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TITLE PAGE

Comparing group-based Acceptance and Commitment Therapy (ACT) with Enhanced Usual Care for adolescents with functional somatic syndromes: Study protocol for a randomised trial

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ABSTRACT (296 words)

Introduction

Functional somatic syndromes (FSS) are common in adolescents, characterised by severe disability and reduced quality of life. Behavioural treatments have shown symptom reduction and increased functioning in adults with FSS, whereas the evidence for treatments in adolescents is sparse. Acceptance and Commitment Therapy (ACT) has shown promising results in children and adolescents with chronic functional pain. The current study will compare the efficacy of group based ACT with that of Enhanced Usual Care (EUC) in adolescents with FSS operationalized by the unifying construct of multi-organ bodily distress syndrome (BDS).

Methods and analysis

A total of 120 adolescents aged 15-19 and diagnosed with multi-organ BDS, of at least 12 months duration, will be assessed and randomised to either: 1. EUC: A manualised consultation with a child and adolescent psychiatrist and individualised treatment plan or 2. Manualised ACT based group therapy plus EUC. The ACT program consists of 9 modules (i.e. 27 hours) and one follow up meeting (3 hours). Primary outcome is physical health, assessed by a SF36 aggregate score 12 months after randomisation. Secondary outcomes include self-reported symptom severity, symptom interference, depression and anxiety, illness worry, perceived stress and global improvement; as well as objective physical activity and bodily stress-response measured by heart rate variability, hair-cortisol and inflammatory biomarkers. Process measures are illness perception, illness related behaviour and psychological flexibility.

Ethics and dissemination

The study is conducted in accordance with the Helsinki Declaration II. Approval has been obtained from the Science Ethics Committee of the Central Denmark Region and the Danish Data Protection. The results will be sought published according to the CONSORT statement in peer-reviewed journals.

Discussion

This is one of the first larger randomised clinical trials evaluating the effect of a group based intervention for adolescents diagnosed with multi-organ BDS.

Registration

ClinicalTrials.gov: NCT02346071

BACKGROUND

Functional somatic syndromes (FSS), including chronic fatigue syndrome, juvenile fibromyalgia, functional gastrointestinal disorders, and idiopathic pain syndromes are well known conditions in adolescents. FSS are diagnostic unities representing clusters of related functional somatic symptoms. Prevalence rates vary considerably due to differences in case definitions, assessment instruments and study populations,(1-3). Studies attempting to cover the whole range of different functional somatic symptoms suggest that 5-10% of children and adolescents in the general population are substantially affected and likely to need care,(4,5). Suffering from FSS during adolescence often has high personal and societal consequences. The adolescents have a higher risk of psychosocial problems such as social isolation, long-term school absence and reduced quality of life,(6) and anxiety and depression are common co-morbidities,(7,8). A substantial proportion show continuity of functional symptoms into adulthood,(9,10) and are less likely to obtain a college education,(9). Furthermore, adolescents diagnosed with FSS have overall higher health care costs due to increased use of medication and health care services,(9,11). The aetiology of FSS remains unknown. Recent studies suggest a potential correlation between physiological stress and FSS, with physical inactivity as a potential covariate,(12-15). It is proposed that a (patho)physiologic response to prolonged or severe mental and/or physical stress in genetically susceptible individuals may trigger symptom development,(16).

High co-occurrence of different types of FSS, especially various pain syndromes, has been shown in children and adolescents,(17-19). Children reporting multiple symptoms have an associated higher frequency of distress and impairment (e.g. higher kindergarten/school absenteeism and consultations with physicians),(20). Moreover, adult patients presenting with multiple symptoms from several organ systems have a poorer prognosis and a higher risk of chronification,(21-23). Thus, an attempt to recognize the most severely affected patients with the highest illness burden may encompass sampling patients with the highest symptom load (i.e. multiple symptoms from several organ systems). Recently, the empirically based unifying diagnostic category Bodily Distress Syndrome (BDS) was introduced,(16). The diagnosis describes specific symptom patterns and includes a multi-organ subtype and four single organ subtypes corresponding to fibromyalgia, irritable bowel syndrome, non cardiac chest pain and chronic fatigue syndrome,(24). Multi-organ BDS comprising multiple symptoms from at least three specific symptom-groups thus offers a diagnostic unity potentially including the most severely affected patients.

Cognitive behavioural therapy (CBT) has been shown to reduce symptoms and increase functioning in adults with FSS,(25-28), whereas the evidence for treatment in adolescents is sparse. Family-based CBT and internet-delivered CBT have proven effective in young patients with specific FSS,(29-34). However, the development of specifically tailored treatments for each FSS or symptom profile seems to be an inefficient strategy due to the costly nature of establishing separate clinics in each medical (sub)-specialty, the fragmented care available, and difficulty to handle multi-symptomatic patients at those clinics,(35-37). Recent studies suggest that adult patients with various FSS can feasibly receive the same treatment delivered in a group format, regardless of their main functional symptom,(38,39). In adolescents, group treatment has been widely used and shown to be feasible in the treatment of both psychiatric and non-psychiatric diseases,(40,41). Group format offers several benefits including peer modelling, diminishment of stigma, increased motivation, and higher acceptance of feedback from peers opposed to professionals,(42). Hence, a unified group-based treatment may be advantageous for adolescents with various FSS due to feasibility, accessibility of treatment, and potential health care savings.

Acceptance and Commitment Therapy (ACT), which derives from CBT, has shown promising results in children and adolescents with chronic functional pain,(43,44). Evidence suggests that acceptance of pain is related to enhanced physical and emotional functioning, whereas attempts to control pain may lead to higher pain and disability,(45,46). By reducing avoidance behaviour and symptom interference, ACT can increase functioning and enhance quality of life, through value driven acceptance and exposure strategies,(47). Symptom avoidance seems to be a general problem leading to disability and lower quality of life in patients with FSS,(48). This provides a rationale for a therapeutic approach focused on reduction of avoidance behaviour and acceptance of somatic symptoms.

The objective of the present trial is to examine the efficacy of ACT-based group therapy for adolescents with a range of FSS grouped under the unifying diagnosis of multi-organ bodily distress syndrome (BDS),(49). To do this, we will examine physical health and a range of other outcomes including level of functioning, symptom interference and emotional distress at baseline, at different time-points throughout the trial, and also at 12-month follow-up. An add-on study includes measurement of physiological stress response and physical activity level.

METHODS

Design

Single-site, non-blinded randomised controlled trial (RCT) with two conditions: 1) Group based ACT and 2) Enhanced usual care (EUC). Overall study design is illustrated in figure 1.

Setting

Patients will be enlisted from the Research Clinic for Functional Disorders and Psychosomatics, situated in a general medicine setting at Aarhus University Hospital, Denmark. The department is a specialist, tertiary service with extra resources allocated for assessment and treatment of patients with debilitating functional somatic symptoms. Enrolment starts in January 2015 and the data collection is expected to be finalised June 2019.

Eligibility

Eligibility criteria are multi-organ BDS, i.e. at least three functional somatic symptoms from at least three organ systems, moderate to severe impairment in daily life and symptom duration of minimum 12 months.

Inclusion and exclusion criteria

The study criteria are summarized in Table 1.

Table 1. In- and exclusion criteria

Inclusion criteria
1. Bodily Distress Syndrome, multi-organ type of at least 12 months duration.
2. 15-19 year-old at referral.
3. Raised since infancy in Denmark or born by Danish parents. Understand, speak and read Danish.
4. Moderate or severe impairment.
Exclusion criteria
1. Not completing informed consent.
2. Acute psychiatric disorder demanding other treatment, or if the patient is suicidal.
3. A lifetime diagnosis of psychosis, mania or depression with psychotic symptoms (ICD-10: F20-29, F30-31, F32.2, F33.3), serious cognitive deficits or developmental disorders such as mental retardation and autism (ICD-10: F70, F84)
4. Substance abuse of e.g. narcotics, alcohol or medication.
5. Pregnancy at the time of inclusion.
6. Not suitable for group-based treatment, e.g. patients with severe ADHD (ICD-10: F90), severe social phobia (ICD-10: F40.1) or conduct disorder (ICD-10: F91).

