Integrated exercise program in opioid agonist therapy clinics and effect on psychological distress: Study protocol for a randomised controlled trial (BAReAktiv)

Einar Furulund (einar.furulund@sus.no)
Stavanger University Hospital: Helse Stavanger HF

Tesfaye Madebo
Stavanger University Hospital: Helse Stavanger HF

Karl Trygve Druckrey-Fiskaaen
Helse Bergen HF

Jørn Henrik Vold
Helse Bergen HF

Mette Hegland Nordbotn
Helse Bergen HF

Eivin Dahl
Stavanger University Hospital: Helse Stavanger HF

Sindre Mikael Dyrstad
University of Stavanger: Universitetet i Stavanger

Torgeir Gilje Lid
Stavanger University Hospital: Helse Stavanger HF

Lars Thore Fadnes
Helse Bergen HF

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Abstract

Background

Substance use disorder is associated with unhealthy lifestyle choices, resulting in adverse social and health consequences. People with opioid use disorder receiving opioid agonist therapy, in particular, have high morbidity and reduced quality of life. Physical activity is recommended as an adjunctive treatment for people with substance use disorder, but there is minimal evidence from randomized controlled trials on effect of this among people with substance use disorder receiving opioid agonist therapy.

Methods

BAReAktiv is a multicentre randomised controlled trial. The study aims to recruit 324 patients receiving opioid agonist therapy (randomised 1:1 to integrated exercise intervention or control). A 16-week group-based integrated exercise intervention with workouts twice a week. The exercise program consists of endurance and resistance training. The target group will be patients 18 years and older receiving opioid agonist therapy in outpatient clinics in several centres in Western Norway. The primary outcome of the study is the effect on psychological distress measured by Hopkins’ symptom checklist with ten items. Secondary outcome measures include physical functioning assessed with a 4-minutes step-test, activity level, fatigue symptoms, quality of life and changes in inflammation markers. This study will provide improved knowledge on the effects of an integrated exercise program in opioid agonist therapy.

Discussion

Systematically integrating exercise programs for people receiving opioid agonist therapy could lead to a shift towards a stronger focus on health behaviours in outpatient care. Integrating exercise could benefit patient recovery and reduce disease burden. Further scale-up will be considered if the provided exercise program is safe and effective.

Trial Registration

: ClinicalTrials.gov.no NCT05242848. Date of registry February 16, 2022. Integrated Exercise Program in Opioid Agonist Therapy Clinics - Full Text View - ClinicalTrials.gov

Administrative Information

Note: The numbers in curly brackets in the protocol refers to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see: http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).
Integrated exercise program in opioid agonist therapy clinics and effect on psychological distress: Study protocol for a randomised controlled trial (BAReAktiv)

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1 Centre for Alcohol and Drug Research, Stavanger University Hospital, Stavanger, Norway;
2 Bergen Addiction Research, Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway;
3 Department of Global Public Health and Primary Care University of Bergen, Bergen, Norway;
4 Department of Respiratory Medicine, Stavanger University Hospital, Stavanger, Norway;
5 Department of addiction, Stavanger University Hospital, Stavanger, Norway;
6 Department of Public Health, University of Stavanger, Stavanger, Norway;
7 Department of Psychiatry, Haukeland University Hospital, Bergen, Norway;
8 Department of Education and Sport Science, University of Stavanger, Stavanger, Norway;
9 List of Members of the ATLAS4LAR Study Group (see acknowledgment)

Western Norway Regional Health Authority, Postboks 303 Forus, 4066 Stavanger, Norway

Funders did not participate in study design, and will not be involved in data collection and analysis, decision to publish, or preparation of the manuscript.

