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EFFECTIVENESS OF INTERDISCIPLINARY COMBINED DERMATOLOGY-GASTROENTEROLOGY-RHEUMATOLOGY CLINICAL CARE COMPARED TO USUAL CARE IN PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES: A parallel group, non-blinded, pragmatic randomized trial

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EFFECTIVENESS OF INTERDISCIPLINARY COMBINED DERMATOLOGY-GASTROENTEROLOGY-RHEUMATOLOGY CLINICAL CARE COMPARED TO USUAL CARE IN PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES: A parallel group, non-blinded, pragmatic randomised trial

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ABSTRACT

Introduction

Immune-Mediated Inflammatory Diseases (IMIDs) are associated with reduced health-related quality of life (HRQol), increased risk of somatic and psychiatric comorbidities, and reduced socioeconomic status. Individuals with one IMID have an increased risk for developing other IMIDs. The unmet needs in the care of patients with IMIDs may result from a lack of patient-centricity in the usual mono-disciplinary siloed approach to these diseases. The advantages of novel interdisciplinary clinics toward the traditional therapeutic approach have not been investigated. The overall aim of this study is to determine the effectiveness of an interdisciplinary combined clinic intervention compared to usual care in a population of patients with the IMIDs: psoriasis, hidradenitis suppurativa, psoriatic arthritis, axial spondyloarthritis, and inflammatory bowel disease. Our hypothesis is, that an interdisciplinary combined clinic intervention will be more effective than usual care in improving clinical and patient reported outcomes, and that a more effective screening and management of other IMIDs and comorbidities can be performed.

Methods and analysis

This is a randomised, usual care controlled, parallel-group pragmatic clinical trial. 300 consecutively enrolled participants with co-occurence of at least two IMIDs are randomly assigned in a 2:1 ratio to either treatment in the interdisciplinary combined clinic or usual care. The study will consist of a 6-month active intervention period and a 6-month follow-up period where no intervention or incentives will be provided by the trial. The primary outcome is the change from baseline to 24-Weeks on the Short-Form Health Survey (SF-36) Physical Component Summary. Additional Patient Reported Outcome measures and clinical measures are assessed as secondary outcomes.

Ethics and dissemination

Ethical approval of this study protocol was established by the institutional review board of the study site. The findings from this trial will be disseminated via conference presentations and publications in peer-reviewed journals, and by engagement with patient organizations.

Registration details

Central Denmark Region Ethical Committee: 1-10-72-176-19
ClinicalTrials.gov: NCT04200690
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Protocol date: 22-DEC-2019

Keywords

Joint Diseases; Inflammatory Bowel Diseases; Skin Diseases; Pragmatic Clinical Trial; Anti-Inflammatory Agents

Strength and limitations of this study (MAX 5 short bullets)

- This is the first randomised, usual-care controlled trial to assess the effectiveness of a coordinated interdisciplinary approach to disease management in patients with IMIDs.
- The focus of the study will be on personalised, preventive and participatory healthcare.
- The pragmatic elements in the design of this trial increase the likelihood that the results can be generalized to everyday practice and support decision-making by patients, providers, and health system leaders.
- Emphasis on generic patient reported outcome measures that can be used across age, disease, and treatment groups enables a meaningful assessment of patients with complex IMIDs and creates a strong focus on patient-centricity.
- Investigators and patients cannot be blinded to participation randomisation outcomes due to pragmatic design limitations.

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) including autoimmune diseases affect up to 10% of the western population.[1] Among these are inflammatory bowel diseases (IBD) including ucerative colitis (UC) and Crohns disease (CD), spondyloarthritis (SpA) including axial spondyloarthrtis (axSpA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA), psoriasis and hidradenitis suppurativa (HS). The aetiology of IMIDs is only scarcely understood, but known to consist of a combination of genetic susceptibility and dysfunctional immunological mechanism resulting in a loss of immunological tolerance towards specific tissues, with a considerable overlap in organ involvement between the different disease-types. The diseases listed above are all associated with cardiometabolic disease, malignancy, infections, ophthalmologic diseases, psychiatric disorders, and reduced socioeconomic status.[2-6] An association between several of the diseases has been shown.[7-11] Additionally, it is generally accepted that individuals with one IMID have an increased risk for developing other IMIDs.

Despite this knowledge, a number of challenges currently exist in providing high-quality care for patients with co-occurrence of more than one IMID. These challenges include: Limited awareness of other autoimmune diseases among patients and health care professionals (HCP)s; lack of screening for other autoimmune diseases; unidisciplinary siloed approach to care; delayed referral from one specialist to the next one, lack of consensus regarding treatment goals and outcome measures; lack of patient centricity; unrecognised, underdiagnosed and undertreated comorbidities; and lack of regular follow-up.[12] The above-mentioned siloed approach to care may lead to a lack of patient centricity and inefficient management of the disease. In a Danish qualitative study, it was reported that some patients experience lack of physician continuity, lack of communication between various HCPs, a need for patients to relay health-related information between various HCPs, contradicting information about disease activity from various HCPs, work-related uncertainties, a lack of knowledge and disease understanding in the social system, and negative consequences in the social system of the delayed diagnostic process.[13, 14]

Recent retrospective studies have reported diagnostic and therapeutic benefits of combined dermatology-rheumatology clinics.[15, 16] Generally, the focus of these clinics is psoriasis and psoriatic arthritis. To our knowledge, no experience with combined clinics including other multidisciplinary professionals such as psychologists, social workers, dieticians, and a broader rheumatology-dermatology-gastroenterology approach has been studied.

The overall aim of this study is to determine the effectiveness of an interdisciplinary combined clinic intervention compared to usual care in a population of patients with complex IMIDs, defined as more than one of the following diagnoses: psoriasis, HS, axSpA including AS, PsA, UC, and CD. Our hypothesis is that an interdisciplinary combined clinic intervention will be more effective than usual care in improving patient reported outcome (PRO) measures (i.e., PROMs, including generic and disease-specific functional status, HRQoL, symptom and symptom burden, and health-related behaviours) and clinical outcomes, and that a more effective screening and management of other autoimmune diseases and comorbidities can be performed in an interdisciplinary combined clinic.

METHODS

Trial design and setting

This is a randomised, usual care controlled, parallel-group clinical trial. Participants are enrolled consecutively and randomly assigned in a 2:1 ratio to either treatment in an interdisciplinary combined clinic or usual care in a hospital clinical setting. In total 300 patients diagnosed with more than one of the selected IMIDs will be randomised to either interdisciplinary combined clinic intervention (200 subjects) or usual care (100 subjects). Work-up and therapy will be at the investigator's/responsible physician's discretion and in accordance with local and national treatment recommendations and guidelines. Thus, diagnostic procedures and therapy are not mandated by the study protocol.

Participants will be recruited based on referrals from hospital clinics and from consultative private practices.

The study will consist of a 6-month active intervention period (assessed after 24 weeks) and a subsequent 6-month follow-up period where no intervention or incentives will be provided by the trial. PROM's will be collected at baseline, 8 Weeks, 16 Weeks, and 24 Weeks, as well as 52 Weeks. Clinical endpoints will be collected at baseline and 24 Weeks.

Figure 1 illustrates the study design. Figure 2 illustrates the trial flow.

Patient and public involvement

Two patient organisations ("De Autoimmune" and "Foreningen for Autoimmune Sygdomme") were part of the original grant proposal, which formed the basis for establishing the National Centre for Autoimmune Diseases (NCAS). The trial described in this protocol is running in the NCAS. Members of the patient organisations provided feedback and comments on the trial concept. Other patients not directly associated with the patient organizations are providing feedback on the content of the interdisciplinary intervention throughout the trial. This feedback is organized through semi-structured interviews and focus groups. Information about the trial is shared with patients through regional and national branches of the aforementioned patient organizations.

Record keeping, monitoring, and data handling

Study data are collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Aarhus University.[17, 18] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Personal data is protected according to the Danish Data Protection Act and The General Data Protection Regulation.

PROM data are collected as surveys through REDCap. The system will send customised emails to participants. It is ensured that participants can complete each survey one time only. Configurable reminders and tracking of responses are in place to minimize the risk of missing data. PRO results are available to investigators on an individual level as a tool to improve the treatment and the consultation. Data will not be available on trial level until database lock.

The Good Clinical Practice (GCP) unit at Aarhus University Hospital is granted access to perform monitoring to confirm that the trial is being conducted in accordance with the currently approved protocol and any other study agreements, International Conference on Harmonisation (ICH) GCP, and all applicable regulatory requirements.

Participants

Inclusion criteria

1. Written informed consent obtained from the participant prior to randomisation.
2. Age 18 and above.
3. Diagnosis of at least two IMIDs* or diagnosis of one IMID and clinical suspicion** of another IMID*

* including and limited to: Psoriasis, HS, UC, CD, axSpA, PsA
** substantiated by e.g. clinical findings, imaging, biochemical results or histological examination at the discretion of the investigator.

Exclusion criteria

1. Non-Danish speaking
2. Expected to be unable to comply with the study protocol

Recruitment and informed consent procedures

Participants will be recruited from the Department of Dermatology, Department of Rheumatology and Department of Hepatology and Gastroenterology, Aarhus University Hospital. Participants will also be recruited based on referrals from other hospital clinics and from consultative private practice.

Referred patients will be discussed at an interdisciplinary preadmission assessment. Patients that are potentially eligible to take part in the trial are invited to attend a clinic appointment. Potential participants will receive verbal and written information regarding the study. Participants will be offered the possibility for bringing a lay representative and will be offered time for reflection to decide whether they wish to participate in the study.

Randomisation and allocation concealment

Eligible participants will be randomised in a 2:1 ratio to either treatment in the interdisciplinary combined clinic or usual care. Participants are randomised by the investigator using a validated REDCap randomisation module. The sequence generation is based on computer-generated random numbers and created by the Clinical Trial Unit at Aarhus University using permuted blocks and no stratification.[19] The investigators are blinded to the allocation sequence.

This is an open-label study and therefore both participants and investigators will be aware of allocation following the first enrolment visit.

Intervention

Interdisciplinary
The intervention in this trial consists of the combined efforts of the interdisciplinary team in the combined clinic arm. The intervention lies in the interdisciplinary organization of workup, treatment, and care for patients with complex IMIDs.
The interdisciplinary team consists of dermatologists, gastroenterologists, rheumatologists, nurses, psychologists, dieticians, social workers, and secretaries. Physiotherapists are involved as needed. Treatment will be individualized based on clinical, biomarker, phenotypic, and psychosocial characteristics. Consultations will be interdisciplinary and coordinated across disciplines. The medical treatment will follow local, national and international guidelines. Thus, the intervention is not a specific pharmaceutical treatment. See online supplementary file for a detailed description of the intervention.

Usual care
Usual care will be carried out by HCPs that are not otherwise involved in the trial. In usual care the patients will not be offered interdisciplinary patient-centred care as described, but rather attend their multiple usual disease-specific departments at the usual appointments. As participants will have complex IMID's this will typically entail attending multiple monodisciplinary specialized clinics. As in the interdisciplinary arm, treatment will be prescribed according to local, national and international guidelines by the treating physicians with no set protocol and no restrictions.

Trial objectives and endpoints
All primary and secondary objectives and endpoints are listed in table 1

Table 1. Objectives and endpoints

Objectives	**Endpoints**
Primary objective	**Primary endpoint**
To compare the change in generic HRQoL from baseline to 24 Weeks	• Change in mean SF-36 PCS from baseline to 24 Weeks
Key Secondary objectives	**Key Secondary endpoints**
To compare the change in generic PROs from baseline to 24 Weeks	• Proportion of subjects achieving MCID in SF-36 PCS at Week 24 • Change in mean SF-36 MCS from baseline to 24 Weeks • Change in mean Facit-Fatigue score from baseline to 24 Weeks • Change in mean WPAI score from baseline to 24 Weeks • Change in mean General Self-Efficacy scale scores from baseline to 24 Weeks • Change in mean HADS-A from baseline to 24 Weeks • Change in mean HADS-D from baseline to 24 Weeks
Additional secondary objectives	
To compare the change in disease-specific PROs from	• Change in mean DLQI from baseline to 24

baseline to 24 Weeks	Weeks • Change in mean HAQ from baseline to 24 Weeks • Change in mean BASDAI from baseline to 24 Weeks • Change in mean BASFI from baseline to 24 Weeks • Change in mean SIBDQ from baseline to 24 Weeks
To compare the change in cardiovascular and metabolic risk factors	• Change in body weight from baseline to 24 Weeks# • BMI response (5% BMI reduction) at 24 Weeks# • Change in waist-hip ratio from baseline to 24 Weeks# • Percent change in LDL-C, TC, TG, and HDL-C at 24 Weeks## • Change in proportion of subjects receiving lipid-lowering agents from baseline to 24 Weeks
To compare changes in signs and symptoms of inflammatory disease from baseline to follow-up	• PASI remission PASI ≤ 3 at Week 24 • PASI 75, 90, and 100 response at 24 Weeks* • Change in PASI, psoriasis BSA and number of psoriatic nails from baseline at 24 Weeks* • ASDAS remission at 24 Weeks (remission <1.3 / not in ASDAS remission >1.3)** • ASAS 20 and 40 response at 24 Weeks** • ACR 20, 50, and 70 at Week 24*** • Change from baseline in DAPSA*** • Change from baseline in MDA*** • HBI remission (HBI < 4) at 24 Weeks**** • SCCAI score < 2 (remission) at 24 weeks***** • Proportion of patients with Hidradenitis Suppurativa Clinical Response (HiSCR) at 24 Weeks******
To assess the change in generic and disease-specific HRQoL from baseline to all other applicable timepoints To assess whether changes in clinical endpoints is associated with changes in HRQoL	

Among patients with

*	Psoriasis at baseline
**	Axial SpA at baseline
***	Psoriatic Arthritis at baseline
****	Crohns disease at baseline
*****	Ulcerative colitis at baseline
******	Hidradenitis Suppurativa at baseline
#	BMI ≥ 35 at baseline
##	LDL-C ≥ 3.0 mmol/l at baseline

Abbreviations, table:
ACR: American College of Rheumatology
ASAS: Assessment of SpondyloArthritis international society
ASDAS: Ankylosing Spondylitis Disease Activity Score
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Function Index
BASMI: Bath Ankylosing Spondylitis Metrology Index
BMI: Body Mass Index
BSA: Body surface area
DAPSA: Disease Activity in PSoriatic Arthritis
DLQI: Dermatology Life Quality Index
HADS: Hospital Anxiety and Depression Scale
HADS-A: Hospital Anxiety and Depression Scale - Anxiety
HADS-D: Hospital Anxiety and Depression Scale - Depression
HAQ-DI: Health assessment questionnaire disability index
HBI: Harvey-Bradshaw index
HDL-C: Cholesterol High Density Lipoprotein
HiSCR: Hidradenitis Suppurativa Clinical Response
HRQoL: Health-Related Quality of Life
IGA: Investigators Global Assesment Scale
LDL-C: Cholesterol Low Density Lipoprotein
MCS: Mental Component Score
MCID: Minimal Clinical Important Difference
MDA: Minimal Disease Activity
PASI: Psoriasis Area Severity Index
PCS: Physical Component Score
PGA: Physician's global assessment
PRO: Patient Reported Outcome
SCCAI: Simple Clinical Colitis Activity Index
SF-36: Short Form Health Survey
SIBDQ: Short Inflammatory Bowel Disease Questionnaire
SJC: Swollen Joint Count
SPARCC: Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system
TC: Total Cholesterol
TG: Triglycerid
TJC: Tender Joint Count
WPAI: Work Productivity and Activity Impairment Questionnaire

Trial schedule and assessments

The study schedule (table 2) details the procedures and tests occurring at specific times throughout the study. Scheduled visits mandated by the protocol are for the purpose of data collection. Additional visits for workup, treatment, and care will be scheduled individually based on the discretion of the treating team in both arms with no restrictions set by the protocol.

Table 2 Study Schedule

Visit/eVisit	Visit 0	eVisit 1	eVisit 2	Visit 3	eVisit 4
Weeks	0	8	16	24	52
Visit window (±weeks)		± 2	± 2	± 4	± 4
Office visits					
Informed consent	X				
Demographics	X				
Inclusion/exclusion criteria	X				
Diagnosis of autoimmune diseases	X				
Smoking/alcohol/drugs consumption	X				
Autoimmune diseases: medical history / previous psoriasis therapies	X				
Other medical history / treatments	X			X	
Concomitant medications	X			X	
Randomisation	X				
Collection of adverse events (see section 25)	X			X	
Physical examination					
General physical examination	X			X	
Height	X				
Weight	X	X[1]	X[1]	X	X[1]
Hip and waist circumference	X			X	
Blood pressure, pulse	X			X	
PASI including BSA	X			X	
IGA	X			X	
Quantitative nail assessment	X			X	
HBI	X			X	
SCCAI	X			X	
TJC (68 joints)	X			X	
SJC (66 joints)	X			X	
BASMI	X			X	
SPARCC	X			X	
Dactylitis count	X			X	
PGA of disease activity (VAS scale)	X			X	
ePROs					
General HRQoL					
SF-36	X	X	X	X	X
Fatigue					
FACIT-Fatigue	X	X	X	X	X
Work productivity					
WPAI	X	X	X	X	X
Self-Efficacy					
General Self-Efficacy scale	X	X	X	X	X
Depression and anxiety					

HADS	X	X	X	X	X
Skin					
DLQI	X	X[2]	X[2]	X	X[2]
Muscoloskeletal					
HAQ-DI	X	X[3]	X[3]	X	X[3]
BASDAI	X	X[3]	X[3]	X	X[3]
BASFI	X	X[3]	X[3]	X	X[3]
Patient's assessment of pain (100 mm VAS scale)	X	X[3]	X[3]	X	X[3]
Patient's assessment of inflammatory back pain (100 mm VAS scale)	X	X[3]	X[3]	X	X[3]
Patient's global assessment of disease activity (100 mm VAS scale)	X	X[3]	X[3]	X	X[3]
Gastrointestinal					
SIBDQ	X	X[4]	X[4]	X	X[4]
Labs					
Serum electrolytes + renal panel	X			X	
Acute-phase proteins	X			X	
Lipids	X			X	
Liver enzymes	X			X	
Glucose metabolism	X			X	
Optional biobank samples	X[5]			X[5]	
Procedures					
Optional punch biopsy	X[5]			X[5]	

Abbreviations table:
BASDAI - Bath Ankylosing Spondylitis Disease Activity Index
BASFI - Bath Ankylosing Spondylitis Function Index
BASMI - Bath Ankylosing Spondylitis Metrology Index
BSA - Body surface area
DLQI - Dermatology Life Quality Index
HADS - Hospital Anxiety and Depression Scale
HAQ-DI - Health assessment questionnaire disability index
HBI - Harvey-Bradshaw index
HRQoL - Health-Related Quality of Life
IGA - Investigators Global Assesment Scale
PASI - Psoriasis Area Severity Index
PGA - Physician's global assessment
PRO – Patient Reported Outcome
SCCAI - Simple Clinical Colitis Activity Index
SF-36 - Short Form Health Survey
SIBDQ - Short Inflammatory Bowel Disease Questionnaire
SJC – Swollen Joint Count
SPARCC - Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system
TJC - Tender Joint Count
VAS – Visual Analog Scale
WPAI - Work Productivity and Activity Impairment Questionnaire

QoL – Quality of Life

[1]As reported by the subject
[2]To be reported by subjects with current or previous psoriasis or HS
[3]To be reported by subjects with axSpA/AS or PsA, diagnosed or suspected
[4]To be reported by subjects with IBD, diagnosed or suspected
[5]Requires additional informed consent

See online supplementary file for additional description of assessments and procedures.