Recruitment procedures

A total of 120 adolescents (aged 15-19) referred from general practitioners (GP), practising medical specialists or hospital wards, will be recruited into the trial. All referrals are initially screened for eligibility by a team of physicians from the Research Clinic for Functional Disorders and Psychosomatics.

Assessment

Patients regarded as eligible undergo a standardized clinical psychiatric and somatic assessment, performed by a physician specialized or trained in child and adolescent psychiatry. The assessment consists of: 1) review of former discharge letters, medical records, and other relevant information, 2) standardized clinical interview, 3) SCAN (Schedules for Clinical Assessment in Neuropsychiatry),(50) which screens for general psychopathology and contains a detailed section on functional somatic symptoms, 4) screening for child and adolescent psychiatric disorders not covered by the SCAN, i.e. ADHD, autism and conduct disorder with specific sections from the child and adolescent psychiatric interview DAWBA (Development and Well Being Assessment),(51), 5) a clinical physical/neurological examination and 6) standard blood tests.
Patients meeting the study criteria (see Table 1) are offered participation in the study and are subsequently asked to complete consent form before enrolment and randomisation. Figure 1. presents the flow of patients during the trial.

Randomisation procedure

Following baseline assessment, patients meeting all study criteria and consenting to participation are randomised to either EUC or group based ACT. The randomisation is conducted by statisticians not involved in treatment. Permuted

block randomisation with block-sizes ranging from 14-16 made by means of a computer algorithm will be used to ensure balanced group sizes and allocation concealment. Patients consenting to participation receive an opaque envelope taken from a sequential order containing information on group allocation, ensuring that initial assessment is not influenced by group allocation.
As the study compares a psychological treatment with EUC, blinding of participants and therapists is not possible.

INTERVENTIONS

Enhanced usual care (EUC)

Patients allocated to EUC will have a psychiatric consultation of 1½ hours duration, approximately 2 weeks after clinical assessment, with participation of the patient and his/her parents or close relatives. The consultation is manualised and includes psycho-education related to the diagnosis of multi-organ BDS, health promoting strategies, advice on medication, or other treatment, supplemented with written information on the BDS diagnosis and general recommendations. The aim of the consultation is to increase the family's understanding of BDS and to optimize management in primary care and social services support by an individualized treatment plan sent to the patient's GP. The consultation is carried out by the child and adolescent psychiatrist doing the initial assessment.

ACT based group therapy

Patients allocated to ACT based group therapy receive the same psychiatric consultation as described above, before starting the manualized ACT treatment developed specifically for this patient group. The therapy is given in groups of 7-8 patients with 9 modules (i.e. 27 hours in total) over a period of 3 months and one follow up meeting (3 hours) three months after module 9. Detailed information on the treatment program is presented in Figure 2. The parents and other relevant close relatives (e.g. siblings, boy/girlfriends) are invited to participate in an information meeting, to support the relatives´ resources to help the adolescent improving his/her functional level and coping with symptoms. One individual consultation with the adolescent and close relatives is offered shortly after module 8. After completed ACT therapy an individualized treatment plan is sent to the patient's GP.
Patients assigned to ACT therapy have to agree not to have any other psychological treatment for BDS while in therapy.

Therapist training and adherence to treatment manual

Therapists are child and adolescent psychiatrists and psychologists with specialist training in ACT. Clinicians well experienced in ACT and group therapy supervise the treatment. Sessions are videotaped and assessed by an external panel to ensure adherence to the treatment manual.

Compliance and attrition

Treatment compliance is assessed by recording the number of completed ACT-modules. When applicable, participants are asked for their reasons for poor compliance or dropout. In the case of dropout from the ACT group therapy, data collection continues as planned with the patients consent.

OUTCOME MEASURES

Outcome measures are obtained at 6 different time points: At baseline (i.e. before assessment and randomisation) and 2, 4, 6, 8, and 12 months after randomisation. These time points have been designed to follow the time schedule of the ACT group therapy to allow for evaluation of process variables. Figure 1 depicts how these time points relate to assessment and treatment. Primary and secondary outcome measures are assessed by web-based questionnaires (see table 2). The questionnaires are distributed simultaneously to the ACT and EUC group i.e. in the randomised blocks. Primary endpoint is 12 months after randomisation.
Due to a study population of adolescents approaching adulthood (15+ years) questionnaires developed and tested in adults are chosen.
Three questionnaires (Limitation Index,(52), Avoidance and Fusion Questionnaire in Youth,(53), and Psychological Inflexibility in Pain Scale,(54)) have been translated with reference to standard procedures with initial translation, synthesis of translations and back-translation,(55).

Table 2. Outcome measures

Respondent: X= Patient P= Parent

	Instrument	Abbreviation	0	2	4	6	8	12
Primary outcome								
Physical health	The Short Form Health Survey,(56,57)	SF-36	X	X	X	X	X	X
Secondary outcomes								
Illness severity	Symptom Checklist Revised-90 – somatisation subscale(58)	SCL-som	X	X	X	X	X	X
	Bodily Distress Syndrome checklist,(59)	BDS checklist	X					X
Symptom interference	Limitation Index (Revised from Pain Interference Index)(52)	LI	XP			XP	X	XP
Depression and anxiety score	Symptom Checklist Revised-90 – depression and anxiety subscales,(58,60-62)	SCL-8-6-4	X			X	X	X
Mental health	The Short Form Health Survey,(56,57)	SF-36	X	X	X	X	X	X
Illness worry	Whiteley-7,(63)		X	X	X	X	X	X
Perceived stress	Perceived Stress Scale,(64)	PSS	X					X
Overall impression of change	Patient Global Impression of Change,(65)	PGIC				XP	X	XP
Process measures								
Illness perception	The Brief Illness Perception Questionnaire,(66)	BIPQ	XP	X	X	XP	X	XP
Illness related behaviour	The Behavioural Response to Illness Questionnaire, short,(67)	BRIQ	X	X	X	X	X	X
Psychological flexibility	Avoidance and Fusion Questionnaire for youth,(53)	AFQ-Y8	X	X	X	X	X	X
	Psychological Inflexibility in Pain Scale,(54)	PIPS-12	X	X	X	X	X	X
Potential moderators								
Family functioning	Family Assessment Devise (general functioning subscale),(68)	FAD	XP					XP
Attachment style	Experience in Close Relationships – Relationship Structure,(69)	ECR-RS	X					
Negative life events	Negative life events,(70)		X					
Physiological measures								
Heart rate variability	HRV measured with Vagus device (resting state, standing, slow breathing, valsalva),(71)		X					X
Hair-cortisol	Measurement of hair-cortisol in 2 strands of hair closest to the scalp (1-2 cm)		X					X
Inflammatory response	IL6, TNF-α, high-sensitive CRP, IL1, neopterin, CD163, HO1, MCP1		X					X
Physical activity	Accelerometer (Actigraph wGT3X-BT) worn for 7 consecutive days,(72)		X					X

Primary outcome
The primary outcome is improvement in physical health 12 months after randomisation, measured with an aggregate score of the SF-36 subscales PF (physical functioning), BP (bodily pain) and VT (vitality),(56,57) with a score range from 15-65. This score has previously been used as the primary outcome in a comparable trial in adults,(38) due to well-known psychometric problems with the existing physical component score (PCS),(73) and based on the rationale that these three subscales have shown to be key-domains affected in this patient group,(74). Danish norm data for adolescents are available,(56).

Self-reported secondary outcomes
Illness severity is measured by two questionnaires. 1. The Somatisation subscale of the Symptom Checklist Revised-90,(58,61), (12 items, 5-point scale), a widely used symptom checklist of commonly experienced physical symptoms. 2. The Bodily Distress Symptom checklist (BDS checklist),(59) (25 items, 5-point scale), a symptom checklist added as a new measure for validation in adolescents. It is developed from the symptoms stated in the BDS criteria, hence evaluating symptom severity in four symptom groups.

The impact of symptoms on functioning i.e. symptom interference is evaluated by self- and parent report using the Limitation Index (LI)),(43,52). LI is a modified version of the Pain Interference Index (PII), (6 items, 7-point scale), a validated questionnaire for children and adolescents measuring impact of pain in performing everyday activities and impact on e.g. mood and sleep. The modification from PII to LI is limited and represents a change in wording from "pain" to "symptoms". Self-reported degree of absence from school or work is being registered.

