Author's response to reviews

Title: Edta chelation therapy for cardiovascular disease: a systematic review

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Author's response to reviews:

Dear Referees,

Thank you for taking the time and effort to review our manuscript. It is clear that this has been done in a thorough and thoughtful manner. Each of the criticisms both major and minor were considered and have been addressed in our resubmission.

First Reviewer: Max H. Pittler
The only major compulsory revisions as required by the first reviewer have been addressed.
. The discussion section (page 19, paragraph 1) now includes a sentence that specifically states the need to warn of potential harm through the use of EDTA. The addition of the last sentence at the end of the paragraph states: "Clinicians should also discuss potential risks associated with EDTA chelation therapy and the current lack of evidence supporting its use in cardiovascular disease."
. The second point requiring modification in the conclusion was addressed by the addition of: ...including the potential for adverse effects attributable directly to EDTA...

Minor revisions have been made to the text as suggested by both reviewers.
1. In the background section, semi-contentious has been replaced with contentious.
1a. An explanation has been added to the background section regarding 'EDTA therapy'. Page 4, paragraph 1 now includes the following addition: "As this is a non-conventional therapy, there is no universally recognized standard therapy. Most protocols, however, share a degree of similarity. A typical protocol might consist of 30 intravenously administered solutions of 3 grams of disodium EDTA with concomitant administration of varying levels of ascorbic acid, B-vitamins, heparin, and the minerals magnesium, copper, zinc, selenium and manganese delivered over 1.5 to 3 hours in 500ml to 1000ml of normal saline. Therapy is often delivered on a weekly or biweekly basis and may be followed up with a much less frequent maintenance schedule.
2. Methods section now includes comment on the authors being contacted with the following addition on page 5: "Authors of some of the trials were contacted to solicit their interpretation of the review and also to comment on any criticism that we had found in non-peer reviewed literature."
3. Report on duplication publication is now included
3a. Reference has been made to the conclusion in Villaruz's Cochrane review in the following statement added to page 7 "The conclusion found by Villaruz et al was that 'there is insufficient evidence to decide on the effectiveness or ineffectiveness of chelation therapy in improving clinical outcomes of patients with atherosclerotic cardiovascular disease"
3b. Beneficial effects and improvements are compared to baseline which has been added appropriately.
3c. Risks of EDTA chelation therapy have been highlighted and added to the Abstract in the results section with the addition of: "Adverse effects were rare but those of note included some cases of hypocalcemia and a single case of increased creatinine in patients on the EDTA intervention."
4 and 5. addressed above.

Second Reviewer: Bongani Mayosi

Minor essential revisions have been addressed below.
1. semi-contentious changed to contentious
2. Abstract now indicates that search was conducted till the end of April and not July.
3. Excluded studies now clearly referenced
4. Abbreviation CAM has been changed to be complementary and alternative medicine.
Discretionary revision suggestion:
1. Mortality was not considered as an outcome measure in the review because it was not an outcome in the primary studies.

Sincerely,

Dugald Seely