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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) are chronic, systemic, inflammatory diseases, primarily in the musculoskeletal system.

Pain and fatigue are key symptoms of RA and AS. Treatment presents a clinical challenge for several reasons, including the progressive nature of the diseases and the involvement of multiple pain mechanisms. Moreover, side effects of pain treatment pose an implicit risk. Currently, no well-controlled studies have investigated how medical cannabis affects pain and cognitive functions in RA and AS. The present study aims to evaluate the efficacy and safety of medical cannabis in the treatment of persistent pain in patients with RA and AS with low disease activity.

Methods and analysis: A double-blinded, randomized, placebo-controlled study of Cannabidiol (CBD), followed by an open label add-on of Tetrahydrocannabinol (THC) with collection of clinical data and biological materials in RA and AS patients treated in routine care. The oral treatment with CBD in the experimental group is compared to placebo in a control group for 12 weeks, followed by an observational 12-week period with an open label add-on of THC in the primary CBD non-responders. Disease characteristics, psychological parameters, demographics, comorbidities, lifestyle factors, blood samples and serious adverse events (SAE) are collected at baseline, after 12 and 24 weeks of treatment, and at a follow-up visit at 36 weeks. Data will be analysed in accordance with a predefined statistical analysis plan.

Ethics and dissemination: The Danish Ethics Committee (S-20170217), the Danish Medicines Agency (S-2018010018) and the Danish Data Protection Agency approved the protocol. The project is registered in the European Clinical Trials Database (EudraCT 2017-004226-15). All participants will give written informed consent to participate prior to any study-related procedures. The results will be presented at international conferences and published in peer-reviewed journals.

Strengths and limitations of this study

Strengths

- The randomised, double-blind and placebo-controlled design aims to determine outcome data (on the defined endpoints) and, thus, reduces the risk of bias, especially selection bias.
- Recruitment in routine care is expected to appropriately reflect the patients and conditions in the two diagnostic groups.
- The performance of a controlled study demands the use of medical Cannabidiol (CBD), and Tetrahydrocannabinol THC instead of plant extracts, i.e. tea or herbal preparations.

Limitations

- There is no clinical evidence for the optimal dosage and application ranges. Thus, the treatment regimens for the drugs used are an extrapolation of expert knowledge
- Both primary and secondary endpoints are based on patient-reported outcome measurements (PROMs) and may be influenced by bias.

INTRODUCTION

The treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) has improved significantly over the last three decades [1, 2, 3]. Chronic pain and fatigue are symptoms typical of these major inflammatory rheumatic disorders [4, 5, 6]. Cognitive dysfunctions, such as concentration and memory problems, are also often reported in patients with chronic pain. These cognitive dysfunctions can be related to pain itself, sleep problems, or reflect a side effect of the pharmacological treatment [4 6]. RA affects the small joints of the hands and feet, but can also involve the larger joints [7]. AS mainly affects the spinal and sacroiliac (SI) joints and is characterised by back pain and stiffness [8]. Pain may involve nociceptive and non-nociceptive components and is based on the interaction between peripheral inflammation and central sensitization [9, 10]. The immediate pain is triggered by the inflammation of the synovial tissue and/or consecutive oedema of the subchondral bone, and leads to a sensitization of the peripheral nociceptors [11].

Thus, chronic pain is likely to be due to peripheral joint and central neuropathic pain mechanisms at various stages [11 -14].

Treatment of moderate to severe chronic pain is difficult to overcome, for several reasons: heterogeneity of the patients in a given diagnostic group, the progressive nature of the disease, involvement of multiple pain mechanisms and the presence of comorbidities, particularly in elderly patients [15]. The rheumatologist is likely to pay full attention to the anti-inflammatory treatment.

This approach implies the fact that chronic pain associated with increased mortality can be overlooked [16, 17].

There is a lack of knowledge about the effect of cannabinoids in rheumatic diseases. Based on a Cochrane meta-analysis, the authors concluded that the existing clinical studies of CBD applied in monotherapy are of such poor quality that there is insufficient data to draw any conclusions about the effectiveness and/or long-term security of the compound [18].

Currently, no well-controlled studies have investigated how medical cannabis affects cognitive functions, such as concentration and attention. A few studies have investigated the impact of illegally obtained cannabis in RA [18]. Furthermore, studies that have assessed medical cannabis did so mostly in the context of multiple sclerosis [18, 19, 20,]. In contrast to studies of recreational cannabis, the studies in persons with multiple sclerosis indicate that medical cannabis does not negatively affect cognition and could improve sleep quality. Given the limited data and the lack of a proper control condition, no definite conclusions of the potential cognitive impact of medical cannabis could be drawn [18, 21].

Hence, concerns about potential negative side effects of medical cannabis on cognition have led the Danish health authorities' attention on a patient's ability to drive safely. [19, 20, 21]. Furthermore, in the treatment of rheumatic diseases, there is no established routine nor rheumatologic competence to prescribe medical cannabis. Consequently, there is considerable uncertainty and caution towards the use of medical cannabis, even in the North American countries, where it is already legal to prescribe these compounds for rheumatologic conditions [19, 20]. This can lead to patients resorting to self-medication with cannabinoids [18, 20, 22]. Thus, there is a strong need for high quality studies of the efficacy and side effects of cannabinoids.

The overall aim of the study is to investigate the effect of medical cannabis on pain in patients with RA and AS, to elaborate on the potential dosage of CBD and THC, and to explore if and how the test compounds affect patients' cognitive functions and sleep.

MATERIALS AND METHODS

Setting and study design

The study is an investigator-initiated, double-blinded, randomized, placebo-controlled intervention study of CBD, followed by an open label add-on of THC. It is designed to evaluate the efficacy and safety of medical cannabis, either as CBD or in the form of the combination treatment of CBD and THC as "add-on" treatment for chronic pain in RA and AS. The patient-reported outcome measurement (PROM), a pain visual analogue scale (VAS) score at a value of at least 50 are the key inclusion criterion. The score range is from 0 – 100; a higher score indicates greater pain intensity. Thus, the null hypothesis, H^0, is that receiving the active treatment with cannabis derivatives does not improve the pain situation in clinical assessment after 12, 24 and 36 weeks.

Figure 1 presents the Consort flow chart.

Clinical data and outcomes are registered in an electronic Case Report Form (eCRF), based on the Reuma-eCRF system available within the Danish nationwide registry DANBIO [23] and biological samples are collected via the Danish Rheumatologic Biobank (DRB) [24]. Patients are recruited from four Danish hospital departments. Patient inclusion is planned to start in November 2018 and is expected to continue for 14 months.

Participants

The study population consists of:

- patients with seropositive RA [1] currently treated with either Conventional Disease Modifying Anti-Rheumatic Drugs (cDMARD) and/or biological Disease Modifying Anti-Rheumatic Drugs (bDMARD), and without clinical signs of arthritis, as assessed by a 40-swollen joint count, and

- patients with AS, according to the modified New York criteria [2], currently receiving either nonsteroidal anti-inflammatory drugs (NSAID) and/or bDMARD, who show an absence of clinical signs of axial and peripheral arthritis and enthesitis, and who have an Ankylosing Spondylitis Disease Activity Score (ASDAS) < 2.1.

Inclusion criteria

a. Minimum Pain VAS 50, both at screening and inclusion
b. Disease duration ≥ 2 years
c. Ongoing treatment or earlier attempt to treat with Paracetamol or NSAIDs without clinical signs of arthritis or spondyloarthritis
d. Analgesic treatment unchanged at least 4 weeks before trial start.

Exclusion criteria

a. Age < 18 years
b. Pregnancy, pregnancy wish or ongoing breastfeeding
c. CRP > 10 mg/L
d. Comorbidities, more specific competitive rheumatologic disorders, such as systemic lupus erythematosus (SLE), scleroderma, polymyositis or chronic pain condition based on a further clinical detectable aetiology (e.g. fibromyalgia)
e. Evidence of serious uncontrolled concomitant cardiovascular, pneumological, neurological, endocrinological, gastroenterological, urogenital, nephrological or hepatic impairment

f. Major surgery performed < 8 weeks before randomization or planned major surgical interventions

g. Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids

h. Evidence of active malignant disease, malignancies diagnosed or treated within the previous 2 years, including hematologic malignancies and solid tumours

i. Actual or previous harmful use of alcohol or drug abuse, in accordance with the WHO definition [25], within the previous 2 years

j. Ongoing treatment with opioids and/or cannabis products and/or neuroleptics, or treatment terminated less than 4 weeks before inclusion

k. Hypersensitivity to the study compounds

l. Suspected for, or evidence of, active schizophrenia, other psychotic illness in the family history (first degree relatives), other significant psychiatric disorder, or treated depression associated with underlying condition

m. Epilepsy or recurrent seizures

n. Use of strong Cytochrome P450 3A4 (CYP3A4) inducers.

Experimental treatment

The treatment starts with oral CBD 10 mg or placebo before bedtime, and increases after two weeks to 10 mg twice daily. Finally, and in case of lack of effect (VAS-pain reduction less than 20) from the beginning of the 5th week, the treatment increases to 10 mg thrice daily.

The clinical assessment after 12 weeks defines how to proceed during the following 12 weeks: in case of a sufficient response, i.e. a VAS-pain reduction of equal/or more than 20, the established treatment continues randomized and without any further adjustment.

In case of insufficient response, i.e. a VAS-pain reduction of less than 20, randomization is terminated. Patients who received placebo are shifted to the active compound, i.e. CBD treatment, and dose adjustment is performed, as mentioned above. In patients who received CBD treatment during the randomised period, the open label follow up combines CBD with THC, i.e. oral THC 2.5 mg daily is added to the ongoing CBD treatment. The THC dose is increased after 2 weeks to 2.5 mg twice daily (in total, 5 mg THC/day), and in case of lack of effect (VAS-pain reduction less than 20, compared to VAS 20, as defined at clinical assessment after 12 weeks), after another two weeks to 2.5 mg thrice daily (in total, 7.5 mg THC/day) from the beginning of the 17th week.

Figure 2 presents the study flow chart.

Randomization procedure

Patients are stratified by diagnosis and by recruiting center. Patients are randomly allocated to one of the two treatment arms – CBD *or* Placebo – by random permuted blocks. Randomization is blinded to the treatment allocation. Allocation is not known to anyone other than Glostrup Pharmacy, who produces and dispatches drug packages on request to each site. Sites receive a sealed, opaque envelope for each patient with the treatment allocation ready to be revealed, should this be required. Treatment is initiated within two weeks after randomization. Measurements of

effect are carried out at baseline before randomization, and post-intervention at 12, 24 and 36-weeks post-randomization. Data analysis and statistical programming are blinded. The randomization procedure and data analysis are performed by an independent statistician at IRS, University of Southern Denmark, Gråsten, Denmark

Designated outcomes and clinical data

Primary outcome is the number of patients achieving an improvement of pain-VAS (Δ VAS-pain ≥ 20) after 12 weeks of treatment.

Secondary outcomes

a. The fraction (%) of RA and AS patients that achieve an improvement in VAS-pain, as assessed by the reduction of Δ VAS ≥ 20 and outcome of the PainDETECT Questionnaire (PD-Q) [26], after 24 and 36 weeks.

b. The fraction (%) of RA and AS patients that achieve an improved quality of life situation, as assessed by Global-VAS with Δ VAS reduction ≥ 20 and by the SF-36 [27], after 24 and 36 weeks.

c. The fraction (%) of AS patients that achieve a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) < 40 or reduction in BASDAI with Δ ≥ 20 after 12, 24 and 36 weeks.

d. A characterization of AS and RA patients' cognition and sleep quality, as assessed by the Trail Making Test (TMT) [28], the Digit Symbol Substitution Test (DSST) [29, 30] and the Pittsburgh Sleep Quality Index [31], performed at baseline and after 12, 24 and 36 weeks.

e. A characterization of the patients' expectation for the treatment effect, as assessed by the Credibility/expectancy Questionnaire (CEQ) and by performing semi-structured interviews [32-36] at baseline and after 12 weeks.

f. A characterization of and a final statement about Serious Adverse Event (SAE) state.

