PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Electroacupuncture plus standard care for managing refractory functional dyspepsia: Protocol of a pragmatic trial with economic evaluation
AUTHORS	Chung, Vincent; Wong, Charlene HL; Ching, Jessica YL; Sun, WZ; Ju, YL; Hung, Zevari SS; Lin, WL; Leung, KC; Wong, Samuel; Wu, Justin

VERSION 1 – REVIEW

REVIEWER	Wei Wei Wangjing Hospital of China Academy of Chinese Medical Sciences, China
REVIEW RETURNED	15-Aug-2017

GENERAL COMMENTS	The clinical trial elaborated in this protocol aims to determine the effectiveness and cost effectiveness of electroacupuncture, and there are several issues that need to be clarified before accepting this protocol. 1. In page 9 of 51, the PDS of FD patients will be enrolled as detailed in the inclusion criteria, however, in the paper of ethical approval supplied in page 35 of 51, the study protocol title is “electoacupuncture plus standard care for managing refractory functional dyspepsia: pragmatic randomized trial with economic evaluation”, and it seems like the potential targeted population is refractory functional dyspepsia patients different with the inclusion criteria. Are there any alterations in the original trial designs? Please supply relative explanations or ethical approval papers. 2. In page 11 of 51, please supply the specific locations of selected acupoints and the standards of locating these acupoints. 3. In page 12 of 51, according to the method of interventions, the CV 12 and ST 42 will not be applied with EA and the BL 20 and BL 21 will be adopted with fast acupuncture, and how to determine and exclude the effects caused by these acupoints which will influence the effects of EA, because the aim of this clinical trial is to explore the effectiveness of EA. 4. In data collection methods, it is only for the primary endpoint to use one method to ensure the consistency, and are there any similar considerations in other outcomes? 5. In page 16 of 51, please supply the specific supports of the conservative estimation of the 10% improvement in control group and 30% improvement in intervention group, and provide the formula or software used in the estimation of sample size.

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	6. In page 17 of 51, based on the blinding designs, blinding of data analysts will be ensured, and please provide the name of the third party of data analysis in corresponding paragraph. 7. Few language mistakes should be rechecked, such as in the 20th line in page 14 of 51.

REVIEWER	Sanjiv Mahadeva University of Malaya Kuala Lumpur Malaysia
REVIEW RETURNED	20-Aug-2017

GENERAL COMMENTS	Summary This is a protocol for a single-centre study in Hong Kong examining the efficacy of Electroaccupuncture (EA) with on-demand antacids (Gastrocaine) (Study group) vs antacids alone in the control group over a 12-week period. EA is an established treatment in this region & there are sufficient qualified EA practitioners for this study to be conducted. Although studies on EA therapy for FD have been published, more data is welcome in this area of gastroenterology. I have a few minor comments on several components of the study protocol. 1. Introduction – 2.1, 3rd paragraph The authors are describing the impact of FD in Hong Kong & perhaps Asia. There is an inappropriate reference to the economic impact of FD in the US – "In US, costs incurred by FD……" I would suggest quoting Asian studies which have described the economic impact of FD – as the relevance of this study is mainly in an Asian setting. 2. Introduction – 2.2 There is insufficient rationale for the use of EA in this study. More should be mentioned in this section. I suggest bringing forward information regarding previous studies on EA, provided in Section 5.1 & 5.6 to this section 3. Objective – 3 The study design is not very clear. Why is the control group labelled as "on a waiting-list for EA"? Does this imply that EA is an established therapy for FD ? In the manner that the protocol is written, the study design is that of EA + Gastrocaine (study group) vs Gastrocaine alone (control group) – it is not clear why the control group is on a waiting list for EA therapy. 4. Trial Design, pg 8 There is no reference provided for the use of Gastrocaine as the control. Antacids are not known to be effective in FD, so there should be some rationale for using this as the control. Would a control group of Proton Pump Inhibitor (PPI) therapy or Prokinetics (especially in PDS) not be better – there is more evidence for PPI use in FD than antacids. The authors mention that the study is designed to provide pragmatic evidence to Gastroenterologists – but Gastroenterologists would not normally use antacids for the treatment of FD.

