STATISTICAL ANALYSIS PLAN for HAPPY HANDS

Administrative information:

Sponsor name	Diakonhjemmet Hospital
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REC no	477746
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SIGNATURE PAGE

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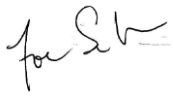

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ABBREVIATIONS

AE	Adverse event
BMI	Body Mass Index
CONSORT	Consolidated Standards of Reporting Trials
eHEALS	The eHealth Literacy Scale
EQ-5D-5L	EuroQol
HOA	Hand osteoarthritis
ICER	incremental cost-effectiveness ratio
MAP-Hand	Measure of Activity Performance of the Hand
NSAIDs	Non-Steroid Anti-Inflammatory Drugs
NRS	Numeric rating scale
OA	Osteoarthritis
OMERACT	Outcome Measures in Rheumatology (Outcome Measures in Rheumatoid Arthritis Clinical Trials)
OARSI	Osteoarthritis Research Society International
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
REK	Regional committee
SAE	Serious adverse event
SUS	System Usability Scale
TSD	Services for sensitive data (Tjeneste for sensitive data)

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1. Introduction

1.1 Background and rationale

Osteoarthritis (OA) is a prominent cause of years lived with disability worldwide [1]. The hand is one of the most commonly affected sites [2] with a lifetime risk of 50% in women and 25% in men for developing hand OA (HOA) [3]. There are no disease-modifying drugs that can cure HOA. Patient education, hand exercises, and assistive devices are the core treatments, while Non-Steroid Anti-Inflammatory Drugs (NSAIDs) can be used for a limited duration to relieve symptoms [4]. Surgery should only be considered if other treatment modalities are ineffective [4]. Core treatment should primarily be provided in primary healthcare, however, research shows that the quality-of-care of OA-services in general is sub-optimal [5], and in particular for people with HOA [6,7].

The use of eHealth is highlighted for self-management and better exploitation of healthcare resources [8]. An observational study suggests that digital delivery of core treatment could be a viable option in people with HOA [9], however, large methodologically sound trials of effect and cost-effectiveness are lacking [10].

In 2020, development of the Happy Hands app was initiated at Diakonhjemmet Hospital, Norway [11], with an overarching goal of delivering a standalone intervention that supports and empowers people with HOA to self-manage their disease, regardless of where they reside [11]. Feasibility of the app has been tested in 71 patients with HOA with promising results [12], and there is now a need to test the app in an RCT to assess the effect and cost-effectiveness.

1.2 Trial Objectives

1.2.1 Primary Objective

The primary objective of this study is to assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective compared to usual care alone in patients with HOA with regards to the **probability of OMERACT/OARSI response** at **3 months**.

1.2.2 Secondary Objectives

Key secondary objectives are:

- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective compared to usual care alone in patients with HOA with regards to the **probability of OMERACT/OARSI response** at **6 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is **cost-effective** compared to usual care alone in patients with HOA at **6 months**.

- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in pain** at **3 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in hand function** at **3 months.**

Other secondary objectives are:

- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in grip strength** at **3 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in quality of care** at **3 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in disease activity** at **3 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in pain** at **6 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in hand function** at **6 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in grip strength** at **6 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in quality of care** at **6 months**.
- To assess whether a 12-week self-management intervention delivered through the Happy Hands app in addition to usual care is more effective than to usual care alone in patients with HOA with regards to **change in disease activity** at **6 months**.

1.2.3 Exploratory Objectives

- To assess the adherence, satisfaction and usability of the Happy Hands
- To identify factors associated with being an OMERACT/OARSI responder at 3 and 6 months

- To identify factors associated with adherence to the self-management intervention delivered through the Happy Hands app.

2. Trial Methods

2.1 Trial Design

The Happy Hands study is designed as a pragmatic, open-labelled, 2-armed, randomized, controlled, multicenter, single-country trial. Participants are randomly allocated to either usual care (control group) or usual care combined with use of the Happy Hands app across a 12-weeks period (intervention group).

2.2 Randomization

Eligible patients are allocated in a 1:1 ratio between control group and intervention group through electronic questionnaires using Nettskjema. Through a build-in Javascript based randomization module, participants are randomly allocated by being forwarded from one questionnaire (the consent form) to one of two baseline questionnaires; one for the control group and one for the intervention group. These questionnaires are identical except for some questions being omitted in the baseline questionnaire for the intervention group as these are answered in the app. After answering the baseline questionnaire, the participants are forwarded to yet another questionnaire, informing them about group allocation. The intervention group is forwarded to yet another questionnaire where they are provided with the link to download the Happy Hands app. Patients (and healthcare provider) are blinded to group allocation until the patient has answered the baseline questionnaire, after that there is no possibility to blind neither patient nor healthcare provider.

The randomization is stratified by recruitment site. A total of 20 sites will recruit participants, thus, altogether 20 identical consent forms, and 20 identical baseline questionnaires for the control group and the intervention group, respectively, have been generated in Nettskjema. Examples of the randomization procedure is provided in Figure 1A and 1B.

