Effect of a Self-Management Intervention for Newly Diagnosed Inflammatory Arthritis: study protocol for a randomized controlled trial {1}

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ABSTRACT

Background

Patients newly diagnosed with inflammatory arthritis (IA) often face substantial physical, psychological, and social challenges despite advances in pharmacological management.

Objective

to investigate the efficacy of the "Newly diagnosed with Inflammatory arthritis—a Self-MAnagement intervention" (NISMA) and usual care, compared to usual care alone (control group), in adults with newly diagnosed IA.

Methods

This pragmatic, multicenter randomized controlled trial (RCT) will enroll 130 adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or axial spondyloarthritis (axSpA) recruited consecutively from three Danish hospitals and randomized 1:1 to NISMA plus usual care or usual care alone. The control group receives ususal care which consists of planned consultations with a rheumatologist and access to nurses. NISMA comprises three mandatory individual nurse-led sessions with two optional multidisciplinary group sessions delivered over 12 months. Assessments occur at baseline, 12 months (primary), and 24 months (extension). The primary outcome is the Health Education Impact Questionnaire (heiQ) 'skill and technique acquisition' domain.

Statistical analysis

Analyses follow the intention-to-treat principle. For the primary analysis, analysis of covariance (ANCOVA) adjusted for baseline, center, and diagnosis will estimate between-group differences with two-sided 95% CIs. Model assumptions (normality, homoscedasticity) will be checked (Q–Q plots, residual diagnostics). If violated, pre-specified alternatives (e.g., transformation, rank-based ANCOVA, or nonparametric tests) will

be used. Missing data will be addressed using multiple imputation. Key secondary endpoints will be assessed in a pre-specified hierarchical (gatekeeping) order; any post-hoc analyses will be exploratory. Extension analyses at 24 months will use linear mixed-effects models.

Discussion

This randomized controlled trial will provide essential insights about the efficacy of a targeted self-management intervention for newly diagnosed patients with inflammatory arthritis. If successful, the NISMA intervention could significantly enhance non-pharmacological management, providing a comprehensive approach to addressing both physical and psychological needs in caring for patients newly diagnosed with IA.

Keywords

Self-management; inflammatory arthritis; randomized controlled trial; patient-centered care; quality of life; rheumatoid arthritis; psoriatic arthritis; axial spondyloarthritis.

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	**Effect of a Self-Management Intervention for Newly Diagnosed Inflammatory Arthritis: study protocol for a randomized controlled trial {1}**
Trial registration {2a and 2b}.	**Clinicaltrials.gov, nr.:** NCT06533423
Protocol version {3}	22.09.2025. Version 2.
Funding {4}	The NISMA trial is supported by grants from the Danish Rheumatism Association (grant nr.: R251-A9062), the Lundbeck Foundation, and the Novo Nordic Foundation (grant nr.: 0096696).

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Name and contact information for the trial sponsor {5b}	Trial sponsor {5b}: There is no sponsor of this study.
Role of sponsor {5c}	Role of sponsor {5c}: This study has no commercial sponsor, and all funding is provided solely by independent foundations that have no involvement in the study's design, data collection, management, analysis, or interpretation. Additionally, these foundations have no role in the writing of the report or the decision to submit it for publication. The research team maintains full independence and ultimate authority over all aspects of the study to ensure objectivity and scientific integrity.

Introduction

Background and rational {6a}

Inflammatory arthritis (IA) (in this trial covering rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA)) constitutes a group of acute and chronic joint diseases characterized by joint pain, swelling, and tenderness caused by underlying inflammation [1–3]. IA affects more than 2% of the population, with considerable variation worldwide [1–3], and can occur at any age and in both sexes. The etiology of IA is incompletely understood, but it involves both genetic and lifestyle factors [1,4,5]. IA mainly presents with joint inflammation, causing leading to pain and stiffness, but can also affect other connective

tissues [2,3,6]. If treated insufficiently, these diseases may progress with functional decline, irreversible joint damage, development of various comorbidities, and increased mortality [7,8]. Pharmacological treatment with disease-modifying anti-rheumatic drugs (DMARDs) early after diagnosis improves short- and long-term outcomes [9,10]. Approximately 60% of patients with RA achieve long-term disease remission [11,12], but even in remission, some patients with IA will experience symptoms, and due to the fluctuating nature of the arthritis, symptoms will come and go throughout life with varying intensity [10,13–15]. Thus, after more than two decades of progress in the pharmacological treatment, some aspects of having IA remain less well managed: patients with IA still confront physiological and psychological distress, impacting daily activities, and overall quality of life (QoL) at disease onset, but also later in the disease course, and even when clinical remission is achieved [15,16].

Patients newly diagnosed with IA are particularly challenged and vulnerable. They are about to begin a life with IA that may involve regular blood tests, lifelong pharmacological treatment, side-effects to treatment, symptoms such as pain, fatigue, sleep disturbances, and increased risk of developing co-morbidities such as depression, cardiovascular disease, diabetes, and osteoporosis [7]. Experiencing altered body image, and changes in the family, work, and social life is common [17–23]. Therefore, a crucial but often insufficient aspect of caring for patients with IA is empowering them to gain a thorough understanding of their condition and develop their capacity to effectively manage the practical, physical, and psychological effects of the disease [24]. Several studies have shown that newly diagnosed patients require regular consultations and support from health professionals (HPs) to deal with physical, emotional and social consequences of the arthritis [17–23]. In addition, they have a wide range of educational needs, such as knowledge and management of the arthritis, and lifestyle recommendations. Previous research suggests that increased self-management - defined as the *individual's ability to manage symptoms, treatments, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition* [25], - can improve the QoL life in patients with chronic illness [26–30].

Self-management in rheumatology has been applied across multiple clinical contexts, including symptom pacing for pain and fatigue; adherence to exercise and physical activity; medication adherence and shared decision-making within treat-to-target care; and navigation of multidisciplinary services. Program formats range from brief nurse-led education to structured group programs that integrate problem-solving, goal-setting, and action planning, with demonstrated benefits in patient-reported outcomes and health service use [31,32].

