Efficacy of electro-acupuncture and manual acupuncture versus sham acupuncture for knee osteoarthritis: statistical analysis plan for a randomized controlled trial

CURRENT STATUS: ACCEPTED

Jian-Feng Tu
Beijing University of Chinese Medicine

Jing-Wen Yang
Beijing University of Chinese Medicine

Li-Qiong Wang
Beijing University of Chinese Medicine

Yang Wang
Shanghai Jiao Tong University

Jin-ling Li
Beijing University of Chinese Medicine

Na Zhang
Beijing University of Chinese Medicine

Lu-Lu Lin
Beijing University of Chinese Medicine

Zhang-Sheng Yu
Shanghai Jiao Tong University

Cun-Zhi Liu
School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine

Corresponding Author

ORCID: https://orcid.org/0000-0001-8031-5667

DOI: 10.21203/rs.2.475/v1

SUBJECT AREAS
KEYWORDS

Acupuncture, Knee osteoarthritis, Statistical analysis plan
Abstract

Background: Acupuncture therapies are widely used for knee osteoarthritis (KOA), despite contradictory evidences. Current study is designed to determine the efficacy of electro-acupuncture and manual acupuncture versus sham acupuncture for KOA. Methods/design: Current study is a multi-center, three-arm, randomized controlled trial which will enroll 480 participants with KOA in China. Participants will be randomly assigned (1:1:1) to receive 24 sessions of electro-acupuncture, manual acupuncture, or sham acupuncture over 8 weeks. The primary outcome is the response rate - the proportion of patients who simultaneously achieve minimal clinically important improvement in pain and function domains at 8 weeks. The primary outcome will be analyzed using Z-test with intention-to-treat set. Secondary outcomes contain pain, function, global patient assessment and quality of life. Full details of the statistical analysis plan for the primary and secondary outcomes will be described in this article. The statistical analysis plan was written and submitted without knowledge of the study data. Discussion: The data will be analyzed according to this pre-specified statistical analysis plan to avoid data-driven analysis and enhance the transparency of current trial. The trial will provide high-quality evidence on the efficacy of acupuncture for KOA. Trial registration: Clinicaltrials.gov, NCT03366363. Registered on 20 November 2017. (https://clinicaltrials.gov/show/NCT03366363)

Background

Knee osteoarthritis (KOA) is one of the leading causes of chronic pain and disability in older adults [1], with symptomatic knee osteoarthritis affecting 8.1% of Chinese [2] and 1.6% - 14.9% of European according to age class [3]. The socioeconomic burden of KOA is large, costing between 1·0% and 2·5% of gross domestic product in developed countries [4]. Since there is no disease-modifying treatment available, current KOA managements are symptomatic [5]. Non-steroid anti-inflammatory drugs are commonly used to treat this disorder. However, limited effect sizes for non-steroid anti-inflammatory drugs of KOA have been shown [6, 7]. Although total knee replacement is an effective treatment for symptomatic end-stage disease, approximately 15% of patients have continuing pain and mobility problems after surgery and the lifespan of prostheses is limited [8].
Acupuncture is increasingly used in clinical practice [9], although evidence of its efficacy is contradictory [10, 11]. Acupuncture has a dose-effect relationship [12]. However the dose of acupuncture in several previous trials is far from adequate [13]. Frequency of acupuncture is one of key factors of dose [14]. A review suggested that the frequency of acupuncture is usually 3-5 sessions per week in China, whereas the frequency is mostly one session per week in Europe and America [15]. Based on previous pilot trial [16], high-dose acupuncture (24 sessions in 8 weeks) may be an effective option for knee osteoarthritis. Electro-acupuncture (EA) combines manual acupuncture (MA) with electric stimulus [17]. Both EA and MA are frequently used in clinical practice. Therefore, current trial is designed to evaluate the effect of EA and MA, compared with sham acupuncture (SA), in patients with knee osteoarthritis.

The protocol of the trial has been published previously [18] and provides more detail on the trial rationale, eligibility criteria, and interventions. This article aims to report in detail the statistical analysis plan (SAP) to reduce the risks of reporting bias and enhance the transparency of the trial. The SAP was approved on 30 October 2017 (Version 1.0) and drafted without knowledge of any of the results.

