PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Electro-acupuncture for post-stroke spasticity (EAPSS): protocol for a randomized controlled trial
AUTHORS	Cai, Yiyi; Zhang, Claire Shuiqing; Ouyang, Wenwei; Li, Jianmin; Nong, Wenheng; Zhang, Anthony; Xue, Charlie; Zehuai, Wen

VERSION 1 – REVIEW

REVIEWER	Javier Mata Son Llàtzer University Hospital, Spain
REVIEW RETURNED	14-Jun-2017

GENERAL COMMENTS	This study is a randomized paralleled controlled trial to determine the add-on effects and safety profile of electro-acupuncture (EA) for post-stroke spasticity (PSS) in addition to routine care (RC). Overall, this is a clear, novel and well-written manuscript. The introduction is relevant and theory based. The methods are generally appropriate. It is a good point that missing data will be replaced by multiple imputation method based on the intent-to-treat principle. Subgroup analysis will be conducted. The outcomes must be defined in the manuscript. The discussion and references must be reviewed. This paper has a potential to be accepted, but some important points have to be clarified or fixed before. Specific comments and recommendations are the following. Page 5 line 60 Trial registration Please update your clinical trial registration. Page 8 line 119. “It is designed following the instructions of SPIRIT 2013 Checklist (Appendix 1)” It must be added: Consolidated Standards of Reporting Trials (CONSORT) guidelines (figure 1) and STRICTA guidelines] for acupuncture studies Page 10 Table 1. EA, EA. The first letter of each word cannot be the definition of an acronym. (Electro-acupuncture) Page 12 line 186 The “routine care” must be change by “usual care”. The usual care intervention should be standardized to reduce bias, a detailed description must be provided, stating how these terms are defined within the trial. In addition, relevant references should be provided.

	In the routine care only the change of RC will be recorded? Page 13 line 194 In the intervention group: the sequence of treatments is EA + usual care or usual care + EA. Both treatments are in the same day? Page 13 line 205 The reference for the systematic Review is: Cai Y, Zhang CS, Liu S, Wen Z, Zhang AL, Guo X, Lu C, Xue CC. Electro-acupuncture for post-stroke spasticity: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2017 Apr 25. pii: S0003-9993(17)30257-5. doi: 10.1016/j.apmr.2017.03.023. [Epub ahead of print]. An acupuncture treatment protocol is a standardized, semi-standardized or fully individualized? The acupuncturists can select acupoints only from the list (LI4, LI10, LI11, LI15, TE5, GB34, LR3, SP6, ST36, ST40) or the can choose others too? Page 14 line 217 Why don´t use a biphasic wave (2Hz/120Hz) (altering every 2 seconds)? Page 14 line 226 Outcome measures and evaluation It is important to explain the rationale for the choice of trial outcomes: The Modified Ashworth Scale and is considered by many as the gold standard for measuring spasticity (Bohannon & Smith, 1987)". It is a 6-point scale (six different joints (shoulder, elbow, wrist, hip, knee and unkle), with a grade score of 0, 1, 2, 3, or 4 or grade "1+",where lower scores represent normal muscle tone and higher scores represent spasticity or increased resistance to passive movement. The rater should extend the patients' limb from a position of maximal flexion to maximal extension until the first soft resistance is felt. The Fugl-Meyer assessment (FMA) is one of the most widely recognized and clinically relevant measures of body function impairment after stroke. The scale is comprised of five domains and there are 155 items in total: motor functioning (in the upper and lower extremities), sensory functioning (evaluates light touch on two surfaces of the arm and leg, and position sense for 8 joints), balance (contains 7 tests, 3 seated and 4 standing), joint range of motion (8 joints), joint pain. The motor domain, which includes items assessing movement, coordination, and reflex action of the shoulder, elbow, forearm, wrist, hand, hip, knee, and ankle, has well-established reliability and validity as an indicator of motor impairment severity across different stroke recovery time points. The Functional Independence Measure (FIM) provides a uniform system of measurement for disability based on the International Classification of Impairment, Disabilities and Handicaps; measures the level of a patient's disability and indicates how much assistance is required for the individual to carry out activities of daily living. Limitations of the outcomes Modified Ashworth Scale • Adequate training is required to ensure inter-rater reliability • Reliability differs from muscle to muscle • Assessment technique must be standardized • Some critics question the validity of the Ashworth scale and Modified Ashworth Scale in measuring spasticity. It may be a description of resistance to passive movement. Therefore, measuring only one aspect of spasticity, not a comprehensive assessment. (Salter et al, 2005)

	• The Ashworth scale produces a global assessment of the resistance to passive movement of an extremity, not just stretch-reflex hyperexcitability. Specifically, the Ashworth score is likely to be influenced by non-contractile soft tissue properties, by persistent muscle activity (dystonia), by intrinsic joint stiffness, and by stretch reflex responses (Kamper et al., 2001) • Ambiguity of wording and lack of standardized procedures limit the scale's usefulness for comparison across studies as well as reliability • The Modified Ashworth scale does not comply with the concept of spasticity (a velocity-dependent increase in muscle tone) (Scholtes, 2007) • The Modified Ashworth Scale measures muscle tone intensity at one, unspecified, velocity which can make comparisons difficult (Scholtes, 2007) Fugl-Meyer (FM) assessment (Gladstone et al, 2002) • The Sensation, Balance, Joint Range of Motion and Joint Pain domains have been criticized as less well suited for this instrument given its intended purpose • Joint Range of Motion may be a confounding variable, so the inclusion of the Joint Pain domain may be unnecessary • Distal fine motor functions may be underrepresented • Finger movement not assessed (but gross hand function is included) • Arm scores are more heavily weighted than the leg scores • Better measure of balance is now available • Inclusion of subjective items on the Sensation and Joint Pain domains may reduce the measures reliability • The Sensory Scale's psychometric properties suggest that is should NOT be used to assess stroke patients (Lin et al, 2004) Funtional independent measure • With Rasch analysis, the FIM instrument had decreased cross-cultural validity of raw motor scores with 7 of 13 items suggesting that FIM Motor Subscale scores should not be pooled in their raw form or compared between countries. (Lawton et al, 2006) • The FIM instrument must be administered by a trained and certified evaluator and ideally scored by consensus with a multi-disciplinary team. Although the FIM instrument was originally developed to address issues of sensitivity and comprehensiveness for Barthel Index (BI), subsequent studies demonstrated that psychometric properties of the FIM instrument and BI are similar (Hsueh et al, 2002; Stroke EDGE task force) Page 17 line 296 ANOVA is "Analysis of Variance", "repeated measures analysis of variance" is rANOVA. DISCUSSION In Discussion, the authors should present studies, discussing the reasons for choosing those acupoints based on previous studies and they should provide an explanation for why they chose usual care versus non-insertive sham acupuncture (devices that mimic acupuncture without skin penetration) as a control for acupuncture when used in a randomised controlled trial (it was found to be a credible control for acupuncture and inert) All below studies and conclusions are with insertive needles (superficial needling of the acupoints for the treated condition, needling of the acupoints not for the treated condition, needling non-acupoints…):