Adverse events

The objective of this study is effectiveness and not risk. Medicines are used in accordance with market authorisations and no specific medicines are being examined. The protocol does not endorse any prespecified treatment; rather medicines will be used at the physician's discretion in both arms of the study. This trial does not fall under the definition of a clinical trial of medicinal products. Thus, suspected adverse drug reaction (ADR)s to medicines used in the trial will be subject to standard reporting to the Danish Medicines Agency according to standard clinical practice.

Reporting of suspected side effects from medicines are pursuant to the Danish executive order no. 381 of 9 April 2014 on the reporting of side effects from medicines etc.

Serious Adverse Events (SAE)'s will be collected systematically in the trial at Week 24 and if spontaneously reported from baseline to Week 24. Drug relatedness of SAE's will be assessed by a trained physician. SAE's will be recorded in the medical record and the eCRF.

[1]An SAE is any untoward medical occurrence that

- results in death.
- is life-threatening.
- requires inpatient hospitalisation or prolongation of existing hospitalisation. (Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is a medically important condition. Events that may not be immediately lifethreatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Sample size

The primary outcome is change in the physical component of HRQoL, measured using SF36 PCS, 24 Weeks after randomisation.

Specification of the sample size calculation, including the target difference, is reported according to the guidance for reporting items available from the DELTA2 guidance on choosing the target difference and undertaking and reporting the sample size calculation.[20] The sample size of 300 patients (randomised: 200-to-100) is designed to provide a high statistical power (>90%) to detect a 5-unit difference in SF36-PCS change

between the groups. All power and sample size calculations were conducted using 'R software version 3.4.3 (The R Foundation for Statistical Computing).

SF36 PCS: for a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05 (P<0.05), assuming a common standard deviation of 10 SF36 points, a sample size of 85 patients per group has a power of 90% to detect a mean difference in the group mean changes of 5 SF36 points (corresponding to a moderate Cohen's effect size of 0.5). Due to a very limited experience with attrition and poor adherence rates it was decided to aim for enrolment of 300 participants in total; with a majority (200 patients) being randomised to the interdisciplinary intervention. With 100 patients in each group in the intention-to-treat (ITT) population, the statistical power might be as high as 94% based on the assumptions above.

Statistical analysis

All P values and 95% confidence intervals (95%CI) will be two sided. We will not apply explicit adjustments for multiplicity, rather we will analyse the key secondary outcomes in a prioritized order (e.g. using "gatekeeping procedure"); i.e., the analyses of the key secondary outcomes will be performed 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.[21] The key secondary statistical tests will be reported with P values for hypothesis tests and claims of statistical significance. The primary statistical model will consist of repeated-measures linear mixed models to compare patient outcomes trajectory over time between the two intervention groups (i.e. Time×Group interaction).

The prespecified efficacy analyses will be based on the ITT population, using data from the full-analysis set, which will include all patients who underwent randomisation, and had at least the outcome of interest measured at baseline.[22] Data will be analysed using R and SAS or STATA, with the particular outcome variable at baseline level as a covariate - using a multilevel repeated measures mixed effects model with participants as the random effect factor based on a restricted maximum likelihood (REML) model. The change in the SF36 PCS value will be the (primary) response variable, and the baseline value (one for each participant), treatment group (2 levels), and time (4 levels: 0, 8, 16, and 24 weeks) will be included as covariates, as well as the interaction between treatment group and time (Group×Time), and Patient ID as a random effects factor. This statistical model will hold all between-group comparisons at all assessment points (incl. baseline) and allows for evaluation of the average effect, as well as the trajectory over the time period from baseline to 24-Weeks follow-up.[23] Results will be reported as the difference between least squares means and their corresponding 95%CI.

Categorical changes for dichotomous end points will be analysed with the use of logistic regression with the same fixed effects and covariates as the respective analysis of continuous outcomes; Odds Ratios (ORs, and 95% CI) will subsequently be converted into Risk Ratios (RRs, and 95%CI).

Handling of Missing Data and Sensitivity Analyses

We plan to conduct both an analysis of the full analysis set (ITT population) and a per protocol analysis, so that any differences between them can be explicitly discussed and interpreted. Using mixed models, like described above, provide valid estimates of treatment

effects even when the missing values are not completely random,[23] and additional methods for handling missing data, such as multiple imputation, are generally not required.

Missing data will be handled by:

1. Attempt to follow up all randomised participants, even if they withdraw from allocated treatment.

2. Perform a main analysis of all observed data that are valid under a plausible assumption about the missing data (i.e. Model-based: data as observed; using linear mixed models assumes that data are "Missing At Random" (MAR).

3. Perform sensitivity analyses to explore the effect of departures from the assumption made in the main analysis (i.e. a non-responder-imputation: using the value at baseline to replace missing data will correspond to a non-responder imputation; these models will potentially be valid even if data are "Missing Not At Random" (MNAR).

4. Account for all randomised participants, at least in the sensitivity analyses (covered by #2 and #3 above plus the corresponding analyses based on the Per protocol population).

The interpretation of the corresponding statistical measures of uncertainty of the treatment effect and treatment comparisons will involve consideration of the potential contribution of bias to the p-value, 95% confidence interval, and inference in general.

Our primary analysis population will be all participants with available data at baseline statistically modelled using repeated-measures linear mixed models (see above). These models will be valid if data are MAR.

#3+4 Sensitivity: We will analyse all variables with missing data being replaced by imputation of the baseline level; i.e. interpreted as assuming that those who dropped out returned to their baseline level; These estimates could potentially be valid even if data are MNAR.

ETHICS AND DISSEMINATION

The risks and burden associated with participating in this clinical trial are considered low and outweighed by the benefit of achieving high-quality scientific knowledge regarding the potential benefits of treating patients with complex IMIDs in an interdisciplinary combined clinic setting. Additionally, on the individual level, participants are expected to experience immediate diagnostic and therapeutic benefit from the interdisciplinary approach. Ethical approval of this study protocol was established by the Central Denmark Region Ethical Committee The findings from this trial will be disseminated via conference presentations and publications in peer-reviewed journals, and by engagement with patient organizations.

DISCUSSION

For the purpose of the current trial a number of prototypical IMIDs have been chosen: Psoriasis, HS, UC, CD, axSpA and AS, and PsA. These diseases will serve as a model for autoimmune diseases in which an interdisciplinary and combined clinical approach will be tested. We believe the model will be scalable with the potential to include other IMIDs in the future.

This study has the potential to address some of the main challenges for IMIDs regarding the management of the complexity of the diseases and comorbidities. The focus of the study will be on personalized, preventive and participatory healthcare.

As described above, patients often have more than one IMID, which lead to patients often need to attend several departments. Patients report communication problems between the departments, experience of neglect regarding comorbidities, and that they are left with the responsibility for coordinating the different treatment courses between the different departments.[12-14]

An increasing body of literature supports that IMIDs share many immunopathogenic features and that there is a considerable clinical and therapeutic overlap between the diseases.[1, 24] This underlines the need to abandon previous perceptions of IMIDs as based on cluster of symptoms and a specific silo in the health-care system. Rather, IMIDs must be seen as chronic conditions that may affect a number of body functions and other patient-relevant social and personal aspects. This calls for an integrated and interdisciplinary approach, which will be in scope for this study. Previous efforts to improve patient-centricity within IMID's through combined clinics have typically included only two medical specialties, e.g. rheumatology and dermatology.[15, 16] The novelty of our concept is firstly, that it includes a broader range of relevant medical specialties spanning a range of inflammatory diseases affecting the skin, musculoskeletal system, and gut. Secondly, the concept adheres to a holistic treatment approach, as other cross-disciplinary professionals are part of the team. Thirdly, the effectiveness of the interdisciplinary combined clinic approach is assessed through data generation in a randomised, usual-care controlled trial setting which has not previously been done.

If it is shown that an interdisciplinary patient-centred approach improves quality of life in these patients compared to usual health care, professionals may rethink the way the health system is organized, and ultimately implement an interdisciplinary approach in the management of IMIDs.

Another aspect that will be explored in this project is whether an interdisciplinary patient-centred approach is associated with a socio-economic benefit e.g. by reducing patients´ sick leave, need for attending to health care and lower medicine costs.

There is currently a political and patient-driven move toward an interdisciplinary treatment approach. However, for this to be broadly generalizable the potential advantages must be proven toward the usual and traditional therapeutic approach.

The pragmatic elements in the design of this trial increase the likelihood that the results can be generalized to everyday practice and support decision-making by patients, providers, and health system leaders. The use of a generic PRO as the primary outcome is remarkable and creates a strong focus on patient-centricity. A generic PRO that can be used across age, disease, and treatment groups enables a meaningful assessment of patients with complex IMIDs.[25-27]

However, there are some limitations in this study. The minimisation of inclusion and exclusion criteria, the potential diversity of individualised treatments, and participants' experience and expectancy of living with a chronic disease may introduce additional variables, which may affect the outcomes. The 24 Weeks duration of the intervention may be insufficient to provide the full benefit in the selected group of patients with chronic, long-standing, complex IMIDs and comorbidities. Sample size calculation is based on the primary outcome, change in SF-36 PCS, whereas the trial may be underpowered to assess changes in

subgroups of participants within each disease domain. Thus, there may be insufficient statistical power to determine the effect of the intervention on certain secondary endpoints.

Furthermore, investigators and patients cannot be blinded to participation randomisation outcomes due to pragmatic design limitations. Increased disease awareness in the usual care group caused by participating in the trial may potentially reduce the difference between the intervention group and the usual care group.

Nonetheless, the results and experience from this study may reveal the benefits of managing patients with complex IMIDs in an interdisciplinary setting. The trial may provide evidence as to whether an interdisciplinary approach to complex autoimmune diseases is beneficial for the patients and lower the socio-economic burden.

This could form the basis for establishing further interdisciplinary autoimmune clinics on a national and international scale.

Trial status

This trial is ongoing. The first participant was enrolled on January 14th 2020.

ACKNOWLEDGMENTS

The authors wish to acknowledge the entire team in the National Center for Autoimmune Diseases for their dedicated work; including current and previous team members: Lise Guld Lerke-Møller, Rikke Edelbo, Mia Marie Remmer, Anja Astrup, Caroline Vinther Hammelsvang, Karen Margrethe Schifter Kirketerp, Helene Almind Pedersen, Louise Gude Jensen, Inger Nielsen Larsen. Sanne Schou. The authors also wish to acknowledge the patient organizations ”De Autoimmune” and ”Foreningen for Autoimmune Sygdomme” for collaboration in establishing the National Center for Autoimmune Diseases.
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Figure legends

Figure 1: Trial design. Two-arm, randomised, usual care controlled, parallel-group pragmatic clinical trial.
Figure 2: Study flow diagram.

Author contributions

KFH is the principal investigator and is responsible for leading the design phase and drafting of the protocol. All authors made contributions to the design of the trial and have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript. LI wrote the project grant application and was awarded funding to establish the center in which the trial is being run.
Non-author contributors: Lise Guld Lerke-Møller, Rikke Edelbo, Mia Marie Remmer, Anja Astrup, and Caroline Vinther Hammelsvang participated in writing or technical editing parts of the protocol.

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Competing interest statement

Anders Dige has received speaking fees from Pfizer.

Anne Gitte Loft has been a consultant and advisor for the following companies: AbbVie, Eli Lilly, MSD, Novartis, Pfizer and UCB and has received speaking fees from: AbbVie, MSD, Novartis, Pfizer and UCB.

Jørgen Agnholt has been consultant, advisory board member or speaker for the following companies: AbbVie, MSD, Bristol Meyer Squibb, Ferring Pharmaceuticals, Pfizer, Janssen-Cilag and Takeda
Kasper Hjuler has been a consultant and advisor for the following companies: AbbVie, LEO Pharma, Novartis and has received speaking fees from: AbbVie, LEO Pharma, Novartis, Janssen, CSL Behring.
Lars Iversen has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by: AbbVie, Almirall, Amgen, Astra Zeneca, BMS, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen Cilag, Kyowa, Leo Pharma, MSD, Novartis, Pfizer, Samsung, UCB.
Louise Faurskov Møller has been advisory board member for Janssen and has received speaking fees from LEO Pharma.
Robin Christensen reports no conflicts of interest.
Trine Bay Laurberg has been a consultant and advisor for UCB.

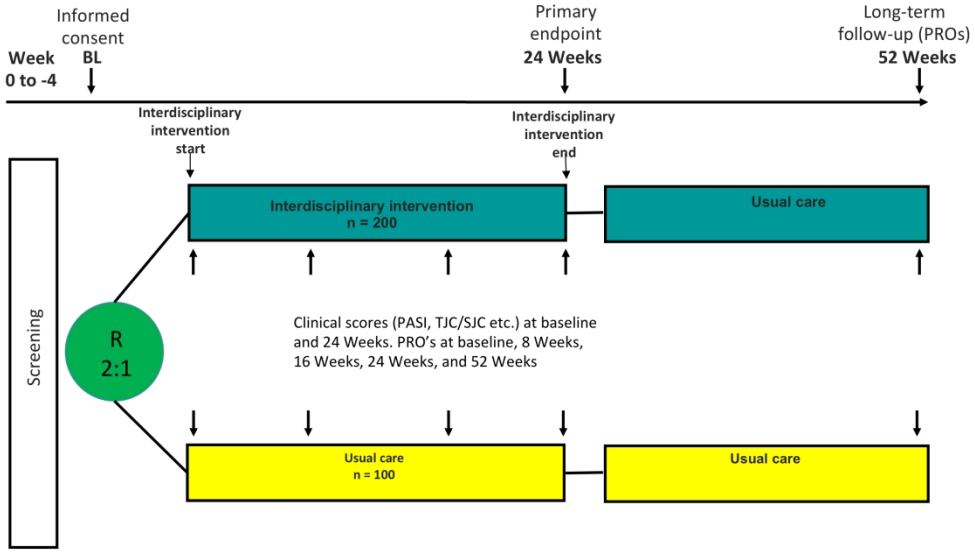

Figure 1: Trial design. Two-arm, randomised, usual care controlled, parallel-group pragmatic clinical trial.

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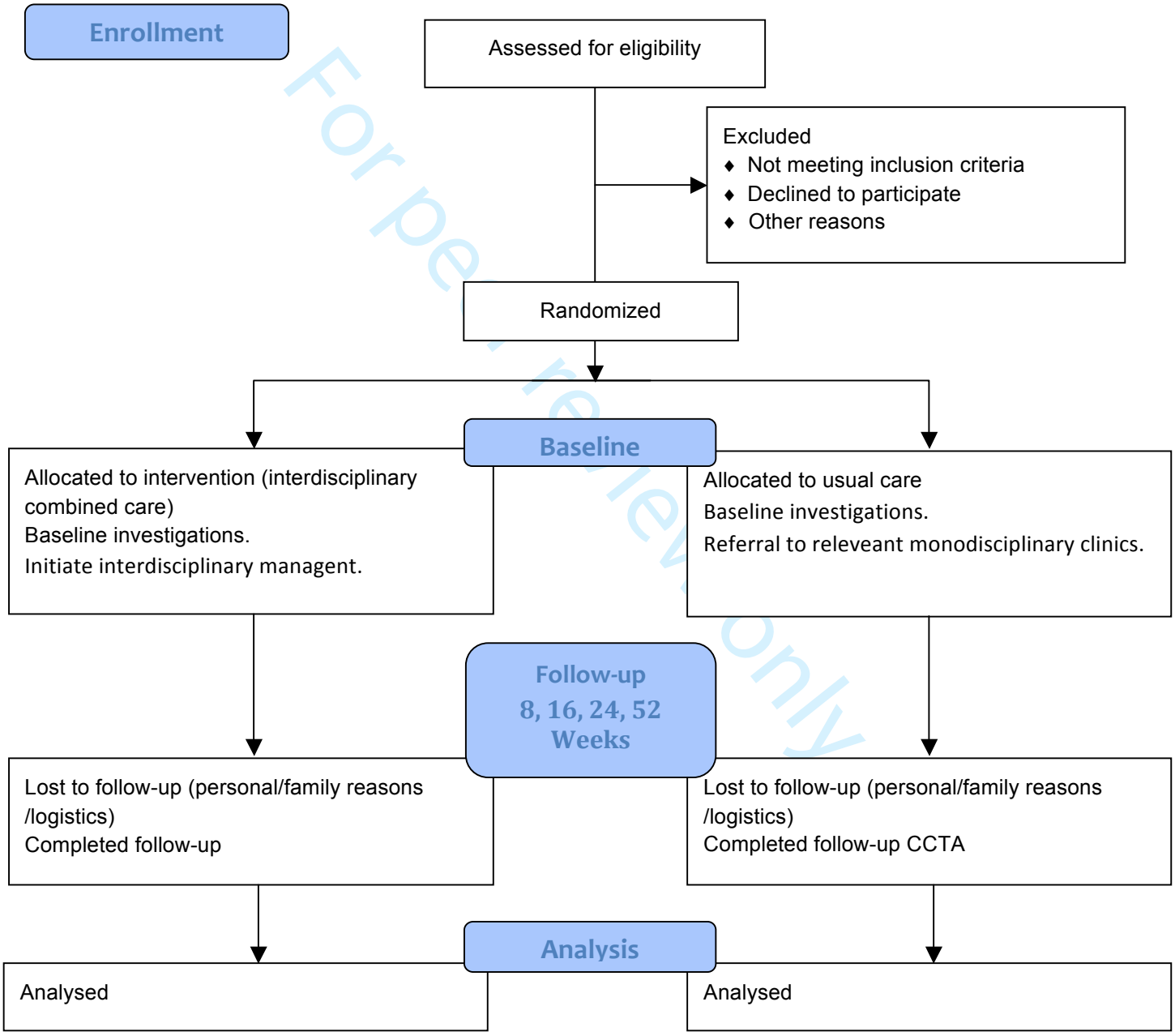

Supplemental appendix

Clinical Trial Protocol

EFFECTIVENESS OF INTERDISCIPLNARY COMBINED DERMATOLOGY-GASTROENTEROLOGY-RHEUMATOLOGY CLINICAL CARE COMPARED TO USUAL CARE IN PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES:

A parallel group, non-blinded, pragmatic randomized trial

National Center for Autoimmune Diseases Aarhus University Hospital		
	Central Denmark Region Ethical Comittee No.	**1-10-72-176-19**
	Date	**22-DEC-2019**
	Version	**1.4.1**

Trial ID: 1-10-72-176-19	Date: 22.12.2019	Page 2 Version 1.4.1

Clinical Trial Approval Statement

1.1 Approval statement sponsor

The following person has approved this clinical trial protocol:

Lars Iversen, MD, DMSc
Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

1.2 Approval statement investigator

The following person has approved this clinical trial protocol:

Kasper Fjellhaugen Hjuler, MD, PhD
Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

1.3 Approval statement co-investigators

The following persons has approved this clinical trial protocol:

Jørgen Agnholt, MD, PhD
Department of Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

Anders Kirch Dige, MD, PhD
Department of Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

Trine Bay Laurberg, MD, PhD
Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark

Anne Gitte Loft, MD, DMSc
Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark

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1.4 Collaboration partner

Biostatistical advice:

Robin Christensen, M.Sc., PhD
Professor of Biostatistics and Clinical Epidemiology, Musculoskeletal Statistics Unit, the Parker Institute, Bispebjerg and Frederiksberg Hospital and the Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark.