Assessing symptoms of anxiety and depression brief versions of the corresponding subscales from Symptom Checklist Revised-90 are used (SCL-8, SCL-6, SCL-4),(58,60-62) (13 items in total, 5 point scale). Level of illness worry is measured by Whiteley-7,(63) (7 items, 5-point scale), a subscale of the Whiteley Index. Mental health is measured with the Mental Component Summary (MCS) from SF-36,(56,57).

Subjective perception of stress is measured by the Perceived Stress Scale (PSS),(64,75) (10 items, 5-point scale). The scale is a widely used measure of the degree, to which situations in life are perceived as stressful. Danish norm data for adolescents are available.

The overall impression of improvement is measured with the Patient Global Impression of Change (PGIC),(65) (1 item, 7-point scale). Answers range from "no change (or condition has gotten worse)" to "a great deal better and a considerable improvement that has made all the difference".

Process measures
The process measures evaluate specific areas hypothesized to play a role in the development and perpetuation of functional somatic symptoms, and are hence addressed directly in the treatment.
Illness perception is measured by the Brief Illness Perceptions Questionnaire (BIPQ),(66) (8 items, 10-point scale and additional item regarding cause of symptoms) which has been widely used in a range of illnesses. The perception of five core components (identity, cause, timeline, consequences, and cure-control) is evaluated as they together form the perception of illness. In a comparable study with adults, changes in illness perceptions partly mediated the effect of treatment on outcome,(76).
Illness related behaviour is measured by the Behavioural Responses to Illness Questionnaire (BRIQ),(67) (13 item, 5-point scale). Specific illness related behaviours have shown to be risk factors for development of FSS in adults,(67).
Psychological flexibility is an area specifically targeted in ACT. It is measured by Avoidance and Fusion Questionnaire in Youth (AFQ-Y8),(53) (8 items, 5-point scale) and Psychological Inflexibility in Pain Scale (PIPS-12),(54) (12 items, 7-point scale).

Potential predictors and moderators
Relevant demographic data and potential important predictors for outcome, e.g. predisposition to functional syndromes and number and kind of life events are obtained as part of the diagnostic assessment,(70).
Family functioning is assessed by the subscale on general functioning from Family Assessment Devise (FAD),(68,77) (12 items, 4-point scale). In addition the patient´s attachment style is assessed dimensionally by Experience in Close Relationships – Relationship Structure (ECR-RS),(69) (9 items, 7-point scale).

Credibility regarding treatment is assessed before the individual standard psychiatric consultation,(78). At end of treatment, i.e. after module 9, the participants complete a standard questionnaire regarding their experience of the service at the clinic.

Concomitant treatment and serious adverse events during the trial period will be registered by self-report one year after randomisation.

Physiological measures

Bodily stress-response is assessed with three different measures:
1) Heart rate variability (HVR) as an indirect measure of the balance between the sympathetic and parasympathetic system. It is measured in various standardized situations (resting state, standing, slow breathing and valsalva) with the handheld device Vagus,(15,71,79).
2) Hair-cortisol as a biological marker for long-term bodily stress. It is measured from two strands of hair cut close to the scalp, since the proximal 1 cm segment of hair represents the cortisol level of the last month,(80).
3) Biomarkers for inflammatory and oxidative stress (including IL6, TNF-α, high-sensitive CRP, IL1, neopterin, CD163, HO1, MCP1 but also newer proteo-based markers),(81-84).

Physical activity

Level of physical activity is assessed by anthropometric measurements with accelerometer (Actigraph wGT3X-BT),(72). The accelerometer is worn on the right hip 24 hours-a-day for 7 consecutive days.

A specific protocol for evaluation of physiological measures and physical activity will be made specifying hypotheses and analytical strategies. A large ongoing epidemiological study in Denmark (DanFunD) will be available for later comparison of results,(85,86).

SAMPLE SIZE ESTIMATION

Power estimation is based on the primary hypothesis regarding changes in self-reported physical health measured with the SF-36 aggregate score. Given the efficacy in a previous RCT study of ACT in adolescents with chronic functional pain,(43) as well as data on a subgroup of patients under 30 years from another RCT study of CBT with BDS,(38), an improvement of self-reported physical health is estimated to be maximum 3 points (from 39-42) in the control group and at least 5 points (from 39-44) in the ACT group from baseline to 12 months after randomisation. Baseline value assumes a standard deviation of 8 referring to the defined groups of patients. Using a random effects model in a simulation setting shows that in order to statistically detect such a difference in improvement (test of no interaction), given a 2-sided alpha of 0.05 and with 95% power, we need to allocate 60 patients to each group.

STATISTICAL ANALYSIS

The efficacy of the ACT treatment will be evaluated on an intention-to-treat basis by means of random effects model regression analysis adjusted for prognostic important baseline characteristics. The main efficacy analysis will pertain to the data obtained at 12 months follow-up. Baseline characteristics will be tabulated by treatment modality in order to evaluate success of randomisation. To judge possible bias due to missing data a random effect model on multiple imputed data will be performed.
An explorative mediation analysis will be performed to investigate to which extend the intervention can affect the primary outcome through each of the process measures. The analytical strategy previously used in a large scale trial will be used,(87).

DISSEMINATION

Results will be reported according to the CONSORT statement for non-pharmacological interventions,(88) and will be submitted for publication in peer-reviewed English-language journals. Positive, inconclusive and negative findings will be published. Trial findings will also be disseminated through conference abstracts.

DATA MONITORING AND MANAGEMENT

This trial is considered a minimal risk study and hence a data and monitoring committee has not been established. Questionnaires are administered electronically and saved in an online database. The database is secured with a password-protected access system, and access to files is limited to research staff that requires direct access. Baseline

information obtained during assessment is registered in a Case Report Form (CRF). All CRF's are stored in locked file cabinets in areas with limited access.

ETHICAL APPROVAL

The project will be conducted in accordance with the Helsinki Declaration II. Approval has been obtained from the Science Ethics Committee of the Central Denmark Region (journal number: 1-10-72-181-14) and the Danish Data Protection (reference number: 1-16-02-290-14).

DISCUSSION

Adolescents with FSS are at risk of continuity of physical problems into adulthood implying reduced quality of life due to potential functional impairment, social withdrawal, lack of education and incapacity to work. To our knowledge the present study will be one of the first larger randomised clinical trials, evaluating the efficacy of a group based treatment for adolescents with a range of FSS grouped under the unifying diagnosis of multi-organ BDS compared to EUC.

Our study design has some limitations. First is the lack of comparison with an evidence based control treatment. However, as the aim of this study is to compare ACT group therapy to the best treatment available (i.e. EUC), we use a pragmatic design that offers systematic clinical assessment and an individual treatment plan also to patients in the usual care arm. Also, a unified treatment for adolescents with a range of FSS has not been tested before. Second, blinding is not possible to the clinician providing the standard psychiatric consultation. However, this is a general problem in trials of behavioural interventions. Third, the assessment and treatment is carried out in a specialised setting, which might not guarantee that the treatment, if proven successful, will work in everyday clinical practice, across different populations, clinical contexts etc.

Important strengths of the study are, that all patients are given a thorough assessment providing them with a positive and evidence based understanding of their illness,(89,90) and that the treatment model is developed based on treatments with proven effect for both paediatric and adult patients with FSS and related disorders,(38,39,43). Bias is minimized by the use of a manualized treatment, different therapists, valid outcome measures, multiple assessment points and by predefining and publishing all outcome measures before study start.

Anticipated difficulties conducting the study includes recruitment problems due to stringent in- and exclusion criteria as well as lack of knowledge of available service for adolescents and social prejudices in terms of receiving psychiatric diagnosis and psychological treatment for functional symptoms,(8).

In conclusion this study will provide important information about efficacy, processes of change and moderators. If the treatment is successful, it will improve the quality of life of adolescents with FSS and may over the life course lead to substantial health and municipal service savings.

COMPETING INTEREST STATEMENT

We have read and understood BMJ Open policy on declaration of interests and declare that we have no competing interests.

CONTRIBUTION OF AUTHORS

Karen Hansen Kallesøe: Took part in designing the study, drafted the initial manuscript and prepared the final manuscript as submitted.

Andreas Schröder: Took part in developing the research idea and in designing the study, contributed with data for statistical power analysis and critically revised the manuscript.