	• Lundeberg T, Lund I, Sing A, et al. Is placebo acupuncture what it is intended to be? Evid Based Complement Alternat Med. 2011; 2011:932407. doi: 10.1093/ecam/nep049. Epub 2011 Jun 18. Conclusions: ACU sham procedures applied are not inert. Should therefore not be interpreted as placebo-controls in RCTs for the test of efficacy The evaluated effects of acupuncture could be compared with standard treatment. • Brown CA, Jones AK. Physiological mechanisms of acupuncture: beyond placebo? Pain. 2009 Dec 15;147(1-3):11-2. doi: 10.1016/j.pain.2009.09.014. Epub 2009 Sep 30. ACU and sham treatments, operate according to different mechanisms, with only ACU exerting long-term therapeutic effects on the Endogenous opioid (EO) system. • Harris RE, Zubieta JK, Scott DJ, et al. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on mu-opioid receptors (MORs). Neuroimage. 2009 Sep;47(3):1077-85. doi: 10.1016/j.neuroimage.2009.05.083. Epub 2009 Jun 6. Long-term increases in MOR binding following ACU are associated with reductions in clinical pain. Pag 19 line 333 “trial is designed to address all the key items recommended by the STRICTA and follow the Consolidated Standards of Reporting Trials (CONSORT) statement”. It must be included in the introduction paragraph. REFERENCES Please ensure the reference section is fully up to date with the relevant literature. A long list of references does not always make the paper of a high quality, at least 85% of the references should be within the last 5 years. The Chinese’s references were not found. Bibliographic references must be reviewed: • European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457-507. Electronic citations Websites are referenced with their URL and access date, and as much other information as is available. Access date is important as websites can be updated and URLs change. The "date accessed" can be later than the acceptance date of the paper, and it can be just the month accessed. • National Stroke Fundation. Clinical Guidelines for Stroke Management 2010. Melbourne Australia. Available in https://informme.org.au/guidelines/clinical-guidelines-for-stroke-management-2010. (Accessed on 07/06/2017) • Stroke Foundation of New Zealand and New Zealand Guidelines Group. Clinical Guidelines for Stroke Management 2010. Wellington: Stroke Foundation of New Zealand; 2010. http://www.stroke.org.nz/resources/NZClinicalGuidelinesStrokeManagement2010ActiveContents.pdf. (Accessed on 07/06/2017) • WHO Regional Office for the Western Pacific: WHO Standard Acupuncture Point Locations in the Western Pacific Region. 2008, Manila: World Health Oraganization (http://www.wpro.who.int/publications/docs/WHOIST_26JUNE_FINAL.pdf) • National Statement on Ethical Conduct in Human Research 2007 (Updated May 2015). The National Health and Medical Research Council, the Australian Research Council and the Australian Vice-Chancellors’ Committee. Commonwealth of Australia, Canberra.

	https://www.nhmrc.gov.au/guidelines-publications/e72. Consideration of these points will, I believe, lead to an improved report. Finally, I would like to congratulate the authors for the manuscript.

REVIEWER	Maria Begoña Criado Instituto Politécnico de Saúde do Norte_IPSN_CESPU. Portugal
REVIEW RETURNED	08-Jul-2017

GENERAL COMMENTS	I think this study is very interesting and important because of the lack of information concerning the effect and safety of acupuncture in stroke patients. But there are a few suggestions: - In my opinion the standardization of the RC treatment will be important to assess the effect of acupuncture. I think the authors should try to standardize as possible. -To make the study more reproducible, authors should explain the EA treatment more in detail: the criteria to choose points, the stimulation frequency, the intensity and the time.

VERSION 1 – AUTHOR RESPONSE

Response to comments of Reviewer #1 (Dr Javier Mata):
• Line 28-29
Trial registration: Please update your clinical trial registration.
Response: Trial registration information was updated in Line 28-29.

• Line 97-98
“It is designed following the instructions of SPIRIT 2013 Checklist (Appendix 1)”
It must be added: Consolidated Standards of Reporting Trials (CONSORT) guidelines (figure 1) and STRICTA guidelines] for acupuncture studies
Response: Thanks for the suggestions. The two statements “CONSORT 2010” and “STRICTA 2010” were added and the whole sentence was revised in Line 97-98.

• Table 1
EA, EA. The first letter of each word cannot be the definition of an acronym. (Electro-acupuncture)
Response: The definition of EA in Table 1 was revised to “electro-acupuncture” in the notes under Table 1.

• Line 165-180
The “routine care” must be change by “usual care”.
The usual care intervention should be standardized to reduce bias, a detailed description must be provided, stating how these terms are defined within the trial. In addition, relevant references should be provided.
In the routine care only the change of RC will be recorded?
Response: “Routine care” was changed to “usual care” through the paper. Although there are huge differences in recommendations among guidelines and complex comorbidities and complications with stroke patients, detailed therapies in usual care would inevitably vary.

Therefore, we added a description of the therapeutic principles for spasticity management without restricting to specific medications or therapies with references in this revision in Line 165-178. Further, changed of RC will be recorded any change of UC will be recorded by clinicians with reasons (Line 178-180).