1.5 GCP responsibilty

The following person take responsibility for enabling GCP monitoring:

Kasper Fjellhaugen Hjuler, MD, PhD
Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

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3 Trial Identification

Central Denmark Region Ethical Committee: 1-10-72-176-19
ClinicalTrials.gov: NCT04200690

4 Trial location

Nationalt Center for Autoimmune Sygdomme
Hud- og kønssygdomme
Aarhus Universitetshospital
Palle Juul-Jensens Boulevard 67
8200 Aarhus N

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5 List of abbreviations:

5-ASA: 5-aminosalicylates
ACR: American College of Rheumatology
AS: ankylosing spondylitis
ASAS: Assessment of SpondyloArthritis
ASDAS: Ankylosing Spondylitis Disease Activity Score
axSpA: axial spondylarthritis
BASDAI: Bath Ankylosing Spondylitis Disease Activity Inex
BASFI: Bath Ankylosing Spondylitis Functional Index
BASMI: Bath Ankylosing Spondylitis Metrology Inde
BMD: Bone mineral density
BSA: Body surface area
CBT: Cognitive Behavioral Therapy
CD: Crohn´s disease
CRP C-reactive protein
CTLA-4: Cytotoxin T-lymphocyte-associated protein 4
CV: Cardiovascular
DAPSA: Disease Activity in PSoriatic Arthritis
DLQI: Dermatology Life Quality Index
EIM: Extraintestinal inflammatory manifestations
ER: endoplasmatic reticulum
HBI: Harvey Bradshaw index
IMD: Immune-meditated diseases
IBD: inflammatory bowel diseases
IMID: immune-mediated inflammatory disease
IPCHS: integrating people-centered health services
HADS: Hospital Anxiety and Depression Scale
HAQ: Health Assessment Questionnaire
HAQ-DI: Health assessment questionnaire disability index
HRQoL: Health-Related Quality of Life
HCPs: health care professionals
HS: Hidrosadenitis Suppurativa
IGA: Investigators Global Assessment Scale
IL: interleukin
IMID: Immune-Mediated Inflammatory Disease
NNR: Nordic Nutrition Recommendation
NSAID: anti-inflammatory drugs
PASI: Psoriasis Area Severity Index
PCC: patient-centeret care
SPACE: SpondyloArthritis Caught Early
PGA VAS: Patient global assessment of pain
PsA: Psoriatic Arthritis
SCCAI: Simple Clinical Colitis Activity Index
SCFA: short chain fatty acids
SF-36: Short Form Health Survey
SIBDQ: Short Inflammatory Bowel Disease Questionnaire
SIJ: Sacroiliac Joints

SJC: Swollen Joint Count
SMR: standardized mortality ratio
SPARCC: Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system
Th: T-helper lymphocyte
TJC: Tender Joint Count
T-regs: regulator T cells
TNF-alfa: tumor necrosis factor alfa
TGF -: Transforming Growth Factor - beta
UC: ulcerative colitis
WHO: World Health Organization

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6 Intervention

6.1 Interdisciplinary combined clinic vs usual care

The intervention in this trial consists of the combined efforts of the multidisciplinary team in the combined clinic arm. All diagnostic procedures and therapy will be carried out according to local, national, and international guidelines as outlined below. This applies to both arms of the trial. Individual choices regarding procedures and therapy are at the investigators discretion and not defined by the protocol. Usual care will be carried out by HCPs that are not otherwise involved in the trial.

6.2 Treatment

Treatment in both the combined clinic arm and the usual care arm adheres to the principles outlined below.

7.1 Dermatology

7.1.1 Psoriasis

The medical treatment of patients with psoriasis will follow local, national and international guidelines in accordance with the treatment principles of Department of Dermatology, Aarhus University Hospital[1] and the Danish National Treatment Recommendations for psoriasis.[2] Treatment with 2nd generation immunomodulating agents including biologics will be carried out in accordance with the latest version of treatment recommendations from the Danish Medicines Council.[3]

Figure 1 provides an overview of the treatment algorithm for psoriasis.

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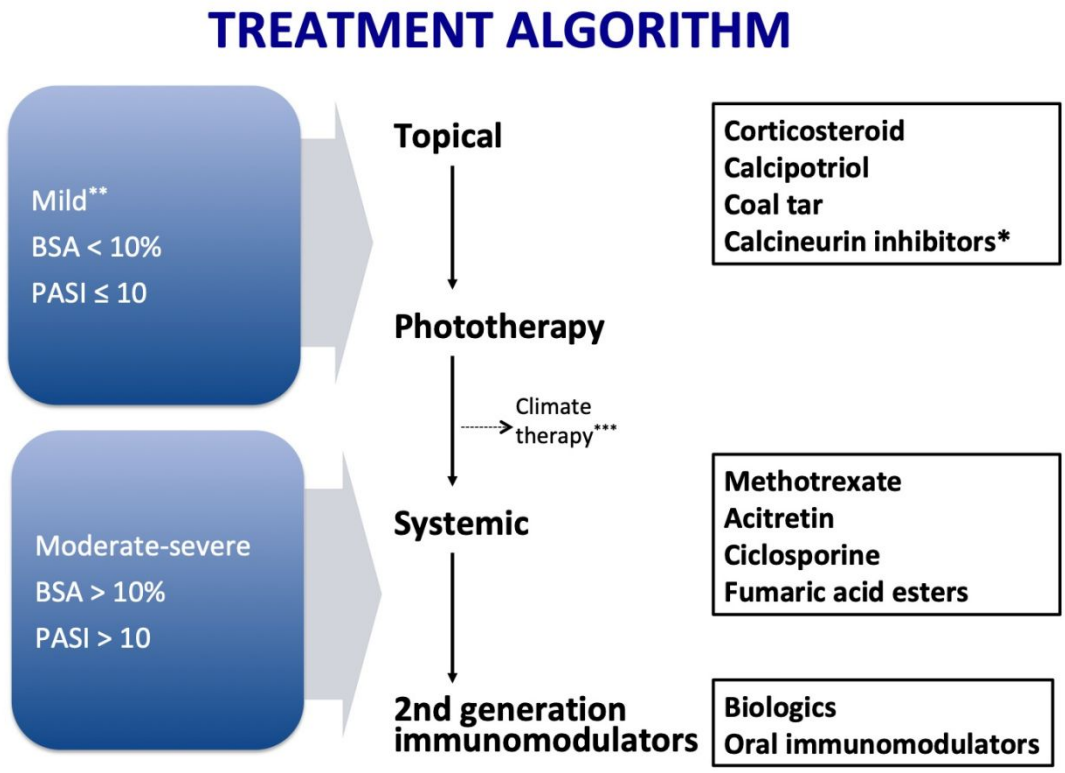

*Off-label
**Involvement of scalp, face, hands, nails, palmoplantar, or genital area may be treated as moderate-severe psoriasis despite PASI < 10[4]
***Adjunctive therapy if needed

7.1.2 HS

The medical treatment of patients with HS will follow local, national and international guidelines in accordance with the treatment principles of Department of Dermatology, Aarhus University Hospital[5] and the Danish Society of Dermatology Treatment Recommendations for HS.[6] Treatment with 2nd generation immunomodulating agents including biologics will be carried out in accordance with the latest version of treatment recommendations from the Danish Medicines Council.[3]

Figure 2 provides an overview of the treatment algorithm for HS.

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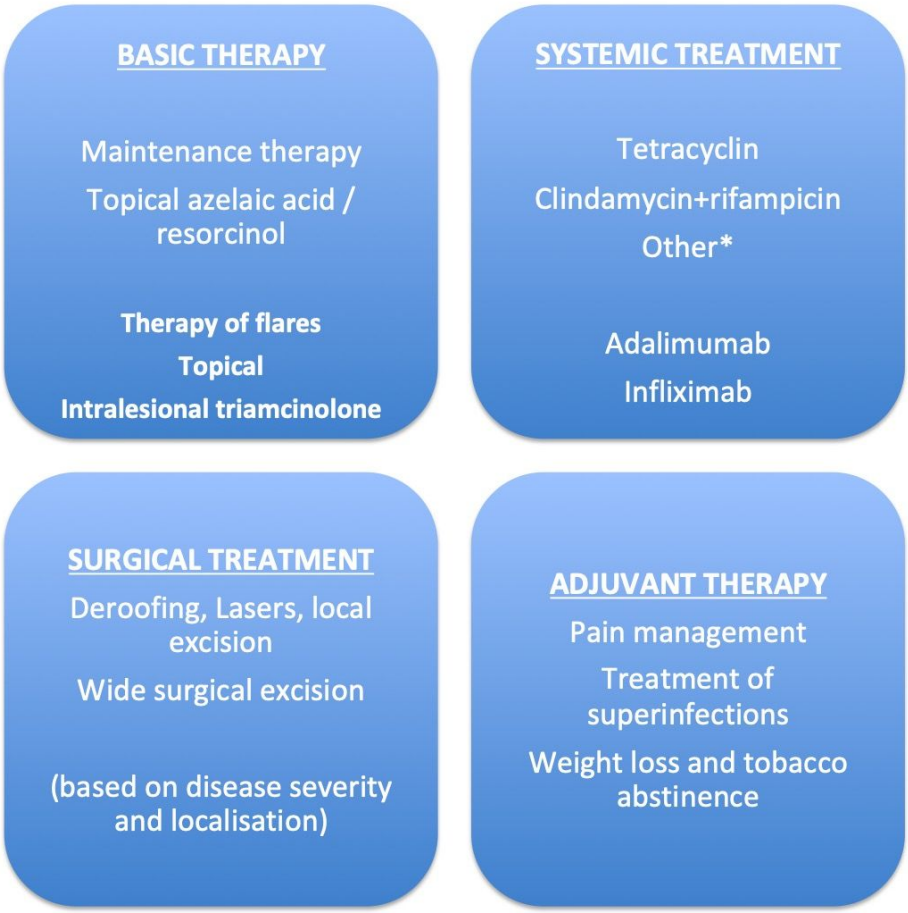


*Metformin (obese), acitretin, dapson

7.2 Gastroenterology

7.2.1 CD and UC

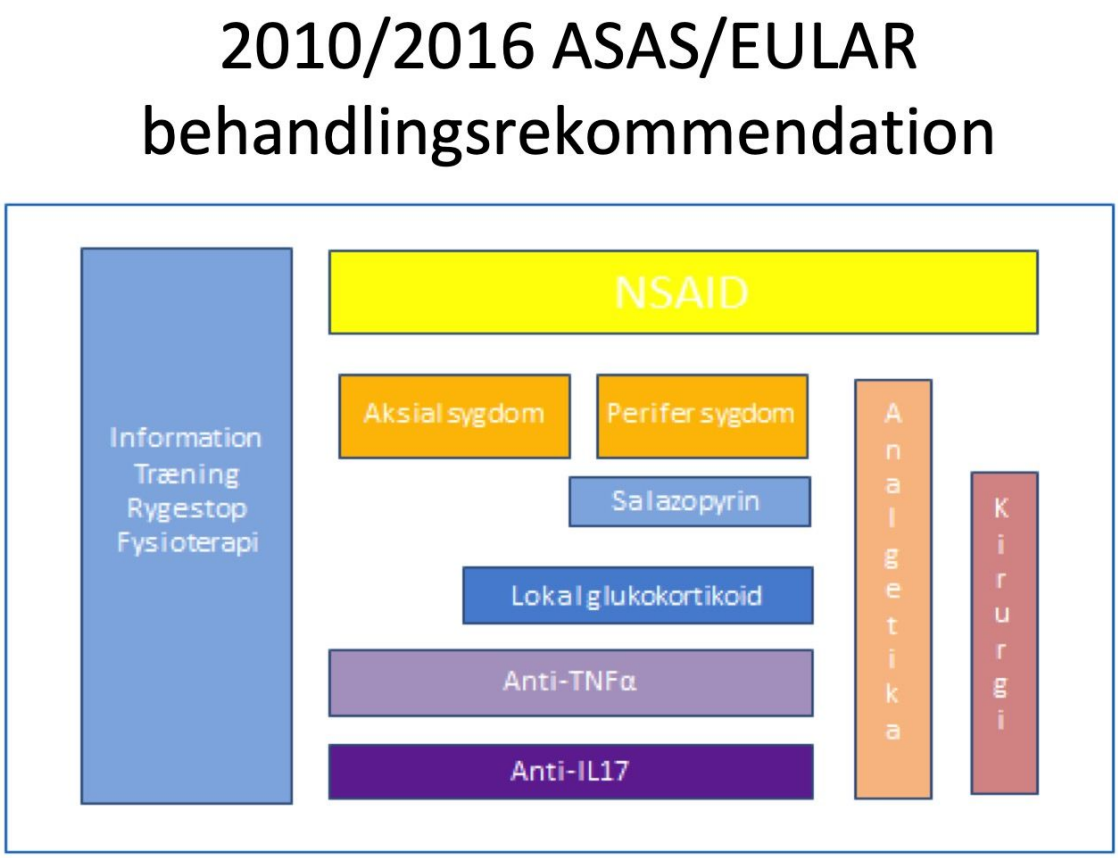
The medical treatment of patients with IBD will follow local, national and international guidelines in accordance with the treatment principles of Department of Gastroenterology and hepatology, (Lever-mave-tarm Sygdomme) Aarhus University Hospital[7] and the European Crohn's and Colitis Organisation.[8, 9] Treatment with 2nd generation immunomodulating agents including biologics will be carried out in accordance with the latest version of treatment recommendations from the Danish Medicines Council.[3]

7.3 Rheumatology

7.3.1 AxSpA/AS and PsA

The medical treatment of patients with axSpA/AS and PsA will follow local, national and international guidelines in accordance with the treatment principles of Department of Rheumatology, Aarhus University Hospital[10] and The National treatment guideline made by Dansk Reumatologisk Selskab.[11] Treatment with 2nd generation immunomodulating agents including biologics will be carried out in accordance with the latest version of treatment recommendations from the Danish Medicines Council.[3]

Figure 3 provides an overview of the treatment algorithm for axSpA and AS.
Non-pharmacological treatment is a cornerstone - especially exercises.



7.4 Cross-disciplinary

As part of the interdisciplinary combined clinic the following disciplines will be a part of the treatment as needed.

7.4.1 Dietetics

There is no specific diet intervention with proven efficacy in IMIDs.[12, 13] However, it is well-known that patients with an IMID have an increased risk of comorbidities.[12, 13]
Studies have shown, that obesity and weight gain is strongly associated with the severity and disease activity among patients with psoriasis and HS. Furthermore, weight loss interventions have shown to improve disease activity and is therefore recommended in these conditions.[13-15]
Among patients with IBD, malnutrition and malabsorption in CD patients may result in micronutrient deficiencies. Furthermore, disease activity in IBD is associated with weight loss and increased protein intake are relevant in some patients.[12]

Dietary treatment is therefore an important supplement to the medical treatment in the management of some IMIDs. It is important that the dietary treatment is based on an individualized approach, where the patient's needs, motivation, behavior, preferences, wishes and life conditions are taken into consideration. Patient education is an important factor in obtaining lasting lifestyle changes.
In patients needing weight loss the goal will be a weight reduction of 5%-10%, which has been shown to improve blood glucose, blood pressure and lipid profile.[16] A weight loss has been associated with reduced disease severity in patients with psoriasis and HS.[14, 17]
In patients with IBD the dietetic counselling will aim to correct and avoid the development of malnutrition. Furthermore, focus will be on identification and subsequently elimination of specific foods, which the patient experience as symptomatic.
All dietary treatment will be in accordance with the national Danish guidelines and the Nordic Nutrition Recommendations (NNR) according to optimal macro- and micronutrient composition.
Dietetic monitoring will consist of weight, waist circumference, BMI, blood glucose, blood pressure, lipid profile, and if relevant micronutrient status.

7.4.2 Psychology

IMIDs are associated with the development of psychological distress, reduced life quality, anxiety, and depression.[18-20]
Preliminary evidence indicates a beneficial effect of psycotherapy in common emotional and psychological disorders associated with IMIDs. Specifically, a number of studies have shown improvements in anxiety, depression, and disease-related stress in patients with IMIDs treated with cognitive behavioral therapy (CBT).[21-24] Moreover, some studies have shown beneficial effect of CBT on clinical disease parameters and a potential antiinflammatory effect of CBT.[25] The latter most likely mediated through positive effect on the systemic inflammatory load through effects on mental and psychological wellbeing. In general, there is consistent supportive evidence for the efficacy of CBT in a variety of problems,[26] however, the evidence-base in IMIDs are still limited.

The aim of the psychological intervention in this trial is to provide relevant patients with different perspectives and tools that can enhance their qualified self-determination when living with a chronic IMID. The aim is hereby to strengthen the patients' self-efficacy[27] and abilities to cope with pain and psychological distress, in order to create a good balance in life – despite having a chronic IMID.

Treatment will involve the application of a range of cognitive and behavioral strategies designed to alter the factors that trigger, maintain, or exacerbate symptoms. Patients are taught to refute or modify unhelpful thoughts and coping patterns. The strategies are aimed to help patients gain control over both psychological and physical symptoms.
A part of this intervention is to help the patients towards a greater awareness of how they deal with their basic psychological needs, and how these needs influence their health and psychological well-being.

If relevant the patients will receive psychoeducation about anxiety, depression and psychological distress.

Patients will be screened with PRO measures, and as part of the clinical assessment. Patients in the interdisciplinary intervention arm will be offered CBT if these assessments indicate significant psychological and social disabilities as assessed by the investigator.

7.4.3 Social work

Studies show that IMIDs have major consequences for education and work. A study by KORA shows that the proportion of people who have dropped out of their education increases with the number of autoimmune diagnoses, and that patients had on average 28 sick days/year due to their IMID(s). A social worker is therefore associated with the center. Patients will be referred to the social worker, if there is a need to clarify personal, social, economic or working issues. The social worker will provide advice and guidance regarding applications for financial or assistive technology support (medical grants and aids). In addition, the social worker can help patients to maintain their attachment to the labor market or education and help those who have lost their attachment to reintegrate[28].

Focus will also be on providing relevant patients with knowledge regarding rights and opportunities. This can provide and ensure them the feeling of social security and prevent escalation of their problems. We will use the Work Productivity and Activity Impairment Questionaire (WPAI) to identify patients who are in risk of losing their attachment to the labor market.

8 Provision for subject care following trial completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, subjects in the combined clinic arm will be treated at the investigator's discretion or referred to other physicians according to clinical practice and national treatment guidelines. This also applies to subjects that dropout or terminates the study before completing all visits.

Participation in the trial will have no influence on the treatment of subjects in the usual care arm during or after the trial.