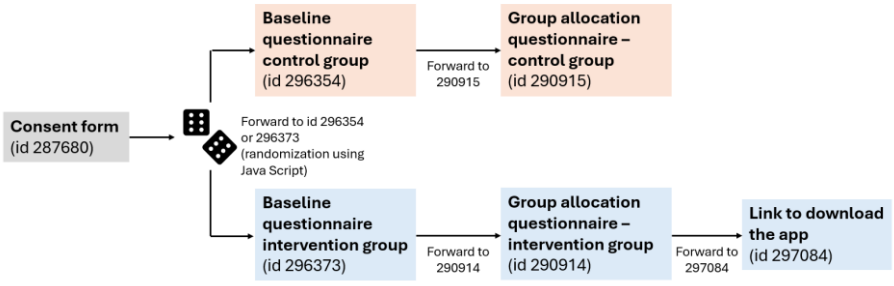

Figure 1A: Example of randomization process for recruitment site 1

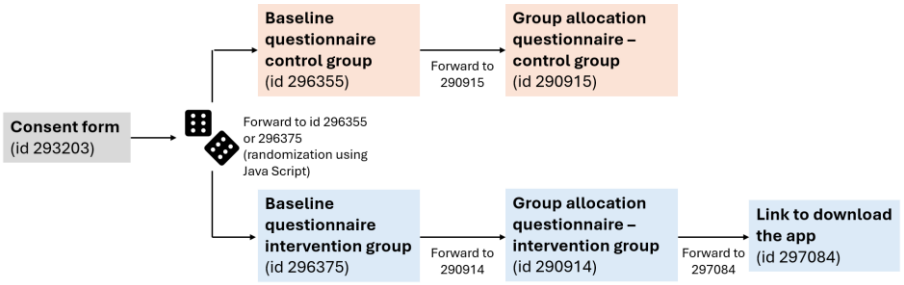

Figure 1B: Example of randomization process for recruitment site 2.

The group allocation questionnaires and the questionnaire containing link to downloading of the app are the same for all recruitment sites as the randomization has been conducted prior to being forwarded to these questionnaires.

2.3 Sample size

The sample size is calculated based on the primary outcome (proportion of OMERACT-OARSI responders) measured at 3 months. An OMERACT-OARSI responder rate between 26-46% is previously shown in hand exercise groups compared to 6-24% in usual care groups [13,14]. The between-group difference in primary outcome is estimated to 20% [15]. To account for multiple testing (primary and key secondary hypotheses), we will use a significance level of 1%, and 90% power. With a between-group difference of 20% and a usual care responder rate of 20%, we need to include 150 patients in each group. To account for a possible drop-out rate of 25% due to the digital nature of the study, a total of 376 patients are needed.

More detailed information is available in the study protocol [12].

2.4 Statistical Framework

2.4.1 Hypothesis Test

This trial is designed to assess if using the Happy Hands app in addition to usual care is superior to usual care alone with regards to probability of OMERACT/OARSI response at 3 months.

- The primary null hypothesis posits that there is no difference in probability of OMERACT/OARSI response between Happy Hands in addition to usual care compared to usual care alone at 3 months.

- The primary alternative hypothesis is that using the Happy Hands app in addition to usual care is superior to usual care alone with regards to probability of OMERACT/OARSI response at 3 months.

2.4.2 Secondary hypotheses

Key secondary hypotheses:

a) To assess the effect of using the Happy Hands app in addition to usual care compared to usual care only with regards to probability of OMERACT-OARSI response at 6 months.
   - The null hypothesis posits that there is no difference in probability of OMERACT/OARSI response between using Happy Hands in addition to usual care compared to usual care alone at 6 months.
   - The alternative hypothesis is that using Happy Hands in addition to usual care is superior to usual care alone with regards to probability of OMERACT/OARSI response at 6 months.

b) To assess the cost-effectiveness of using the Happy Hands app in addition to usual care compared to usual care alone at 6 months.
   - The null hypothesis is that the Happy Hands intervention is not cost-effective compared to usual care alone at 6 months.
   - The alternative hypothesis is that using the Happy Hands app is cost-effective compared to usual care alone at 6 months.

c) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in pain from baseline to 3 months.
   - The null hypothesis is that there is no difference in change in pain from baseline to 3 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
   - The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in pain from baseline to 3 months follow-up compared to usual care alone.

d) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in function from baseline to 3 months.
   - The null hypothesis is that there is no difference in change in function from baseline to 3 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
   - The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in function from baseline to 3 months follow-up compared to usual care alone.

Additional secondary hypotheses:

a) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in grip strength from baseline to 3 months.

- The null hypothesis is that there is no difference in change in grip strength from baseline to 3 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
- The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in grip strength from baseline to 3 months follow-up compared to usual care alone.

b) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in disease activity from baseline to 3 months.
   - The null hypothesis is that there is no difference in change in disease activity from baseline to 3 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
   - The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in disease activity from baseline to 3 months follow-up compared to usual care alone.

c) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in quality of care from baseline to 3 months.
   - The null hypothesis is that there is no difference in change in quality of care from baseline to 3 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
   - The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in quality of care from baseline to 3 months follow-up compared to usual care alone.

d) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in pain from baseline to 6 months.
   - The null hypothesis is that there is no difference in change in pain from baseline to 6 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
   - The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in pain from baseline to 6 months follow-up compared to usual care alone.

e) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in function from baseline to 6 months.
   - The null hypothesis is that there is no difference in change in function from baseline to 6 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
   - The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in function from baseline to 6 months follow-up compared to usual care alone.

f) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in grip strength from baseline to 6 months.
   - The null hypothesis is that there is no difference in change in grip strength from baseline to 6 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.