• Line 182-183
In the intervention group: the sequence of treatments is EA + usual care or usual care + EA. Both treatments are in the same day?
Response: Electro-acupuncture will be performed three times per day, whereas usual care, including pharmacotherapy (such as blood pressure control and lipid lowering medications) and treatments for spasticity (such as stretching and splinting) will be carried out according to their conventional treatment frequency. Therefore, when EA is performed, usual care would also be conducted.

• Line 194
The reference for the systematic Review is:
Cai Y, Zhang CS, Liu S, Wen Z, Zhang AL, Guo X, Lu C, Xue CC. Electro-acupuncture for post-stroke spasticity: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2017 Apr 25. pii: S0003-9993(17)30257-5. doi: 10.1016/j.apmr.2017.03.023. [Epub ahead of print].
Response: The reference was added to Line 194 in this revision.

• Line 193-204
An acupuncture treatment protocol is a standardized, semi-standardized or fully individualized? The acupuncturists can select acupoints only from the list (LI4, LI10, LI11, LI15, TE5, GB34, LR3, SP6, ST36, ST40) or the can choose others too?
Response: Electro-acupuncture treatment protocol in this trial will be semi-standardized. Selection of acupoints will not be restricted to the list. Further clarification of acupoint selection was added to Line 193-204.

• Line 359-369
Why don´t use a biphasic wave (2Hz/120Hz) (altering every 2 seconds)?
Response: Reasons for the selection of electro-acupuncture stimulation wave was illustrated in Line 359-369.

• Line 223-240, Line 390-407
Outcome measures and evaluation
It is important to explain the rationale for the choice of trial outcomes:
The Modified Ashworth Scale and is considered by many as the gold standard for measuring spasticity (Bohannon & Smith, 1987)". It is a 6-point scale (six different joints (shoulder, elbow, wrist, hip, knee and unkle), with a grade score of 0, 1, 2, 3, or 4 or grade "1+",where lower scores represent normal muscle tone and higher scores represent spasticity or increased resistance to passive movement. The rater should extend the patients' limb from a position of maximal flexion to maximal extension until the first soft resistance is felt.

The Fugl-Meyer assessment (FMA) is one of the most widely recognized and clinically relevant measures of body function impairment after stroke. The scale is comprised of five domains and there are 155 items in total: motor functioning (in the upper and lower extremities), sensory functioning (evaluates light touch on two surfaces of the arm and leg, and position sense for 8 joints), balance (contains 7 tests, 3 seated and 4 standing), joint range of motion (8 joints), joint pain. The motor domain, which includes items assessing movement, coordination, and reflex action of the shoulder, elbow, forearm, wrist, hand, hip, knee, and ankle, has well-established reliability and validity as an indicator of motor impairment severity across different stroke recovery time points.

The Functional Independence Measure (FIM) provides a uniform system of measurement for disability based on the International Classification of Impairment, Disabilities and Handicaps; measures the level of a patient's disability and indicates how much assistance is required for the individual to carry out activities of daily living.

Limitations of the outcomes
Modified Ashworth Scale
• Adequate training is required to ensure inter-rater reliability
• Reliability differs from muscle to muscle
• Assessment technique must be standardized
• Some critics question the validity of the Ashworth scale and Modified Ashworth Scale in measuring spasticity. It may be a description of resistance to passive movement. Therefore, measuring only one aspect of spasticity, not a comprehensive assessment. (Salter et al, 2005)
• The Ashworth scale produces a global assessment of the resistance to passive movement of an extremity, not just stretch-reflex hyperexcitability. Specifically, the Ashworth score is likely to be influenced by non-contractile soft tissue properties, by persistent muscle activity (dystonia), by intrinsic joint stiffness, and by stretch reflex responses (Kamper et al., 2001)
• Ambiguity of wording and lack of standardized procedures limit the scale's usefulness for comparison across studies as well as reliability
• The Modified Ashworth scale does not comply with the concept of spasticity (a velocity-dependent increase in muscle tone) (Scholtes, 2007)
• The Modified Ashworth Scale measures muscle tone intensity at one, unspecified, velocity which can make comparisons difficult (Scholtes, 2007)
Fugl-Meyer (FM) assessment
(Gladstone et al, 2002)
• The Sensation, Balance, Joint Range of Motion and Joint Pain domains have been criticized as less well suited for this instrument given its intended purpose
• Joint Range of Motion may be a confounding variable, so the inclusion of the Joint Pain domain may be unnecessary
• Distal fine motor functions may be underrepresented
• Finger movement not assessed (but gross hand function is included)
• Arm scores are more heavily weighted than the leg scores
• Better measure of balance is now available
• Inclusion of subjective items on the Sensation and Joint Pain domains may reduce the measures reliability
• The Sensory Scale's psychometric properties suggest that is should NOT be used to assess stroke patients (Lin et al, 2004)
Functional independent measure
• With Rasch analysis, the FIM instrument had decreased cross-cultural validity of raw motor scores with 7 of 13 items suggesting that FIM Motor Subscale scores should not be pooled in their raw form or compared between countries. (Lawton et al, 2006)
• The FIM instrument must be administered by a trained and certified evaluator and ideally scored by consensus with a multi-disciplinary team. Although the FIM instrument was originally developed to address issues of sensitivity and comprehensiveness for Barthel Index (BI), subsequent studies demonstrated that psychometric properties of the FIM instrument and BI are similar (Hsueh et al, 2002; Stroke EDGE task force)
Response: Thanks for the comprehensive summary of the three outcome measures with references. After discussion with all the other research team members, we decided to replace one of the secondary outcome measures Functional Independence Measure (FIM) with Barthel Index (BI), due to the following reasons: 1) Compared to FIM, BI has been more widely accepted, used, studied and reported in China.[1]

Therefore, comparison of results from our trial and other studies could be applicable whereas FIM was seldom reported in trials conducted in Chinese population with post-stroke spasticity; 2) a validated Chinese version of BI is available while FIM has not been officially translated and validated in Chinese language yet;[1] 3) subsequent studies demonstrated that psychometric properties of the FIM instrument and BI are similar.[2] Introduction to the three outcome measures (Modified Ashworth Scale, Fugl-Meyer Assessment and Barthel Index) was added to "outcome measures and evaluation" under the "METHODS AND ANALYSIS" section in Line 223-240, while the reliability and validity of the three outcome measures, together with the rationale of the outcome selection for this randomized controlled trial was further discussed in the "Selection of outcome measures" under the "DISCUSSION" section in Line 390-407. The contents of FIM in the original version were replaced with those of BI in this new version through the whole manuscript.