Clinical data

At baseline, and after 12, 24 and 36 weeks, respectively, data are collected in the DANBIO Reuma-eCRF system. Furthermore, two additional nurse consultations are performed after 4 and 16 weeks, to obtain safety information and VAS-pain and to possibly perform a treatment increase from the beginning of the 5th and/or 17th week, respectively, as presented in the section above, Experimental treatment. The following data are collected at the time points as presented in Figure 3:

1) Clinical measurements, i.e. in RA the Disease Activity Score 28-joints (DAS28-CRP), Health Assessment Questionnaire (HAQ) and, in AS, the (ASDAS) and Bath Ankylosing Spondylitis (BAS)-scores for disease activity (BASDAI), function (BASFI) and measures (BASMI) are registered [37, 38, 39]. In both patient groups, additional Patient Reported Outcome Measures (PROMs) are obtained: visual analogue scales (VAS) for pain, fatigue, patient's global Quality of Life (QoL) score SF-36 and pain-score PainDETECT [26]. Furthermore, the effect of intervention on attention and concentration is investigated using the TMT and DSST [28, 29, 30]. Additionally, sleep quality is evaluated with the Pittsburgh Sleep Quality Index. [31]. The expected effect of treatment is measured with the Credibility/expectancy Questionnaire and semi-structured interviews.

2) Exposures, i.e. all concomitant treatment, especially current treatments with cDMARDs, bDMARDs and/or analgesics, including dosing schedule and treatment onset.

3) Comorbidities, e.g., cardiovascular disease, diabetes and hypertension

4) Lifestyle (blood pressure, exercise habits and smoking status)

5) Patient demographics, e.g., diagnosis, age, gender, height, weight, Body Mass Index (BMI), disease duration, smoking status, educational level, marital status, sick leave, occupation and ethnicity are obtained at baseline.

Biological samples

Blood samples are obtained at baseline, and at 12, 24 and 36 weeks. In addition to routine blood tests blood samples are collected in one EDTA tube (9 ml), two serum tubes (2x9 ml) and one PAXgene blood RNA tube (2.5 ml, Becton & Dickinson, Lyngby, Denmark), as described previously [40]. These are collected for definition of drug concentration of CBD and THC, i.e. monitoring of compliance, possible adverse events and for further future analyses.

Statistical Analysis Plan

The power calculation is based on the following assumptions for the primary outcome:

- An expected proportion with a response of 50% or more in the CBD group and expected 20% in the placebo group (OR = 4). Response is defined as a reduction in VAS-pain of at least 20 (range 0-100) after 12 weeks of treatment.
- A significance level of 0.05 in a two-sided z-test of proportions.
- A total of 180 patients will be included in two balanced groups, each consisting of 90 patients.

This setup gives a statistical power of 0.98 for the primary outcome. The power is reduced if the true difference between the groups is less than the expected 30 percentage points, and if more than an expected 10% of the patients drop out of the experiment. Balanced groups of 45 patients will yield a power of 83% for two-group comparisons on binary outcomes, such as the primary outcome. Slight deviations in sample sizes might occur because of block randomization.

The primary outcome is tested by a z-test in a logistic regression model. The main parameter estimates the ratio of the odds of response for the intervention group relative to the control group. All tests are two-sided. Secondary outcomes are analysed using logistic and linear regression, depending on the data type. In the case of deviations from the normality assumption, a non-parametric proportional odds model will be used. The secondary outcomes measured at baseline and post-intervention, 12, 24

and 36 weeks (follow-up) will be analysed using mixed-effects models, controlling for time of measurement. The random effects parameter is estimated for the clustering of repeated observations within patients. Analysis for the direct effects of CBD, THC and the interaction between those will be carried out separately, with placebo as the reference group for CBD.

Baseline measurements are reported as proportions of categorical variables, average and standard deviation (SD) for normally distributed data, and median (range) scores for non-normal numerical data. All variables are reported for the two intervention groups. Baseline variables with a tendency ($p < .25$) to coincide with the intervention group will be included as control variables in the test of the primary and secondary outcomes. The relationship between the tested variables at baseline and intervention allocation will be analysed with parametric (t-test) and non-parametric tests ($\chi 2$ and the Mann-Whitney test). Correction for multiple tests will be based on a gatekeeping model of access. This means that significant results for the secondary outcomes are interpreted solely as exploratory findings in case of a non-significant finding for the primary outcome.

ETHICS AND DISSEMINATION

The protocol is approved by the Danish Ethics Committee (S-20170217), the Danish Data Protection Agency (2018-41-5388)and the Danish Medicines Agency (2018-010018). All patients receive verbal and written information and give their written consent before enrolment, in accordance with Danish Ethics Committee guidelines. All patients are informed that they can withdraw from the study at any time. Although this would lead to the termination of project medication, patient withdrawal will have no consequences for regular course of treatment. In case of withdrawal, no subsequent patient-related registrations will be obtained.

The two cannabis derivatives used in this study are comparable to the authorized compounds in the drug Sativex® [41]. The treatment consists of CBD tablets and THC herbal capsule preparation,

which are produced based on natural raw materials by Glostrup Pharmacy's laboratory. The drugs are manufactured according to quality-ensured standardized procedures specifying the exact ingredients in mg. This makes dosage and monitoring of the therapy safe according to Danish national Good Clinical Practice (GCP) guidelines. The side effects, are well known and well described [41]. The study subjects are patients who are already associated to one of the four participating outpatient clinics. The blood samples at baseline, after 12 weeks and 24 weeks respectively, will be realized in connection with routine blood tests, in accordance with an a priori arranged outpatient visit and thus will not pose increased risks.

The patients will be contacted and informed regarding the overall study results if they indicate interest in this, and in accordance with the patient study consent form and as directed by the Danish Ethics Committee guidelines. The physician in charge of the project at each participating outpatient clinic is responsible for conducting the study in accordance with the 5th edition of the Helsinki declaration. Study participation does not affect the established anti-inflammatory treatment course of individual patients.

Results will be presented at international conferences and published in international and peer-reviewed medical journals. Negative, positive as well as inconclusive results will be published.

DISCUSSION AND POTENTIAL LIMITATIONS

CBD and THC are two of more than 80 active compounds in the marijuana plant [42].

In contrast to THC, CBD does not exhibit a narcotic effect and/or intoxication [42, 43]. The biochemical effect of the cannabinoids is explained by the compounds´ interaction with specific receptors; the CB1 receptor is located on neurons and glial cells in different parts of the central nervous system, whereas the CB2 receptor is found in structures of the immune system. The stimulating and narcotic effects of THC are considered to be caused by activation of CB-1 receptors. CBD has a very low affinity for these receptors [42]. Thus, CBD binding to the CB-1 receptors causes little to no narcotic effect. New studies show evidence that CBD affects autoimmune signalling pathways and that these mechanisms may be relevant to CBD's therapeutic profile [44, 45].

The effect of CBD is studied in a placebo-controlled design, whereas the effect of a combination of CBD and THC is an open label continuation of the study. This design represents the balance between a wish to assess the effect of both CBD and THC correctly, while recognizing risks, including traffic safety issues, especially due to the THC treatment. Also, the possible negative effect on cognitive functioning can have a large impact on job functioning. Therefore, a more definite answer as to whether medical cannabis negatively affects cognition is important in relation to job functioning and autonomy.

The trial population is monitored regularly at the participating outpatient clinics and the individual longitudinal treatment is registered. DANBIO is the nationwide clinical quality database for rheumatology [23]. All adult patients treated with biological drugs are registered. Furthermore, patients with AS and RA are registered, regardless of treatment. Thus, the DANBIO based Reuma-eCRF system provides particularly good conditions for the collection and monitoring of validated data.

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Contributors

OH wrote the protocol for the European and the Danish Medicines Agency and the Research Ethics Committee. TEA, AAC, JP, EMH, TJE, TH, AGB, AGL, ABB, MØ, MLH, KKR, KHP and OH contributed to study concept. KHP, MØ and OH drafted and revised the manuscript after feedback from all authors. All authors contributed to the review of the present manuscript and approved the final version of the manuscript.

Competing interests

None

Provenance and peer review

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FIGURE 1: Consort flow chart