9 Trial schedule and assessments

9.4 Assessments performed only at screening/baseline

9.4.1 Demographics

The following demographic data will be recorded:
- Month and year of birth
- Sex
- Race: Asian, Black or African American, Middle East and North Africa, White, Other

9.4.2 Medical history

Relevant past and concurrent medical history must be recorded and includes:
- Diagnosis of psoriasis, PsA, HS, axSpA, CD, UC
- Diagnosis of other autoimmune diseases
- Information regarding CV and metabolic risk factors
- Previous and current CV and/or metabolic diseases
- Previous and current immunomodulating agents (systemic and topical)
- Concomitant medication (categorised: antidiabetic, antihypertensive, lipid-lowering, diuretics, NSAID), procedures and diagnoses

9.4.3 Height and weight

The subject's height must be measured (without shoes) and weight must be determined (in indoor clothing and without shoes).

9.4.4 Hip and Waist circumference

Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor (108).

9.5 Generic HRQoL PRO's

PROs are increasingly used in clinical trials, in registries, and, to a lesser extent, in daily clinical practice.[29] There is an increasing awareness that health care should not only reduce symptom severity or reverse disease progression, but also improve how patients feel and function in daily life. There's a growing awareness on PRO data among clinicians, patient organizations, health systems, and regulatory authorities.[29-31]

9.5.1 SF-36

SF-36 is a multipurpose generic health survey that works across various age groups, diseases, and treatments. It has been used worldwide in a variety of studies including a large number of different diseases and it is reported as the most frequently used PRO instrument in clinical trials today.[32] A large body of evidence supports the validity and reliability of SF-36.[33] It has been validated and widely used in a large number of conditions including IMIDs, and it is generally accepted as a measure of disease burden.[33-36]
SF-36 is comprised of 36 items that assess eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions. Physical and mental health summary scores are also derived from the eight SF-36 scales. Scores can be compared to general population norms or between groups and clinically important difference for SF-36 scales and summary measures has been published.[33-36]
Clinically meaningful differences are based on definitions for Minimal Clinically Important Differences (MCID) of 2.5–5 points in Physical Component Score (PCS) and Mental Component Score (MCS) of SF-36 derived from published randomized controlled trials in relevant IMIDs.[34, 37, 38]

9.5.2 Work Productivity and Activity Impairment Questionnaire (WPAI:GH)

The WPAI questionnaire is a well-validated instrument to measure impairments in work and activities.[39, 40] The WPAI assess the impact of disease on work productivity and daily activities during the past seven days, using 6 questions regarding: 1 (if currently employed); 2 (hours missed due to disease); 3 (hours missed other reasons); 4 (hours actually worked); 5 (degree disease affected productivity while working); 6 (degree disease affected regular activities). WPAI generates four main outcomes: 1 percentage of work time missed (absenteeism); percentage of impairment while working (presentisms); percentage of overall work impairment (absenteeism and presentisms combined); and percentage of activity impairment. Scores for WPAI range from 0% to 100%, where 0 % indicates no impairment and 100% is total loss of work productivity/activity.

9.5.3 FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale) is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function.[41] It has been employed in many published studies including a large number of subjects, including patients with psoriasis, PsA, HS, AxSpA, IBD, and other IMIDs[41-47].
All FACIT scales are scored so that a high score is good. As each of the 13 items of the FACIT-Fatigue Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst

possible score and 52 the best. To obtain the 0-52 score each negatively-worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score.
The average score in the US general population is 40, with a standard deviation (SD) of approximately 10. Studies have shown that a FACIT-Fatigue score of 30, which is 1.0 SD below the average for the general population, may be considered significantly below the normal level. An increase or decrease of 3-4 points on the scale may reasonable be considered a relevant change in the score.[42, 48]

9.5.4 General Self-Efficacy Scale

The General Self-Efficacy Scale is a 10-item psychometric scale that is designed to assess optimistic self-beliefs to cope with a variety of life difficulties. The scale has been used in many studies with hundred thousand of participants. In contrast to other scales that were designed to assess optimism, this one explicitly refers to personal agency, i.e., the belief that one's actions are responsible for successful outcomes. Perceived self-efficacy is a prospective and operative construct.[49]

9.6 Psoriasis efficacy assessments

9.6.1 Investigator assessments

9.6.1.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of the subject's global psoriasis and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA score will be assessed according to the Schedule of procedures (Section 6). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit (static form of IGA). Assessment is performed by a trained investigator.

Investigator's Global Assessment

Score	**Disease severity**
0	Clear
1	Almost clear
2	Mild disease
3	Moderate disease
4	Severe disease

9.6.1.2 Psoriasis Area and Severity Index

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The most widely used and best validated instrument for assessment of psoriasis disease severity is the *Psoriasis Area Severity Index* (PASI). The PASI score rests on a physician's evaluation of the skin area involved, erythema, induration and scaling; and scores range from 0 to 72. Treatment response is assessed as PASI reduction in percentage. Even though there is no definite consensus, moderate-to-severe psoriasis is often defined as a PASI score ≥ 10. Assessment is performed by a trained investigator.

Plaque characteristic	Rating score	Body region (and weighting factor)			
		Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Thickness					
Scaling					
Add together each of the 3 scores for each of the body regions to give 4 separate sub totals.					
Sub Totals		A1=	A2=	A3=	A4=
Multiply each sub total by amount of body surface area represented by that region i.e. A1 x 0.1 for head, A2 x 0.2 for upper limbs, A3 x 0.3 for trunk, A4 x 0.4 for lower limbs to give a value B1, B2, B3 and B4 for each body region respectively					
		A1 x 0.1 = B1	A2 x 0.2 = B2	A3 x 0.3 = B3	A4 x 0.4 = B4
		B1=	B2=	B3=	B4=
Degree of involvement as % for each body region affected; (score each region with score between 0–6)	0 = None 1 = 1–9% 2 = 10–29% 3 = 30–49% 4 = 50–69% 5 = 70–89% 6 = 90–100%				
For each body region multiply sub total B1, B2, B3 and B4 by the score (0–6) of the % of body region involved to give 4 subtotals C1, C2, C3 and C4					
		B1 x score = C1	B2 x score = C2	B3 x score = C3	B4 x score = C4
		C1=	C2=	C3=	C4=
The patient's PASI score is the sum of C1+C2+C3+C4				PASI=	

9.6.1.3 Body surface area involvement

The total BSA affected by psoriasis will be assessed. Assessment is performed by a trained investigator.

9.6.1.4 Quantitative nail assessment

The total number of nails affected by psoriasis will be assessed. The nails are assessed for both nail matrix psoriasis and nail bed psoriasis. Features of nail matrix psoriasis includes nail pitting, leukonychia, red spots in the lunula, and crumbling of the nail. Features of nail bed psoriasis includes onycholysis, oil drop (salmon patch), dyschromia, splinter hemorrhages, and nail bed hyperkeratosis.

Assessment is performed by a trained investigator.

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9.6.2 Subject assessments

9.6.2.1 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their HRQoL over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment. Each item is scored on a 4 point Likert scale (0 = not at all /not relevant; 1 = a little; 2 = a lot; 3 = very much). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor HRQoL. The DLQI will be completed according to the Schedule of procedures. The DLQI is included in the appendix.

9.7 HS efficacy assessments

9.7.1 Investigator assessment

Three types of lesions will be assessed: abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion) and draining fistulas (sinus tracts, with communications to skin surface, draining purulent fluid). Number of each type of lesions are counted.

Hidradenitis Suppurativa Clinical Response (HiSCR) is a dichotomous definition of responders to treatment. HiSCR achievers are defined as the following changes from baseline: (i) at least a 50% reduction in total abscess and inflammatory nodule count, (ii) no increase in the number of abscesses, and (iii) no increase in the number of draining fistulas.[50]

9.7.2 Subject assessment

DLQI will be used.

9.8 IBD efficacy assessments

9.8.1 Disease activity

The disease activity indexes for inflammatory bowel diseases are based on symptoms and general wellbeing. The Harvey Bradshaw index (HBI) and Simple Clinical Colitis activity index (SCCAI) will be applied in patients with Crohn´s Disease and ulcerative colitis, respectively. Both indexes are widely used and well-established in IBD research.

9.8.2 Biochemical parameters

Because patients with IBD or suspected IBD can demonstrate subclinical disease activity, i.e. low degree of intestinal inflammation, which does not elicit any symptoms of disease activity blood sampling investigating the presence of systemic inflammation but also signs of malnutrition is part of usual IBD care. With respect to the presence of systemic inflammation C-reactive protein (CRP) is a well-established marker. The presence of malnutrition is estimated by measurements of albumin and hemoglobin. If anemia is observed blood samples will be supplemented with analysis for iron and vitamin deficiency (ferritin, transferrin, vitamin B12 and folic acid). The fecal marker calprotectin will be used to estimate the presence of intestinal inflammation. All of these parameters are part of routine clinical care.

9.8.3 Endoscopy and histology

Endoscopy will be performed in patients referred for diagnosis of suspected IBD. For patients suspected for ulcerative colitis a sigmoidoscopy will be performed. For patients suspected for Crohn´s disease an ileocolonoscopy (and in selected patients: capsule endoscopy) will be performed, as this compared to a sigmoidoscopy enables the inspection of both the (terminal) ileum and colon - the intestinal locality for which CD has a predilection.
As a part of the endoscopy intestinal biopsies will be obtained and evaluated regarding degree of intestinal inflammation. The histological characteristics of UC and CD will be used in the establishment of a diagnosis of inflammatory bowel disease in patients with symptoms but without prior diagnosis.

9.8.4 Patient reported outcomes

Patient reported outcomes will be evaluated by a Danish version of the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).[51] This questionnaire, has been validated to the quite extensive Inflammatory Bowel Disease Questionaire (32 questions), which is regarded to be the golden standard for evaluating quality of life in IBD. The SIBDQ consists of only 10 questions regarding bowel function, systemic symptoms, social function and emotional status. The SIBDQ has predominantly been developed in Crohn´s Disease, but has also been shown to perform well in ulcerative colitis.[52]

9.9 AxSpA and PsA efficacy assessments

9.9.1 Investigator assessments

9.9.1.1 BASMI (The Bath Ankylosing spondylitis Metrology Index)

Measurement of tragus-wall distance, flexion and lateral flexion of the lumbar spine, intermalleolar distance and cervical rotation

9.9.1.2 Thorax expansion

Measured at the maximum inspiration followed by maximum expiration corresponding to the fourth intercostal space in men and just below the breast in women

9.9.1.3 Swollen (66) and tender (68) joint count

The following joints are examined: Right and left jaw joint, sternoclavicular joint, acromioclavicular joint, humeral articulation, elbow joint, wrist, 10 MCP-joints, 10 PIP-joints in the hands and 10 MTP-joints, ankle joint, knee joint, hip joint (for tenderness only).

9.9.1.4 SPARCC Enthesitis Index

Examined at: Insertion of supraspinatus, lateral and medial epicondyle of humerus, greater trochanter, quadriceps tendon into superior border of patella, Patellar tendon insertion into tibial tubercle, Achilles tendon and plantar fascia insertion on calcaneus (score 0-16).

9.9.1.5 Physician global assessment (VAS 0-100)

An evaluation of the overall disease activity of the patient on the 0-100 VAS scale.

9.9.1.6 Dactylitis count

The dactylitis count is defined as the sum of 20 fingers/toes that exhibit dactylitis (absent 0, present 1).

9.9.1.7 Symptomatic SpA features

Information from the patient about symptoms of anterior uveitis, inflammatory bowel disease and objective signs of psoriasis at skin and/or nails and, dactylitis will be recorded at part of the medical history.

9.9.2 Subject assessments

9.9.2.1 BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)

The patient indicates the severity of six types of discomfort related to disease activity on six individual VAS scales.

9.9.2.2 BASFI (The Bath Ankylosing Spondylitis Functional Index)

The patient indicates the ability to perform 10 actions or movements on VAS scales

9.9.2.3 HAQ (Health Assessment Questionnaire)

20 questions that assesses how difficult it is for the patient to perform eight different functions. The questions are primarily related to peripheral joints. A score (i.e. HAQ score) is calculated.

9.9.2.4 VAS scales

Patient global assessment of arthritis disease activity (PtGA, 0-100 VAS); Patient global assessment of joint pain (0-100 VAS); Patient's assessment of inflammatory back pain (0-100 VAS).

9.10 Composite scores

The following composite scores will be calculated when applicable.

ASAS (Assessment of SpondyloArthritis) 20/40
ASAS is composed of four domains:

- The patient's global assessment of arthritis disease activity (0-100 VAS).
- The patient's assessment of inflammatory back pain (0-100 VAS scale).
- A function component measured by the BASFI. The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values.
- The inflammation component determined as the mean of questions 5 and 6 of the BASDAI.

ASAS20 response is defined as an improvement of ≥20% and absolute improvement of ≥1 unit (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening by ≥20% in the remaining domain; ASAS40 response is defined as an improvement of ≥40% and absolute improvement of ≥2 units (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening in the remaining domain.
ASAS 20/40 is relevant in subjects with axSpA / AS.

ASDAS (Ankylosing Spondylitis Disease Activity Score)
ASDAS parameters include spinal pain (BASDAI question 2), patient's global assessment of disease activity (VAS), peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6) and C-reactive protein (CRP) in mg/L.
ASDAS is relevant in subjects with axSpA / AS.

ACR (American College of Reumatology) 20/50
A positive ACR 20/50 response is defined as at least 20%/50% improvement from baseline in both tender/painful (68 joints) and swollen joint counts (66 joints), and a 20%/50% or more improvement in at least 3 of the following 5 criteria: physician global assessment of arthritis disease activity (PhGA, 0-100 VAS), patient global assessment of arthritis disease activity (PtGA, 0-100 VAS), patient global assessment of joint pain (0-100 VAS), HAQ, and acute phase reactant: erythrocyte sedimentation rate (ESR) or C-Reactive Protein (CRP), whichever has greater improvement.
ACR 20/50 is relevant in subjects with PsA.

DAPSA (Disease Activity in PSoriatic Arthritis)
DAPSA is a joint-specific PsA composite measure of disease activity calculated by summing swollen + tender joint counts + patient pain + patient global assessments + CRP, using 66/68 joint counts, as defined below.
DAPSA is relevant in subjects with PsA.

MDA (Minimal Disease Activity)
A PsA patient is classified as achieving MDA when meeting 5 of the 7 following criteria: tender joint count < or =1; swollen joint count < or =1; PASI < or =1 or BSA < or =3; patient pain visual analogue score (VAS) < or =15; patient global disease activity VAS < or =20; HAQ < or =0.5; tender entheseal points < or =1.
MDA is relevant in subjects with PsA.

HiSCR (Hidradenitis Suppurativa Clinical Response)

HiSCR is a dichotomous definition of responders to treatment. HiSCR achievers are defined as the following changes from baseline: (i) at least a 50% reduction in total abscess and inflammatory nodule count, (ii) no increase in the number of abscesses, and (iii) no increase in the number of draining fistulas.
HiSCR is relevant in subjects with HS.

SCCAI (Simple Clinical Colitis Activity Index)
The SCCAI includes 6 variables: bowel frequency during the day and night, urgency of defecation, blood in the stool, general well-being, and extracolonic manifestations of UC.
SCCAI is relevant in subjects with UC.

HBI (Harvey Bradshaw index)
The HBI includes 5 variables that assess general well-being, abdominal pain, diarrhea, abdominal mass, and complications. Score is total of 1) subject well-being (0=very well; 4=terrible); 2) abdominal pain (0=none; 3=severe); 3) diarrhea (number of time per day); 4) abdominal mass (0=none; 3=definite and tender); 5) complications (number).
HBI is relevant in subjects with CD.

9.11 Clinical and laboratory assessments

9.11.1 Physical examination

A physical examination of the subject including whole body inspection of the skin and assessment of height, weight, hip and waist circumference, blood pressure, and pulse will be performed according to the schedule of procedures. Additional physical examination including auscultation of heart, lungs and abdomen; palpation of the abdominal organs and basic neurological status will be performed by a physician if needed.

Blood pressure and pulse (vital signs) will be measured following at least 5 minutes rest.
If an abnormal vital sign at screening is considered by the investigator to be clinically significant, it will be up to the investigator's discretion if the subject should be randomized into the trial.
In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects resting in a supine position. Only the last value measured and considered as correct will be recorded in the eCRF.

9.11.2 Laboratory testing

The following standard analyses will be performed at baseline and Week 24 at the Biochemical laboratory Aarhus University Hospital:
Blood-Hemoglobin
Blood-Leukocytes
Blood-leukocytes (differential counting)
Blood-Platelets

Blood-Alanine transaminase
Plasma-Albumin
Plasma-C reactive protein
Plasma-creatinine
eGFR / 1.73m^2 (CKD-EPI)
Hemoglobin(blood) - Hemoglobin A1c
Blood-Hydroxy-Vitamin D (D3 + D2)
Blood-basic phosphatase
Plasma-Cholesterol
Plasma-cholesterol HDL
Plasma-cholesterol LDL
Plasma-Triglyceride
Plasma-Glucose
Plasma-Thyroid-screening

Patients will have their HLA-B27 tissue type determined if this has not previously been done and recorded in the medical chart.
Additional analyses (e.g. rheumatoid factor) may be performed at the physician's discretion.

All of the above-mentioned analyses are part of routine clinical care for patients with IMIDs.

Blood samples will be batched for the analysis of a coagulation profile.

Further, three samples of 10 mL blood in EDTA-tubes, one sample 10 mL serum, and one 2.5 mL PAXgene blood RNA tube are collected for storage at visit 1 (screening) and visit 3 (week). Plasma is separated from erythrocytes by centrifugation and stored at -80°C or -150°C for later analysis of inflammatory markers. No analyses are performed on these blood samples as part of this trial.

9.11.3 Procedures

Punch biopsies will be performed as optional procedures. A supplementary informed consent form must be signed. A lesional and a non-lesional 4 mm punch biopsy will be performed in local anesthesia (approximately 1 mL/per injection 2% lidocaine with epinephrine solution) according to institutional guidelines. The punch biopsies will be performed at baseline and at 24 Weeks. Subjects will have the option to accept or decline punch biopsies. The acceptance or rejection of this procedure does not otherwise affect the eligibility of subjects. Punch biopsies will be snap frozen in liquid nitrogen and stored at -150°C for later analysis.

9.11.4 Research biobank

Blood samples for future research and optional punch biopsies for future research will be collected and stored in an existing biobank (Central Denmark Region / Region Midtjylland sagsnr. 1-16-02-601-16). Collection and storage of blood samples for future research requires a signature of a separate informed consent if the subject agrees to participate.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2 (in part / N/A)
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	1 + 18

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 + 14
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	4, 7, 8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and			

outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A (pragmatic trial)
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5-6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A (pragmatic trial)
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see	Figure 1 + table 2

		Figure)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5 Through eCRF (REDCap)
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Non-blinded usual-care controlled pragmatic trial
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	N/A

		during the trial	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Table 2 + supplementary information
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13+14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14

Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	GCP monitoring plan on file
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2 Approved
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Will be communicated to Ethical Committee before implemented. Reported to clinicaltrials.gov immediately after.
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5 According to Danish legislation

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Supplementary information
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5-6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Principal investigator+sponsor
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Supplementary information
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	According to ICMJE
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	This publication shares the protocol. Data sharing declation.
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	On file. Approved by Ethical Committee
Biological	#33	Plans for collection, laboratory evaluation, and	Supplementary information

specimens	storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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EFFECTIVENESS OF INTERDISCIPLINARY COMBINED DERMATOLOGY-GASTROENTEROLOGY-RHEUMATOLOGY CLINICAL CARE COMPARED TO USUAL CARE IN PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES: A parallel group, non-blinded, pragmatic randomized trial

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ABSTRACT

Introduction

Immune-Mediated Inflammatory Diseases (IMIDs) are associated with reduced health-related quality of life (HRQol), increased risk of somatic and psychiatric comorbidities, and reduced socioeconomic status. Individuals with one IMID have an increased risk for developing other IMIDs. The unmet needs in the care of patients with IMIDs may result from a lack of patient-centricity in the usual mono-disciplinary siloed approach to these diseases. The advantages of novel interdisciplinary clinics toward the traditional therapeutic approach have not been investigated. The overall aim of this study is to determine the effectiveness of an interdisciplinary combined clinic intervention compared to usual care in a population of patients with the IMIDs: psoriasis, hidradenitis suppurativa, psoriatic arthritis, axial spondyloarthritis, and inflammatory bowel disease. Our hypothesis is, that an interdisciplinary combined clinic intervention will be more effective than usual care in improving clinical and patient reported outcomes, and that a more effective screening and management of other IMIDs and comorbidities can be performed.

