Author’s response to reviews

Title: A randomised controlled feasibility trial to evaluate local heat preconditioning on wound healing after reconstructive breast surgery: the preHEAT trial

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Author’s response to reviews:

Dear Dr. Mayo,

Submission: PAFS-D-18-00129

A randomised controlled feasibility trial to evaluate local heat preconditioning on wound healing after reconstructive breast surgery: the preHEAT trial Saahil Mehta; Suzie Cro; Billie Coomber; Rachel Rolph; Victoria Cornelius; Jian Farhadi Pilot and Feasibility Studies

Thank you for your recent correspondence regarding our submission and the reviewers comments. We would like to respond to the comments and hope that the manuscript is accepted for publication. The updated manuscript is labelled ver 1.10.
Reviewer 1:

- I wonder if there are too many objectives. What is the net goal of the paper? I sit to get the groundwork and necessary data to then set up the larger trial? Why such a large number of secondary objectives that cover a broad range of unrelated issues? how were these chosen?

The goal of the paper is to create a robust protocol that can be used for a definitive multicentre trial. We have added this overarching aim to the background section (page 5, paragraph 2 “preHEAT was a feasibility study for a trial that will evaluate local heat preconditioning with respect to its effects on skin necrosis in patients with breast cancer undergoing SSM and NSM. The overarching aim of preHEAT was to create a robust protocol that can be used for a larger definitive multicentre trial.”) There are very few randomised controlled trials in breast reconstruction and we included the secondary outcomes to better understand whether an RCT is in fact feasible at all. We do not believe that these are unrelated as they will all be important for the design of the larger multicentre RCT.

- How long before surgery were the patients asked to start heat application?

The patients were asked to perform the heating procedure 12-hours before surgery. This was at around 7-8pm the night before surgery. This is in the text on page 7, paragraph 2 “Patients were asked to perform the heating procedure as close to 12 hours before surgery at home. Patients attended for surgery as normal the following day.”

- Do we know how adherent they were (frequency, length of time for heat application, consistency in achieving and maintaining 43 degrees, etc.)?

Yes, there was an overall compliance of 76% to the heating protocol. We asked patients to document the times and temperatures of the protocol as they performed it. We have added the compliance form as a supplementary document to this resubmission and this is referenced in the text page 8, paragraph 2.

- Do you have a definition of necrosis that was used by your assessors to then give a yes/no assessment? Were the assessors standardized within themselves and consistent? Was there any pre-trial training done to the assessors on this?

One of the main aims of the study was to determine how to measure necrosis in the definitive trial. We considered different approaches to do this. As we described on page 8, paragraph 3, we assessed the current method of measuring skin necrosis of any depth (superficial, partial thickness, full thickness) and clinical opinion as a yes/no measure. There was no definition used
for yes/no as the aim was to compare the reliance on clinical experience to do with other measures (depth and area). However, in this study our nurses are standardised to the extent that they are all plastic surgery nurses who manage post-operative wounds on a daily basis and are trained specifically to do so. We would ensure the clinical outcome assessors in the main trial will also have experience in post-operative wounds. There was pre-trial training and this was focussed on explaining the assessment methods (yes/no, SKIN Score, wound grid) and the importance of blinding in assessment.

- I don't see any clear and objective assessment of cosmetic outcomes. This was not an aim of this trial but it is certainly something of interest we will look into for the definitive multicentre trial.

- Is the 30% flap necrosis rate in line with published data on this? Yes, several references are included in the text to support this and are referenced on page 21, paragraph 1.

- Can you explain the 5 days of length of stay? Seems a bit long. Length of stay can vary widely and will depend to some extent on local hospital policy. The range of length of stay for patients undergoing breast reconstruction is between 3-5.5 days. We have included some references here to support this. We do not feel that our length of stay is an outlier to other studies 1–4.

- Did you explore an important patient-centered outcome: pain/discomfort at heat pad application and after surgery? This was not included in this study but we did in a previous smaller study. The intervention was acceptable overall 5.
Reviewer, Shelley Potter:

Abstract

1. The last line in the results section should read '15% of patients experiencing necrosis in the control group required surgical intervention

We have checked our calculation of 17% (4/23) for patients experiencing necrosis in the control group requiring surgical intervention which we believe holds correctly.

Background

2. The authors state that SSM/NSM and reconstruction are the 'standard of care' in most patients requiring mastectomy for breast cancer. This is not accurate. NICE guidelines state that all patients requiring mastectomy should be offered immediate breast reconstruction (IBR) but rates of IBR vary significantly across the UK. This statement should be revised and the current guidelines referenced.

Thank you for raising this important point. We have now corrected this and referenced the NICE guidelines. This can be found on page 4, paragraph 1. “According to the most recent NICE guidance, immediate breast reconstruction should be to all women requiring a mastectomy for breast cancer in the UK.”

3. The authors are correct in stating that MSFN may result in further surgical procedures, but as the majority of patients undergoing mastectomy and IBR are having surgery for breast cancer, a further concern is that complications may delay the delivery of adjuvant cancer treatment and compromise oncological outcomes. This should be added as a further (arguably more important) justification for reducing the incidence of necrosis.

Thank you for this important suggestion. We have now included this on page 4, paragraph 1. “This can require further surgical interventions, delayed recovery and an increased length of stay (LOS) in hospital, which can cause a delay in the delivery of adjuvant cancer treatment and compromise oncological outcomes.”