As per recommendations from EULAR (European Alliance of Associations for Rheumatology) (10), self-management should be included in daily rheumatology care to support patients to become active partners in handling the disease [24]. This should include patient education and e.g., key self-management approaches such as problem-solving, goal-setting and action planning. However, when reviewing the numerous systematic reviews of arthritis-specific self-management interventions [33–37], we found it challenging to compare the included studies due to their heterogeneous study designs, program foci, and outcomes. Furthermore, despite the well-documented need for patient guidance following diagnosis [34], we found no IA-specific self-management interventions that have been systematically and specifically developed with a focus on newly diagnosed patients and subsequently tested in a Randomized Controlled Trial (RCT).
NISMA is a systematically developed, theory-informed self-management program for adults newly diagnosed with IA, described in detail elsewhere [38]. Development of NISMA followed the Medical Research Council framework, [39,40] with feasibility and process evaluations subsequently undertaken (manuscripts submitted [41,42]. The present RCT evaluates the program's efficacy compared with usual care.
The hypothesis is that the adapted NISMA intervention will be superior to usual care in increasing self-management skills and techniques and thereby improve symptoms among others. Therefore, the next step will be to test this hypothesis in a randomized NISMA trial. Further, if the intervention proves to be effective, we will conduct a cost-effectiveness analysis subsequently.
Rationale: Compared with usual care NISMA provides structured, individualized coaching with continuity from a dedicated nurse, explicit behavior-change techniques (problem-solving, goal-setting, action planning),

and optional peer-supported group sessions. Grounded in Social Cognitive Theory (SCT) and informed by Acceptance and Commitment Therapy (ACT) questioning techniques, NISMA targets self-efficacy, adaptive coping, and healthcare service navigation—mechanisms expected to improve heiQ domains and downstream clinical and psychosocial outcomes.

Objectives {7}

The primary objective of this trial is to compare the short-term efficacy of the NISMA intervention and usual care, relative to usual care alone, on the HeiQ 'self-management skills and techniques' domain in patients newly diagnosed with inflammatory arthritis, from baseline to 12 months from randomization.
Our key secondary objectives are to compare the short-term efficacy of the NISMA intervention and usual care, relative to usual care on self-management skills, anxiety and depression, fatigue, pain self-efficacy, pain intensity, patient global assessment, medication adherence, quality of life, loneliness, and physical function from baseline to completion of the intervention (12 months from baseline).

In the extension study we will explore the longer-term efficacy of the intervention relative to usual care on self-management skills, anxiety and depression, fatigue, pain self-efficacy, pain intensity, patient global assessment, medication adherence, quality of life, loneliness, and physical function at follow-up 24-months from baseline.

Trial design {8}

The trial is designed as a pragmatic, multicenter randomized trial with a two-group parallel design in a superiority framework. Participants will be allocated in a 1:1 ratio; after providing informed consent and completing baseline assessments, they will be randomized to either the NISMA intervention (experimental group) or usual care (control group) with no protocolized added treatment.

The protocol is approved by the Regional Committee on Health Research Ethics for the Capital Region of Denmark (H-24046135) and the Danish Data Protection Agency (p-2024-15846).

Methods

Setting {9}

Patients will be included from the following 3 centers: the Center for Rheumatology and Spine Diseases, Rigshospitalet University Hospital, Copenhagen, and the Department of Rheumatology and Spinal Diseases, Holbæk Hospital and Slagelse Hospital; all in Denmark. These three departments cover most of the Zealand, which covers an area of 2.5 million residents.

Eligibility criteria {10}

Inclusion Criteria

Patients will be included if they are adults aged 18 years or older with one of the following conditions:

- RA diagnosed within the last 6 months
- PsA diagnosed within the last 6 months
- AxSpA diagnosed within the last 12 months, and has initiated biological treatment

Patients with axSpA will have unique inclusion criteria due to NSAIDs being the first-line pharmacological treatment [43]. For those effectively treated with NSAIDs and exercise, treatment is transitioned to their general practitioner. Therefore, we only those who has initiated biological treatment will be included.

Exclusion criteria

• Severe mental illness that, in the investigator's judgment, precludes participation

• Pregnancy

• Current chemotherapy for malignancy

• Insufficient Danish language proficiency to participate (operationalized as inability to read the written information and explain study procedures in own words during consent; assessed via a brief comprehension check by the project manager)

Who will take informed consent {26a}

If patients meet the above criteria, the rheumatologist and/or other HPs will briefly inform patients about the trial and hand out written information. Interested patients will have the possibility to contact the project manager (LHL) by telephone or e-mail. Oral information about the trial will take place at the hospital or by telephone based on the patient's preferences. The project manager will ensure that the information is given in an undisturbed setting if conducted at the hospital. Patients will be informed of their right to bring a relative to the information session. If still interested after oral information, a consent statement must be filled out. Based on the recruitment rates from the prior feasibility study, we estimate that recruitment will take 10-12 months.

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

This item does not apply as there will be no collection of biological specimens.