Rikard Wicksell: Took part in designing the study, contributed with data for statistical power analysis and critically revised the manuscript.

Per Fink: Took part in developing the research idea and critically revised the manuscript.

Eva Ørnbøl: Took part in the statistical design of the study, made the power analysis and description of the statistical method and critically revised the manuscript.

Charlotte Ulrikka Rask: Came up with the original research idea, took part in designing the study, drafted the initial treatment protocol and critically revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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FINANCIAL DISCLOSURE

None of the authors have any financial interests to declare in relation to this study.

TRIAL REGISTRATION

ClinicalTrials.gov: NCT02346071

Legend figure 2:

The overall focus of the treatment is to increase the patients´ physical and emotional self-awareness, and to teach them skills to manage the distress associated with difficult thoughts, emotions, and bodily sensations. Practical exercises throughout the treatment includes experiential exercises focusing on identification of own values, barriers and avoidance behaviour, and mindfulness exercises focusing on allowance of the experience of here and now as it is and of being present.

Gradual exposure is implemented through individually customized homework assignments in accordance with the identified personal values.

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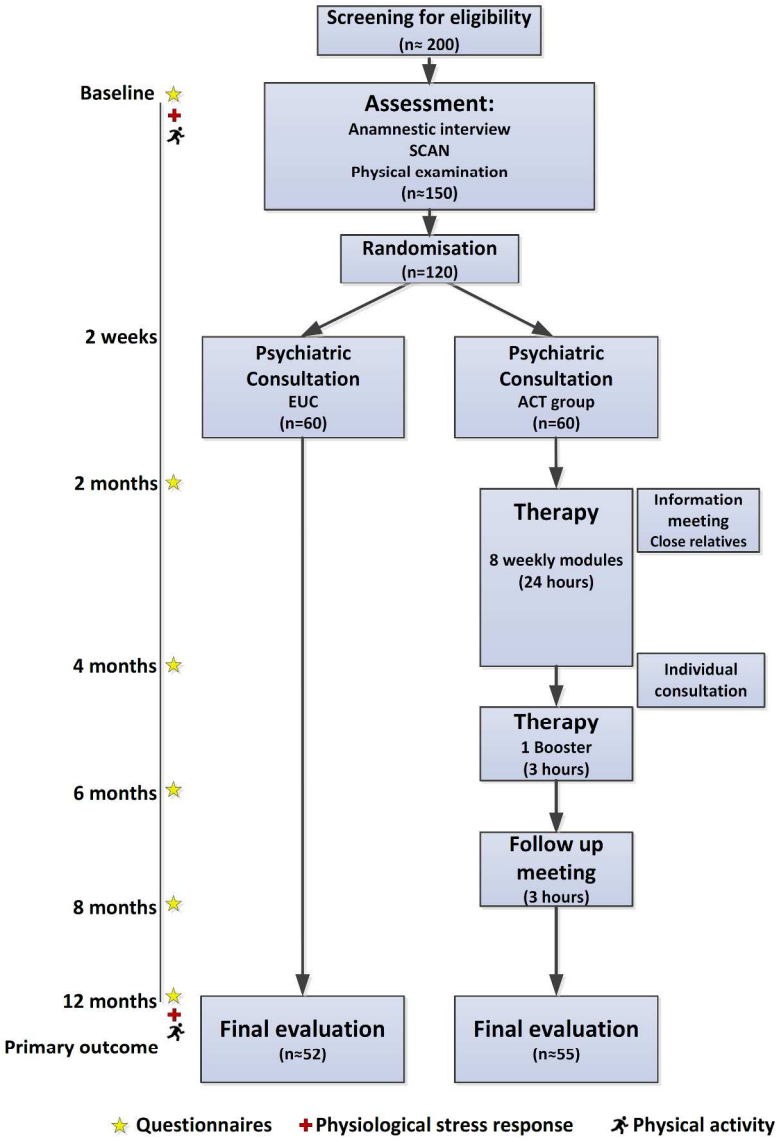
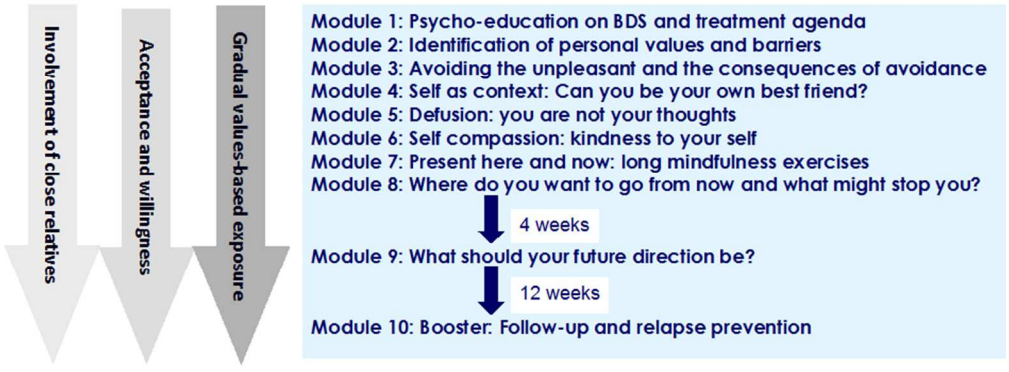


Figure 1. Flowchart of participants with estimated numbers at each level

831x1083mm (96 x 96 DPI)



Caption: Figure 2. Overview of the group-based Acceptance and Commitment Therapy treatment program

Legend: The overall focus of the treatment is to increase the patients´ physical and emotional self-awareness, and to teach them skills to manage the distress associated with difficult thoughts, emotions, and bodily sensations. Practical exercises throughout the treatment includes experiential exercises focusing on identification of own values, barriers and avoidance behaviour, and mindfulness exercises focusing on allowance of the experience of here and now as it is and of being present.
Gradual exposure is implemented through individually customized homework assignments in accordance with the identified personal values.

249x96mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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	1 (title page)__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1 (title page)
	2b	All items from the World Health Organization Trial Registration Data Set	Enclosed WHO supplement
Protocol version	3	Date and version identifier	Enclosed WHO supplement
Funding	4	Sources and types of financial, material, and other support	10_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	9-10_____
	5b	Name and contact information for the trial sponsor	Enclosed WHO supplement___
	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	10_____

	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)	Not applicable
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	3_____
	6b	Explanation for choice of comparators	5 and 9_____
Objectives	7	Specific objectives or hypotheses	3_____
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)	4_____
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	4_____
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)	4_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5 plus fig 1+2___
	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)	5 (dropout) or else not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5_____

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	5-7 incl. table 2
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)	Figure 1
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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
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	4-5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4-5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
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	4-7
	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	5
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	8-9
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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	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)	8
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	8
	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	Not applicable
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	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not planned
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9_____
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)	Enclosed WHO supplement
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	8-9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10_____
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	8-9_____
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	Not applicable_
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	8_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable_
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request in Danish.

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	Will be published in separate protocol

*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

Comparing group-based Acceptance and Commitment Therapy (ACT) with Enhanced Usual Care for adolescents with functional somatic syndromes: Study protocol for a randomised trial

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TITLE PAGE

Comparing group-based Acceptance and Commitment Therapy (ACT) with Enhanced Usual Care for adolescents with functional somatic syndromes: Study protocol for a randomised trial

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Keywords: Functional somatic syndromes, adolescents, randomised controlled trial, study protocol, psychotherapy

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Trial registration:
ClinicalTrials.gov: NCT02346071

ABSTRACT (291 words)

Introduction

Functional somatic syndromes (FSS) are common in adolescents, characterised by severe disability and reduced quality of life. Behavioural treatments such as Acceptance and Commitment Therapy (ACT), has shown promising results in children and adolescents with FSS, but has focused on specific syndromes such as functional pain. The current study will compare the efficacy of group based ACT with that of Enhanced Usual Care (EUC) in adolescents with a range of FSS operationalized by the unifying construct of multi-organ bodily distress syndrome (BDS).