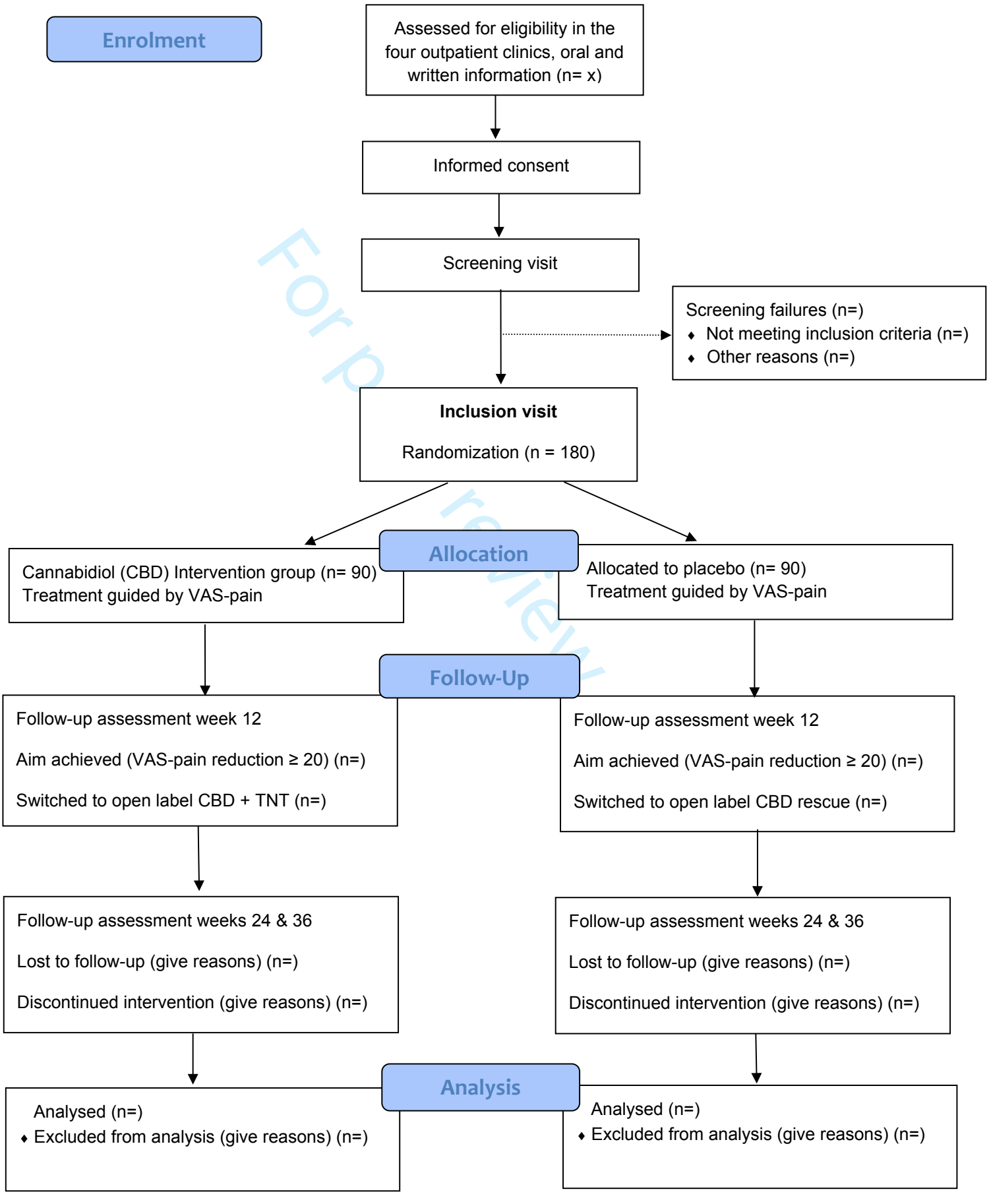

FIGURE 2: Treatment flow chart

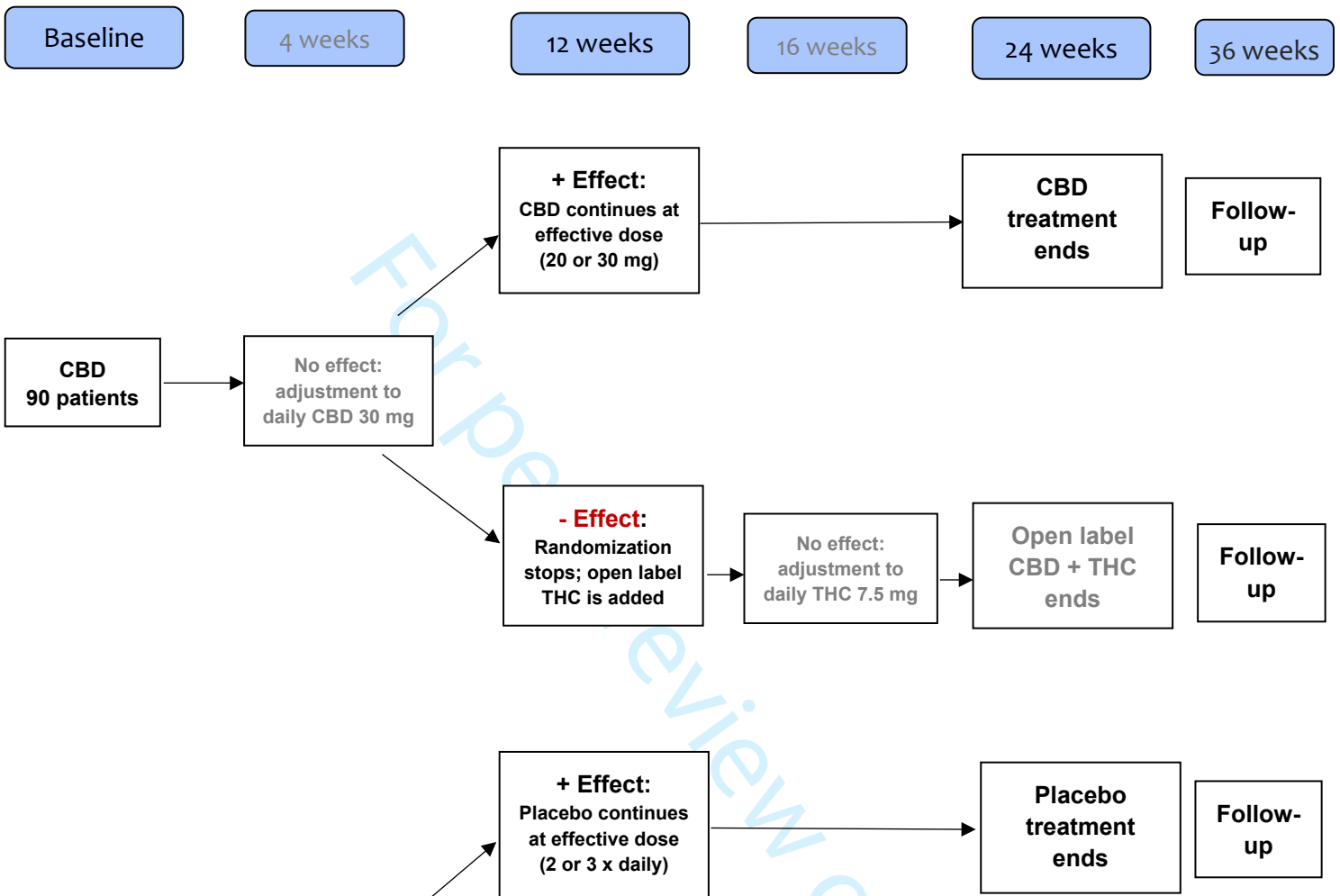

FIGURE 3: Schedule of assessments and procedures

Visit	Screening Visit	Baseline Visit	Nurse Consultation A	Assessment Consultation A	Nurse Consultation B	Assessment Consultation B	Follow-up
Week	-2	0	4	12	16	24	36
Inclusion/ Exclusion	(X)	X					
Demography	(X)	X					
Medical History	(X)	X					
Concomitant medication	(X)	X		X		X	
Physical examination	(X)	X		X		X	
BP, pulse, temperature	(X)	X		X		X	
Hematology/ Biochemistry	(X)	X		X		X	X
CRP	X	X		X		X	X
Serum/blood bank		X		X		X	X
ECG	(X)	X		X		X	X
Check up on fulfilled classification	(X)	X					
40 joint score or BAS score	(X)	X		X		X	X
Patient's pain score (VAS)	X	X	X	X	X	X	X
Patient's global score (VAS)	(X)	X		X		X	X
Doctors' global score (VAS)	(X)	X		X		X	X
HAQ or BAS	(X)	X		X		X	X
DAS 28 CRP or ASDAS	(X)	X		X		X	X
Check up on potential AE or SAE			X	X	X	X	X
PainDETECT		X		X		X	X
SF-36		X		X		X	X
Cognitive tests (TMT, DSST)		X		X		X	X
Sleep quality		X		X		X	X
CEQ Expectation		X		X			

BMJ Open

The efficacy and safety of Cannabidiol followed by an open label add-on of Tetrahydrocannabinol for the treatment of chronic pain in patients with Rheumatoid arthritis or Ankylosing spondylitis Protocol for a multicentre, randomized, placebo-controlled study

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The efficacy and safety of Cannabidiol followed by an open label add-on of Tetrahydrocannabinol for the treatment of chronic pain in patients with Rheumatoid arthritis or Ankylosing spondylitis

Protocol for a multicentre, randomized, placebo-controlled study

Running title: CANART

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) are chronic, systemic, inflammatory diseases, primarily in the musculoskeletal system.

Pain and fatigue are key symptoms of RA and AS. Treatment presents a clinical challenge for several reasons, including the progressive nature of the diseases and the involvement of multiple pain mechanisms. Moreover, side effects of pain treatment pose an implicit risk. Currently, no well-controlled studies have investigated how medical cannabis affects pain and cognitive functions in RA and AS. The present study aims to evaluate the efficacy and safety of medical cannabis in the treatment of persistent pain in patients with RA and AS with low disease activity.

Methods and analysis: A double-blinded, randomized, placebo-controlled study of Cannabidiol (CBD), followed by an open label add-on of Tetrahydrocannabinol (THC) with collection of clinical data and biological materials in RA and AS patients treated in routine care. The oral treatment with CBD in the experimental group is compared to placebo in a control group for 12 weeks, followed by an observational 12-week period with an open label add-on of THC in the primary CBD non-responders. Disease characteristics, psychological parameters, demographics, comorbidities, lifestyle factors, blood samples and serious adverse events (SAE) are collected at baseline, after 12 and 24 weeks of treatment, and at a follow-up visit at 36 weeks. Data will be analysed in accordance with a predefined statistical analysis plan.

Ethics and dissemination: The Danish Ethics Committee (S-20170217), the Danish Medicines Agency (S-2018010018) and the Danish Data Protection Agency approved the protocol. The project is registered in the European Clinical Trials Database (EudraCT 2017-004226-15). All participants will give written informed consent to participate prior to any study-related procedures. The results will be presented at international conferences and published in peer-reviewed journals.

Strengths and limitations of this study

Strengths

- The randomised, double-blind and placebo-controlled design aims to determine outcome data (on the defined endpoints) and, thus, reduces the risk of bias, especially selection bias.
- Recruitment in routine care is expected to appropriately reflect the patients and conditions in the two diagnostic groups.
- The performance of a controlled study demands the use of medical Cannabidiol (CBD), and Tetrahydrocannabinol THC instead of plant extracts, i.e. tea or herbal preparations.

Limitations

- There is no clinical evidence for the optimal dosage and application ranges. Thus, the treatment regimens for the drugs used are an extrapolation of expert knowledge
- Both primary and secondary endpoints are based on patient-reported outcome measurements (PROMs) and may be influenced by bias.

INTRODUCTION

The treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) has improved significantly over the last three decades [1, 2, 3]. Chronic pain and fatigue are symptoms typical of these major inflammatory rheumatic disorders [4, 5, 6]. Cognitive dysfunctions, such as concentration and memory problems, are also often reported in patients with chronic pain. These cognitive dysfunctions can be related to pain itself, sleep problems, or reflect a side effect of the pharmacological treatment [4, 6]. RA affects the small joints of the hands and feet, but can also involve the larger joints [7]. AS mainly affects the spinal and sacroiliac (SI) joints and is characterised by back pain and stiffness [8]. Pain may involve nociceptive and non-nociceptive components and is based on the interaction between peripheral inflammation and central sensitization [9, 10]. The immediate pain is triggered by the inflammation of the synovial tissue and/or consecutive oedema of the subchondral bone, and leads to a sensitization of the peripheral nociceptors [11].

Thus, chronic pain is likely to be due to peripheral joint and central neuropathic pain mechanisms at various stages [11 -16].

Treatment of moderate to severe chronic pain is difficult to overcome, for several reasons: heterogeneity of the patients in a given diagnostic group, the progressive nature of the disease, involvement of multiple pain mechanisms and the presence of comorbidities, particularly in elderly patients [17]. The rheumatologist is likely to pay full attention to the anti-inflammatory treatment. This approach implies the fact that chronic pain associated with increased mortality can be overlooked [18, 19].

There is a lack of knowledge about the effect of cannabinoids in rheumatic diseases. Based on a Cochrane meta-analysis, the authors concluded that the existing clinical studies of CBD applied in monotherapy are of such poor quality that there is insufficient data to draw any conclusions about the effectiveness and/or long-term security of the compound [20].

Currently, only very few studies have investigated how medical cannabis affects cognitive functions, such as concentration and attention [21]. A few studies have investigated the impact of illegally obtained cannabis in RA [20]. Furthermore, studies that have assessed medical cannabis did so mostly in the context of multiple sclerosis [20, 22, 23]. In contrast to studies of recreational cannabis, the studies in persons with multiple sclerosis indicate that medical cannabis does not negatively affect cognition and could improve sleep quality. Given the limited data and the lack of a proper control condition, no definite conclusions of the potential cognitive impact of medical cannabis could be drawn [20, 24].

Hence, concerns about potential negative side effects of medical cannabis on cognition have led the Danish health authorities' attention on a patient's ability to drive safely [20, 23]. Furthermore, in the treatment of rheumatic diseases, there is no established routine nor rheumatologic competence to prescribe medical cannabis. Consequently, there is considerable uncertainty and caution towards the use of medical cannabis, even in the North American countries, where it is already legal to prescribe these compounds for rheumatologic conditions [23, 24]. This can lead to patients resorting to self-medication with cannabinoids [20, 24, 25]. Thus, there is a strong need for high quality studies of the efficacy and side effects of cannabinoids.

The overall aim of the study is to investigate the effect of medical cannabis on pain in patients with RA and AS, to elaborate on the potential dosage of CBD and THC, and to explore if and how the test compounds affect patients' cognitive functions and sleep.

MATERIALS AND METHODS

Setting and study design

The study is an investigator-initiated, double-blinded, randomized, placebo-controlled intervention study of CBD, followed by an open label add-on of THC. It is designed to evaluate the efficacy and safety of medical cannabis, either as CBD or in the form of the combination treatment of CBD and THC as "add-on" treatment for chronic pain in RA and AS. The patient-reported outcome measurement (PROM) [26], a pain visual analogue scale (VAS) score [27] at a value of at least 50 are the key inclusion criterion. The score range is from 0 – 100; a higher score indicates greater pain intensity. Thus, the null hypothesis, H^0, is that receiving the active treatment with cannabis derivatives does not improve the pain situation in clinical assessment after 12, 24 and 36 weeks.

Figure 1 presents the Consort flow chart.

Clinical data and outcomes are registered in an electronic Case Report Form (eCRF), based on the Reuma-eCRF system available within the Danish nationwide registry DANBIO [15, 28] and biological samples are collected via the Danish Rheumatologic Biobank (DRB) [29]. Patients are recruited from four Danish university hospital departments. Patient inclusion is planned to start in November 2018 and is expected to continue for 14 months.

Participants

The study population consists of:

- patients with seropositive RA [1] currently treated with either Conventional Disease Modifying Anti-Rheumatic Drugs (cDMARD) and/or biological Disease Modifying Anti-Rheumatic Drugs (bDMARD), and without clinical signs of arthritis, as assessed by a 40-swollen joint count, and

- patients with AS, according to the modified New York criteria [2], currently receiving either nonsteroidal anti-inflammatory drugs (NSAID) and/or bDMARD, who show an absence of clinical signs of axial and peripheral arthritis and enthesitis, and who have an Ankylosing Spondylitis Disease Activity Score (ASDAS) < 2.1.

Inclusion criteria

a. Minimum Pain VAS 50, both at screening and inclusion
b. Disease duration ≥ 2 years
c. Ongoing treatment or earlier attempt to treat with Paracetamol or NSAIDs without clinical signs of arthritis or spondyloarthritis
d. Analgesic treatment unchanged at least 4 weeks before trial start.

Exclusion criteria

a. Age < 18 years
b. Pregnancy, pregnancy wish or ongoing breastfeeding
c. CRP > 10 mg/L
d. Comorbidities, more specific competitive rheumatologic disorders, such as systemic lupus erythematosus (SLE), scleroderma, polymyositis or chronic pain condition based on a further clinical detectable aetiology (e.g. fibromyalgia)
e. Evidence of serious uncontrolled concomitant cardiovascular, pneumological, neurological, endocrinological, gastroenterological, urogenital, nephrological or hepatic impairment
f. Major surgery performed < 8 weeks before randomization or planned major surgical interventions
g. Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
h. Evidence of active malignant disease, malignancies diagnosed or treated within the previous 2 years, including hematologic malignancies and solid tumours
i. Actual or previous harmful use of alcohol or drug abuse, in accordance with the WHO definition [30], within the previous 2 years
j. Ongoing treatment with opioids and/or cannabis products and/or neuroleptics, or treatment

terminated less than 4 weeks before inclusion

k. Hypersensitivity to the study compounds

l. Suspected for, or evidence of, active schizophrenia, other psychotic illness in the family history (first degree relatives), other significant psychiatric disorder, or treated depression associated with underlying condition

m. Epilepsy or recurrent seizures

n. Use of strong Cytochrome P450 3A4 (CYP3A4) inducers.

