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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 monodisciplinary siloed approach to these diseases. The advantages of novel interdisciplinary clinics towards 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 with 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 organisations.

Trial registration number NCT04200690.

Strength and limitations of this study

- This is the first randomised, usual-care controlled trial to assess the effectiveness of a coordinated interdisciplinary approach to disease management in patients with immune-mediated inflammatory diseases (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 generalised 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 Crohn's 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 healthcare professionals (HCPs); 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 PsA. To the best of 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 with 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 (ie, 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. PROMs will be collected at baseline, 8, 16 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 organisations are providing feedback on the content of the interdisciplinary intervention throughout the trial. This feedback is organised through semistructured interviews and focus groups. Information about the trial is shared with patients through regional and national branches of the aforementioned patient organisations.

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)

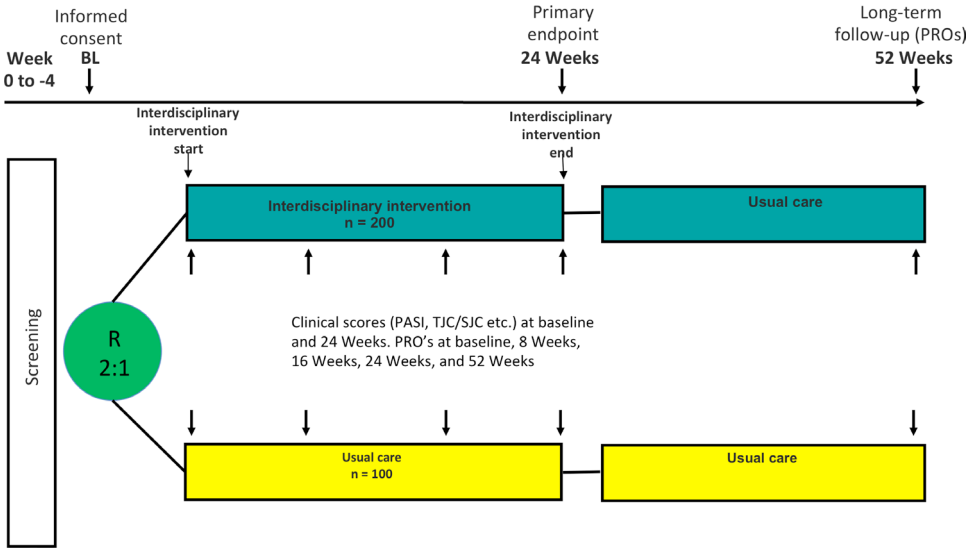

Figure 1 Trial design. Two-arm, randomised, usual care controlled, parallel-group pragmatic clinical trial.

procedures for data integration and interoperability with external sources.

Personal data are 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 minimise 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

