after mild head injuries.

3.3 Study aim 3 (in connection with separate study. Procedures for ANS testing included in separate protocol)

To explore whether self-reported and measures exercise intolerance is associated with abnormal autonomic nervous system (ANS) functioning in patients with PCS/PTH.

Objective: To utilize data on exercise tolerance from this study with data on ANS functioning in a related study and perform analyses of correlation between these measures.

3.4 Study aim 4 (in connection with separate study. Procedures for ANS testing included in separate protocol)

To explore whether sub symptom-threshold exercise is associated with normalisation of ANS functioning.

Objective: to study the change in ANS functioning in relation to the change in BCTT measures

3.5 Study endpoints and outcomes

3.5.1 Study primary endpoints are:

- change in HR at BCTT/BCCT test termination, as a measure of exercise tolerance.

3.5.2 Secondary outcomes are in addition:

- Change in days of headache of at least moderate intensity,
- Change score on Rivermead postconcussion symptom questionnaire[25], a list of 13 common postconcussion somatic, emotional and cognitive symptoms
- Change on the Patient-specific Function Scale (PSFS)[26] at 3 months of follow-up after the end of intervention. The patient is asked to write down activities that they have difficulty with due to their PCS/PTH. They can report up to three activities. Then they are asked to rate their current ability to complete the activity on 11-point scale from 0 “unable to perform” to 10 “able to perform at prior level”. Prior refers to the level

experienced before the injury. At follow-up, the activities they reported the first time are then presented to them, and they are asked to rate them on the same 11-point scale. The first activity the patient lists is used for scoring. A change of two points or more at follow-up is considered a clinically meaningful change[27].

- Change on the Quality of life after brain injury - Overall Scale (QOLIBRI - OS). Quality of life after brain injury (QOLIBRI) will be used to examine health-related quality of life (HRQL). The questionnaire assesses 6 dimensions of HRQL: Cognition, Self, Daily life and Autonomy, Social relationships, Emotions and Physical problems. Each item is scored on a 5-point scale, from 1 (not-at-all satisfied) to 5 (very satisfied).
- Change in depressive symptoms measured with the Patient Health Questionnaire (PHQ-9). The questionnaire consists of 9 items on a 4 point scale ranging from 0-27 (best-worst). PHQ-9 is validated and often used in people with TBI.
- Change in anxiety measured with the Generalized Anxiety Disorder Scale (GAD-7) The questionnaire consists of 7 items ranging from 0-21 (best-worst).
- Change in impact of headaches on life measured with the Headache Impact Test (HIT). The questionnaire has 6 questions that address the severity of the headache and the headache's impact on daily activities, psychosocial and cognitive functioning. The six items is scored on a 5 point scale ranging fram never to always (best-worst).
- Change in fatigue measured with the Fatigue Severity Scale (FSS). The Fatigue Severity Scale (FSS) consists of 9 questions about the physical and cognitive effects of fatigue. It is scored on a seven point scale where 1 = strongly disagree and 7 = strongly agree. The total score ranges from 9 to 63, the higher the score, the more severe fatigue.
- Change in physical activity measured with the International Physical Activity Questionnaire (IPAQ). The IPAQ is a 7 item questionnaire The response can be categorized into three categories: 1 = inactive, 2 = minimally active, 3 = Health Enhancing Physical Activity (HEPA) active.
- Change in balance measured with the Single leg stance test (SLS). SLS tests the balance ability in patients with vestibular conditions and can detect changes over time.
- Adherence to training measured with the The Problematic Experience of Therapy scale (PETS). PETS is a brief quantitative measure developed to reflect the most commonly reported reasons for discontinuing therapy/training given by patients undergoing self-managed home-based rehabilitation/training.

4 STUDY DESIGN AND SETTING

4.1 Overall design

The clinical trial in this study (aim 1) study is a pragmatic, randomized controlled trial with two arms. A parallel group design is applied.

4.2 Study setting

The study is run in an outpatient setting at the Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Norway. All patients are also participants in the observational study: “Minimal and mild head injury: an exercise and outpatient follow-up study at St. Olavs Hospital” (REK number 2018/2159).