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	5. Methods – 5.4.3 The evaluation of Anxiety & Depression is to be commended. Would the Hospital Anxiety & Depression (HAD) questionnaire not be sufficient for this purpose? 6. Sample size – 5.6 This is based on an estimated 20% difference in symptoms between study & control groups – does this refer to global symptoms or individual dyspepsia symptoms ? 7. Blinding – 6.4 The lack of blinding by assessors will be an obvious limitation in the study design. I believe the authors have covered this limitation appropriately

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comment 1:
In page 9 of 51, the PDS of FD patients will be enrolled as detailed in the inclusion criteria, however, in the paper of ethical approval supplied in page 35 of 51, the study protocol title is "electoacupuncture plus standard care for managing refractory functional dyspepsia: pragmatic randomized trial with economic evaluation", and it seems like the potential targeted population is refractory functional dyspepsia patients different with the inclusion criteria. Are there any alterations in the original trial designs? Please supply relative explanations or ethical approval papers.

Response to Comment 1:
We have amended the title of the manuscript so it is now consistent with the registration title as well as the title we used for applying ethical approval. The current title is "Electroacupuncture plus standard care for managing refractory functional dyspepsia: Protocol of a pragmatic trial with economic evaluation".
With regards with inclusion criteria, we would like to clarify that we only recruited functional dyspepsia patient who are refractory to conventional treatment. This is defined as voluntary discontinuation of any conventional pharmacological treatments for their functional dyspepsia 2 weeks prior to enrolment, due to perceived ineffectiveness. This has been clarified in Section 5.2 of the revised manuscript.

Comment 2:
2. In page 11 of 51, please supply the specific locations of selected acupoints and the standards of locating these acupoints.

Response to Comment 2:
For acupoints locations and standards for locating these points, we followed the WHO Western Pacific Region standard.[1] Detailed information can be found in Table 1 in the revised manuscript. This has been clarified in the Section 5.3.1 of the revised manuscript.

Comment 3:
3. In page 12 of 51, according to the method of interventions, the CV 12 and ST 42 will not be applied with EA and the BL 20 and BL 21 will be adopted with fast acupuncture, and how to determine and exclude the effects caused by these acupoints which will influence the effects of EA, because the aim of this clinical trial is to explore the effectiveness of EA.

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Response to Comment 3:
We chose not to apply EA at ST42 and CV12, respectively due to its proximity with the dorsalis pedis artery, and a lack of coupling acupoint. Also, we did not apply electro-simulation at BL20 and BL21 as it is impossible for patients at supine position to receive EA at these two points over the course of treatment. That said, EA remains to be the main modality evaluated in this trial as electro-simulation at the acupoints of ST34, ST36, ST40 and PC6 remained to be much longer than the brief mechanical simulation at BL20 and BL21. We did not locate any high quality evidence demonstrating the impact of mechanical acupoint simulation on the treatment outcome of EA. This has been clarified in the Section 5.3.1 of the revised manuscript.

Comment 4:
4. In data collection methods, it is only for the primary endpoint to use one method to ensure the consistency, and are there any similar considerations in other outcomes?

Response to Comment 4:
To ensure consistency in data collection method, all data for all outcomes will be collected via standardized interview by trained, blinded assessors. This has been clarified in Section 5.4.

Comment 5:
5. In page 16 of 51, please supply the specific supports of the conservative estimation of the 10% improvement in control group and 30% improvement in intervention group, and provide the formula or software used in the estimation of sample size.

Response to Comment 5:
The sample size was calculated on the basis of the following hypothesized change in primary outcome (binary assessment of adequate relief, see Section 5.4.1 for details): intervention group is superior to control group by 20% in providing adequate relief of symptoms in patients with FD of PDS subtype. Investigation of the natural history of FD demonstrates that 60% of patients will remain symptomatic over a long period of time.[2] Conservatively, it can be expected that only 10% of patients in the control group would improve, given the fact that their condition is of refractory nature and no active treatment were provided. Taking into account expert consensus based minimally important clinical difference of 20%,[3] it is expected that 30% of intervention group patients would improve if additional EA were deemed valuable. Our estimation of an improvement of 30% from baseline among intervention group patients should be considered conservative, as results from previous published trials using EA for FD showed much larger effect sizes. In a trial conducted by Zeng et al.,[4] FD patient receiving EA showed 53.8% improvement in distension; and 61.0% improvement in early satiety. In another trial conducted by Ma et al.,[5] 70.7% of FD patients receiving EA showed marked improvement or had become symptom free.

In order to achieve 80 % power, with a significant level at 5 %, 118 patients are required. Assuming that refusal of follow-up will occur in 10% of patients, a minimum of 66 patients are required in each arm of the study. The total number of patient to be enrolled will therefore be 132. The power calculation was based on two independent proportion test, using PASS 13 (v13.0.13), NCSS Statistical Software.
The above has been clarified in Section 5.6.

