Statistical Analysis Plan

NCT 06583980: INSELMA – a Randomised Controlled Trial

Full title: The Efficacy of a Complex Interdisciplinary Nurse-Coordinated SELf-MAnagement Intervention for People with Substantial Impact from their Inflammatory Arthritis: a Multicenter, Randomized Pragmatic Trial

ACRONYM: INSELMA Trial

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ADMINISTRATIVE INFORMATION

Trial and trial registration

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INTRODUCTION

Background and rationale

Some patients with inflammatory arthritis (IA) experience substantial disease impact despite optimal pharmacological treatment**.** To be able to manage these challenges effectively, these patients could benefit from interdisciplinary tailored self-management support. We thus developed a six-month nurse-coordinated interdisciplinary self-management intervention (INSELMA), in collaboration with patients, clinicians and managers.

We have performed a feasibility test of the INSELMA intervention on 18 participants from two hospitals, Rigshospitalet-Glostrup in Copenhagen, and the Danish Hospital for Rheumatic Diseases in Sønderborg. In total, 17 completed the intervention. Eight hours support in average from the health professionals (HPs) led to a tendency towards increase of the participants' quality of life, mental well-being, self-efficacy, assessment of global impact of the disease and a decrease in symptoms of anxiety, depression, fatigue, and pain (1). Individual interviews with participants revealed that they experienced the INSELMA intervention as a great opportunity to reduce long-held challenges they had fought alone, until now. They felt the intervention was adapted to their specific needs and considered the empathic and goal-oriented support from the same coordinating nurse during all six months and from physio- and occupational therapist, to be essential. It was important for the participants with time in between consultations to work towards the goals they had agreed upon. The participants experienced decreased impact of their disease and improved self-management ability (2). A scientific article reporting the participants perspective is published (2) as well as an article reporting the staffs positive experiences (3). The quantitative results from the feasibility study indicated improvement in quality of life, mental well-being, anxiety, depression, pain and fatigue (1). Based on these very positive results, we consider the intervention to be feasible, meaningful, and promising. The staff consider they need additional training in goal setting and ACT. It is now relevant to test these proof-of-concept findings in a larger trial with a control group.

OBJECTIVES

The primary objective of the trial is to compare the efficacy of the INSELMA intervention, relative to a usual care control group, on changes in health-related quality of life measured by EQ-5D-5L VAS from baseline to month 6, in patients with substantial impact from their inflammatory arthritis.

- The key secondary objectives are to compare, relative to the usual care control group, the efficacy on changes in the following key secondary outcome measures from baseline to 6 months: mental well-being (WHO-5)
- Number of participants achieving the Patient Acceptable Symptom State (PASS)
- fatigue coping (BRAF NRSv2 coping)

Other secondary objectives include comparing the efficacy of INSELMA, relative to usual care, on

A. changes from baseline to 6 months in:
    - anxiety and depression (HADS)
    - fatigue severity (BRAF NRSv2 severity)
    - fatigue impact (BRAF NRSv2 impact)

- pain (VAS pain)
- pain self-efficacy (PSEQ)
- global impact of the disease (VAS global)
- physical function (MDHAQ in RA and PsA and BASFI in axSpA)
- sleep problems (ISI)
- health related quality of life index (EQ-5D-5L index)

B. changes from baseline to 12 months after baseline
    - Health related quality of life (EQ5D-5L VAS)
    - Mental well-being (WHO-5)
    - Acceptable Symptoms (PASS)
    - Fatigue coping (BRAF-NRSv2 Coping)
    - Anxiety and depression (HADS)
    - Fatigue (BRAF-NRSv2)
        - Severity
        - Impact
    - Pain (VAS pain)
    - Pain self-efficacy (PSEQ)
    - Physical disability (MDHAQ in RA and PsA) (BASFI in axSpA)
    - Impact of the disease (VAS-global)
    - Sleep problems (ISI)
    - Health related quality of life (EQ5D-5L index)

METHODS

Trial design

The study is conducted as a pragmatic, investigator-initiated, multicenter randomized clinical trial with a two-group parallel design (INSELMA-RCT). The trial was designed as a superiority trial to assess whether the experimental (INSELMA) intervention yields superior outcomes compared with usual care at 6 months after baseline at the primary and key secondary outcome measures.

Interventions

The INSELMA intervention (experimental intervention group)

The intervention group will receive the INSELMA intervention in addition to usual care. After inclusion, each participant is assigned a coordinating rheumatology nurse, who is specifically trained to deliver the intervention. The coordinating nurse will follow the participant throughout the six months intervention period. The coordinating nurse performs an initial biopsychosocial assessment and based on this, the nurse and the patient define up to five activities the participant finds it hard to perform using the Patient Specific Functional Scale (PSFS) (4). In addition, the nurse and the participant agree on goals for the following six months based on shared decision-making.