4.3 Scientific rationale for study design

There is still a need for more controlled studies of exercise interventions for patients with PCS/PTH. Studies that compare a structured exercise intervention with treatment as usual are needed, and such a study is currently conducted at Oslo University Hospital. In contrast, in our study we compare two types of delivery of exercise. This design was chosen, since we, in the clinic, already tend to offer an exercise intervention guided by BCTT/BCCT to patients with exercise intolerance, based on our own previous pilot study and increasing evidence from international studies. Our study and the study at Oslo University Hospital together therefore add important new knowledge to the field.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.
A participant is considered to have completed the study if he/she has completed the first and the last visit.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, will be avoided as far as possible, but may be discussed if changes are needed in order to maximize the quality of the study. Such changes will be reflected in new protocol versions and reported to clinical.trials.gov.

5.1 Inclusion criteria

- Age 18-65 years
- Having sustained a minimal HI or MTBI at least 2 weeks ago.
- PCS/ PTH (at least one postconcussion symptoms, of at least moderate degree, occurring within the first week after the head injury).
- Intolerance for physical activity (self-reported and measured; including symptom exacerbation later on the test day) (see also 5.5.3.
- Capable of giving informed consent.

5.2 Exclusion criteria:

- More than 2 years since last injury.
- The symptoms are better explained by other conditions.
- Severe communication problems, typically due to poor knowledge of Norwegian.
- Severe psychiatric, neurological, somatic, or substance abuse disorders that will make it problematic to function in a group and/or will complicate follow-up and outcome assessment.
- Safety concerns according to the medical checklist.
- Pregnancy

5.3 Determining eligibility

The BCTT/BCCT will be used to diagnose exercise intolerance. When the tests is terminated before Borg 16, criteria are met.

5.3.1 The Buffalo treadmill test

The participant will perform an incremental treadmill exercise test according to a standard Balke protocol to the first sign of symptom exacerbation or submaximal exertion. The treadmill speed is typically 5 km/hour, but can be adjusted, to obtain a comfortable walking speed for each person. Each minute, the grade is increased by 1.0% while maintaining the same speed. HR and ratings of perceived exertion (Borg scale) is measured every minute. The test shall be terminated at report of exacerbation of PCS symptoms of ≥ 3 points on NRS scale 0-10, or when reaching 16 on Borg scale. A physiotherapist, a physician or a master student will conduct the test, and an additional person will be present if needed. Before the test, we will measure resting HR. After 12 weeks and 6 months, there will be a repeated BCTT.

5.3.2 The Buffalo Cycle test

For test procedures regarding the BCTT and the BCCT

5.3.3 Exercise intolerance

Participants where the BCTT/BCCT is terminated due to symptom increase, or who report an increase of ≥ 2 points on NRS scale at the end of the test or during the next 60 minutes, but could continue to 16 on the Borg Scale, diagnosed with exercise intolerance and eligible for the study.

5.4 Lifestyle considerations

5.4.1 Dietary and stimulant restrictions

None

5.4.2 Activity restrictions

None

5.5 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. These will typically be those who do not have exercise by definition as measured with the BCTT/BCCT or where medical contraindications are revealed during initial testing. A minimal set of screen failure information will be collected to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing. Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.6 Criteria for temporarily delaying

If we reveal a family or medical history, symptoms or signs during the screening that warrant additional medical examinations, baseline testing will be delayed until such concerns have been addressed according to clinical standards.

In case of any life circumstances occur, not related to the health condition, that temporarily prevents the participant from engaging in the study activities, baseline testing will be delayed until the participant is ready, provided that the study is still recruiting, and that eligibility criteria are still met.

6 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational interventions, marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

ARM Name	**A**	**B**
Intervention Name	**Follow-up face-to face**	**Follow-up over the phone**
Type	Exercise	Exercise
Description of intervention	Home-based and in-house exercise, supervised both by telephone and face-to-face. Every week the first three weeks participants will exercise one session at the hospital, and the BCTT/BCCT will be performed every 3rd week, at the hospital in order to be able to shape the intervention.	Home-based exercise only, supervised by telephone. The participants will exercise solely in the home setting and will be contacted by telephone, every week during the first three weeks, thereafter every third week. Based on the therapist's evaluation during these calls, the intervention is shaped.
Dosage	3-5 times per week at 80-90% HR of HR at test termination, or individually adjusted to lower intensity after therapist judgement.	3-5 times per week at 80-90% HR of HR at test termination, or individually adjusted to lower intensity after therapist judgement.
Sourcing	Provided by a physical therapist at Clinic of Physical Medicine and Rehabilitation at St. Olavs Hospital.	Provided by a physical therapist at Clinic of Physical Medicine and Rehabilitation at St. Olavs Hospital.