Experimental treatment

The treatment starts with oral CBD 10 mg or placebo before bedtime, and increases after two weeks to 10 mg twice daily. Finally, and in case of lack of effect (VAS-pain reduction less than 20) from the beginning of the 5th week, the treatment increases to 10 mg thrice daily.

The clinical assessment after 12 weeks defines how to proceed during the following 12 weeks: in case of a sufficient response, i.e. a VAS-pain reduction of equal/or more than 20, the established treatment continues randomized and without any further adjustment.

In case of insufficient response, i.e. a VAS-pain reduction of less than 20, randomization is terminated. Patients who received placebo are shifted to the active compound, i.e. CBD treatment, and dose adjustment is performed, as mentioned above. In patients who received CBD treatment during the randomised period, the open label follow up combines CBD with THC, i.e. oral THC 2.5 mg daily is added to the ongoing CBD treatment. The THC dose is increased after 2 weeks to 2.5 mg twice daily (in total, 5 mg THC/day), and in case of lack of effect (VAS-pain reduction less than 20, compared to VAS 20, as defined at clinical assessment after 12 weeks), after another two weeks to 2.5 mg thrice daily (in total, 7.5 mg THC/day) from the beginning of the 17th week.

Figure 2 presents the study flow chart.

Randomization procedure

Patients are stratified by diagnosis and by recruiting center. Patients are randomly allocated to one of the two treatment arms – CBD *or* Placebo – by random permuted blocks. Randomization is blinded to the treatment allocation. Allocation is not known to anyone other than Glostrup Pharmacy, who produces and dispatches drug packages on request to each site. Sites receive a sealed, opaque envelope for each patient with the treatment allocation ready to be revealed, should this be required. Treatment is initiated within two weeks after randomization. Measurements of effect are carried out at baseline before randomization, and post-intervention at 12, 24 and 36-weeks post-randomization. Data analysis and statistical programming are blinded. The randomization procedure and data analysis are performed by an independent statistician at IRS, University of Southern Denmark, Gråsten, Denmark

Designated outcomes and clinical data

Primary outcome is the number of patients achieving an improvement of pain-VAS (Δ VAS-pain ≥ 20) after 12 weeks of treatment.

Secondary outcomes

a. The fraction (%) of RA and AS patients that achieve an improvement in VAS-pain, as assessed by the reduction of Δ VAS ≥ 20 and outcome of the PainDETECT Questionnaire (PD-Q) [31, 32], after 24 and 36 weeks.

b. The fraction (%) of RA and AS patients that achieve an improved quality of life situation, as assessed by Global-VAS with Δ VAS reduction ≥ 20 and by the SF-36 [33], after 24 and 36 weeks.

c. The fraction (%) of AS patients that achieve a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) < 40 or reduction in BASDAI with Δ ≥ 20 after 12, 24 and 36 weeks [34].

d. A characterization of AS and RA patients' cognition and sleep quality, as assessed by the Trail Making Test (TMT) [35], the Digit Symbol Substitution Test (DSST) [36, 37] and the Pittsburgh Sleep Quality Index [38], performed at baseline and after 12, 24 and 36 weeks.

e. A characterization of the patients' expectation for the treatment effect, as assessed by the Credibility/expectancy Questionnaire (CEQ) and by performing semi-structured interviews [39-43] at baseline and after 12 weeks.

f. A characterization of and a final statement about Serious Adverse Event (SAE) state.

The outcome measures include parameters recommended by the IMMPACT paper. [44]

Clinical data

At baseline, and after 12, 24 and 36 weeks, respectively, data are collected in the DANBIO Reuma-eCRF system. Furthermore, two additional nurse consultations are performed after 4 and 16 weeks, to obtain safety information and VAS-pain and to possibly perform a treatment increase from the beginning of the 5th and/or 17th week, respectively, as presented in the section above, Experimental treatment. The following data are collected at the time points as presented in Figure 3:

1) Clinical measurements, i.e. in RA the Disease Activity Score 28-joints (DAS28-CRP) [45, 46], Health Assessment Questionnaire (HAQ) and, in AS, the (ASDAS) and Bath Ankylosing Spondylitis (BAS)-scores for disease activity (BASDAI), function (BASFI) and measures (BASMI) are registered [47, 48]. In both patient groups, additional Patient Reported Outcome Measures (PROMs) are obtained: visual analogue scales (VAS) for pain, fatigue, patient's global Quality of Life (QoL) score SF-36 and pain-score PainDETECT [31, 32]. Furthermore, the effect of intervention on attention and concentration is investigated using the TMT and DSST [35-37]. Additionally, sleep quality is evaluated with the Pittsburgh Sleep Quality Index. [38]. The expected effect of treatment is measured with the Credibility/expectancy Questionnaire and semi-structured interviews.

2) Exposures, i.e. all concomitant treatment, especially current treatments with cDMARDs, bDMARDs and/or analgesics, including dosing schedule and treatment onset.

3) Comorbidities, e.g., cardiovascular disease, diabetes and hypertension

4) Lifestyle (blood pressure, exercise habits and smoking status)

5) Patient demographics, e.g., diagnosis, age, gender, height, weight, Body Mass Index (BMI), disease duration, smoking status, educational level, marital status, sick leave, occupation and ethnicity are obtained at baseline.

Biological samples

Blood samples are obtained at baseline, and at 12, 24 and 36 weeks. In addition to routine blood tests blood samples are collected in one EDTA tube (9 ml), two serum tubes (2x9 ml) and one PAXgene blood RNA tube (2.5 ml, Becton & Dickinson, Lyngby, Denmark), as described previously [49]. These are collected for definition of drug concentration of CBD and THC, i.e. monitoring of compliance, possible adverse events and for further future analyses.

Statistical Analysis Plan

The power calculation is based on the following assumptions for the primary outcome:

- An expected proportion with a response of 50% or more in the CBD group and expected 20% in the placebo group (OR = 4). Response is defined as a reduction in VAS-pain of at least 20 (range 0-100) after 12 weeks of treatment.
- A significance level of 0.05 in a two-sided z-test of proportions.
- A total of 180 patients will be included in two balanced groups, each consisting of 90 patients.

This setup gives a statistical power of 0.98 for the primary outcome. The power is reduced if the true difference between the groups is less than the expected 30 percentage points, and if more than an

expected 10% of the patients drop out of the experiment. Balanced groups of 45 patients will yield a power of 83% for two-group comparisons on binary outcomes, such as the primary outcome. Slight deviations in sample sizes might occur because of block randomization.

The primary outcome is tested by a z-test in a logistic regression model. The main parameter estimates the ratio of the odds of response for the intervention group relative to the control group. All tests are two-sided. Secondary outcomes are analysed using logistic and linear regression, depending on the data type. In the case of deviations from the normality assumption, a non-parametric proportional odds model will be used. The secondary outcomes measured at baseline and post-intervention, 12, 24 and 36 weeks (follow-up) will be analysed using mixed-effects models, controlling for time of measurement. The random effects parameter is estimated for the clustering of repeated observations within patients. Analysis for the direct effects of CBD, THC and the interaction between those will be carried out separately, with placebo as the reference group for CBD.

Baseline measurements are reported as proportions of categorical variables, average and standard deviation (SD) for normally distributed data, and median (range) scores for non-normal numerical data. All variables are reported for the two intervention groups. Baseline variables with a tendency ($p < .25$) to coincide with the intervention group will be included as control variables in the test of the primary and secondary outcomes. The relationship between the tested variables at baseline and intervention allocation will be analysed with parametric (t-test) and non-parametric tests ($\chi 2$ and the Mann-Whitney test). Correction for multiple tests will be based on a gatekeeping model of access. This means that significant results for the secondary outcomes are interpreted solely as exploratory findings in case of a non-significant finding for the primary outcome.

PATIENT AND PUBLIC INVOLVEMENT

King Christian X's Hospital for Rheumatic diseases involves patients with inflammatory rheumatic diseases actively in both quality assurance projects, research projects and in the development of educational programmes. Furthermore, a User Council was established in 2013 in the research department. The project is a consequence of rheumatic patient's pain reality and the idea of the project was originally presented to the User Council back in autumn 2017. Since then, two patients have been involved in the processing of the project. So far, the patient information brochures have been developed based on the integration of the patient's perspectives. PROMS, especially the patient's pain VAS, are the main focus of the outcome measurements. Thus, both the burden and consequence of the intervention and the results of the given intervention are transparent.

Meetings with the projects patient representatives will be arranged twice a year and the progress of the project is presented continuously for the User Council.

ETHICS AND DISSEMINATION

The protocol (*version 8.1., November 22nd 2018*) is approved by the Danish Ethics Committee (S-20170217), the Danish Data Protection Agency (2018-41-5388) and the Danish Medicines Agency (2018-010018). All patients receive verbal and written information and give their written consent before enrolment, in accordance with Danish Ethics Committee guidelines. Appendix 1 presents the projects consent statement in English. All patients are informed that they can withdraw from the study at any time. Although this would lead to the termination of project medication, patient withdrawal will have no consequences for regular course of treatment. In case of withdrawal, no subsequent patient-related registrations will be obtained.

The two cannabis derivatives used in this study are comparable to the authorized compounds in the drug Sativex® [50]. The treatment consists of CBD tablets and THC herbal capsule preparation,

which are produced based on natural raw materials by Glostrup Pharmacy's laboratory. The drugs are manufactured according to quality-ensured standardized procedures specifying the exact ingredients in mg. This makes dosage and monitoring of the therapy safe according to Danish national Good Clinical Practice (GCP) guidelines. The side effects, are well known and well described [51]. The study subjects are patients who are already associated to one of the four participating outpatient clinics. The blood samples at baseline, after 12 weeks and 24 weeks respectively, will be realized in connection with routine blood tests, in accordance with an a priori arranged outpatient visit and thus will not pose increased risks. At all visits, participants will asked about events and/or reactions. Based on this information the investigator will assess whether there is an adverse event (AE), an adverse reaction (AR), a serious adverse event (SAE), or a suspected unexpected serious adverse reaction (SUSAR). The GCP unit of the University of Southern Denmark monitors the study independently.

The patients will be contacted and informed regarding the overall study results if they indicate interest in this, and in accordance with the patient study consent form and as directed by the Danish Ethics Committee guidelines. The physician in charge of the project at each participating outpatient clinic is responsible for conducting the study in accordance with the 5th edition of the Helsinki declaration. Study participation does not affect the established anti-inflammatory treatment course of individual patients.

Results will be presented at international conferences and published in international and peer-reviewed medical journals. Negative, positive as well as inconclusive results will be published.

DISCUSSION AND POTENTIAL LIMITATIONS

CBD and THC are two of more than 80 active compounds in the marijuana plant [52].

In contrast to THC, CBD does not exhibit a narcotic effect and/or intoxication [53, 54]. The biochemical effect of the cannabinoids is explained by the compounds´ interaction with specific receptors; the CB1 receptor is located on neurons and glial cells in different parts of the central nervous system, whereas the CB2 receptor is found in structures of the immune system. The stimulating and narcotic effects of THC are considered to be caused by activation of CB-1 receptors. CBD has a very low affinity for these receptors [52]. Thus, CBD binding to the CB-1 receptors causes little to no narcotic effect. New studies show evidence that CBD affects autoimmune signalling pathways and that these mechanisms may be relevant to CBD's therapeutic profile [53, 54].

The effect of CBD is studied in a placebo-controlled design, whereas the effect of a combination of CBD and THC is an open label continuation of the study. This design represents the balance between a wish to assess the effect of both CBD and THC correctly, while recognizing risks, including traffic safety issues, especially due to the THC treatment. Also, the possible negative effect on cognitive functioning can have a large impact on job functioning. Therefore, a more definite answer as to whether medical cannabis negatively affects cognition is important in relation to job functioning and autonomy.

The trial population is monitored regularly at the participating outpatient clinics and the individual longitudinal treatment is registered. DANBIO is the nationwide clinical quality database for rheumatology [16, 29]. All adult patients treated with biological drugs are registered. Furthermore, patients with AS and RA are registered, regardless of treatment. Thus, the DANBIO based Reuma-eCRF system provides particularly good conditions for the collection and monitoring of validated data.

