STATISTICAL ANALYSIS PLAN for TASKSHIFT

Administrative information:

Sponsor name	Norwegian research council
Sponsor address	Diakonhjemmet Hospital Postboks 23 Vinderen 0319 Oslo Norway
EudraCT number / REC no	2017/742/REK sør-øst A
Trial title	A randomized controlled non-inferiority trial to evaluate the safety and effectiveness of osteoarthritis management by occupational therapists compared to management by rheumatologists: The TASKSHIFT study
Trial ID	TASKSHIFT in HOA. ES638040 Project Number: 300823
Trial registration number	NCT03102788 https://clinicaltrials.gov/ct2/show/NCT03102788?term=Kjeken&draw=2&rank=1

SAP and protocol version:

SAP version and date:	This SAP is version 2.0, and has been written based on Gamble C, et al. *Guidelines for the content of statistical analysis plans in clinical trials* (1).
Protocol version	This document has been written based on information contained in Kjeken I, et al. *Task shifting in the care for patients with hand osteoarthritis. Protocol for a randomized controlled non-inferiority trial* (2).

SAP revision history:

Protocol version	SAP version	Section number changed	Description and reason for change	Date changed
1.0	2.0	NA	The Statistical Analysis Plan (SAP) for the Randomized Controlled Trial (RCT)	19 June 2024

			was revised due to the identification of certain ambiguities and the need to incorporate additional analyses. Upon review, several sections of the initial SAP lacked clarity, which could potentially affect the interpretation and reproducibility of the study results. To ensure comprehensive and precise documentation, these sections were refined. Furthermore, to address emerging research questions and enhance the robustness of the study outcomes, supplementary analyses were deemed necessary and included in the updated SAP. This revision aims to improve the overall quality and integrity of the trial's data analysis process.	
1.0	1.0	NA	Original file	30 Mai 2022
NA	NA			

SIGNATURE PAGE

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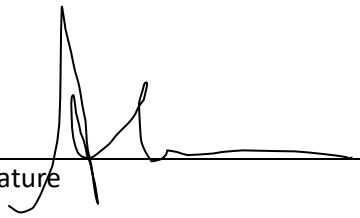

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ABBREVIATIONS

OA	Osteoarthritis
OT	Occupational Therapist
QALY	Quality-adjusted life years
ICER	Incremental cost-effectiveness ratio

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1 Introduction

1.1 Background and rationale

The availability of specialist health care is limited, and thus efficient management of available resources is needed. A promising approach for improving resource management is task shifting, where tasks are delegated from specialists to allied health professions. Tasks suitable for delegation need to be identified and the safety, effectiveness and cost efficiency of task shifting evaluated. This study evaluates the suitability of shifting the management of hand osteoarthritis (OA) from rheumatologist to occupational therapy (OT) specialists through a randomized controlled non-inferiority trial.

1.2 Trial Objectives

1.2.1 Primary Objective

The primary objectives of this study are to assess whether OT-led hand OA care is non-inferior to rheumatologist-led OA care with regards to the proportion of patients with disease improvement 6 months after the study visit, and whether OT-led hand OA care is more cost effective than rheumatologist-led care.

1.2.2 Secondary Objectives

To assess the characteristics of patients with hand OA referred to specialist health care with regards to a) joint affection, b) disease activity, c) symptoms and d) function as well as demographic features.

To identify predictors for symptom improvement 6 and 12 months after baseline.

1.2.3 Exploratory Objectives

To identify predictors for treatment response 6 and 12 months after baseline.

2 Trial Methods

2.1 Trial Design

The TASKSHIFT study is designed as a randomized, controlled, multi- center, single-country, non-inferiority comparative study. Management allocation is a 1:1 ratio. Patients are randomised to either OT-led or rheumatologist-led care.

2.2 Randomisation

Eligible patients are allocated in a 1:1 ratio between OT-led and rheumatologist-led care, using two computer-generated randomization lists with a block size of 10, one for each participating center.