6.1 Content and shaping of the exercise

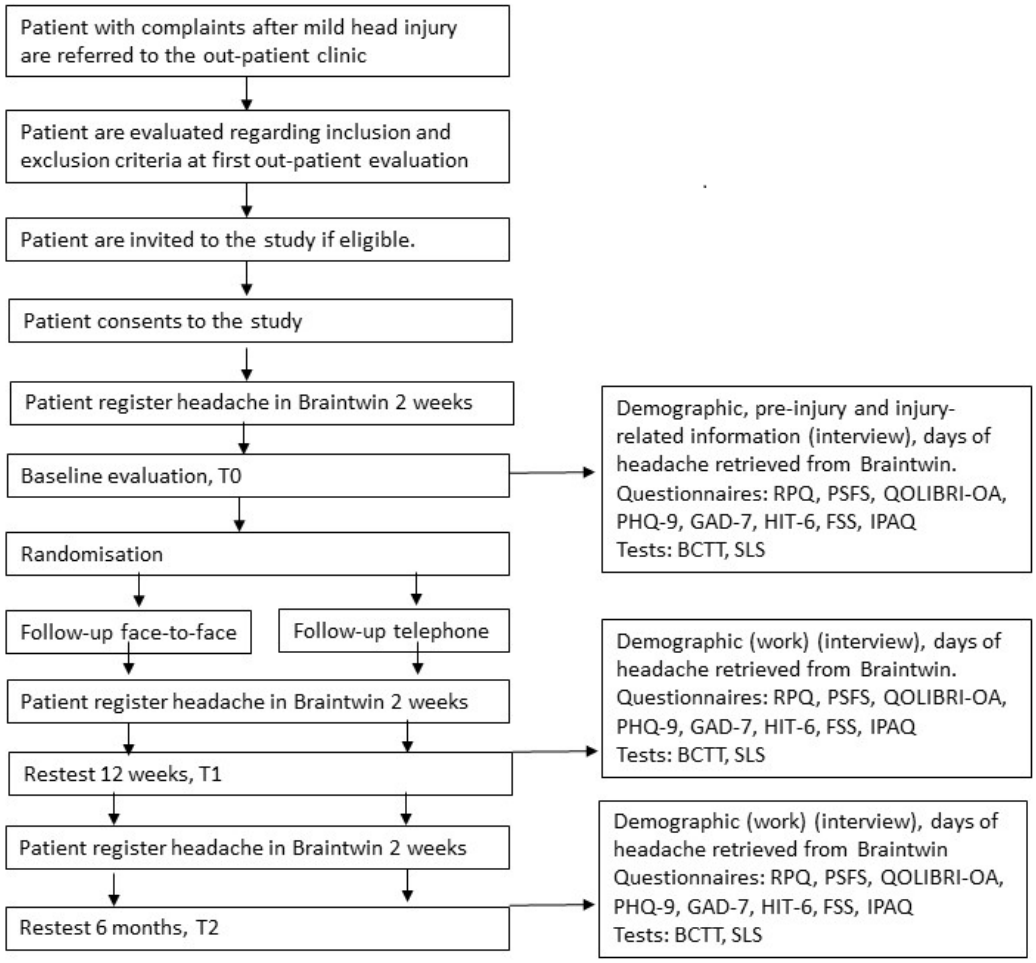
The type of exercise will be discussed with the participant and can be any activity which implies a rise in HR to the desired level. The participant will exercise alone or with friends / family without any supervision from the study personnel.

a. Participants who are used to regular exercise, will start exercising at 80-90 % of the HR at test completion, 2-3 times per week, 15-20 minutes the first 2 weeks, then increase to 3-5 times per week if there is no symptom exacerbation lasting until the following day.

b. Participants, who likely are deconditioned after long lasting inactivity and rest, will start exercising at a lower intensity (70-80%) of the symptom threshold, 5-10 minutes, and 2-3 times per week the first 2 weeks, then increase gradually to 3-5 times per week if there is no symptom exacerbation lasting until the following day.