Figure Legends

Figure 1 presents the Consort flow chart

Figure 2 presents the treatment flow chart

Figure 3 presents the schedule of assessments and procedures

Funding

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Contributors

OH wrote the protocol for the European and the Danish Medicines Agency and the Research Ethics Committee. TEA, AAC, JP, EMH, TJE, TH, AGB, AGL, ABB, MØ, MLH, NSK, KKR, KHP and OH contributed to study concept. KHP, MØ and OH drafted and revised the manuscript after feedback from all authors. All authors contributed to the review of the present manuscript and approved the final version of the manuscript.

Competing interests

None

Provenance and peer review

Not commissioned; externally peer-reviewed

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FIGURE 1: Consort flow chart

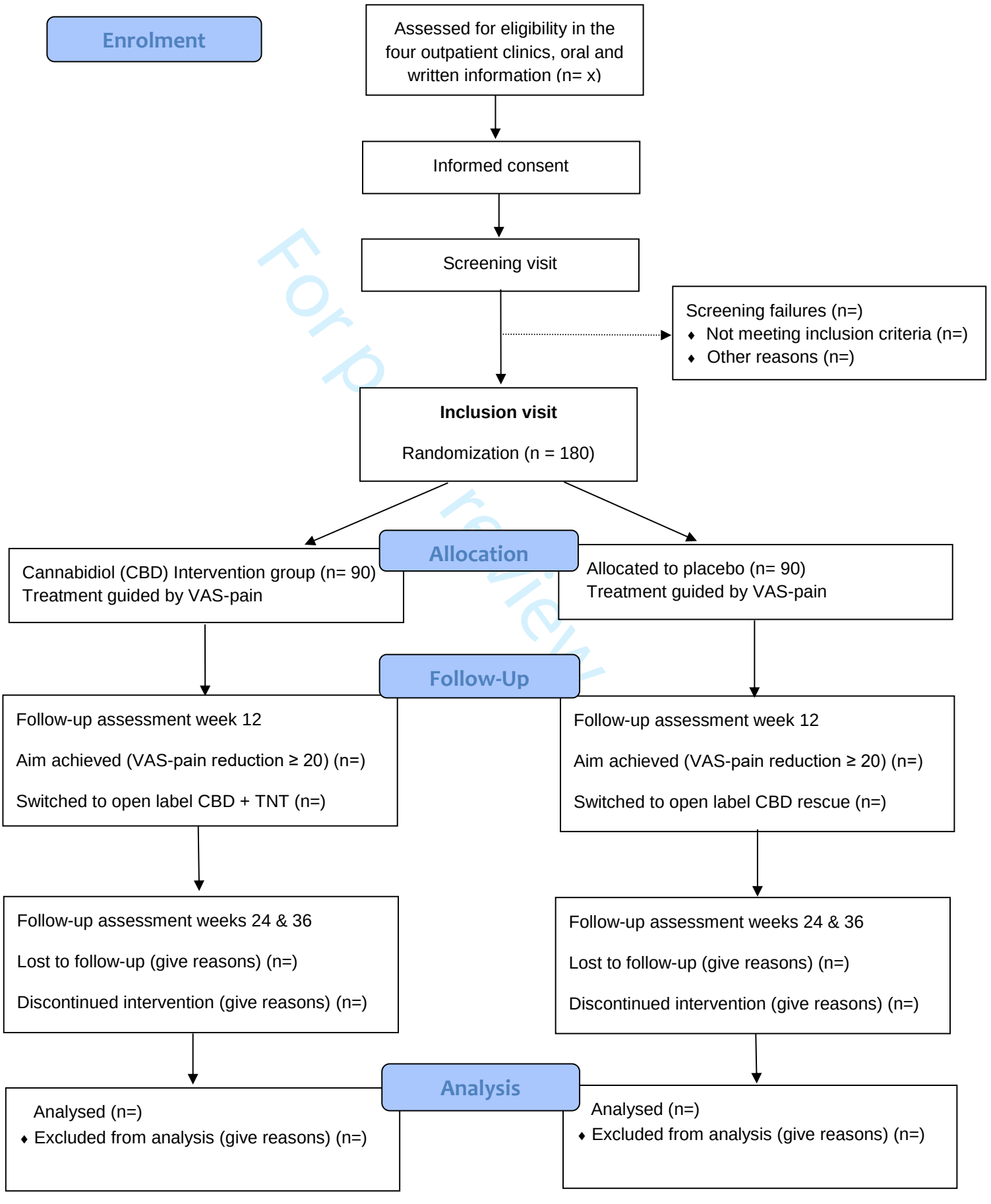

FIGURE 2: Treatment flow chart

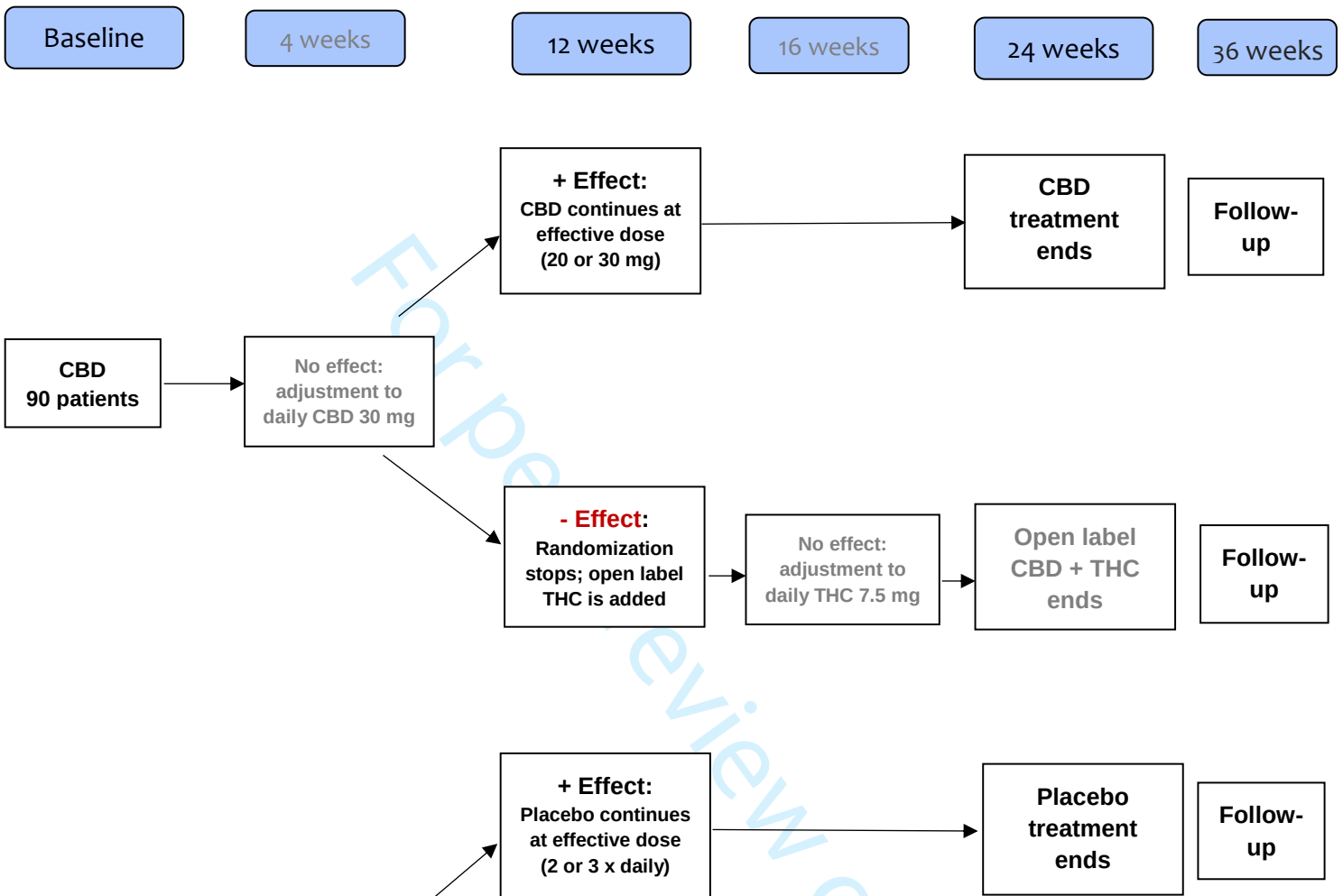

FIGURE 3: Schedule of assessments and procedures

Visit	Screening Visit	Baseline Visit	Nurse Consultation A	Assessment Consultation A	Nurse Consultation B	Assessment Consultation B	Follow-up
Week	-2	0	4	12	16	24	36
Inclusion/ Exclusion	(X)	X					
Demography	(X)	X					
Medical History	(X)	X					
Concomitant medication	(X)	X		X		X	
Physical examination	(X)	X		X		X	
BP, pulse, temperature	(X)	X		X		X	
Hematology/ Biochemistry	(X)	X		X		X	X
CRP	X	X		X		X	X
Serum/blood bank		X		X		X	X
ECG	(X)	X		X		X	X
Check up on fulfilled classification	(X)	X					
40 joint score or BAS score	(X)	X		X		X	X
Patient's pain score (VAS)	X	X	X	X	X	X	X
Patient's global score (VAS)	(X)	X		X		X	X
Doctors' global score (VAS)	(X)	X		X		X	X
HAQ or BAS	(X)	X		X		X	X
DAS 28 CRP or ASDAS	(X)	X		X		X	X
Check up on potential AE or SAE			X	X	X	X	X
PainDETECT		X		X		X	X
SF-36		X		X		X	X
Cognitive tests (TMT, DSST)		X		X		X	X
Sleep quality		X		X		X	X
CEQ Expectation		X		X			

THE DANISH BIOMEDICAL RESEARCH ETHICS COMMITTEE SYSTEM

Standard consent statement prepared by the Danish Biomedical Research Ethics Committee System, December 2011. (S4)

Informed consent to participate in a health science research project

Title of the research project:

Can-Art

Pain treatment with medical CANnabis in patients with inflammatory ARThritis

Statement by Research Subject:

I have been given written and oral information and I know enough about the purpose and method, and about the advantages and disadvantages of participation.

I know that participation is voluntary and that I can withdraw my consent at any time without losing my current or future rights to treatment.

I consent to participate in the research project and that my biological data be extracted for storage in a research bio-bank. I have received a copy of this consent form and a copy of the written information about the project for my own records.

Research subject's name: _____

Date _____ Signature: _____

If new, essential health information about you comes to light in the research project, you will be informed. If you would prefer *not* to be informed about new, essential health information, should it come to light in the research project, please mark here: _ (mark with an x)

Do you want to be informed about the results of the research project and any consequences for you?

Yes _____ (mark with an x) No _____ (mark with an x)

Declaration by the person providing this information:

I declare that the research subject has received oral and written information about the research project.

In my opinion, sufficient information has been provided to the research subject for the decision to be made regarding participation in the research project.