Methods and analysis

A total of 120 adolescents aged 15-19 and diagnosed with multi-organ BDS, of at least 12 months duration, will be assessed and randomised to either: 1. EUC: A manualised consultation with a child and adolescent psychiatrist and individualised treatment plan or 2. Manualised ACT based group therapy plus EUC. The ACT program consists of 9 modules (i.e. 27 hours) and one follow up meeting (3 hours). Primary outcome is physical health, assessed by a SF36 aggregate score 12 months after randomisation. Secondary outcomes include self-reported symptom severity, symptom interference, depression and anxiety, illness worry, perceived stress and global improvement; as well as objective physical activity and bodily stress-response measured by heart rate variability, hair-cortisol and inflammatory biomarkers. Process measures are illness perception, illness related behaviour and psychological flexibility.

Ethics and dissemination

The study is conducted in accordance with the Helsinki Declaration II. Approval has been obtained from the Science Ethics Committee of the Central Denmark Region and the Danish Data Protection. The results will be sought published according to the CONSORT statement in peer-reviewed journals.

Discussion

This is one of the first larger randomised clinical trials evaluating the effect of a group based intervention for adolescents with a range of severe FSS.

Registration

ClinicalTrials.gov: NCT02346071

Strengths and limitations

Strengths:

- Large-scale study in an area with limited knowledge.
- Evaluation of psychosocial and biological predictors and moderators of outcomes.
- Thorough assessment of all patients providing them with evidence based understanding of their illness.
- Treatment model developed based on treatments with proven effect for both paediatric and adult patients with FSS and related disorders.
- Minimization of bias by the use of a manualized treatment, different therapists, valid outcome measures, multiple assessment points and by predefining and publishing all outcome measures before study start.

Limitations:

- Lack of comparison with an evidence based control treatment.
- Blinding of clinicians not possible.
- Study design does not allow for determination of which treatment components are most important in achieving change.
- Assessment and treatment is carried out in a specialised setting, which might affect generalization.
- Results not automatically applicable to younger adolescents given the developmental perspective, with multiple symptoms being less common in children and younger adolescents.

BACKGROUND

Functional somatic syndromes (FSS), including chronic fatigue syndrome, juvenile fibromyalgia, functional gastrointestinal disorders, and idiopathic pain syndromes are well known conditions in adolescents. FSS are diagnostic unities representing clusters of related functional somatic symptoms. Prevalence rates vary considerably due to differences in case definitions, assessment instruments and study populations.(1-3) Studies attempting to cover the whole range of different functional somatic symptoms suggest that 5-10% of children and adolescents in the general population are substantially affected and likely to need care.(4, 5) Suffering from FSS during adolescence often has high personal and societal consequences. The adolescents have a higher risk of psychosocial problems such as social isolation, long-term school absence and reduced quality of life(6) and anxiety and depression are common co-morbidities.(7, 8) A substantial proportion show continuity of functional symptoms into adulthood(9-11) and are less likely to obtain a college education.(9) Furthermore, adolescents diagnosed with FSS have overall higher health care costs due to increased use of medication and health care services.(9, 12) The aetiology of FSS remains unknown. Recent studies suggest a potential correlation between physiological stress and FSS, with physical inactivity as a potential covariate.(13-16) It is proposed that a (patho)physiologic response to prolonged or severe mental and/or physical stress in genetically susceptible individuals may trigger symptom development.(17)

High co-occurrence of different types of FSS, especially various pain syndromes, has been shown in children and adolescents.(18-20) Children reporting multiple symptoms have an associated higher frequency of distress and impairment (e.g. higher kindergarten/school absenteeism and consultations with physicians).(21) Moreover, adult patients presenting with multiple symptoms from several organ systems have a poorer prognosis and a higher risk of chronification.(22-24) Thus, an attempt to recognize the most severely affected patients with the highest illness burden may encompass sampling patients with the highest symptom load (i.e. multiple symptoms from several organ systems). Recently, the empirically based unifying diagnostic category Bodily Distress Syndrome (BDS) was introduced.(25) The diagnosis describes specific symptom patterns and includes a multi-organ subtype and four single organ subtypes and has in adult samples been shown to capture a range of FSS including fibromyalgia, irritable bowel syndrome, non cardiac chest pain and chronic fatigue syndrome.(26) Multi-organ BDS comprising multiple symptoms from at least three specific symptom-groups thus offers a diagnostic unity potentially including the most severely affected patients.

Cognitive behavioural therapy (CBT) has been shown to reduce symptoms and increase functioning in adults with FSS,(27-30) whereas the evidence for treatment in adolescents is sparse. Family-based CBT and internet-delivered CBT have proven effective in young patients with specific FSS.(31-36) However, the development of specifically tailored treatments for each FSS or symptom profile seems to be an inefficient strategy due to the costly nature of establishing separate clinics in each medical (sub)-specialty, the fragmented care available, and difficulty to handle multi-symptomatic patients at those clinics.(17, 37, 38) Recent studies suggest that adult patients with various FSS can feasibly receive the same treatment delivered in a group format, regardless of their main functional symptom.(39, 40) In adolescents, group treatment has been widely used and shown to be feasible in the treatment of both psychiatric and non-psychiatric diseases.(41, 42) Group format offers several benefits including peer modelling, diminishment of stigma, increased motivation, and higher acceptance of feedback from peers opposed to professionals.(43) Hence, a unified group-based treatment may be advantageous for adolescents with various FSS due to feasibility, accessibility of treatment, and potential health care savings.

Acceptance and Commitment Therapy (ACT), which derives from CBT, has shown promising results in children and adolescents with chronic functional pain.(44, 45) Evidence suggests that acceptance of pain is related to enhanced physical and emotional functioning, whereas attempts to control pain may lead to higher pain and disability.(46, 47) By reducing avoidance behaviour and symptom interference, ACT can increase functioning and enhance quality of life, through value driven acceptance and exposure strategies.(48) Symptom avoidance seems to be a general problem leading to disability and lower quality of life in patients with FSS.(49) This provides a rationale for a therapeutic approach focused on reduction of avoidance behaviour and acceptance of somatic symptoms.

The objective of the present trial is to examine the efficacy of ACT-based group therapy for adolescents with a range of FSS grouped under the unifying diagnosis of multi-organ bodily distress syndrome (BDS).(17) To do this, we will examine physical health and a range of other outcomes including level of functioning, symptom interference and emotional distress at baseline, at different time-points throughout the trial, and also at 12-month follow-up. An add-on study includes measurement of physiological stress response and physical activity level.

METHODS

Design

Single-site, non-blinded randomised controlled trial (RCT) with two conditions: 1) Group based ACT and 2) Enhanced usual care (EUC). Overall study design is illustrated in figure 1.

Setting

Patients will be enlisted from the Research Clinic for Functional Disorders and Psychosomatics, situated in a general medicine setting at Aarhus University Hospital, Denmark. The department is a specialist, tertiary service with extra resources allocated for assessment and treatment of patients with debilitating functional somatic symptoms. Enrolment starts in January 2015 and the data collection is expected to be finalised June 2019.
Prior to enrolment an uncontrolled pilot study was performed to test the applicability of the multi-organ BDS diagnosis for this specific age group as well as the feasibility of the new group based treatment programme. Twenty-one patients were included in the uncontrolled pilot study.

Eligibility

Eligibility criteria are multi-organ BDS, i.e. at least three functional somatic symptoms from at least three symptom groups, moderate to severe impairment in daily life and symptom duration of minimum 12 months (see table 1).(22, 26)

Table 1. Diagnostic criteria for multi-organ Bodily Distress Syndrome (BDS) (25, 26)
Functional symptoms from at least 3 out of 4 symptom groups and at least 3 symptoms from each of the symptom groups.

Gastrointestinal	**Cardiopulmonal** (including autonomic symptoms)
Abdominal pain	Palpitations / heart pounding
Nausea	Hot or cold sweats
Frequent loose bowel movements	Breathlessness without exertion
Diarrhoea	Hyperventilation
Feeling bloated	Dry mouth
Regurgitations	Trembling/shaking
Burning sensation in chest	Churning in stomach
Constipation	Flushing or blushing
Vomiting	Precordial discomfort
Musculoskeletal	**General symptoms**
Muscular ache or pain	Headache
Pain in the joints	Concentration difficulties
Feeling of paresis or localized weakness	Impairment of memory
Back ache	Excessive fatigue
Pain moving from one place to another	Dizziness
Unpleasant numbness or tingling sensations	
Pain in arms or legs	

Inclusion and exclusion criteria

The study criteria are summarized in Table 2.