• Line 310
ANOVA is "Analysis of Variance", "repeated measures analysis of variance" is rANOVA.
Response: Thanks for the correction. Correspondent revision was available in Line 310.

• Line 342-407
In Discussion, the authors should present studies, discussing the reasons for choosing those acupoints based on previous studies and they should provide an explanation for why they chose usual care versus non-insertive sham acupuncture (devices that mimic acupuncture without skin penetration) as a control for acupuncture when used in a randomized controlled trial (it was found to be a credible control for acupuncture and inert)
Response: The discussion section was revised with three paragraphs, respectively illustrating a summary of trial (Line 342-349), rationale of electro-acupuncture treatment protocol (Line 351-369), control method selection (Line 371-380), as well as selection of outcome measures in this trial (Line 382-407).

• Line 371-380
All below studies and conclusions are with insertive needles (superficial needling of the acupoints for the treated condition, needling of the acupoints not for the treated condition, needling non-acupoints…):
• Lundeberg T, Lund I, Sing A, et al. Is placebo acupuncture what it is intended to be? Evid Based Complement Alternat Med. 2011; 2011:932407. doi: 10.1093/ecam/nep049. Epub 2011 Jun 18.
Conclusions: ACU sham procedures applied are not inert. Should therefore not be interpreted as placebo-controls in RCTs for the test of efficacy The evaluated effects of acupuncture could be compared with standard treatment.
• Brown CA, Jones AK. Physiological mechanisms of acupuncture: beyond placebo? Pain. 2009 Dec 15;147(1-3):11-2. doi: 10.1016/j.pain.2009.09.014. Epub 2009 Sep 30.
ACU and sham treatments, operate according to different mechanisms, with only ACU exerting long-term therapeutic effects on the Endogenous opioid (EO) system.
• Harris RE, Zubieta JK, Scott DJ, et al. Traditional Chinese acupuncture and placebo (sham) acupuncture are differentiated by their effects on mu-opioid receptors (MORs). Neuroimage. 2009 Sep;47(3):1077-85. doi: 10.1016/j.neuroimage.2009.05.083. Epub 2009 Jun 6.
Long-term increases in MOR binding following ACU are associated with reductions in clinical pain.
Response: There has been controversy over the control methods for research with acupuncture and electro-acupuncture. Some of the above studies (Brown 2009, Harris 2009) indicated sham acupuncture on non-acupoints might not achieve the same therapeutic effects as that from penetrating needing in true acupoints. However, there is evidence questioned the sham acupuncture was not completely inert (Lundeberg 2011). Therefore, the treatment effects of acupuncture might be underestimated when compared with pseudo or sham acupuncture. The concern was discussed in the "control method for EA trial" under the discussion section in Line 371-380.

• Line 98
“Trial is designed to address all the key items recommended by the STRICTA and follow the Consolidated Standards of Reporting Trials (CONSORT) statement”.
It must be included in the introduction paragraph.
Response: The “CONSORT 2010” and “STRICTA 2010” were added to the “limitations in previous trials” under the “Introduction” section in Line 98.

• REFERENCES
Please ensure the reference section is fully up to date with the relevant literature. A long list of references does not always make the paper of a high quality; at least 85% of the references should be within the last 5 years.
Response: We tried our best to update the references without impacting on the contents of the text. The number of references was changed accordingly. Unfortunately, the proportion of references within the last five years was only 38%, and that within 10 years was around 81%. This might partially result from the citations related to studies of the three outcome measures, some of which were conducted more than 10 years ago. The other possible reason is that the number of mechanism studies of acupuncture specifically for post-stroke spasticity is relatively small compared to other post-stroke complications or conditions.

• The Chinese’s references were not found.
Response: References in Chinese were articles published in Chinese journals and may not be identified from English databases. These articles were searched and identified through Chinese databases. Full texts of these articles were available if required.

• Bibliographic references must be reviewed:
• European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457-507.
Electronic citations
Websites are referenced with their URL and access date, and as much other information as is available. Access date is important as websites can be updated and URLs change. The "date accessed" can be later than the acceptance date of the paper, and it can be just the month accessed.
• National Stroke Fundation. Clinical Guidelines for Stroke Management 2010. Melbourne Australia. Available in https://informme.org.au/guidelines/clinical-guidelines-for-stroke-management-2010. (Accessed on 07/06/2017)
• Stroke Foundation of New Zealand and New Zealand Guidelines Group. Clinical Guidelines for Stroke Management 2010. Wellington: Stroke Foundation of New Zealand; 2010. http://www.stroke.org.nz/resources/NZClinicalGuidelinesStrokeManagement2010ActiveContents.pdf. (Accessed on 07/06/2017)
• WHO Regional Office for the Western Pacific: WHO Standard Acupuncture Point Locations in the Western Pacific Region. 2008, Manila: World Health Organization (http://www.wpro.who.int/publications/docs/WHOIST_26JUNE_FINAL.pdf)
• National Statement on Ethical Conduct in Human Research 2007 (Updated May 2015). The National Health and Medical Research Council, the Australian Research Council and the Australian Vice-Chancellors’ Committee. Commonwealth of Australia, Canberra. https://www.nhmrc.gov.au/guidelines-publications/e72.
Consideration of these points will, I believe, lead to an improved report. Finally, I would like to congratulate the authors for the manuscript.
Response: Thanks for the correction. Correspondent and related references formats were revised (Reference No. 6, 8, 10, 22, 23, 28, 30, 38, 47, 50-53).

