PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Objective assessment of clinical, oncological & cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery: protocol for a systematic review
AUTHORS	Hu, Jesse; Rainsbury, Richard; Segaran, Ashvina; Predescu, Oana; Roy, Pankaj

VERSION 1 – REVIEW

REVIEWER	Shelley Potter Bristol Centre for Surgical Research, Bristol Medical School, UK
REVIEW RETURNED	10-Dec-2017

GENERAL COMMENTS	This is a protocol for a systematic review of volume replacement techniques in oncoplastic breast surgery. While this is a worthwhile question, there are a number of methodological issues that require consideration: 1. Introduction The first 2 paras are well written but the 3rd para would benefit from more detail about the types of volume replacement (e.g mini LDs, LiCAPs etc) and where these may be indicated (e.g small breasts). The table summarising previous systematic reviews is not labelled and is uninformative. What types of study and procedures were included in each review? Have any reviews just focused on volume replacement? It would be helpful to include additional columns with more detail such as number of papers reporting outcomes of volume replacement techniques; procedures evaluated etc. There have also been other recent SRs including one which is good quality which are not included e.g Adv Radiat Oncol. 2016 Sep 21;1(4):205-215. doi: 10.1016/j.adro.2016.09.002. eCollection 2016 Oct-Dec;. Ann Surg Oncol. 2016 Oct;23(10):3247-58. doi: 10.1245/s10434-016-5313-1. Epub 2016 Jun 29. 2. Outcomes There is inconsistency throughout the manuscript regarding the primary and secondary outcomes to be evaluated throughout the manuscript and with those stated on PROSPERO. The abstract states that the primary outcomes are 'oncological safety and cosmetic outcomes' but the 'Objectives' (page 6, line 47-9) and PROSPERO record state the primary objectives are to evaluate the 'clinical, oncological and cosmetic outcomes'. The methods again state 'oncological safety and cosmetic outcome.' The objectives also state a secondary objective is to 'A secondary objective is to review the patient-reported outcomes associated with oncoplastic breast surgery to help refine patient selection for the procedure and to

develop an algorithm for identifying patients suitable for volume replacement rather than volume displacement during OBS'. There is no further mention of patient reported outcomes in the methods. There is nothing in the proposed data extraction about patient selection so it is unclear how this objective would be achieved.

The outcomes are not clearly defined. The authors need to clearly define what they mean by 'oncological safety' above 'includes overall survival and local recurrence rates'. There is also the need to define 'cosmetic outcomes'. The title of the manuscript states 'objective' assessment but there is no other reference to 'objective assessment' anywhere in the methods. Are the authors going to exclude studies assessing patient reported cosmetic outcome? This needs to be defined and justified.

3. Inclusion and exclusion criteria
The inclusion and exclusion criteria for the review are unclear. Does the 10 patients refer to the whole study or just the number of patients undergoing volume replacement techniques? It would be helpful some of the techniques to be included were listed e.g. LiCAP flaps, TDAP flaps, mini LDs. The exclusion criteria need to be more specific – i.e. women undergoing volume displacement techniques (such as therapeutic mammaplasty) and those undergoing mastectomy and total breast reconstruction will be excluded. What about indication for surgery and gender – these are also included on PROSPERO and should be included in the methods

The strengths and weaknesses section and the PROSPERO record states that the search will be restricted to studies published in English – this should be included in inclusion and exclusion criteria section of the methods.

Are the authors planning to include abstracts and grey literature or just full text published papers? This needs clarification.

4. Search strategy
This is different from that stated on PROSPERO. In the manuscript the search interval is from inception until 31st June 2018?? PROSPERO states 'The search will include all publications from January 1990' . June 2018 is after the proposed end date of the study. This needs to be consistent.

The search strategy does not appear comprehensive. The authors should also include search terms for the individual procedures (LiCAP, TDAP, mini LD) etc to avoid missing potentially relevant papers.

5. Study registration
The PROSPERO registration needs to be included in the main test in the methods section.

6. Risk of bias assessment
The ACROBAT-NRSI is being used to assess risk of bias in non - randomised studies – the ROBINS-1 tool would be better as the authors state that they are using Cochrane methodology.

7. Data extraction
The field for data extraction do not appear adequate to address the study objectives, especially regarding patient selection. How are the authors going to classify 'level of evidence'? There is little detail on

	the type of procedure and more detail is required regarding what data they are planning to extract regarding the outcomes. This section is currently inadequate. 8. Statistics This section requires elaboration. Are the authors going to pool the data and perform a meta-analysis; if not why not? The statement regarding funnel plots in inappropriate without additional information. Again there is disparity between this manuscript and the PROSPERO record which needs to be addressed. 9. Discussion There is a need for a discussion section at the end of the manuscript which is currently lacking. 10. Strengths and weaknesses This section needs to include some strengths as well as weaknesses. E.g first review to specifically focus on volume replacement techniques

REVIEWER	Michael Rose Department of Surgery, Section of Plastic Surgery, Hospital of Southwest Jutland, Denmark
REVIEW RETURNED	30-Jan-2018

GENERAL COMMENTS	In my opinion the oncological outcome after breast conserving surgery and oncoplastic replacement techniques for breast cancer is expected to have equal oncological results as patients threated with other oncoplastic techniques. However, studies on longtime oncological results are few. Regarding the cosmetic outcomes it can be expected, or it´s possible, that the results of oncoplastic replacement techniques may be poorer as the surgery is more extensive. And also here, there´s very few studies on cosmetic outcome with validated instruments. In conclusion a review of studies including the outcome regarding oncological as well as cometic outcome of the replacement technique in oncoplastic breast cancer surgery will be useful.