Methods and analysis

This is a randomised, usual care controlled, parallel-group pragmatic clinical trial. 300 consecutively enrolled participants with co-occurrence of at least two IMIDs are randomly assigned in a 2:1 ratio to either treatment in the interdisciplinary combined clinic or usual care. The study will consist of a 6-month active intervention period and a 6-month follow-up period where no intervention or incentives will be provided by the trial. The primary outcome is the change from baseline to 24-Weeks on the Short-Form Health Survey (SF-36) Physical Component Summary. Additional Patient Reported Outcome measures and clinical measures are assessed as secondary outcomes.

Ethics and dissemination

Ethical approval of this study protocol was established by the institutional review board of the study site. The findings from this trial will be disseminated via conference presentations and publications in peer-reviewed journals, and by engagement with patient organizations.

Registration details

Central Denmark Region Ethical Committee: 1-10-72-176-19
ClinicalTrials.gov: NCT04200690
Protocol version: 1.4.1
Protocol date: 22-DEC-2019

Keywords

Joint Diseases; Inflammatory Bowel Diseases; Skin Diseases; Pragmatic Clinical Trial; Anti-Inflammatory Agents

Strength and limitations of this study (MAX 5 short bullets)

- This is the first randomised, usual-care controlled trial to assess the effectiveness of a coordinated interdisciplinary approach to disease management in patients with IMIDs.
- The focus of the study will be on personalised, preventive and participatory healthcare.
- The pragmatic elements in the design of this trial increase the likelihood that the results can be generalized to everyday practice and support decision-making by patients, providers, and health system leaders.
- Emphasis on generic patient reported outcome measures that can be used across age, disease, and treatment groups enables a meaningful assessment of patients with complex IMIDs and creates a strong focus on patient-centricity.
- Investigators and patients cannot be blinded to participation randomisation outcomes due to pragmatic design limitations.

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) including autoimmune diseases affect up to 10% of the western population.[1] Among these are inflammatory bowel diseases (IBD) including ulcerative colitis (UC) and Crohns disease (CD), spondyloarthritis (SpA) including axial spondyloarthrtis (axSpA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA), psoriasis and hidradenitis suppurativa (HS). The aetiology of IMIDs is only scarcely understood, but known to consist of a combination of genetic susceptibility and dysfunctional immunological mechanism resulting in a loss of immunological tolerance towards specific tissues, with a considerable overlap in organ involvement between the different disease-types. The diseases listed above are all associated with cardiometabolic disease, malignancy, infections, ophthalmologic diseases, psychiatric disorders, and reduced socioeconomic status.[2-6] An association between several of the diseases has been shown.[7-11] Additionally, it is generally accepted that individuals with one IMID have an increased risk for developing other IMIDs.

Despite this knowledge, a number of challenges currently exist in providing high-quality care for patients with co-occurrence of more than one IMID. These challenges include: Limited awareness of other autoimmune diseases among patients and health care professionals (HCP)s; lack of screening for other autoimmune diseases; unidisciplinary siloed approach to care; delayed referral from one specialist to the next one, lack of consensus regarding treatment goals and outcome measures; lack of patient centricity; unrecognised, underdiagnosed and undertreated comorbidities; and lack of regular follow-up.[12] The above-mentioned siloed approach to care may lead to a lack of patient centricity and inefficient management of the disease. In a Danish qualitative study, it was reported that some patients experience lack of physician continuity, lack of communication between various HCPs, a need for patients to relay health-related information between various HCPs, contradicting information about disease activity from various HCPs, work-related uncertainties, a lack of knowledge and disease understanding in the social system, and negative consequences in the social system of the delayed diagnostic process.[13, 14]

Recent retrospective studies have reported diagnostic and therapeutic benefits of combined dermatology-rheumatology clinics.[15, 16] Generally, the focus of these clinics is psoriasis and psoriatic arthritis. To our knowledge, no experience with combined clinics including other multidisciplinary professionals such as psychologists, social workers, dieticians, and a broader rheumatology-dermatology-gastroenterology approach has been studied.

The overall aim of this study is to determine the effectiveness of an interdisciplinary combined clinic intervention compared to usual care in a population of patients with complex IMIDs, defined as more than one of the following diagnoses: psoriasis, HS, axSpA including AS, PsA, UC, and CD. Our hypothesis is that an interdisciplinary combined clinic intervention will be more effective than usual care in improving patient reported outcome (PRO) measures (i.e., PROMs, including generic and disease-specific functional status, HRQoL, symptom and symptom burden, and health-related behaviours) and clinical outcomes, and that a more effective screening and management of other autoimmune diseases and comorbidities can be performed in an interdisciplinary combined clinic.

METHODS

Trial design and setting

This is a randomised, usual care controlled, parallel-group clinical trial. Participants are enrolled consecutively and randomly assigned in a 2:1 ratio to either treatment in an interdisciplinary combined clinic or usual care in a hospital clinical setting. In total 300 patients diagnosed with more than one of the selected IMIDs will be randomised to either interdisciplinary combined clinic intervention (200 subjects) or usual care (100 subjects). Work-up and therapy will be at the investigator's/responsible physician's discretion and in accordance with local and national treatment recommendations and guidelines. Thus, diagnostic procedures and therapy are not mandated by the study protocol.

Participants will be recruited based on referrals from hospital clinics and from consultative private practices.

The study will consist of a 6-month active intervention period (assessed after 24 weeks) and a subsequent 6-month follow-up period where no intervention or incentives will be provided by the trial. PROM's will be collected at baseline, 8 Weeks, 16 Weeks, and 24 Weeks, as well as 52 Weeks. Clinical endpoints will be collected at baseline and 24 Weeks.

Figure 1 illustrates the study design. Figure 2 illustrates the trial flow.

Patient and public involvement

Two patient organisations ("De Autoimmune" and "Foreningen for Autoimmune Sygdomme") were part of the original grant proposal, which formed the basis for establishing the National Centre for Autoimmune Diseases (NCAS). The trial described in this protocol is running in the NCAS. Members of the patient organisations provided feedback and comments on the trial concept. Other patients not directly associated with the patient organizations are providing feedback on the content of the interdisciplinary intervention throughout the trial. This feedback is organized through semi-structured interviews and focus groups. Information about the trial is shared with patients through regional and national branches of the aforementioned patient organizations.

Record keeping, monitoring, and data handling

Study data are collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Aarhus University.[17, 18] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Personal data is protected according to the Danish Data Protection Act and The General Data Protection Regulation.

PROM data are collected as surveys through REDCap. The system will send customised emails to participants. It is ensured that participants can complete each survey one time only. Configurable reminders and tracking of responses are in place to minimize the risk of missing data. PRO results are available to investigators on an individual level as a tool to improve the treatment and the consultation. Data will not be available on trial level until database lock.

The Good Clinical Practice (GCP) unit at Aarhus University Hospital is granted access to perform monitoring to confirm that the trial is being conducted in accordance with the currently approved protocol and any other study agreements, International Conference on Harmonisation (ICH) GCP, and all applicable regulatory requirements.

Participants

Inclusion criteria

1. Written informed consent obtained from the participant prior to randomisation.
2. Age 18 and above.
3. Diagnosis of at least two IMIDs* or diagnosis of one IMID and clinical suspicion** of another IMID*

* including and limited to: Psoriasis, HS, UC, CD, axSpA/AS, PsA
** substantiated by e.g. clinical findings, imaging, biochemical results or histological examination at the discretion of the investigator.

Exclusion criteria

1. Non-Danish speaking
2. Expected to be unable to comply with the study protocol

Recruitment and informed consent procedures

Participants will be recruited from the Department of Dermatology, Department of Rheumatology and Department of Hepatology and Gastroenterology, Aarhus University Hospital. Participants will also be recruited based on referrals from other hospital clinics and from consultative private practice.

Referred patients will be discussed at an interdisciplinary preadmission assessment. Patients that are potentially eligible to take part in the trial are invited to attend a clinic appointment. Potential participants will receive verbal and written information regarding the study. Participants will be offered the possibility for bringing a lay representative and will be offered time for reflection to decide whether they wish to participate in the study.

Randomisation and allocation concealment

Eligible participants will be randomised in a 2:1 ratio to either treatment in the interdisciplinary combined clinic or usual care. Participants are randomised by the investigator using a validated REDCap randomisation module. The sequence generation is based on computer-generated random numbers and created by the Clinical Trial Unit at Aarhus University using permuted blocks and no stratification.[19] The investigators are blinded to the allocation sequence.

This is an open-label study and therefore both participants and investigators will be aware of allocation following the first enrolment visit.

Intervention

Interdisciplinary
The intervention in this trial consists of the combined efforts of the interdisciplinary team in the combined clinic arm. The intervention lies in the interdisciplinary organization of workup, treatment, and care for patients with complex IMIDs.
The interdisciplinary team consists of dermatologists, gastroenterologists, rheumatologists, nurses, psychologists, dieticians, social workers, and secretaries. Physiotherapists are involved as needed. Treatment will be individualized based on clinical, biomarker, phenotypic, and psychosocial characteristics. Consultations will be interdisciplinary and coordinated across disciplines. The medical treatment will follow local, national and international guidelines. Thus, the intervention is not a specific pharmaceutical treatment. See online supplementary file for a detailed description of the intervention.

Usual care
Usual care will be carried out by HCPs that are not otherwise involved in the trial. In usual care the patients will not be offered interdisciplinary patient-centred care as described, but rather attend their multiple usual disease-specific departments at the usual appointments. As participants will have complex IMID's this will typically entail attending multiple monodisciplinary specialized clinics. As in the interdisciplinary arm, treatment will be prescribed according to local, national and international guidelines by the treating physicians with no set protocol and no restrictions.

Trial objectives and endpoints
All primary and secondary objectives and endpoints are listed in table 1

Table 1. Objectives and endpoints

Objectives	**Endpoints**
Primary objective	**Primary endpoint**
To compare the change in generic HRQoL from baseline to 24 Weeks	• Change in mean SF-36 PCS from baseline to 24 Weeks
Key Secondary objectives	**Key Secondary endpoints**
To compare the change in generic PROs from baseline to 24 Weeks	• Proportion of subjects achieving MCID in SF-36 PCS at Week 24 • Change in mean SF-36 MCS from baseline to 24 Weeks • Change in mean Facit-Fatigue score from baseline to 24 Weeks • Change in mean WPAI score from baseline to 24 Weeks • Change in mean General Self-Efficacy scale scores from baseline to 24 Weeks • Change in mean HADS-A from baseline to 24 Weeks • Change in mean HADS-D from baseline to 24 Weeks
Additional secondary objectives	
To compare the change in disease-specific PROs from	• Change in mean DLQI from baseline to 24

baseline to 24 Weeks	Weeks • Change in mean HAQ from baseline to 24 Weeks • Change in mean BASDAI from baseline to 24 Weeks • Change in mean BASFI from baseline to 24 Weeks • Change in mean SIBDQ from baseline to 24 Weeks
To compare the change in cardiovascular and metabolic risk factors	• Change in body weight from baseline to 24 Weeks# • BMI response (5% BMI reduction) at 24 Weeks# • Change in waist-hip ratio from baseline to 24 Weeks# • Percent change in LDL-C, TC, TG, and HDL-C at 24 Weeks## • Change in proportion of subjects receiving lipid-lowering agents from baseline to 24 Weeks
To compare changes in signs and symptoms of inflammatory disease from baseline to follow-up	• PASI remission PASI ≤ 3 at Week 24 • PASI 75, 90, and 100 response at 24 Weeks* • Change in PASI, psoriasis BSA and number of psoriatic nails from baseline at 24 Weeks* • ASDAS remission at 24 Weeks (remission <1.3 / not in ASDAS remission >1.3)** • ASAS 20 and 40 response at 24 Weeks** • ACR 20, 50, and 70 at Week 24*** • Change from baseline in DAPSA*** • Change from baseline in MDA*** • HBI remission (HBI < 4) at 24 Weeks**** • SCCAI score < 2 (remission) at 24 weeks***** • Proportion of patients with Hidradenitis Suppurativa Clinical Response (HiSCR) at 24 Weeks******
To assess the change in generic and disease-specific HRQoL from baseline to all other applicable timepoints To assess whether changes in clinical endpoints is associated with changes in HRQoL	

Among patients with

*	Psoriasis at baseline
**	AxSpA/AS at baseline
***	Psoriatic Arthritis at baseline
****	Crohns disease at baseline
*****	Ulcerative colitis at baseline
******	Hidradenitis Suppurativa at baseline
#	BMI ≥ 35 at baseline
##	LDL-C ≥ 3.0 mmol/l at baseline

Abbreviations, table:
ACR: American College of Rheumatology
ASAS: Assessment of SpondyloArthritis international society
ASDAS: Ankylosing Spondylitis Disease Activity Score
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Function Index
BASMI: Bath Ankylosing Spondylitis Metrology Index
BMI: Body Mass Index
BSA: Body surface area
DAPSA: Disease Activity in PSoriatic Arthritis
DLQI: Dermatology Life Quality Index
HADS: Hospital Anxiety and Depression Scale
HADS-A: Hospital Anxiety and Depression Scale - Anxiety
HADS-D: Hospital Anxiety and Depression Scale - Depression
HAQ-DI: Health assessment questionnaire disability index
HBI: Harvey-Bradshaw index
HDL-C: Cholesterol High Density Lipoprotein
HiSCR: Hidradenitis Suppurativa Clinical Response
HRQoL: Health-Related Quality of Life
IGA: Investigators Global Assesment Scale
LDL-C: Cholesterol Low Density Lipoprotein
MCS: Mental Component Score
MCID: Minimal Clinical Important Difference
MDA: Minimal Disease Activity
PASI: Psoriasis Area Severity Index
PCS: Physical Component Score
PGA: Physician's global assessment
PRO: Patient Reported Outcome
SCCAI: Simple Clinical Colitis Activity Index
SF-36: Short Form Health Survey
SIBDQ: Short Inflammatory Bowel Disease Questionnaire
SJC: Swollen Joint Count
SPARCC: Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system
TC: Total Cholesterol
TG: Triglycerid
TJC: Tender Joint Count
WPAI: Work Productivity and Activity Impairment Questionnaire

Trial schedule and assessments

The study schedule (table 2) details the procedures and tests occurring at specific times throughout the study. Scheduled visits mandated by the protocol are for the purpose of data collection. Additional visits for workup, treatment, and care will be scheduled individually based on the discretion of the treating team in both arms with no restrictions set by the protocol.

Table 2 Study Schedule

Visit/eVisit	Visit 0	eVisit 1	eVisit 2	Visit 3	eVisit 4
Weeks	0	8	16	24	52
Visit window (±weeks)		± 2	± 2	± 4	± 4
Office visits					
Informed consent	X				
Demographics	X				
Inclusion/exclusion criteria	X				
Diagnosis of autoimmune diseases	X				
Smoking/alcohol/drugs consumption	X				
Autoimmune diseases: medical history / previous psoriasis therapies	X				
Other medical history / treatments	X			X	
Concomitant medications	X			X	
Randomisation	X				
Collection of adverse events (see section 25)	X			X	
Physical examination					
General physical examination	X			X	
Height	X				
Weight	X	X[1]	X[1]	X	X[1]
Hip and waist circumference	X			X	
Blood pressure, pulse	X			X	
PASI including BSA	X			X	
IGA	X			X	
Quantitative nail assessment	X			X	
HBI	X			X	
SCCAI	X			X	
TJC (68 joints)	X			X	
SJC (66 joints)	X			X	
BASMI	X			X	
SPARCC	X			X	
Dactylitis count	X			X	
PGA of disease activity (VAS scale)	X			X	
ePROs					
General HRQoL					
SF-36	X	X	X	X	X
Fatigue					
FACIT-Fatigue	X	X	X	X	X
Work productivity					
WPAI	X	X	X	X	X
Self-Efficacy					
General Self-Efficacy scale	X	X	X	X	X
Depression and anxiety					

HADS	X	X	X	X	X
Skin					
DLQI	X	X[2]	X[2]	X	X[2]
Muscoloskeletal					
HAQ-DI	X	X[3]	X[3]	X	X[3]
BASDAI	X	X[3]	X[3]	X	X[3]
BASFI	X	X[3]	X[3]	X	X[3]
Patient's assessment of pain (100 mm VAS scale)	X	X[3]	X[3]	X	X[3]
Patient's assessment of inflammatory back pain (100 mm VAS scale)	X	X[3]	X[3]	X	X[3]
Patient's global assessment of disease activity (100 mm VAS scale)	X	X[3]	X[3]	X	X[3]
Gastrointestinal					
SIBDQ	X	X[4]	X[4]	X	X[4]
Labs					
Serum electrolytes + renal panel	X			X	
Acute-phase proteins	X			X	
Lipids	X			X	
Liver enzymes	X			X	
Glucose metabolism	X			X	
Optional biobank samples	X[5]			X[5]	
Procedures					
Optional punch biopsy	X[5]			X[5]	

Abbreviations table:
BASDAI - Bath Ankylosing Spondylitis Disease Activity Index
BASFI - Bath Ankylosing Spondylitis Function Index
BASMI - Bath Ankylosing Spondylitis Metrology Index
BSA - Body surface area
DLQI - Dermatology Life Quality Index
HADS - Hospital Anxiety and Depression Scale
HAQ-DI - Health assessment questionnaire disability index
HBI - Harvey-Bradshaw index
HRQoL - Health-Related Quality of Life
IGA - Investigators Global Assesment Scale
PASI - Psoriasis Area Severity Index
PGA - Physician's global assessment
PRO – Patient Reported Outcome
SCCAI - Simple Clinical Colitis Activity Index
SF-36 - Short Form Health Survey
SIBDQ - Short Inflammatory Bowel Disease Questionnaire
SJC – Swollen Joint Count
SPARCC - Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system
TJC - Tender Joint Count
VAS – Visual Analog Scale
WPAI - Work Productivity and Activity Impairment Questionnaire

QoL – Quality of Life

[1]As reported by the subject
[2]To be reported by subjects with current or previous psoriasis or HS
[3]To be reported by subjects with axSpA/AS or PsA, diagnosed or suspected
[4]To be reported by subjects with IBD, diagnosed or suspected
[5]Requires additional informed consent

See online supplementary file for additional description of assessments and procedures.