Response to comments of Reviewer #2 (Dr Maria Begoña Criado):

• Line 165-180
I think this study is very interesting and important because of the lack of information concerning the effect and safety of acupuncture in stroke patients.
But there are a few suggestions:
- In my opinion the standardization of the RC treatment will be important to assess the effect of acupuncture. I think the authors should try to standardize as possible.
Response: Thanks for the comments. Due to the inconsistency of different guidelines in specific therapies recommended for post-stroke spasticity, and the complex complications and comorbidities with stroke patients, it would be difficult to restrict the interventions that might be received by participants. But we tried to set a therapeutic principle for spasticity management in the usual care of the trial. Besides, as recommended by the other reviewer, the term “routine care (RC)” was also replaced by “usual care (UC)” with the same meaning. The revised introduction to usual care in this trial is available in Line 165-180.

• Line 193-204, 212, 213, 182-183
To make the study more reproducible, authors should explain the EA treatment more in detail: the criteria to choose points, the stimulation frequency, the intensity and the time.
Response: Detailed information was added to describe the correspondent parameters of electro-acupuncture therapy: selection of acupoints (Line 193-204), electrical stimulation frequency and intensity (Line 212), stimulation time in each treatment section (Line 213), total treatment period (Line 182-183).

Other changes
• List of abbreviation
Abbreviation was revised according to the contents of the manuscript.

• Changes in spelling and wording
The highlighted contents were rephrased or reworded (Line 8-9, 12, 14-16, 19, 26, 53-66, 72-78, 81, 89, 93-96, 99-102, 106-107, 115-116, 126, 186, 204-205, 251-253, 288, 290, 308, 314, 316, 322).

• Line 426-428
The Funding named “Specific Research Fund for TCM Science and Technology of Guangdong Provincial Hospital of Chinese Medicine (2016)' (No. YN2016QL01)” was added to the supporting funding in Line 426-428.

• Line 431
CZ (Claire Shuiqing Zhang) and TZ (Anthony Lin Zhang) was added to the ones that designed or conceptualized the trial protocol in Line 431.

References
1. Leung SO, Chan CC, Shah S. Development of a Chinese version of the Modified Barthel Index--validity and reliability. Clinical rehabilitation 2007;21(10):912-22.
2. Hsueh IP, Lin JH, Jeng JS, et al. Comparison of the psychometric characteristics of the functional independence measure, 5 item Barthel index, and 10 item Barthel index in patients with stroke. Journal of neurology, neurosurgery, and psychiatry 2002;73(2):188-90.

VERSION 2 – REVIEW

REVIEWER	Javier Mata Estévez Son Llàtzer University Hospital Palma de Mallorca Spain
REVIEW RETURNED	04-Sep-2017

GENERAL COMMENTS	Reviewer Comments for Manuscript ID: bmjopen-2017-017912 Electro-acupuncture for post-stroke spasticity (EAPSS): protocol for a randomized controlled trial (Manuscript ID: bmjopen-2017-017912) The authors have been responsive to the reviewers' comments and the manuscript has improved as a result. I recommend the manuscript for publication after some adjustments have been taken into account. Comment -1: page 5. Line 68 The limitations of the study are those characteristics of design or methodology that impacted or influenced the interpretation of the findings from your research (study design limitation, impact limitation, statistical or data limitations). There are no limitations in this study, are there? For example: • Usual care is not the same for everyone • Some critics question the validity of the Ashworth scale and Modified Ashworth Scale in measuring spasticity. Comment -2: page 10 line 156. Inclusion criteria • "The inclusion criteria of participants are: 1) with first-ever stroke confirmed by Computed Tomography or Magnetic Resonance Imaging". CT is instead of MRI or in addition • "Baseline Modified Ashworth Scale (MAS)". Some critics question the validity of the Ashworth scale and Modified Ashworth Scale in measuring spasticity. It may be a description of resistance to passive movement. Therefore, measuring only one aspect of spasticity, not a comprehensive assessment. (Salter et al, 2005). It was concluded that the Ashworth scale is of limited use in the assessment of spasticity in the lower limb of patients with spinal cord injury. The Ashworth scale produces a global assessment of the resistance to passive movement of an extremity, not just stretch-reflex hyperexcitability. Specifically, the Ashworth score is likely to be influenced by non-contractile soft tissue properties, by persistent muscle activity (dystonia), by intrinsic joint stiffness, and by stretch reflex responses (Kamper et al., 2001). Ambiguity of wording and lack of standardized procedures limit the scale's usefulness for comparison across studies as well as reliability. The Modified Ashworth scale does not comply with the concept of spasticity (a velocity-dependent increase in muscle tone) (Scholtes, 2007). The Modified Ashworth Scale measures muscle tone intensity at one, unspecified, velocity which can make comparisons difficult (Scholtes, 2007). Aloraini SM, Gäverth J, Yeung , MacKay-Lyons. Assessment of spasticity after stroke using clinical measures: a systematic review. Disabil Rehabil. 2015;37(25):2313-23. doi: 10.3109/09638288.2015.1014933. Epub 2015 Feb 18. CONCLUSION: This systematic review found limited evidence to support the use of most of clinical measures of spasticity for people post-stroke. Future research examining the application and psychometric properties of these measures is warranted. Implications for Rehabilitation There is a need for objective clinical tools for measuring spasticity that are clinically feasible and easily interpreted by clinicians. This review identified various clinical measures of spasticity that have been investigated in people after stroke. Insufficient evidence of psychometric properties precludes recommending one tool over the others. Future research should focus on investigating the psychometric properties of clinical measures of spasticity. Comment -3: page 14 line 239.