Background And Rationale

Substance use disorder is associated with unhealthy lifestyle choices, resulting in adverse social and health consequences (1, 2). People with opioid use disorder have particularly high morbidity, reduced physical fitness and quality of life (3-5), and a higher risk of premature death (6, 7).
Physical activity is defined as any bodily movement produced by skeletal muscles which requires energy expenditure. Exercise is planned, structured, repetitive, and intentional physical activity intended to improve or maintain physical fitness (8). Exercise has been suggested as an adjunctive treatment strategy for people with substance use disorder (7) due to its positive effects on health, quality of life and reducing the burden of substance use disorder patterns (9, 10). Physical activity and exercise can be effective adjunctive treatment methods for reducing nicotine, alcohol and drug use (7, 11, 12). Still, we need more knowledge about the effects of exercise as part of opioid agonist therapy (OAT) and how to best integrate an exercise program into OAT (13). Few studies have investigated the effects of an exercise program on OAT patients (14-19) and none of these are randomised controlled trials with power to assess effects. Results from these studies suggest that exercise interventions could be desirable on physical fitness (17), substance use (14), and quality of life (17). However, the potential effect is uncertain. Further research on exercise intervention would therefore be beneficial (18).

**Objectives {7}**

This paper describes the BAReAktiv protocol. The primary objective is to evaluate the effect of a 16-week exercise intervention on the level of psychological distress among people receiving opioid agonist therapy.

We will also assess adherence to physical activity recommendations, physical functioning, symptoms of lung disease, assessment of changes in quality of life, fatigue and inflammatory markers from a blood sample.

**Trial design {8}**

A multicentre individually randomised controlled trial.

**Methods: Participants, Interventions And Outcomes**

This protocol is developed from preliminary experiences from a multicentre pilot study evaluated with a mixed-method design (not yet published). In summary, the ATLAS4LAR study group conducted a 6-week pilot intervention with a group-based exercise program for people receiving OAT. This pilot study was conducted from May 2021 to June 2021. We will now evaluate a prolonged scaled-up version of this intervention.

**Study setting and participants {9}**

Recruitment will take place in OAT outpatient clinics in Bergen and Stavanger, two of the four largest cities in Norway. Department of Addiction Medicine at Haukeland University Hospital in Bergen and OAT-clinic in Stavanger has adopted an integrated treatment and care model for patients receiving OAT. In Bergen, OAT outpatient clinics are established in each district. A consultant and a doctor specialising in addiction medicine, nurses, social workers, and psychologists staff the OAT clinics. The patients are
followed up almost daily with an observed intake of the OAT medications (20). The model in Stavanger is similar. The treatment model in Bergen and Stavanger is a good platform to test the integration of additional interventions aiming to improve the health of a vulnerable group and gather knowledge, which traditionally has been very difficult to reach (21).

**Eligibility criteria {10}**

The participants will be recruited from OAT outpatient clinics in Bergen and Stavanger inclusion criteria are as follow:

- Adults receiving OAT from the outpatient OAT clinics with weekly follow-ups
- Giving informed consent

Exclusion criteria:

- Not able to participate in the physical exercise intervention due to health disabilities
- Being imprisoned or hospitalised

**Who will take informed consent? {26a}**

Research nurses from the included OAT clinics will recruit patients and obtain informed consent.

**Additional consent provisions for collection and use of participant data and biological specimens {26b}**

Not applicable.

**Interventions**

**Explanation for choice of comparators {6b}**

To reduce selection bias, participants in the intervention and comparison groups are recruited from the same OAT clinics.

**Intervention {11a}**

The intervention is a supervised group-based exercise intervention for 16 weeks, which includes two outdoor sessions per week. The workout consists of two parts, endurance and resistance training. Every workout follows the same structure and lasts for approximately 45 minutes. The exercise starts with roughly 15 minutes of endurance warm-up, followed by moderate to high intensity running or walking intervals. Eight repetitions of 30 seconds uphill, and the participants can freely choose between running and walking. The preferred intensity of the intervals is \( >13 \) on Borg-score 20, meaning at least moderate-intensity activity (22). The participants will be guided in using the Borg scale to identify exercise intensity, and the perceived exertion will be measured at the end of the endurance section. The resistance training
consists of four exercises focusing on strengthening the large muscle groups, including pectoralis major, rectus abdominis, quadriceps femoris, gluteus maximus and latissimus dorsi. The strength-training program follows the same structure as the intervals, 30 seconds of active time and approximately 60 seconds of break, four rounds.

Clinical staff, research staff, and people with user experience will supervise the exercise sessions. The supervisors have been trained to carry out this exercise program, and the research team will provide weekly guidance to these supervisors. The intervention is designed on the World Health Organization 2020 guidelines on physical activity (23) and national guidelines for chronic obstructive pulmonary disorder (24). In addition, a clinical therapist panel and user with extensive experience in exercise as therapy for drug and mental health disorders from Stavanger and Haukeland University Hospitals, and preliminary experiences of patients and research personnel from the pilot study.