Methods

4. Further details are required regarding how patients were identified and approached regarding study participation.
We have included a clearer explanation of this on page 6, paragraph 3. “All referrals to Plastic Surgery were screened and patients referred for mastectomy and immediate breast reconstruction were identified. These patients were approached to participate in the study during a weekly breast reconstruction clinic.”

5. The authors state that necrosis area was measured 'on the day of occurrence' - more accurately, this is probably the day at which it was initially identified as the injury would have occurred in theatre at the time of mastectomy.

We agree that this is not clear and have edited this on page 9, paragraph 1.

Further details are required regarding the assessment of compliance with the heating procedure. It would be helpful to include the assessment tool as an appendix.

We have included the compliance form as another supplementary material document.

6. I am slightly confused by the sample size calculation. The primary aim of the study was to determine how to assess the primary outcome, but this sample size calculation is exploring issues around recruitment and also it appears as if it may be a power calculation for the primary outcome of the main trial (skin necrosis).

The reviewer is correct. The main aim of the feasibility was to determine how to assess the primary outcome for the definitive trial, but we were also interested in a number of other feasibility parameters including estimating recruitment and retention rates and estimating other feasibility parameters. No power calculation was performed as no statistical hypothesis testing was planned or performed. That is we first established the anticipated the number of cases we would see over a two year recruitment period: we anticipated 300 potentially eligible participants and a recruitment rate of 60%, resulting in an anticipated sample size of 180. We wanted a sample size that was large enough to allows us to estimate the feasibility parameters with reasonable precision. At the time of the trial design we did not have the decision matrix developed, which is how we subsequently put some structure to the decision making process for the necrosis outcome. This was a suggested addition made by the TSC at the start of the trial. As a result, the original sample size calculation was based on providing some reassurance that the recruitment duration would result in a ‘large enough’ sample size to provide meaningful estimates that would be informative for the feasibility parameters.

We have updated the sample size section so that our approach to sample size is clearer.
Results

7. The rates of MSFN reported in this study are 26-35%. This seems very high compared to other studies and requires comment in the discussion as the majority of the group are low risk (non smokers, non obese, no prev RT). These figures have also been used to inform the potential sample size for the main trial.

We have checked the literature and there is a wide variation in skin necrosis rates. We have included these references on page 21 paragraph 1. Further to this very few studies define what they report as skin necrosis. The results of the study indicate the most reliable method of reporting skin necrosis is yes/no (any depth) and we have suggested that the need for surgical intervention is an effective comparator.

8. Rates of non-compliance with the heating are high (25%). When calculating the rates of MSFN - did the authors do an ITT analysis or a per protocol analysis as this would influence the results and subsequent power calculation. If informing a sample size calculation was also a 2nd objective this should be clarified in this section of the methods (it does appear to be as stated in the discussion)

Data were analysed following the intention-to-treat principle i.e. all participants with a recorded outcome were included in the analysis according to the treatment group to which they were randomised regardless of treatment actually received. We have added this detail to the statistical analysis section. We do not agree that the non-compliance level is high.

In the sample size section of the methods, we have added that the estimated events rates will be used to calculate the required sample size for a larger adequately powered definitive study so this is clear. Above this the background indicates that the estimated necrosis event rates in each treatment group will be used to inform the design of a definitive trial. These changes can be found on pages 10-12)

9. Further information is required about the 30 serious adverse events

We have described the serious adverse events in line with the updated CONSORT guidelines in reporting harm. These are clearly detailed in table 4. In addition to this, we have clearly documented the single adverse reaction related to the heating protocol on page 23, paragraph 2. We have also suggested why this may have happened and what we have learned. We feel we have provided adequate descriptions but if the reviewer still feels we need to describe more then we would ask what specifically they would like us to describe.
Discussion

10. The majority of mastectomies are performed for breast cancer so the main problem with skin necrosis is its impact on adjuvant treatments and oncological outcomes. Scarring is an issue but one of lesser importance.

Thank you for this important point. We agree with this and hope that our additional statement as mentioned in point 3 indicates this.

11. The discussion is very repetitive of the background - the first 4 paragraphs can be removed. The remaining discussion could be significantly reduced to aid the reader.

We have relooked at the discussion session in light of the reviewers comments and as a result we have substantially revised. We have removed the first 4 paragraphs and have edited the remaining text.

12. The authors should consider some of the limitations of the study and include a para discussing these

This has been included on page 24, paragraph 2. “This feasibility study was not powered to detect a significant difference in MSFN and heat preconditioning. However, the study has demonstrated a positive signal that shows a possible beneficial effect of heat preconditioning on MSFN rates. The future plans for this trial are to expand to a definitive multicentre RCT through further grant applications such as the Health Technology Assessment funding stream with the NIHR”.

13. It is not clear what the next steps will be, it would be helpful to have a para discussing these - e.g. a multicentre RCT

The next step is to expand this into a multicentre RCT and we have elaborated on this on page 24 paragraphs 2 and 3. “We have subsequently started funding applications to the NIHR.”

We hope that the above satisfies the reviewers and yourself. We look forward to receiving your response.

Kind regards,
Mr. Saahil Mehta BSc Hons MBBS MRCS

On behalf of the preHEAT research team

Bibliography