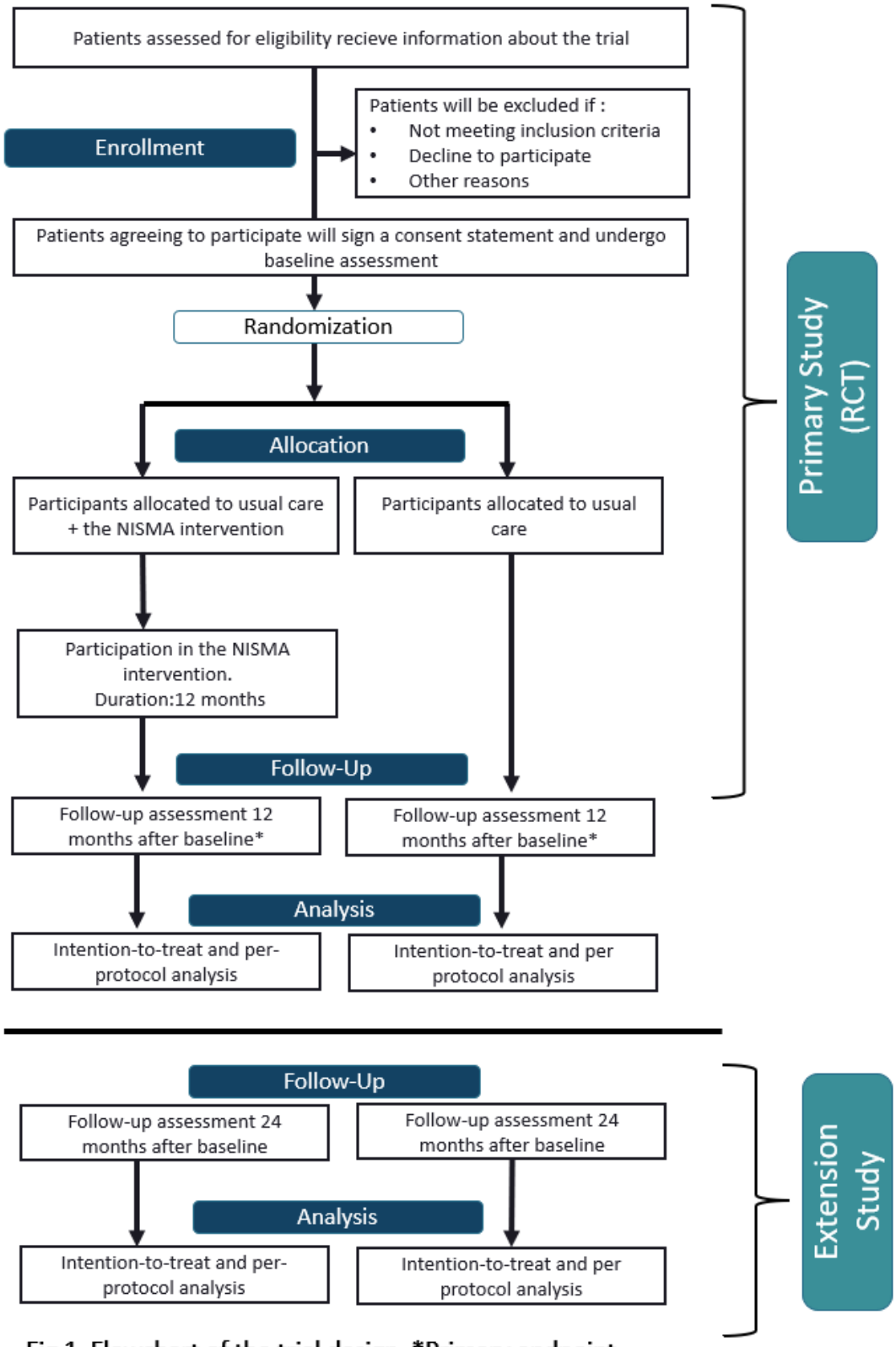

Fig 1. Flowchart of the trial design. *Primary endpoint

The interventions

Explanation for the choice of comparators {6b}

Both groups will continually receive relevant treatment for her IA. There are no established standards for identifying and addressing self-management needs in rheumatology outpatient consultations. Participants allocated to the control group will receive usual care, which consists of planned sessions with a rheumatologist and occasionally a nurse, a physiotherapist, and an occupational therapist. Those who started DMARDs of any type had an appointment with a nurse and a follow-up phone call. All participants will have the possibility to contact the outpatient clinic and consult a nurse. Participants in the control group will be encouraged to maintain their usual daily routines and self-management practices until the follow-up assessment is conducted. Participants allocated to the intervention group will receive the NISMA Intervention in addition to usual care. See Table 1 for summary of interventions (NISMA vs usual care)

Table 1. Summary of interventions (NISMA vs usual care)

Arm	Provider(s)	Dose & format	Session characteristics	Core content	Adherence & fidelity	Medical management / usual care
Usual care (control)	Rheumatologist; nurse; PT/OT as clinically indicated	Consultations per clinical need; for DMARD starts. Nurse education visit + follow-up phone call	Routine outpatient consultations; ad-hoc education/support; access to clinic/nurse advice line as needed	Guideline-concordant medical management; opportunistic self-management advice (no structured program)	Not applicable (no structured program; routine attendance recorded in clinical systems)	Treat-to-target DMARD management and monitoring per local practice
Usual care + NISMA	Usual care Nurse (individual). Nurse + physiotherapist + occupational therapist co-facilitate group sessions	Usual care + 3× individual (60–90 min) over 12 months; 2× optional group (120 min; ~5–8 participants)	Usual care + Individual: consistent nurse; first session in person, then in-person/online as appropriate. Group: fixed time points; rolling enrolment	Usual care + Person-centered coaching; problem-solving; goal-setting; action planning; ACT-informed questioning; lifestyle & symptom management	Attendance logs; session checklists in REDCap; ~10% session fidelity review with feedback; automated reminders and active rescheduling	Usual care + Guideline-concordant care including DMARDs and access to nurse advice (as part of usual care)

The NISMA-intervention (experimental group) {11a}

The NISMA intervention is a flexible intervention and comprises three mandatory individual sessions with a nurse, supplemented by two optional group sessions over a period of 12 months, to provide comprehensive support tailored to each participant's needs.

In brief, the intervention is delivered by a registered nurse for the individual sessions, with a physiotherapist and an occupational therapist co-facilitating the group sessions. The planned dose and format are three individual sessions of 60–90 minutes over 12 months and two optional group sessions of 120 minutes with approximately five to eight participants. Core content includes person-centered coaching; structured problem-solving, goal-setting, and action planning; ACT–informed questioning; and guidance on lifestyle and symptom management.

Adherence and fidelity are promoted through attendance logs, session checklists entered in REDCap, and independent reviews of approximately 10% of sessions, alongside automated reminders and active rescheduling. Usual care (control) comprises guideline-concordant medical management, including DMARDs and nurse access, without a structured self-management program. See Figure 2 for an overview of the session sequence and content.

Our intervention is grounded in the theoretical framework SCT [44] and inspired by the questioning techniques in ACT [45,46]. These methods play a crucial role in helping participants enhance their self-efficacy. The key components of our approach include: a person-centered approach by addressing challenges identified by each participant to foster self-efficacy through targeted problem-solving, goal-setting, and action planning. This is utilized by interviewing techniques derived from ACT to assist participants in accepting and committing to self-management. The program is designed to last between 12 months, allowing for gradual skill development and adaptation.