The randomization process is described in full within the clinical trial protocol. Details of the randomization including the final random allocation list are held securely and unavailable to unauthorized trial personnel.

2.3 Sample size

Based on an extensive literature review (Table 1), we have conservatively estimated the six-month response rate for rheumatologist-led care to be 35%. Responders are defined according to the OMERACT-OARSI criteria (3).
The non-inferiority margin is set to 15 percentage points. To ensure adequate statistical power, a sample size of 400 patients (200 per arm) is required. This calculation assumes 80% power that a two-sided 95% confidence interval will demonstrate that OT-led care is not more than 15 percentage points inferior to rheumatologist-led care, given a response rate of 35% in both groups.
An assumed drop-out rate of 20% has been included in the sample size determination, based on observed attrition rates in comparable studies, typically ranging from 20% to 25%. Randomization will be stratified by center to account for inter-site variability.
More detailed information is available in the study protocol (2).

Publication	Type of intervention	Control group	Proportion of responders (intervention/control)			
			4 weeks	3 months	6 months	12 months
Østerås 2014 (4)	Hand exercises	Treatment as usual		46 % / 16%	30% / 28%	
Hennig 2015 (5)	Hand exercises	Treatment as usual		43% / 6%		
Dziedzic 2015 (6)	Joint protection	No joint protection		28% / 22%	42% / 27%	34% / 27%
Dziedzic 2015 (6)	Exercises	No exercises		26% / 24%	36% / 32%	38% / 34%
Wenham 2012 (7)	Prednisolone	Placebo	57% / 57%			

Table 1: Overview of the literature review used to estimate the expected number of responders.

2.4 Statistical Framework

2.4.1 Hypothesis Test

This trial is designed to assess the non-inferiority of OT-led OA management compared to rheumatologist-led OA management with regards to disease improvement based on OMERACT/OARSI responder criteria (3) measured 6 months after the study visit.

The primary hypothesis test is:

- Null hypothesis: The probability of a patient fulfilling the OMERACT/OARSI responder criteria (3) at 6 months with OT-led management is at-least 15 percentage points below that of rheumatologist-led management.
- Alternative hypothesis: The probability of a patient fulfilling the OMERACT/OARSI responder criteria (3) at 6 months with OT-led management is no more 15 percentage points below that of rheumatologist-led management.

2.4.2 Additional analysis

This trial will also compare the cost effectiveness of OT-led OA management compared to rheumatologist-led OA management.

2.4.3 Decision Rule

Non-inferiority of treatment response rate is claimed if the null hypothesis is rejected on the significance level (alpha) of 0.025 (one-sided). That is, if the upper limit of the two-sided 95% confidence interval for the treatment difference (probability of response under RT minus OT management) is less than 15%.

2.5 Statistical Interim Analyses and Stopping Guidance

There will be no interim analyses in this trial.

2.6 Timing of Final Analysis

The main analysis is planned when all patients have concluded 182 days post baseline, all data have been entered, verified and validated and the primary database has been locked.

2.7 Timing of Outcome Assessments

Outcomes are assessed at a second visit 6 months after the primary visit. Additionally, they are reassessed via a mailed questionnaires 12 months after the primary visit.

Visit Label	Target Day	Definition (Day window)
V1. Screening	Day – 21 (app 3 weeks before BL assessment)	Day - 21

V1. Randomisation	Day – 21 (by project leader who randomised the participant and booked an appointment at either rheumatologist or OT, thereafter put the allocation information in a closed and sealed envelope, which was opened by the Research assistant after baseline assessment)	Day - 21
V1. Baseline	Day 0 Baseline assessment	Day 0
V2 Follow-up Last study visit	Day 182 Main outcome measurement timepoint	
Mail Follow-up	Day 364	

3 Statistical Principles

3.1 Confidence Intervals and p-values

See section 2.4

3.2 Adherence and Protocol Deviations

3.2.1 Adherence to Allocated Treatment

Only participation in the primary visit is registered as adherence, it is not registered whether suggestions/instructions are adhered to.