- The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in grip strength from baseline to 6 months follow-up compared to usual care alone.

g) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in disease activity from baseline to 6 months.
   - The null hypothesis is that there is no difference in change in disease activity from baseline to 6 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
   - The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in disease activity from baseline to 6 months follow-up compared to usual care alone.

h) To assess the effect of using the Happy in addition to usual care compared to usual care alone on the change in quality of care from baseline to 6 months.
   - The null hypothesis is that there is no difference in change in quality of care from baseline to 6 months follow-up between using Happy Hands in addition to usual care compared to usual care alone.
   - The alternative hypothesis is that using the Happy Hands app in addition to usual care in more effective regarding change in quality of care from baseline to 6 months follow-up compared to usual care alone.

2.4.3 Other objectives

Other objectives are considered to be supportive or exploratory, thus, they are not subject to hypothesis testing.

2.4.4 Decision Rule

For the primary outcome, superiority of probability of OMERACT/OARSI response is claimed if the null hypothesis is rejected at the significance level (alpha) of 0.01 (Bonferroni corrected due to multiple testing of one primary and four key secondary hypotheses; 0.05/5= 0.01. The result is deemed clinically relevant if the lower limit of the 95% confidence interval is more than 20% (see figure 2).

A significance level of <0.01 will also be used for the four key secondary hypotheses due to multiple testing.

For the additional secondary outcomes, multiple testing adjustment will not be carried out. The listed hypotheses will be assessed by their (unadjusted) p-values though no formal acceptance/rejection of these hypotheses will be done.

The intervention will be considered cost-effective if the incremental cost effectiveness ratio is below the threshold for cost-effectiveness, recommended in Norway. In the health economic evaluation, we will not consider p-values or confidence intervals for the ICER but instead plot bootstrapped ICERs on the cost-effectiveness plane and calculate a cost-effectiveness acceptability curve [16].

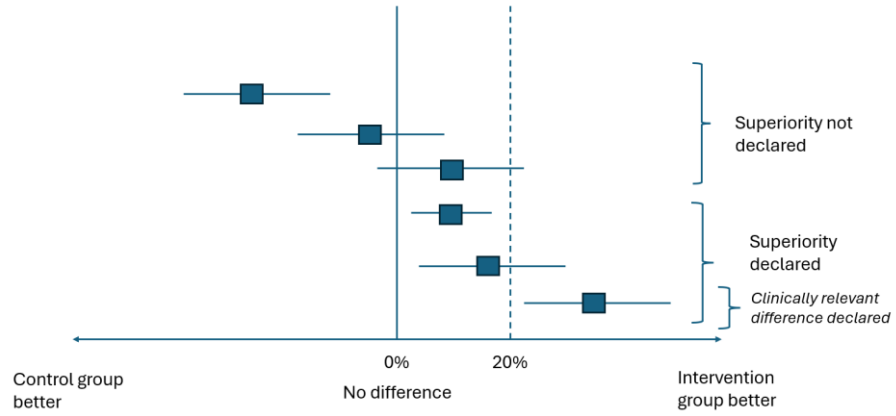

Figure 2: Visualization of superiority and clinically relevant difference.

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 are finished with the data collection, 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 baseline, 3 and 6 months. In addition, the intervention group will answer questionnaires as part of the Happy Hands app at a monthly basis and after each exercise session.

Visit Label	Target Day	Definition (Day window)
T0. Consent	The day they consult a healthcare provider at one of the recruitment sites	Day 0
T0. Randomization	After receiving information about the study, the participants are asked to sign a digital consent, thereafter the participants are randomly allocated to two groups based	Day 0

	on baseline questionnaire (see section 2.2.)	
T0. Baseline	Day 0 Baseline assessment	Day 0
T3. 3-months follow-up	Day 90 Follow-up (digital/face-to-face)	Day 90 +/- 45
T6. 6-months follow-up	Day 180 Follow-up (digital)	Day 180 +/- 45

3. Statistical Principles

3.1 Adherence and Protocol Deviations

3.1.1 Adherence to Allocated Treatment

e-self-management intervention:

Adherence will be evaluated by tracking the number of exercise and informational videos viewed, as well as the number of quizzes completed each week. Each time a participant watches a video or submits quiz answers; this activity will be recorded in Nettskjema. Participants will also document each instance of exercise completion in the app. Recognizing that not all participants will view the same exercise videos multiple times, adherence to the exercise regimen will be based on self-reported exercise completion. As there is no consensus regarding what constitute adequate adherence to hand exercises, the American College of Sports Medicine guidelines will be used [17]. Adherence to the exercise program will be considered adequate if participants compete ≥2 exercise sessions per week for a duration of least 8 weeks (67%)[18]. Adherence to information videos and quizzes will be deemed adequate if participants have watched 19 of 26 videos and completed 9 of 12 quizzes, corresponding to approximately 75% utilization.