The coordinating nurse provides individually adapted self-management support in face-to-face, telephone or online consultations. The form and scheduling of the consultations depend on the participant's preferences and needs during the following six months. At each face-to-face consultation with the nurse, the PSFS activities and the goals are evaluated and documented in the participants' medical journal.

The coordinating nurse uses communication tools from the comprehensive intervention manual including questions to address biopsychosocial areas, elements from Acceptance and Commitment Therapy (ACT) (5, 6) and how to support the patient's self-management ability based on self-efficacy theory (7). In addition, the nurse can use the Conversational Health Literacy Assessment Tool (CHAT) (8) to assess and support the participant's challenges in different aspects of Health Literacy.

Each participant is assigned up to 2.5 hours of individual support from the nurse during the six months intervention including time for documentation. The coordinating nurse coordinates relevant support from interdisciplinary partners, e.g., physiotherapist, occupational therapist, or a social worker either at the hospital or in primary health care. In addition, the nurse helps identify relevant services in the participant's municipality to reach their goals.

During the six months intervention period, the coordinating nurse can plan up to two interdisciplinary conferences to discuss progress and actions to achieve the goals with involved professionals at the hospital and or in the municipality, the patient and maybe relatives. The conferences can be held physical, online or by telephone depending on the participants' availabilities. A final consultation with the coordinating nurse after the six-month intervention includes a status and a discussion of the participant's future need for support.

Usual Care (control comparator group)

Usual care consists of planned consultations every 6-12 months by a rheumatologist or a rheumatology nurse and access to support from a rheumatology nurse by telephone. The planned consultations encompass review of blood tests, joint examinations, review of completed answers to questionnaires in DANBIO (9), adherence and evaluation of whether pharmacological adjustment is necessary. In addition, the planned nursing consultations sporadically encompass education in relation to management of the disease, symptoms, and the pharmacological treatment. At the outpatient departments at the Danish Hospital for Rheumatic Diseases, Rigshospitalet-Glostrup and Frederiksberg Hospital, patients who have specific challenges can be offered an additional nursing consultation for non-pharmacological support. At Rigshospitalet-Glostrup it is also possible to refer a patient to see a physiotherapist and/or an occupational therapist in a single consultation in the outpatient department for advice.

Randomization and blinding

The patients are randomly allocated after signing informed consent to either the INSELMA intervention (intervention group) or usual care (control group). A research assistant informs the participants about group allocation. Baseline measures are securely collected before the result from the randomization is revealed. Participants are allocated in ratio 1:1 in permuted blocks of 2 to 6 stratified by trial site (three centers) and diagnosis (RA, axSpA or PsA). The randomization sequences are generated in the customized REDCap system.

It is not possible to blind the intervention to the participants and the healthcare professionals in this trial. To ensure blinding in the analyses, all patient participants are given a number for reference and the person performing the statistical analyses will be blinded to allocation group.

Sample size and Power considerations

This superiority trial was powered to show a statistically significant difference between the participants allocated to the INSELMA intervention and those allocated to usual care. Using data from our previous feasibility study (N=17), we estimated the EQ5D-5L VAS on a 0-100 scale at baseline to have a mean of 44 points (Standard Deviation [SD] 15) in the target population (1).

Target Difference: Based on an estimated minimal important difference between groups of 8.0 EQ5D-5L VAS units, and an SD of 15 (1) (corresponding to a Cohen's effect size of >0.50), a statistical power of at least 80%, and a two-sided statistical significance level of 0.05, 114 patients would be required for the intention-to-treat population (approximately 57 participants in each group). It was decided to enroll 120 patients in the intention-to-treat population (i.e., 60 patients in each group), potentially corresponding to a statistical power of more than 83% to detect a difference between groups in the intention-to-treat population.

Framework

The trial was designed as a 2-group, superiority framework. The primary null hypothesis is that there is no immediate difference between the groups (H0: μ[I] = μ[C]) on change in health-related quality of life (HRQoL) (primary outcome) measured by EQ-5D-5L VAS as a change 6 months from baseline.

Timing of outcome assessments

Outcomes are collected at three time points for each participant; at baseline, 6 and 12 months after baseline (Table 1).