Criteria for discontinuing or modifying allocated interventions (11b)

If the participant asks for discontinuing the allocated interventions, the intervention will be discontinued or modified within our limits of the study design.

Strategies to improve adherence to interventions (11c)

Intervention will be linked to additional follow-up treatments to improve adherence, and short text message reminders will be sent.

Relevant concomitant care permitted or prohibited during the trial (11d)

See eligibility criteria.

Provisions for post-trial care (30)

At their local OAT clinic, participants will receive yearly health assessments following the trial.

Outcomes Measures (12)

Primary outcome measure:

Psychological distress

- The primary outcome is psychological distress 12-16 weeks after intervention initiation assessed with the Norwegian validated translation then item version of the Hopkins Symptom Checklist (SCL-10) (25). SCL-10 will be evaluated with mean SCL-10 item score, and compared between the intervention and control arm.

Secondary outcome measures 12 to 16 weeks after intervention initiation:
• Physical functioning assessed with a 4-minutes step-test measuring the number of steps climbed in the period (26).
• Physical activity assessed using the Norwegian validated translation of the International physical activity questionnaire (IPAQ) (27).
• Changes in fatigue will be assessed with the Fatigue Symptom Scale (FSS-3) (28).
• Changes in health-related quality of life assessed with EuroQoL EQ-5D-5L (29) in addition to a self-reported question on happiness on a 0 to 10 scale.
• Biochemical indicators of inflammation (measured with C-reactive protein in serum and total leukocyte count in blood).

Participant timeline (13)

See Table 1: Flow chart of the study outlining follow-up visits and assessment at each visit.

Sample Size (14)

Based on a cohort study in the same population (30), we assume that psychological distress assessed with a mean item score of SCL-10 score is 2.2 with a standard deviation of 0.8. To detect a reduction in psychological distress to a mean level of SCL-10 of 1.95 (corresponding to mean level of SCL-10 of 1.8 among a proportion of 62.5% taking active part in intervention among those randomized to intervention groups), with 80% power, a 1:1 intervention: control ratio, a two-sided test, and alpha (\( \alpha \)) error of 5%. Based on these assumptions, 324 persons are required in total, including 162 persons in the intervention arm and 162 persons in the control arm (statistical power calculations in Stata SE 17.0).

Recruitment (15)

All patients receiving OAT from included OAT outpatient clinics will be considered the reference target population. As part of an annual health assessment related to the ATLAS4LAR project (31), patients will be informed about the trial and invited to participate. Study personnel provides an extended clinical evaluation for those patients giving informed consent and fulfilling the study eligibility criteria.

Assignment of interventions: allocation

Sequence generation (16a)

We will use 1:1 randomisation that will be electronically registered using a randomization algorithm made through Stata that is linked to electronic number for each patient (linked to CheckWare).

Concealment mechanism (16b)
After all eligibility criteria have been met and consent has been obtained, a unique patient identifier number will be entered into a randomization spreadsheet to determine which study arms the participant will receive.

**Implementation (16c)**

In order to enrol and assign participants, research nurses will use a randomization algorithm created through Stata linked to a patient's electronic number.

**Assignment of interventions: Blinding**

**Who will be blinded (17a)**

Blinding of patients is regarded as complex and infeasible. Patients will be informed of the follow-up they will receive, but not on other follow-up alternatives that are used or the exact hypotheses for the study. Outcomes assessor will be blinded.

**Procedure for unblinding if needed (17b)**

Not applicable. The research nurses know patient assignment.

**Data collection and management**

**Plans for assessment and collection of outcomes (18a)**

Outcome measures will be measured/collected at the OAT clinics through a structured interview and clinical assessment for participants randomised to standard or intervention. Research personnel with health professional background will perform the data collection. Data collection and follow-up will be given in line with *Table 1* and *Figure 1*.

