

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prospective Pilot Study Protocol Evaluating Safety and Feasibility of Robot-assisted Nipple Sparing Mastectomy (RNSM)
AUTHORS	Park, Ko Un; Lee, Sandy; Sarna, Angela; Chetta, Matthew; Schulz, Steven; Agnese, Doreen; Grignol, Valerie; Carson, William; Skoracki, Roman

VERSION 1 – REVIEW

REVIEWER	Park, Hyung Seok Yonsei University College of Medicine, Department of Surgery
REVIEW RETURNED	15-Apr-2021

GENERAL COMMENTS	<p>This is a protocol of a pilot study evaluating RNSM for patients with early breast cancer. This study would have an important role to generate hypotheses for further prospective studies, and the protocol of the study is also valuable to researchers who are planning prospective studies of RNSM in the world. Therefore, the reviewer believes that this protocol can be accepted in the BMJopen and added to the literature. However, there are some minor issues to be addressed before publication</p> <ol style="list-style-type: none">1. This study would be the first prospective study for use of RNSM in patients with early breast cancer in the United State. However, there is another IDE study on clinicaltrials.gov, which is evaluating the role of RNSM in risk-reduction for high-risk women. (https://clinicaltrials.gov/ct2/show/NCT03892980). Therefore the sentence “This is the first US trial assessing the safety and feasibility of RNSM.” may be revised.2. Postoperative pictures after RNSM would be informative for evaluating objective cosmetic outcomes. Please consider collecting postoperative pictures after RNSM in your protocol.3. Recording the whole procedure of RNSM after docking would be also informative, please consider it.4. Which type of robotic surgical system would you apply? Si, X, Xi, and SP? Please specify if possible.5. Cite a recent article related to RNSM in the reference, please Front. Oncol., 08 January 2021 https://doi.org/10.3389/fonc.2020.594388
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REVIEWER	Ludwig, Kandice K Indiana University School of Medicine
REVIEW RETURNED	26-Apr-2021

GENERAL COMMENTS	I think that this study is worthwhile as more institutions seek expanded use for robots in the operating room. I believe that your goal of the protocol is to prove (1) feasibility and (2) track outcomes
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	<p>when compared to open technique. Some things to consider as this protocol is developed:</p> <ol style="list-style-type: none"> 1. Interesting eligibility criteria includes only patients with small breasts, even though the introduction speaks extensively of benefits for RNSM in large breasted patients. Would edit the intro as such. 2. How to address axilla in patients who have SLNB or ALND in same operation 3. Size of incision (realizing it may be extended, but what is the usual start) 4. Frozen sectioning of nipple base? 5. An important outcome metric would be cost-- for institutions that don't currently own a robot for other reasons would be significant investment of dollars.
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REVIEWER	Ko, BeomSeok University of Ulsan College of Medicine, Surgery
REVIEW RETURNED	30-Apr-2021

GENERAL COMMENTS	<p>As a pilot study, this study is considered to be well-purposed. If you need to do axillary dissection, will you use a robot? It seems necessary to mention some limitations.</p> <ol style="list-style-type: none"> 1. As the number of subjects included in the study is small, difficulties are expected in the analysis of safety and effectiveness. 2. As a single group study, there is a limitation in that it is difficult to compare with conventional surgical methods. 3.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Hyung Seok Park, Yonsei University College of Medicine Comments to the Author:

This is a protocol of a pilot study evaluating RNSM for patients with early breast cancer. This study would have an important role to generate hypotheses for further prospective studies, and the protocol of the study is also valuable to researchers who are planning prospective studies of RNSM in the world. Therefore, the reviewer believes that this protocol can be accepted in the BMJopen and added to the literature. However, there are some minor issues to be addressed before publication

1. This study would be the first prospective study for use of RNSM in patients with early breast cancer in the United State. However, there is another IDE study on clinicaltrials.gov, which is evaluating the role of RNSM in risk-reduction for high-risk women.

([https://urldefense.com/v3/__https://clinicaltrials.gov/ct2/show/NCT03892980__;!!Cjnu1T6GFXg!_JeGtpuooF8nod5avTvzjUMBPE3EhJ-q74bYwcQx6vI5z4VsuvzLYhtbDWkoqgPOw\\$](https://urldefense.com/v3/__https://clinicaltrials.gov/ct2/show/NCT03892980__;!!Cjnu1T6GFXg!_JeGtpuooF8nod5avTvzjUMBPE3EhJ-q74bYwcQx6vI5z4VsuvzLYhtbDWkoqgPOw$)). Therefore the sentence “This is the first US trial assessing the safety and feasibility of RNSM.” may be revised.

Response: We have clarified this bullet point in the “Strengths and Limitations of this Study” section.

2. Postoperative pictures after RNSM would be informative for evaluating objective cosmetic outcomes. Please consider collecting postoperative pictures after RNSM in your protocol.