Comment 6:
6. In page 17 of 51, based on the blinding designs, blinding of data analysts will be ensured, and please provide the name of the third party of data analysis in corresponding paragraph.

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Response to Comment 6:
Prof Ben Yip and Dr Irene Wu from the Chinese University of Hong Kong, who are not involved in the conduct of this trial, will perform the data analysis. This has been clarified in Section 6.4.

Comment 7:
7. Few language mistakes should be rechecked, such as in the 20th line in page 14 of 51.

Response to Comment 7:
We would like to thanks the reviewer for pointing out the mistakes, and careful editing on the current submission has been conducted.

Reviewer: 2
Comment 1:
Summary
This is a protocol for a single-centre study in Hong Kong examining the efficacy of Electroaccupuncture (EA) with on-demand antacids (Gastrocaine) (Study group) vs antacids alone in the control group over a 12-week period. EA is an established treatment in this region & there are sufficient qualified EA practitioners for this study to be conducted. Although studies on EA therapy for FD have been published, more data is welcome in this area of gastroenterology. I have a few minor comments on several components of the study protocol.
1. Introduction – 2.1, 3rd paragraph
The authors are describing the impact of FD in Hong Kong & perhaps Asia. There is an inappropriate reference to the economic impact of FD in the US – "In US, costs incurred by FD……"
I would suggest quoting Asian studies which have described the economic impact of FD – as the relevance of this study is mainly in an Asian setting.

Response to Comment 1:
Thanks very much this suggestion and we have searched for relevant Asian studies but there were only a few publications in this area. We have added the following in Section 2.1 to replace the US study results:
"In a Malaysian study, the annual cost of dyspepsia in 1,000 population was $USD14,816.10 and $USD59,282.20 respectively in rural and urban populations. Among rural and urban adults, respectively the cost per quality adjusted life year was $USD16.30 and $USD69.75.[6] It is probable that differences in sociodemographic, health service utilization pattern, and clinical factors are contributing to cost variation in different settings.[7] In South Korea, economic analysis using data from the National Health Insurance Corporation database also indicated that functional GI disorder represents a severe burden to the health system.[8]"

Comment 2:
2. Introduction – 2.2
There is insufficient rationale for the use of EA in this study. More should be mentioned in this section. I suggest bringing forward information regarding previous studies on EA, provided in Section 5.1 & 5.6 to this section

Response to Comment 2:
We have brought forward information regarding previous studies on EA at Section 5.6 to this section. Also, we have quoted additional evidence on the effectiveness of EA for functional dyspepsia in this Section to support the role of EA. The following has been added in Section 2.2.:
Existing trials support the effectiveness of EA in managing functional dyspepsia. In a trial conducted by Zeng et al.,[4] FD patient receiving EA showed 53.8% improvement in distension; and 61.0% improvement in early satiety.

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In another trial conducted by Ma et al.,[5] 70.7% of FD patients receiving EA showed marked improvement or had become symptom free. In a recent network meta-analysis, it is demonstrated that EA is superior to using itopride alone for symptom relief.[9]

Comment 3:
3. Objective – 3
The study design is not very clear.

Response to Comment 3:
The study design is randomized controlled trial. The flow of the trial is reported in accordance to the CONSORT requirement, and details are provided in Figure 1.

Comment 4:
Why is the control group labelled as “on a waiting-list for EA”? Does this imply that EA is an established therapy for FD ? In the manner that the protocol is written, the study design is that of EA + Gastrocaine (study group) vs Gastrocaine alone (control group) – it is not clear why the control group is on a waiting list for EA therapy.

Response to Comment 4:
In order to incentivize control group patients to stay in the trial, we offered the same EA package as patient in the intervention group does once they complete all follow-up assessment. This is an essential step in ensuring low drop-out rate the control group. As shown in Figure 1, all measurements are performed prior to the receipt of EA treatment for control group patients, and therefore this will not contaminate trial results. It should be emphasised that in Hong Kong, EA is an established treatment modality in Chinese medicine practice, which is under statutory regulation of the Chinese Medicine Council of Hong Kong.[10]
We have highlighted this point at Section 5.3.2.

Comment 5:
Would a control group of Proton Pump Inhibitor (PPI) therapy or Prokinetics (especially in PDS) not be better – there is more evidence for PPI use in FD than antacids.

Response to Comment 5:
Since we are recruiting patients who would like to discontinue conventional pharmacological treatment due to perceived ineffectiveness, the regular use of PPI and prokinetics as control will not be an appropriate for these patients. We have highlighted this point at Section 5.3.2.