Table 1: Data collection in the INSELMA RCT

Intervention period 0-6 months, follow-up at 12 months				
		Intervention period		Follow-up
Time point in months after baseline		Baseline	6 months	12 months
Variable (Domain)	**Outcome measurement**			
Hospital and diagnosis	Hospital, diagnosis, year of diagnosis	X		
Socio-demographics	Age (years) and gender (male/female/other) *(from medical journal)* Living status (living with partner (yes/no); Living with others apart from partner (yes/no), Kids living at home (yes/no), Kids living away from home (yes/no) School and educational level (8 years or less, 9 years, 10-11 years. High school level or other, highest attained education (no education, vocational, short higher education, medium-term higher education, long university education) Income level (5 levels and "do not want to disclose")	X		
Smoking habits	Do you smoke? (never, previous smoker, occasional smoker, daily smoker, uses other nicotine products) Number of cigarettes/cigars etc. daily	X	X	X

Alcohol habits	Units per week (n); How often do you drink? (I do not drink alcohol, maximum once a month, 2-4 times a month, 2-3 times a week or four times a week or more often); How often do you drink five units or more on the same occasion? (daily or almost daily, weekly, monthly, rarely, never)	X	X	X
Work	Sick-leave during the past three months (yes/no), sick-leave at present (yes/no) Work status (employee, independent, unemployed, on sick-leave/early retirement/retired/student)	x	x	x
Disease activity	Disease activity (DAS28-CRP*) Disease activity (BASDAI**) *(from medical journal)*	X		
Pharmacological treatment *(from medical journal)*	cDMARD bDMARD glucocorticoids	X	X	X
Primary outcome				
Health-related quality of life	Health-Related Quality of Life (EQ5D-5L-VAS)	X	X	X
Key secondary outcomes				
Mental well-being	WHO-5	X	X	X
Symptom burden	PASS	X	X	X
Coping with fatigue	BRAF NRSv2 coping	X	X	X
Other secondary outcomes				
Anxiety and depression	HADS	X	X	X
Fatigue	BRAF NRSv2 severity, and impact	X	X	X
Pain	VAS-pain	X	X	X
Self-efficacy for managing pain	PSEQ	X	X	X
Impact of the disease	VAS-patient global impact of the disease	X	X	X
Physical disability	MD-HAQ* BASFI**	X	X X	X X
Sleep problems	ISI	X	X	X
Health-related quality of life for later cost-effectiveness analyses	EQ5D-5L index			
Other outcomes				
Health literacy	HLQ subscales 3 and 6	X	X	X

*in participants diagnosed with Rheumatoid arthritis and Psoriatic arthritis ** in participants with Axial Spondyloarthritis; DAS28-CRP: Disease activity score 28 joints, c-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cDMARD: conventional disease modifying anti-rheumatic drug; bDMARD: biologic disease modifying anti-rheumatic drug; EQ5D-5L: European Quality of Life 5 dimensions, 5 levels; VAS: Visual Analogue Scale; WHO-5: World Health Organisation 5 mental health index; HADS: Hospital Anxiety and Depression Scale; BRAF-NRSv2: Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale version 2; PSEQ: Pain Self-Efficacy Questionnaire; MD-HAQ: Multidimensional Health Assessments Questionnaire; BASFI; ISI: Insomnia Severity Index; PASS: Patient Acceptable Symptom State; HLQ: Health Literacy Questionnaire

Statistical interim analysis and stopping guidance

As we do not expect any serious adverse events, no statistical interim analyses are planned on any of the outcomes and no guidelines for stopping the trial early are described. All participants will continue usual care and will be monitored by the coordinating nurse throughout the intervention period to detect any unintended events. Specific attention will be towards covering any serious adverse events, and mortalities.

Timing of final analysis

Analysis of the primary outcome and key secondary outcomes will be conducted when data from six-month follow-up after baseline from the included participants have been collected and are cleaned. The analyses of the primary outcome measure, key secondary outcome measures, and other secondary outcome measures will be conducted on data from 12-month follow-up for the included participants when they have been collected and cleaned. Last patient last visit is anticipated by 31th August 2027.