Response: We agree with this comment and have clarified this point in the “Trial Procedures: Post-operative phase” section.

3. Recording the whole procedure of RNSM after docking would be also informative, please consider it.

Response: We agree with this comment and have clarified that the entire robotic portion of the surgery will be recorded in the “Trial Procedures: Surgery and biospecimen collection” section.

4. Which type of robotic surgical system would you apply? Si, X, Xi, and SP? Please specify if possible.

Response: We have specified the use of the da Vinci Xi surgical system in the “Trial Procedures: Surgery and biospecimen collection” section.

5. Cite a recent article related to RNSM in the reference, please

Front. Oncol., 08 January 2021 |

[https://urldefense.com/v3/__https://doi.org/10.3389/fonc.2020.594388__;!!Cjnu1T6GFXg!_JeGtpuooF8nod5avTvzjUMBpSE3EhJ-q74bYwcQx6v15z4VsuvzLYhtbDUhoEkDvA\\$](https://urldefense.com/v3/__https://doi.org/10.3389/fonc.2020.594388__;!!Cjnu1T6GFXg!_JeGtpuooF8nod5avTvzjUMBpSE3EhJ-q74bYwcQx6v15z4VsuvzLYhtbDUhoEkDvA$)

Response: We have cited this article in the “Introduction” and updated the list of references.

Reviewer: 2

Dr. Kandice K Ludwig, Indiana University School of Medicine Comments to the Author:

I think that this study is worthwhile as more institutions seek expanded use for robots in the operating room. I believe that your goal of the protocol is to prove (1) feasibility and (2) track outcomes when compared to open technique. Some things to consider as this protocol is developed:

1. Interesting eligibility criteria includes only patients with small breasts, even though the introduction speaks extensively of benefits for RNSM in large breasted patients. Would edit the intro as such.

Response: While this pilot study is limited to smaller breasted women (traditional open NSM candidates), we plan to expand the cohort in future studies. We clarify this point in the “Methods and Analysis” section. We believe that once we establish basic safety and feasibility of RNSM, we will be able to conduct RNSM on larger breasted women.

2. How to address axilla in patients who have SLNB or ALND in same operation

Response: A small separate axillary incision will be made for the SLNB and ALND (similar approach we take during open NSM). We added this information in the “Trial Procedures: Surgery and biospecimen collection” section.

3. Size of incision (realizing it may be extended, but what is the usual start)

Response: The incision location and size are clarified in “Study design” section.

4. Frozen sectioning of nipple base?

Response: Our institutional practice does not include routine frozen sectioning of the nipple base. This specimen is evaluated under permanent H&E evaluation. However, patients are carefully selected pre-operatively to assure that the tumor is situated far away from the base of the nipple.

5. An important outcome metric would be cost-- for institutions that don't currently own a robot for other reasons would be significant investment of dollars.

Response: We agree with the reviewer that cost, more importantly cost-effectiveness of the robotic technique is absolutely an important outcome to consider. Given this is a small feasibility study, we are not explicitly measuring cost-effectiveness. While the initial amortization will be high for the robotic system, we hypothesize that with the reduced rate of complication compared to open (especially with skin necrosis) and high patient satisfaction, the use of the robotic technique will be cost effective. We plan to measure this in our future studies. This has been included in the “Study objectives and outcomes” section.

Reviewer: 3

Dr. BeomSeok Ko, University of Ulsan College of Medicine Comments to the Author:

As a pilot study, this study is considered to be well-purposed.

If you need to do axillary dissection, will you use a robot?

Response: Currently we do not intend to use the robot for axillary surgery. This is clarified in the 'Study Design' section.

It seems necessary to mention some limitations.

1. As the number of subjects included in the study is small, difficulties are expected in the analysis of safety and effectiveness.

Response: We agree with this comment that there is a need to mention limitations, and that difficulties may arise in the analysis due to small sample size. We have included this limitation in the "Strengths and Limitations of this Study" section. Furthermore, we emphasize this as a pilot study designed to assess initial feasibility and safety of RNSM and results will lead to a larger scale study (see "Study Objectives and Outcomes" section).

2. As a single group study, there is a limitation in that it is difficult to compare with conventional surgical methods.

Response: We agree with the reviewer comments that this study is not powered to compare the robotic technique to open NSM. However, in the US due to safety concerns, in discussion with the FDA, we have designed this initial feasibility and safety study to assure that the breast can be removed en bloc. The intent is that absent major safety signals, the results of this study will lead to a larger scale study.

VERSION 2 – REVIEW

REVIEWER	Ludwig, Kandice K Indiana University School of Medicine
REVIEW RETURNED	29-Jul-2021
GENERAL COMMENTS	Thank you for addressing all of the comments of the reviewers. The manuscript in its current state is ready for publication.