	• Number of needle insertions per subject per session ((mean and range)? Comment -4: page 14 line 248. “Upon the needling sensation, 248 EA will be applied through a stimulator with a stimulation frequency of 50-100 Hz 249 and at the maximum tolerable intensity for 20-30 minutes”. The type of wave must be mentioned in this paragraph (monophasic, in this case) Comment -5: page 14 line 253. “For the remaining four-week post treatment phase, participants in both groups will continue to receive RC” Replace “RC” with “UC”. Comment -6: page 14 line 258. Outcome measures and evaluation A validated Chinese version of MAS and FMA are available? I did not find officially translated and validated in Chinese language. Modified Barthel Index in Chinese (Leung, Cha, & Shah, 2007) Comment -7: page 17 line 305. “Information of the participants, instrument measures, AEs and other relevant data will be collected at the initial”, Can be adverse events collected at the initial? Comment -8: page 2 line 419. Selection of outcome measures You can add: Compared to FIM, BI has been more widely accepted, used, studied and reported in China. Therefore, comparison of results from our trial and other studies could be applicable whereas FIM was seldom reported in trials conducted in Chinese population with post-stroke spasticity; 2) a validated Chinese version of BI is available while FIM has not been officially translated and validated in Chinese language yet; subsequent studies demonstrated that psychometric properties of the FIM instrument and BI are similar. Figure 1. Flow chart. Change “Routine care” with “usual care” Checklist for items in STRICTA • Acupuncture rationale. Traditional Chinese Medicine is supposed to be the Style of acupuncture in the study. • Number of needle insertions per subject per session (mean and range where relevant) Consideration of these points will, I believe, lead to an improved report. Finally, I would like to congratulate the authors for the manuscript.

VERSION 2 – AUTHOR RESPONSE

Response to comments of Reviewer #1 (Dr Javier Mata Estévez):

• Comment 1: Line 68

The limitations of the study are those characteristics of design or methodology that impacted or influenced the interpretation of the findings from your research (study design limitation, impact limitation, statistical or data limitations). There are no limitations in this study, are there?

For example:

• Usual care is not the same for everyone

• Some critics question the validity of the Ashworth scale and Modified Ashworth Scale in measuring spasticity.

Response: Two limitations (the variation of usual care and the validity of Modified Ashworth Scale) were added to the ‘strength and limitations’ sections in Line 71-78. Correspondent discussion of the validity of Modified Ashworth Scale was also revised in Line 431-439.

• Comment 2: Line 157 Inclusion criteria
“The inclusion criteria of participants are: 1) with first-ever stroke confirmed by Computed Tomography or Magnetic Resonance Imaging”. CT is instead of MRI or in addition
Response: For participants included in this trial, stroke could be confirmed only by CT, or only confirmed by MRI, or both. To clarify this inclusion criterion, CT or MRI was revised to “CT or/and MRI” in Line 157.

• Line 431-439
“Baseline Modified Ashworth Scale (MAS)”. Some critics question the validity of the Ashworth scale and Modified Ashworth Scale in measuring spasticity. It may be a description of resistance to passive movement. Therefore, measuring only one aspect of spasticity, not a comprehensive assessment. (Salter et al, 2005). It was concluded that the Ashworth scale is of limited use in the assessment of spasticity in the lower limb of patients with spinal cord injury. The Ashworth scale produces a global assessment of the resistance to passive movement of an extremity, not just stretch-reflex hyperexcitability. Specifically, the Ashworth score is likely to be influenced by non-contractile soft tissue properties, by persistent muscle activity (dystonia), by intrinsic joint stiffness, and by stretch reflex responses (Kamper et al., 2001). Ambiguity of wording and lack of standardized procedures limit the scale’s usefulness for comparison across studies as well as reliability. The Modified Ashworth scale does not comply with the concept of spasticity (a velocity-dependent increase in muscle tone) (Scholtes, 2007). The Modified Ashworth Scale measures muscle tone intensity at one, unspecified, velocity which can make comparisons difficult (Scholtes, 2007).
Aloraini SM, Gäverth J, Yeung , MacKay-Lyons. Assessment of spasticity after stroke using clinical measures: a systematic review. Disabil Rehabil. 2015;37(25):2313-23. doi: 10.3109/09638288.2015.1014933. Epub 2015 Feb 18.
CONCLUSION:
This systematic review found limited evidence to support the use of most of clinical measures of spasticity for people post-stroke. Future research examining the application and psychometric properties of these measures is warranted. Implications for Rehabilitation There is a need for objective clinical tools for measuring spasticity that are clinically feasible and easily interpreted by clinicians. This review identified various clinical measures of spasticity that have been investigated in people after stroke. Insufficient evidence of psychometric properties precludes recommending one tool over the others. Future research should focus on investigating the psychometric properties of clinical measures of spasticity.
Response: Thanks for the references. Discussion of the validity of Modified Ashworth Scale was also revised in Line 431-439.

• Comment 3: Line 237-239
Number of needle insertions per subject per session ((mean and range)?
Response: The exact number of needle insertions per subject per session in this trial would not be a fix number, which would be determined by the acupuncture practioners. But we limit the number of acupoints used in each EA treatment session to three pairs. Further clarification was added to Line 237-239.

• Comment 4: Line 249
“Upon the needling sensation, EA will be applied through a stimulator with a stimulation frequency of 50-100 Hz and at the maximum tolerable intensity for 20-30 minutes”.
The type of wave must be mentioned in this paragraph (monophasic, in this case)
Response: Thanks for the suggestion. Biphasic wave will be used in this study. Information of wave type was added to Line 249.

• Comment 5: Line 254

“For the remaining four-week post treatment phase, participants in both groups will continue to receive RC”
Replace “RC” with “UC”.
Response: Thanks for the correction. “RC” was replaced with “UC” in Line 254.

• Comment 6: Line 259 Outcome measures and evaluation
A validated Chinese version of MAS and FMA are available? I did not find officially translated and validated in Chinese language.
Modified Barthel Index in Chinese (Leung, Cha, & Shah, 2007)
Response: Although there has not been an officially translated Chinese version of MAS and FMA yet , the outcome assessor of our trial is a professional rehabilitation therapist who has many years’ experience of using MAS and FMA in clinical practice, we consider the use of these outcome measures are acceptable in this trial.

• Comment 7: Line 307-308
“Information of the participants, instrument measures, AEs and other relevant data will be collected at the initial”,
Can be adverse events collected at the initial?
Response: Thanks for the correction. Adverse events could not be collected at baseline. Correspondent revision was available in Line 307-308.