Adverse events

The objective of this study is effectiveness and not risk. Medicines are used in accordance with market authorisations and no specific medicines are being examined. The protocol does not endorse any prespecified treatment; rather medicines will be used at the physician's discretion in both arms of the study. This trial does not fall under the definition of a clinical trial of medicinal products. Thus, suspected adverse drug reaction (ADR)s to medicines used in the trial will be subject to standard reporting to the Danish Medicines Agency according to standard clinical practice.

Reporting of suspected side effects from medicines are pursuant to the Danish executive order no. 381 of 9 April 2014 on the reporting of side effects from medicines etc.

Serious Adverse Events[1] (SAE)'s will be collected systematically in the trial at Week 24 and if spontaneously reported from baseline to Week 24. Drug relatedness of SAE's will be assessed by a trained physician. SAE's will be recorded in the medical record and the eCRF.

[1]An SAE is any untoward medical occurrence that

- results in death.
- is life-threatening.
- requires inpatient hospitalisation or prolongation of existing hospitalisation. (Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- is a medically important condition. Events that may not be immediately lifethreatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Sample size

The primary outcome is change in the physical component of HRQoL, measured using SF36 PCS, 24 Weeks after randomisation.

Specification of the sample size calculation, including the target difference, is reported according to the guidance for reporting items available from the DELTA2 guidance on choosing the target difference and undertaking and reporting the sample size calculation.[20] The assumptions regarding variation and expected effect assessed by changes in SF-36 are largely based on experience from previous pharmaceutical trials using SF-36 as a

secondary outcome measure. Also, we have based our assumptions on Minimal Clinical Important Difference estimations from previous publications.[21-23]

The sample size of 300 patients (randomised: 200-to-100) is designed to provide a high statistical power (>90%) to detect a 5-unit difference in SF36-PCS change between the groups. All power and sample size calculations were conducted using 'R software version 3.4.3 (The R Foundation for Statistical Computing).

SF36 PCS: for a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05 (P<0.05), assuming a common standard deviation of 10 SF36 points, a sample size of 85 patients per group has a power of 90% to detect a mean difference in the group mean changes of 5 SF36 points (corresponding to a moderate Cohen's effect size of 0.5). Due to a very limited experience with attrition, to utilize the capacity of the clinic, to maximise data generation in the combined clinic arm, and to increase external validity of the study it was decided to aim for enrolment of 300 participants in total; with a majority (200 patients) being randomised to the interdisciplinary intervention. With 100 patients in each group in the intention-to-treat (ITT) population, the statistical power might be as high as 94% based on the assumptions above.

Statistical analysis

All P values and 95% confidence intervals (95%CI) will be two sided. We will not apply explicit adjustments for multiplicity, rather we will analyse the key secondary outcomes in a prioritized order (e.g. using "gatekeeping procedure"); i.e., the analyses of the key secondary outcomes will be performed 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.[24] The key secondary statistical tests will be reported with P values for hypothesis tests and claims of statistical significance. The primary statistical model will consist of repeated-measures linear mixed models to compare patient outcomes trajectory over time between the two intervention groups (i.e. Time×Group interaction).

The prespecified analyses will be based on the ITT population, using data from the full-analysis set, which will include all patients who underwent randomisation, and had at least the outcome of interest measured at baseline.[25] Data will be analysed using R and SAS or STATA, with the particular outcome variable at baseline level as a covariate - using a multilevel repeated measures mixed effects model with participants as the random effect factor based on a restricted maximum likelihood (REML) model. The primary outcome analyses for continuous outcomes will be based on the following model: The dependent variable (e.g. change in the SF36 PCS value) will be the response variable, and the baseline value (one for each participant) will be applied as a covariate, with a fixed effect (main effect) for treatment group (2 levels), IMID condition (5 levels; corresponding to psoriasis, hidradenitis suppurativa, psoriatic arthritis, axial spondyloarthritis, and inflammatory bowel disease), and time (4 levels: 0, 8, 16, and 24 weeks) will be included as covariates, as well as the interaction between treatment group and time (Group×Time), and Patient ID as a random effects factor. This statistical model will hold all between-group comparisons at all assessment points (incl. baseline) and allows for evaluation of the average effect, as well as the trajectory over the time period from baseline to 24-Weeks follow-up.[26] Results will be reported as the difference between least squares means and their corresponding 95%CI. Categorical changes for dichotomous end points will be analysed with the use of logistic regression with the same fixed effects and covariates as the respective analysis of continuous

outcomes; Odds Ratios (ORs, and 95% CI) will subsequently be converted into Risk Ratios (RRs, and 95%CI).

Handling of Missing Data and Sensitivity Analyses

We plan to conduct both an analysis of the full analysis set (ITT population) and a per protocol analysis, so that any differences between them can be explicitly discussed and interpreted. Using mixed models, like described above, provide valid estimates of treatment effects even when the missing values are not completely random,[26] and additional methods for handling missing data, such as multiple imputation, are generally not required.

Missing data will be handled by:

1. Attempt to follow up all randomised participants, even if they withdraw from allocated treatment.

2. Perform a main analysis of all observed data that are valid under a plausible assumption about the missing data (i.e. Model-based: data as observed; using linear mixed models assumes that data are "Missing At Random" (MAR).

3. Perform sensitivity analyses to explore the effect of departures from the assumption made in the main analysis (i.e. a non-responder-imputation: using the value at baseline to replace missing data will correspond to a non-responder imputation; these models will potentially be valid even if data are "Missing Not At Random" (MNAR).

4. Account for all randomised participants, at least in the sensitivity analyses (covered by #2 and #3 above plus the corresponding analyses based on the Per protocol population).

The interpretation of the corresponding statistical measures of uncertainty of the treatment effect and treatment comparisons will involve consideration of the potential contribution of bias to the p-value, 95% confidence interval, and inference in general.

Our primary analysis population will be all participants with available data at baseline statistically modelled using repeated-measures linear mixed models (see above). These models will be valid if data are MAR.

#3+4 Sensitivity: We will analyse all variables with missing data being replaced by imputation of the baseline level; i.e. interpreted as assuming that those who dropped out returned to their baseline level; These estimates could potentially be valid even if data are MNAR.

ETHICS AND DISSEMINATION

The risks and burden associated with participating in this clinical trial are considered low and outweighed by the benefit of achieving high-quality scientific knowledge regarding the potential benefits of treating patients with complex IMIDs in an interdisciplinary combined clinic setting. Additionally, on the individual level, participants are expected to experience immediate diagnostic and therapeutic benefit from the interdisciplinary approach. Ethical approval of this study protocol was established by the Central Denmark Region Ethical Committee The findings from this trial will be disseminated via conference presentations and publications in peer-reviewed journals, and by engagement with patient organizations.

DISCUSSION

For the purpose of the current trial a number of prototypical IMIDs have been chosen: Psoriasis, HS, UC, CD, axSpA and AS, and PsA. These diseases will serve as a model for autoimmune diseases in which an interdisciplinary and combined clinical approach will be tested. We believe the model will be scalable with the potential to include other IMIDs in the future.

This study has the potential to address some of the main challenges for IMIDs regarding the management of the complexity of the diseases and comorbidities. The focus of the study will be on personalized, preventive and participatory healthcare.

As described above, patients often have more than one IMID, which lead to patients often need to attend several departments. Patients report communication problems between the departments, experience of neglect regarding comorbidities, and that they are left with the responsibility for coordinating the different treatment courses between the different departments.[12-14]

An increasing body of literature supports that IMIDs share many immunopathogenic features and that there is a considerable clinical and therapeutic overlap between the diseases.[1, 27, 28] This underlines the need to abandon previous perceptions of IMIDs as based on cluster of symptoms and a specific silo in the health-care system. Rather, IMIDs must be seen as chronic conditions that may affect a number of body functions and other patient-relevant social and personal aspects. This calls for an integrated and interdisciplinary approach, which will be in scope for this study. Previous efforts to improve patient-centricity within IMID's through combined clinics have typically included only two medical specialties, e.g. rheumatology and dermatology.[15, 16] The novelty of our concept is firstly, that it includes a broader range of relevant medical specialties spanning a range of inflammatory diseases affecting the skin, musculoskeletal system, and gut. Secondly, the concept adheres to a holistic treatment approach, as other cross-disciplinary professionals are part of the team. Thirdly, the effectiveness of the interdisciplinary combined clinic approach is assessed through data generation in a randomised, usual-care controlled trial setting which has not previously been done.

If it is shown that an interdisciplinary patient-centred approach improves quality of life in these patients compared to usual health care, professionals may rethink the way the health system is organized, and ultimately implement an interdisciplinary approach in the management of IMIDs.

Another aspect that will be explored in this project is whether an interdisciplinary patient-centred approach is associated with a socio-economic benefit e.g. by reducing patients´ sick leave, need for attending to health care and lower medicine costs.

There is currently a political and patient-driven move toward an interdisciplinary treatment approach. However, for this to be broadly generalizable the potential advantages must be proven toward the usual and traditional therapeutic approach.

The pragmatic elements in the design of this trial increase the likelihood that the results can be generalized to everyday practice and support decision-making by patients, providers, and health system leaders. The use of a generic PRO as the primary outcome is remarkable and creates a strong focus on patient-centricity. A generic PRO that can be used across age, disease, and treatment groups enables a meaningful assessment of patients with complex IMIDs.[29-31]

However, there are some limitations in this study. The minimisation of inclusion and exclusion criteria, the potential diversity of individualised treatments, and participants'

experience and expectancy of living with a chronic disease may introduce additional variables, which may affect the outcomes. The 24 Weeks duration of the intervention may be insufficient to provide the full benefit in the selected group of patients with chronic, long-standing, complex IMIDs and comorbidities. Sample size calculation is based on the primary outcome, change in SF-36 PCS, whereas the trial may be underpowered to assess changes in subgroups of participants within each disease domain. Thus, there may be insufficient statistical power to determine the effect of the intervention on certain secondary endpoints.

Furthermore, investigators and patients cannot be blinded to participation randomisation outcomes due to pragmatic design limitations. Increased disease awareness in the usual care group caused by participating in the trial may potentially reduce the difference between the intervention group and the usual care group.

A potential bias may be introduced as patients might be inclined to report improvements in generic and disease-related PROs based simply on the fact that they have been assigned to one study arm or the other. However, findings from published psychobehavioral literature suggest that cognitively, respondents are not prone to altering the content of their self-reports of symptoms associated with treatments that they are receiving,[32] and an analysis of the trustworthiness of PROs in unblinded cancer clinical trials did not find evidence of a bias associated with knowledge of treatment allocation.[33] Furthermore, patients in this study is not assigned to placebo but will receive medical care no matter of trial arm allocation. In fact, patients in the usual care arm may likely improve due to medical treatment decisions as they will likely by referred to the trial in a period with disease activity and thus indications for treatment modifications.

Nonetheless, the results and experience from this study may reveal the benefits of managing patients with complex IMIDs in an interdisciplinary setting. The trial may provide evidence as to whether an interdisciplinary approach to complex autoimmune diseases is beneficial for the patients and lower the socio-economic burden.

This could form the basis for establishing further interdisciplinary autoimmune clinics on a national and international scale.

Trial status

This trial is ongoing. The first participant was enrolled on January 14th 2020.

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Figure legends

Figure 1: Trial design. Two-arm, randomised, usual care controlled, parallel-group pragmatic clinical trial.
Figure 2: Study flow diagram.

Author contributions

KFH is the principal investigator and is responsible for leading the design phase and drafting of the protocol. All authors (KFH, AKD, JA, TBL, AGL, LFM, RC, LI) made contributions to the design of the trial and have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors (KFH, AKD, JA, TBL, AGL, LFM, RC, LI) read and approved the final manuscript. LI wrote the project grant application and was awarded funding to establish the center in which the trial is being run.

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Competing interest statement

Anders Dige has received speaking fees from Pfizer.
Anne Gitte Loft has been a consultant and advisor for the following companies: AbbVie, Eli Lilly, MSD, Novartis, Pfizer and UCB and has received speaking fees from: AbbVie, MSD, Novartis, Pfizer and UCB.

Jørgen Agnholt has been consultant, advisory board member or speaker for the following companies: AbbVie, MSD, Bristol Meyer Squibb, Ferring Pharmaceuticals, Pfizer, Janssen-Cilag and Takeda
Kasper Hjuler has been a consultant and advisor for the following companies: AbbVie, LEO Pharma, Novartis and has received speaking fees from: AbbVie, LEO Pharma, Novartis, Janssen, CSL Behring.
Lars Iversen has served as a consultant and/or paid speaker for and/or participated in clinical trials sponsored by: AbbVie, Almirall, Amgen, Astra Zeneca, BMS, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Janssen Cilag, Kyowa, Leo Pharma, MSD, Novartis, Pfizer, Samsung, UCB.

Louise Faurskov Møller has been advisory board member for Janssen and has received speaking fees from LEO Pharma.
Robin Christensen reports no conflicts of interest.
Trine Bay Laurberg has been a consultant and advisor for UCB.

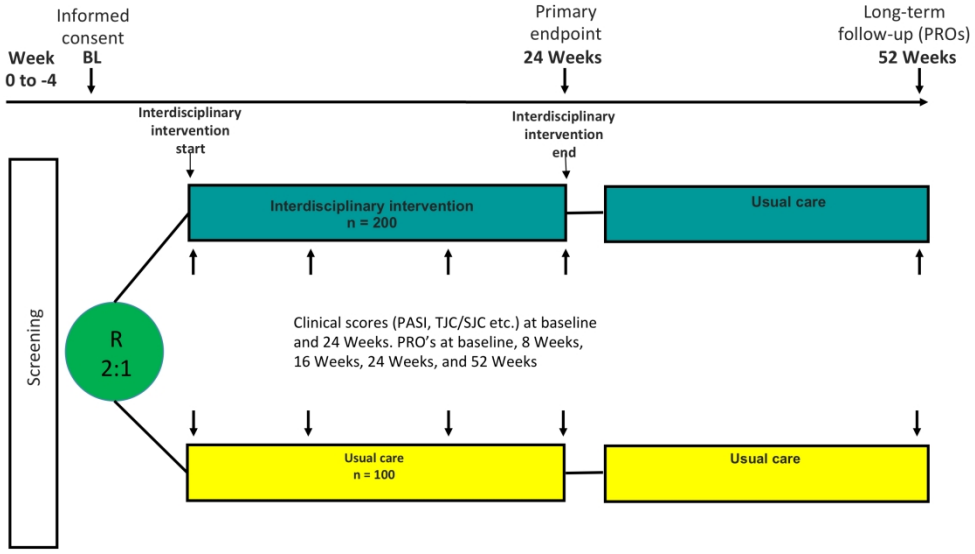

Figure 1: Trial design. Two-arm, randomised, usual care controlled, parallel-group pragmatic clinical trial.

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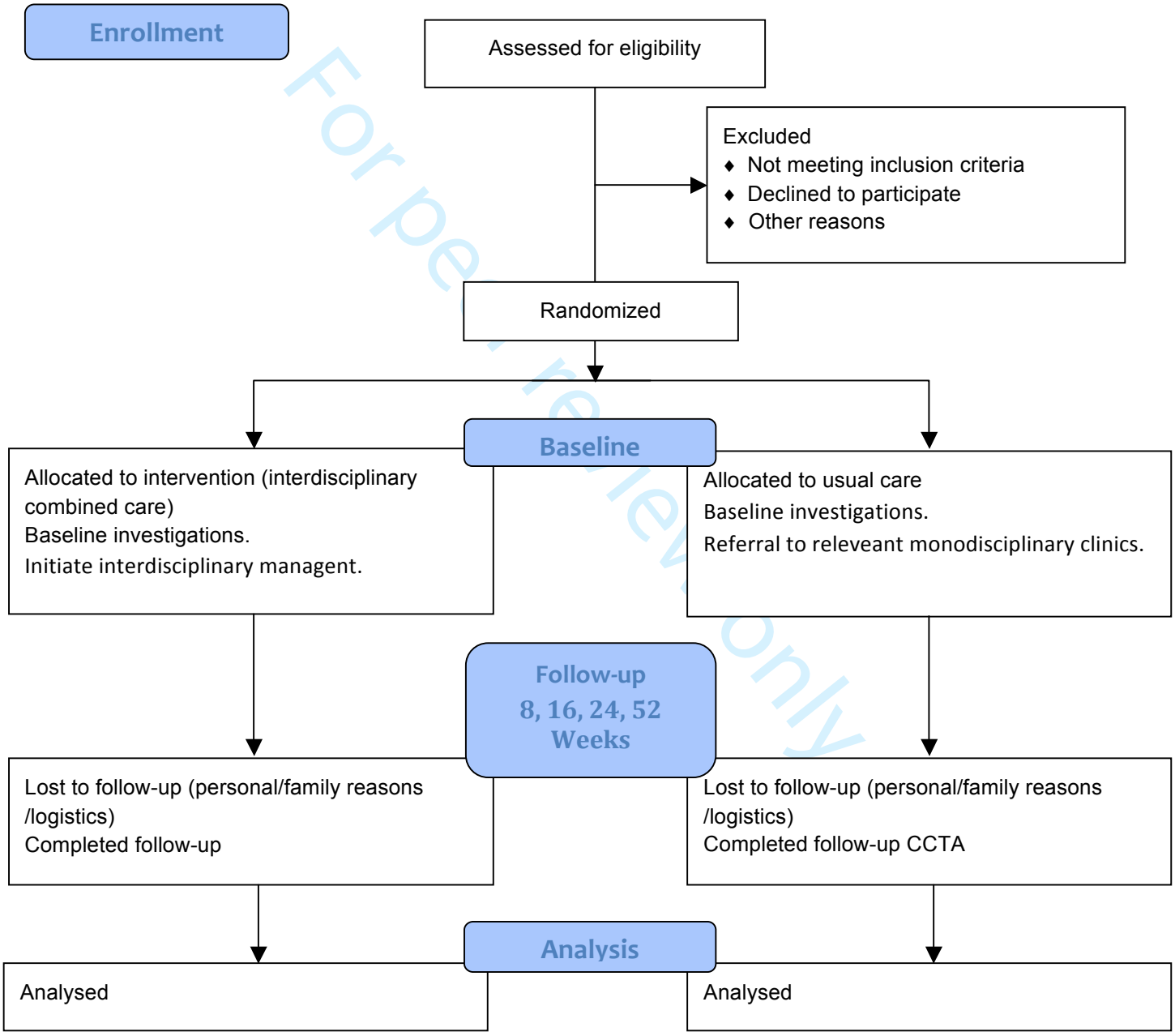

Supplemental appendix

Clinical Trial Protocol

EFFECTIVENESS OF INTERDISCIPLNARY COMBINED DERMATOLOGY-GASTROENTEROLOGY-RHEUMATOLOGY CLINICAL CARE COMPARED TO USUAL CARE IN PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES:

A parallel group, non-blinded, pragmatic randomized trial

National Center for Autoimmune Diseases Aarhus University Hospital		
	Central Denmark Region Ethical Comittee No.	**1-10-72-176-19**
	Date	**22-DEC-2019**
	Version	**1.4.1**

Trial ID: 1-10-72-176-19	Date: 22.12.2019	Page 2 Version 1.4.1

Clinical Trial Approval Statement

1.1 Approval statement sponsor

The following person has approved this clinical trial protocol:

Lars Iversen, MD, DMSc
Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

1.2 Approval statement investigator

The following person has approved this clinical trial protocol:

Kasper Fjellhaugen Hjuler, MD, PhD
Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

1.3 Approval statement co-investigators

The following persons has approved this clinical trial protocol:

Jørgen Agnholt, MD, PhD
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1.4 Collaboration partner

Biostatistical advice:

Robin Christensen, M.Sc., PhD
Professor of Biostatistics and Clinical Epidemiology, Musculoskeletal Statistics Unit, the Parker Institute, Bispebjerg and Frederiksberg Hospital and the Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark.

