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• Commentary

The methodology flaws in Hinman's acupuncture clinical trial, Part III: Sample size calculation

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In the October 2014 publication of *JAMA*, Dr. Hinman and colleagues published the study "*Acupuncture for Chronic Knee Pain: A Randomized Clinical Trial*," in which the authors concluded that "in patients older than 50 years with moderate or severe chronic knee pain, neither laser nor needle acupuncture conferred benefit over sham for pain or function. Our findings do not support acupuncture for these patients"[1]. We strongly disagree with such a conclusion.

As pointed out in my former articles[2,3], serious flaws exist in the trial design, statistics, interpretation of the results, as well as the use of Zelen study design itself, as reported by Hinman *et al*[1]. In Part II of the critique[3] I discussed problems in sample size calculation of the Hinman study[1] due to the variance introduced by multiple groups, multiple therapists, as well as the characteristics of intervention therapies. In this article, I discuss these aspects in more detail.

1 The sample size calculation based on the pre–requisites in the article

The article[1] stated that the authors: *aimed to detect a minimal clinically important difference (MCID) of 1.8 units in NRS pain (0–10 scale, 100 mm in length and marked at 10-mm increments). ...Calculations were based on an analysis of covariance adjusting for baseline outcome scores, assuming between-patient SDs of 3.0 units for pain and 12.0 units for function, conservative intra-therapist correlation of 0.10, 15% nonconsent rate for participants randomized to an intervention group and 15% attrition rate. To achieve 80% power at a 2-sided 5% significance level, 66 patients were required in each group, which we rounded up to 70.*

MCID was determined by six rheumatology experts as a 35% reduction in baseline pain score[1], which is equal to an effect size (ES) of 0.6 for function measures, as per calculation by White and Cummings[4]. An ES of 0.6 is higher than the generic value of 0.5 recommended by the National Institute for Health and Care Excellence (NICE) for testing non-steroidal anti-inflammatory drugs (NSAIDs)[5]. The selection of an ES of 0.6 in the study[1] establishes a more strict requirement to prove the efficacy of acupuncture than is used in the evaluation of NSAIDs.

Additionally, using online sample size calculation software[6], we calculated a minimum sample size of 45; with the accommodation of a 15% nonconsent and a 15% attrition rate, we also arrived at 66 patients per group, which is in agreement with Hinman *et al*[1]. However, their calculation did not consider the four groups and the six comparisons among these four groups although they did mention in above cited statements[1].

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2 Sample size adjustment based on the multiple group comparisons

If we use the sample size that Hinman's trial had used[1], also considering the factor there were six comparisons of the means among the four groups, then the significance level changes to 0.83%, but no longer at 5% (*i.e.*, 5% must be divided by 6)[7]; the power level is also reduced to 55.97% from 80%. In order to maintain the significance level at 5% and the power level at 80% as the original trial[1] wanted, appropriate adjustments should be made to the sample size. Using the formula specifically for six comparisons among four groups $26 \times s^2/d^2 + 1$[7] (here s represents assumed between-patient SD 3.0[1], d represents MCID 1.8[1], so $26 \times 3^2/1.8^2 + 1 = 74$, plus the adjustment of 15% nonconsent and 15% attrition rate), we find n = 106 per group, which is also confirmed by the online sample size calculation[6].

3 Sample size adjustment with the consideration of the factor of intra-therapists

In the study conducted by Hinman *et al*[1], treatments were applied by eight therapists. For a well-designed study, the variance of among therapists has to be considered. The adjustment should be based on the sample size multiplied by an inflation factor (IF)[8]: $1+ (m - 1)r$. Here, m = 8 (m represents that the therapist numbers were 8[1]), and r = 0.10[1] (r represents the intra-therapist correlation 0.10 mentioned by Hinman *et al*[1]). Therefore, IF is 1.70, and the sample size adjusted for the IF should be 126 (74 × 1.70). Including the adjustment of 15% nonconsent and 15% attrition rate, I calculate n = 180 per group. In the study by Hinman *et al*[1], four groups of patients were included; so, the appropriate sample size should be 720, which is 2.56 times the sample used in Hinman's clinical trial[1].

