PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparing group-based Acceptance and Commitment Therapy (ACT) with Enhanced Usual Care for adolescents with functional somatic syndromes: Study protocol for a randomised trial
AUTHORS	Kallesøe, Karen; Schröder, Andreas; Wicksell, Rikard; Fink, Per; Ørnbøl, Eva; Rask, Charlotte

VERSION 1 - REVIEW

REVIEWER	M Elena Garralda Imperial College London, United Kingdom
REVIEW RETURNED	11-Jun-2016

GENERAL COMMENTS	This paper describes a RCT of a novel psychological therapy – Acceptance and Commitment Therapy or ACT- for young people with combined functional somatic syndromes (FSS), a neglected but potentially highly impairing clinical condition. As the authors rightly state we know comparatively little about aetiological pathways, and there is a dearth of evaluation treatment studies in older adolescents with multiple somatic syndromes. This trial is therefore should help fill an important gap in knowledge. The intervention under evaluation has already been used in children and adolescents with chronic functional pain. The treatment ingredients are multiple and varied, and if the trial is successful, this will make it difficult to disentangle helpful from redundant strategies. Nevertheless given the present state of knowledge about maintaining factors and effective interventions, the combined use of motivational, stress management and behavioural techniques all seem appropriate and in line with clinical thinking, and the comparator treatment involving systematized enhanced usual care by a child psychiatrist acceptable. The background and justification for the study are clearly outlined, as are the objective and trial design and methods (setting, eligibility and interventions; primary and secondary outcomes, study timeline, sample size and recruitment). The assignment of interventions seems fit-for- purpose. There is no blinding but the authors explain the rationale for this. The data collection, management methods and analytic strategy are adequate. The study does not have data and monitoring committees, on the basis that it is considered a minimal risk study, but the database is carefully secured, registered and stored. The study has been ethically approved and plans for dissemination are adequate. A particular strength of the study is the evaluation of potential psychosocial and biological predictors and moderators of outcomes. In addition to the lack of blindness, limitations noted by the authors

	include the lack of a placebo control treatment and possible recruitment problems, partly due to the reluctance by many young people with functional symptoms to accept psychological treatments. Whilst the lack of a placebo group may be unavoidable, recruitment may indeed prove challenging. Previous evaluations of psychological treatments in children and adolescents with functional symptoms have usually involved family rather than peer group based treatments. This older age sample will be more amenable to group work, but it would be helpful to know whether the authors have piloted the study and have good reason to believe that the necessary appropriate and large sample is likely to be available and retained for the study. Of the functional disorders chosen for this study irritable bowel syndrome and non-cardiac chest pain are comparatively uncommon in children and adolescents. To make results more applicable to younger adolescents, broader pain syndromes such as severe and impairing recurrent abdominal pains and headaches could have been included. Nevertheless the study will be relevant for the older adolescent age group. The sample has been powered to pick up quite small numerical changes in the primary outcome measure, which may not reflect clinically significant improvements, but the data available will no doubt provide sufficient information to document this.

REVIEWER	Karin Janssens Postdoctoral researcher, Interdisciplinary Center Psychopathology and Emotion regulation, University of Groningen, University Medical Center Groningen, CC 72, PO Box 30001, 9700 RB, Groningen, The Netherlands
REVIEW RETURNED	23-Jun-2016

GENERAL COMMENTS	This is a well-designed and carefully described RCT on group ACT in adolescents with bodily distress syndrome. The study outcomes are well-described and all standards for completing an RCT are met. Some concerns are addressed below. *The last sentence of the abstract is a bit confusion. It states “this is one of the first larger randomized clinical trials evaluating the effect of a group based intervention for adolescents diagnosed with multi-organ BDS”. It is not clear from the introduction what other studies are performed and if, what the current study adds to previously performed studies. *As the authors already mention, the largest disadvantage of the study design is a lack of control group that received an evidence based treatment. This disables finding out whether it is actually the group element or the acceptance-commitment element or a combination of both that makes the treatment successful if proven successful. It would be good if the authors mention to which extent ACT elements are incorporated in the enhanced usual care. *The add-on study on physiological stress measures could be a bit more extensive. It appears from Table 2 that the researchers are going to compare pre- en post-treatment physiology. It would be good to mention this in the text. Given the large variability in physiology researchers can best focus on differences within

	individuals. Minor comments: *Somehow a comma (,) seems to be inserted before all literature references *It would be clear if the numbers in Table 2 in top are labeled. I guess they refer to the months of follow-up.