1.5 GCP responsibilty

The following person take responsibility for enabling GCP monitoring:

Kasper Fjellhaugen Hjuler, MD, PhD
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3 Trial Identification

Central Denmark Region Ethical Committee: 1-10-72-176-19
ClinicalTrials.gov: NCT04200690

4 Trial location

Nationalt Center for Autoimmune Sygdomme
Hud- og kønssygdomme
Aarhus Universitetshospital
Palle Juul-Jensens Boulevard 67
8200 Aarhus N

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5 List of abbreviations:

5-ASA: 5-aminosalicylates
ACR: American College of Rheumatology
AS: ankylosing spondylitis
ASAS: Assessment of SpondyloArthritis
ASDAS: Ankylosing Spondylitis Disease Activity Score
axSpA: axial spondylarthritis
BASDAI: Bath Ankylosing Spondylitis Disease Activity Inex
BASFI: Bath Ankylosing Spondylitis Functional Index
BASMI: Bath Ankylosing Spondylitis Metrology Inde
BMD: Bone mineral density
BSA: Body surface area
CBT: Cognitive Behavioral Therapy
CD: Crohn´s disease
CRP C-reactive protein
CTLA-4: Cytotoxin T-lymphocyte-associated protein 4
CV: Cardiovascular
DAPSA: Disease Activity in PSoriatic Arthritis
DLQI: Dermatology Life Quality Index
EIM: Extraintestinal inflammatory manifestations
ER: endoplasmatic reticulum
HBI: Harvey Bradshaw index
IMD: Immune-meditated diseases
IBD: inflammatory bowel diseases
IMID: immune-mediated inflammatory disease
IPCHS: integrating people-centered health services
HADS: Hospital Anxiety and Depression Scale
HAQ: Health Assessment Questionnaire
HAQ-DI: Health assessment questionnaire disability index
HRQoL: Health-Related Quality of Life
HCPs: health care professionals
HS: Hidrosadenitis Suppurativa
IGA: Investigators Global Assessment Scale
IL: interleukin
IMID: Immune-Mediated Inflammatory Disease
NNR: Nordic Nutrition Recommendation
NSAID: anti-inflammatory drugs
PASI: Psoriasis Area Severity Index
PCC: patient-centeret care
SPACE: SpondyloArthritis Caught Early
PGA VAS: Patient global assessment of pain
PsA: Psoriatic Arthritis
SCCAI: Simple Clinical Colitis Activity Index
SCFA: short chain fatty acids
SF-36: Short Form Health Survey
SIBDQ: Short Inflammatory Bowel Disease Questionnaire
SIJ: Sacroiliac Joints

SJC: Swollen Joint Count
SMR: standardized mortality ratio
SPARCC: Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system
Th: T-helper lymphocyte
TJC: Tender Joint Count
T-regs: regulator T cells
TNF-alfa: tumor necrosis factor alfa
TGF -β: Transforming Growth Factor - beta
UC: ulcerative colitis
WHO: World Health Organization

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6 Intervention

6.1 Interdisciplinary combined clinic vs usual care

The intervention in this trial consists of the combined efforts of the multidisciplinary team in the combined clinic arm. All diagnostic procedures and therapy will be carried out according to local, national, and international guidelines as outlined below. This applies to both arms of the trial. Individual choices regarding procedures and therapy are at the investigators discretion and not defined by the protocol. Usual care will be carried out by HCPs that are not otherwise involved in the trial.

6.2 Treatment

Treatment in both the combined clinic arm and the usual care arm adheres to the principles outlined below.

7.1 Dermatology

7.1.1 Psoriasis

The medical treatment of patients with psoriasis will follow local, national and international guidelines in accordance with the treatment principles of Department of Dermatology, Aarhus University Hospital[1] and the Danish National Treatment Recommendations for psoriasis.[2] Treatment with 2nd generation immunomodulating agents including biologics will be carried out in accordance with the latest version of treatment recommendations from the Danish Medicines Council.[3]

Figure 1 provides an overview of the treatment algorithm for psoriasis.

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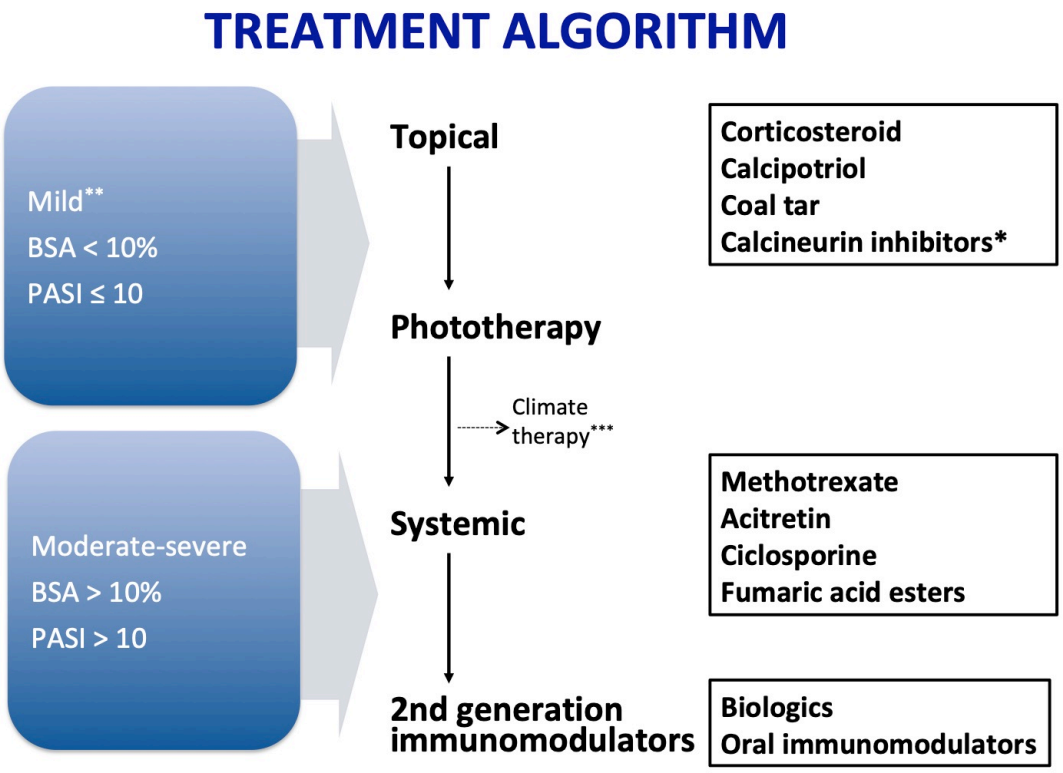

*Off-label
**Involvement of scalp, face, hands, nails, palmoplantar, or genital area may be treated as moderate-severe psoriasis despite PASI < 10[4]
***Adjunctive therapy if needed

7.1.2 HS

The medical treatment of patients with HS will follow local, national and international guidelines in accordance with the treatment principles of Department of Dermatology, Aarhus University Hospital[5] and the Danish Society of Dermatology Treatment Recommendations for HS.[6] Treatment with 2nd generation immunomodulating agents including biologics will be carried out in accordance with the latest version of treatment recommendations from the Danish Medicines Council.[3]

Figure 2 provides an overview of the treatment algorithm for HS.

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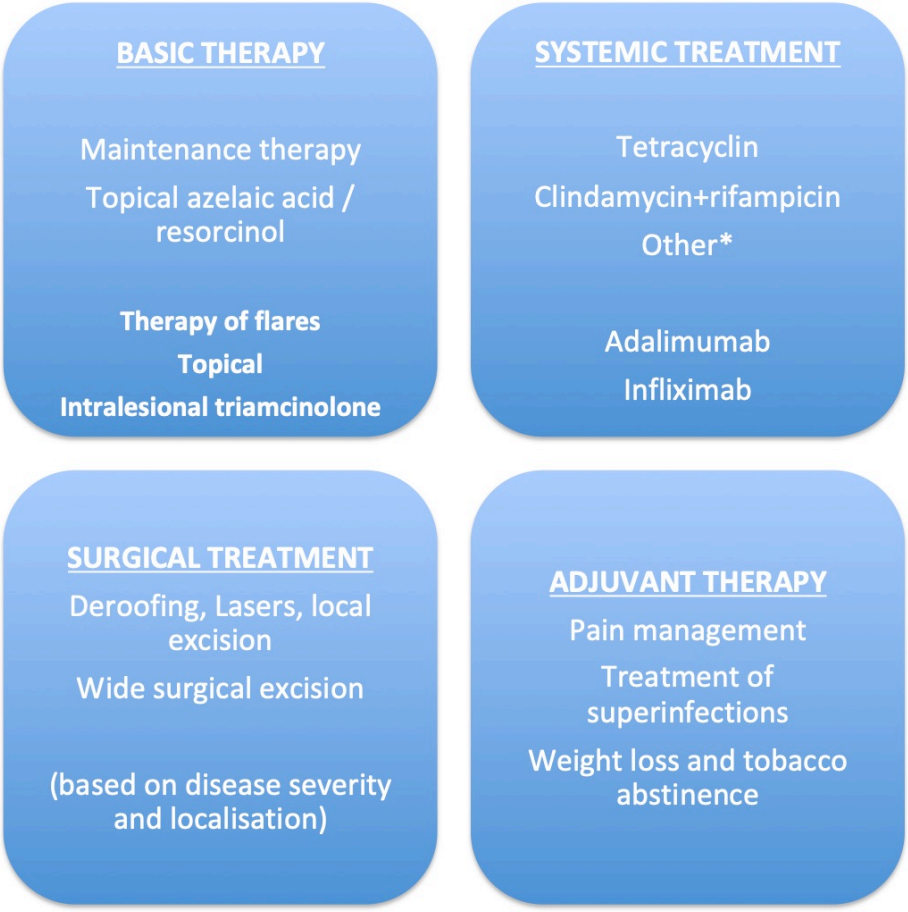

*Metformin (obese), acitretin, dapson

7.2 Gastroenterology

7.2.1 CD and UC

The medical treatment of patients with IBD will follow local, national and international guidelines in accordance with the treatment principles of Department of Gastroenterology and hepatology, (Lever-mave-tarm Sygdomme) Aarhus University Hospital[7] and the European Crohn's and Colitis Organisation.[8, 9] Treatment with 2nd generation immunomodulating agents including biologics will be carried out in accordance with the latest version of treatment recommendations from the Danish Medicines Council.[3]

7.3 Rheumatology

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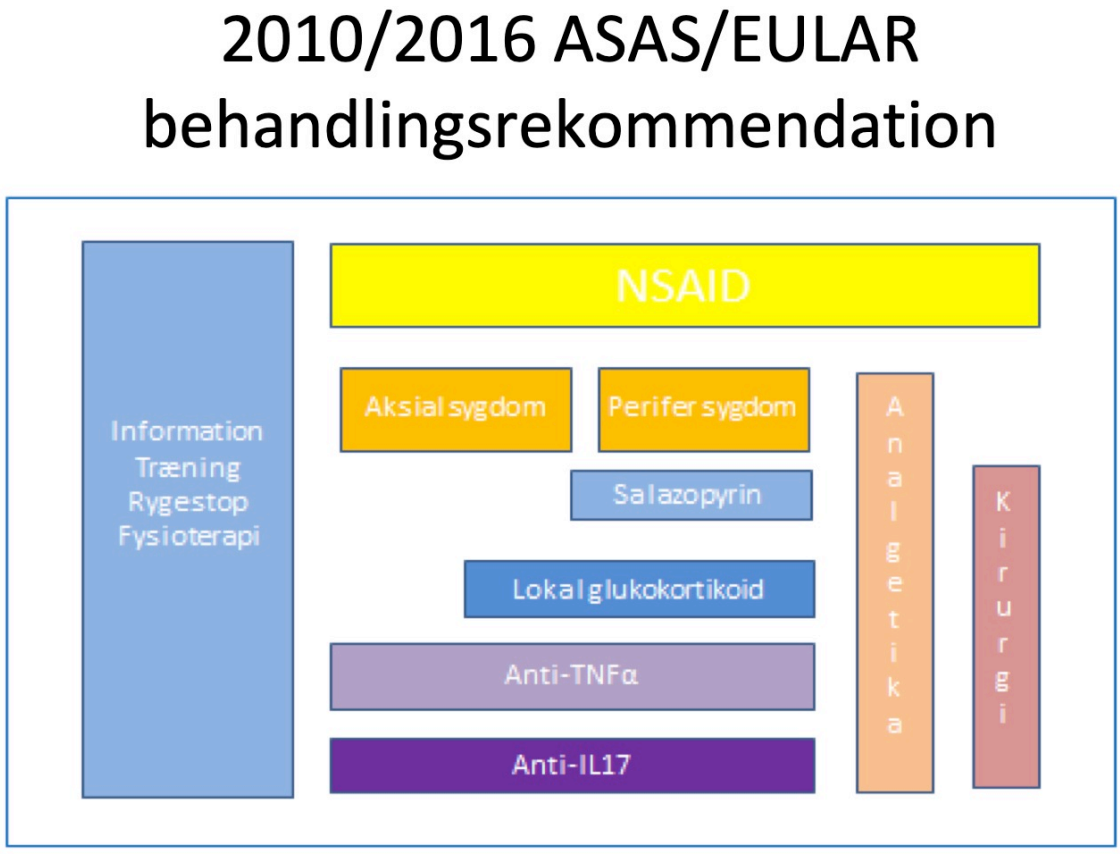
7.3.1 AxSpA/AS and PsA

The medical treatment of patients with axSpA/AS and PsA will follow local, national and international guidelines in accordance with the treatment principles of Department of Rheumatology, Aarhus University Hospital[10] and The National treatment guideline made by Dansk Reumatologisk Selskab.[11] Treatment with 2nd generation immunomodulating agents including biologics will be carried out in accordance with the latest version of treatment recommendations from the Danish Medicines Council.[3]

Figure 3 provides an overview of the treatment algorithm for axSpA and AS.
Non-pharmacological treatment is a cornerstone - especially exercises.



7.4 Cross-disciplinary

As part of the interdisciplinary combined clinic the following disciplines will be a part of the treatment as needed.

7.4.1 Dietetics

There is no specific diet intervention with proven efficacy in IMIDs.[12, 13] However, it is well-known that patients with an IMID have an increased risk of comorbidities.[12, 13]
Studies have shown, that obesity and weight gain is strongly associated with the severity and disease activity among patients with psoriasis and HS. Furthermore, weight loss interventions have shown to improve disease activity and is therefore recommended in these conditions.[13-15]
Among patients with IBD, malnutrition and malabsorption in CD patients may result in micronutrient deficiencies. Furthermore, disease activity in IBD is associated with weight loss and increased protein intake are relevant in some patients.[12]

Dietary treatment is therefore an important supplement to the medical treatment in the management of some IMIDs. It is important that the dietary treatment is based on an individualized approach, where the patient's needs, motivation, behavior, preferences, wishes and life conditions are taken into consideration. Patient education is an important factor in obtaining lasting lifestyle changes.
In patients needing weight loss the goal will be a weight reduction of 5%-10%, which has been shown to improve blood glucose, blood pressure and lipid profile.[16] A weight loss has been associated with reduced disease severity in patients with psoriasis and HS.[14, 17]
In patients with IBD the dietetic counselling will aim to correct and avoid the development of malnutrition. Furthermore, focus will be on identification and subsequently elimination of specific foods, which the patient experience as symptomatic.
All dietary treatment will be in accordance with the national Danish guidelines and the Nordic Nutrition Recommendations (NNR) according to optimal macro- and micronutrient composition.
Dietetic monitoring will consist of weight, waist circumference, BMI, blood glucose, blood pressure, lipid profile, and if relevant micronutrient status.

7.4.2 Psychology

IMIDs are associated with the development of psychological distress, reduced life quality, anxiety, and depression.[18-20]
Preliminary evidence indicates a beneficial effect of psycotherapy in common emotional and psychological disorders associated with IMIDs. Specifically, a number of studies have shown improvements in anxiety, depression, and disease-related stress in patients with IMIDs treated with cognitive behavioral therapy (CBT).[21-24] Moreover, some studies have shown beneficial effect of CBT on clinical disease parameters and a potential antiinflammatory effect of CBT.[25] The latter most likely mediated through positive effect on the systemic inflammatory load through effects on mental and psychological wellbeing. In general, there is consistent supportive evidence for the efficacy of CBT in a variety of problems,[26] however, the evidence-base in IMIDs are still limited.

The aim of the psychological intervention in this trial is to provide relevant patients with different perspectives and tools that can enhance their qualified self-determination when living with a chronic IMID. The aim is hereby to strengthen the patients' self-efficacy[27] and abilities to cope with pain and psychological distress, in order to create a good balance in life – despite having a chronic IMID.

Treatment will involve the application of a range of cognitive and behavioral strategies designed to alter the factors that trigger, maintain, or exacerbate symptoms. Patients are taught to refute or modify unhelpful thoughts and coping patterns. The strategies are aimed to help patients gain control over both psychological and physical symptoms.
A part of this intervention is to help the patients towards a greater awareness of how they deal with their basic psychological needs, and how these needs influence their health and psychological well-being.

If relevant the patients will receive psychoeducation about anxiety, depression and psychological distress.

Patients will be screened with PRO measures, and as part of the clinical assessment. Patients in the interdisciplinary intervention arm will be offered CBT if these assessments indicate significant psychological and social disabilities as assessed by the investigator.

7.4.3 Social work

Studies show that IMIDs have major consequences for education and work. A study by KORA shows that the proportion of people who have dropped out of their education increases with the number of autoimmune diagnoses, and that patients had on average 28 sick days/year due to their IMID(s). A social worker is therefore associated with the center. Patients will be referred to the social worker, if there is a need to clarify personal, social, economic or working issues. The social worker will provide advice and guidance regarding applications for financial or assistive technology support (medical grants and aids). In addition, the social worker can help patients to maintain their attachment to the labor market or education and help those who have lost their attachment to reintegrate[28].

Focus will also be on providing relevant patients with knowledge regarding rights and opportunities. This can provide and ensure them the feeling of social security and prevent escalation of their problems. We will use the Work Productivity and Activity Impairment Questionaire (WPAI) to identify patients who are in risk of losing their attachment to the labor market.

8 Provision for subject care following trial completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, subjects in the combined clinic arm will be treated at the investigator's discretion or referred to other physicians according to clinical practice and national treatment guidelines. This also applies to subjects that dropout or terminates the study before completing all visits.

Participation in the trial will have no influence on the treatment of subjects in the usual care arm during or after the trial.