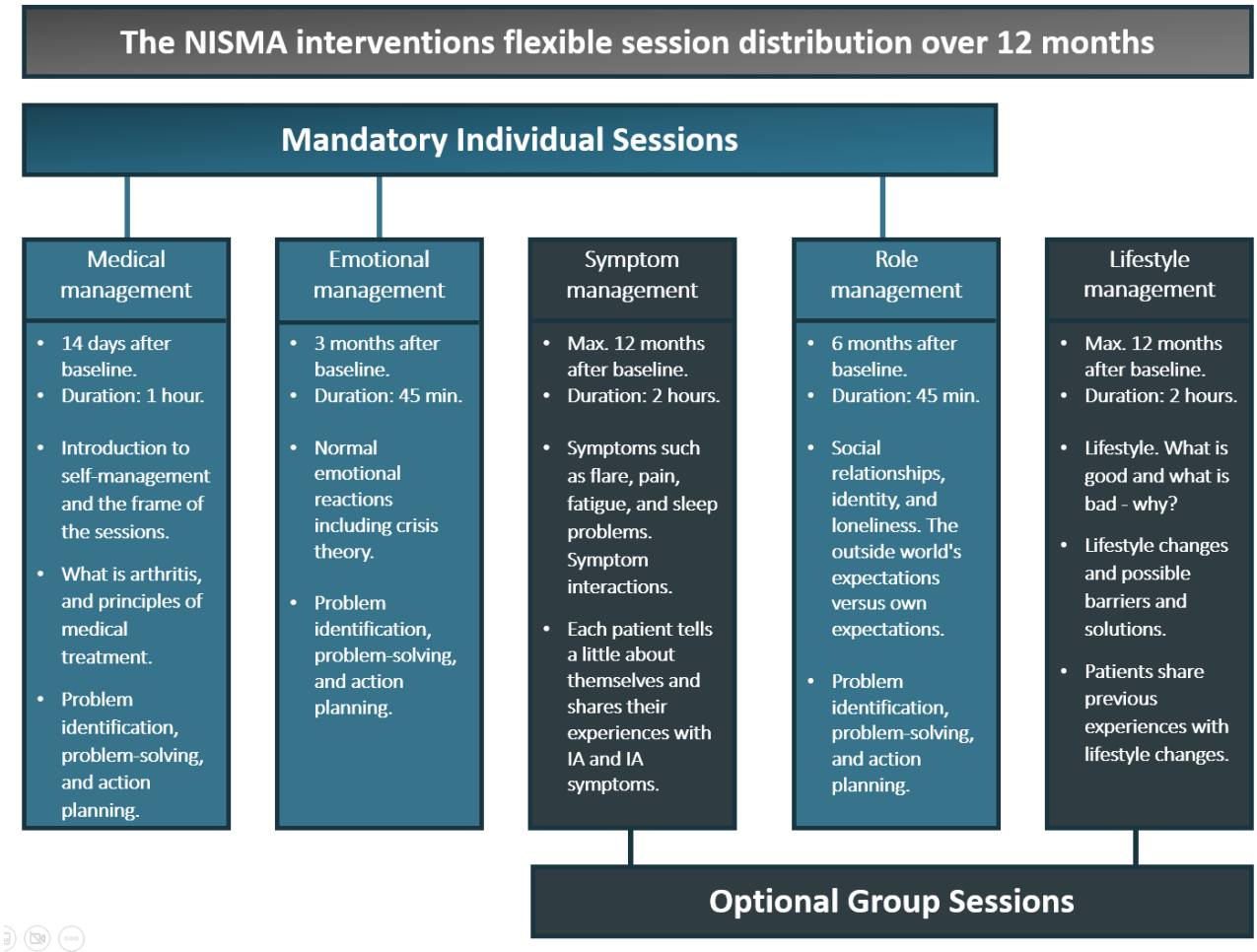

Fig. 2. The NISMA intervention

The structured sessions are as follows:

Individual sessions

The first individual session focuses on what IA is, medical management, providing essential knowledge and strategies for managing the condition effectively.

The second session addresses emotional management, recognizing the unique challenges faced by newly diagnosed patients. Our intervention places a particular emphasis on themes of crisis and acceptance management.

The third session aims to address role management, aiding participants in adjusting their roles in personal and professional life.

The individual sessions are conducted by a specially trained registered nurse , who remains consistent throughout the individual sessions to provide continuity of care. Individual sessions can be conducted either as online meetings or face-to-face. However, the initial meeting will be in person to establish a solid foundation for the relationship.

Group sessions (optional)

Participants are invited to attend two optional group sessions (two hours each), each designed to accommodate five to eight individuals. The group sessions are scheduled at fixed time points. This arrangement enables participants to register for these sessions at their convenience., facilitating their active engagement in the program. Group sessions are co-facilitated by a team comprising a nurse, an occupational therapist, and a physiotherapist, offering a multidisciplinary approach to address various aspects of self-management (see Fig. 2 for overview of sessions).

Group sessions delve into lifestyle and symptom management, offering practical advice and peer support. The themes of symptom management and lifestyle adjustments are central to the group discussions, aiming to equip participants with practical strategies for day-to-day management of their condition.

To ensure the fidelity of the intervention, we have developed a comprehensive manual, and to secure the validity of its content, our experts in rheumatology and self-management (members of the project group) have reviewed the manual. Further, to train the HPs to deliver the intervention, we have designed a competence development program, where the HPs will be trained in ACT questioning techniques and group facilitation and in addition get familiar with the manual. To further increase fidelity, we offered the HPs ongoing supervision with both the project manager (LHL) and a psychologist trained in ACT.

Criteria for discontinuing or modifying allocated intervention {11b}

As this is a minimal-risk intervention, no modification or discontinuation of interventions is anticipated. Participants voluntarily participate in the intervention and can withdraw their consent and exit the trial at any time. If a participant in the intervention group is unable to attend a scheduled session due to unforeseen circumstances, a new individual session will be arranged at the earliest possible convenience. Patients who fail to attend the three individual sessions will be classified as non-completers.

Strategies to improve adherence to the intervention {11c}

Participants will receive SMS/e-mail appointment reminders; missed sessions will be actively rescheduled. Interventionists will complete structured session checklists and upload to REDCap; a 10% sample of sessions will be reviewed for fidelity with feedback to providers. To enhance adherence throughout the trial period, several strategies will be employed. Participants will be encouraged to practice self-management skills through follow-ups during sessions. For the HPs delivering the intervention, we will monitor fidelity to research protocols by requiring HPs will complete an evaluation form after each session. Also, the HPs will provide feedback on the delivery of the intervention, participant engagement, and report any adverse events.

Relevant concomitant care permitted or prohibited during the trial {11d}

No specific concomitant care is restricted during the trial.

Provisions for post-trial care {30}

Post-trial care is usual care.

Outcomes {12}

Self-management is a complex concept that primarily has been utilized in the research of patients with chronic diseases. There is no consensus on how to measure self-management in IA (or any other chronic disease) [47]. Early IA presents multidimensional challenges (symptoms, function, mental health, self-efficacy, service navigation). The outcome set captures these domains while prioritizing a single primary endpoint (heiQ 'skill and technique acquisition'). Key secondary endpoints follow a pre-specified hierarchy based on feasibility results; interpretation will consider heterogeneity of scales.

Primary outcome and endpoint

The primary outcome is self-management skills assessed with the heiQ "skill and technique acquisition" domain [48]. We consider the" self-management skill and technique acquisition" domain to best reflect the changes we aim to achieve through our intervention, and therefore it is considered our primary outcome. This domain captures knowledge-based skills and techniques used to manage disease-related symptoms and health problems. The heiQ comprises eight independent domains (health-directed activity; positive and active engagement in life; emotional wellbeing; self-monitoring and insight; constructive attitudes and approaches; skill and technique acquisition; social integration and support; health service navigation), each scored 1–4, where higher values reflect better self-management (note: emotional wellbeing is reverse-scored). The heiQ demonstrates sound internal consistency, construct validity, and responsiveness across chronic-disease and rheumatology settings [49,50]. The primary endpoint is the between-group difference in least-squares means (LS-means) for the heiQ "skill and technique acquisition" score at 12 months from baseline, reported with two-sided 95% confidence intervals and p values (superiority defined as $p<0.05$).