Table 2. In- and exclusion criteria

Inclusion criteria
1. Bodily Distress Syndrome, multi-organ type of at least 12 months duration.
2. 15-19 year-old at referral.
3. Raised since infancy in Denmark or born by Danish parents. Understand, speak and read Danish.
4. Moderate or severe impairment.
Exclusion criteria
1. Not completing informed consent.
2. Acute psychiatric disorder demanding other treatment, or if the patient is suicidal.
3. A lifetime diagnosis of psychosis, mania or depression with psychotic symptoms (ICD-10: F20-29, F30-31, F32.2, F33.3), serious cognitive deficits or developmental disorders such as mental retardation and autism (ICD-10: F70, F84)
4. Substance abuse of e.g. narcotics, alcohol or medication.
5. Pregnancy at the time of inclusion.
6. Not suitable for group-based treatment, e.g. patients with severe ADHD (ICD-10: F90), severe social phobia (ICD-10: F40.1) or conduct disorder (ICD-10: F91).

Recruitment procedures

A total of 120 adolescents (aged 15-19) referred from general practitioners (GP), practising medical specialists or hospital wards, will be recruited into the trial. All referrals are initially screened for eligibility by a team of physicians from the Research Clinic for Functional Disorders and Psychosomatics.

Assessment

Patients regarded as eligible undergo a standardized clinical psychiatric and somatic assessment, performed by a physician specialized or trained in child and adolescent psychiatry. The assessment consists of: 1) review of former discharge letters, medical records, and other relevant information, 2) standardized clinical interview, 3) SCAN (Schedules for Clinical Assessment in Neuropsychiatry),(50) which screens for general psychopathology and contains a detailed section on functional somatic symptoms, 4) screening for child and adolescent psychiatric disorders not covered by the SCAN, i.e. ADHD, autism and conduct disorder with specific sections from the child and adolescent psychiatric interview DAWBA (Development and Well Being Assessment),(51) 5) a clinical physical/neurological examination and 6) standard blood tests.

Patients meeting the study criteria (see Table 2) are offered participation in the study and are subsequently asked to complete consent form before enrolment and randomisation. Figure 1. presents the flow of patients during the trial.

Randomisation procedure

Following baseline assessment, patients meeting all study criteria and consenting to participation are randomised to either EUC or group based ACT. The randomisation is conducted by statisticians not involved in treatment. Permuted block randomisation with block-sizes ranging from 14-16 made by means of a computer algorithm will be used to ensure balanced group sizes and allocation concealment. Patients consenting to participation receive an opaque envelope taken from a sequential order containing information on group allocation, ensuring that initial assessment is not influenced by group allocation.

As the study compares a psychological treatment with EUC, blinding of participants and therapists is not possible.

INTERVENTIONS

Enhanced usual care (EUC)

Patients allocated to EUC will have a psychiatric consultation of 1½ hours duration, approximately 2 weeks after clinical assessment, with participation of the patient and his/her parents or close relatives. The consultation is manualised and includes psycho-education related to the diagnosis of multi-organ BDS, health promoting strategies, advice on medication, or other treatment, supplemented with written information on the BDS diagnosis and general recommendations. ACT elements are not incorporated or used in the consultation. The aim of the consultation is to increase the family's understanding of BDS and to optimize management in primary care and social services support

by an individualized treatment plan sent to the patient's GP. The consultation is carried out by the child and adolescent psychiatrist doing the initial assessment.

ACT based group therapy

Patients allocated to ACT based group therapy receive the same psychiatric consultation as described above, before starting the manualized ACT treatment developed specifically for this patient group. The therapy is given in groups of 7-8 patients with 9 modules (i.e. 27 hours in total) over a period of 3 months and one follow up meeting (3 hours) three months after module 9. Detailed information on the treatment program is presented in Figure 2. The parents and other relevant close relatives (e.g. siblings, boy/girlfriends) are invited to participate in an information meeting, to support the relatives´ resources to help the adolescent improving his/her functional level and coping with symptoms. One individual consultation with the adolescent and close relatives is offered shortly after module 8. After completed ACT therapy an individualized treatment plan is sent to the patient's GP.

Patients assigned to ACT therapy have to agree not to have any other psychological treatment for BDS while in therapy.

Therapist training and adherence to treatment manual

Therapists are child and adolescent psychiatrists and psychologists with specialist training in ACT. Clinicians well experienced in ACT and group therapy supervise the treatment. Sessions are videotaped and assessed by an external panel to ensure adherence to the treatment manual.

Compliance and attrition

Treatment compliance is assessed by recording the number of completed ACT-modules. When applicable, participants are asked for their reasons for poor compliance or dropout. In the case of dropout from the ACT group therapy, data collection continues as planned with the patients consent.

OUTCOME MEASURES

Outcome measures are obtained at 6 different time points: At baseline (i.e. before assessment and randomisation) and 2, 4, 6, 8, and 12 months after randomisation. These time points have been designed to follow the time schedule of the ACT group therapy to allow for evaluation of process variables. Figure 1 depicts how these time points relate to assessment and treatment. Primary and secondary outcome measures are assessed by web-based questionnaires (see table 3). The questionnaires are distributed simultaneously to the ACT and EUC group i.e. in the randomised blocks. Primary endpoint is 12 months after randomisation.

Due to a study population of adolescents approaching adulthood (15+ years) questionnaires developed and tested in adults are chosen.

Three questionnaires (Limitation Index,(52) Avoidance and Fusion Questionnaire in Youth,(53) and Psychological Inflexibility in Pain Scale,(54)) have been translated with reference to standard procedures with initial translation, synthesis of translations and back-translation.(55)

Table 3. Outcome measures

Respondent: X= Patient P= Parent

	Instrument	Abbreviation	Mos.	0	2	4	6	8	12
Primary outcome									
Physical health	The Short Form Health Survey(56, 57)	SF-36		X	X	X	X	X	X
Secondary outcomes									
Illness severity	Symptom Checklist Revised-90 – somatisation subscale(58)	SCL-som		X	X	X	X	X	X
	Bodily Distress Syndrome checklist(59)	BDS checklist		X					X
Symptom interference	Limitation Index (Revised from Pain Interference Index)(52)	LI		XP			XP	X	XP
Depression and anxiety score	Symptom Checklist Revised-90 – depression and anxiety subscales(58, 60-62)	SCL-8-6-4		X			X	X	X
Mental health	The Short Form Health Survey(56, 57)	SF-36		X	X	X	X	X	X
Illness worry	Whiteley-7(63)			X	X	X	X	X	X
Perceived stress	Perceived Stress Scale(64)	PSS		X					X
Overall impression of change	Patient Global Impression of Change(65)	PGIC					XP	X	XP
Process measures									
Illness perception	The Brief Illness Perception Questionnaire(66)	BIPQ		XP	X	X	XP	X	XP
Illness related behaviour	The Behavioural Response to Illness Questionnaire, short(67)	BRIQ		X	X	X	X	X	X
Psychological flexibility	Avoidance and Fusion Questionnaire for youth(53)	AFQ-Y8		X	X	X	X	X	X
	Psychological Inflexibility in Pain Scale(54)	PIPS-12		X	X	X	X	X	X
Potential moderators									
Family functioning	Family Assessment Devise (general functioning subscale)(68)	FAD		XP					XP
Attachment style	Experience in Close Relationships – Relationship Structure(69)	ECR-RS		X					
Negative life events	Negative life events(70)			X					
Physiological measures									
Heart rate variability	HRV measured with Vagus device (resting state, standing, slow breathing, valsalva)(71)			X					X
Hair-cortisol	Measurement of hair-cortisol in 2 strands of hair closest to the scalp (1-2 cm)			X					X
Inflammatory response	IL6, TNF-α, high-sensitive CRP, IL1, neopterin, CD163, HO1, MCP1			X					X
Physical activity	Accelerometer (Actigraph wGT3X-BT) worn for 7 consecutive days(72)			X					X

Primary outcome
The primary outcome is improvement in physical health 12 months after randomisation, measured with an aggregate score of the SF-36 subscales PF (physical functioning), BP (bodily pain) and VT (vitality)(56, 57) with a score range from 15-65. This score has previously been used as the primary outcome in a comparable trial in adults(39) due to well-known psychometric problems with the existing physical component score (PCS)(73) and based on the rationale that these three subscales have shown to be key-domains affected in this patient group.(74) Danish norm data for adolescents are available.(56)

Self-reported secondary outcomes
Illness severity is measured by two questionnaires. 1. The Somatisation subscale of the Symptom Checklist Revised-90(58, 61) (12 items, 5-point scale), a widely used symptom checklist of commonly experienced physical symptoms. 2. The Bodily Distress Symptom checklist (BDS checklist)(59) (25 items, 5-point scale), a symptom checklist added as a new measure for validation in adolescents. It is developed from the symptoms stated in the BDS criteria, hence evaluating symptom severity in four symptom groups.

