BMJ Open

Prospective Pilot Study Evaluating Safety and Feasibility of Robot-assisted Nipple Sparing Mastectomy (RNSM)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050173
Article Type:	Protocol
Date Submitted by the Author:	16-Feb-2021
Complete List of Authors:	Park, Ko Un; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Lee, Sandy; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Sarna, Angela; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Chetta, Matthew; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery Schulz, Steven; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery Sisk, Geoffroy; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery Agnese, Doreen; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Grignol, Valerie; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Carson, William; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Skoracki, Roman; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery
Keywords:	Breast surgery < SURGERY, PLASTIC & RECONSTRUCTIVE SURGERY, Breast tumours < ONCOLOGY, ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Prospective Pilot Study Evaluating Safety and Feasibility of Robot-assisted Nipple Sparing Mastectomy (RNSM)

Authors: Ko Un Park MD[1], Sandy Lee BA[1], Angela Sarna BS[1], Matthew Chetta MD[2], Steven Schulz MD[2], Geoffroy Sisk MD[2], Doreen Agnese MD[1], Valerie Grignol MD[1], William Carson MD[1], and Roman J Skoracki MD[2]

Author Affiliations:
1. Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center James Cancer Hospital, Columbus, OH
2. Department of Plastic and Reconstructive Surgery, The Ohio State University Wexner Medical Center James Cancer Hospital, Columbus, OH

Brief title: Robot-assisted Nipple Sparing Mastectomy

Financial and conflict of interest disclosure: The authors have no relevant financial disclosure. The authors declare that there are no competing interests.

Corresponding Author:
Ko Un Park, MD
Assistant Professor of Surgery
The Ohio State University Wexner Medical Center
The James Cancer Hospital
410 W 10th Ave, N908 Doan Hall
Columbus, Ohio 43210
Tel: 614-293-6708
Fax: 614-293-3465
koun.park@osumc.edu

Requests for reprints should be addressed to:
Ko Un Park
410 W 10th Ave, N908 Doan Hall
Columbus, Ohio 43210
Tel: 614-293-6708

Word Count: 2759

ABSTRACT

Introduction

Nipple sparing mastectomy (NSM) can be performed for treatment of breast cancer and risk reduction, but total mammary glandular excision in NSM can be technically challenging. Minimally invasive robot assisted NSM (RNSM) has the potential to improve the ergonomic challenges of open NSM. Recent studies in RNSM demonstrate the feasibility and safety of the procedure but this technique is still novel in the United States.

Methods and analysis

This is a single arm prospective pilot study to determine safety, efficacy, and potential risks of RNSM. Up to 12 RNSM will be performed to assess the safety and feasibility of the procedure. Routine follow-up visits and study assessments will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months. The primary outcome is to assess feasibility of removing the breast gland en bloc using the RNSM technique. To assess safety, postoperative complication information will be collected. Secondary outcomes include defining benefits and challenges of RNSM for both surgeons and patients utilizing surveys, as well as defining the breast and nipple areolar complex (NAC) sensation recovery following RNSM. Mainly descriptive analysis will be used to report the findings.

Ethics and dissemination The RNSM protocol was reviewed and approved by the U.S. Food and Drug Administration (FDA) using the Investigational Device Exemption (IDE) mechanism (reference number G200096). In addition, the protocol was registered with clinicaltrials.gov (NCT04537312) and approved by The Ohio State University institutional review board (IRB), reference number 2020C0094 (8/18/2020). The results of this study will be distributed through peer-reviewed journals and presented at surgical conferences.

Trial registration number: NCT04537312

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first US trial assessing the safety and feasibility of RNSM.
- Patient reported outcome data including nipple sensation after surgery are collected.
- If RNSM proves to be safe and feasible, the results will form the basis for a subsequent multi-center trial measuring oncologic outcomes.

INTRODUCTION

Breast cancer is the most common solid tumor in women. With advances in breast reconstruction after mastectomy for the treatment of breast diseases including breast cancer, surgical techniques have evolved to preserve the skin flaps and nipple areolar complex (NAC) to give better aesthetic outcome without compromising oncologic outcome.[1, 2] Nipple sparing mastectomy (NSM) preserves the skin and nipple areolar complex for improved body image and patient satisfaction.[3-6] However, total mammary glandular excision for oncologic purposes in NSM can be technically challenging particularly due to small incision size in relation to the operative field and poor visualization of the dissection plane due to the curvature of the breast parenchyma and suboptimal illumination.[7] Surgeons experience greater physical symptoms such as neck and lower back pain, mental strain, and fatigue from performing NSM.[8] A more ergonomically sound technique with greater visualization is needed to improve surgeon ergonomics but also to improve the ease of the operation.

