Author's response to reviews

Title: Development of a validated Patient Reported Symptom Metric for Pediatric Eosinophilic Esophagitis: Qualitative Methods

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Version: 2 Date: 26 August 2011

Author's response to reviews: see over
Dear members of the Biomed Central editorial staff and reviewers,

We appreciate the thoughtful review of this manuscript and have revised the manuscript in accordance with all of the reviewers’ questions and suggestions. The specific responses to each item are detailed below.

Response to Reviewers:

Editor

Comment 1. Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate. Please also indicate whether patients gave informed consent to participate in the study. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

Response: The manuscript has been revised to reflect these important points. These statements have been included in the Methods section, lines 123-127.

Referee #1

Comment 1. Overall this is a well conducted study which addresses an important issue. The manuscript is generally well written and clear. The authors are the first to rigorously develop such a metric for children with eosinophilic esophagitis and as such I believe this paper to be of importance to the scientific community. There is a discrepancy between the numbering of tables in the text and on the tables themselves. This appears to be a simple numbering error, in the section “Methods - Cognitive Interviews” the paper refers to table 2, I believe they mean table 1. In the section “Results – Cognitive Interview
Patient Self-Report” the paper refers to table 3, I believe they mean table 2. My apologies if I have misunderstood this but I do believe that it needs review and correction. This comment has been addressed in the response to the editor comment #1.

**Response:** Thank you for your review of our manuscript. We have carefully reviewed all of the numbering of tables in the text and on the tables themselves and have corrected all inconsistencies. Specifically, lines 150, 176, 185, 215 and 243.

**Comment 2.** Participants the authors do not mention GERD as a co-morbidity which was excluded from the population studied. Was GERD excluded? If not, a brief explanation of the reasons for this would be helpful.

**Response:** We have reviewed all of the abstraction forms for past medical history, and there were no patients with a clinical diagnosis of GERD and eosinophilic esophagitis. We have added this to the exclusion criteria in lines 145-146.

**Comment 3.** In the section “Methods – Cognitive Interviews” the authors should provide a brief description of the demographic details of this population of 39 children. This could be placed either in the methods but may be more appropriate in the results section. Age and sex data should be included, as well as the number of children in the 8-12 age category and the number in the 13-18 category.

**Response:** The manuscript has been revised to reflect these important points and is noted a new Table 3, line 497.

**Comment 3.** In the pdf document I was able to review there is an unlabeled table which I presume to be table 3. In the final column, the question “How bad is the trouble swallowing?” is repeated, I believe that the upper should read something along the lines of “How often do you have trouble swallowing?” but this needs to be corrected. The bottom of Table 3 appears to be cut off the page but I presume this is an issue with manuscript conversion.

**Response:** The manuscript has been revised to reflect these important points in the revised Table 4.

**Comment 4.** In the section “Methods – Focus Interviews” the authors describe how disagreements were resolved through discussion. Was there an arbiter who held the final decision when disagreements arose? If so, this could be noted.

**Response:** Disagreements were minor and easily resolved by further discussion and then consensus within the group in lines 159-160.

**Comment 5.** In the section “Methods – Expert Opinion” it would be helpful to know how many experts were consulted on this and how many were outside the authorship of the paper. I am presuming the 4 acknowledged experts are the ones referred to but this could be clarified in the manuscript.
Response: The manuscript has been revised to reflect the number of experts consulted that are listed in the acknowledgements in lines 163, and lines 363-364.

Comment 6. I would argue that in the section “Conclusion” the authors could go further with their statement and suggest that PROs are more important as an outcome measure than histological findings, given the nature of this condition.

Response: Thank you. We have revised the manuscript in lines 338-340.

Referee #2

Comment 1. This paper described the development of the PEESS™ v2.0, a patient-reported symptom assessment tool for children with EoE. Given that the PEESS version 1.0 was developed without patient input, a key step in developing patient-reported outcomes, the authors performed concept elicitation interviews with patients and parents to identify any missing content and to draft the PEESS™ v2.0 instrument. Cognitive interviews were then conducted to address issues with understanding and interpretation, and revisions were made based on these results.

The authors should note that this is not the first study to assess content validity of patient and parent-completed symptom assessment tools or EoE. See Flood et al., Patient and caregiver perspective on pediatric eosinophilic esophagitis and newly developed symptom questionnaires. Curr Med Res Opin. 2008 Dec; 24(12):3369-81.