Usual care:

Usual care will vary between the different recruitment sites, from nothing to a single consultation, information courses or adaptation of orthosis. Thus, all participants are considered to have received usual care.

3.1.2 Protocol Deviations

Not all recruitment sites have the possibility to summon the participants for a face-to-face follow-up consultation. Thus, there will be a deviation from the protocol regarding the assessment of follow-up grip strength.

3.2 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 baseline questionnaire.

The Full Analysis Set will be the same as the Enrolled set as the different questionnaires are linked together at baseline, thus, the patients will answer both consent, baseline questionnaire and be randomly allocated in one action.

The Per protocol set will include those who are deemed adherent based on the number of exercise session they have conducted and the number of informational videos they have seen.

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 (Figure 3) 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 3 months
- lost to follow-up 6 months

Reasons will be provided where possible.

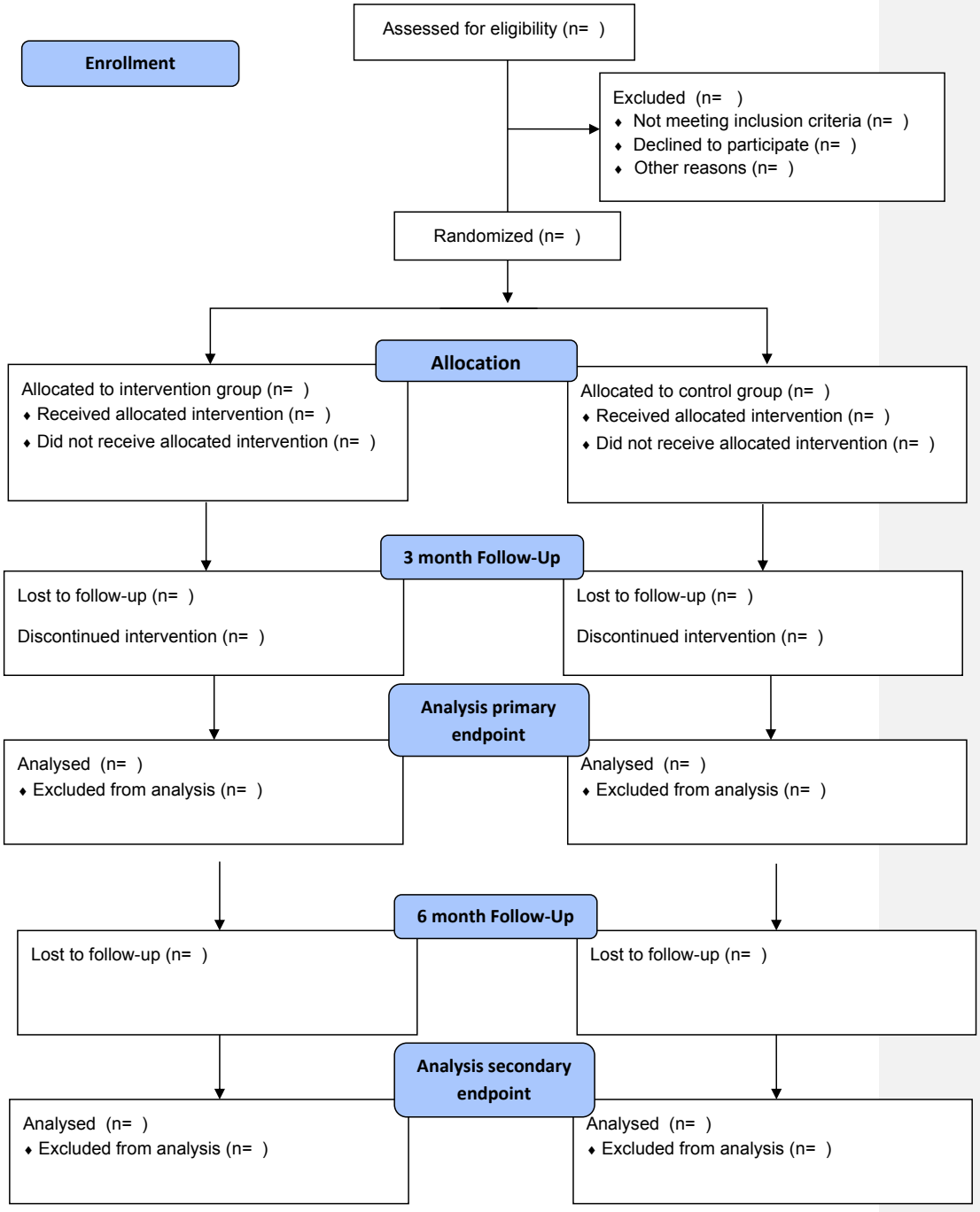

Figure 3 Flow chart

4.2 Withdrawal/Follow-up

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

- withdrawn 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, gender, living arrangement, education, occupational status, smoking, height and weight (calculated to BMI), most painful hand, other painful joints, previous treatment including surgery, medication, comorbidities, (e)Health literacy, joint mobility, pain at rest and in activity, disease activity, hand function, quality of care, health-related quality of life, motivation for exercising, grip strength.

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

Reported as age in years

5.1.1.2 Gender

Reported as male/ female/ other.

5.1.1.3 Living arrangements

Reported as living alone / living together with someone.