**Methods**

This three-arm, randomized, sham-controlled trial has been approved by ethics committees at all 9 hospitals. Eligible KOA participants diagnosed according to the American College of Rheumatology criteria [19] are randomly assigned (1:1:1) to receive 24 sessions of electro-acupuncture, manual acupuncture, or sham acupuncture over 8 weeks. Block randomization with random block size of 6 and 9, is stratified by study centre, and is performed via a web-based randomization system. The nature of acupuncture means that acupuncturists are not blinded to treatment allocation; however, patients, outcome assessors and statisticians remain masked where possible. Informed consent is obtained from each participant before randomization. The trial has been registered with ClinicalTrials.gov (NCT03366363).

**Objectives**

The objective of current study is to determine if EA and MA improve the outcome at 8 weeks in
patients with knee osteoarthritis. The following two null hypotheses are tested: there is no difference in patients’ response rate between EA group and SA group; there is no difference in patients’ response rate between MA group and SA group.

**Outcomes**

**Primary outcome**

The primary outcome is the response rate [20] - the proportion of patients who simultaneously achieve minimal clinically important improvement (MCII) in pain and function domains at 8 weeks post-randomization. The average pain over the previous week is assessed using an 11-point Numerical Rating Scale (NRS) [21] with scores ranging from 0 to 10. The MCII in pain domain is defined as 2 points in NRS [11, 22]. The average function over the previous week is measured using Western Ontario and McMaster Universities osteoarthritis index (WOMAC) function subscale [23] with scores ranging from 0 to 68. The MCII in function domain is defined as 6 points in WOMAC function subscale [11, 22]. The criteria of responder are presented in Fig 1. The response rate is also measured at weeks 4, 16, and 26 after randomization.

**Secondary outcomes**

Numerical Rating Scale [21]: an 11-point patient reported outcome measure (PROM) with scores ranging from 0 (no pain) to 10 (worst pain).

WOMAC [23] pain subscale: a 5-item PROM with total scores ranging from 0 to 20. Higher scores indicate worse pain.

WOMAC [23] function subscale: a 17-item PROM with total scores ranging from 0 to 68. Lower scores indicate better physical function.

WOMAC [23] stiffness subscale: a 2-item PROM with total scores ranging from 0 to 8. Higher scores indicate more stiffness.

Patient global assessment [24]: a 5-point Likert scale. Participants are asked how their knee symptoms were during the past week. The answers include ‘extremely improved’, ‘slightly improved’, ‘not changed’, ‘slightly aggravated’, and ‘extremely aggravated’.

12-item Short Form Health Survey (SF-12) [25] physical dimension: total score range from 0 to 100.
Lower scores indicate a worse quality of life.

SF-12 [25] mental dimension: total score range from 0 to 100. Higher scores indicate a better quality of life.

NRS, WOMAC, Patient global assessment and SF-12 is measured at 4, 8, 16, and 26 weeks after randomization. Blinding assessment is measured at 4 and 8 weeks after randomization. Credibility and expectancy of participants are measured 5 minutes after the first acupuncture [26]. The use of rescue medicine is also counted throughout the trial.

**Safety outcome**

Adverse events are recorded throughout the trial. Based on the potential relationship between acupuncture and adverse events, adverse events are categorized as treatment-related or not.

**Sample size**

Based on the results of a previous trial [16], the response rates of EA, MA and SA group are assumed to be 70%, 60% and 40%, respectively. With a 2-sided significance level of 2.5% and power of 80%, 128 participants in each group will be required to detect a difference as small as 20% between each acupuncture group and control group. With an estimated loss-to-follow-up rate of 20%, 480 participants in the three groups will be recruited.

**Statistical analysis**

**Statistical analysis population**

Full analysis set (FAS), per-protocol set (PPS), and safety set (SS) will be used in current trial.

FAS will consist of all randomized participants who have at least one post-baseline measurement according to modified intention-to-treat principle. Logistic regression will be used to exam whether the data are missing at random or not [27]. If data is missing at random, multiple imputation method will be used [28]. FAS will be the primary analysis set, and all analyses will be conducted for this population if not otherwise stated. Analyses on FAS will provide an estimate of the effect of electro-acupuncture and manual acupuncture.

