Reviewer’s report

**Title:** The Efficacy and Safety Study of Electro-acupuncture for Severe Chronic Functional Constipation - a Multicenter, Randomized Controlled Trial

**Version:** 1  **Date:** 15 March 2013

**Reviewer:** Michael Camilleri

**Reviewer’s report:**

The protocol manuscript follows closely the sections proposed by the journal except for a minor change in the order with acknowledgements ahead of authors' contributions and authors' information located on the title page.

**Comments:**

1. **Will the study design adequately test the hypothesis?**

   In general, the study design would adequately test the hypothesis although there are enhancements to the study that would enhance the quality of the result and make the study more consistent with recent high quality RCTs in chronic functional constipation. It is relevant to note that the sample size proposed is appropriate for the primary endpoint and effect size to be demonstrated, if one accepts the proposed endpoint. Therefore, it is acknowledged that the current design would adequately test the proposed hypothesis. However, the endpoint does not reflect current state-of-the-art.

   The areas of enhancement of the clinical trial are listed below:

   **A.** Given that it is estimated that ~25% of patients with chronic constipation patients evaluated in gastroenterology practice have evidence of pelvic floor dysynergia or rectal evacuation disorder (Gut 61:1132-1139, 2012), the exclusion criteria should detail how such patients will be either excluded or equally distributed in the two treatment arms. Symptoms criteria for chronic functional constipation are insufficient to exclude evacuation disorder e.g. they permit up to 25% of days with sense of incomplete evacuation in the Rome criteria of functional constipation.

   **B.** Duration of trial: the recent literature and FDA guidance suggests that trials should be of 12 weeks’ duration

   **C.** Primary Endpoint: The current recommendation is to use a composite endpoint of at least 3CSBM per week plus at least 1 CSBM per week over baseline (2 week observation with diary, not just recall); this composite result has to be recorded in at least 9 of 12 weeks including at least 3 of the last 4 weeks (9-12) of the 12 week trial. The current primary endpoint would be an appropriate secondary endpoint.
D. Power: The sample size will have to be adjusted according to the revised primary endpoint

E. Missing data imputation by the “multiple imputation method” needs to be more clearly spelled out and any correction for alpha based on the number of data imputed will be relevant.

2. Are sufficient details provided to allow replication of the work or comparison with related analyses: if not, what is missing?

The protocol provides sufficient detail to allow replication. Additional details of the follow up period after the 8 week RCT period are needed e.g. how will treatment be standardized, what about concomitant medications. If this is not “controlled” the data at 12, 16 and 20 weeks cannot be used to appraise longer term efficacy after cessation of the active treatment period.

3. Is the planned statistical analysis appropriate?

The proposal of the statistical analysis of the main efficacy outcome is to use a one-side because the study is designed to demonstrate superiority. This is unacceptable for most RCTS and it is certainly conceivable that the active treatment arm may show worse outcomes than the sham arm. Therefore 2-sided tests should be applied to the primary endpoint, as authors propose for the secondary endpoints.

4. Is the writing acceptable?

English language editing is required e.g. portion of participants should be proportion. Reference 3 and 15 are identical.