6.2 Participants timeline

Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants.



Rivermead post-concussion symptoms questionnaire (RPQ), Pasient-spesifikk funksjons skala (PSFS), Quality of life after TBI (Qolibri), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder Scale (GAD-7), , Headache Impact Test (HIT) HIT 6, Fatigue Severity Scale (FSS), International physical activity questionnaire (IPAQ). Problematic Experience of Therapy Scale (PETS). Tester: Bufallo Concussion Treadmill Test (BCTT), Ett-bens stående (SLS).

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to randomized study intervention. A web-based randomization system developed and administered by a third party (KlinForsk) will perform the randomization. Block randomization, varying block size, will be performed to generate two groups with equal number of participants, group A and group B. The date of randomization will be recorded as well as the intervention group.

This is an open-label study, where only the assessor of the primary endpoint is blinded for study intervention.

6.4 Continued access to intervention after the end of the study

After the end of the study, participants will receive limited advice on further exercise, in line with the public advice to the general population. No further individual supervision will be given to participants

6.5 Study intervention compliance

Compliance with the intervention will be assessed at each visit/phone call with a short interview. The individual workouts will be registered to an app connected to the HR monitor, and participants will be asked for number of workouts, duration of workouts, average HR during each workout and how they felt during and after workout. Information will also be noted in the hospital's medical record.

6.6 Dose modification

The decision to proceed to the next intensity level of exercise, or to reduce the intensity, will be made by the Study Team based on the participant's feedback regarding the experience with the current intensity. Such modification is part of the exercise program, as described in 6.1.

6.7 Treatment of persistent symptom exacerbation

Participants are encouraged to get in contact with us if they experience symptom exacerbation that lasts longer than 24 hours. We will in such cases schedule a consultation with physiotherapist or physician within 10 days, and a reduction in workload will be initiated immediately.

6.8 Concomitant therapy

Participants cannot engage in similar therapy (exercise programs) concomitant with the exercise intervention in this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of study intervention

In rare instances, it may be necessary for a participant to discontinue study intervention permanently. If study intervention is permanently discontinued, the participant will remain in the study, to be evaluated for already collected data. Date and cause of discontinuation

7.2 Withdrawal criteria BCTT

If a patient feels ill, or there are abnormal heart rate responses (the HR does not increase gradually as expected), during testing (as evaluated by the tester), the test shall be discontinued, and the patient shall be examined by a physician who decides further action. New test or continued exercise shall only occur after a medical evaluation.

7.3 Withdrawal criteria exercise

When a participant experiences feeling worse the day after the test, or feeling worse the following day after workouts in the initial week of the program. If so, the protocol should be changed to exercising at a lower HR, 5-10 minutes less frequently. If the patient feels worse also after reducing intensity and frequency, exercise shall be stopped and the patient shall receive a new evaluation.

7.4 Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study personell.

The following actions must be taken if a participant fails to return to the clinic for a required study visit / is unavailable for scheduled telephone calls :

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and councel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, by telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENT AND PROCEDURES

• Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions should be avoided if possible, and if they occur, they should be logged.

• Immediate safety concerns should be discussed with the physician responsible for the study immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

• Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

• All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

• Procedures conducted as part of the participant's routine clinical management (e.g., medical examinations) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy and outcome assessments

Tests and outcome measures	Description	Baseline T0	12 uker T1	6 mnd. T2
Main outcome				
Rivermead post-concussion symptoms questionnaire (RPQ)	Generelle post-commotio symptomer, alvorlighetsgrad	X	X	X
Secondary outcomes				
Bufallo Concussion Treadmill Test (BCTT)	Exercise intolerance	X	X	X
Andre utfallsmål				
Patient Specific Functional Scale (PSFS)	Patient-specific functional limitations	X	X	X
Quality of life after TBI (Qolibri-OA)	Healthrelated quality of life	X	X	X
Patient Health Questionnaire (PHQ-9)	Depression	X	X	X
Generalized Anxiety Disorder Scale (GAD-7)	Anxiety	X	X	X
Headache Impact Test (HIT) HIT 6	Headache, consequences	X	X	X
Fatigue Severity Scale (FSS)	Fatigue	X	X	X