PPS will include those who complete the treatment and follow-up timely according to protocol without major violations. Major violations of protocol will be judged during the audit of data, including but not
limited to: not meeting the inclusion criteria / meeting the exclusion criteria, receiving other treatments which might affect symptoms of KOA during the trial, completing ≥ 20 sessions of acupuncture. PPS will be the secondary analysis set and be used for sensitivity analyses. Those who receive randomization and at least one session of acupuncture will be defined as SS, which is used for safety analyses.

**General analysis principles**

All data will be summarized by treatment group. Numbers (percentages) will be used to describe categorical data. Either means (standard deviations) or medians (interquartile ranges) will be used for quantitative data depending on whether the variables are normally distributed or not. If not otherwise stated, the significance level will be set at 0.05. The significance level will be adjusted for the multiple comparisons for the primary outcome. The conclusion will be based on the analysis of primary outcome, and all secondary outcomes will be analyzed to support the primary analysis. All analyses will be carried out using SAS 9.3 (Cary, NC).

**Descriptive analyses**

The number of participants screened, excluded, randomly assigned to each group, interviewed at each follow up, and analyzed will be summarized using a flow diagram recommended by CONSORT [29] (Fig. 2). Reasons for the losses to follow-up and withdrawals will also be listed by treatment arm. Demographic characteristics and clinical outcomes at baseline will be presented in Table 1. When testing differences among the three groups, either one-way analysis of variance (ANOVA) or Krusal-Wallis one-way ANOVA (if normality is violated) will be used for continuous variables. Chi-square test or Fisher exact test will be used for categorical variables.

**Analysis of primary outcome**

For the analysis of primary outcome, the response rates of the three groups at 8 weeks will be calculated and the Z-test for comparisons of proportions will be used with FAS. There will be two comparisons. The first comparison is the one between electro-acupuncture group and sham acupuncture group. The second comparison is the one between manual acupuncture group and sham acupuncture group. The significance level will be adjusted at 0.025 for the multiple comparisons.
**Analysis of secondary outcomes**

For NRS score, comparisons among three groups will be assessed by mixed-effect model with repeated measurement (MMRM) analysis using NRS scores at all follow up time points as dependent variable, treatment as main factor, baseline value as a covariate. The same approach will be used to analyze WOMAC pain subscale, function subscale, and stiffness subscale, and SF-12. If there is a normality violation in the continuous variables, a transformation will be performed before the comparison. Chi-square test will be used for patient global assessment. These outcomes will be shown in Table 2.

**Safety analyses**

Based on the potential relationship between acupuncture and adverse events, adverse events are categorized as treatment-related or not. Acupuncture-related adverse events will be summarized by group and compared using Chi-square test (or Fisher exact test).

**Blinding analyses**

Kappa analysis will be used to determine whether participants correctly guessed their group assignment at a higher rate than would be expected by chance.

**Additional analyses**

Sensitivity analysis of primary outcome and secondary outcomes will be carried out with PPS to examine the robustness of conclusion. Several researches have shown that the center stratified randomization lead to the correlation among treatment groups. Therefore, we will discuss the generalized linear mixed-effect model for primary outcome to analyze the group effect, in which centre effects is included. Subgroup analysis based on Kellgren - Lawrence grade will be performed.

**Discussion And Trial Status**

The trial will provide high-quality evidence on the efficacy of electro-acupuncture and manual acupuncture for KOA. This paper provides details of the planned statistical analyses for current trial and will help reduce the risks of outcome reporting bias and data-driven results [30]. This paper has been prepared in accordance with the published guidelines for the content of statistical analysis plans [31]. As of October 2018, 480 patients from 9 centers were randomized. Follow-up is currently
ongoing and expected to finish on 10 April 2019. The final analysis will be conducted thereafter.

**Abbreviations**

ANOVA: One-way analysis of variance; EA: electro-acupuncture; FAS: Full analysis set; KOA: knee osteoarthritis; MA: manual acupuncture; MCII: minimal clinically important improvement; MMRM: mixed-effect model with repeated measurement; NRS: Numerical Rating Scale; PPS: per-protocol set; PROM: patient reported outcome measure; SA: sham acupuncture; SAP: statistical analysis plan; SF-12: 12-item Short Form Health Survey; SS: safety set; WOMAC: Western Ontario and McMaster Universities osteoarthritis index.