5.1.1.4 Education

Reported as elementary school / high school / college, university less than 4 years / college, university 4 years or more. Will be dichotomized into less than (elementary school/ high school) or more than (college, university) 12 years.

5.1.1.5 Occupation status
Reported as working fulltime / working parttime / fulltime sick leave / parttime sick leave / retired / disability benefit / work assessment allowance / seeking work / unpaid, staying at home /student. Will be dichotomized to working/ not working.

5.1.1.6 Smoking
Reported as smoking/ smoking previously/ not smoking.

5.1.1.7 Height and weight (Body mass index, BMI)
Reported as body height (cm) and body weight (kg). Calculated as BMI = Body weight in kilograms divided by the square of the height in meters.

5.1.1.8 Most troublesome joint
Reported as left hand/ right hand/ both hands/ none of the hands.

5.1.1.9 Other troublesome joints
Reported as right hip/ left hip/ right knee/ left knee/ right ankle or foot/ left ankle or foot. Will be summarized into number of other troublesome joints (0-6)

5.1.1.10 Previous treatment
Reported as having received previous treatment (yes/no) and a description of the treatment if reporting yes. Additionally, reported as previously having hand surgery (yes/no), and if yes, with hand (right/ left / both).

5.1.1.11 Medication
Reported as using medication due to hand OA (yes/no), with description of type and dose if answering yes.

5.1.1.12 Comorbidities
Reported as any problems affecting health (yes/no) for the following reasons: high blood pressure/ angina, infarction, other heart disease/ asthma, bronchitis, other lung disease/ allergy, eczema/ sciatic pain/ stroke, cerebral haemorrhage/ cancer/ neurological disease/ diabetes/ metabolic disease/ mental disease/ kidney disease/ liver disease/ ulcer, other stomach disease/ anaemia. Summarized as having comorbidity (yes/no), and number of comorbidities (0-15).

5.1.1.13 (e)Health literacy
Measured by eHEALS [19,20], consisting of eight statements answered on 5-point scale (from “totally agree” to “totally disagree”) with a total score ranging from 8 to 40 (higher score representing higher health literacy). Additionally, the participants are asked about their knowledge/experience with using technology and digital services like smartphone, tablets, apps, video consultation, and digital services (Helsenorge.no). The knowledge/experience with using measured on a 5-point scale (very poorly to very good) with an additional alternative of 'never tried'

5.1.1.14 Joint mobility
Measured using a numeric rating scale (NRS) from 0 to 10 with 0 being very good joint mobility. Reported separately for left and right hand. In baseline, 3- and 6-month questionnaires, the

participants are asked to rate their pain the last week. In the Happy Hands app, the participants are asked to rate their pain after exercising.

5.1.1.15 Pain

Measured using an NRS from 0 to 10 with 0 being no pain. Reported separately for right and left hand at rest and in activity. In baseline, 3- and 6-month questionnaires, the participants are asked to rate their pain the last week. In the Happy Hands app, the participants are asked to rate their pain after exercising.

5.1.1.16 Disease activity

Measured using an NRS from 0 to 10 with 0 being no disease activity.

5.1.1.17 Hand function

Measured by the Measure of Activity of the Hand (MAP-Hand) questionnaire, containing 18 questions about problems with different activities (no problems/ some problems/ large problems /cannot perform). A mean score (from 1 to 4 with 1 being no problems) is calculated from the answers, with at least 15 of 18 items having to be answered for a valid score [21].

5.1.1.18 Quality of care

Measured by a modified version of the OsteoArthritis Quality Indicator questionnaire v2 [22], modified to hand OA. Containing 20 items related to treatment recommendations for hand OA, answered with yes/no/not relevant, do not have pain, do not remember. Scored as a pass rate (0-100%, with 100% being best quality of care), calculated as the number of yes-answers, divided by the total number of yes- and no-answers.

5.1.1.19 Health-related quality of life

Measured by EuroQol EQ-5D-5L [23], five items (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) scored at a 5-level scale ("no problems" to "unable to do"), calculated as a utility index 0-1, 1= best health-related quality of life. Visual analogue scale (EQ VAS), 0-100, 100= perfect health.

5.1.1.20 Grip strength

Maximum grip strength measured as the mean of two measures for left and right hand separately, using the JAMAR dynamometer. Grip strength is given in kg.

5.1.1.21 Motivation for exercising

Reported on an NRS from 0 to 10 with 0 being no motivation.

5.1.1.22 Costs

Costs connected to patient care pathways will be self-reported by the patient using open-ended questions.

5.1.2 Primary Outcome Definitions

The primary outcome will be defined as OMERACT/OARSI responder [24], which is a composite index reported as a single variable (yes/no) based on one of the two following criteria:

- High improvement on pain or function
  - ≥50% improvement + absolute change of ≥2 points in pain (NRS 0-10, 0=no pain), OR
  - ≥50% improvement + absolute change of ≥0.6 point in hand function (MAP-Hand 1-4, 1=no disability)
- Improvement in at least two of the three following
  - ≥20% improvement + absolute change of ≥1 points in pain (NRS 0-10, 0=no pain)
  - ≥20% improvement + absolute change of ≥0.3 point in hand function (MAP-Hand 1-4, 1=no disability)
  - ≥20% improvement + absolute change of ≥1 points in disease activity (NRS 0-10, 0=no disease activity)

5.1.3 Secondary Outcomes Definitions

Secondary outcomes are listed in Table 1.
For assessment of cost-effectiveness, we will use healthcare costs (as listed under Costs in Table 1) and scores from EQ-5D-5L calculated into a utility index.

