STATISTICAL ANALYSIS PLAN for NCT05506579

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1 Introduction

1.1 Background and rationale

Overuse injuries are common among competitive Norwegian rhythmic gymnasts with a mean weekly prevalence of 37% [95% CI: 36% to 39%] and incidence of 4.2 new overuse injuries [95% CI: 3.6 to 4.9] per gymnast per year (Gram, M., Clarsen, B., & Bø, K., 2021). The knees, lower back and hip/groin were the most common injury locations. It has been postulated that reduced physical capacity (e.g strength, flexibility, stability) in the knees, lower back and hip/groin can increase the risk of injuries in rhythmic gymnastics.

In addition, more than 30% of the Norwegian rhythmic gymnasts experience urinary incontinence (UI), and 70% reported that UI negatively affected sports performance (Gram, M., & Bø, K., 2020). Few of the rhythmic gymnasts had any knowledge about the pelvic floor.

Hence, this assessor blinded cluster randomized controlled trial aims to find out whether the implementation of exercises targeting reduced physical capacity and pelvic floor dysfunction can prevent/reduce the prevalence of overuse injuries and UI.

The results from this RCT will be presented in two separate publications: **Publication I** on overuse injuries and **Publication II** on UI.

1.2 Trial Objectives

1.2.1 Primary Objective

Publication I: The primary objective is to assess if implementation of exercises targeting reduced capacity in the lower back, knees and hip/groin reduces the prevalence of overuse injuries in these areas compared with no targeted intervention.

Publication II: The primary objective is to assess if implementation of pelvic floor muscle training (PFMT) reduces the bother of UI compared with no targeted intervention.

1.2.2 Secondary Objectives

Publication I: The secondary objectives are:

  I. To assess if implementation of exercises targeting reduced capacity in the lower back, knees and hip/groin reduces the prevalence of substantial overuse injuries in these areas compared with no targeted intervention.
 II. The primary objective and the secondary objective number I) including overuse injuries in the calf/ankle/foot in addition to lower back, knees and hip/groin.
III. To assess the self-experienced effect and progress of the exercise program related to overuse injuries in the knees, lower back and hip/groin in the intervention group.

Publication II: The secondary objectives are:

   I.   To assess if implementation of PFMT reduces the prevalence of UI compared with no targeted intervention.
  II.   The primary objective and the secondary objective number I) but restricted to gymnasts having UI.
 III.   The primary objective and the secondary objective number I) but restricted to gymnasts having SUI.
 IV.   To assess the self-experienced effect and progress of the exercise program related to UI in the intervention group.

1.2.3   Subgroup analysis

Subgroup analysis of gymnasts with more than/less than 15 hours weekly training load will be conducted on the following primary and secondary objectives:

Publication I: The secondary outcome number II)

Publication II: The primary outcome and all the secondary outcomes except number IV).

2   Trial Methods

2.1   Trial Design

This is an assessor blinded cluster randomized controlled trial with rhythmic gymnastics clubs as the unit of randomization. Two different interventions (preventive exercises for the knees, lower back and hip/groin and pelvic floor muscle training (PFMT)) for two different conditions (overuse injuries and UI) are combined in this design. After inclusion, all rhythmic gymnastics clubs will be randomly allocated 1:1 to preventive exercises for knee, lower back and hip/groin and PFMT or a control group with no intervention.

2.2   Randomisation

Eligible rhythmic gymnastics clubs are allocated in a 1:1 ratio between preventive exercises for knee, lower back and hip/groin and PFMT (intervention group) or a control group with no intervention, using a computer randomization procedure stratified by club size (less than 10 gymnasts/10 or more gymnasts). The randomization is blocked within each stratum, with block sizes 4 and 6 in random order.

2.3   Sample size

The power calculation for Publication I (overuse injuries) is based on average prevalence in our previous study (Gram, M., Clarsen, B., & Bø, K., 2021) and previous studies with a

similar design (Olsen, et.al, 2005). With 80% power, 5% significance level and a decrease in the primary outcome measure from 40% to 20% in the intervention group and no change in the control group at least 158 gymnasts are required. In addition, to account for randomization at the cluster level, the total number were multiplied with an inflation factor (DE) of 1.4 (based on the following assumptions; average number of gymnasts per club (cluster) m = 9, ICC = 0.05, DE = 1+(m – 1)*ICC = 1+(9 – 1)*0.05 = 1.4), resulting in a required total sample size of 220 gymnasts (110 in each group).

The power calculation for Publication II (UI) is based on average prevalence in our previous study (Gram, M., & Bø, K., 2020) and studies with a similar design (Ferreira, et.al, 2014). With 80% power, 5% significance level and a decrease in the total sum score of ICIQ from 4.7 to 2.5 (SD 2.1) in the intervention group and no change in the control group at least 30 gymnasts are required. Multiplied with the same DE, the total required sample size will be 42 gymnasts (with 21 in each group).