9 Trial schedule and assessments

9.4 Assessments performed only at screening/baseline

9.4.1 Demographics

The following demographic data will be recorded:
· Month and year of birth
· Sex
· Race: Asian, Black or African American, Middle East and North Africa, White, Other

9.4.2 Medical history

Relevant past and concurrent medical history must be recorded and includes:

- Diagnosis of psoriasis, PsA, HS, axSpA, CD, UC
- Diagnosis of other autoimmune diseases
- Information regarding CV and metabolic risk factors
- Previous and current CV and/or metabolic diseases
- Previous and current immunomodulating agents (systemic and topical)
- Concomitant medication (categorised: antidiabetic, antihypertensive, lipid-lowering, diuretics, NSAID), procedures and diagnoses

9.4.3 Height and weight

The subject's height must be measured (without shoes) and weight must be determined (in indoor clothing and without shoes).

9.4.4 Hip and Waist circumference

Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor (108).

9.5 Generic HRQoL PRO's

PROs are increasingly used in clinical trials, in registries, and, to a lesser extent, in daily clinical practice.[29] There is an increasing awareness that health care should not only reduce symptom severity or reverse disease progression, but also improve how patients feel and function in daily life. There's a growing awareness on PRO data among clinicians, patient organizations, health systems, and regulatory authorities.[29-31]

9.5.1 SF-36

SF-36 is a multipurpose generic health survey that works across various age groups, diseases, and treatments. It has been used worldwide in a variety of studies including a large number of different diseases and it is reported as the most frequently used PRO instrument in clinical trials today.[32] A large body of evidence supports the validity and reliability of SF-36.[33] It has been validated and widely used in a large number of conditions including IMIDs, and it is generally accepted as a measure of disease burden.[33-36]
SF-36 is comprised of 36 items that assess eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions. Physical and mental health summary scores are also derived from the eight SF-36 scales. Scores can be compared to general population norms or between groups and clinically important difference for SF-36 scales and summary measures has been published.[33-36]
Clinically meaningful differences are based on definitions for Minimal Clinically Important Differences (MCID) of 2.5–5 points in Physical Component Score (PCS) and Mental Component Score (MCS) of SF-36 derived from published randomized controlled trials in relevant IMIDs.[34, 37, 38]

9.5.2 Work Productivity and Activity Impairment Questionnaire (WPAI:GH)

The WPAI questionnaire is a well-validated instrument to measure impairments in work and activities.[39, 40] The WPAI assess the impact of disease on work productivity and daily activities during the past seven days, using 6 questions regarding: 1 (if currently employed); 2 (hours missed due to disease); 3 (hours missed other reasons); 4 (hours actually worked); 5 (degree disease affected productivity while working); 6 (degree disease affected regular activities). WPAI generates four main outcomes: 1 percentage of work time missed (absenteeism); percentage of impairment while working (presentisms); percentage of overall work impairment (absenteeism and presentisms combined); and percentage of activity impairment. Scores for WPAI range from 0% to 100%, where 0 % indicates no impairment and 100% is total loss of work productivity/activity.

9.5.3 FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale) is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function.[41] It has been employed in many published studies including a large number of subjects, including patients with psoriasis, PsA, HS, AxSpA, IBD, and other IMIDs[41-47].
All FACIT scales are scored so that a high score is good. As each of the 13 items of the FACIT-Fatigue Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst

possible score and 52 the best. To obtain the 0-52 score each negatively-worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score.
The average score in the US general population is 40, with a standard deviation (SD) of approximately 10. Studies have shown that a FACIT-Fatigue score of 30, which is 1.0 SD below the average for the general population, may be considered significantly below the normal level. An increase or decrease of 3-4 points on the scale may reasonable be considered a relevant change in the score.[42, 48]

9.5.4 General Self-Efficacy Scale

The General Self-Efficacy Scale is a 10-item psychometric scale that is designed to assess optimistic self-beliefs to cope with a variety of life difficulties. The scale has been used in many studies with hundred thousand of participants. In contrast to other scales that were designed to assess optimism, this one explicitly refers to personal agency, i.e., the belief that one's actions are responsible for successful outcomes. Perceived self-efficacy is a prospective and operative construct.[49]

9.6 Psoriasis efficacy assessments

9.6.1 Investigator assessments

9.6.1.1 Investigator's Global Assessment

The IGA is an instrument used in clinical trials to rate the severity of the subject's global psoriasis and is based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA score will be assessed according to the Schedule of procedures (Section 6). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit (static form of IGA). Assessment is performed by a trained investigator.

Investigator's Global Assessment

Score	**Disease severity**
0	Clear
1	Almost clear
2	Mild disease
3	Moderate disease
4	Severe disease

9.6.1.2 Psoriasis Area and Severity Index

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The most widely used and best validated instrument for assessment of psoriasis disease severity is the *Psoriasis Area Severity Index* (PASI). The PASI score rests on a physician's evaluation of the skin area involved, erythema, induration and scaling; and scores range from 0 to 72. Treatment response is assessed as PASI reduction in percentage. Even though there is no definite consensus, moderate-to-severe psoriasis is often defined as a PASI score ≥ 10. Assessment is performed by a trained investigator.

Plaque characteristic	Rating score	Body region (and weighting factor)			
		Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Thickness					
Scaling					
Add together each of the 3 scores for each of the body regions to give 4 separate sub totals.					
Sub Totals		A1=	A2=	A3=	A4=
Multiply each sub total by amount of body surface area represented by that region i.e. A1 x 0.1 for head, A2 x 0.2 for upper limbs, A3 x 0.3 for trunk, A4 x 0.4 for lower limbs to give a value B1, B2, B3 and B4 for each body region respectively					
		A1 x 0.1 = B1	A2 x 0.2 = B2	A3 x 0.3 = B3	A4 x 0.4 = B4
		B1=	B2=	B3=	B4=
Degree of involvement as % for each body region affected; (score each region with score between 0–6)	0 = None 1 = 1–9% 2 = 10–29% 3 = 30–49% 4 = 50–69% 5 = 70–89% 6 = 90–100%				
For each body region multiply sub total B1, B2, B3 and B4 by the score (0–6) of the % of body region involved to give 4 subtotals C1, C2, C3 and C4					
		B1 x score = C1	B2 x score = C2	B3 x score = C3	B4 x score = C4
		C1=	C2=	C3=	C4=
The patient's PASI score is the sum of C1+C2+C3+C4				PASI=	

9.6.1.3 Body surface area involvement

The total BSA affected by psoriasis will be assessed. Assessment is performed by a trained investigator.

9.6.1.4 Quantitative nail assessment

The total number of nails affected by psoriasis will be assessed. The nails are assessed for both nail matrix psoriasis and nail bed psoriasis. Features of nail matrix psoriasis includes nail pitting, leukonychia, red spots in the lunula, and crumbling of the nail. Features of nail bed psoriasis includes onycholysis, oil drop (salmon patch), dyschromia, splinter hemorrhages, and nail bed hyperkeratosis.

Assessment is performed by a trained investigator.

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9.6.2 Subject assessments

9.6.2.1 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a validated questionnaire with content specific to those with dermatology conditions. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their HRQoL over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment. Each item is scored on a 4 point Likert scale (0 = not at all /not relevant; 1 = a little; 2 = a lot; 3 = very much). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor HRQoL. The DLQI will be completed according to the Schedule of procedures. The DLQI is included in the appendix.

9.7 HS efficacy assessments

9.7.1 Investigator assessment

Three types of lesions will be assessed: abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion) and draining fistulas (sinus tracts, with communications to skin surface, draining purulent fluid). Number of each type of lesions are counted.

Hidradenitis Suppurativa Clinical Response (HiSCR) is a dichotomous definition of responders to treatment. HiSCR achievers are defined as the following changes from baseline: (i) at least a 50% reduction in total abscess and inflammatory nodule count, (ii) no increase in the number of abscesses, and (iii) no increase in the number of draining fistulas.[50]

9.7.2 Subject assessment

DLQI will be used.

9.8 IBD efficacy assessments

9.8.1 Disease activity

The disease activity indexes for inflammatory bowel diseases are based on symptoms and general wellbeing. The Harvey Bradshaw index (HBI) and Simple Clinical Colitis activity index (SCCAI) will be applied in patients with Crohn´s Disease and ulcerative colitis, respectively. Both indexes are widely used and well-established in IBD research.

9.8.2 Biochemical parameters

Because patients with IBD or suspected IBD can demonstrate subclinical disease activity, i.e. low degree of intestinal inflammation, which does not elicit any symptoms of disease activity blood sampling investigating the presence of systemic inflammation but also signs of malnutrition is part of usual IBD care. With respect to the presence of systemic inflammation C-reactive protein (CRP) is a well-established marker. The presence of malnutrition is estimated by measurements of albumin and hemoglobin. If anemia is observed blood samples will be supplemented with analysis for iron and vitamin deficiency (ferritin, transferrin, vitamin B12 and folic acid). The fecal marker calprotectin will be used to estimate the presence of intestinal inflammation. All of these parameters are part of routine clinical care.

9.8.3 Endoscopy and histology

Endoscopy will be performed in patients referred for diagnosis of suspected IBD. For patients suspected for ulcerative colitis a sigmoidoscopy will be performed. For patients suspected for Crohn´s disease an ileocolonoscopy (and in selected patients: capsule endoscopy) will be performed, as this compared to a sigmoidoscopy enables the inspection of both the (terminal) ileum and colon - the intestinal locality for which CD has a predilection.
As a part of the endoscopy intestinal biopsies will be obtained and evaluated regarding degree of intestinal inflammation. The histological characteristics of UC and CD will be used in the establishment of a diagnosis of inflammatory bowel disease in patients with symptoms but without prior diagnosis.

9.8.4 Patient reported outcomes

Patient reported outcomes will be evaluated by a Danish version of the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).[51] This questionnaire, has been validated to the quite extensive Inflammatory Bowel Disease Questionaire (32 questions), which is regarded to be the golden standard for evaluating quality of life in IBD. The SIBDQ consists of only 10 questions regarding bowel function, systemic symptoms, social function and emotional status. The SIBDQ has predominantly been developed in Crohn´s Disease, but has also been shown to perform well in ulcerative colitis.[52]

9.9 AxSpA and PsA efficacy assessments

9.9.1 Investigator assessments

9.9.1.1 BASMI (The Bath Ankylosing spondylitis Metrology Index)

Measurement of tragus-wall distance, flexion and lateral flexion of the lumbar spine, intermalleolar distance and cervical rotation

9.9.1.2 Thorax expansion

Measured at the maximum inspiration followed by maximum expiration corresponding to the fourth intercostal space in men and just below the breast in women

9.9.1.3 Swollen (66) and tender (68) joint count

The following joints are examined: Right and left jaw joint, sternoclavicular joint, acromioclavicular joint, humeral articulation, elbow joint, wrist, 10 MCP-joints, 10 PIP-joints in the hands and 10 MTP-joints, ankle joint, knee joint, hip joint (for tenderness only).

9.9.1.4 SPARCC Enthesitis Index

Examined at: Insertion of supraspinatus, lateral and medial epicondyle of humerus, greater trochanter, quadriceps tendon into superior border of patella, Patellar tendon insertion into tibial tubercle, Achilles tendon and plantar fascia insertion on calcaneus (score 0-16).

9.9.1.5 Physician global assessment (VAS 0-100)

An evaluation of the overall disease activity of the patient on the 0-100 VAS scale.

9.9.1.6 Dactylitis count

The dactylitis count is defined as the sum of 20 fingers/toes that exhibit dactylitis (absent 0, present 1).

9.9.1.7 Symptomatic SpA features

Information from the patient about symptoms of anterior uveitis, inflammatory bowel disease and objective signs of psoriasis at skin and/or nails and, dactylitis will be recorded at part of the medical history.

9.9.2 Subject assessments

9.9.2.1 BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)

The patient indicates the severity of six types of discomfort related to disease activity on six individual VAS scales.

9.9.2.2 BASFI (The Bath Ankylosing Spondylitis Functional Index)

The patient indicates the ability to perform 10 actions or movements on VAS scales

9.9.2.3 HAQ (Health Assessment Questionnaire)

20 questions that assesses how difficult it is for the patient to perform eight different functions. The questions are primarily related to peripheral joints. A score (i.e. HAQ score) is calculated.

9.9.2.4 VAS scales

Patient global assessment of arthritis disease activity (PtGA, 0-100 VAS); Patient global assessment of joint pain (0-100 VAS); Patient's assessment of inflammatory back pain (0-100 VAS).

9.10 Composite scores

The following composite scores will be calculated when applicable.

ASAS (Assessment of SpondyloArthritis) 20/40
ASAS is composed of four domains:

- The patient's global assessment of arthritis disease activity (0-100 VAS).
- The patient's assessment of inflammatory back pain (0-100 VAS scale).
- A function component measured by the BASFI. The patient provides self-assessment of 10 questions on a 100 mm VAS. The BASFI score is the mean of these values.
- The inflammation component determined as the mean of questions 5 and 6 of the BASDAI.

ASAS20 response is defined as an improvement of ≥20% and absolute improvement of ≥1 unit (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening by ≥20% in the remaining domain; ASAS40 response is defined as an improvement of ≥40% and absolute improvement of ≥2 units (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening in the remaining domain.
ASAS 20/40 is relevant in subjects with axSpA / AS.

ASDAS (Ankylosing Spondylitis Disease Activity Score)
ASDAS parameters include spinal pain (BASDAI question 2), patient's global assessment of disease activity (VAS), peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6) and C-reactive protein (CRP) in mg/L.
ASDAS is relevant in subjects with axSpA / AS.

ACR (American College of Reumatology) 20/50
A positive ACR 20/50 response is defined as at least 20%/50% improvement from baseline in both tender/painful (68 joints) and swollen joint counts (66 joints), and a 20%/50% or more improvement in at least 3 of the following 5 criteria: physician global assessment of arthritis disease activity (PhGA, 0-100 VAS), patient global assessment of arthritis disease activity (PtGA, 0-100 VAS), patient global assessment of joint pain (0-100 VAS), HAQ, and acute phase reactant: erythrocyte sedimentation rate (ESR) or C-Reactive Protein (CRP), whichever has greater improvement.
ACR 20/50 is relevant in subjects with PsA.

DAPSA (Disease Activity in PSoriatic Arthritis)
DAPSA is a joint-specific PsA composite measure of disease activity calculated by summing swollen + tender joint counts + patient pain + patient global assessments + CRP, using 66/68 joint counts, as defined below.
DAPSA is relevant in subjects with PsA.

MDA (Minimal Disease Activity)
A PsA patient is classified as achieving MDA when meeting 5 of the 7 following criteria: tender joint count < or =1; swollen joint count < or =1; PASI < or =1 or BSA < or =3; patient pain visual analogue score (VAS) < or =15; patient global disease activity VAS < or =20; HAQ < or =0.5; tender entheseal points < or =1.
MDA is relevant in subjects with PsA.

HiSCR (Hidradenitis Suppurativa Clinical Response)

HiSCR is a dichotomous definition of responders to treatment. HiSCR achievers are defined as the following changes from baseline: (i) at least a 50% reduction in total abscess and inflammatory nodule count, (ii) no increase in the number of abscesses, and (iii) no increase in the number of draining fistulas.
HiSCR is relevant in subjects with HS.

SCCAI (Simple Clinical Colitis Activity Index)
The SCCAI includes 6 variables: bowel frequency during the day and night, urgency of defecation, blood in the stool, general well-being, and extracolonic manifestations of UC.
SCCAI is relevant in subjects with UC.

HBI (Harvey Bradshaw index)
The HBI includes 5 variables that assess general well-being, abdominal pain, diarrhea, abdominal mass, and complications. Score is total of 1) subject well-being (0=very well; 4=terrible); 2) abdominal pain (0=none; 3=severe); 3) diarrhea (number of time per day); 4) abdominal mass (0=none; 3=definite and tender); 5) complications (number).
HBI is relevant in subjects with CD.

9.11 Clinical and laboratory assessments

9.11.1 Physical examination

A physical examination of the subject including whole body inspection of the skin and assessment of height, weight, hip and waist circumference, blood pressure, and pulse will be performed according to the schedule of procedures. Additional physical examination including auscultation of heart, lungs and abdomen; palpation of the abdominal organs and basic neurological status will be performed by a physician if needed.

Blood pressure and pulse (vital signs) will be measured following at least 5 minutes rest.
If an abnormal vital sign at screening is considered by the investigator to be clinically significant, it will be up to the investigator's discretion if the subject should be randomized into the trial.
In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later with subjects resting in a supine position. Only the last value measured and considered as correct will be recorded in the eCRF.

9.11.2 Laboratory testing

The following standard analyses will be performed at baseline and Week 24 at the Biochemical laboratory Aarhus University Hospital:
Blood-Hemoglobin
Blood-Leukocytes
Blood-leukocytes (differential counting)
Blood-Platelets

Blood-Alanine transaminase
Plasma-Albumin
Plasma-C reactive protein
Plasma-creatinine
eGFR / 1.73m^2 (CKD-EPI)
Hemoglobin(blood) - Hemoglobin A1c
Blood-Hydroxy-Vitamin D (D3 + D2)
Blood-basic phosphatase
Plasma-Cholesterol
Plasma-cholesterol HDL
Plasma-cholesterol LDL
Plasma-Triglyceride
Plasma-Glucose
Plasma-Thyroid-screening

Patients will have their HLA-B27 tissue type determined if this has not previously been done and recorded in the medical chart.
Additional analyses (e.g. rheumatoid factor) may be performed at the physician's discretion.

All of the above-mentioned analyses are part of routine clinical care for patients with IMIDs.

Blood samples will be batched for the analysis of a coagulation profile.

Further, three samples of 10 mL blood in EDTA-tubes, one sample 10 mL serum, and one 2.5 mL PAXgene blood RNA tube are collected for storage at visit 1 (screening) and visit 3 (week). Plasma is separated from erythrocytes by centrifugation and stored at -80°C or -150°C for later analysis of inflammatory markers. No analyses are performed on these blood samples as part of this trial.

9.11.3 Procedures

Punch biopsies will be performed as optional procedures. A supplementary informed consent form must be signed. A lesional and a non-lesional 4 mm punch biopsy will be performed in local anesthesia (approximately 1 mL/per injection 2% lidocaine with epinephrine solution) according to institutional guidelines. The punch biopsies will be performed at baseline and at 24 Weeks. Subjects will have the option to accept or decline punch biopsies. The acceptance or rejection of this procedure does not otherwise affect the eligibility of subjects. Punch biopsies will be snap frozen in liquid nitrogen and stored at -150°C for later analysis.

9.11.4 Research biobank

Blood samples for future research and optional punch biopsies for future research will be collected and stored in an existing biobank (Central Denmark Region / Region Midtjylland sagsnr. 1-16-02-601-16). Collection and storage of blood samples for future research requires a signature of a separate informed consent if the subject agrees to participate.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2 (in part / N/A)
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	1 + 18

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 + 14
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	4, 7, 8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and			

outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A (pragmatic trial)
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5-6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A (pragmatic trial)
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see	Figure 1 + table 2

		Figure)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5 Through eCRF (REDCap)
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Non-blinded usual-care controlled pragmatic trial
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	N/A

		during the trial	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Table 2 + supplementary information
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13+14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14

Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	GCP monitoring plan on file
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2 Approved
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Will be communicated to Ethical Committee before implemented. Reported to clinicaltrials.gov immediately after.
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5 According to Danish legislation

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Supplementary information
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5-6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Principal investigator+sponsor
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Supplementary information
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	According to ICMJE
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	This publication shares the protocol. Data sharing declation.
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	On file. Approved by Ethical Committee
Biological	#33	Plans for collection, laboratory evaluation, and	Supplementary information

specimens	storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable