----Original Message----
From: XXX YYY<xxx@yyy.zzz>
Sent: Wed, Apr 10, 2013 at 6:49 PM
To: Managing Editor
Subject: RE: FW: Request for evaluation of revised paper, reference number: 2013 BJMMR 3208

Attached are Dr. Manchikanti's comments on the revision. Please let me know if you need anything further.

XXX YYY

REVIEW FOR NECESSITY OF RANDOMIZED CLINICAL TRIALS

COMMENTS:
The authors have significantly expanded the manuscript to address multiple concerns raised in the review. However, the major issue remains in reference to placebos when conducting trials, what is a true placebo, and misinterpretation of an active-controlled trial as a placebo-controlled trial based on a methodologist's or reviewer's view.

COMPULSORY REVISIONS:
The authors, while presenting an excellent case for the necessity of randomized, clinical trials, along with expansion of the text to include multiple issues, still continue to miss the importance of methodologists which drives policy.

Overall the manuscript is pertinent for newer interventions; however, it may be somewhat redundant and confusing for existing interventions.

If an intervention is used for long periods of time, such an intervention should not be excluded based on the conduct of randomized trials based on a misguided or lack of understanding of the clinical effects of placebos.

As an example, the authors should realize that injecting sodium chloride solution into a disc or muscle or into a closed space such, as the epidural space or intraarticular space, can produce a multitude of effects. Some are clinically relevant and equivalent to an active substance. Consequently, a placebo is not a true placebo in this case. The authors should emphasize that the design for a placebo should be explicit in that no active effect is produced by injecting an inactive substance into an active structure. This is extremely important for interventional techniques (Manchikanti L, et al. Guidelines warfare over interventional techniques: Is there a lack of discourse or straw man? *Pain Physician* 2012; 15:E1-E26).

Further, in reference to active-control trials, the authors added the wording that a treatment backed by sufficient evidence which is extremely vague. This will once again empower misguided reviewers to exclude all types of interventions and consider them as placebos. This also gives them an excuse to require a placebo-controlled trial, whether it is properly performed or not, prior to considering an active-controlled trial. Consequently, we may never be able to have any active-controlled trials except for highly proven techniques, which may not require any such studies.

I would like to point the authors to the recent systematic review by Pinto et al published in *Annals of Internal Medicine* (Pinto RZ, et al. Epidural corticosteroid injections in the management of sciatica: A systematic review and meta-analysis. *Ann Intern Med* 2012; 157:865-877) which considers a local anesthetic injection into the epidural space as a placebo even though approximately 80% of the patients were shown to respond with significant improvement over a period of 2 years and they showed a defined amount of relief of 13 to 16 weeks with each injection.

This is not new for budding methodologists who do not have any sense of a technique and biased administrative clinicians. The same can be applied to Chou and Huffman's review of guidelines for APS, sponsored by the opioid industry, which appeared as multiple publications.

Please also look at what do interventions tell us (Levin JH. Prospective, double-blind, randomized placebo-controlled trials in interventional spine: What the highest quality literature tells us. *Spine J* 2009; 9:690-703). This manuscript converts all local anesthetics into placebo and consequently claims nothing works even though the interventions were effective for several years on a continuous basis based upon a randomized study performed for a period of 2 years in an appropriately selected sample (Manchikanti L, Shah RV, Datta S, Singh V. Critical evaluation of interventional pain management literature provides inaccurate conclusions. *Spine J* 2009; 9:706-708).

The effects of placebo solutions and electromagnetic effects have been well described (Pham Dang C, et al. Effect on neurostimulation of injectates used for perineural space expansion before placement of a stimulating catheter: Normal saline versus dextrose 5% in water. *Reg Anesth Pain Med* 2009; 34:398-403, Tsui BC et al. Dextrose 5% in water: Fluid medium maintaining electrical stimulation of peripheral nerve during stimulating catheter placement. *Acta Anaesthesiol Scand* 2005; 49:1562-1565, Indahl A, et al. Interaction between the porcine lumbar intervertebral disc, zygapophysial joints, and paraspinal muscles. *Spine (Phila Pa 1976)* 1997; 22:2834-2840, Indahl A, et al. Electromyographic response of the porcine multifidus musculature after nerve stimulation. *Spine (Phila Pa 1976)* 1995; 20:2652-2658).

The authors also should specify what the sample size should be and what is an adequate sample.

Further, the authors state that randomization is able to construct a perfect control, which, at baseline, becomes fully comparable to the experimental group regarding all known and unknown prognostic factors – provided that the randomized groups become large enough. The authors probably need to clarify the sentence – there is no such thing as a perfect control. It has been shown in numerous studies that baseline groups do not correlate. Consequently, we are tempted to exclude these studies and the results. However, when randomization is performed based on established criteria, and if these differences do not make any difference in the outcomes, the study should be considered as proper (Manchikanti L, Pampati V. Research designs in interventional pain management: Is randomization superior, desirable or essential? *Pain Physician* 2002; 5:275-284).

Reviewer Details:

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Note: Modification was done in this email ONLY to hide the identity.