• Comment 8: Line 445-452. Selection of outcome measures
You can add: Compared to FIM, BI has been more widely accepted, used, studied and reported in China. Therefore, comparison of results from our trial and other studies could be applicable whereas FIM was seldom reported in trials conducted in Chinese population with post-stroke spasticity; 2) a validated Chinese version of BI is available while FIM has not been officially translated and validated in Chinese language yet; subsequent studies demonstrated that psychometric properties of the FIM instrument and BI are similar.
Response: Thanks for the suggestion. We condensed the above information and revised correspondent sentences in Line 445-452.

• Figure 1 Flow chart
Change “Routine care” with “usual care”
Response: Thanks for the correction. “Routine care” was replaced with “usual care” in Figure 1.

• Checklist for items in STRICTA
• Acupuncture rationale. Traditional Chinese Medicine is supposed to be the Style of acupuncture in the study.
• Number of needle insertions per subject per session (mean and range where relevant)
Response: The rationale to conduct the trial with electro-acupuncture was illustrated in Line 104-113. In terms of the number of needle insertions per subject per session, response was available under “Comment 3” and clarification was available in Line 237-239.

Yours sincerely,

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VERSION 3 – REVIEW

REVIEWER	Javier Mata Hospital Universaity Son Llàtzer Palma (Balearic Islands) Spain
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	The authors have been responsive to the reviewers' comments and the manuscript has improved as a result. In general, I believe this manuscript merits publication, and have only a few comments and suggestions to the authors before publication. LINE 145. Table1. Schedule of enrollment, interventions and assessments. Adverse effects (AEs) should not be collected in baseline assessment. LINE 240. "Maximum number of acupuncture points used in each EA treatment on the affected side of the body will be limited to three pairs", but what is the maximum total number of needles in each session (mean and range)? LINE 249. "EA will be applied through a stimulator with biphasic waves" but in LINE 398. "We referred to the results of our systematic review [18] and select monophasic waveform (50-100Hz) at patients' maximum tolerable intensity". LINE 406. "we decided to use monophasic waveform (50-100Hz) in this trial". And you say in the answer of our question: Thanks for the suggestion. Biphasic wave will be used in this study. Information of wave type was added to Line 249. You need to explain this. LINE 440. You should include: Although there has not been an officially translated Chinese version of MAS and FMA yet, the outcome assessor of our trial is a professional rehabilitation therapist who has many years' experience of using MAS and FMA in clinical practice, we consider the use of these outcome measures are acceptable in this trial. Consideration of these points will, I believe, lead to an improved report. Finally, I would like to congratulate the authors for the manuscript.

VERSION 3 – AUTHOR RESPONSE

Response to comments of Reviewer #1 (Dr Javier Mata):
The authors have been responsive to the reviewers' comments and the manuscript has improved as a result. In general, I believe this manuscript merits publication, and have only a few comments and suggestions to the authors before publication.

• Comment 5: Table 1
Schedule of enrollment, interventions and assessments: Adverse effects (AEs) should not be collected in baseline assessment.
Response: Thanks for the correction. Adverse event (AE) was excluded from baseline assessment in Table 1. We also condensed and revised the format of Table 1(Line 141).

• Comment 6: Line 224-225
"Maximum number of acupuncture points used in each EA treatment on the affected side of the body will be limited to three pairs", but what is the maximum total number of needles in each session (mean and range)?

Response: The exact number of needle insertions per subject per session in this trial would not be a fix number, which would be determined by the acupuncture practioners. But we suggested the maximum total number of needles in each session to be ten. This information was added to Line 224-225.

• Comment 7: Line 235, 384-385, 391, 393
LINE 249. “EA will be applied through a stimulator with biphasic waves” but in LINE 398. “We referred to the results of our systematic review [18] and select monophasic waveform (50-100Hz) at patients’ maximum tolerable intensity”. LINE 406. “we decided to use monophasic waveform (50-100Hz) in this trial”. And you say in the answer of our question: Thanks for the suggestion. Biphasic wave will be used in this study. Information of wave type was added to Line 249. You need to explain this.
Response: Sorry for the inconsistence and confusion with the description of electrical stimulation waveform. (1) Biphasic continuous waveform (50-100 Hz) will be applied in this trial. (2) Since biphasic waveform was pre-set in the electric acupuncture apparatus, we will not be able to select monophasic or biphasic waveform in electro-acupuncture treatment. However, selection of waveform include continuous/discontinuous wave. (3) For waveform reported in the included studies in the systematic review (Cai Y, Zhang CS, Liu S, et al. Electroacupuncture for Poststroke Spasticity: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil 2017.), continuous waveform was used in all included trials, but whether the waveform was monophasic or biphasic was not mentioned. (4) Correspondent revision was in Line 235, 384-385, 391 and 393.

• Comment 8: Line 425-429
You should include: Although there has not been an officially translated Chinese version of MAS and FMA yet, the outcome assessor of our trial is a professional rehabilitation therapist who has many years’ experience of using MAS and FMA in clinical practice, we consider the use of these outcome measures are acceptable in this trial.
Response: This sentence was added to Line 425-429.

• Other Changes:
Figure 1 was simplified.
SPIRIT 2013 Checklist: The page numbers were changed accordingly.

Changes were also made to correct spelling, clarify confusion and improve readability of the manuscript as indicated with highlights in Line 38, 44-45, 81, 95-99, 114, 117, 119-120, 126, 129, 152, 157, 159, 163-170, 174-176, 178, 182-184, 193-194, 205-212, 215-216, 220, 224-225, 228-229, 231, 233-236, 239-241, 246-248, 251-252, 265-267, 274, 277-278, 286-289, 293-295, 303-305, 309-312, 326-331, 336-338, 341, 355-356, 361, 366-367, 372, 376, 382-383, 387, 397-404, 407-412, 417-424, 432-442, 445.