5.1.4 Overview of Outcomes

Table 1 Primary and secondary outcomes

	Data collection instrument and scale	Timepoints
Primary outcome		
Probability of OMERACT-OARSI response	The responder classification is a composite index reported as a single variable (yes/no)	t0, mo, t3, t6
Secondary outcomes		
Hand pain at rest	Pain left/right hand last week, NRS 0-10, 0= no pain	t0, ex, mo, t3, t6
Pain in activity	Pain left/right hand last week, NRS 0-10, 0= no pain	t0, ex, mo, t3, t6
Stiffness	Stiffness left/right hand last week, NRS 0-10, 0= no stiffness	t0, ex, mo, t3, t6
Grip strength	Maximum grip strength, mean of two measures left/right hand, in kg using the JAMAR dynamometer	t0, t3
Activity performance of the hands (hand function)	Measured by the Measure of Activity Performance of the Hand (MAP-Hand); mean of 18 standardized activities, rating scale 1 ("no difficulty") to 4 ("cannot perform")	t0, mo, t3, t6
Health-related quality of life	Measured by EuroQol EQ-5D-5L, five items (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) scored at a five level scare ("no problems" to "unable to do"), calculated as an utility index 0-1, 1= best health-related quality of life. Visual analogue scale (EQ VAS), 0-100, 100= perfect health	t0, t3, t6
Global assessment of disease activity	Disease activity last week, NRS 0-10, 0=no disease activity	t0, mo, t3, t6
Global assessment of change	5-point Likert scale from "Much better" to "Much worse"	t3, t6
Quality of care	Modified version of the OsteoArthritis Quality Indicator questionnaire, 15 questions rated as yes/no/unsure or not applicable, scored as pass rate 0-100, 100=best quality of care	t0, t3, t6
Motivation for hand exercises	NRS 0-10, 10=highly motivated	t0, t3, t6

Hand exercises	Approximately number of exercise sessions each week for the last 3 months	t3, t6
Costs		
Healthcare use	Number of consultations with healthcare providers last 3 months	t3, t6
Medication use	Type and dosage last 3 months	t0, t3, t6
Hand surgery	Conducted hand surgery last 3 months (yes/no), if yes, reported sick leave due to hand surgery	t3, t6
Hospitalization	Number of hospital admissions	t3, t6
Medical equipment	Any medical equipment (i.e. hand orthoses, exercise equipment) bought last 3 months (type and cost)	t3, t6
Technical equipment	Any technical equipment (i.e. bread knife, jar key, sissors, electric toothbrush) bought last 3 months (type and cost)	t3, t6
Work status	Reported as yes/no on the following options: working, sick leave, retired, disability pension, work assessment allowance, unemployed, not working, student	t0, t3, t6
Use of the Happy Hands app *(intervention group only)*		
Usability	Measured by System Usability Scale (SUS), 10 statements scored on a 5-point scale from "strongly disagree" to "strongly agree"	t3, t6
Satisfaction with use of the app	NRS 0-10, 10=highly satisfied	t3, t6
Usefulness of the app	NRS 0-10, 10=highly useful	t3, t6
Adherence to hand exercises	Number of exercises conducted	t3, (t6)
Adherence to informational videos	Number of informational videos watched	t3, (t6)
Adherence to quizzes	Number of quizzes answered	t3
Continued use	Plans to continue using the app, measured as yes/no/unsure	t3, t6
Adverse events	Description of any complaints related to hand exercises	t3
Baseline characteristics		
Age	Years	t0
Gender	Female, male, other	t0
Living arrangement	Living alone, living together with someone	t0
Education	Elementary school, high school, university/college <4 years, university/college ≥ 4 years	t0
Smoking	No, previously, yes	t0
Height	Cm	t0
Weight	Kg	t0
Most troublesome hand	Left, right, both	t0
Other painful joints	Hip, knee, foot/ankle	t0
Previous treatment for HOA	Yes, no	t0
Previous hand surgery	Yes, no	t0
Comorbidities	High blood pressure, heart disease, lung disease, allergy, back pain, stroke, cancer, neurological disease, diabetes, metabolic disease, mental disease, kidney disease, liver disease, ulcer, blood disease	t0

Health Literacy	eHEALS, 5-point scale with a total score ranging from 8 to 40 (higher score representing higher health literacy)	t0
Experience with using technology and digital services	Experience with smartphone, tablets, apps, video consultation, and digital services (Helsenorge.no), measured on a 5-point scale (very poorly to very good) with an additional alternative of 'never tried'	t0
Motivation for digital treatment/follow-up	NRS 0-10, 10=to a large degree	t0

t0=baseline; t3=3 months; t6=6 months; ex=after each exercise session (in the app/intervention group only); mo=monthly (in the app/intervention group only); NRS=numeric rating scale; MAP-Hand=Measure of Activity Performance of the Hand; HOA=hand osteoarthritis

5.2 Analysis Methods

5.2.1 Primary Outcome

5.2.1.1 Primary Analysis

For analysis of the primary outcome a logistic regression with group as independent variable and OMERACT/OARSI response (yes/no) at 3 months as dependent variable will be conducted. The analysis will adjust for study center, the stratification factor used in the randomization. Probability of being a responder as well as risk difference will be calculated using the adjusted risk and risk difference estimators [25].

Kommentert [JS1]: Skal center justeres for? Vanlig å justere for stratifiseringsvariabler brukt i randomiseringen.

5.2.1.2 Additional analysis

Besides sensitivity analyses, no additional analyses are planned.

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 trough the study design. (OMERACT/OARSI responder criteria, calculated into a binary yes or no score).
- Independence: This assumption is fulfilled through the study design.
- No severe multicollinearity: This assumption is fulfilled through the study design.
- Sufficient number of observations: The sample size was calculated based on approximately 20% responders in the control group and 40% responders in the intervention group, which would provide 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 utilize multiple imputation, including variables such as gender, age, pain, function and disease activity at baseline and 3 months.

5.2.1.6 Sensitivity Analyses

For the primary endpoint, a sensitivity analysis will be carried out adjusting for recruitment site (, baseline pain, disease activity and function (which are the measures included in the OMERACT/OARSI responder criteria). Additional sensitivity analyses may be conducted, adjusting for variety in usual care (participating in osteoarthritis courses).

If deemed necessary, sensitivity analyses will also be conducted to address missing data and subgroup data.

5.2.1.7 Subgroup Analyses

No subgroup analyses are planned outside of the sensitivity analyses.

5.2.2 Secondary Outcomes

5.2.2.1 Secondary Analyses

a) OMERACT/OARSI responders at 6 months

For the secondary outcome of probability of OMERACT/OARSI response in the two groups at 6 months, we will conduct the same analysis as for the primary outcome.

Secondary continuous outcomes will be analysed using linear regression. The analyses will, in addition to randomization group, adjust for baseline level of the outcome and study center. Missing values will be handled using multiple imputation.

b) Health economic evaluation

Aim: To assess whether the Happy Hands app in combination with usual care is a cost-effective treatment strategy for patients with hand OA compared to usual care alone.

Statistical software: Mainly STATA. Excel for bootstrap, plotting results on the cost-effectiveness plane and for construction the cost-effectiveness acceptability curve.

Perspective on costs: health care perspective as primary analysis, inclusion of production loss in explorative analysis.

Cost of the intervention: The Happy Hands app is not yet commercially available, hence has no official list price or yearly fee. Based on the cost of development and maintenance and the size of the eligible patient population, we assume that the app will be offered at an annual subscription fee of NOK 150 (EUR 13).

Identification of resources: patient self-reported in questionnaire, asked about resource use items as displayed in Table 1.

Measurement of resource use: patient self-reported in questionnaire. May add information from clinical expertise if needed, e.g. patient reports a rehabilitation stay, but not duration.

Valuation of resource use data: As far as possible, we will use unit prices reported in the Directorate of Medical Products database for use in health technology assessments (https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.dmp.no%2Fglobalassets%2Fdocuments%2Foffentlig-finansiering-og-pris%2Fdokumentasjon-til-metodevurdering%2Fenhetskostnader-v1.5.xlsx&wdOrigin=BROWSELINK), this includes the price per in-patient day at hospital.

If some unit price is not available in this database, we will use publicly available reimbursement rates. For visits to an occupational therapist in primary care, we will assume an average duration of visit and wage of therapist. Medical and technical equipment, such as a bread knife or vegetable knife with built-up handles, key for opening jars, or self-opening scissors, will be based on market prices (e.g. https://www.velferdsbutikken.no/categories/hjelpemidler-kjokken).

Identification of outcomes: self-reported in questionnaires.

Measurement of outcomes: Health related quality of life measured by the EQ-5D-5L. In the analysis of EQ-5D-5L, we will adjust for baseline imbalances using the method recommended by Manca and co-workers [26], if warranted.

Valuation of outcomes: Primary analysis based on the Norwegian EQ-5D-5L tariff by Garratt and co-corkers [27], sensitivity analysis with the UK Devlin tariff [28].

Analysis population: primary analysis with ITT population, may explore PP as sensitivity analysis.

Timing: Health-related quality of life is measured at baseline, 3 and 6 months, while costs are measured at 3 and 6 months.

Discounting: not relevant due to trial duration

Cost-effectiveness threshold: threshold suggested for Norway at time of analysis, currently NOK, 275,000 per QALY for patients with osteoarthritis

Statistical decision rule: Cost-effective if incremental cost-effectiveness ratio below threshold and if intervention has a higher probability of being cost-effective than comparator based on bootstrap results.

Analysis of resource use: mean cost per patient reported in 2024 EUR, will use valuta converter provided by "Norges Bank" to convert NOK to EUR using the average exchange rate in 2024 (https://www.norges-bank.no/tema/Statistikk/valutakurser/?tab=currency&frequencyTab=3).

Analysis of outcomes: mean QALY per patient. We expect no effect on mortality, hence any QALY gain will be a result of improvements in function and well-being. QALYs will be calculated based on the area under the curve approach. We will assume that transition between different health utility values will take place halfway between two measurements.

Missing data: if whole questionnaire of EQ-5D-5L is missing, multiple imputation, if single questions are missing, simple imputation. Costs are assumed to be missing only if the whole questionnaire is missing, if the questionnaire is missing, we will impute using multiple imputation.

Analysis of cost-effectiveness: ICER=difference in mean costs/difference in mean QALY

Sampling uncertainty: We will use non-parametric bootstrapping to assess the degree of uncertainty around the ICER. We bootstrap costs and QALY 10,000 times with replacement, recalculate ICERS and plot the results on the cost-effectiveness plane. The likelihood of cost-effectiveness will then be calculated as the proportion of all bootstrapped samples below the cost-effectiveness threshold value. A cost-effectiveness acceptability curve will be constructed to illustrate how sensitive the conclusion is to varying levels of threshold values. This approach is one of several alternatives recommended for trial-based cost-effectiveness analyses [16].

Subgroup analysis: Per protocol population

Sensitivity analysis: Devlin tariff for the EQ-5D-5L

Explorative analysis: including loss of production

c) Effect on secondary outcomes (pain, hand function, grip strength, disease activity and quality of care)
To assess the effect of using the Happy Hands app in addition to usual care compared to usual care only on secondary outcomes of pain, hand function, grip strength, disease activity and quality of care, we will use multiple linear regression with the mean change scores at 3 and 6 months as dependent variables and group as independent variable, adjusting for baseline values for the variable of interest and recruitment sites.

5.2.2.2 Summary Measures

See 5.1.1

5.2.2.3 Assumption Checks

A logistic regression includes the following assumptions:

- Binary dependent variable: This assumption is fulfilled trough the study design. OMERACT/OARSI responder criteria, calculated into a binary yes or no score.
- Independence: This assumption is fulfilled through the study design.
- No severe multicollinearity: This assumption is fulfilled through the study design.
- Sufficient number of observations: The sample size was calculated based on approximately 20% responders in the control group and 40% responders in the intervention group, which would provide sufficient number of patients per group.

A linear regression includes the following assumptions:

- Continuous dependent variable: This assumption is fulfilled through the study design.
- Independence: This assumption is fulfilled through the study design.
- Homoscedasticity: The spread of the residuals should be roughly the same across the regression line and should rather not exceed +3 and -3.
-

- Multicollinearity: The independent variables should not be highly correlated (r<0.7)

In case the outcome variable or the residuals are severly skewed, transformation (eg log-transformation) of the outcome variable will be carried out.

5.2.2.4 Missing Data

We are expecting the amount of missing data to increase with time, but we cannot retrace the individual reasons for missingness. The cost-effectiveness analysis will utilize multiple imputation for missing whole questionnaires of EQ-5D. Costs will be assumed to be missing if the whole questionnaire is missing. If the questionnaire is answered without reporting costs, it will be assumed that the costs are 0. The other secondary analyses will be based on complete case analysis.

5.2.2.5 Sensitivity Analyses

If deemed necessary, sensitivity analyses will also be conducted to address missing data and subgroup data.

5.2.2.6 Subgroup Analyses

No subgroup analyses are planned outside of the sensitivity analyses.

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 additional questions/analyses are raised during the analysis process, we will add them to this list of exploratory analyses.

a) To assess the adherence, satisfaction and usability with use of the Happy Hands app, we will only include participants allocated to the intervention group. Adherence will be described with mean and SD or median and interquartile range, as well as the proportion of participants with adequate adherence to the exercise sessions and the information videos. Satisfaction and usability will be described with mean and SD or median and interquartile range.
b) To identify relevant factors associated with being an OMERACT/OARSI responder at 3 and 6 months we will use multiple logistic regression and select variables based previous research and clinical relevance.
c) To identify factors associated with adherence to the interventions (exercise and information videos) in the Happy Hands app, both multiple linear and logistic regression may be used.

6. Safety Analyses

6.1 Adverse Events/Safety

AEs is based on self-report in open-ended questions in the 3-months follow-up questionnaire and e-mails or phone calls from patients and will be categorised as mild to moderate depending on the

description in the questionnaire. Brief transitory pain/discomfort will be regarded as mild AEs and persistent pain/discomfort will be considered moderate AEs.

Per definition, any events caused by the intervention that results in significant disability, prolonged hospitalization, life threatening events or death are categorized as serious adverse events (SAE). As we did not expect that the intervention would cause any SAEs, we did not ask the patients for permission to retrieve information from their medical journal. Thus, information on life threatening events or death are not included in the study. Participants were asked about surgery and hospitalization due to hand osteoarthritis, however, planned surgery will not be considered an AE/SAE as this may be part of the treatment for these patients.

7. Statistical Software

All data handling and statistical analyses will be performed using Stata (*StataCorp. 2015. College Station, TX, USA*).

8. Ethics

The project is granted approval by the Regional Committees for Medical and Health Research Ethics (REK) in Norway (REK no 477746)

The study is funded by the Dam Foundation (2022/FO387170). The funders have no role in the study other than providing funding.

Data is stored in Services for sensitive data (TSD) at the University of Oslo and in a secure research server at Diakonhjemmet Hospital.

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