4 The sample size calculation should consider the differences of intervention groups

As pointed out in Part II, in Hinman's clinical trial, the sample size calculation was not based on either previously published studies of laser acupuncture and acupuncture, or on the author's own previous studies in laser acupuncture and acupuncture[3]. In that clinical trial at week 12[1], the drop-out rates were 2.82% (2/71) in the control group, 22.86% (16/70) in the acupuncture group, 18.31% (13/71) in the laser acupuncture group, and 22.86% (16/70) for the sham laser acupuncture group. The dilution rates were 31.27% in the acupuncture group, 21.87% in the laser acupuncture group and 13.80% in the sham laser acupuncture group[3]. I use the base sample size 126 per group (from the above calculation), multiplied by (1.0 plus the drop-out rate, and dilution rate), and then I can calculate sample sizes that would have been needed for each group given the real drop-out rate and dilution rates from the study. The sum of drop-out rate and dilution rate for the control, acupuncture, laser acupuncture and sham laser acupuncture were 2.82%, 54.13%, 40.18% and 33.66, respectively at 12 weeks. Thus I calculate 130, 195, 177 and 168 in the control, acupuncture, laser acupuncture and sham laser acupuncture groups, for a total sample size of 670 patients. If we consider the follow-up at the end of 6 month, 3 month after the last treatment at the week 12, we can add 15% additional attrition rate, and we can get 150, 225, 204 and 194 in the control, acupuncture, laser acupuncture, and sham laser acupuncture groups, respectively. According to this calculation, the total sample size would be 773. I do not think the follow-up at one year[1] is appropriate for this study, because chronic knee pain is a degenerative condition and the effectiveness from either acupuncture or laser acupuncture would not last a full year after cessation of treatment.

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6 Competing interests

The author is an independent researcher, and declares that he has no competing interests.

REFERENCES

1 Hinman RS, McCrory P, Pirotta M, Relf I, Forbes A, Crossley KM, Williamson E, Kyriakides M, Novy K, Metcalf BR, Harris A, Reddy P, Conaghan PG, Bennell KL. Acupuncture for chronic knee pain: a randomized clinical trial. *JAMA*. 2014; 312(13): 1313–1322.

2 Fan AY. The methodology flaws in Hinman's acupuncture clinical, Part I: Design and results interpretation. *J Integr Med*. 2015; 13(2): 65–68.

3 Fan AY. The methodology flaws in Hinman's acupuncture clinical trial, Part II: Zelen design and effectiveness dilutions. *J Integr Med*. 2015 April; Epub ahead of print.

4 White A, Cummings M. Acupuncture for knee osteoarthritis: study by Hinman *et al* represents missed opportunities. *Acupunct Med*. 2015; 33(1): 84–86.

5 National Institute for Health and Care Excellence (NICE). *Osteoarthritis: care and management in adults*. (2014-02) [2015-04-05]. http://www.nice.org.uk/guidance/cg177.
6 Dallal J. *Approximate sample size calculator: comparing two means*. (2012-05-23) [2015-04-05]. http://www.jerrydallal.com/lhsp/SIZECALC.HTM.
7 Dallal J. *Sample size calculations simplified: control trials*. (2012-05-23) [2015-04-05]. http://www.jerrydallal.com/lhsp/SIZE.HTM.
8 Friedman LM, Furberg CD, DeMets DL. Sample size. In: *Fundamentals of clinical trials*. 4th ed. New York: Springer. 2010: 133–162.

• Corrigendum

Corrigendum: Bioactivity of five components of Chinese herbal formula Jiangzhi granules against hepatocellular steatosis

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In the initially published version of this paper in *Journal of Integrative Medicine*, Volume 11, Issue 4, the doses of the components were miswritten (5, 10, 20, 50, 100, 200, and 500 μmol/L) in several places (pages 262, 263 and 264). The miswritten doses are all ten times of the original doses (0.5, 1, 2, 5, 10, 20, and 50 μmol/L).

The errors happened on page 262, in METHODS and RESULTS; on page 263, "2.3 Cytotoxicity assay of the five components", and "2.4 Induction of HepG2 cellular steatosis and treatment with TCM components"; on page 264, "3.1 Experimental dose determination of the five components by cytotoxicity assay" and the title of Table 1.

The authors apologize for those errors.

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