2.4 Statistical Framework

2.4.1 Hypothesis Test
This RCT is designed to establish superiority of the intervention.

Publication I:

- The primary null hypothesis is that the prevalence of overuse injuries in the lower back, knees and hip/groin in the intervention group is the same as the prevalence of overuse injuries in the lower back, knees and hip/groin in the control group.
- The alternative hypothesis corresponding to the primary null hypothesis is that the prevalence of overuse injuries in the lower back, knees and hip/groin in the intervention group is lower or higher than the prevalence of overuse injuries in the lower back, knees and hip/groin in the control group.

There is only one identified primary analysis in this publication. All other efficacy analyses will be regarded as supportive or exploratory.

Publication II:

- The primary null hypothesis is that the bother of UI in the intervention group is the same as the bother of UI in the control group.
- The alternative hypothesis corresponding to the primary null hypothesis is that the bother of UI in the intervention group is less or more than the bother of UI in the control group.

There is only one identified primary analysis in this publication. All other efficacy analyses will be regarded as supportive or exploratory.

2.4.2 Decision Rule

This RCT is designed to address a single primary outcome for each publication. Superiority of the intervention is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.05 (two-sided).

2.5 Timing of Outcome Assessments

Publication I:

- Primary outcome: To assess the prevalence of overuse injuries in the lower back, knees and hip/groin, the Oslo Sports Trauma Research Center Questionnaire on Health Problems (OSTRC-H2) was used. The gymnasts in both groups answered the OSTRC-H2 at baseline (October 2022) and one time each month (last Sunday during the moth) throughout the intervention period (November 2022 - June 2023).
- Secondary outcome:
    I.   To assess the prevalence of substantial overuse injuries in the lower back, knees and hip/groin, the same assessment method and time frame as listed above for the primary outcome was used.
    II.   To assess the primary outcome and the secondary outcome number I) including overuse injuries in the calf/ankle/foot in addition to lower back, knees and hip/groin, the same assessment method and time frame as listed above for the primary outcome was used.
    III. To assess self-experienced effect and progress of the exercise program related to overuse injuries in the knees, lower back and hip/groin, a global rating of change (GRC) 11-point numerical scale was used. The gymnasts in the intervention group answered the GRC one time when the intervention period had ended (June 2023).

Publication II:

- Primary outcome: To assess the bother of UI, The International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI-SF) was used. The gymnasts in both groups answered the ICIQ-UI-SF one time at baseline (October 2022) and one time when the intervention period had ended (June 2023).
- Secondary outcome:
    I.   To assess the prevalence of UI, the same assessment method and time frame as listed above for the primary outcome was used.
    II.   To assess the primary outcome and the secondary outcome number I) restricted to gymnasts having UI, the same assessment method and time frame as listed above for the primary outcome was used.
    III. To assess the primary outcome and the secondary outcome number I) restricted to gymnasts having SUI, the same assessment method and time frame as listed above for the primary outcome was used.
    IV.   To assess self-experienced effect and progress of the exercise program related to UI, a global rating of change (GRC) 11-point numerical scale was used. The gymnasts in the intervention group answered the GRC one time when the intervention period had ended (June 2023).

<u>Subgroup analysis variable:</u> Weekly training load (hours/week) was reported by the gymnasts in the baseline questionnaire (October 2022).

3   Statistical Principles

3.1   Confidence Intervals and p-values

All calculated p-values will be two-sided and compared to a 5% significance level. If a p-value is less than 0.05, the corresponding group difference will be denoted as statistically significant. All efficacy estimates will be presented with two-sided 95% confidence intervals. As there is only one primary null hypothesis to be tested per publication, there will be no adjustments for multiplicity.

3.2   Adherence and Protocol Deviations

3.2.1   Adherence to Allocated Intervention

Adherence is assessed based on the percent of gymnasts who have conducted 65% or more of the required intervention sessions per week:

% adherence = (mean number of completed intervention sessions per week / number of weekly RG training sessions) *100%.

The number of weekly RG training sessions will be calculated based on training load stated in the baseline questionnaire (weekly hours of training / 3 hours (average length of an RG training)).

The number and % of gymnasts performing 65% or more of the required intervention sessions per week will be presented.

3.2.2   Protocol Deviations

The following are pre-defined major protocol deviations regarded to affect the efficacy of the intervention:

- Discontinuation of conducting weekly intervention sessions (adherence <65%, see more details in 3.2.1)

The number and % of gymnasts with major protocol deviations will be stated in the publications.