**Table 1**: Flow chart of the study outlining follow-up visits and assessments at each visit
<table>
<thead>
<tr>
<th>Research nurse assessment</th>
<th>Screening (research nurse)</th>
<th>Treatment follow-up week 0 to 16 (nurses/social workers)</th>
<th>Intervention end-assessment (12-16 weeks after initiation)</th>
<th>Intervention post-assessment (10-30 weeks after intervention initiation)</th>
<th>Annual follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Informed consent</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>- Eligibility assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>- Follow-up by OAT staff</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>- Clinical assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Biochemical tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical funct. (4-min step-test)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical funct. (IPAQ)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SCL-10 (mental Health)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FSS-3 (fatigue symptoms)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EQ-5D-5L (quality of life)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Plans to promote participant retention and complete follow-up (18b)**

We will show appreciation to all participants who agree to take part in the trial. During the study period, participants will be able to build rapport with the research staff. A positive relationship could provide an opportunity for information and communication about issues concerning the trial. We will aim to make participants feel like they are part of a community and that they are involved in research. Patients who discontinue will be offered a consultation without obligation with the research nurse to explore reasons for discontinuing. In the event that participants discontinue the trial, they will be offered a health
assessment at the next yearly assessment. As the trial is integrated into routine care in OAT, patients will receive weekly follow-ups and reminders of appointments.

**Data management** (19)

Research nurses will collect all data using electronic data collection software (Checkware®). This information will be stored on the University Hospital of Bergen's secure servers. This study will collect clinical data from electronic medical records (DIPS®).

**Confidentiality** (27)

All personal data is stored on a secure, access restricted research server. The senior investigators LTF and JHV will import data from the collection software (Checkware®) and from the electronic medical record to a common file using each participant’s Norwegian personal identification number. Each participant is then given a computer-generated identification number for further analysis. Only anonymized data will be published.

Research nurses use paper forms for collecting the data during the trial and before data is plotted into the collection software. Appointments are made using the medical record system. The research nurses store all paper forms that may be connected to a participant in a locked file in a room with restricted access.

For documentation and follow-up purposes data will be stored until the end of the project on the 31th of December 2029, and then deleted.

**Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use** (33)

Not applicable.

**Statistical methods**

**Statistical methods for primary and secondary outcomes** (20a)

A detailed plan for analysis will be developed before data export and analysis. We will in this section outline some of the principles which will be used to guide decisions during data analysis. Analysis methods will follow the CONSORT and SPIRIT guidelines as far as possible (32-34). All tests will be two-sided. Descriptive results and efficacy estimates will be presented with 95% confidence intervals, and the statistical significance is set at $p < 0.05$. Potential confounders may be considered for adjustment if they are imbalanced at baseline, with assumed meaningful differences. Missing data will be considered and appropriate imputations based on pre-defined assumptions, will be done when necessary, as described in a detailed analysis plan. Categorical variables will be summarised as percentages and continuous variables as medians with interquartile ranges or means with standard deviation for variables with a Gaussian distribution. The primary outcomes will be analysed with generalised linear models, Gaussian distribution. The main analyses will be analysed as intention-to-treat.
Interim analyses \{21b\}

There will be weekly meetings between the research nurses and the investigators throughout the study period. The meetings will evaluate the progression of the trial and adverse events. The principal investigator, LTF will decide to terminate the trial.

Methods for additional analyses (e.g. subgroup analyses) \{20b\}

We will also conduct per protocol analyses including only intervention participants taking actively part of the intervention at least for 8 of the weeks. This will be conducted for both primary and secondary outcomes. We will also conduct sub-group analyses for participants with less or more than median number of steps in the 4-minute step test.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data \{20c\}

Missing data will be considered and appropriate imputations based on pre-defined assumptions, will be done when necessary, as described in a detailed analysis plan.

Plans to give access to the full protocol, participant level-data and statistical code \{31c\}

Access to the complete protocol anonymized participant-level dataset and statistical code is granted upon request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee \{5d\}

The principal investigator, investigators, research nurses and user representatives will meet once a week (study coordination unit). Research nurses and the primary investigator will meet weekly during the study period. The clinical team, including the research nurse, at each OAT clinic will meet daily.

Composition of the data monitoring committee, its role and reporting structure \{21a\}

There will not be an independent data monitoring committee, but the study coordination unit will ensure safety, adherence to the protocol, quality of the study, and ethical conduct.