The name of the person who provided this information:

Date _____Signature: _____

Project identification: (VEK Project ID 61 187, EUdraCT no. 2017-2017-004226-15)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1;line 1 - 4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P1, line 24
	2b	All items from the World Health Organization Trial Registration Data Set	P1, line 24 & P3, line 82, 83
Protocol version	3	Date and version identifier	P14, line 349
Funding	4	Sources and types of financial, material, and other support	P17, line 414 - 417
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1, line 6 – 22 & P17, line 419 - 424
	5b	Name and contact information for the trial sponsor	P1, line 28
	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	P17, line 414 - 417
	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)	P16, line 401 –406 & Danish Medicines Agency (S-2018010018)

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	P5, line 114 - 134
	6b	Explanation for choice of comparators	P6, line 144 - 150
Objectives	7	Specific objectives or hypotheses	P6, line 152 – 154 & P7, line 167- 168
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, noninferiority, exploratory)	P7, line 160 – 164
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	P7, line 172 – 173 EudraCT 2017-004226-15
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)	P8 & 9, line 185 – 215
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P9, line 217 – 232
	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)	P9, line 217 – 232, P15, line 365 - 368
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P12, 299 - 300
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P7, line 164

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	P10 -11, line 245 - 270
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)	P9, line 232: Figure 2
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	P12, line 302 - 308
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P16, line 403 - 406
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	P10, line 233 –243 & Danish Medicines Agency (S-2018010018)
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	P10, line 233 - 243
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P10, line 233 - 243
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P10, line 233 - 243
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P10, line 233 – 243 & Figure 2

Methods: Data collection, management, and analysis

Data collection methods	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	Page11 & 12, line 272 – 293
	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	Page16, line 401 – 406
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	Page19, line 500 – 502
Statistical methods	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	Page13, line 314 – 329
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page13, line 317 – 322
	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)	Page 13, line 314 – 329 & Danish Medicines Agency (S-2018010018)

Methods: Monitoring

Data monitoring	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	P15, 369 P19, 500 – 501

	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	Danish Medicines Agency (S-2018010018)
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	Danish Medicines Agency (S-2018010018)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 15, line 369 Danish Medicines Agency (S-2018010018)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 3, line 81 – 83
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)	Page 3, line 81, Danish Ethics Committee (S-20170217)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P14, line 349 – 353, Appendix 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P19, line 500 -502
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	P19, line 500-501
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 17, line 425 - 426

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 3, line 81, Danish Ethics Committee (S-20170217)
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	Page 3, line 81, Danish Ethics Committee (S-20170217)
Dissemination policy	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	Page 3, line 84 – 85 & p15, line 373 – 374
	31b	Authorship eligibility guidelines and any intended use of professional writers	Danish Ethics Committee (S-20170217
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None declared
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached Appendix 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 12, line 295 – 300

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The efficacy and safety of Cannabidiol followed by an open label add-on of Tetrahydrocannabinol for the treatment of chronic pain in patients with Rheumatoid arthritis or Ankylosing spondylitis: Protocol for a multicentre, randomized, placebo-controlled study

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Primary Subject Heading:	Rheumatology

Secondary Subject Heading:	Pharmacology and therapeutics, Patient-centred medicine
Keywords:	Rheumatoid Arthritis, Ankylosing Spondylitis, Chronic Pain, Treatment with Medical Cannabis

The efficacy and safety of Cannabidiol followed by an open label add-on of Tetrahydrocannabinol for the treatment of chronic pain in patients with Rheumatoid arthritis or Ankylosing spondylitis: Protocol for a multicentre, randomized, placebo-controlled study

Running title: CANART

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) are chronic, systemic, inflammatory diseases, primarily in the musculoskeletal system.

Pain and fatigue are key symptoms of RA and AS. Treatment presents a clinical challenge for several reasons, including the progressive nature of the diseases and the involvement of multiple pain mechanisms. Moreover, side effects of pain treatment pose an implicit risk. Currently, no well-controlled studies have investigated how medical cannabis affects pain and cognitive functions in RA and AS. The present study aims to evaluate the efficacy and safety of medical cannabis in the treatment of persistent pain in patients with RA and AS with low disease activity.

Methods and analysis: A double-blinded, randomized, placebo-controlled study of Cannabidiol (CBD), followed by an open label add-on of Tetrahydrocannabinol (THC) with collection of clinical data and biological materials in RA and AS patients treated in routine care. The oral treatment with CBD in the experimental group is compared to placebo in a control group for 12 weeks, followed by an observational 12-week period with an open label add-on of THC in the primary CBD non-responders. Disease characteristics, psychological parameters, demographics, comorbidities, lifestyle factors, blood samples and serious adverse events (SAE) are collected at baseline, after 12 and 24 weeks of treatment, and at a follow-up visit at 36 weeks. Data will be analysed in accordance with a predefined statistical analysis plan.

Ethics and dissemination: The Danish Ethics Committee (S-20170217), the Danish Medicines Agency (S-2018010018) and the Danish Data Protection Agency approved the protocol. The project is registered in the European Clinical Trials Database (EudraCT 2017-004226-15). All participants will give written informed consent to participate prior to any study-related procedures. The results will be presented at international conferences and published in peer-reviewed journals.

Strengths and limitations of this study

Strengths

- The randomised, double-blind and placebo-controlled design aims to determine outcome data (on the defined endpoints) and, thus, reduces the risk of bias, especially selection bias.
- Recruitment in routine care is expected to appropriately reflect the patients and conditions in the two diagnostic groups.
- The performance of a controlled study demands the use of medical Cannabidiol (CBD), and Tetrahydrocannabinol THC instead of plant extracts, i.e. tea or herbal preparations.

Limitations

- There is no clinical evidence for the optimal dosage and application ranges. Thus, the treatment regimens for the drugs used are an extrapolation of expert knowledge
- Both primary and secondary endpoints are based on patient-reported outcome measurements (PROMs) and may be influenced by bias.

INTRODUCTION

The treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) has improved significantly over the last three decades [1, 2, 3]. Chronic pain and fatigue are symptoms typical of these major inflammatory rheumatic disorders [4, 5, 6]. Cognitive dysfunctions, such as concentration and memory problems, are also often reported in patients with chronic pain. These cognitive dysfunctions can be related to pain itself, sleep problems, or reflect a side effect of the pharmacological treatment [4, 6]. RA affects the small joints of the hands and feet, but can also involve the larger joints [7]. AS mainly affects the spinal and sacroiliac (SI) joints and is characterised by back pain and stiffness [8]. Pain may involve nociceptive and non-nociceptive components and is based on the interaction between peripheral inflammation and central sensitization [9, 10]. The immediate pain is triggered by the inflammation of the synovial tissue and/or consecutive oedema of the subchondral bone, and leads to a sensitization of the peripheral nociceptors [11].

Thus, chronic pain is likely to be due to peripheral joint and central neuropathic pain mechanisms at various stages [11 -16].

Treatment of moderate to severe chronic pain is difficult to overcome, for several reasons: heterogeneity of the patients in a given diagnostic group, the progressive nature of the disease, involvement of multiple pain mechanisms and the presence of comorbidities, particularly in elderly patients [17]. The rheumatologist is likely to pay full attention to the anti-inflammatory treatment. This approach implies the fact that chronic pain associated with increased mortality can be overlooked [18, 19].

There is a lack of knowledge about the effect of cannabinoids in rheumatic diseases. Based on a Cochrane meta-analysis, the authors concluded that the existing clinical studies of CBD applied in monotherapy are of such poor quality that there is insufficient data to draw any conclusions about the effectiveness and/or long-term security of the compound [20].

Currently, only very few studies have investigated how medical cannabis affects cognitive functions, such as concentration and attention [21]. A few studies have investigated the impact of illegally obtained cannabis in RA [20]. Furthermore, studies that have assessed medical cannabis did so mostly in the context of multiple sclerosis [20, 22, 23]. In contrast to studies of recreational cannabis, the studies in persons with multiple sclerosis indicate that medical cannabis does not negatively affect cognition and could improve sleep quality. Given the limited data and the lack of a proper control condition, no definite conclusions of the potential cognitive impact of medical cannabis could be drawn [20, 24].

Hence, concerns about potential negative side effects of medical cannabis on cognition have led the Danish health authorities' attention on a patient's ability to drive safely [20, 23]. Furthermore, in the treatment of rheumatic diseases, there is no established routine nor rheumatologic competence to prescribe medical cannabis. Consequently, there is considerable uncertainty and caution towards the use of medical cannabis, even in the North American countries, where it is already legal to prescribe these compounds for rheumatologic conditions [23, 24]. This can lead to patients resorting to self-medication with cannabinoids [20, 24, 25]. Thus, there is a strong need for high quality studies of the efficacy and side effects of cannabinoids.

The overall aim of the study is to investigate the effect of medical cannabis on pain in patients with RA and AS, to elaborate on the potential dosage of CBD and THC, and to explore if and how the test compounds affect patients' cognitive functions and sleep.

MATERIALS AND METHODS

Setting and study design

The study is an investigator-initiated, double-blinded, randomized, placebo-controlled intervention study of CBD, followed by an open label add-on of THC. It is designed to evaluate the efficacy and safety of medical cannabis, either as CBD or in the form of the combination treatment of CBD and THC as "add-on" treatment for chronic pain in RA and AS. The patient-reported outcome measurement (PROM) [26], a pain visual analogue scale (VAS) score [27] at a value of at least 50 are the key inclusion criterion. The score range is from 0 – 100; a higher score indicates greater pain intensity. Thus, the null hypothesis, H^0, is that receiving the active treatment with cannabis derivatives does not improve the pain situation in clinical assessment after 12, 24 and 36 weeks.

Figure 1 presents the Consort flow chart.

Clinical data and outcomes are registered in an electronic Case Report Form (eCRF), based on the Reuma-eCRF system available within the Danish nationwide registry DANBIO [15, 28]. DANBIO contains actualized data on ongoing treatment regiments, which therefore easily can be monitored. Biological samples are collected via the Danish Rheumatologic Biobank (DRB) [29]. Patients are recruited from four Danish university hospital departments. Patient inclusion is planned to start in November 2018 and is expected to continue for 14 months.

Participants

The study population consists of:

- patients with seropositive RA [1] currently treated with either Conventional Disease Modifying Anti-Rheumatic Drugs (cDMARD) and/or biological Disease Modifying Anti-Rheumatic Drugs (bDMARD), and without clinical signs of arthritis, as assessed by a 40-swollen joint count, and

- patients with AS, according to the modified New York criteria [2], currently receiving either nonsteroidal anti-inflammatory drugs (NSAID) and/or bDMARD, who show an absence of

clinical signs of axial and peripheral arthritis and enthesitis, and who have an Ankylosing Spondylitis Disease Activity Score (ASDAS) < 2.1.

Inclusion criteria

a. Minimum Pain VAS 50, both at screening and inclusion
b. Disease duration ≥ 2 years
c. Ongoing treatment or earlier attempt to treat with Paracetamol or NSAIDs without clinical signs of arthritis or spondyloarthritis
d. Analgesic treatment unchanged at least 4 weeks before trial start.

Exclusion criteria

a. Age < 18 years
b. Pregnancy, pregnancy wish or ongoing breastfeeding
c. CRP > 10 mg/L
d. Comorbidities, more specific competitive rheumatologic disorders, such as systemic lupus erythematosus (SLE), scleroderma, polymyositis or chronic pain condition based on a further clinical detectable aetiology (e.g. fibromyalgia)
e. Evidence of serious uncontrolled concomitant cardiovascular, pneumological, neurological, endocrinological, gastroenterological, urogenital, nephrological or hepatic impairment
f. Major surgery performed < 8 weeks before randomization or planned major surgical interventions
g. Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
h. Evidence of active malignant disease, malignancies diagnosed or treated within the previous 2 years, including hematologic malignancies and solid tumours

i. Actual or previous harmful use of alcohol or drug abuse, in accordance with the WHO definition [30], within the previous 2 years

j. Ongoing treatment with opioids and/or cannabis products and/or neuroleptics, or treatment terminated less than 4 weeks before inclusion

k. Hypersensitivity to the study compounds

l. Suspected for, or evidence of, active schizophrenia, other psychotic illness in the family history (first degree relatives), other significant psychiatric disorder, or treated depression associated with underlying condition

m. Epilepsy or recurrent seizures

n. Use of strong Cytochrome P450 3A4 (CYP3A4) inducers.

Experimental treatment

The treatment starts with oral CBD 10 mg or placebo before bedtime, and increases after two weeks to 10 mg twice daily. Finally, and in case of lack of effect (VAS-pain reduction less than 20) from the beginning of the 5th week, the treatment increases to 10 mg thrice daily.

The clinical assessment after 12 weeks defines how to proceed during the following 12 weeks: in case of a sufficient response, i.e. a VAS-pain reduction of equal/or more than 20, the established treatment continues randomized and without any further adjustment.

In case of insufficient response, i.e. a VAS-pain reduction of less than 20, randomization is terminated. Patients who received placebo are shifted to the active compound, i.e. CBD treatment, and dose adjustment is performed, as mentioned above. In patients who received CBD treatment during the randomised period, the open label follow up combines CBD with THC, i.e. oral THC 2.5 mg daily is added to the ongoing CBD treatment.

The THC dose is increased after 2 weeks to 2.5 mg twice daily (in total, 5 mg THC/day), and in case of lack of effect (VAS-pain reduction less than 20, compared to VAS 20, as defined at clinical assessment after 12 weeks), after another two weeks to 2.5 mg thrice daily (in total, 7.5 mg THC/day) from the beginning of the 17th week.

Figure 2 presents the study flow chart.

Randomization procedure

Patients are stratified by diagnosis and by recruiting center. Patients are randomly allocated to one of the two treatment arms – CBD *or* Placebo – by random permuted blocks. Randomization is blinded to the treatment allocation. Allocation is not known to anyone other than Glostrup Pharmacy, who produces and dispatches drug packages on request to each site. Sites receive a sealed, opaque envelope for each patient with the treatment allocation ready to be revealed, should this be required. Treatment is initiated within two weeks after randomization. Measurements of effect are carried out at baseline before randomization, and post-intervention at 12, 24 and 36-weeks post-randomization. Data analysis and statistical programming are blinded. The randomization procedure and data analysis are performed by an independent statistician at IRS, University of Southern Denmark, Gråsten, Denmark

Designated outcomes and clinical data

Primary outcome is the number of patients achieving an improvement of pain-VAS (Δ VAS-pain ≥ 20) after 12 weeks of treatment.