Non-adherence is defined as not participating in visit 1, and will be presented in the CONSORT diagram.

3.2.2 Protocol Deviations

Given the definition of adherence, no protocol deviations after visit 1 are registered. Please see the study protocol (2) for details regarding study design.

3.3 Analysis Populations

The Enrolled set will include all patients who have provided informed consent, have been included into the study data base, randomly assigned to one of the two groups and completed the first visit. Given the study design, the Enrolled set will be equal to the Full Analysis Set (FAS).

4 Trial Population

4.1 Screening Data, Eligibility and Recruitment

The total number of screened patients and reasons for not entering the trial will be summarised and tabulated.

A CONSORT flow diagram (details in study protocol (2)) will be used to summarise the number of patients who were:

- assessed for eligibility at screening
- eligible at screening
- ineligible at screening*
- eligible and randomised
- eligible but not randomised*
- received the randomised allocation
- lost to follow-up* 6 months
- lost to follow-up* 12 months

*reasons will be provided.

4.2 Withdrawal/Follow-up

The status of eligible and randomised patients at trial end will be tabulated by group according to

- completed intervention and assessments
- withdrew consent
- lost to follow-up

This will be presented in the CONSORT diagram.

4.3 Baseline Patient Characteristics

The patient demographics and baseline characteristics to be summarised include age in years, gender, marital status, education, occupational status, BMI, number of interphalangeal joints with bony enlargements, degree of hand OA (based on radiological assessment using the Kellgren Lawrence method), function, hand strength, duration of symptoms, comorbidities and medication, laboratory inflammation markers as well as site of treatment.

Patient demographics and baseline characteristics will be summarised by randomised treatment arm and overall using descriptive statistics (N, mean, standard deviation, median, 25/75 percentiles, minimum, and maximum) for continuous variables, and number and percentages of patients for

categorical variables. Any clinically important imbalance between the treatment groups will be noted.

5 Analysis

5.1 Outcome Definitions

5.1.1 General Definitions and Derived Variables

5.1.1.1 Gender

Dichotomized as “male/female”.

5.1.1.2 Age

Age in years

5.1.1.3 Education

Dichotomized into less than/more than 12 years.

5.1.1.4 Civil status

Living alone “yes/no”.

5.1.1.5 BMI

Body Mass Index (BMI) = Body weight in kilograms divided by the square of the height in meters.

5.1.1.6 Function

Based on the MAP-hand questionnaire. A mean score is calculated from the answers, at least 15 of 18 items must be answered

5.1.1.7 Analgetics

Dichotomized to “Usage yes/no”

5.1.1.8 Duration of symptoms

Duration in years

5.1.1.9 Occupation status

Dichotomized to “Is working yes/no”.

5.1.1.10 Average hand strength

Mean score for left and right hand separately, units are given in kg.

5.1.1.11 Number of painful joints

Sum score of both hands combined, has a maximum score of 30.

5.1.1.12 Number of joints other than hand affected by OA

Dichotomized into “yes/no”.

5.1.1.13 Comorbidities

Dichotomized into “yes/no” (Yes = one or more comorbidities).

5.1.1.14 Hospital

Which of the participating sites the patient was allocated to, coded as 1 or 2.

5.1.1.15 QALY

Quality-adjusted life years, calculated based on scores in the utility measure EQ-5D-5L.

5.1.2 Primary Outcome Definitions

The primary outcome treatment effectiveness will be defined as OMERACT/OARSI response (3) coded as yes/no. The outcome regarding cost efficiency will be defined using the utility measure EQ-5D-5L. Both scores are described in detail in the study protocol (2).

5.1.3 Secondary Outcomes Definitions

The number of painful joints, function (measured by the MAP-hand questionnaire) and hand strength (measured by JAMAR dynamometer) will be reported at baseline and 6 months. Information about adverse events will be collected from patients' medical records and used in the evaluation of safety.