The impact of symptoms on functioning i.e. symptom interference is evaluated by self- and parent report using the Limitation Index (LI)).(44, 52) LI is a modified version of the Pain Interference Index (PII), (6 items, 7-point scale), a validated questionnaire for children and adolescents measuring impact of pain in performing everyday activities and impact on e.g. mood and sleep. The modification from PII to LI is limited and represents a change in wording from "pain" to "symptoms". Self-reported degree of absence from school or work is being registered.

Assessing symptoms of anxiety and depression brief versions of the corresponding subscales from Symptom Checklist Revised-90 are used (SCL-8, SCL-6, SCL-4)(58, 60-62) (13 items in total, 5 point scale). Level of illness worry is measured by Whiteley-7(63) (7 items, 5-point scale), a subscale of the Whiteley Index. Mental health is measured with the Mental Component Summary (MCS) from SF-36.(56, 57)

Subjective perception of stress is measured by the Perceived Stress Scale (PSS)(64, 75) (10 items, 5-point scale). The scale is a widely used measure of the degree, to which situations in life are perceived as stressful. Danish norm data for adolescents are available.

The overall impression of improvement is measured with the Patient Global Impression of Change (PGIC)(65) (1 item, 7-point scale). Answers range from "no change (or condition has gotten worse)" to "a great deal better and a considerable improvement that has made all the difference".

Process measures
The process measures evaluate specific areas hypothesized to play a role in the development and perpetuation of functional somatic symptoms, and are hence addressed directly in the treatment.
Illness perception is measured by the Brief Illness Perceptions Questionnaire (BIPQ)(66) (8 items, 10-point scale and additional item regarding cause of symptoms) which has been widely used in a range of illnesses. The perception of five core components (identity, cause, timeline, consequences, and cure-control) is evaluated as they together form the perception of illness. In a comparable study with adults, changes in illness perceptions partly mediated the effect of treatment on outcome.(76)
Illness related behaviour is measured by the Behavioural Responses to Illness Questionnaire (BRIQ)(67) (13 item, 5-point scale). Specific illness related behaviours have shown to be risk factors for development of FSS in adults.(67)
Psychological flexibility is an area specifically targeted in ACT. It is measured by Avoidance and Fusion Questionnaire in Youth (AFQ-Y8)(53) (8 items, 5-point scale) and Psychological Inflexibility in Pain Scale (PIPS-12)(54) (12 items, 7-point scale).

Potential predictors and moderators
Relevant demographic data and potential important predictors for outcome, e.g. predisposition to functional syndromes and number and kind of life events are obtained as part of the diagnostic assessment,(70).
Family functioning is assessed by the subscale on general functioning from Family Assessment Devise (FAD)(68, 77) (12 items, 4-point scale). In addition the patient´s attachment style is assessed dimensionally by Experience in Close Relationships – Relationship Structure (ECR-RS)(69) (9 items, 7-point scale).

Credibility regarding treatment is assessed before the individual standard psychiatric consultation.(78) At end of treatment, i.e. after module 9, the participants complete a standard questionnaire regarding their experience of the service at the clinic.

Concomitant treatment and serious adverse events during the trial period will be registered by self-report one year after randomisation.

Physiological measures

Bodily stress-response is assessed with three different measures pre- and post-treatment:
1) Heart rate variability (HVR) as an indirect measure of the balance between the sympathetic and parasympathetic system. It is measured in various standardized situations (resting state, standing, slow breathing and valsalva) with the handheld device Vagus.(16, 71, 79)
2) Hair-cortisol as a biological marker for long-term bodily stress. It is measured from two strands of hair cut close to the scalp, since the proximal 1 cm segment of hair represents the cortisol level of the last month.(80)
3) Biomarkers for inflammatory and oxidative stress (including IL6, TNF-α, high-sensitive CRP, IL1, neopterin, CD163, HO1, MCP1 but also newer proteo-based markers).(81-84)

Physical activity

Level of physical activity is assessed pre- and post-treatment by anthropometric measurements with accelerometer (Actigraph wGT3X-BT).(72) The accelerometer is worn on the right hip 24 hours-a-day for 7 consecutive days.

A specific protocol for evaluation of physiological measures and physical activity will be made specifying hypotheses and analytical strategies. A large ongoing epidemiological study in Denmark (DanFunD) will be available for later comparison of results.(85)

SAMPLE SIZE ESTIMATION

Power estimation is based on the primary hypothesis regarding changes in self-reported physical health measured with the SF-36 aggregate score. Given the efficacy in a previous RCT study of ACT in adolescents with chronic functional pain(44) as well as data on a subgroup of patients under 30 years from another RCT study of CBT with BDS,(39) an improvement of self-reported physical health is estimated to be maximum 3 points (from 39-42) in the control group and at least 5 points (from 39-44) in the ACT group from baseline to 12 months after randomisation. Baseline value assumes a standard deviation of 8 referring to the defined groups of patients. Using a random effects model in a simulation setting shows that in order to statistically detect such a difference in improvement (test of no interaction), given a 2-sided alpha of 0.05 and with 95% power, we need to allocate 60 patients to each group.

STATISTICAL ANALYSIS

The efficacy of the ACT treatment will be evaluated on an intention-to-treat basis by means of random effects model regression analysis adjusted for prognostic important baseline characteristics. The main efficacy analysis will pertain to the data obtained at 12 months follow-up. Baseline characteristics will be tabulated by treatment modality in order to evaluate success of randomisation. To judge possible bias due to missing data a random effect model on multiple imputed data will be performed.
An explorative mediation analysis will be performed to investigate to which extend the intervention can affect the primary outcome through each of the process measures. The analytical strategy previously used in a large scale trial will be used.(86)

DISSEMINATION

Results will be reported according to the CONSORT statement for non-pharmacological interventions,(87) and will be submitted for publication in peer-reviewed English-language journals. Positive, inconclusive and negative findings will be published. Trial findings will also be disseminated through conference abstracts.

DATA MONITORING AND MANAGEMENT

This trial is considered a minimal risk study and hence a data and monitoring committee has not been established. Questionnaires are administered electronically and saved in an online database. The database is secured with a password-protected access system, and access to files is limited to research staff that requires direct access. Baseline

information obtained during assessment is registered in a Case Report Form (CRF). All CRF's are stored in locked file cabinets in areas with limited access.

ETHICAL APPROVAL

The project will be conducted in accordance with the Helsinki Declaration II. Approval has been obtained from the Science Ethics Committee of the Central Denmark Region (journal number: 1-10-72-181-14) and the Danish Data Protection (reference number: 1-16-02-290-14).

DISCUSSION

Adolescents with FSS are at risk of continuity of physical problems into adulthood implying reduced quality of life due to potential functional impairment, social withdrawal, lack of education and incapacity to work. To our knowledge the present study will be one of the first larger randomised clinical trials, evaluating the efficacy of a group based treatment for adolescents with a range of FSS grouped under the unifying diagnosis of multi-organ BDS compared to EUC.

Our study design has some limitations. First is the lack of comparison with an evidence based control treatment. However, as the aim of this study is to compare ACT group therapy to the best treatment available (i.e. EUC), we use a pragmatic design that offers systematic clinical assessment and an individual treatment plan also to patients in the usual care arm. Also, a unified treatment for adolescents with a range of FSS has not been tested before. Second, blinding is not possible to the clinician providing the standard psychiatric consultation. However, this is a general problem in trials of behavioural interventions. Third, the study design does not allow us to determine which treatment components are most important in achieving change. Accordingly, our aim is to assess whether the whole complex intervention as delivered is more effective than EUC in improving physical health. Fourth, the assessment and treatment is carried out in a specialised setting, which might not guarantee that the treatment, if proven successful, will work in everyday clinical practice, across different populations, clinical contexts etc. Lastly the results from the study cannot automatically be applied to younger adolescents given the developmental perspective, with multiple symptoms being less common in children and younger adolescents.