VERSION 1 – AUTHOR RESPONSE

We do have some minor changes in regards to references:
1. The original reference numbers 16, 35 and 49 were referring to the same article. This has been corrected to just one reference, number 17.
2. In the background section, paragraph 1, in the sentence: “A substantial proportion show continuity of functional symptoms into adulthood” we forgot to include the Steinhausen reference (new reference number 11). We would like to add this reference since it refers to the whole spectrum of functional symptoms.
3. In the background section, paragraph 2, in the sentence “Recently, the empirically based unifying diagnostic category Bodily Distress Syndrome (BDS) was introduced” the reference has been corrected to the original paper describing the BDS diagnosis (new reference number 25).
4. The original reference numbers 85 and 86 have been updated since they were referring to home-pages under revision. They have been combined in just one reference number 85.

Reviewer 1’s comments regarding the selected patients have made it clear to us, that our description of the criteria for the diagnostic concept of Bodily Distress Syndrome (BDS) is not thorough enough. We therefore kindly ask for permission to include a table with the diagnostic criteria in the protocol to enhance the understanding of the diagnosis.

Reviewers comments
Reviewer #1
This paper describes a RCT of a novel psychological therapy – Acceptance and Commitment Therapy or ACT- for young people with combined functional somatic syndromes (FSS), a neglected but potentially highly impairing clinical condition. As the authors rightly state we know comparatively little about aetiological pathways, and there is a dearth of evaluation treatment studies in older adolescents with multiple somatic syndromes. This trial is therefore should help fill an important gap in knowledge.

The intervention under evaluation has already been used in children and adolescents with chronic functional pain. The treatment ingredients are multiple and varied, and if the trial is successful, this will make it difficult to disentangle helpful from redundant strategies. Nevertheless given the present state of knowledge about maintaining factors and effective interventions, the combined use of motivational, stress management and behavioural techniques all seem appropriate and in line with clinical thinking, and the comparator treatment involving systematized enhanced usual care by a child psychiatrist acceptable.

**We agree that the multiple and varied treatment ingredients will make it difficult to disentangle helpful from redundant treatment elements. Accordingly, the current study presents a pragmatic design where the aim is to assess whether the whole complex intervention as delivered is acceptable and effective in improving functioning and health-related quality of life in young patients with severe FSS. We acknowledge that it has not been noted in the paper and have therefore added it to the limitations section. Still, we believe the study is an important step towards providing more evidence based treatment to this young patient group that currently are offered limited both specialized

assessment and treatment.**

The background and justification for the study are clearly outlined, as are the objective and trial design and methods (setting, eligibility and interventions; primary and secondary outcomes, study timeline, sample size and recruitment). The assignment of interventions seems fit-for- purpose. There is no blinding but the authors explain the rationale for this. The data collection, management methods and analytic strategy are adequate. The study does not have data and monitoring committees, on the basis that it is considered a minimal risk study, but the database is carefully secured, registered and stored. The study has been ethically approved and plans for dissemination are adequate. A particular strength of the study is the evaluation of potential psychosocial and biological predictors and moderators of outcomes.

Thank you for pointing out your view on the particular strength of the study. This has been added to the discussion.

In addition to the lack of blindness, limitations noted by the authors include the lack of a placebo control treatment and possible recruitment problems, partly due to the reluctance by many young people with functional symptoms to accept psychological treatments. Whilst the lack of a placebo group may be unavoidable, recruitment may indeed prove challenging. Previous evaluations of psychological treatments in children and adolescents with functional symptoms have usually involved family rather than peer group based treatments. This older age sample will be more amenable to group work, but it would be helpful to know whether the authors have piloted the study and have good reason to believe that the necessary appropriate and large sample is likely to be available and retained for the study.

**The assessment including the use of the multi-organ BDS diagnosis for this age group and the group based treatment program have been pilot tested in an uncontrolled pilot study prior to the RCT. A total of 21 patients (3 groups) were included. Feasibility of the treatment program as tested in the pilot study will be described in a separate paper.

