

## PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The Systemic Exertion Intolerance Disease (SEID) diagnostic criteria applied on an adolescent Chronic Fatigue Syndrome (CFS) cohort: evaluation of subgroup differences and prognostic utility
<b>AUTHORS</b>	Asprusten, Tarjei; Sulheim, Dag; Fagermoen, Even; Winger, Anette; Skovlund, Eva; Wyller, Vegard

## VERSION 1 - REVIEW

<b>REVIEWER</b>	Crawley, Esther University of Bristol Competing Interests: I do not have any competing interests.
<b>REVIEW RETURNED</b>	04-Oct-2017

<b>GENERAL COMMENTS</b>	<p>This is an important paper testing a new clinical definition in a cohort of patients. I enjoyed reading it.</p> <p>My major issues are:</p> <ol style="list-style-type: none"><li>1. Whilst the authors did a sample size calculation, this was only to look at differences between those diagnosed SEID positive and those diagnosed as SEID negative in a relatively small, predefined cohort. I am not convinced by the authors second aim. They say "2) evaluate the discriminant validity of the SEID criteria by investigating differences in baseline characteristics and disease markers between SEID-positive and SEID-negative patients." As these are all patients who the authors have diagnosed as having CFS/ME, I do not believe they are evaluating the discriminant validity but I think they are comparing differences.....I would therefore change this aim to: "evaluate the SEID criteria by investigating differences in baseline characteristics and disease markers between SEID-positive and SEID-negative patients."</li><li>2. In the abstract, the authors say they used the outcome at 30 weeks to "investigate prognostic validity of the criteria". Given these patients have CFS/ME and the SEID definition is post hoc, I think they are merely investigating differences at 30 weeks between those who were given the SEID diagnosis compared to those who weren't. This is also true for the statistical methods section on page 9 and elsewhere.</li><li>3. In the strengths and limitations, please remove "relatively high number". This is not a high number in a pre-defined cohort to investigate diagnostic criteria in an illness which is heterogenous....</li></ol> <p>I have a few minor comments: The paragraph in the introduction needs to be softened: "The pathophysiology of CFS remains poorly understood, but multiple studies have demonstrated</p>
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	<p>certain characteristics such as: Attenuation of the hypothalamus–pituitary–adrenal axis (HPAaxis)[8,9] which may be associated with PEM,[10] altered autonomic cardiovascular control,[8,11,12] and impaired cognitive function</p> <p>Page 4, line 24 “neither” should be “either”. The sentence at the end of the introduction: “we based inclusion on a broad case definition, and hypothesized differences between the SEID-positive and SEID-negative groups regarding disease markers and prognosis.” Does not add anything to this paper....What were your hypotheses prior to analyses?</p> <p>The authors make a very important point that they excluded those with clinically diagnosed depression from the project. This is important in terms of understanding the issues, and could be strengthened in the abstract and elsewhere.</p>
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<b>REVIEWER</b>	Reviewer 2
<b>REVIEW RETURNED</b>	11-Oct-2017

<b>GENERAL COMMENTS</b>	<p>I must congratulate you on your comprehensive analysis of what seems to be a large cohort of 120 patients. I see this paper not as a criticism of SEID criteria but an addition to the SEID criteria. Apart from a couple of typos (on page 12, you meant fatigue or fatigued?), there are no major corrections that i would advise. Once again, congratulations!</p>
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<b>REVIEWER</b>	Ridout, Deborah Institute of Child Health, Paediatric Epidemiology Biostatistics Competing Interests: None
<b>REVIEW RETURNED</b>	22-Oct-2017