**Declarations**

**Acknowledgements**

None.

**Funding**

The trial is funded by Beijing Municipal Science & Technology Commission (D171100003217003) and Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding (XMLX201607). The funders have no role in study design, data collection, analysis and interpretation, decision to publish, or preparation of the manuscript.

**Availability of data and materials**

Of the current detailed statistical analysis plan no original data are available. The datasets used during the current study will be available from the corresponding author on reasonable request.

**Contributors**

JF Tu, JW Yang, ZS Yu and CZ Liu proposed the statistical analysis plan. JF Tu and Y Wang drafted the manuscript. CZ Liu led the trial concept and assembled the study group. All authors revised and approved the final manuscript.

**Ethical Approval and Consent**

Ethics approval was granted at the Research Ethical Committee of Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University (2017BL-077-01) and at each participating site. Written informed consent will be obtained from each participant prior to enrolment in the study.
Competing interests
None declared.

References
1. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. Lancet. 2015;386:376-87.
2. Tang X, Wang S, Zhan S, et al. The Prevalence of Symptomatic Knee Osteoarthritis in China: Results From the China Health and Retirement Longitudinal Study. Arthritis Rheumatol 2016;68:648-653.
3. Guillemin F, Rat AC, Mazieres B, et al. Prevalence of symptomatic hip and knee osteoarthritis: a two-phase population-based survey. Osteoarthritis Cartilage 2011;19:1314-1322.
4. Hiligsmann M, Cooper C, Arden N, Boers M, Branco JC, Luisa Brandi M, et al. Health economics in the field of osteoarthritis: an expert's consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Semin Arthritis Rheum. 2013;43:303-13.
5. Mahler E, Minten MJ, Leseman-Hoogenboom MM, Poortmans P, Leer J, Boks SS, et al. Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: a randomised, double-blinded, sham-controlled trial. Ann Rheum Dis. 2019;78:83-90.
6. da Costa BR, Reichenbach S, Keller N, Narrey L, Wandel S, Jüni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390:e21-21e33.
7. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363-388.
8. Jones CA, Beaupre LA, Johnston DW, Suarez-Almazor ME. Total joint arthroplasties:
current concepts of patient outcomes after surgery. Rheum Dis Clin North Am. 2007;33:71-86.

9. Su D, Li L. Trends in the use of complementary and alternative medicine in the United States: 2002-2007. J Health Care Poor Underserved 2011;22:296-310.

10. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med 2012;172:1444-1453.

11. Hinman RS, McCrory P, Pirotta M, et al. Acupuncture for chronic knee pain: a randomized clinical trial. JAMA 2014;312:1313-1322.

12. White A, Cummings M, Barlas P, et al. Defining an adequate dose of acupuncture using a neurophysiological approach--a narrative review of the literature. Acupunct Med 2008;26:111-120.

13. Zhang Q, Yue J, Lu Y. Acupuncture treatment for chronic knee pain: study by Hinman et al underestimates acupuncture efficacy. Acupunct Med 2015;33:170.

14. Armour M, Smith CA. Treating primary dysmenorrhea with acupuncture: a narrative review of the relationship between acupuncture 'dose' and menstrual pain outcomes. Acupunct Med 2016;34:416-424.

15. He W, Zhu B, Yu X, Liu B, Xu N, Jing X. [Comparison between western and Chinese acupuncture and its enlightenment]. Zhongguo Zhen Jiu. 2015;35:105-8.

16. Lin LL, Li YT, Tu JF, Yang JW, Sun N, Zhang S, et al. Effectiveness and feasibility of acupuncture for knee osteoarthritis: a pilot randomized controlled trial. Clin Rehabil. 2018:269215518790632.

17. Noordergraaf A, Silage D. Electroacupuncture. IEEE Trans Biomed Eng. 1973;20:364-6.

18. Tu JF, Yang JW, Lin LL, Wang TQ, Du YZ, Liu ZS, et al. Efficacy of electro-acupuncture and manual acupuncture versus sham acupuncture for knee osteoarthritis: study
protocol for a randomised controlled trial. Trials. 2019;20:79.

19. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology. Arthritis Rheum 1995;38:1541-1546.

20. Forestier R, Desfour H, Tessier JM, et al. Spa therapy in the treatment of knee osteoarthritis: a large randomised multicentre trial. Ann Rheum Dis 2010;69:660-665.

21. Hawker GA, Mian S, Kendzerska T, et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S240-252.

22. Tubach F, Ravaud P, Baron G, et al. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005;64:29-33.

23. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-1840.

24. Berman BM, Lao L, Langenberg P, et al. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. Ann Intern Med 2004;141:901-910.

25. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220-33.

26. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy
questionnaire. J Behav Ther Exp Psychiatry 2000;31:73-86.

27. Vach W, Blettner M. Logistic regression with incompletely observed categorical covariates--investigating the sensitivity against violation of the missing at random assumption. Stat Med. 1995;14:1315-29.

28. Li P, Stuart EA, Allison DB. Multiple Imputation: A Flexible Tool for Handling Missing Data. JAMA. 2015;314:1966-7.

29. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152:726-32.

30. Finfer S, Bellomo R. Why publish statistical analysis plans. Crit Care Resusc. 2009;11:5-6.

31. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318:2337-43.

Tables
Table 1 Baseline characteristics
| Baseline characteristic          | Type       | Levels or scale       |
|----------------------------------|------------|-----------------------|
| Gender                           | Categorical| Male; Female           |
| Age                              | Continuous | Years                 |
| Nationality                      | Categorical| Han, Others           |
| Duration of disease              | Continuous | Years                 |
| Kellgren - Lawrence grade        | Categorical| Grade II; Grade III   |
| Body mass index                  | Continuous | kg/m²                 |
| Years of education               | Categorical| 9; 9-12; 12           |
| Affected knee                    | Categorical| Unilateral; Bilateral |
| Past treatment                   | Categorical| Injections; Medication; Physical therapy; Acupuncture; Exercise, etc. |
| Concomitant diseases             | Categorical| Hypertension; Coronary heart disease; Diabetes mellitus; Hyperlipidemia, etc. |
| Numerical Rating Scale           | Continuous | point                 |
| WOMAC pain subscale              | Continuous | point                 |
| WOMAC function subscale          | Continuous | point                 |
| WOMAC stiffness subscale         | Continuous | point                 |
| Physical health, SF-12           | Continuous | point                 |
| Mental health, SF-12             | Continuous | point                 |

WOMAC: Western Ontario and McMaster Universities osteoarthritis index; SF-12: 12-item Short Form Health Survey

Table 2 Primary and Secondary Outcomes
| Outcomes                  | EA (n= ) | MA (n= ) | SA (n= ) | P value |
|--------------------------|----------|----------|----------|---------|
|                           |          |          |          |         |
| **Success rate, No. (%)**|          |          |          |         |
| 4 weeks                  | x (xx.x) | x (xx.x) | x (xx.x) | -       | xx.x (xx.x-xx.x) | xx.x |
| 8 weeks                  | x (xx.x) | x (xx.x) | x (xx.x) | -       | xx.x (xx.x-xx.x) | xx.x |
| 16 weeks                 | x (xx.x) | x (xx.x) | x (xx.x) | -       | xx.x (xx.x-xx.x) | xx.x |
| 26 weeks                 | x (xx.x) | x (xx.x) | x (xx.x) | -       | xx.x (xx.x-xx.x) | xx.x |
| **Numerical Rating Scale, mean (SD)** |          |          |          |         |
| Baseline                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 4 weeks                  | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 8 weeks                  | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 16 weeks                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 26 weeks                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| **WOMAC pain subscale, mean (SD)** |          |          |          |         |
| Baseline                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 4 weeks                  | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 8 weeks                  | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 16 weeks                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 26 weeks                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| **WOMAC function subscale, mean (SD)** |          |          |          |         |
| Baseline                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 4 weeks                  | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 8 weeks                  | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 16 weeks                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |
| 26 weeks                 | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) | xx.x | xx.x (xx.x-xx.x) | xx.x |

**Figures**
Figure 1. Responder criteria

Responder criteria
Figure 2. Flow diagram