Adverse event reporting and harms \{22\}

All grade 3 (severe) and grade 4 (potentially life threatening) adverse events are considered serious adverse events and will be reported. Some might have adverse reactions to physical exercises. Participating in trials with an exercise-based intervention increases the risk of non-serious adverse events but not serious adverse events (37). For safety evaluation, all serious adverse events occurring during the trial follow-up period will be recorded. According to current treatment guidelines, all serious adverse events will be followed until resolution, or a stable clinical endpoint is reached.
Frequency and plans for auditing trial conduct (23)

There are no plans for independent trial auditing. However, internal bi-annual audit procedures for study conduct and intervention will take place.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) (25)

Important protocol amendments must be submitted to the ethical committee.

Dissemination plans (31a)

Outcomes of the trial will be published in peer-reviewed journals. We will also submit abstracts to relevant national and international congresses. Summaries of the outcomes will be provided to participants and clinical staff at the participating OAT-clinics.

Ethics (24)

In the study, participation is not assumed to pose a substantial risk. However, blood collection might be unpleasant, and exercise can be exhausting. The regional ethical committee has approved the study (no. 155386 REK sør/øst C, dated 23.09.2020/05.04.2022). The study is also registered online ClinicalTrials.gov identifier: NCT05242848. The trial will be conducted according to the Declaration of Helsinki and other international conventions, GCP and GLP standards (35, 36). Each participant will be required to provide written informed consent and assent.

Discussion

This multicentre randomised controlled trial aims to evaluate the effects of an integrated group-based physical exercise intervention on psychological distress in people with substance use disorders receiving OAT. To the best of our knowledge, no large randomised controlled trials with exercise interventions have been developed and tested among patients receiving OAT (13).

If successful, an exercise program could be integrated into treatment service. Integrated treatment models could be an alternative to increase adherence to OAT and lifestyle-related disorders, such as cardiovascular and cardiometabolic disease. However, barriers to succeeding with exercise programs in clinical settings in this population include difficulties with adherence to the exercise program, difficulty devising a suitable intervention, and the relatively high cost of intervention related to personnel, equipment, or facilities (16, 37, 38).

Improving health seems to be one of the most important motives to start exercising for people with opioid use disorders. These findings are important factors taken into account when designing exercise
intervention and using an already familiar setting to deliver treatment may lower the participation threshold to increase engagement (39).

Our trial contains some limitations and several strengths. As mentioned earlier, complete blinding is hard to achieve. However, we aim to blind the outcome assessor in this study, and the data collectors have a strict manuscript to follow when performing physical function tests (26). All participants will receive the same instruction, reducing the possibility of external motivation from the data collector ongoing the 4-minute step-test. Additionally, since the study is individually randomised, the risk of confounding factors is minimized. The study population receiving OAT is large enough to answer the primary objectives accurately, and the associated accuracy for secondary objectives is assumed to be adequate.

If successful, this approach has the potential for widespread application through health care services for people in opioid agonist therapy.

**Trial Status**

Trial protocol version 1, 19. April 2022. Start of recruitment 19. April 2022. Estimated completion of recruitment December 2022

**Abbreviations**

OAT
Opioid Agonist Therapy
SCL-10
Hopkins Symptom Checklist
IPAQ
International Physical Activity Questionnaire
FSS-3
Fatigue Symptom Scale

**Declarations**

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Authors’ contributions (31b)

Each of the authors contributed to designing, implementing, and writing the protocol for the study. The authors both contributed to designing, implementing, and drafting the protocol for the study. EF wrote the first draft and led the design process. All authors have read and approved the final manuscript.

Funding (4)

The study was funded by Western Norway Regional Health Authority («Strategiske forskningsmidler» through ATLAS4LAR-project) with Department of Addiction Medicine, Haukeland University Hospital as responsible institution. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and material (29)

The final trial dataset will be made available to the authors mentioned under acknowledgments.

Consent for publication (32)

The authors have all given their consent for publication.

Competing interests (28)

The authors have no competing interests.

References


Figures

![Figure 2](image)

**Figure 2**

Overview of follow-up for the study

*The arrows indicate when measurements are timed.

**Supplementary Files**
This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010ChecklistMSWord.doc