Author’s response to reviews

Title: The Effect of Post Mastectomy Radiation Therapy on Breast Reconstruction with and without Acellular Dermal Matrix: A Systematic Review and Meta-analysis Protocol

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Author’s response to reviews:

Dear Dr. Malic:

We thank you and the reviewers for your thoughtful appraisal and constructive feedback. At your request, we have addressed every point you requested we improve. Please note that in our point-by-point response below, the indicated pages and line numbers apply to the revised unmarked version.

Reviewer #1: This research protocol has an interesting idea, but the manuscript has many failing.

First, It’s no clear why the final search date is in 2016 (right now it is outdated). Authors should correct the date.

We have updated the final search date (Line 344).

Do not include articles in several languages or gray literature is a significant limitation in a Systematic Review. Please, review and take the better decision.
We thank the reviewer for this feedback to broaden the search. We will now include articles in English, French (reviewer AC bilingual) and other languages were translation possible with the resources of our institution (Lines 565 – 566).

I do not know what the authors want to say with this phrase "The references of selected works will be reviewed using SCOPUS to identify additional articles that meet inclusion criteria". Please review and use the consistent search strategy described in the literature to search for articles based on the references of other articles.

The authors will independently review the references of selected works and compare results to identify additional articles (Lines 349 - 451).

I recommend that 2 authors carry out the search and then compare the results, before evaluating the titles and summaries.

We will adopt this approach (Line 348-349).

Primary outcomes are poorly described. I recommend improve the definition. The authors should mention the statistical measure used for each outcome. The flaw is that there is no clear definition of complications, therefore it is difficult to know the level of measurement of each outcome.

We thank the reviewer for the chance to better define the outcomes.

We changed the primary outcome to be reconstructive failure defined as the need to have the implant removed as this is a more objective endpoint and clinically relevant. Table 2 outlines how the complications are defined.

Line 694 describes that complications will be analyzed as proportions with Odds Ratios calculated.
Please, it isn’t necessary describe the form to data extraction. It is enough to say that they will use it. Delete all related to this. "Data will be extracted using predesigned forms using Excel (Microsoft) for the following items..." change for "Data will be extracted using predesigned forms."

We have made this change (Line 683-684).

<50% does not mean that there is no heterogeneity, please review.

Thank you for this correction. We have changed this to reflect low-moderate heterogeneity (Line 699).

It is important to describe if the results will be presented according to the type of study from which the information was extracted. The results of controlled studies are not the same as of observational studies

We have changed the manuscript to reflect that the results will be analyzed by study type. (Line 693-694).

Authors describe that they will use the Cochrane RoB tool for randomized studies and NOS for Non-randomized studies. Why are not authors using the ROBINS tool?

We now recognize that this is the tool recommended by the Cochrane group. Changed Line (824-825).

Remove: "The results of this study will be published in an appropriate plastic surgery, breast surgery or oncology journal. This work will also be presented at conferences in these fields."

We have removed this accordingly (Line 828).
I don't agree with this phrase: "If there are an insufficient number of articles, the review will proceed as a descriptive narrative." The authors are conducting a systematic review and do not understand that regardless of the number of items identified, it will remain a SR. Another point is whether they can perform a meta-analysis, which will ultimately depend on the number of articles and the heterogeneity.

We have removed reference to this (Line 828). The point that we attempted to convey was that we would still continue with a review but would not conduct a meta-analysis. We would attempt to summarize the results of the studies found in the structured search.

Reviewer #2:

Abstract

1. Re: "Implant-based breast reconstruction has undergone advancements including" - perhaps change to "Implant-based breast reconstruction has undergone several changes including...". You imply that ADMs are a positive/beneficial 'advancement' in the field and yet the literature does not support this conjecture (and indeed this is why you're doing this much needed review).

We changed the phrase to “broadened“ in an attempt to avoid bias (Line 97).

Intro

Very nice. One suggestion only Re: "Several studies have demonstrated additional benefits including: lower risk of capsular contracture and implant migration" - this isn't quite correct, the above review by Hallberg shows equipoise re: capsular contracture. The article you cite is a narrative review which should be replaced.