International physical activity questionnaire (IPAQ)	Physical activity	X	X	X
The Problematic Experience of Therapy Scale (PETS)	Adherence		X	X
Single Leg Stance (SLS)	Balance	X	X	

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

Safety assessment comprise asking questions about symptom exacerbation, falls or other problems in connection with the exercise. If such are reported, further examinations will be considered by the physician in charge of the study:

8.2.1 Vital signs and physical examinations

A physical examination will include assessments of BP and HR in the supine and upright position, assessment of the skin, heart and lung auscultation, abdominal palpation, a brief neurological evaluation and repeat balance testing. Pulse oximetry will be performed during the BCTT/ BCCT in cases of dyspnea during the initial part of the testing.

8.2.2 Vital signs

8.2.3 Electrocardiogram

ECG will be performed in cases with HR outside the expected boundaries, if the patient experiences any chest pain or discomfort or if the medical checklist reveals any risk factors. One of the physicians in the study will decide when ECG should be perfprmed.

8.3 Adverse events (AE)

According to a systematic review and meta-analysis, participating in an exercise intervention increased the relative risk of non-serious adverse events, but not of serious adverse events. Exercise therapy may therefore be recommended as a relatively safe intervention. However, as 51% of all primary studies in the study did not report adverse events, there is a need to systematically monitor adverse events in all future exercise therapy studies [28]. Hence, the current study will systematically monitor and report adverse events.

AEs will be reported by the participant. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up.

8.3.1 Methods and timing for determining AE

The participants will be asked as part of the study interventions and are also encouraged to contact us between scheduled appointments if they feel that their symptoms have worsened, they do not tolerate the exercise, they have had falls or other events during exercise.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow up of AE

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed and treated until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Reporting of AE

AEs will be reported to the physician in charge of the study, logged in the participants Schema and also described in the hospital's medical record. No regulatory reporting is required; however, all participants are covered by the Norwegian Patient Injury Compensation. SAEs might be reported there if they result in permanent sequelae.

8.3.4 Pregnancy

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and the patient will be withdrawn from the study. Any abnormal pregnancy outcome will not be reported as AE, since exercise at this intensity level is not considered to increase risk.

8.3.5 Disease-related events/outcomes not qualifying as AEs

PCS/PTH tend to fluctuate, and symptom exacerbation may be triggered by a range of stimuli and strains, not only exercise. In case of symptom exacerbation, it will be evaluated by therapist or physician whether an event/ worsening is likely caused by the exercise, or other factors. In the latter case, the event/worsening will not be listed as AE but reported in the record and in the study CRF.

8.4 Biomarkers

As part of the overarching PCS study, some participants will have blood drawn for storage. This is performed at the Clinic of Laboratory Medicine at St Olavs Hospital, regulated via a separate agreement, and blood test is optional.

8.5 Neurophysiological testing

Testing of autonomic functioning and pain thresholds will be performed in some participants as part of a separate study (Appendix X). They consent separately to that study, however timing of the examinations will be harmonized with T0, T1 and T2 in this exercise study.

8.6 Assessment of eligibility and allocation to study group

Potential participants are patients who have been referred for evaluation and treatment of PCS /PTH and have consented to be registered in the observational study. Eligibility criteria will be evaluated by the physician at the outpatient clinic or by physicians or other research staff participating in the observational study. Patients, who may be eligible, will receive the study information sheet and a brief description of the study. If they express a preliminary interest, a contact with the study coordinator or physiotherapist will be arranged, where they will receive information that is more detailed. Consent will thereafter be given electronically on the platform E-forsk.

8.7 Implementation

When the eligible patient has signed the consent for this intervention study, the coordinator will ensure the first baseline assessment, and the first BCTT/BCCT will be performed. Randomisation will then occur by KlinForsk. The result will be given to the patient either directly or by telephone by one of the project collaborators at the Department of Acquired Brain Injury, where the patient has been enrolled in the main observational study prior to the invitation to participate in the current study.