Comment 6:
4. Trial Design, pg 8
There is no reference provided for the use of Gastrocaine as the control. Antacids are not known to be effective in FD, so there should be some rationale for using this as the control… The authors mention that the study is designed to provide pragmatic evidence to Gastroenterologists – but Gastroenterologists would not normally use antacids for the treatment of FD.

Response to Comment 6:
In this trial, gastrocaine is a rescue medication to be used in an on-demand basis in both groups. It can only be considered as a baseline treatment for both groups, not a control treatment. While evidence on antacids for FD is unclear due to a lack of placebo controlled trial, it continues to be used by many clinicians and patients worldwide.[11] Antacids can alleviate acid-related symptoms such as abdominal pain and burning sensations, and it may also enhance angiogenesis, bind to bile acid and also reduce peptic activity.

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[12] From the pragmatic perspective of this trial, antacid is a suitable baseline treatment for a recurrent condition like FD as they are available without prescription, and are affordable.[13] This choice will allow us to generate real world evidence on the value of EA in routine practice.
We have highlighted this point at Section 5.3.2.

Comment 7:
5. Methods – 5.4.3
The evaluation of Anxiety & Depression is to be commended. Would the Hospital Anxiety & Depression (HAD) questionnaire not be sufficient for this purpose?

Response to Comment 7:
We did not choose HAD as the underlying structure of this questionnaire is inconsistent across samples, and is highly dependent on the statistical methods used to establish that structure. This implies that the HADS is not a dependable means of differentiating anxiety and depression for the purposes of assessing the absolute or relative levels of these variables.[14] Recently, there has been call for abonnement of HAD[15] [16], and therefore we have chosen PHQ9 and GAD7 instead. We have highlighted this point at Section 5.4.3.

Comment 8:
6. Sample size – 5.6
This is based on an estimated 20% difference in symptoms between study & control groups – does this refer to global symptoms or individual dyspepsia symptoms?

Response to Comment 8:
As mentioned in the original submission, the sample size was calculated on the basis of the following hypothesized change in primary outcome, which is the binary assessment of adequate relief (see section 5.4.1). This has been highlighted in Section 5.6.

Comment 9:
7. Blinding – 6.4
The lack of blinding by assessors will be an obvious limitation in the study design. I believe the authors have covered this limitation appropriately

Response to Comment 9:
Thanks very much for your comment.

References:
[1] World Health Organization. WHO standard acupuncture point locations in the Western Pacific Region. WHO standard acupuncture point locations in the Western Pacific region 2008.
[2] Halder SL, Locke GR, Schleck CD, et al. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. Gastroenterology 2007;133(3):799-807.
[3]Talley NJ, Locke GR, Herrick LM, et al. Functional Dyspepsia Treatment Trial (FDTT): a double-blind, randomized, placebo-controlled trial of antidepressants in functional dyspepsia, evaluating symptoms, psychopathology, pathophysiology and pharmacogenetics. Contemporary clinical trials 2012;33(3):523-33.
[4] Zeng F, Qin W, Ma T, et al. Influence of acupuncture treatment on cerebral activity in functional dyspepsia patients and its relationship with efficacy. The American journal of gastroenterology 2012;107(8):1236-47.
[5] Ma T, Yu S, Li Y, et al. Randomised clinical trial: an assessment of acupuncture on specific meridian or specific acupoint vs. sham acupuncture for treating functional dyspepsia. Alimentary pharmacology & therapeutics 2012;35(5):552-61.

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[6] Mahadeva S, Yadav H, Everett SM, et al. Economic impact of dyspepsia in rural and urban Malaysia: a population-based study. Journal of neurogastroenterology and motility 2012;18(1):43-57.
[7] Mahadeva S, Goh KL. East–West differences in the economic impact of functional dyspepsia. Alimentary pharmacology & therapeutics 2013;38(6):655-55.
[8] Jung H-k, Jang B, Kim YH, et al. Health care costs of digestive diseases in Korea. The Korean Journal of Gastroenterology 2011;58(6):323-31.
[9] Ho RS, Chung VC, Wong CH, et al. Acupuncture and related therapies used as add-on or alternative to prokinetics for functional dyspepsia: overview of systematic reviews and network meta-analysis. Scientific Reports 2017;7(1):10320.
[10] Griffiths S. Development and regulation of traditional Chinese medicine practitioners in Hong Kong. Perspectives in public health 2009;129(2):64-67.
[11] Overland MK. Dyspepsia. Medical Clinics 2014;98(3):549-64.
[12] Chen SL. A review of drug therapy for functional dyspepsia. Journal of digestive diseases 2013;14(12):623-25.
[13] Abdar Esfahani M, Ahmadi N, Keikha M, et al. Antacids, sucralfate and bismuth salts for functional dyspepsia. The Cochrane Library 2017
[14] Cosco TD, Doyle F, Ward M, et al. Latent structure of the Hospital Anxiety And Depression Scale: a 10-year systematic review. Journal of psychosomatic research 2012;72(3):180-84.
[15] Coyne JC, van Sonderen E. The Hospital Anxiety and Depression Scale (HADS) is dead, but like Elvis, there will still be citings. Journal of Psychosomatic Research 2012;73(1):77-78.
[16] Coyne JC, van Sonderen E. No further research needed: abandoning the Hospital and Anxiety Depression Scale (HADS). Journal of Psychosomatic Research 2012;72(3):173-74.