Response: Thank you for your careful review of our manuscript. We have included the reference by Flood et al., “Patient and caregiver perspective on pediatric eosinophilic esophagitis and newly developed symptom questionnaires.” Curr Med Res Opin. 2008 Dec; 24(12):3369-81. We have revised the manuscript to reflect this important point in lines 95-116, lines 302-304, and lines 417-420. However, our manuscript is unique in that the symptoms were generated from patients themselves in the focus interview phase, and then reviewed by a separate cohort in the cognitive interview phase. The Flood et al. metric was generated by experts first, and then patients were asked to review this metric and comment on this metric (only a cognitive interview phase). The inclusion/exclusion of specific details in this metric was determined by experts and not by the patients themselves. In contrast, the PEESS™ v2.0 really began with open ended questions and specific patient generated language was used to develop questions. The general categories of symptoms in the PEESS v1.0 were used in open-ended question format that are similar categories to what Flood et al. had developed. Examples of specific patient generated items and language are described in Table 4. We clarify these differences in lines 95-98, 117-120, 150-151 and 257-262.

Comment 2. Additionally, with respect to symptom assessment tools, there is a general move toward daily assessments through electronic diaries, at least in the trial setting.

Response: Daily assessments through electronic diaries are another option to capture patient reported outcomes. However, this in no way negates the validity of
numerous validated metrics with different methodologies that include what is being described in this manuscript. In addition, the PEESS™ v2.0 is intended for use both in and outside the clinical trial setting. We considered using daily electronic diaries, but we have found the patient response burden too high, and that they are impractical for any research but a highly funded and closely regulated clinical trials. This has been included in the discussion lines 311-317.

Comment 3. The one-month recall period is of particular concern.

Response: Thank you for this important comment. The use of a 1 month recall period has been widely utilized by Varni and others in over 625 Pediatric Quality of Life Inventory™ (PedsQL™) peer-reviewed journal publications since 2001. This is also true of the widely used SF-36 for adult patients. In addition, The Mayo Dysphagia Questionnaire developed by Romero and colleagues was shown not to be responsive over a 14 day recall period, but was responsive over a 30 day (1 month) recall period (reference 26). In future studies, we will be conducting responsiveness testing of the PEESS™ v2.0 metric, and will be assessing different recall periods – 1 week, 2 week and 1 month. This has been included in the discussion lines 305-311 and references 18-26 have been provided (lines 427-457).

Comment 4. And finally, per FDA, parent proxy tools are generally not accepted. Parent observer tools are accepted, but the items can only be symptoms that would be clearly observed by the parent. Pain, for example, would not be included in a parent observer tool.

Response: Thank you for this important comment. The PEESS™ v2.0 is intended for use both in and outside the clinical trial setting. We agree that the current thinking at the FDA is that for child ages 2-7 years of age that parent observer tools are recommended for symptoms that would be clearly observed by the parent. For FDA endorsed clinical trials that would use the PEESS™ v2.0, it may be that we are only able to obtain specific PRO based labeling for children ages 8-18 years of age. Another possibility is that the symptoms within the PEESS™ v2.0 that are “observable” such as vomiting, long time to eat, drinking a lot of liquids to swallow food may represent a subscale of questions that are able to be used for clinical trials in children 2-7 years of age who have these particular symptoms. However, it is also important to recognize that the thinking around PROs in the FDA for labeling purposes has changed significantly in the past several decades. Therefore, the current thinking on parent-proxy metrics that are widely supported by many psychometricians and clinicians alike may also change. In future studies, we will be conducting responsiveness testing of the PEESS™ v2.0 metric, we can further assess the parent proxy metric and specific subscales. This has been included in the discussion lines 277-292.

Comment 5. Consider replacing “focus interviews” with “concept elicitation interviews”, which is now the commonly used term in PRO research
**Response:** We have added this in parentheses after the term focus interviews is first presented in line 148, but we prefer the term focus interviews given the widespread use of this term in the larger survey research literature.

**Comment 6.** Objective should be clarified. As I understand it, your objective was to assess the content validity of the PEESS™ v2.0 and revise it based on patient and parent input, thereby establishing its content validity.