VERSION 1 – AUTHOR RESPONSE

Reply to Editorial Requirements:

- PRISMA-P check-list completed and attached
- Strengths and Limitations section revised and included at the end of the abstract

Reply to Reviewer 1:

1. Introduction was revised to include more details about the types of volume replacement. For example, we listed some of the techniques used and the indication which is largely for patients with small-moderate non-ptotic breasts with large tumour to breast ratio.

Table 1 was revised to include more details and the latest SRs. Most of the SRs are focusing on oncoplastic techniques in general with volume displacement cases forming the main bulk of the cases.

2. Outcomes were reviewed and revised to be in line with those stated on PROSPERO. The outcomes were also further elaborated in various subgroups under clinical, oncological and cosmetic outcomes.

The primary objective remains the same which is to evaluate the clinical, oncological and cosmetic outcomes following volume replacement in patients undergoing oncoplastic breast conserving surgery. We have further elaborated on the primary objective. Early clinical outcomes include clinical complications such as flap necrosis, infection, re-admission, re-excision and completion mastectomy rates. Later clinical outcomes include correction of symmetry (contralateral augmentaion/reduction), nipple reconstruction, correction of deformity (lipomodelling, scar revision etc), mastectomy for recurrence, and any other procedures. Oncological outcomes include overall survival and local recurrence rate in the follow-up period. Cosmetic outcomes include cosmetic results and cosmetic evaluation method.

A secondary objective is to review the patient-reported outcomes (PROMs) associated with oncoplastic breast surgery to help identify any unmet needs and to consider refining the existing PROMs to suit women undergoing volume replacement surgery. PROMs include patient satisfaction and quality of life. We would also be looking at parameters, if reported in the published studies, optimising patient selection for these surgical procedures such as age, smoking history, co-morbidity such as diabetes mellitus, tumour size and location, and pre-operative breast/bra size.

3. Inclusion and exclusion criteria were reviewed to be more specific.

Only women with breast cancer who are undergoing partial breast reconstruction using volume replacement in breast conserving surgery will be included. Males, patients who underwent mastectomy and patients who underwent surgery for benign breast conditions will be excluded. We will include all randomized controlled trials (RCTs), cohort and case-control studies. Single group cohorts and case series will be included if there are more than 10 patients who underwent volume replacement after oncoplastic breast conserving surgery

4. Search strategy is consistent with that stated on PROSPERO which is from January 1990 to 31 December 2017. Additional search terms for individual procedures such as chest wall perforator flaps, latissimus dorsi mini flap, omental flap and further logical combinations of these and related terms will be used to maximize sensitivity.

5. Study registration was included in the methods section.

6. Risk of bias assessment was changed as suggested. We will use the Cochrane Risk of Bias Tool for RCTs and the ROBINS-1 tool for non-randomised studies. We will compare study protocols with final papers where possible and key missing information across all study types will be presented.

7. Data extraction was expanded to include more variables to address the study objectives.

New variables such as history of diabetes, smoking history, location of tumour, technical details and further definitions of outcomes are included.

8. Statistics section was reviewed and revised. We feel that it is unlikely that we are able to perform a meta-analysis due to the large disparity in literature and small numbers in studies. Hence, we will provide a narrative synthesis of the findings from the included studies, structured around the type of intervention, target population characteristics, type of outcome and intervention content. We will provide summaries of intervention effects for each study by calculating risk ratios (for dichotomous outcomes) or standardised mean differences (for continuous outcomes).

9. Discussion was not included as this is a study protocol.

10. Strengths and weaknesses was reviewed and included at the end of the abstract.

Reply to reviewer 2:

We do hope that our study will help address some of the concerns too.

VERSION 2 – REVIEW

REVIEWER	Shelley Potter Population Health Sciences, Bristol Medical School, UK
REVIEW RETURNED	10-Apr-2018

GENERAL COMMENTS	Many thanks for making the suggested changes. There is still inconsistency regarding the outcomes to be evaluated in this paper - the title states 'oncological and cosmetic' and the remainder of the paper states 'clinical, oncological and cosmetic'. This needs to be addressed. Page 7 line 39 - remove the word 'etc' - would be better to precisely include the techniques or state 'other volume replacement techniques'. Although this is a protocol, there is still a need for a discussion. It should summarise the study, what it will add to the literature.

VERSION 2 – AUTHOR RESPONSE

Thank you for reviewing our manuscript.

We have submitted a revised manuscript along with the editorial requirments requested.

In particular, the following changes have been made:

1. A draft search strategy has been included as a supplementary file

2. The title of the paper has been modified slightly.

3. 'etc' has been removed in page 7 line 39.

We hope to hear a favorable reply from you soon.