9 STATISTICAL CONSIDERATIONS, DATA MANAGEMENT AND MONITORING

9.1 Sample size

Regarding the primary outcome, a sample size of 40 patients in each group is sufficient to detect a difference between the two groups of 10 in HR, which is considered a clinically meaningful gain in exercise tolerance, allowing for exercise at a higher intensity level. To account for some patents with poor compliance, we plan to include 45 in each arm. Sample size calculations has also been based on the Patient-specific Functional Scale (PSFS). A change of 2 points has been suggested as a clinically significant change. The expected standard deviation (SD) of 2.5 was based on data from a large Norwegian cohort of patients with complex musculoskeletal complaints (Fysioprim). We used an alpha level of 0.05 and power of 0.90. The sample size calculations were performed two ways. First, we conducted a simple calculation assuming a single measure at end of follow-up; this suggested a sample size of 66 (33 in each group). However, repeated measures have dramatic effects on power, increasing the number of measurements from one to four can reduce the sample size by 30-50% depending on the correlation between measures, indicating that 34 to 46 participants are needed. Second, we performed a simulation using 1000 repetitions of a mixed model regression for repeated measures, assuming four data-points per participant (baseline, start of intervention, end of intervention and 3 months after the intervention) and a correlation between measures of 0.4. This gave an estimated power of 0.90 (95% CI 0.88-0.92) for a total sample of 40 participants (20 in each group). Taken together, we therefore aim to include a total of 48 participants (24 in each arm) allowing for a dropout rate of 20% at 3 months of follow-

9.2 Planned statistical analyses

The main effect of the intervention will be analyses according to the intention to treat principle (i.e. include all randomized participants) using parametric or non-parametric tests for comparison of independent samples. Patient-specific Functional Scale scores will be analyzed with linear mixed models. This model includes all available data for all participants at each time point (i.e. baseline, end of intervention and at three months). Baseline levels will be pooled for the two intervention groups assuming that any baseline differences are due to chance; this also controls for any baseline differences in the outcome variable. For the other secondary outcomes, we will use parametric or non-parametric tests for comparison of independent samples. Linear mixed models for continuous outcomes and generalized estimated equations (GEE) for binary outcomes may also be applied.

Precision of the estimated effects of the intervention will be assessed by a 95% confidence interval, and the effect will be described as a point estimate (mean difference or odds ratio) with accompanying confidence limits. A statistical analysis plan (SAP) will be published (Clinical Trials.gov) before any of the analyses are initiated.

9.3 Data management and data protection

A data management plan, a living document has been developed. The tool at NSD was used and the plan can be accessed here: https://dmp.nsd.no/plan/7f000001-8315-1d43-8183-c7167f501125/export
and a recent PDF version will also will be kept in the eMTF.

9.3.1 Electronic data management systems

Study documents are stored electronically in St. Olav Hospital's research server, and in the hospital archive, Elements (2020/2429), and they are listed in the Master Trial Form.

The list of participants, their contact information and a log of their appointments is stored electronically in St. Olav Hospital's research server and can only be accessed by research personnel who need it for executing tasks in the study. A list of the people who have access to the different folders is archived in Elements, and also kept in the MTF.

The study data collected at testing and as part of clinical interviews during the intervention and follow-up will be entered into **WebCRF3,** run by the "KlinForsk". Data agreement is stored electronically, see MTF.
The study data collected with questionnaires (participant reported) are entered directly by the participant into **E-forsk**, via Helsenorge.
Data will be extracted from WebCRF and E-forsk, and delevered as SPSS files via Filsender, or encrypted as….
The datafiles will be stored in the project **study data folder** at the **research server** at St. Olavs Hospital strictly separated from the identification key. Data protection
When data are delivered to the students and researchers for analyses, a document is signed, where the recipient of data state that they have read the regulation for storage of sensitive data and that they apply for data.
The appointed secretary for data file management will keep a log of delivery of data. When studies have been finished, the recipient of data return the files and state that no data are longer stored privately.

9.4 Monitoring

There is no external monitoring in the study. The study coordinator and the principal investigator will ensure that internal monitoring is performed every 6th month.

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