<b>GENERAL COMMENTS</b>	<p>The background detail regarding the need for validation of the SEID is described well and possibly this should be reflected more clearly in the title. The methodology however is difficult to follow, particularly with regards to this study utilising data from an earlier clinical trial. The implication of the clinical trial is not considered sufficiently and it is not always clear exactly what data is being referred to. I have some specific comments:</p> <ol style="list-style-type: none"> <li>1. How were CFS patients identified for the RCT, what scale was used? Furthermore in order to validate any scale it is important to understand the specificity to ensure non-cases are identified as such and as far as I can tell the present study does not address this important and fundamental issue.</li> <li>2. Patients are divided in to SEID positive and negative but it is not explicitly stated this is at baseline, furthermore reference to baseline characteristics in the background (this is probably not in the correct section) is confusing because we do not know what this baseline is for. Similarly aim 3 is to evaluate prognostic validity – but we do not know what outcome this is for and for when.</li> <li>3. A brief sentence explaining the aim of the RCT would be helpful</li> <li>4. Mood and SEID are confounded so I am not sure what conclusions can be drawn</li> <li>5. It is good the authors have considered the impact of multiple testing on their results and have corrected for 44 tests. I think it</li> </ol>
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	<p>would have been preferable to have a more focussed study question and hypothesis.</p> <p>6. I am not sure the Difference column in Table 4 accurately reflects the adjusted effect, although I see the footnote explains that certain factors were controlled for in the analysis.</p>
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## VERSION 1 – AUTHOR RESPONSE

### Reviewer: 1

#### Comments to the Author

This is an important paper testing a new clinical definition in a cohort of patients. I enjoyed reading it. My major issues are:

1. Whilst the authors did a sample size calculation, this was only to look at differences between those diagnosed SEID positive and those diagnosed as SEID negative in a relatively small, predefined cohort. I am not convinced by the authors second aim. They say “2) evaluate the discriminant validity of the SEID criteria by investigating differences in baseline characteristics and disease markers between SEID-positive and SEID-negative patients.” As these are all patients who the authors have diagnosed as having CFS/ME, I do not believe they are evaluating the discriminant validity but I think they are comparing differences.....I would therefore change this aim to: “evaluate the SEID criteria by investigating differences in baseline characteristics and disease markers between SEID-positive and SEID-negative patients.”

*We agree, and have rephrased the aim accordingly. Also, the title and abstract of the manuscript have been altered.*

2. In the abstract, the authors say they used the outcome at 30 weeks to “investigate prognostic validity of the criteria”. Given these patients have CFS/ME and the SEID definition is post hoc, I think they are merely investigating differences at 30 weeks between those who were given the SEID diagnosis compared to those who weren’t. This is also true for the statistical methods section on page 9 and elsewhere.

*We agree, and have revised the paper – including the title and the abstract- accordingly*

3. In the strengths and limitations, please remove “relatively high number”. This is not a high number in a pre-defined cohort to investigate diagnostic criteria in an illness which is heterogenous....

*Done!*

I have a few minor comments:

The paragraph in the introduction needs to be softened: “The pathophysiology of CFS remains poorly understood, but multiple studies have demonstrated certain characteristics such as: Attenuation of the hypothalamus–pituitary–adrenal axis (HPAaxis)[8,9] which may be associated with PEM,[10] altered autonomic cardiovascular control,[8,11,12] and impaired cognitive function

*The paragraph has been softened in the revised version of the manuscript*

Page 4, line 24 “neither” should be “either”.

*Done*

The sentence at the end of the introduction: “we based inclusion on a broad case definition, and hypothesized differences between the SEID-positive and SEID-negative groups regarding disease markers and prognosis.” Does not add anything to this paper....What were your hypotheses prior to analyses?

*The sentence has been removed, as suggested.*

The authors make a very important point that they excluded those with clinically diagnosed depression from the project. This is important in terms of understanding the issues, and could be strengthened in the abstract and elsewhere.

*Thank you, the paper – including the abstract - has been revised accordingly.*

## **Reviewer: 2**

### Comments to the Author

I must congratulate you on your comprehensive analysis of what seems to be a large cohort of 120 patients. I see this paper not as a criticism of SEID criteria but an addition to the SEID criteria. Apart from a couple of typos (on page 12, you meant fatigue or fatigued?), there are no major corrections that I would advise. Once again, congratulations!