We have added two additional papers, Chun 2010 and Parks 2012 illustrating the increased risk of seroma formation and infection seen with ADM use (Line 203).
Methods

1. I fear if you build your searches using terms concerning radiotherapy then you will miss a great deal of information. Many articles concerning ADMs for implant-based breast reconstruction do not explicitly mention neoadjuvant or adjuvant therapy in the title and nor will these terms necessary be reflected in the keywords / MESH terms. I suggest your search is broadened to capture all studies using implant-based breast reconstruction with ADMs; you could then manually remove irrelevant papers and of those included they aren't obviously RT ADM vs. noRT ADM studies, extract subgroup data from broader articles pertaining to irradiated ADM patients. Thoughts?

We thank the reviewer for these comments. We tried this approach initially with out librarian but this yielded too many irrelevant results.

2. "Only peer-reviewed papers written in English will be included. " - It is good practice not to limit searches to a language; if you have funds for translation, helpful multilingual students in your institution or access to Google Translate, etc then articles should be translated where possible.

We will now include articles in English, French (reviewer AC bilingual) and other languages were translation possible with the resources of our institution (Lines 565 – 566).

3. Re: "The types of study to be included are control trials, quasi randomized studies, cohort studies, case-control, case series" do you mean "The types of study to be included are randomised controlled trials, quasi randomized studies..."?

Yes, we have changed this (Line 562).

4. The primary outcome should be a single event. eg., the most important end-point of failure of the reconstruction / implant loss. All other outcomes are of secondary interest (infection, seroma, haematoma, etc). At the moment I'm not clear what you will count as a "post operative complication" and this is critical, as the figures could be massaged (eg. you choose not to include
seroma as it shows ADMs unfavourably or vice versa). I suggest these outcomes are examined individually and you select one as the primary end-point.

We have changed the primary outcome to reconstruction failure defined by implant loss as this has a defined endpoint and clinically relevant (Line 572). We will report additional complications separately as described in Table 2.

5. You don't need to detail this "Dichotomous data will be analyzed using odds ratios (OR) with 95% CI. For continuous data, mean differences (MD) with 95% confidence interval (CI) will be calculated. " as this is tacit. Your decision or whether to use fixed/random effects is not solely based on statistically heterogeneity as this fails to account for clinical heterogeneity (ie. a study of using one brand of ADM may be statistically the same as another ADM but there are clearly important clinical differences which must be accounted for). I imagine there will be need for random effects given the expected clinical heterogeneity. Consequently you can remove reference 22 which is passe.

This reference has been deleted.

6. Cochrane recommends the use of the ROBINS-I tool for the risk of bias assessment in observational studies - please amend.

This has been changed (Line 824).

7. Please add methods on your GRADE assessment.

We have added a section on GRADE assessment (Line 825).

8. What will you do if data are missing? Will you contact authors? Exclude the paper? This should be detailed.
In the case of missing data or data that cannot be extracted, we will contact the author (Line 684).

9. What will be your unit of analysis? The breast or patient? This is a hotly debated topic and the majority of clinicians, statisticians and the literature suggest that the patient should be the unit of analysis. None-the-less you must expect some studies to report the units differently and have a plan of how to deal with this data.

The unit of analysis will be by patient as opposed to by breast. For studies reporting outcomes by breast, the data will be converted to reflect the complications by patient where possible (Line 689).

10. Will you consider 2-stage implant-based reconstruction or straight to implant only with ADM +/- RT studies? How will you handle immediate versus delayed reconstructions? And what is the evidence underpinning these decisions?

In order to understand the impact of radiation we will include studies on 2-stage and straight to implant reconstruction, as well as immediate vs delayed reconstructions. We will group each type of reconstruction separately (Line 691).

Throughout the protocol and within the letter to the Editor, there is an flavour of bias in favour of ADMs. My sincerest apologies if my observation is incorrect but still, I wonder if the authors could state their position/preference/biases/conflicts regarding ADMs and their clinical practice? Ideally, the author team is composed of individuals with equipoise on the matter and conflicts of interest/preferences, etc are stated upfront.

ADMds are used at our institution for reconstructions. The authors affiliations are listed and there are no conflicts of interest. Reviewer AC in general practice (not in a surgical speciality) and AG is in plastic surgery and we hope this provides a balance.