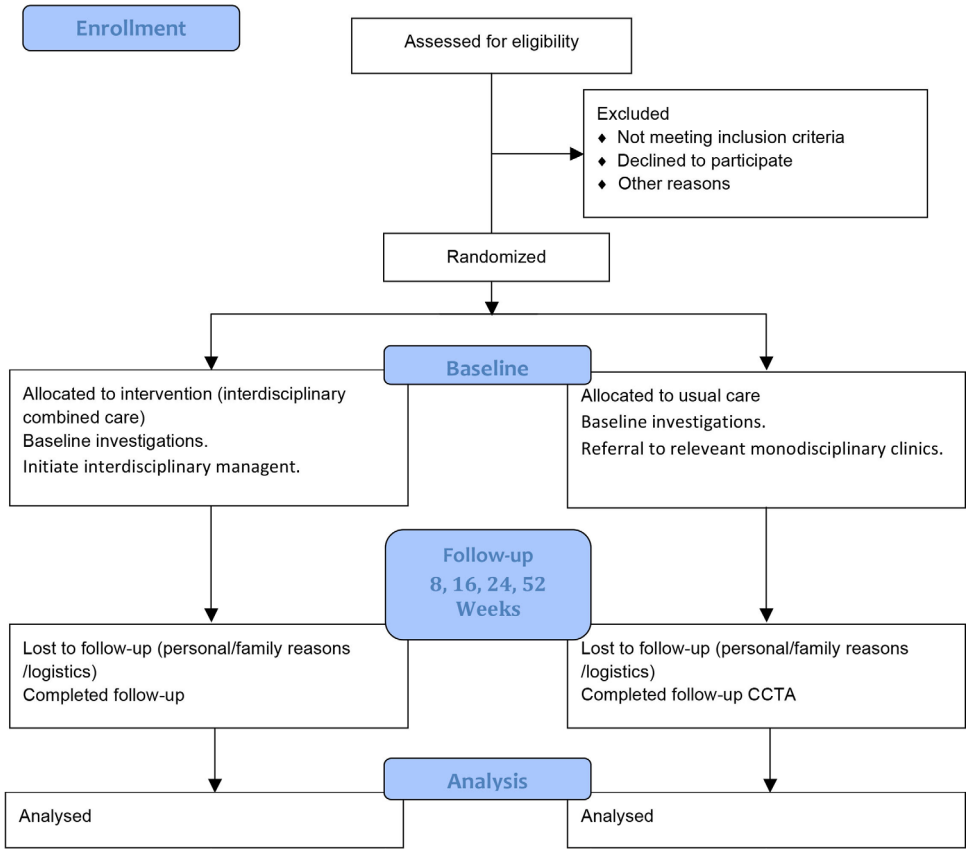

Figure 2 Study flow diagram.

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 and PsA.
   **Substantiated by, for example, 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 who 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 organisation 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 individualised 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 who 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 IMIDs, this will typically entail attending multiple monodisciplinary specialised 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

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.

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 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 SAEs will be assessed by a trained physician. SAEs will be recorded in the medical record and the eCRF.

[1]An SAE is any untoward medical occurrence that

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 baseline to 24 weeks	► Change in mean DLQI from baseline to 24 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, ****Crohn's disease at baseline, *****Ulcerative colitis at baseline, ******Hidradenitis Suppurativa at baseline, #BMI≥35 at baseline, ##LDL-C ≥3.0 mmol/L at baseline.
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; MCID, Minimal Clinical Important Difference; MCS, Mental Component Score ; 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.

- 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 life threatening or result in death or hospitalisation but may jeopardise the subject or

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*	X*	X	X*
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†	X†	X	X†
Muscoloskeletal					
HAQ-DI	X	X‡	X‡	X	X‡
BASDAI	X	X‡	X‡	X	X‡

Continued

Table 2 Continued

Visit/eVisit	Visit 0	eVisit 1	eVisit 2	Visit 3	eVisit 4
BASFI	X	X‡	X‡	X	X‡
Patient's assessment of pain (100 mm VAS scale)	X	X‡	X‡	X	X‡
Patient's assessment of inflammatory back pain (100 mm VAS scale)	X	X‡	X‡	X	X‡
Patient's global assessment of disease activity (100 mm VAS scale)	X	X‡	X‡	X	X‡
Gastrointestinal					
SIBDQ	X	X§	X§	X	X§
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¶			X¶	
Procedures					
Optional punch biopsy	X¶			X¶	

See online supplementary file for additional description of assessments and procedures.
*As reported by the subject.
†To be reported by subjects with current or previous psoriasis or HS.
‡To be reported by subjects with axSpA/AS or PsA, diagnosed or suspected.
§To be reported by subjects with IBD, diagnosed or suspected.
¶Requires additional informed consent.
AS, ankylosing spondylitis ; axSpA, axial spondyloarthrtis ; 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; HS, hidradenitis suppurativa ; IBD, inflammatory bowel diseases; 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 Analogue Scale; WPAI, Work Productivity and Activity Impairment Questionnaire.

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 V.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 SD 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 utilise 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% CIs will be two sided. We will not apply explicit adjustments for multiplicity, rather we will analyse the key secondary outcomes in a prioritised order (eg, using 'gatekeeping procedure'); that is, 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 (ie, 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 model. The primary outcome analyses for continuous outcomes will be based on the following model: the dependent variable (eg, 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 (two levels), IMID condition (five levels; corresponding to psoriasis, HS, PsA, axial spondyloarthritis and IBD) and time (four levels: 0, 8, 16 and 24weeks) 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 24Weeks 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; 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 (ie, 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 (ie, 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% CI 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; that is, 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 organisations.

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 personalised, 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 healthcare 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, for example, rheumatology and dermatology.[15 16] The novelty of our concept is first that it includes a broader range of relevant medical specialties spanning a range of inflammatory diseases affecting the skin, musculoskeletal system and gut. Second, the concept adheres to a holistic treatment approach, as other cross-disciplinary professionals are part of the team. Third, 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 with usual healthcare, professionals may rethink the way the health system is organised 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 socioeconomic benefit, for example, by reducing patients' sick leave, need for attending to healthcare and lower medicine costs.

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

The pragmatic elements in the design of this trial increase the likelihood that the results can be generalised 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 socioeconomic 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 14 January 2020.

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