Key secondary outcomes and endpoints

Secondary outcomes are the following PROMs:

- Self-management skills measured by seven of the heiQ domains: health-directed activity; positive and active engagement in life; emotional wellbeing; self-monitoring and insight; constructive attitudes and approaches; social integration and support, and health service navigation [49,50]. The corresponding endpoints is the between-group difference in least squares means from the 6 heiQ domains after 12 months. Endpoints in the extension study are the between-group difference in least squares means in heiQ domain 1, 2, 3, 4, 5, 6, 7, and 8 after 24 months.
- Anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS), that has good reliability and factorial validity across medical populations, including rheumatology [51,52]. The corresponding endpoint is the between-group difference in least squares means from HADS after 12 months. Endpoint in the extension study is between group difference in HADS 24 months after baseline.
- Fatigue measured by the Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale (BRAF-NRS), that is validated, including Danish versions, with good construct validity and responsiveness [53], and VAS-fatigue (0-100). The corresponding endpoint is the between-group difference in least squares means from VAS and BRAF-NRS after 12 months. Endpoint in the extension study is between group difference in VAS and BRAF-NRS 24 months after baseline.
- Pain self-efficacy measured by the Arthritis specific Self-Efficacy measurement tool (ASES-pain). The scale has established internal consistency and predictive validity in arthritis [54,55]. The corresponding endpoint is the between-group difference in least squares means from ASES-pain after 12 months. Endpoint in the extension study is between group difference in ASES-pain 24 months after baseline.
- Pain Intensity measured by VAS (0-100), a simple, reliable single-item measures with strong convergent validity in IA [56,57]The corresponding endpoint is the between-group difference in least squares means from VAS after 12 months. Endpoint in the extension study is between group difference in VAS 24 months after baseline.

- Patient global assessment measured by VAS-Global, which is validated within rheumatology [58]. The corresponding endpoint is the between-group difference in least squares means from VAS after 12 months. Endpoint in the extension study is between group difference in VAS 24 months after baseline.
- Medication adherence will be measured by the Compliance Questionnaire Rheumatology (CQR)-5-item scale, that has acceptable reliability and criterion validity for identifying non-adherence [59,60] The corresponding endpoint is the between-group difference in least squares means from CQR after 12 months. Endpoint in the extension study is between group difference in CQR 24 months after baseline.
- Health Related Quality of Life measured by European Quality of Life (EQ5D-5L), that has validity supported across rheumatic diseases; Danish value set applied [61,62]. The corresponding endpoint is the between-group difference in least squares means from EQ5D-5L after 12 months. Endpoint in the extension study is between group difference in EQ5D-5L 24 months after baseline.
- Loneliness will be measured by the Three Item Loneliness Scale, a short scale validated for measuring loneliness [63]. The corresponding endpoint is the between-group difference after 12 months. Endpoint in the extension study is between group difference 24 months after baseline.
- Physical function measured by Modified Health Assessment Questionnaire (MD-HAQ) , is well-validated and responsive across rheumatology) [64]. The corresponding endpoint is the between-group difference in least squares means from MD-HAQ after 12 months. Endpoint in the extension study is between group difference in MD-HAQ 24 months after baseline.

Other secondary outcomes and endpoints

- Disease activity measured by the percentage improvement from baseline using various composite scores depending on the rheumatic diagnoses. For RA: Disease Activity Score in 28 joints (DAS28) [65], for axSpA: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [66], and for PsA: the Disease Activity index for Psoriatic Arthritis (DAPSA) [67].These indices have established reliability, construct

validity, and responsiveness in their target populations, and are analyzed as between-group LS-means differences at 12 months; the extension study repeats these analyses at 24 months.

All primary and secondary outcomes will be measured at baseline (t=0 months), 12 months after baseline. The extension study will report all outcomes, presenting the long-term effect and sustainability at 24 months from baseline.

Participant timeline {13}

The participant timeline is shown in Table 2.

Sample size and power calculation {14}

As no established thresholds exist for clinically relevant changes in heiQ domains, we refer to prior research [68,69]. I prior research in the skills acquisition domain, we found mean differences between groups ranging from 0.22 to 0.38. Therefore, we decided that a minimal important difference probably correspond to a target difference of 0.30 with a standard deviation (SD) of 0.55 for the heiQ 'skill and technique acquisition' domain (primary endpoint) from baseline to 12 months after baseline. To achieve a statistical power of 80% and a significance level set at an alpha of 0.05, our calculations indicated a need for 54 patients per group (i.e., enrolling 108 patients in the Intention to Treat Population (ITT)). Incorporating an anticipated dropout rate of 15% from our feasibility study [41], the sample size would correspond to 127. Consequently, we revised the necessary sample size to approximately 65 patients per group (i.e., 130 patients in the ITT population) to achieve a reasonable statistical power to identify a statistically significant difference between the intervention and control group (i.e., corresponding to a statistical power of 87% in the best-case scenario).

Recruitment {15}

Eligible patients will be identified in the outpatient clinic, the rheumatologist and/or other HPs will briefly inform patients about the trial and hand out written information.

Sequence generation {16a} and concealment mechanism {16b}

Randomization in a 1:1 ratio will be performed after the patient has signed informed consent and completed baseline assessments. A computerized random number generator algorithm obtained from the Sealed Envelope website [70] will be used to provide customized randomization tables. Randomization will be stratified by site (3 centers) and type of inflammatory condition (3 diagnoses). To facilitate this, the customized randomization tables will be uploaded for each site to Research Electronic Data Capture (REDCap) [71] allowing for stratification across three individual IA conditions. The REDCap randomization module will be used for allocation generation and to securely maintain the sequence until the intervention is assigned.

Implementation {16c}

The project manager will enroll participants at the individual sites and inform them whether they have been allocated to the intervention group or the control group (see Fig. 1 for participants flow through the trial). For participants randomized to the intervention group, the first individual session will be scheduled as soon as possible after allocation.

Who will be blinded {17a}

Due to the nature of the intervention, it is not possible to blind participants or HPs to the allocated intervention. Outcome assessors abstracting clinical indices from DANBIO/electronic records will be blinded to group allocation wherever feasible. Analyses will be performed with groups masked until the primary analysis is finalized.

Procedure for unblinding if needed {17b}

This item does not apply as participants and HPs knew the group allocation.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Socio-demographic and lifestyle data will be collected at baseline. For the primary analyses, outcomes will be measured at baseline and 12 months after baseline. An additional 24-month follow-up assessment will be included in the extension study (See Fig. 1 and Table 2). Diagnosis and disease duration will be obtained from the electronic Danish Rheumatology Database DANBIO [72–74]. Data on pharmacological treatment will be obtained from the electronic medical record (Sundhedsplatformen), and data on disease activity from DANBIO using the nearest value to the current measurement timepoint. Data will be extracted from DANBIO/electronic records by trained staff blinded to allocation; a 10% random sample will be re-abstracted to evaluate agreement (kappa/ICC).

The self-administered questionnaires will be entered by the participants into the electronic project manager tool REDCap [75]. Patients will have the flexibility to complete the questionnaire either on-site at the hospital

or through their official digital mailbox ('e-Boks'), based on their preference. All other data will be entered into REDCap by the project manager (LHL).

Table 2. Diagram of enrolment, interventions, and assessments – study period 0-12 (and 24 months)

	Measurement	Enrolment	Baseline	End of intervention (primary endpoint)	Follow-up (extension study)
Time point		**Before Baseline**	**Week -2 to 0**	**12 months after baseline**	**24 months after baseline**
Enrolment					
Eligibility criteria		X			
Informed consent		X			
Allocation			X		
Intervention					
NISMA-intervention			X	X	
Usual care			X	X	
Assessments					
Outcomes					
Primary outcome					
Self-management skills and technique measured by HeiQ[1]	HeiQ: Domain 6: Skill and technique acquisition		X	X	X
Key secondary outcomes					
Self-management skills	HeiQ: Domain 1: Health-directed activities		X	X	X
	HeiQ: Domain 2: Positive and active engagement in life		X	X	X
	HeiQ: Domain 3. Emotional distress		X	X	X
	HeiQ: Domain 4: Self-monitoring and insight		X	X	X
	HeiQ: Domain 5: Constructive attitudes and approaches		X	X	X
	HeiQ: Domain 7: Social integration and support		X	X	X
	HeiQ: Domain 8: Health service navigation		X	X	X
Anxiety and depression	HADS Anxiety		X	X	X
	HADS Depression		X	X	X
Fatigue	BRAF-NRS severity		X	X	X
	BRAF-NRS impact		X	X	X
	BRAF-NRS coping		X	X	X
	VAS-fatigue		X	X	X
Pain self-efficacy	ASES-pain		X	X	X
Pain intensity	VAS-pain		X	X	X
Global assessment by	VAS-global		X	X	X
Medication adherence	CQR-5-item scale		X	X	X
Quality of life by	EQ5D-5L		X	X	X
Loneliness by	Three-Item Loneliness Scale		X	X	X
Physical function by	MD-HAQ		X	X	X
Other Secondary outcomes					
Disease activity by condition	DAS28 for RA		X	X	X
	BASDAI for axSpA		X	X	X
	DAPSA for PsA		X	X	X

Acute phase reactant value	C-reactive protein		X	X	X
Additional measures					
Age, sex, educational level, cohabitation, work status	Questionnaire		X		
Diagnoses	Medical record		X		
Pharmacological treatment of arthritis (DMARDS)	Medical record		X		
Use of pain medication	Medical record		X		
Use of glucocorticoids	Medical record		X		
Co-morbidity*	Medical record and Questionnaire		X		
Smoking	Questionnaire		X		
Alcohol	Questionnaire		X		

*Diabetes, hypertension, myocardial infarction, chronic obstructive pulmonary disease, cancer, osteoarthritis, osteoporosis, asthma, depression, or anxiety.

ASES (Arthritis Self-Efficacy Scale); axSpA (axial spondyloarthritis); BASDAI (Bath Ankylosing Spondylitis Disease Activity Index); BRAF-NRS (Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale); CQR-5 (Compliance Questionnaire Rheumatology, 5-item); DAS28 (Disease Activity Score in 28 joints); DAPSA (Disease Activity in Psoriatic Arthritis); DMARDs (disease-modifying antirheumatic drugs); EQ5D-5L (EuroQol 5 Dimensions 5 Levels); HADS (Hospital Anxiety and Depression Scale); heiQ (Health Education Impact Questionnaire); MD-HAQ (Modified Health Assessment Questionnaire); PsA (psoriatic arthritis); RA (rheumatoid arthritis); VAS (visual analogue scale).

Plans to promote participants retention and complete follow-up {18b}

To promote participant retention and ensure complete follow-up participants will be thoroughly informed about the data collection process and timepoints and the importance of data completeness for the project. Further, questionnaires will be re-sent after two weeks.

Data management {19}

Collected data will be stored securely, physically, and digitally, anonymized using a unique participant research ID, and accessed only by the team members trained in data management.

Confidentiality {27}

Data will be stored on password-protected computers and entered into a computer database (REDCap). For all analyses, subjects will be identified by their unique study ID. Limited information will be retained on

patients who are pre-screened and do not qualify, or who are approached and decline participation, to generate a CONSORT flow diagram.

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

This item does not apply as no biological specimens will be collected.

Statistical methods for primary and secondary outcomes {20a}

Descriptive statistics for baseline data will be reported in a Table 1 format; reported separately for each treatment group. These descriptive statistics will summarize the characteristics of participants at baseline, including demographic information and outcome variables relevant to the trial. Descriptive statistics include the mean and standard deviation (SD), or median and interquartile ranges (if applicable). For categorical data we will report the count and percentages.

If ANCOVA assumptions are not met, we will consider rank-based ANCOVA (aligned ranks) or transformation as pre-specified alternatives; any post-hoc analyses will be labeled exploratory.

The primary endpoint will be based on the change in heiQ from baseline to 12 after baseline, estimated as the difference between least squares means. In our main analyses, estimations of between-group differences for all continuous outcomes will be conducted after 12 months. The primary endpoint will be analyzed using analysis of covariance (ANCOVA), adjusting for baseline values, trial site, and type of IA diagnosis as covariates. The analyses of the secondary endpoints will be performed and interpreted in sequence until one of the analyses fails to show the statistically significant difference, or until all analyses have been completed at a statistical significance level of 0.05 ($P<0.05$). All analyses in the statistical hierarchy will be based on the treatment policy estimand (the primary estimand, i.e., the ITT principle), which quantify the average treatment effect regardless of adherence to treatment or initiation of rescue interventions

between baseline and month 12. Key assumptions for statistical tests, including normality of residuals in ANCOVA, will be assessed using studentized residuals scattered against the predicted values, and other graphical methods (e.g., Q-Q plots, histograms). If assumptions are violated, alternative methods such as nonparametric tests (e.g., Wilcoxon rank-sum test) or transformation of variables will be considered.

The extension study

Given the availability of repeated measures in the extension study, missing data will be addressed implicitly using repeated-measures mixed-effects models. The primary and key secondary (continuous) outcomes will be analyzed using linear mixed-effects models (LMMs) with repeated measures, incorporating: Treatment group (2 levels: intervention, control), time (0, 12, and 24 months after baseline [3 levels]), group × time interaction, baseline values of the respective outcome as a covariate, and stratification factors: center (3 levels) and diagnosis (3 levels)

This approach ensures that all intergroup differences at each timepoint are adjusted for baseline levels, thereby minimizing random variation. Least squares means (LSMs), and their standard errors will be reported for each group, with between-group differences presented as adjusted LSM differences with two-sided 95% CIs and P values. Superiority will be defined as $P < 0.05$.

Interim analyses {21b}

This item does not apply as there will be no interim analyses.

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

This item does not apply as no additional analyses are planned.

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

The main analyses will be based on the ITT population, i.e., including all randomized patients with a baseline measure available [76]. The ITT principle asserts the effect of a treatment policy (that is, the planned treatment regimen), rather than the actual treatment given (i.e., it is independent of treatment adherence) [9]. Accordingly, participants allocated to a treatment group (NISMA and Control, respectively) will be followed up, assessed, and analyzed as members of that group, irrespective of their adherence to the planned course of treatment (i.e., independent of withdrawals and cross-over phenomena).

All 95% confidence intervals and P values will be two sided. We will not apply explicit adjustments for multiplicity, rather we will analyze the key secondary outcomes and interpret these as endpoints in a prioritized order (e.g., "gatekeeping procedure").

A multiple imputation approach will be used in which missing data are imputed from month 12 measurements from participants in the same treatment group. A series of complete data sets will be generated and analyzed, and the results will be combined using the Rubin formula [77] to obtain overall estimates. While binary outcomes will be analyzed and initially reported using Odds Ratios with 95%confidence intervals (95%Cis), all between-group differences 95%Cis for continuous outcomes will be based on the least square means, adjusted for baseline levels and stratifying factors to minimize random variation [78].

Continuous outcome measures will be analyzed using analysis of covariance, with randomized treatment, trial site, and type of IA diagnoses as factors, and baseline (pre-exposure) value as a covariate. Categorical end points will be analyzed using logistic regression, with the same factors and covariates.

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

Any changes to eligibility criteria, outcomes, or analyses during the study will be reported to ClinicalTrials.gov, and participants as needed.

Due to the Italian data protection laws and GDPR regulations, access to participant-level data is restricted. The full study protocol and statistical analysis plan will be made available upon reasonable request to authorized regulatory authorities, ethics committees, and academic institutions in compliance with legal and ethical requirements.

Oversight and monitoring

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

We have established a project group to ensure the timely execution, progress, and quality of the project. The group consists of one patient research partners, a professor in rheumatology nursing and self-management, a professor in rheumatology, a professor in rheumatology nursing and epidemiology, a professor in physiotherapy, a professor in biostatistics, a postdoc in occupational therapy and a postdoc in nursing. The project group has expertise within rheumatology, patients with chronic diseases, patient education, rehabilitation, health promotion, coping and telemedicine. The group expertise represents extended experience of RCT's, qualitative research, and epidemiology.

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

Data monitoring committee is not required for this study.

Adverse event reporting and harms {22}

This is a non-drug intervention trial using educational elements, behavioral therapies, and self-efficacy training strategies – all elements included in the daily work of many HPs and clinical practice. Participants will be monitored throughout the period of the intervention in order to detect any unintended events and to optimize security. Adverse events occurring in the sessions will be reported and registered by the HPs. All serious adverse events will be reported to the Research Ethics Committee [79].

Frequency and plans for auditing trial conduct {23}

There are no procedures for auditing trial conduct.

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

All protocol amendments must be submitted to the Danish Ethical Committee for approval before implementation in the ongoing trial. The Principal Investigator (PI) is responsible for communicating these amendments and obtaining the necessary approvals. Once approved, an updated version of the protocol will be distributed to all study sites. The PI will ensure that amendments are reflected by updating the protocol's date and version number. Additionally, all amendments will be documented within the protocol, and clinical trial registries will be updated accordingly to maintain transparency and compliance.

Dissemination plans {31a}

The dissemination of results from our trial will be comprehensive and multifaceted, ensuring broad visibility irrespective of the results' alignment with the initial hypothesis—whether they support the intervention, favor the comparator, or are ambiguous. Our communication strategy includes the publication of scientific papers in peer-reviewed journals and presentations at pertinent academic conferences. Additionally, we aim to engage a wider audience by leveraging news outlets, social media platforms, and both online and offline educational resources, including multimedia materials and printed literature. These efforts will be complemented by oral presentations and articles in popular science magazines to make our research accessible to the public.

In terms of authorship, our policy aligns with the guidelines set forth by the International Committee of Medical Journal Editors (ICMJE), ensuring that all contributors who meet these criteria are recognized appropriately. Every author will be granted full access to the study data, promoting transparency and collaboration.

Should there be any significant modifications to the trial protocol, these changes will be formally communicated to the Committee on Health Research Ethics for The Capital Region of Denmark. Moreover, all amendments will be duly registered on ClinicalTrials.gov and detailed in the primary report of the RCT, maintaining the integrity and transparency of the research process.

Patient involvement

This trial is designed with a solid patient focus. From the very beginning, three patients were involved in the initial design and development of the NISMA intervention (reported elsewhere [38]). During the feasibility testing and process evaluation (Phase 2), all patients were interviewed to include their views on the intervention [42]. We have also involved a patient with RA as research partner in the project group in all

project phases of NISMA. Studies have shown that this supports maintain the patient perspective, the relevance of the project focus and structure, and the results and implementation [80].

Discussion

Several studies have highlighted the need for targeted interventions for newly diagnosed patients with IA [17–23]. Newly diagnosed patients are considered as a particularly vulnerable group and strengthening their self-management skills from the outset can lead to better long-term outcomes and increased self-management abilities. However, evidence on effective intervention components remains limited. The NISMA RCT is designed to address this gap by evaluating a systematically developed intervention) within the framework of the Medical Research Council [39,40]. Building on our prior feasibility study [81] and a comprehensive process evaluation [42] that examined contextual influences on delivery, fidelity, mechanisms of impact, and acceptability. Together, these preparatory studies indicate that the intervention is relevant, acceptable, and feasible to implement in routine care, providing a clear rationale for definitive evaluation in an RCT. Compared with conventional care—which typically prioritizes rapid pharmacologic control alongside variable, often ad hoc education—NISMA offers a structured, manualized program delivered early after diagnosis, integrating group facilitation with individual goal-setting, action planning, problem-solving, and cognitive-behavioral strategies.

This targeted timing and method are intended to accelerate patient activation, improve navigation of services, and embed sustainable behaviors within routine clinical pathways, potentially yielding benefits beyond symptom control (e.g., mental health, coping, and engagement with care) [30,82].

Plausible mechanisms span both psychosocial, and physical domains. Reducing threat appraisal and stress reactivity, improving sleep, and increasing regular physical activity may modulate central pain processing and fatigue, supporting better symptom control. Psychosocially, gains in self-efficacy, insight, constructive attitudes, and social integration (as captured by heiQ domains) can enhance coping, resilience, and shared

decision-making. Physically, improved adherence, joint protection, pacing, and graded activity may preserve function and reduce flares. Together, these pathways are hypothesized to translate into fewer complications, lower symptom burden, and better quality of life [36,83], with potential downstream reductions in unplanned care and hospitalizations [84].