The setting, i.e. the Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, where the treatment for adolescents in this study is being carried out, has for several years offered specialized treatment for adults (+20 years) with multi-organ BDS. Due to several requests to the clinic from parents and referrals from doctors of adolescents it was estimated that a treatment offer for multi-symptomatic adolescents would be relevant.**

Of the functional disorders chosen for this study irritable bowel syndrome and non-cardiac chest pain are comparatively uncommon in children and adolescents. To make results more applicable to younger adolescents, broader pain syndromes such as severe and impairing recurrent abdominal pains and headaches could have been included. Nevertheless the study will be relevant for the older adolescent age group.

**We recognize from this comment that our description of the symptoms encompassed by the multi-organ BDS diagnosis is not clear enough. The main purpose of mentioning specific FSS in our description of the BDS diagnosis is to show the connection between the BDS diagnosis and the more widely known FSS. Irritable bowel syndrome and non-cardiac chest pain are simply examples of specific FSS that among others have shown a high diagnostic agreement with the BDS diagnosis (reference 26). The specific syndromes more commonly seen in children and adolescents such as recurrent abdominal pain have not been tested in regards to the BDS diagnosis. However, symptoms such as abdominal pain and headache are present in the diagnostic criteria.
As a consequence we made a minor change to the text concerning the diagnosis in the background section and have asked for permission to include a table with the diagnostic criteria.

We also acknowledge that 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. This is now also mentioned in the section on limitations.**

The sample has been powered to pick up quite small numerical changes in the primary outcome measure, which may not reflect clinically significant improvements, but the data available will no doubt provide sufficient information to document this.

Very relevant comment, that the power calculation is based on quite small numerical changes. From the existing literature regarding adolescents it has not been possible to find a generally accepted measure for a clinically relevant change. Our power calculation has therefore been based on existing clinical data available from comparative studies. In the estimation we have also taken into account the possibility of spontaneous remission and the potential effect of psycho-education in the group receiving enhanced usual care.

Reviewer #2
This is a well-designed and carefully described RCT on group ACT in adolescents with bodily distress syndrome. The study outcomes are well-described and all standards for completing an RCT are met. Some concerns are addressed below.

The last sentence of the abstract is a bit confusion. It states “this is one of the first larger randomized clinical trials evaluating the effect of a group based intervention for adolescents diagnosed with multi-organ BDS”. It is not clear from the introduction what other studies are performed and if, what the current study adds to previously performed studies.

We have made some changes to the abstract and hope this clarifies the confusion and pinpoints what this study adds to previously performed studies.

As the authors already mention, the largest disadvantage of the study design is a lack of control group that received an evidence based treatment. This disables finding out whether it is actually the group element or the acceptance-commitment element or a combination of both that makes the treatment successful if proven successful. It would be good if the authors mention to which extent ACT elements are incorporated in the enhanced usual care.

We have added a sentence to the description of enhanced usual care stating that ACT elements are not incorporated in this treatment arm.

The add-on study on physiological stress measures could be a bit more extensive. It appears from Table 2 that the researchers are going to compare pre- en post-treatment physiology. It would be good to mention this in the text. Given the large variability in physiology researchers can best focus on differences within individuals.

**The fact that we measure physiological measures and physical activity both at baseline and at primary endpoint has been added to the text in the section describing these measures.
We also thank you for the good advice regarding the focus on differences within individuals. This will be incorporated in the specific protocol regarding physiological stress measures.**

Minor comments:

Somehow a comma (,) seems to be inserted before all literature references *It would be clear if the numbers in Table 2 in top are labeled. I guess they refer to the months of follow-up.

Thank you for noting this. The comma has been corrected and label with months added to table 2 (new table 3).

VERSION 2 – REVIEW

REVIEWER	Karin Anne Maria Janssens Interdisciplinary Center Psychopathology and Emotion regulation, University Medical Center Groningen, Groningen, the Netherlands I co-authored an (unpublished) manuscript with these authors.
REVIEW RETURNED	23-Aug-2016

GENERAL COMMENTS	Thank you for adequately addressing my comments. Final minor comment: Plural and singular is mixed in the following sentence of the abstract: 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.