5.1.4 Overview of Outcomes

Level	Outcome	Timeframe	Type
Primary	OMERACT/OARSI response (3)	182/364 days	Dichotomous
	EQ-5D-5L (8)	182/364 days	Discrete/Continuous
Safety	Adverse events	182 days	Discrete

5.2 Analysis Methods

5.2.1 Primary Outcome

5.2.1.1 Primary Analysis

For the analysis of the primary outcome, a logistic regression with treatment provider as independent and OMERACT/OARSI responder classification (3) as dependent variable will be conducted, adjusting for treatment center (the stratification factor used in the randomization). Response probability as well as risk difference will be calculated using the adjusted risk and risk difference estimators (9) using bootstrapping to estimate standard errors to form normal based 95%

confidence intervals. As a sensitivity analysis, an analysis will also be carried out adjusting for baseline pain, disease activity and function.

5.2.1.2 Additional analysis

For the analysis of cost-effectiveness, the total cost-effectiveness will be calculated as total health effect of the two strategies. The outcome of interest is the incremental cost-effectiveness ratio (ICER), which is defined by the incremental cost (ΔC = cost OT-led OA management – cost of rheumatologist-led OA management) per incremental QALY (ΔU = QALYs with OT-led OA – cost of rheumatologist-led OA). If the cost-per-QALY of the ICER is less than the cost-effectiveness acceptability threshold, the OT-led OA management may be considered a cost-effective alternative to the rheumatologist-led OA management. This criterion is usually summarised in the net-monetary benefit static:

(1) NMB = W*ΔU- ΔC, where W is the acceptability threshold value, and ΔU is the incremental utilities/QALYs gained and ΔC is the incremental cost. If the NMB is positive (NMB > 0), the new programme is considered to have acceptable cost-effectiveness for the decision maker, otherwise not.

As there is no current official acceptability threshold value (W), we will follow the approach of the Norwegian Medicines Agency (10) to calculate an absolute prognosis loss for the patients under the current treatment strategy. This static has been discussed in the official White Paper on priority setting and is often used as a proxy for the upper limit of willingness to pay per QALY, also known as the cost-effectiveness acceptability threshold.

Healthcare costs are a function of resource use and the unit cost of those resources. In this study, resource use is defined as the number and type of contact with healthcare personnel, administered treatment (such as injections or surgical interventions) and assistive devices, patient education and exercise options as well as work absence, taking a healthcare perspective. We will use official tariffs and rates as unit costs in valuing the resource use.

To calculate QALYs, we follow the recommended approach by the Norwegian Directorate of Health (11). The patients' description of their own health is taken from the collected EQ-5D data. These scores are subsequently weighted with preference weights from the general population. In the absence of a survival-effect from treatment, the calculated utility of health will serve as the measure of the QALY.

Finally, we will use non-parametric bootstrapping to assess the degree of uncertainty around the likelihood of cost-effectiveness (12). This allows assessing uncertainty without having to impose parametric assumptions on our highly skewed data. We will perform 10,000 bootstrap samples with replacement of the sample outcomes. For each bootstrapped sample replica, we calculated the net monetary benefit (1) using the assumed acceptability threshold (W). The likelihood of cost-effectiveness will then be calculated as the proportion of all bootstrapped samples in which OT-led OA management conferred a positive net monetary benefit.

5.2.1.3 Summary Measures

See 5.1.1

5.2.1.4 Assumption Checks and Alternative Analyses

A logistic regression includes the following assumptions:

- Binary dependent variable: This assumption is fulfilled via the study design.
- Independence: This assumption is fulfilled via the study design.
- No severe multicollinearity: This assumption is fulfilled via the study design.
- Sufficient number of observations: We are expecting a rate of approximately 35% responders, which would provide a sufficient number of patients per group.