Important strengths of the study are the evaluation of potential psychosocial and biological predictors and moderators of outcomes. Furthermore all patients are given a thorough assessment providing them with a positive and evidence based understanding of their illness,(88, 89) and the treatment model is developed based on treatments with proven effect for both paediatric and adult patients with FSS and related disorders.(39, 40, 44)
Bias is minimized by the use of a manualized treatment, different therapists, valid outcome measures, multiple assessment points and by predefining and publishing all outcome measures before study start.

Anticipated difficulties conducting the study include recruitment problems due to stringent in- and exclusion criteria as well as lack of knowledge of available service for adolescents and social prejudices in terms of receiving psychiatric diagnosis and psychological treatment for functional symptoms.(8)

In conclusion this study will provide important information about efficacy, processes of change and moderators. If the treatment is successful, it will improve the quality of life of adolescents with FSS and may over the life course lead to substantial health and municipal service savings.

COMPETING INTEREST STATEMENT

We have read and understood BMJ Open policy on declaration of interests and declare that we have no competing interests.

CONTRIBUTION OF AUTHORS

Karen Hansen Kallesøe: Took part in designing the study, drafted the initial manuscript and prepared the final manuscript as submitted.

Andreas Schröder: Took part in developing the research idea and in designing the study, contributed with data for statistical power analysis and critically revised the manuscript.

Rikard Wicksell: Took part in designing the study, contributed with data for statistical power analysis and critically revised the manuscript.

Per Fink: Took part in developing the research idea and critically revised the manuscript.

Eva Ørnbøl: Took part in the statistical design of the study, made the power analysis and description of the statistical method and critically revised the manuscript.

Charlotte Ulrikka Rask: Came up with the original research idea, took part in designing the study, drafted the initial treatment protocol and critically revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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FINANCIAL DISCLOSURE

None of the authors have any financial interests to declare in relation to this study.

TRIAL REGISTRATION

ClinicalTrials.gov: NCT02346071

Legend figure 2:
The overall focus of the treatment is to increase the patients´ physical and emotional self-awareness, and to teach them skills to manage the distress associated with difficult thoughts, emotions, and bodily sensations. Practical exercises throughout the treatment includes experiential exercises focusing on identification of own values, barriers and avoidance behaviour, and mindfulness exercises focusing on allowance of the experience of here and now as it is and of being present.
Gradual exposure is implemented through individually customized homework assignments in accordance with the identified personal values.

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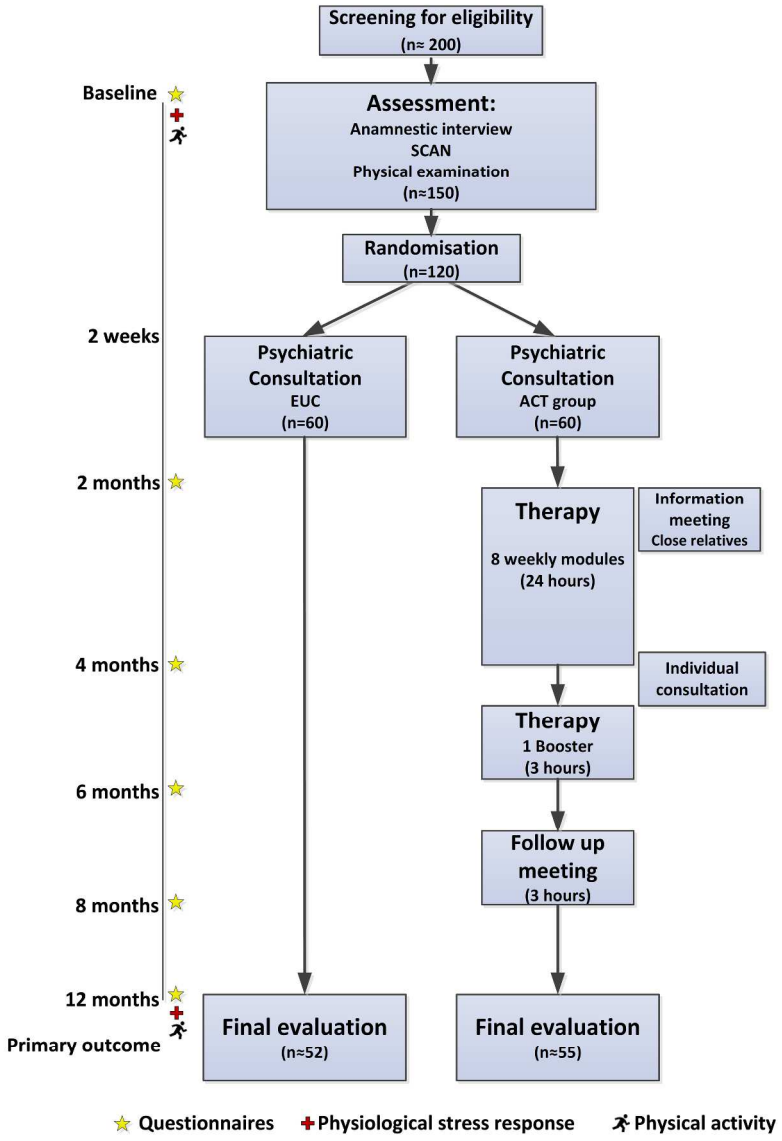
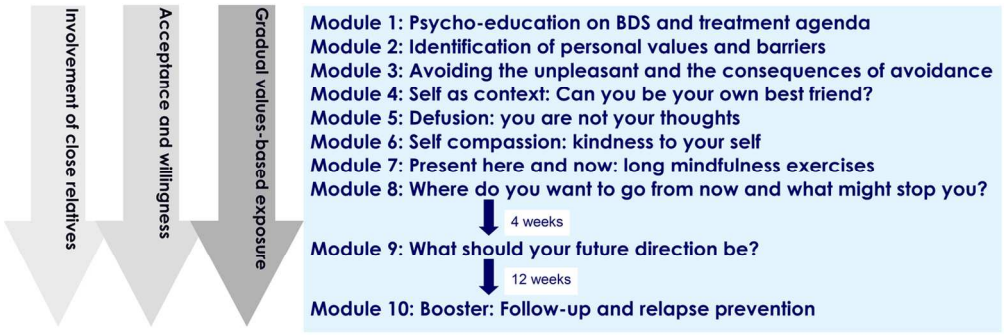


Caption: Figure 1. Flowchart of participants with estimated numbers at each level

260x337mm (300 x 300 DPI)



Caption: Figure 2. Overview of the group-based Acceptance and Commitment Therapy treatment program
Legend: The overall focus of the treatment is to increase the patients´ physical and emotional self-awareness, and to teach them skills to manage the distress associated with difficult thoughts, emotions, and bodily sensations. Practical exercises throughout the treatment includes experiential exercises focusing on identification of own values, barriers and avoidance behaviour, and mindfulness exercises focusing on allowance of the experience of here and now as it is and of being present. Gradual exposure is implemented through individually customized homework assignments in accordance with the identified personal values.

134x44mm (300 x 300 DPI)

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	1 (title page)__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1 (title page)
	2b	All items from the World Health Organization Trial Registration Data Set	Enclosed WHO supplement
Protocol version	3	Date and version identifier	Enclosed WHO supplement
Funding	4	Sources and types of financial, material, and other support	10_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	9-10_____
	5b	Name and contact information for the trial sponsor	Enclosed WHO supplement___
	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	10_____

	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)	Not applicable
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	3_____
	6b	Explanation for choice of comparators	5 and 9_____
Objectives	7	Specific objectives or hypotheses	3_____
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)	4_____
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	4_____
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)	4_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5 plus fig 1+2___
	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)	5 (dropout) or else not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5_____

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	5-7 incl. table 2
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)	Figure 1
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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
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	4-5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4-5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
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	4-7
	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	5
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	8-9
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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	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)	8
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	8
	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	Not applicable
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	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not planned
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9_____
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)	Enclosed WHO supplement
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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	8-9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10_____
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	8-9_____
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	Not applicable_
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	8_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable_
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request in Danish.

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	Will be published in separate protocol

*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.