Secondary outcomes

a. The fraction (%) of RA and AS patients that achieve an improvement in VAS-pain, as assessed by the reduction of Δ VAS ≥ 20 and outcome of the PainDETECT Questionnaire (PD-Q) [31, 32], after 24 and 36 weeks.

b. The fraction (%) of RA and AS patients that achieve an improved quality of life situation, as assessed by Global-VAS with Δ VAS reduction ≥ 20 and by the SF-36 [33], after 24 and 36 weeks.

c. The fraction (%) of AS patients that achieve a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) < 40 or reduction in BASDAI with Δ ≥ 20 after 12, 24 and 36 weeks [34].

d. A characterization of AS and RA patients' cognition and sleep quality, as assessed by the Trail Making Test (TMT) [35], the Digit Symbol Substitution Test (DSST) [36, 37] and the Pittsburgh Sleep Quality Index [38], performed at baseline and after 12, 24 and 36 weeks.

e. A characterization of the patients' expectation for the treatment effect, as assessed by the Credibility/expectancy Questionnaire (CEQ) and by performing semi-structured interviews [39-43] at baseline and after 12 weeks.

f. A characterization of and a final statement about Serious Adverse Event (SAE) state.

The outcome measures include parameters recommended by the IMMPACT paper. [44]

Clinical data

At baseline, and after 12, 24 and 36 weeks, respectively, data are collected in the DANBIO Reuma-eCRF system. Furthermore, two additional nurse consultations are performed after 4 and 16 weeks, to obtain safety information and VAS-pain and to possibly perform a treatment increase from the beginning of the 5th and/or 17th week, respectively, as presented in the section above, Experimental treatment. The following data are collected at the time points as presented in Figure 3:

1) Clinical measurements, i.e. in RA the Disease Activity Score 28-joints (DAS28-CRP) [45, 46], Health Assessment Questionnaire (HAQ) and, in AS, the (ASDAS) and Bath Ankylosing Spondylitis (BAS)-scores for disease activity (BASDAI), function (BASFI) and measures (BASMI) are

registered [47, 48]. In both patient groups, additional Patient Reported Outcome Measures (PROMs) are obtained: visual analogue scales (VAS) for pain, fatigue, patient's global Quality of Life (QoL) score SF-36 and pain-score PainDETECT [31, 32]. Furthermore, the effect of intervention on attention and concentration is investigated using the TMT and DSST [35-37]. Additionally, sleep quality is evaluated with the Pittsburgh Sleep Quality Index. [38]. The expected effect of treatment is measured with the Credibility/expectancy Questionnaire and semi-structured interviews.

2) Exposures, i.e. all concomitant treatment, especially current treatments with cDMARDs, bDMARDs and/or analgesics, including dosing schedule and treatment onset.

3) Comorbidities, e.g., cardiovascular disease, diabetes and hypertension

4) Lifestyle (blood pressure, exercise habits and smoking status)

5) Patient demographics, e.g., diagnosis, age, gender, height, weight, Body Mass Index (BMI), disease duration, smoking status, educational level, marital status, sick leave, occupation and ethnicity are obtained at baseline.

Biological samples

Blood samples are obtained at baseline, and at 12, 24 and 36 weeks. In addition to routine blood tests blood samples are collected in one EDTA tube (9 ml), two serum tubes (2x9 ml) and one PAXgene blood RNA tube (2.5 ml, Becton & Dickinson, Lyngby, Denmark), as described previously [49]. These are collected for definition of drug concentration of CBD and THC, i.e. monitoring of compliance, possible adverse events and for further future analyses.

Statistical Analysis Plan

The power calculation is based on the following assumptions for the primary outcome:

- An expected proportion with a response of 50% or more in the CBD group and expected 20% in the placebo group (OR = 4). Response is defined as a reduction in VAS-pain of at least 20 (range 0-100) after 12 weeks of treatment.
- A significance level of 0.05 in a two-sided z-test of proportions.
- A total of 180 patients will be included in two balanced groups, each consisting of 90 patients.

This setup gives a statistical power of 0.98 for the primary outcome. The power is reduced if the true difference between the groups is less than the expected 30 percentage points, and if more than an expected 10% of the patients drop out of the experiment. Balanced groups of 45 patients will yield a power of 83% for two-group comparisons on binary outcomes, such as the primary outcome. Slight deviations in sample sizes might occur because of block randomization.

The primary outcome is tested by a z-test in a logistic regression model. The main parameter estimates the ratio of the odds of response for the intervention group relative to the control group. All tests are two-sided. Secondary outcomes are analysed using logistic and linear regression, depending on the data type. In the case of deviations from the normality assumption, a non-parametric proportional odds model will be used. The secondary outcomes measured at baseline and post-intervention, 12, 24 and 36 weeks (follow-up) will be analysed using mixed-effects models, controlling for time of measurement. The random effects parameter is estimated for the clustering of repeated observations within patients. Analysis for the direct effects of CBD, THC and the interaction between those will be carried out separately, with placebo as the reference group for CBD.

Baseline measurements are reported as proportions of categorical variables, average and standard deviation (SD) for normally distributed data, and median (range) scores for non-normal numerical data. All variables are reported for the two intervention groups. Baseline variables with a tendency (p

<.25) to coincide with the intervention group will be included as control variables in the test of the primary and secondary outcomes. The relationship between the tested variables at baseline and intervention allocation will be analysed with parametric (t-test) and non-parametric tests ($\chi 2$ and the Mann-Whitney test). Correction for multiple tests will be based on a gatekeeping model of access. This means that significant results for the secondary outcomes are interpreted solely as exploratory findings in case of a non-significant finding for the primary outcome.

PATIENT AND PUBLIC INVOLVEMENT

King Christian X's Hospital for Rheumatic diseases involves patients with inflammatory rheumatic diseases actively in both quality assurance projects, research projects and in the development of educational programmes. Furthermore, a User Council was established in 2013 in the research department. The project is a consequence of rheumatic patient's pain reality and the idea of the project was originally presented to the User Council back in autumn 2017. Since then, two patients have been involved in the processing of the project. So far, the patient information brochures have been developed based on the integration of the patient's perspectives. PROMS, especially the patient's pain VAS, are the main focus of the outcome measurements. Thus, both the burden and consequence of the intervention and the results of the given intervention are transparent.

Meetings with the projects patient representatives will be arranged twice a year and the progress of the project is presented continuously for the User Council.

ETHICS AND DISSEMINATION

The protocol (*version 8.1., November 22nd 2018*) is approved by the Danish Ethics Committee (S-20170217), the Danish Data Protection Agency (2018-41-5388) and the Danish Medicines Agency (2018-010018).

All patients receive verbal and written information and give their written consent before enrolment, in accordance with Danish Ethics Committee guidelines. Appendix 1 presents the projects consent statement in English. All patients are informed that they can withdraw from the study at any time. Although this would lead to the termination of project medication, patient withdrawal will have no consequences for regular course of treatment. In case of withdrawal, no subsequent patient-related registrations will be obtained.

The two cannabis derivatives used in this study are comparable to the authorized compounds in the drug Sativex®, which is a registered drug in DK [50]. The patients will receive the information that efficacy of the applied test compound, as well as potential side effect may be comparable to Sativex®. The patient's rheumatologist will provide relevant project information in an outpatient setting. Chronicity of the chosen diseases and the inclusion criteria implies the typical project patient to be well known with a serious burden of disease. Investigators and study nurses are specialists in the rheumatic field.

The treatment consists of CBD tablets and THC herbal capsule preparation, which are produced based on natural raw materials by Glostrup Pharmacy's laboratory. The drugs are manufactured according to quality-ensured standardized procedures specifying the exact ingredients in mg. This makes dosage and monitoring of the therapy safe according to Danish national Good Clinical Practice (GCP) guidelines. The side effects, are well known and well described [51]. The study subjects are patients who are already associated to one of the four participating outpatient clinics. The blood samples at baseline, after 12 weeks and 24 weeks respectively, will be realized in connection with routine blood tests, in accordance with an a priori arranged outpatient visit and thus will not pose increased risks. At all visits, participants will asked about events and/or reactions. Based on this information the investigator will assess whether there is an adverse event (AE), an adverse reaction (AR), a serious

adverse event (SAE), or a suspected unexpected serious adverse reaction (SUSAR). The GCP unit of the University of Southern Denmark monitors the study independently.

The patients will be contacted and informed regarding the overall study results if they indicate interest in this, and in accordance with the patient study consent form and as directed by the Danish Ethics Committee guidelines. The physician in charge of the project at each participating outpatient clinic is responsible for conducting the study in accordance with the 5th edition of the Helsinki declaration. Study participation does not affect the established anti-inflammatory treatment course of individual patients.

Results will be presented at international conferences and published in international and peer-reviewed medical journals. Negative, positive as well as inconclusive results will be published.

DISCUSSION AND POTENTIAL LIMITATIONS

The project's focus is on chronic pain, which cannot be attributed to inflammatory activity.

Conventional and biologic DMARDs possess the potential to treat inflammation sufficiently. Thus, a treatment situation characterized by inflammatory disease activity should be treated according to the existing guidelines, i.e. by adjusting the treatment to an adequate DMARD regiment [1, 2]. Consequently, the absence of inflammation is a major inclusion criteria. Potential participants are well known as the study demands that their course of treatment has taken place for at least 2 years. Thus, we assume that alcohol or drug abuse, as well as information about ongoing opioid and/ or cannabis treatment are accessible information for the involved investigators. Furthermore, the demand of a disease duration of at least 2 years is supposed to ensure the presence of chronical pain. CBD and THC are two of more than 80 active compounds in the marijuana plant [52].

In contrast to THC, CBD does not exhibit a narcotic effect and/ or intoxication [53, 54]. The biochemical effect of the cannabinoids is explained by the compounds´ interaction with specific

receptors; the CB1 receptor is located on neurons and glial cells in different parts of the central nervous system, whereas the CB2 receptor is found in structures of the immune system. The stimulating and narcotic effects of THC are considered to be caused by activation of CB-1 receptors. CBD has a very low affinity for these receptors [52]. Thus, CBD binding to the CB-1 receptors causes little to no narcotic effect. New studies show evidence that CBD affects autoimmune signalling pathways and that these mechanisms may be relevant to CBD's therapeutic profile [53, 54].

The effect of CBD is studied in a placebo-controlled design, whereas the effect of a combination of CBD and THC is an open label continuation of the study. The scientifically ideal solution would have been a randomised study comparing both CBD, THC and placebo, for instance in a cross over design. Such a design would be characterized by the implicit risks of THC for all patients during the entire study period and it would require a significantly larger study. The actual design represents the balance between a wish to assess the effect of both CBD and THC correctly, while recognizing risks, including traffic safety issues, especially due to the THC treatment. Also, the possible negative effect on cognitive functioning can have a large impact on job functioning. Therefore, a more definite answer as to whether medical cannabis negatively affects cognition is important in relation to job functioning and autonomy. We feel our design will provide important information on THC, despite the design, and it has the advantage that we know when THC is applied, and thereby can take the necessary precautions.

The trial population is monitored regularly at the participating outpatient clinics and the individual longitudinal treatment is registered. DANBIO is the nationwide clinical quality database for rheumatology [16, 29]. All adult patients treated with biological drugs are registered. Furthermore, patients with AS and RA are registered, regardless of treatment. Thus, the DANBIO based Reuma-eCRF system provides particularly good conditions for the collection and monitoring of validated data.

Figure Legends

Figure 1 presents the Consort flow chart

Figure 2 presents the treatment flow chart

Figure 3 presents the schedule of assessments and procedures

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Contributors

OH wrote the protocol for the European and the Danish Medicines Agency and the Research Ethics Committee. TEA, AAC, JP, EMH, TJE, TH, AGB, AGL, ABB, MØ, MLH, NSK, KKR, KHP and OH contributed to study concept. KHP, MØ and OH drafted and revised the manuscript after feedback from all authors. All authors contributed to the review of the present manuscript and approved the final version of the manuscript.

