Author's response to reviews

Title: Systematic review: conservative treatments for secondary lymphedema

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Author's response to reviews: see over
Dear Ms. Manibo:

We would like to thank the reviewers for their time and comments.

Below is a list of reviewers’ and editor’s comments, as well as our responses to these comments.

**Reviewer 1**

1. *No (there is no clear definition of primary and secondary outcome measures which renders further review of this paper pointless).*

Please see our response to comment 3 below.

2. *I am of the opinion that the subject matter is very relevant and deserve proper investigation.*

Thank you.

3. *I would recommend that the authors decided on a few important outcome measures: E.g. Objective measurements of circumference/volume & subjective patient comfort/pain/function and then re-evaluated the papers found in the literature search with that in mind. The literature analysis should focus on prospective blinded randomised comparative studies.*

Our manuscript is based on the assignment given to us by the Agency for Healthcare Research and Quality and Centers for Medicare and Medicaid Services. The purpose of the assignment was to evaluate the published evidence regarding conservative treatment for secondary lymphedema, regardless of outcome. To arbitrarily decide on a hierarchy of outcomes, especially when the lymphedema research community does not have an accepted gold standard outcome or set of outcomes, would have allowed our
normative judgments to dictate an important parameter of the review, i.e., the exclusion of potentially relevant papers because they did not contain outcomes that fell within our predefined hierarchy of outcomes. Since the technology assessment upon which the manuscript is based was presented at a policy-making meeting (i.e., Medicare Evidence Development & Coverage Advisory Committee), arbitrarily reducing the scope of included studies could have been deleterious to policy deliberations. This is because our conclusions would have been based on a highly-selective subgroup of studies.

We do believe the reviewer raised a valid concern about the multiplicity of outcomes in lymphedema research and we already raised this issue in the previous iteration of the manuscript (p. 14, lines 7-9).

The issue of including non-RCTs in systematic reviews generates debate; however, inclusion of observational studies in systematic reviews is justified if these studies can address gaps in the evidence from RCTs. This is especially so when a review seeks to assess adverse effects. We included observational studies precisely to facilitate examination of evidence for adverse effects; we added a paragraph to the text to clarify this point (p. 6, lines 7-9). Inclusion of observational studies in this regard is justified according to the Agency for Healthcare Research and Quality’s Methods Guide for Effectiveness and Comparative Effectiveness Reviews (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=454). Please also see a recent publication in Journal of Clinical Epidemiology (PubMed ID: 21636246).

Reviewer 2

Minor Essential Revisions:
1. On page 9 and 10 you describe two additional methods that are not mentioned on page 3: a special diet with low fat and an interesting approach using bone marrow stromal cell transplantation. Please add these in to the according section on page 3.

We added low-fat diet (p. 4, lines 1-2). In reference # 23, the conservative treatment is decongestive therapy and stromal cell transplantation is a novel treatment that does not fall into the ‘conservative’ category. Therefore, we elected not to mention stromal cell transplantation in the section mentioned by the reviewer (this section lists conservative therapies only).

2. On page 26 at the legends for table 1 you wrote the explanation for RT twice. At table 2 misspelling for “Bone Marrow Stromal Cell Transplantation”.

We corrected these two errors.

3. Please give in the background section some facts on the incidence or
prevalence for secondary lymphedema

We added some facts (p. 3, lines 12-16).

4. It would be interesting if the results could be analysed according to initial treatment causing SE. Would there be a different outcome for patients who were irradiated or treated by lymphadenectomy for the effectiveness of the different treatment approaches? Could you comment on this aspect in the discussion section?

We added a comment to the discussion (p. 15, lines 1-5).

Discretionary Revisions:
1. Please consider to add page numbers and to use short captions for table 1 and 2.

We are uncertain as to what the reviewer means by “short captions” and we added page numbers to the table files.

Editor

Please ensure that the order in which your tables are cited is the same as the order in which they are provided. Every table must be cited in the text, using Arabic numerals. Please do not use ranges when listing tables. Tables must not be subdivided, or contain tables within tables. Please note that we are unable to display vertical lines or text within tables, no display merged cells: please re-layout your table without these elements. Tables should be formatted using the Table tool in your word processor. Please ensure the table title is above the table and the legend is below the table. For more information, see the instructions for authors on the journal website.

We confirmed that our tables meet these requirements.

We notice that you have included tables as additional files. If you want the tables to be visible within the final published manuscript please include them in the manuscript in a tables section following the references. Alternatively, please cite the files as Additional file 1 etc., and include an additional files section in the manuscript.

We included our literature search strategy as an additional file. We identified this file as such in the text (p. 5, lines 4-5) and included an additional materials section in the manuscript (p. 16, top of page).

We are submitting two copies of the revised manuscript: a copy with track changes showing our revisions and a clean copy without track changes.
Sincerely,

Parminder Raina, PhD