3.3   Analysis Populations

The Enrolled set will include all gymnasts who have provided informed consent and have been included into the study data base.

The Full Analysis Set (FAS) will be defined as all gymnasts randomly assigned to either the intervention or control group and who have responded to:

- Publication I: The OSTRC-H2 questionnaire either at baseline (Oct 2022) or Nov 2022 + one or more of April, May and June 2023.
- Publication II: The ICIQ-UI-SF questionnaire at baseline and in June 2023.

The Per Protocol Analysis Set (PPS) will include all randomised gymnasts meeting the study eligibility criteria and with no major protocol deviations affecting the intervention efficacy (FAS + completed 65% or more of the intervention sessions per week).

4 Trial Population

4.1 Screening Data, Eligibility and Recruitment

The total number of invited clubs (with their gymnasts) and reasons for not entering the RCT will be summarised and tabulated.

A CONSORT flow diagram will be used to summarise the number of rhythmic gymnastics clubs/gymnasts who were:

- assessed for eligibility at screening (all rhythmic gymnastics clubs in Norway)
- eligible at screening (all rhythmic gymnastics clubs in Norway having gymnasts ≥12 years of age training ≥3 days per week)
- ineligible at screening*
- eligible and randomised (including number of gymnasts per club)
- eligible but not randomised* (including number of gymnasts per club)
- received the randomised allocation (including number of gymnasts per club)
- did not receive the randomised allocation* (N/A)
- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

4.2 Baseline Patient Characteristics

The gymnast demographics and baseline characteristics to be summarised include age in years, weight, height, BMI, age when they started RG, competition level, weekly training load in hours, history of previous injuries and menstrual history.

Gymnast demographics and baseline characteristics will be summarised by randomised group and overall using descriptive statistics for continuous variables, and number and percentages of gymnasts for categorical variables. There will be no statistical analysis of group differences at baseline. Any clinical important imbalance between the groups will be noted.

5 Analysis

5.1 Outcome Definitions

All outcomes will be analyzed on the full analysis set. An additional analysis of the primary outcome (in both publications) and the secondary outcomes I) (publication I) and I)-III) (publication II) will be performed on the per protocol set.

5.1.1 Primary Outcome Definition

Publication I: The primary outcome is the prevalence of overuse injuries in the lower back, knees and hip/groin during the intervention period. In the OSTRC-H2 a health problem is defined as: "any condition that you consider to be a reduction in your normal state of full health, irrespective of its consequences on your sports participation or performance, or whether you have sought medical attention. This may include, but is not limited to, injury, illness, pain or mental health conditions." Furthermore, an overuse injury is defined as: "an injury caused by multiple accumulative bouts of energy transfer without a single, clearly identifiable event responsible for the injury." (Clarsen, et.al, 2020; Clarsen, et.al 2014). The primary outcome is dichotomous.

Publication II: The primary outcome is the bother of UI before and after the intervention period. Degree of bother is defined with the ICIQ-UI-SF sum score (0-21 points). The primary outcome is continuous.

5.1.2 Secondary Outcomes Definitions

Publication I: The secondary outcomes are:

I. The prevalence of substantial overuse injuries in the lower back, knees and hip/groin during the intervention period. A substantial overuse injury is defined as "an overuse injury leading to moderate or severe reductions in sports performance or participation, or time loss" in the OSTRC-H2 (Clarsen, et.al, 2020; Clarsen, et.al 2014). The secondary outcome is dichotomous.
II. The primary outcome and the secondary outcome number I) including overuse injuries in the calf/ankle/foot in addition to lower back, knees and hip/groin. The same definitions as listed above apply. The secondary outcome is dichotomous.
III. The self-experienced effect and progress of the exercise program related to overuse injuries in the knees, lower back and hip/groin. The secondary outcome is continuous (score of -5 to 5).

Publication II: The secondary outcomes are:

I. The prevalence of UI before and after the intervention period. The prevalence is defined by question 6 in the ICIQ-UI-SF. The secondary outcome is dichotomous.
II. The primary outcome and the secondary outcome number I) restricted to gymnasts having UI. The secondary outcome is continuous.
III. The primary outcome and the secondary outcome number I) restricted to gymnasts having SUI. The secondary outcome is continuous.

IV. The self-experienced effect and progress of the exercise program related to UI. The secondary outcome is continuous (score of -5 to 5).