5.2.1.5 Missing Data

We are expecting the amount of missing data to increase with time, but we cannot retrace the individual reasons for missingness. The primary analysis will be based on complete case analysis, whereas the cost-efficiency analysis will utilize imputation.

5.2.1.6 Sensitivity Analyses

If deemed necessary, sensitivity analyses will be conducted to address missing data, if needed also on subgroup data. Further, analyses adjusted for baseline status of disease activity, pain and function will be conducted to evaluate a possible effect on response rate within the two treatment arms.

5.2.1.7 Subgroup Analyses

No subgroup analyses are planned outside of the sensitivity analyses.

5.2.2 Continuous Secondary Outcomes

5.2.2.1 Main Analysis

To identify clinically relevant predictors for symptom improvement 6 and 12 months after baseline, we will fit a regression model and select variables based on standardized beta-values as well as clinical usefulness based previous research and clinical relevance.

5.2.2.2 Summary Measures

See 5.1.1

5.2.2.3 Assumption Checks

Regression models entail four key assumptions:

- Independence: Given the study design, we are confident that this assumption is met.
- Linear relationship: If this assumption is violated, we will apply a logarithmic transformation.
- Normality: If this assumption is violated, we will apply a logistic transformation

- Homoscedasticity: If this assumption is violated, we will apply a logistic transformation to the dependent variable or explore alternative options depending on the data characteristics.

5.2.2.4 Missing Data

Same as 5.2.1.4

5.2.2.5 Sensitivity Analyses

Same as 5.2.1.5

5.2.2.6 Subgroup Analyses

Same as 5.2.1.6

5.2.3 Additional Analyses

5.2.3.1 Exploratory Analyses

The following additional, hypothesis-generating exploratory analyses will be conducted in addition to the above-stated analyses. If during the course of the data analyses additional questions will be raised, we will add them to this list of exploratory analyses.

1) To explore the potential influence of disease activity on treatment response, we will compare participants with erosive hand OA to those with less active inflammation, as defined by Xray scorings. Comparative analyses as well as additional regression models will be calculated for this.
2) To explore associations between different disease-related factors, we will investigate the relationships between various factors using correlation analyses.
3) To understand the disease trajectory of the participants, we will explore time and treatment dependent changes in different disease-related factors and compare these between the groups using comparative statistics and regression models.

6 Safety Analyses

6.1 Adverse Events/Safety

The main considerations in this study relate to safety and non-inferiority. Since this study does not include novel interventions, we are not expecting any adverse events connected to the study design. We will therefore focus on the safety aspects of the two treatment approaches and evaluate them in

the health economics section of the analysis. For both groups the healthcare usage (including additional contact to healthcare professionals as well as supportive devices) related to hand OA between baseline and six months as well as twelve months will be registered, compared and used to evaluate cost-effectiveness.

6.2 Clinical Laboratory Parameters

Standard clinical laboratory parameters were collected and assessed at baseline, but only used to verify that exclusion criteria were not met. Clinical laboratory parameters will be summarised by treatment group and time point.

7 Statistical Software

All data handling and statistical analyses will be performed using Stata (*StataCorp. 2015. College Station, TX, USA*), R (*R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)* as well as Microsoft Office.

8 References

8.1 Literature References

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8.2 Reference to Data Handling Plan

The data handling plan is only available in Norwegian and has been sent to the Norwegian research council in conjunction with the original funding application. A summary in English is given in the study plan (2).

8.3 Reference to the Trial Master File and Statistical Documentation

The Statistical Documentation contain a copy of the Trial Master File and is stored on the research server at Diakonhjemmet Hospital with access restricted to the researchers that need the data to perform the statistical analyses.

As agreed with the Norwegian Regional Committee for Medical Research Ethics (2017/742/REK sør-øst A), the data will be stored deidentified in the project period, which ends 31.12.2023, after which it will be stored anonymized or deleted.

The data protection officers at Diakonhjemmet Hospital have ensured that the study comply with the requirements in the General Data Protection Regulation, (2020/00184).

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