*Thanks a lot! The typos have been corrected.*

## **Reviewer: 3**

### Comments to the Author

The background detail regarding the need for validation of the SEID is described well and possibly this should be reflected more clearly in the title. The methodology however is difficult to follow, particularly with regards to this study utilising data from an earlier clinical trial. The implication of the clinical trial is not considered sufficiently and it is not always clear exactly what data is being referred to. I have some specific comments:

1. How were CFS patients identified for the RCT, what scale was used? Furthermore in order to validate any scale it is important to understand the specificity to ensure non-cases are identified as such and as far as I can tell the present study does not address this important and fundamental issue.

*We agree that the recruitment procedure and inclusion/exclusion criteria for the original RCT (and thus for the present study) should be explained in more detail. In the revised version of the manuscript, the relevant paragraph has been expanded.*

*As for the SEID subgrouping, no single scale was used; instead, we developed operationalized SEID-criteria based upon multiple inventories, and applied these criteria to our patient material. This approach has been specified in the revised version of the manuscript. Furthermore, the operationalized SEID-criteria is published as an online supplementary.*

2. Patients are divided into SEID positive and negative but it is not explicitly stated this is at baseline, furthermore reference to baseline characteristics in the background (this is probably not in the correct section) is confusing because we do not know what this baseline is for. Similarly aim 3 is to evaluate prognostic validity – but we do not know what outcome this is for and for when.

*We agree. In the revised version of the manuscript, these points have been clarified.*

3. A brief sentence explaining the aim of the RCT would be helpful

*We agree, and have included a sentence on aim of the original RCT in the revised version of the manuscript.*

4. Mood and SEID are confounded so I am not sure what conclusions can be drawn

*We agree with the reviewer that mood and SEID are confounded. In the revised manuscript, we therefore emphasize that patients with clinically depression were not allowed to enter the original RCT; still, the SEID criteria tends to select patients with higher depression symptom burden.*

5. It is good the authors have considered the impact of multiple testing on their results and have corrected for 44 tests. I think it would have been preferable to have a more focussed study question and hypothesis.

*Thank you. The study aim and hypothesis has been rephrased according to recommendations from reviewer #1, cf. above.*

6. I am not sure the Difference column in Table 4 accurately reflects the adjusted effect, although I see the footnote explains that certain factors were controlled for in the analysis.

*Both the differences and the p-values have been adjusted in ANCOVA models, as has been specified in the revised version of the manuscript.*

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Crawley, Esther University of Bristol Competing interests: None
<b>REVIEW RETURNED</b>	22-Dec-2017

<b>GENERAL COMMENTS</b>	<p>Thank you for making the changes. I think this is now a better paper. Just a couple of minor comments to improve the readability:</p> <p>In the abstract you say: Despite clinically depressed patient were excluded I think you mean: Despite the fact that clinically depressed patients....</p> <p>You also say "suggesting mood disorder" when you mean "suggesting a mood disorder". In the introduction please delete "Despite ample research". There is good evidence that there is insufficient research, particularly for biomarkers.</p> <p>In the discussion: please change "A strength of this study is few missing data." to "A strength of this study is the low rate of missing data" or something similar.</p>
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#### VERSION 2 – AUTHOR RESPONSE

##### Reviewer: 1

In the abstract you say: Despite clinically depressed patient were excluded  
I think you mean: Despite the fact that clinically depressed patients....

*We agree, the sentence has been changed, as suggested.*

You also say "suggesting mood disorder" when you mean "suggesting a mood disorder".

*We have changed the phrase accordingly the three times it occurs in the text.*

In the introduction please delete "Despite ample research". There is good evidence that there is insufficient research, particularly for biomarkers.

*Done!*

In the discussion: please change "A strength of this study is few missing data." to "A strength of this study is the low rate of missing data" or something similar.

*The sentence has been changed as suggested.*