Competing interests

None

Provenance and peer review

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FIGURE 1: Consort flow chart

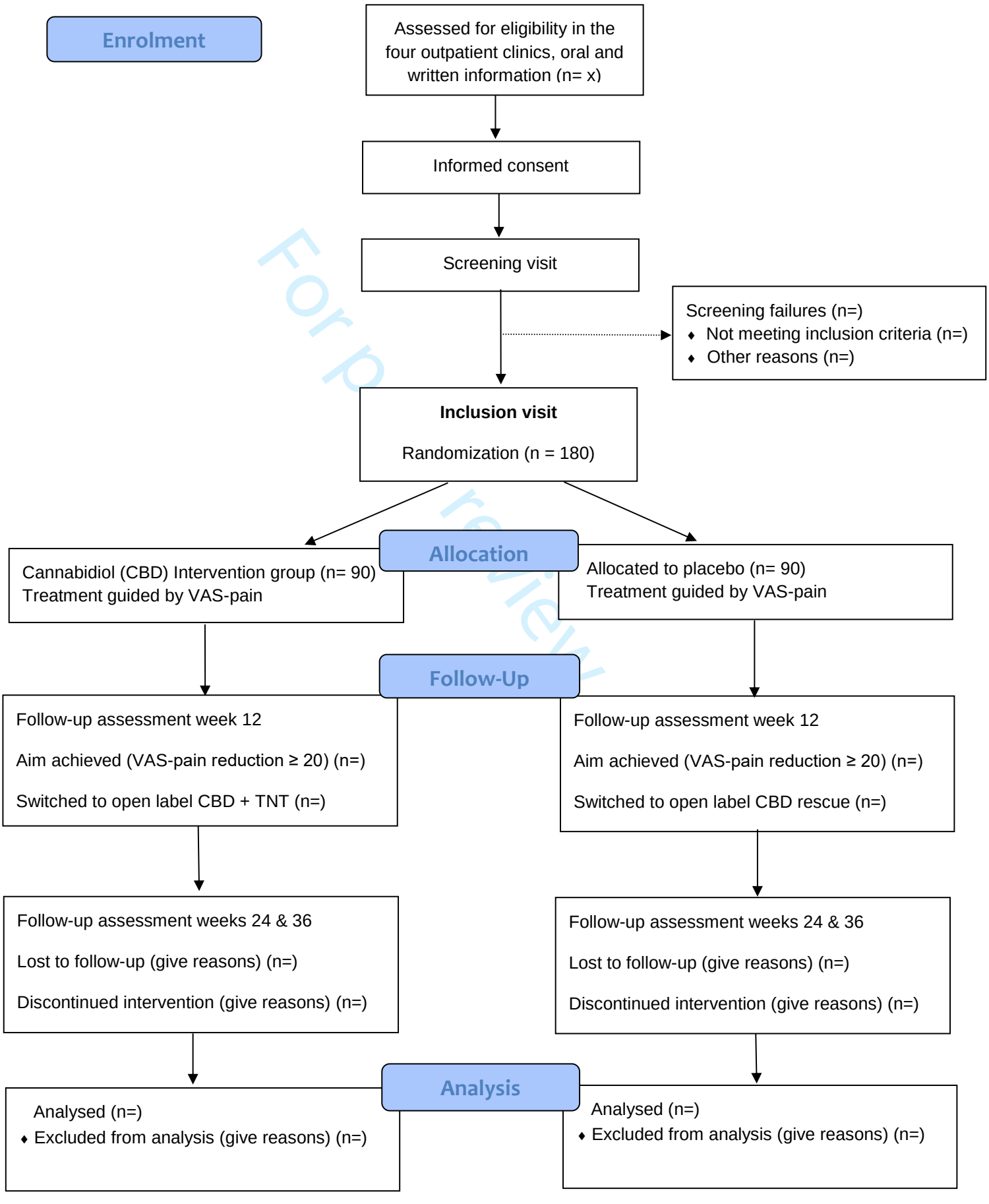

FIGURE 2: Treatment flow chart

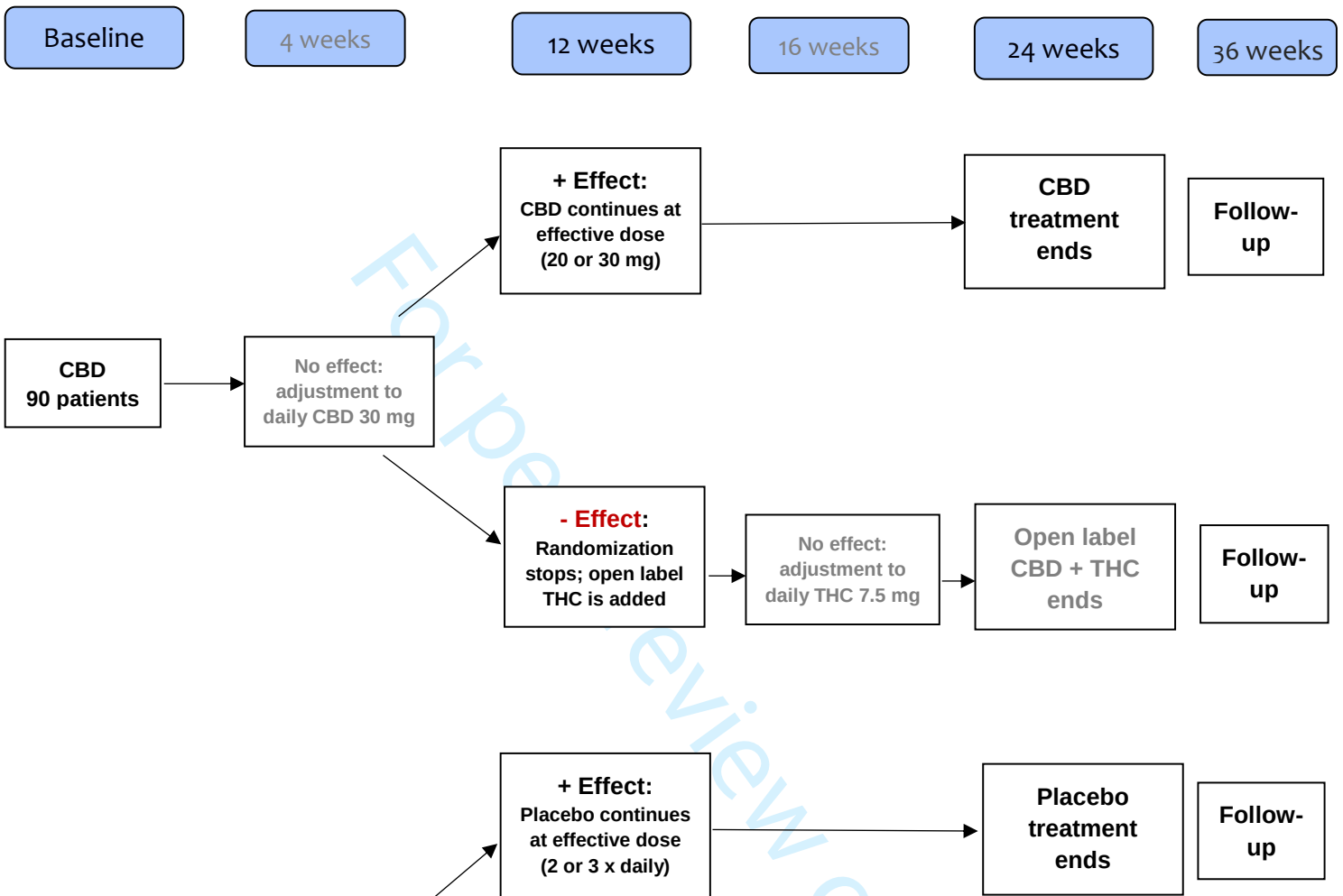

FIGURE 3: Schedule of assessments and procedures

Visit	Screening Visit	Baseline Visit	Nurse Consultation A	Assessment Consultation A	Nurse Consultation B	Assessment Consultation B	Follow-up
Week	-2	0	4	12	16	24	36
Inclusion/ Exclusion	(X)	X					
Demography	(X)	X					
Medical History	(X)	X					
Concomitant medication	(X)	X		X		X	
Physical examination	(X)	X		X		X	
BP, pulse, temperature	(X)	X		X		X	
Hematology/ Biochemistry	(X)	X		X		X	X
CRP	X	X		X		X	X
Serum/blood bank		X		X		X	X
ECG	(X)	X		X		X	X
Check up on fulfilled classification	(X)	X					
40 joint score or BAS score	(X)	X		X		X	X
Patient's pain score (VAS)	X	X	X	X	X	X	X
Patient's global score (VAS)	(X)	X		X		X	X
Doctors' global score (VAS)	(X)	X		X		X	X
HAQ or BAS	(X)	X		X		X	X
DAS 28 CRP or ASDAS	(X)	X		X		X	X
Check up on potential AE or SAE			X	X	X	X	X
PainDETECT		X		X		X	X
SF-36		X		X		X	X
Cognitive tests (TMT, DSST)		X		X		X	X
Sleep quality		X		X		X	X
CEQ Expectation		X		X			

THE DANISH BIOMEDICAL RESEARCH ETHICS COMMITTEE SYSTEM

Standard consent statement prepared by the Danish Biomedical Research Ethics Committee System, December 2011. (S4)

Informed consent to participate in a health science research project

Title of the research project:

Can-Art

Pain treatment with medical CANnabis in patients with inflammatory ARThritis

Statement by Research Subject:

I have been given written and oral information and I know enough about the purpose and method, and about the advantages and disadvantages of participation.

I know that participation is voluntary and that I can withdraw my consent at any time without losing my current or future rights to treatment.

I consent to participate in the research project and that my biological data be extracted for storage in a research bio-bank. I have received a copy of this consent form and a copy of the written information about the project for my own records.

Research subject's name: _____

Date _____ Signature: _____

If new, essential health information about you comes to light in the research project, you will be informed. If you would prefer *not* to be informed about new, essential health information, should it come to light in the research project, please mark here: _ (mark with an x)

Do you want to be informed about the results of the research project and any consequences for you?

Yes _____ (mark with an x) No _____ (mark with an x)

Declaration by the person providing this information:

I declare that the research subject has received oral and written information about the research project.

In my opinion, sufficient information has been provided to the research subject for the decision to be made regarding participation in the research project.

The name of the person who provided this information:

Date _____Signature: _____

Project identification: (VEK Project ID 61 187, EUdraCT no. 2017-2017-004226-15)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1;line 1 - 4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P1, line 24
	2b	All items from the World Health Organization Trial Registration Data Set	P1, line 24 & P3, line 82, 83
Protocol version	3	Date and version identifier	P14, line 349
Funding	4	Sources and types of financial, material, and other support	P17, line 414 - 417
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1, line 6 – 22 & P17, line 419 - 424
	5b	Name and contact information for the trial sponsor	P1, line 28
	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	P17, line 414 - 417
	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)	P16, line 401 –406 & Danish Medicines Agency (S-2018010018)

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	P5, line 114 - 134
	6b	Explanation for choice of comparators	P6, line 144 - 150
Objectives	7	Specific objectives or hypotheses	P6, line 152 – 154 & P7, line 167- 168
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, noninferiority, exploratory)	P7, line 160 – 164
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	P7, line 172 – 173 EudraCT 2017-004226-15
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)	P8 & 9, line 185 – 215
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P9, line 217 – 232
	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)	P9, line 217 – 232, P15, line 365 - 368
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P12, 299 - 300
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P7, line 164

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	P10 -11, line 245 - 270
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)	P9, line 232: Figure 2
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	P12, line 302 - 308
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P16, line 403 - 406
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	P10, line 233 –243 & Danish Medicines Agency (S-2018010018)
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	P10, line 233 - 243
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P10, line 233 - 243
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P10, line 233 - 243
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P10, line 233 – 243 & Figure 2

Methods: Data collection, management, and analysis

Data collection methods	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	Page11 & 12, line 272 – 293
	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	Page16, line 401 – 406
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	Page19, line 500 – 502
Statistical methods	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	Page13, line 314 – 329
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page13, line 317 – 322
	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)	Page 13, line 314 – 329 & Danish Medicines Agency (S-2018010018)

Methods: Monitoring

Data monitoring	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	P15, 369 P19, 500 – 501

	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	Danish Medicines Agency (S-2018010018)
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	Danish Medicines Agency (S-2018010018)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 15, line 369 Danish Medicines Agency (S-2018010018)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 3, line 81 – 83
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)	Page 3, line 81, Danish Ethics Committee (S-20170217)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P14, line 349 – 353, Appendix 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P19, line 500 -502
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	P19, line 500-501
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 17, line 425 - 426

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 3, line 81, Danish Ethics Committee (S-20170217)
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	Page 3, line 81, Danish Ethics Committee (S-20170217)
Dissemination policy	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	Page 3, line 84 – 85 & p15, line 373 – 374
	31b	Authorship eligibility guidelines and any intended use of professional writers	Danish Ethics Committee (S-20170217
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None declared
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached Appendix 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 12, line 295 – 300

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.