STATISTICAL PRINCIPLES

Confidence intervals and P values

All results from statistical analyses on the primary, key secondary, and other secondary endpoints on change from baseline to 6 months will be accompanied by two-sided 95% Confidence Intervals (95%CIs) and corresponding *P* values. Superiority is defined as $P<0.05$ for the primary endpoint. To account for multiplicity and preserve the overall type I error for the key secondary and other secondary outcomes, a hierarchical (gatekeeping) strategy will be used (listed in mockup table 2 below). Changes from baseline to 6 months are prioritized over changes from baseline to 12 months. Key secondary endpoints will be tested based on change from baseline to 6 months in the following order: mental well-being (WHO-5, continuous outcome measure), Number of participants achieving the Patient Acceptable Symptom State (PASS, binary outcome measure) and coping with fatigue (BRAF-NRSv2 coping, continuous outcome measure) followed by other secondary endpoints estimated as change from baseline to 6 months in the following order: Anxiety and Depression (HADS), fatigue severity and impact (BRAF-NRSv2 severity and impact), pain (VAS-pain), self-efficacy to manage pain (PSEQ), the impact of the disease (VAS-patient global) , physical disability (MDHAQ/BASFI), sleep problems (ISI), and health related quality of life (EQ-5D-5L index). Additionally, changes from baseline to 12-month follow-up will be tested for the primary, key secondary, and other secondary outcome measures. The 95%CIs will not be adjusted for multiplicity and should not be used in place of hypothesis testing.

Adherence and Protocol deviations

Adherence to the intervention is defined as participation in an initial assessment by the coordinating nurses and ongoing contact with the coordinating nurse for a minimum of five months (six months +/- 1 month)

followed by a status consultation. Number of participants who adhered and did not adhere to the intervention will be summarized and reported.

Analysis of populations

The treatment policy estimand: We will quantify the average treatment effect among all randomly assigned patients, regardless of adherence to treatment or initiation of rescue intervention (i.e., the intention to treat [ITT] population). The ITT principle asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given (10, 11).

The hypothetical estimand: What would the treatment effect be if a specific event or intercurrent event did not occur? The treatment effect of INSELMA versus usual care, measured by the change from baseline to month 6 in the primary and key secondary endpoints, assuming participants remained on their randomized treatment throughout the planned trial duration without changing their (*i*) DMARDs or (*ii*) steroid regimen, (*iii*) attending a rehabilitation stay at e.g., Sano, Danish Hospital for Rheumatic Diseases or Montebello, (*iv*) seeking support at a pain or sleep clinic, or (*v*) undergoing surgery requiring hospital admission during the trial period.

Screening data

Number of patients screened for participation will be reported. This includes number of patients who were shown the pop-up text in the DANBIO registry after completing the usual questionnaires, number who showed interest to hear more about the study (added their phone number and patients identified in the clinic), the number who were considered eligible after the initial screening by a research nurse and who were sent the participant information, number contacted, number of contacted patients who did not meet the eligibility criteria, number of patients who met the eligibility criteria who declined and the number who accepted to participate.

Eligibility

Details of how eligibility data is collected will be presented in a CONSORT 'Trial profile diagram' (flow-chart) to provide details of the number of patients screened followed by a breakdown of how many patients showed interest, how many were eligible and how many were excluded due to violating each inclusion/exclusion criteria.

Inclusion criteria

- Adults aged 18 years or older
- Diagnosed with RA, PsA, or axSpA by a rheumatologist for at least 24 months.
- Answer "no" to the Patient Acceptable Symptom State (PASS), "Think about all the ways your arthritis has affected you during the last 48 hours. If you were to remain in the next few months as you were during the last 48 hours, would this be acceptable to you?" and/or
- Report ≥ 60 on at least one Visual Analogue Scale (VAS) (0–100) for fatigue, pain, or global assessment of the impact of the disease

Exclusion criteria

• Planned change or a change during the past three months in treatment with disease modifying anti-rheumatic drugs (DMARDs) or glucocorticoids
• Participation in other studies of relevance for the outcomes in INSELMA (i.e. TRACE, WORK-ON, SPINCODE, COMFI, PLATE or KRAM (Frederiksberg))
• Not able to speak and understand Danish sufficiently to participate without a translator
• Unstable psychiatric illness, cognitive impairment or other physical or mental issues that impede the ability to give informed consent to participation
• Current alcohol or drug use disorder documented in their medical journal
• Pregnant or nursing a baby
• Planned or ongoing rehabilitation at the Danish Hospital for Rheumatic Diseases or Sano, a pain or sleep clinic
• Ongoing application for early retirement or planned surgery requiring admission
• Participated in the INSELMA feasibility study or is a patient research partner in INSELMA

Recruitment

Participants are recruited through the national Danish Rheumatology Database DANBIO based on their responses to the standard questionnaires in DANBIO. If their responses fulfil the initial inclusion criteria (age, diagnosis and response to Patient Acceptable Symptom State, fatigue, -pain and global health), a popup text will appear on the screen with a short information about the INSELMA trial. If the patients are interested to hear more, they can add their telephone number.

In addition, eligible participants can be identified during outpatient consultations with a rheumatology nurse or a rheumatologist/physician. A research assistant will send out participant information to the patients who have indicated interest to their electronic mailbox (e-Boks) or by postal mail if the patient does not have e-Boks.

Next, a research assistant will contact the interested patients by phone within 10 working days to offer more information about the trial. If the patient is still interested to participate, consent material is sent through REDCap or by postal mail. After written consent has been obtained, baseline questionnaires are sent to the participant's electronic mailbox (e-Boks) through REDCap or by postal mail if the patient does not have e-Boks.

The CONSORT Trial profile diagram will comprise the number of people screened, eligible, consented, randomized, receiving their allocated treatment, withdrawing/lost to follow-up across all time points.

Withdrawal and follow-up

Participants can withdraw until data are analysed. Number of withdrawals after consent, group allocation, socio-demographic and disease characteristics, and time of withdrawal/ loss to follow-up data will be reported. We will attempt to follow up all randomized participants if they withdraw from allocated treatment. The level of consent withdrawal will be tabulated, classified as; consent to continue follow-up and data collection, consent to continue data collection only, or complete – no further follow-up or data collection.

Baseline patient characteristics

Baseline characteristics (socio-demographics including work status, disease activity, pharmacological treatment, and comorbidities in accordance with Table 1 above) will be descriptively summarized. Baseline demographic and clinical characteristics will be reported separately for each group using descriptive

statistics. Continuous variables will be summarized as mean (standard deviation) if approximately normally distributed, or as median (interquartile range) if skewed. Categorical variables will be presented as counts and percentages. No formal hypothesis testing or P-values will be reported for baseline comparisons, in accordance with the CONSORT statement recommendations.

Outcome definitions

Please see Table 1.

ANALYSIS

Descriptive statistics will be reported stratified by group as Means and (SDs, or medians with Interquartile ranges depending on the empirical data distribution. Categorical variables will be reported as absolute counts and proportions (percentages) for each group. Minimum and maximum values will also be reported for continuous data.

Inferential statistical analyses will be based on the intention-to-treat (ITT) population, including all randomized participants with baseline data collected before randomization, regardless of subsequent missing data or adherence (11): We will (*i*) Attempt to follow up all randomized participants, even if they withdraw from allocated treatment; (*ii*) Perform a main analysis of all observed data that are valid under a plausible assumption about the missing data (i.e., Missing At Random' [MAR]); (*iii*) Perform sensitivity analyses to explore the effect of departures from the assumption made in the main analysis (i.e., testing the hypothetical estimand and also applying a non-responder imputation [informative even if data is Missing Not At Random]); and (*iv*) Account for all randomized participants, at least in the sensitivity analyses (11).

Because of the availability of repeated measures collected over time, missing data will be handled indirectly by using repeated measures mixed effects models for the main analyses (12). The continuous outcomes listed as primary and secondary endpoints will be analyzed according to the ITT principle using repeated-measures linear mixed effects models (12), including a factor for treatment group (2 levels) and time (0, 6, and 12 months after baseline [3 levels]), the interaction between group and time (Group×Time), with adjustments for the stratifying factors (Center [3 levels]; Diagnosis [3 levels]) while the level at baseline will be applied as a covariate to reduce the random variation. For all the continuous outcome measures the statistical model describes the long-term trajectory of the outcomes while accounting for within-subject correlation over time using a spatial Gaussian-type correlation structure implemented via the linear mixed-effects model (e.g., PROC MIXED, REML method). For the primary endpoint, the analysis models the change in EQ5D-5L VAS as a function of baseline EQ5D-5L VAS, site, stratifying factors, treatment group, time, and their interaction (Group × Time). A random intercept is included for each patient (PtID) to account for individual-level variability. The repeated measure's structure models within-subject correlation using a spatial Gaussian correlation function over time, allowing correlation to decay smoothly as time points become more distant. Least-squares mean (LSMean) estimates are derived from the main model for group and time-by-group interactions, with group comparisons presented alongside confidence intervals at 6 and 12 months (see endpoint hierarchy). For the continuous outcome measures, this approach should ensure robust estimation of treatment effects over time, incorporating both between- and within-subject variability while improving precision in longitudinal outcome assessments. All results from statistical analyses on the primary and secondary endpoints will be based on the differences in least squares means, accompanied by two-sided 95% CIs and corresponding *P* values (superiority defined as $P<0.05$ for the primary endpoint).

Categorical endpoints will be analyzed by logistical regression at the individual time points (6 and 12 months post baseline, respectively) using randomized treatment, stratification groups, and the baseline value as a covariate. By default, odds ratios with 95% CIs will be estimated from these models and subsequently converted to approximate risk ratios and risk differences, facilitating interpretation as numbers needed to treat (NNT) when appropriate.

Missing data

As stated above, we will attempt to follow up all randomized participants, even if they withdraw from allocated treatment; missing data will be reported and graphically presented in the Trial profile flow diagram. For the primary and secondary endpoints, we will refer to the average causal effect (treatment policy estimand) as the main analysis of all observed data that are valid under a plausible assumption about the missing data: we assume data are 'Missing At Random' (MAR), meaning the probability of missingness depends only on observed data and not on unobserved data. If this assumption holds, valid inferences can be made by modeling the relationship between observed data and missingness. A mixed methods model addresses missing data under MAR by combining fixed and random effects to account for variability within and between subjects (12). The responder indices (categorical outcomes) will be analyzed using logistic regression models, including a factor for group and adjustment for stratification factors, and conservatively assuming missing data to be from non-responders.

For the primary and key secondary endpoints, we will perform sensitivity analyses to explore the effect of departures from the assumption made in the main analysis. The hypothetical estimand defines what the treatment effect would be if a specific intercurrent event did not occur, allowing for clearer and more relevant interpretation of clinical trial results (i.e., excluding outcome data collected after an individual has experienced one of the specified intercurrent events). This approach enhances transparency and consistency by explicitly stating the conditions under which the treatment effect is estimated, making it easier to align the estimand with clinical objectives and decision-making. If data were assumed to be 'Missing Not At Random' (MNAR), the probability of missingness depends on unobserved data, making standard methods like multiple imputation potentially biased. In this context, non-responder imputation can be informative because it takes a conservative approach by assuming that participants with missing data are non-responders (i.e., they did not achieve the desired improvement). This method is useful because it provides a worst-case scenario, reflecting a cautious interpretation of treatment effectiveness. It explicitly acknowledges that missing data may be related to poor outcomes and avoids overly optimistic estimates. As a result, non-responder imputation can strengthen the robustness of conclusions by accounting for potential biases associated with MNAR data. See Supplementary table B.

Harms

The number (and percentage) of patients discontinuing from the trial, discontinuation because of adverse events, serious adverse events, and possible deaths will be presented for each treatment arm. The number (and percentage) of occurrences of each adverse event will also be presented for each treatment arm. No formal statistical testing will be undertaken. Discontinuation due to AEs, deaths, SAEs and their individual (sub) components.

Statistical software

The software programs SAS and SPSS will be used to carry out analyses.

ANTICIPATED MANUSCRIPT OUTLINE

CONSORT 2010 Flow Diagram (Figure 1)

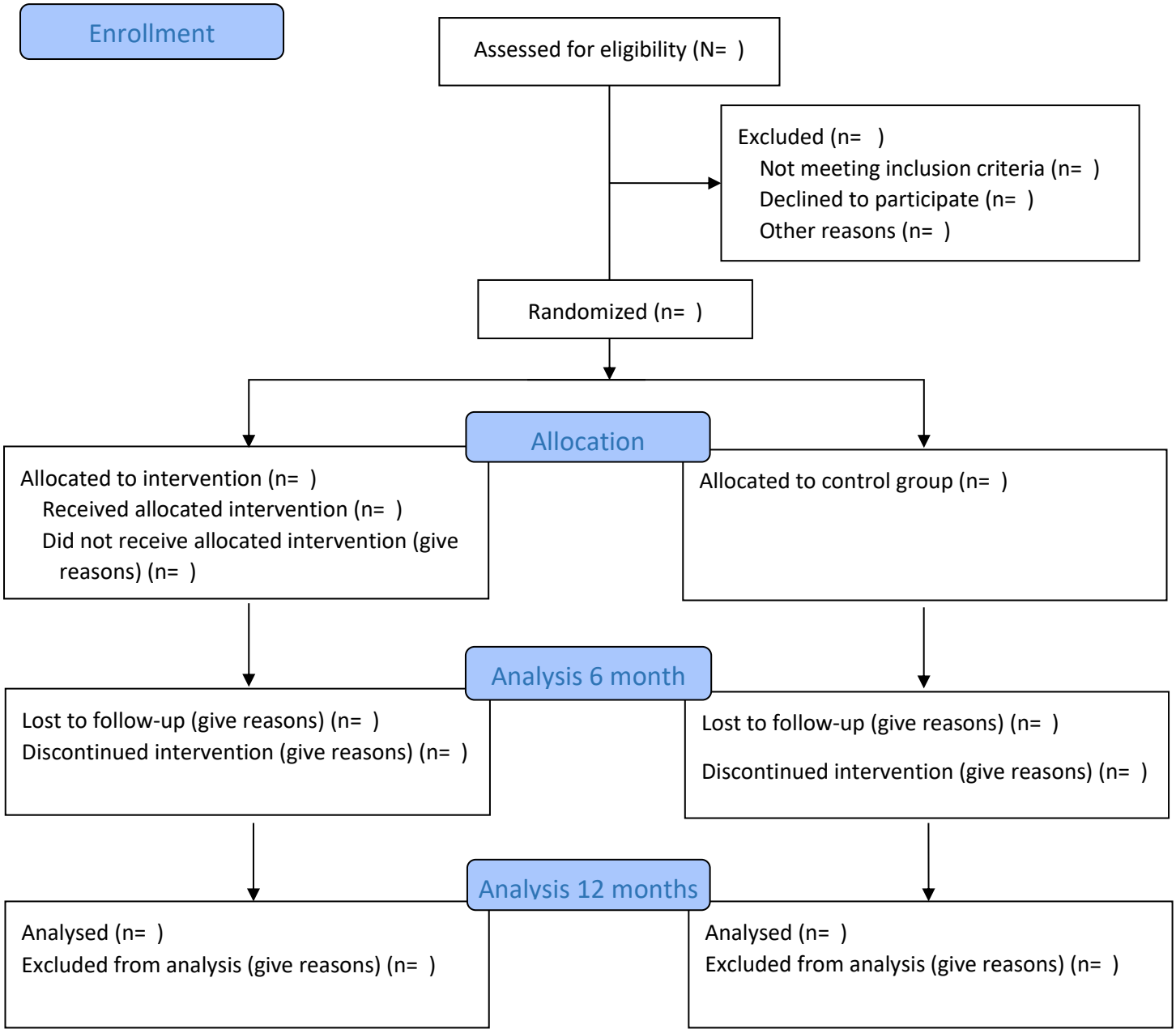

Table 1 (Mockup): Baseline characteristics of the participants

Characteristics	Intervention group (N=?)	Control group (N=?)	Total population (N=?)
Age			
Female sex, N (%)			
Diagnosis, no. (%)			
Rheumatoid arthritis			
Psoriatic arthritis			
Axial Spondyloarthritis			
Disease duration, (Years)			
Comorbidities, no. (%):			
None			
1 comorbidity			
≥2 comorbidities			
Smokers, no. (%)			
Present, no. (%)			
Previous or never, no. (%)			
Other (e-cigarettes, snuff etc)			
Alcohol, >10 units/week, no (%)			
More than 5 units per day, no (%)			
Living with partner, no(%)			
Kids living at home			
Income			
<300.000 DKK			
300.000-700.000 DKK			
More than 700.000 Dkk			
Work status			
In work/self-employed			
On sick leave, no (%)			
Retired			
Unemployed/student			
School level above high school, no (%)			
Primary outcome:			
Health related quality of life (EQ5D-5L VAS)			
Key secondary outcomes:			
Mental well-being (WHO-5)			
Acceptable symptoms (PASS)			
Fatigue coping (BRAF NRSv2 Coping)			
Other outcomes			
Anxiety and depression (HADS)			
Anxiety			
Depression			
Fatigue (BRAF-NRSv2)			
Severity			
Impact			
Pain (VAS pain)			
Pain self-efficacy (PSES)			
Physical disability MD-HAQ (RA and PsA)			

BASFI (axSpA)
Impact of the disease (VAS-global)
Sleep problems (ISI)
Health literacy
  HLQ subscale 3
  HLQ subscale 6

EQ5D-5L: European Quality of Life 5 dimensions, 5 levels; VAS: Visual analogue scale; HADS: Hospital Anxiety and Depression Scale; BRAF-NRSv2: Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales version 2; PSES: Pain Self-Efficacy Scale; MD-HAQ: Modified Health Assessment Questionnaire; BASFI: Bath Ankylosing Spondylitis Functinal Index; ISI: Insomnia Severity Index; PASS: Patient Acceptable Symptom State; HLQ: Health Literacy Questionnaire. Plus–minus values will be means ±SD unless otherwise indicated. Percentages may not total 100 because of rounding. IQR will be use to denotes interquartile range.

Table 2 (Mockup) Changes in outcomes at 6 and 12 months after baseline in the Intention-to-Treat population*

	Intervention group (N=?)	Control group (N=?	Difference (95% CI) P-value
Primary endpoint (0-6 months):			
Health related quality of life (EQ5D-5L VAS)			
Key secondary outcome measures (0-6 months):			
Mental well-being (WHO-5) (0-20)			
Acceptable symptoms (PASS), no. (%)			
Fatigue coping (BRAF-NRSv2 Coping) (0-100)			
Other secondary outcome measures (0-6 months):			
Anxiety and depression (HADS) (0-42)			
Fatigue (BRAF-NRSv2)			
Severity (0-100)			
Impact (0-100)			
Pain (VAS pain) (0-100)			
Pain self-efficacy (PSEQ) (0-60)			
Physical disability (% change in disability)			
(MDHAQ in RA and PsA and BASFI in axSpA)			
Global impact of the disease (VAS-global)(0-100)			
Sleep problems (ISI) (0-28)			
Health related quality of life (EQ5D-5L index)			
Primary endpoint (0-12 months)			
Health related quality of life (EQ5D-5L VAS)			
Key secondary outcome measures			
(0-12 months)			
Mental well-being (WHO-5) (0-20)			
Acceptable Symptoms (PASS), no. (%)			
Fatigue coping (BRAF-NRSv2 Coping) (0-100)			
Other secondary outcome measures			
(0-12 months)			
Anxiety and depression (HADS) (0-42)			
Fatigue (BRAF-NRSv2)			
Severity (0-100)			
Impact (0-100)			
Pain (VAS pain) (0-100)			
Pain self-efficacy (PSEQ) (0-60)			
Physical disability (% change in disability)			
(MDHAQ in RA and PsA and BASFI in axSpA)			
Impact of the disease (VAS-global) (0-100)			
Sleep problems (ISI) (0-28)			
Health related quality of life (EQ5D-5L index)			

The gatekeeping strategy is hierarchically demonstrated, numerated from 1 to 25. EQ5D-5L: European Quality of Life 5 dimensions, 5 levels; VAS: Visual analogue scale; HADS: Hospital Anxiety and Depression Scale; BRAF-NRSv2: Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales version 2; PSES: Pain Self-Efficacy Scale; MD-HAQ: Modified Health Assessment Questionnaire; BASFI: Bath Ankylosing Spondylitis Functinoal Index; ISI: Insomnia Severity Index; PASS: Patient Acceptable Symptom State; HLQ: Health Literacy Questionnaire. Percentages may not total 100 because of rounding. IQR will be use to denotes interquartile range. Values are reported as Least Squares Means with Standard Errors unless otherwise indicated based on the RM Mixed effects model derived from the interaction term Group×Time.

Table 3 (Mockup). Safety, Harms and Adverse Events assessed up to 12 months from baseline

	Intervention group N=??	Control group N=??	Risk Difference (95% CI)
Withdrawals, no. (%)			
Participants ≥ 1 AEs, no. (%)			
Total SAEs, no. (%)			
Withdrawals due to AEs, no. (%)			
Deaths, no. (%)			

AE: Adverse Event;

Supplementary table A

Estimates based on the 6-month assessment: Hypothetical estimand analysis excluding participants with intercurrent events from the time of the event to 12 months after baseline

	Intervention group (N=?)	Control group (N=?)	Contrast between groups (95% CI) (N=?)
Primary endpoint:			
EQ5D-5L VAS			
Key secondary outcome measures:			
Mental well-being (WHO-5) (0-20)			
PASS, no. (%)			
BRAF-NRSv2 Coping (0-100)			

EQ5D-5L: European Quality of Life 5 dimensions, 5 levels; VAS: Visual analogue scale; PASS: Patient Acceptable Symptom State; BRAF-NRSv2: Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales version 2

Supplementary table B

Estimates based on the 6-month assessment: Non-responder imputation* will be used to replace missing data in the ITT Population (informative if data is MNAR)

	Intervention group (N=?)	Control group (N=?)	Contrast between groups (95% CI) (N=?)
Primary endpoint:			
EQ5D-5L VAS			
Key secondary outcome measures:			
Mental well-being (WHO-5) (0-20)			
PASS, no. (%)			
BRAF-NRSv2 Coping (0-100)			

EQ5D-5L: European Quality of Life 5 dimensions, 5 levels; VAS: Visual analogue scale; PASS: Patient Acceptable Symptom State; BRAF-NRSv2: Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales version 2

* For continuous outcome measures, missing data at 6 and 12 months will be conservatively imputed using baseline values, corresponding to a non-responder assumption when calculating change from baseline. For the binary outcome measure, missing data at 6 months will be imputed repeatedly using worst-case, best-case, worst–best case, and best–worst case scenarios to reflect all extreme assumptions; the resulting estimates will be combined using Rubin's rules.

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