Yours sincerely,

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VERSION 4 – REVIEW

REVIEWER	Javier Mata Son Llatzèr University Hospital
REVIEW RETURNED	21-Nov-2017

GENERAL COMMENTS	General comments The authors have considered the various suggestions made by the reviewers and have accordingly rewritten the manuscript. However, the manuscript cannot be published in its current form. As detailed below, a moderate revision is necessary before it can be accepted. Specific comments: Page 12. It is not clear which acupuncture points are mandatory and which of them are optional. “It is a semi-standardised treatment protocol where acupuncturists will be permitted to select points”. For example: Upper limb: LI4, LI10, LI11, LI15, TE5. Lower limb: GB34, LR3, SP6, ST36, and ST40 The acupoints selection may depend on the treatment of upper/lower limb spasticity (mandatory?) and additional acupuncture points not involved in the above list may be selected by acupuncturists based on the individualised condition of patients (optional?) Page 13 and table 1. “Follow-ups Participants in both groups will continue to receive UC during the four-week follow-up phase” UC will continue in the follow up phase. You need to show it in table 1. (items required not appears in 6 weeks and 8 weeks for UC (both groups)). Page 15. Line 277. “Should participants develop an AE during the trial…” This sentence is not clear… Page 22. Line 420. “While the ability of the MAS to distinguish between functional and mechanical properties of muscle has been”. The sentence is unfinished… Discussion At the end of the discussion there should be a paragraph with the summary of the objectives of the study Table S1. You need to explain the method of point location, the proportional (B-cun) method: This method divides the height of the human body into 75 equal units. Using joints on the surface of the body as the primary landmarks, the length and width of every body part is measured by such proportions. The specific method is as follows: divide the height of the human body into 75 equal units and then estimate the length and width of a certain part of the body according to such units. One unit is equal to one cun. Flow chart You need to specify more clearly the different steps of the study in the diagram boxes (for example, number of treatments per week)

VERSION 4 – AUTHOR RESPONSE

Response to comments of the editorial board and Reviewer #1 (Dr Javier Mata):
Editorial comments
Whilst we normally allow a maximum of two revisions, we are willing to consider one more revision of this manuscript since reviewer 4's comments below are addressable. We urge you to make all the necessary revisions at this stage in an effort to convince the reviewer and editorial team that your work is suitable for publication in BMJ Open.

Comments of Reviewer #1 (Dr Javier Mata)
The authors have considered the various suggestions made by the reviewers and have accordingly rewritten the manuscript. However, the manuscript cannot be published in its current form. As detailed below, a moderate revision is necessary before it can be accepted. Specific comments:

• Comment 1: Line 205-211
It is not clear which acupuncture points are mandatory and which of them are optional. “It is a semi-standardised treatment protocol where acupuncturists will be permitted to select points”.
For example:
Upper limb: LI4, LI10, LI11, LI15, TE5.
Lower limb: GB34, LR3, SP6, ST36, and ST40
The acupoints selection may depend on the treatment of upper/lower limb spasticity (mandatory?) and additional acupuncture points not involved in the above list may be selected by acupuncturists based on the individualised condition of patients (optional?)
Response: For EA treatment in this trial, acupoints selection will be determined by acupuncturists. Based on our systematic review of published EA trials for PSS, we identified a list of acupuncture points and suggested them to be used in correspondent joints affected by spasticity in the trial (Table S1). Meanwhile, acupuncturists will be permitted to select points out of the list based on the individualised condition of patients. Correspondent revision is available in Line 205-211 in the main text file.

• Comment 2: Table 1 in Line 134
“Follow-ups Participants in both groups will continue to receive UC during the four-week follow-up phase”. UC will continue in the follow up phase. You need to show it in table 1. (items required not appears in 6 weeks and 8 weeks for UC (both groups)).
Response: Thanks for the correction. UC was added in follow-up phase in Table 1 and the row “medications and therapies” was deleted from Table 1. We also replaced “X” with “×” in Table 1.

• Comment 3: Line 264-266
“Should participants develop an AE during the trial…” This sentence is not clear.
Response: The sentence was revised to “If participants develop an AE during the trial, they will be advised to seek medical advice from their physicians and cease the EA treatment if the AE is considered to be EA related and becomes intolerable” in Line 264-266.

• Comment 4: Line 396-398
“While the ability of the MAS to distinguish between functional and mechanical properties of muscle has been”. The sentence is unfinished.
Response: The sentence was revised to “While the ability of the MAS to distinguish between functional and mechanical properties of muscle has been questioned, it is considered as the primary measure of muscle spasticity with widespread clinical acceptance” in Line 396-398.

• Comment 5: Line 417-419
At the end of the discussion there should be a paragraph with the summary of the objectives of the study.
Response: Thanks for the suggestion. A paragraph with a summary of the objectives of the study was added to the end of the discussion in Line 417-419. The aim of the study could also be found in Line 118-122 in the main text file. In fact, a brief summary of the study objectives following the discussion section was included in the first submitted version. Then it was removed according to the editorial board's suggestion. Whether this summary should be presented in the final format might be determined following the journal requirement.

• Comment 6: Table S1
You need to explain the method of point location, the proportional (B-cun) method: This method divides the height of the human body into 75 equal units. Using joints on the surface of the body as the primary landmarks, the length and width of every body part is measured by such proportions. The specific method is as follows: divide the height of the human body into 75 equal units and then estimate the length and width of a certain part of the body according to such units. One unit is equal to one cun.
Response: Thanks for the detailed explanation. We added a note to illustrate the proportional method to locate acupoints at the end of Table S1 as suggested. Besides, a column indicating correspondent joints affected by spasticity for the use of listed acupoints was also added to the table.

• Comment 7: flow chart
You need to specify more clearly the different steps of the study in the diagram boxes (for example, number of treatments per week).
Response: Treatment frequency of electro-acupuncture was added to the flow chart. Besides, different steps of the study was summarized with the boxes "enrolment", "allocation", "treatment", "follow-up" and "analysis" on the left side in the flow chart.

Other changes: Line 171
To make the meaning clearer, we rephrased the "central internet randomisation service system" to "central web-based interactive randomisation service system".

Other changes: Line 306-307
More information of SAS 9.2 was added to Line 306-307.

VERSION 5 – REVIEW

REVIEWER	Dr Javier Mata Son Llàtzer University Hospital Palma de Mallorca Balearic Islands Spain
REVIEW RETURNED	22-Dec-2017

GENERAL COMMENTS	The authors have satisfactorily responded to all the questions and made the necessary changes to the manuscript. The paper has been improved considerably, so it can be suitable for publication in BMJ Open.