In line with EULAR recommendations, it foregrounds the role of HPs in symptom control, patient-reported outcomes, and psychosocial/lifestyle support, with training in group facilitation, problem-solving, goal-setting, action planning, and cognitive-behavioral techniques [85,86]. This skill set strengthens multidisciplinary collaboration, streamlines workflows, and enables more personalized care, improving patient experience and clinician satisfaction [86].

The trial also incorporates an economic evaluation to inform scalability and adoption. When the NISAM trial is completed, we will conduct a cost-utility analysis using EQ5D-5L (Danish value set) to estimate QALYs, alongside a cost-consequence summary of key outcomes, from the healthcare payer perspective over 12 and 24 months, with prespecified sensitivity analyses [87]. If efficacy is confirmed, implementation work will examine feasibility, workforce requirements (including HP upskilling), reach, and sustainability across settings, supporting routine integration and equitable access [88,89].

The trial's scope and implications extend beyond IA symptom management. If NISMA proves effective and cost-effective, it will support embedding structured self-management at the diagnostic window as standard practice, strengthen multidisciplinary collaboration, and provide a replicable training model for HPs. Findings will also clarify which components and mechanisms matter most, guiding adaptation for heterogeneous IA phenotypes and informing policy and service design in rheumatology.

In sum, NISMA has the potential to improve outcomes that matter to patients and to the health system, while providing robust evidence on effectiveness, and value for money.

Limitations

Key limitations include the risk of contamination between arms within shared services, variability in disease trajectories early after diagnosis, and reliance on PROMs that may be influenced by expectancy and context. We mitigate these through a manualized curriculum, fidelity monitoring and supervision, prespecified analyses (including sensitivity and mediation analyses), and triangulation with clinical indices. Generalizability will be examined across participating sites, with attention to implementation contexts. Concomitant care was not restricted or systematically recorded; however, we trust that randomization distributed such practices evenly across groups, thereby minimizing the risk of systematic bias. Due to the nature of the NISMA intervention blinding of participants is impossible. However, the outcome assessor will be blinded, and participants will be asked not to disclose their group to the assessor. Second, spillover effect can be occurring, the participants in the control group may be receiving intervention fragments in the outpatient clinic or seek for additional support e.g., patient organizations. Moreover, the dose and content of usual care may be different among participants. Also, we cannot report the precise intervention content delivered to each participant, as the intervention is individually adjusted to individual challenges.

Trial status

The latest protocol version approval date is September 2025. Recruitment began 09-12-2024 with an expected completion date in December 2025. Therefore, the last patient first visit is expected to be around 30-12-2025.

Abbreviations

ACT — Acceptance and Commitment Therapy
ANCOVA — analysis of covariance
ASES / ASES-pain — (Arthritis) Self-Efficacy Scale / pain subscale
axSpA — axial spondyloarthritis
BASDAI — Bath Ankylosing Spondylitis Disease Activity Index
BRAF-NRS — Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale

CONSORT — Consolidated Standards of Reporting Trials
CQR-5 / CQR-5-item — Compliance Questionnaire Rheumatology (5-item)
DANBIO — Danish nationwide rheumatology registry
DAPSA — Disease Activity in Psoriatic Arthritis
DAS28 — Disease Activity Score in 28 joints
DMARDs — disease-modifying anti-rheumatic drugs
EQ5D-5L — EuroQol 5 Dimensions, 5 Levels
EULAR — European Alliance of Associations for Rheumatology
GDPR — General Data Protection Regulation
HADS — Hospital Anxiety and Depression Scale
heiQ / HeiQ — Health Education Impact Questionnaire
HPs — health professionals
IA — inflammatory arthritis
ICC — intraclass correlation coefficient
ITT — intention-to-treat
LHL — Luise Holberg Lindgren
LS-means — least-squares means
MD-HAQ — Modified Health Assessment Questionnaire
NISMA — Newly diagnosed with Inflammatory arthritis — a Self-MAnagement intervention
PI — Principal Investigator
PROMs — patient-reported outcome measures
PsA — psoriatic arthritis
PT / OT — physiotherapist / occupational therapist
QALYs — quality-adjusted life years
Q–Q (plots) — quantile–quantile (plots)
QoL — quality of life
RA — rheumatoid arthritis
RCT — randomized controlled trial
REDCap — Research Electronic Data Capture
SCT — Social Cognitive Theory
SD — standard deviation
SPIRIT — Standard Protocol Items: Recommendations for Interventional Trials
VAS / VAS-Global — visual analogue scale / patient global assessment by VAS

Acknowledgements

We would like to thank all patients and HPs who contributed to the development and feasibility test of the NISMA intervention, which laid the foundation for the final RCT design.

We also thank the patient research partner Sara Danshøj Christensen who approved the participant information, contributed to discussions on trial concept and collaborated on the intervention in NISMA as recommended by the European League Against Rheumatism.

Authors' contributions {31b}

All authors contributed to the trial concept and the design. LHL and BAE performed the draft. All the authors (LHL, TT, AT, MA, MLH, RC, and BAE) read, critically revised, and approved the final version of the manuscript. All the authors are accountable for all aspects of the work.

Funding {4}

The NISMA trial is supported by grants from the Danish Rheumatism Association (grant nr.: R251-A9062), the Lundbeck Foundation, and the Novo Nordic Foundation (grant nr.: 0096696).

Availability of data and material {29}

All requests of data will be made available at reasonable request to the PI.

Declarations

Ethics approval and consent to participate {24}

The trial was approved by the Regional Committee on Health Research Ethics for the Capital Region of Denmark nr H-24046135. Furthermore, the RCT was approved by the Danish Data Protection Agency of the Capital Region of Denmark (Nr.: p-2024-15846) and was registered at ClinicalTrials.gov. nr.: NCT06533423.

All data will be treated confidentially and in accordance with EU legislation and data security regulations, and legislation (GDPR). The principles of the Declaration of Helsinki will be followed. We will secure informed consent from participants. The trial sponsor and the project manager will secure that all information collected during the study will be kept confidential in accordance with Danish Data Protection Agency rules. This trial protocol has been prepared as outlined in the PREPARE guide [90], and reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [91].

All potential patients will receive oral and written information about the trial. Participation is voluntary, and participants can at any time and without justification leave the trial without affecting their rheumatological their treatment. The participants will give the primary investigator and project manager permission to obtain data from the patients' journals in the informed consent. Informed consent material is available in Danish.

Consent for publication {32}

The informed consent form is available from the corresponding author on request.

Competing interests {28}

The authors declare that they have no competing interests.

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