5.1.3 Overview of Outcomes Publication I

Level	Outcome	Timeframe	Type
Primary	Prevalence overuse injuries in the lower back, knees and hip/groin	Baseline (Oct 2022) + monthly for eight months (Nov 2022 – June 2023)	Dichotomous
Secondary	Prevalence substantial overuse injuries in the lower back, knees and hip/groin	Baseline (Oct 2022) + monthly for eight months (Nov 2022 – June 2023)	Dichotomous
	Prevalence overuse injuries and substantial overuse injuries in the lower back, knees, hip/groin, calf, ankle and foot	Baseline (Oct 2022) + monthly for eight months (Nov 2022 – June 2023)	Dichotomous
	Self-experienced effect and progress	After intervention (June 2023)	Continuous
Sub-group analysis	Prevalence overuse injuries and substantial overuse injuries in the lower back, knees, hip/groin, calf, ankle and foot for gymnasts training less or more than 15 hours per week	Baseline (Oct 2022) + monthly for eight months (Nov 2022 – June 2023)	Dichotomous

5.1.4 Overview of Outcomes Publication II

Level	Outcome	Timeframe	Type
Primary	Bother of UI	Baseline (Oct 2022) + after intervention (June 2023)	Continuous
Secondary	Prevalence of UI	Baseline (Oct 2022) + after intervention (June 2023)	Dichotomous
	Bother and prevalence of UI restricted to gymnasts having UI	Baseline (Oct 2022) + after intervention (June 2023)	Continuous / Dichotomous
	Bother and prevalence of UI restricted to gymnasts having SUI	Baseline (Oct 2022) + after intervention (June 2023)	Continuous / Dichotomous
	Self-experienced effect and progress	After intervention (June 2023)	Continuous
Sub-group analysis	Bother and prevalence of UI for all gymnasts training less or more than 15 hours per week	Baseline (Oct 2022) + after intervention (June 2023)	Continuous/ Dichotomous
	Bother and prevalence of UI restricted to gymnasts having UI training less or more than 15 hours per week	Baseline (Oct 2022) + after intervention (June 2023)	Continuous/ Dichotomous
	Bother and prevalence of UI restricted to gymnasts having SUI training less or more than 15 hours per week	Baseline (Oct 2022) + after intervention (June 2023)	Continuous/ Dichotomous

5.2 Analysis Methods

5.2.1 Publication 1

The outcomes prevalence of overuse injuries (primary outcome) and prevalence of substantial overuse injuries (secondary outcome) will be analyzed with multilevel mixed effect logistic regression models. The models will be fitted with outcome data from all time points (Nov, Dec, …, June) except the baseline (Oct). The models will have a fixed effect for group (intervention vs control) and two random intercepts: gymnast and club, with gymnast nested within club. Based on the fitted model, we will present the odds ratio (OR) for injury (with 95% confidence interval [CI]) for intervention vs control and the P-value for the null hypothesis of an OR = 1.

The observed prevalence of injuries (with 95% CI) for each time point (Oct, Nov, …, June) for the primary outcome and the secondary outcome I) and II) will be presented in a figure.

Self-experienced effect and progress is measures on a -5 to 5 scale and only measured after end of the intervention (June) and only for the gymnasts in the intervention group. We will present the observed number and percentage of responses in each category (-5, -4, …, 4, 5) and also the mean and standard deviation of the responses.

5.2.2 Publication 2

Bother of UI (primary outcome) at the end of the intervention (June) will be analyzed with linear regression, with the June measurement as the dependent variable and group (intervention vs control) and the baseline (Oct) measurement as independent variables (ANCOVA). The standard errors in the model will be adjusted for the clustering of gymnasts within clubs. We will present the mean and standard deviation of the baseline and end-of-intervention measurements for each group and the estimated between-group difference in changes from baseline to end-of-intervention with a 95% CI. We will also give the P-value for the null hypothesis of a zero between-group difference.

The prevalence of UI (secondary outcome) at the end of the intervention (June) will be analyzed with a mixed effect logistic regression model with the June measurement as dependent variable and group (intervention vs control) and the baseline (Oct) measurement as independent variables. The model will contain a random intercept for club to account for the clustering of gymnasts within clubs. We will present the observed prevalence of UI for each group for each of the two time points, the OR for UI (with 95% CI) for intervention vs control and the P-value for the null hypothesis of an OR = 1.

Self-experienced effect and progress will be analyzed as described in section 5.2.1.

5.2.3 Sensitivity analyses

A sensitivity analysis of the prevalence of injuries (primary outcome in publication 1) will be performed with a mixed effect logistic regression model where only the June measurement is used as an outcome. The model will have a fixed effect for group (intervention vs control) and a random intercept for club to account for the clustering of gymnasts within clubs.

A sensitivity analysis of the bother of UI (primary outcome in publication 2) will be performed with a quantile (median) regression model with the June measurement as dependent variable and group (intervention vs control) and the baseline (Oct) measurement as independent variables.

6   Statistical Software

All statistical analyses will be done in Stata version 17 (StataCorp LLC, College Station, TX, USA).

7   References

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