VERSION 2 – REVIEW

REVIEWER	Wei Wei Wangjing Hospital of China Academy of Chinese Medical Sciences, China
REVIEW RETURNED	19-Dec-2017

GENERAL COMMENTS	I'm satisfied with those responses to my previous reviews and have no further comments.

REVIEWER	Sanjiv Mahadeva University of Malaya Kuala Lumpur Malaysia
REVIEW RETURNED	13-Dec-2017

GENERAL COMMENTS	The authors have addressed my comments satisfactorily

VERSION 2 – AUTHOR RESPONSE

Response to Comment 1:
We have amended the abstract with the following sections: Introduction; Methods and analysis; Ethics and dissemination. We have included registration details as a final section. The updated abstract is shown below:

Abstract
Introduction:

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This trial proposes to compare the effectiveness and cost effectiveness of electroacupuncture (EA) plus on-demand gastrocaine with waiting list for EA plus on-demand gastrocaine in providing symptom relief and quality of life improvement among functional dyspepsia (FD) patients.

Methods and analysis:
Single-centre, pragmatic, randomized parallel-group, superiority trial comparing the outcomes of (1) EA plus on-demand gastrocaine group, and (2) waiting list to EA plus on-demand gastrocaine group. 132 (66/arm) endoscopically confirmed, H. pylori negative FD patients will be recruited. Enrolled patients will respectively be receiving (1) 20 sessions of EA over 10 weeks plus on-demand gastrocaine; or (2) on-demand gastrocaine and being nominated on to a waiting list for EA, which entitles 20 sessions of EA over 10 weeks after 12 weeks of waiting. Primary outcome will be the between group difference in proportion of patients achieving adequate relief of symptoms over 12 weeks. Secondary outcomes will include patient reported change in global symptoms and individual symptoms, Nepean Dyspepsia index (NDI), nutrient drink test (NDT), Patient Health Questionnaire (PHQ) 9, and PHQ section for anxiety (GAD7). Adverse events will be assessed formally. Results on direct medical cost and EuroQol (EQ-5D) questionnaire will be also used to assess cost effectiveness. Analysis will follow intention-to-treat principle using appropriate univariate and multivariate methods. A mixed model analysis taking into account missing data of these outcomes will be performed. Cost effectiveness analysis will be performed using established approach.

Ethics and Dissemination
The study is supported by the Health and Medical Research Fund, Government of the Hong Kong Special Administrative Region of China. It has been approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. Results will be published in peer-reviewed journals and be disseminated in international conference.

Trial registration number: ChiCTR-IPC-15007109

Comment 2:
2. The strengths and limitations section on page 4 needs shortening. As a reminder, this section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods of the study reported (see: http://bmjopen.bmj.com/site/about/guidelines.xhtml#articletypes). It should not be a summary of the study and its findings.

Response to Comment 2:
We have shortened the strengths and limitations section on page 4. Five short bullet points, which were specifically related to the methods of the study, were provided in this session. The updated strengths and limitations are shown below:

Strengths and Weaknesses of this study
• We did not use sham control in this trial as we aimed to determine the overall add-on benefit of electroacupuncture, where on demand gastrocaine is often used as a rescue treatment.
• From a pragmatic perspective, nonspecific benefits of acupuncture characterized by patient-reported outcomes may be interpreted as clinical effect instead of bias.
• To circumvent potential bias caused by the lack of blinding, we have included assessor-blinded objective outcomes (Nutrient Drink Test).
• We chose a 12-week follow-up duration, which is in line with current recommendations for trials on functional dyspepsia patients.
• In the future, multi-center trials will provide further evidence on the generalizability of study results.

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