**Response:** This is a very important point that we have hoped to clarify in our revisions in lines 150-151. Please see the response to comment #1.

**Comment 7.** Results section seems to include methods and conclusions and few results. Second-to-last sentence describes the methods. The last sentence is more of a conclusion. I would recommend that you report what the patients told you about symptoms and the specific changes you needed to make after cog debriefing. Background: First paragraph, last sentence. Not accurate per above.

**Response:** We have revised the methods and results section in lines 187-193 and in 219-220.

**Comment 8.** “Proxy” should be replaced with parent “observer” throughout. As noted above, proxy measures are not acceptable by FDA. Only symptoms that the parent can observe should be included in the measure (i.e., a parent cannot assess pain, or difficulty swallowing, etc. Only things like vomiting, trouble sleeping, etc., should be included.)

**Response:** Please see response to Comment 4. The term “Parent proxy-report” is widely used in the pediatric HRQOL research literature, and is the preferred term for consistency with this larger literature.

**Comment 9.** Clarify the objective as noted above. Are you developing a new PRO or assessing content validity of an existing PRO and updating it based on your findings?

**Response:** Please see responses above. This has been added to the discussion lines 256-262. This is a new metric.

**Comment 10.** Need a description of the sample – number per age group, males/females, etc.

**Response:** We have included a new Table 3 and in lines 184-185 to address these important points.

**Comment 11.** More details on concept elicitation results would be useful. What symptoms were reported and how frequently? How were they described by children? Which ones were considered most severe or most troubling? What symptoms were missing from PEESS v1? Any differences by age group: 8-12 vs. 13-17?
Response: Please see response to comment 1 and Table 4. The PEESS v1.0 general categories of symptoms were used as a guide for open ended questions - how patients described nausea, vomiting, abdominal pain, chest pain, heartburn, regurgitation, dysphagia, food impaction, poor appetite and early satiety. The key issue of the PEESS v1.0 vs PEESS™ v2.0 was that the PEESS v1.0 used medical terminology that was incomprehensible to the patients. Not necessarily what symptoms were not included, rather the difference between how patients and physicians view them. This has been added to the discussion lines 259-262.

Comment 12. Sample size could be considered low, particularly given the age range and variability of symptoms. Did you reach information saturation? Assessment of saturation should be added.

Response: Item saturation assessment was provided by the cognitive interviews with the specific questions provided in Table 4. In particular the items question, “how would you change the questions words to make it easier to understand,” and the overall assessment, question “is there things that we forgot to ask about that you feel are important?” These questions were asked to the patients themselves in the 8-18 year old age range, and to the parents in the 2-18 year old age range. Item saturation was achieved for each question and the questionnaire as a whole during the cognitive interviews for each age range as determined by the fact that no new information was requested by subsequent participants. This has been added to the manuscript in lines 2903-304.

Comment 13. Recall period is of particular concern. One month is quite long, particularly for children, and in trials, symptoms are generally assessed in a daily diary format with a 24-hour recall period. Was recall explored during cognitive debriefing? If so, results should be included. Do you have a rationale for a one-month recall period?

Response: Please see response to comment 2, 3 and Table 4. Yes was explored in cognitive debriefing, and has also been added to the discussion in lines 305-314.

Comment 14. There is mention of a VAS, but the graphic doesn’t seem to have a VAS. Do children provide their responses using a VAS?

Response: It is more correct to describe our scale as a combination of a pictorial scale and a Likert’s scale rather than a visual analog scale. The manuscript has been revised to reflect these important points in lines 274-276.

Comment 15. If you do not want to include the measures themselves, a more detailed description of the final versions of each would be useful – X items covering the following symptoms, scored on a Likert? VAS? scale, etc.

Response: We have provided the metrics for your review. The metrics have been copyrighted, and will not be published with the manuscript, but available at (www.mapitrust.org). This has been added to lines 328-329.
**Comment 16.** Discussion is a bit lean. Would add reference to Flood et al and compare findings with respect to symptoms assessed in the respective measures. Also perhaps discuss differences by age, if any exist.

**Response:** We have revised the discussion as suggested in lines 256-262, and in lines 277-329.

**Comment 17.** Need to add study limitations.

**Response:** We have provided study limitations as suggested in lines 318-329.