Open NSM results in variable rate of sensation in the nipple-areolar complex. In a study by Chirappapha et al, evaluation of 55 NSM for sensory recovery demonstrated 11 patients with partial sensation recovery in first 6 months.[9] Women undergoing risk reducing mastectomy with reconstruction report the breast feeling numb and lacking in sensation.[10] These changes in bodily sensations can have long-lasting quality of life repercussions and can actually cause harm as the skin acts as a functional protection against thermal injuries.[11, 12] Thus, understanding the sensation of the breast after RNSM from a patient-centered research perspective is important.

Additionally, traditional open NSM is associated with higher rates of mastectomy skin flap and nipple areolar complex necrosis if performed in larger breasted women.[13] While bra cup size is not a reliable marker for increased risk of complication, breast volume measured using the area visualized on mammogram can predict large volume associated with higher necrosis rate.[14] For instance, 45% of patients with breast volume on mammogram of 675 cc or larger had mastectomy flap or nipple areolar complex necrosis.[13] Currently, there is a need to develop innovative approach to NSM in women with larger breast size.

Minimally invasive robot assisted NSM (RNSM) has the potential to improve the safety and efficacy of NSM. Studies in RNSM demonstrate the feasibility and safety of performing a minimally invasive NSM using the da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA). Preliminary data from a randomized clinical study comparing 40 open to 40 robotic NSM cases indicate the safety of RNSM with regards to low perioperative complication rate and none of the patients had any mastectomy flap necrosis or loss of nipple due to complication.[15] In a recent publication of the updated series by Toesca et al, between June 2014 and January 2019, 73 women underwent 94 RNSM with immediate implant based breast reconstruction.[15] There were 39 patients with invasive breast cancer, 17 with ductal carcinoma in situ (DCIS), and 17 without cancer diagnosis but with BRCA mutation. The mean surgery time was 3 hours and 32 minutes. The most common complication after surgery was seroma (N=5) followed by eschar (N=4). The rates of infection and hematoma were low (N=2 each). Only 1 patient had necrosis after surgery. There was one patient in the series who had Stage IV disease at the time of surgery and died 4 months after surgery. Excluding this patient with metastatic disease, the disease-free survival rate was 100% with a median follow-up was 19 months (range 3.1–44.8). Long term oncologic safety of RNSM will take time for data to mature.

To study the technical feasibility and safety of RNSM, we performed a series of cadaveric RNSM and assessed the mastectomy flap for presence of residual breast tissue.[16] We were able to demonstrate that RNSM is technically feasible. Residual breast tissue was only

detectable in the NAC, and none was detectable in the mastectomy flap outside the NAC.

The technique of RNSM is still novel for U.S. surgeons and to date there are no published studies from US institutions because the use of the da Vinci surgical system is not FDA approved for use in breast surgery. This is partly due to the safety concerns expressed by the FDA, which stems from the inferior outcomes of minimally invasive surgery compared to open hysterectomy for cervical cancer.[17] In response to the safety concerns, our institution has received FDA approval of an Investigational Device Exemption (IDE) to initiate the RNSM clinical trial described here. This study aims to define the anatomic challenges and technical feasibility of RNSM and demonstrate its initial safety and efficacy profile. These data will inform a future, larger study of the procedure and help surgeons determine whether to consider the procedure for their practice.

METHODS AND ANALYSIS

Study design

This is a single arm prospective pilot study to determine safety, efficacy, and potential risks of Robotic Nipple Sparing Mastectomy (RNSM), funded by an Ohio State Intramural Research Program IDEA award and National Center for Advancing Translational Sciences award. Up to 20 subjects will be enrolled in order to perform 12 procedures of RNSM. This study will be performed in a single center, at The Ohio State University Wexner Medical Center James Comprehensive Cancer Center. All eligible interested patients must sign consent for enrollment into the robotic nipple sparing mastectomy clinical study.

Eligible patients will undergo RNSM as previously described.[16] Briefly, the anterior axillary incision will be used for dissection. A subcutaneous dissection will be performed to create a working space. The single port system (GelPOINT Mini, Applied Medical, Rancho Santa Margarita, CA) will be inserted into the incision and the three 8-mm-diameter robot ports will be inserted and secured into the GelSeal Cap connected to an insufflator to keep the pressure at 8 mm Hg. Once the robot is docked, subcutaneous dissection will be performed using the monopolar-curved scissors and bipolar grasping forceps for traction and exposure. Using similar technique, the gland will be separated from the pectoralis major muscle. The specimen will be removed from the anterior axillary incision. All breast specimens will be evaluated by pathology through the institutional usual specimen processing protocol. To reconstruct the mound of the breast, plastic surgery will perform an immediate direct to implant-based reconstruction or TE placement using the anterior axillary line incision following the standard technique.

Patients will be recovered in the postoperative phase following the usual standard of care. Routine follow-up visits and study assessments will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months, as well as standard of care follow-up for surveillance for a minimum of 5 years after surgery.

Study population and eligibility criteria

Patients who present to the breast surgical oncology clinic will be screened for eligibility for robot-assisted nipple sparing mastectomy (RNSM). These patients typically have small breasts (bra cup size B or smaller, less than 500 grams of breast tissue) and no extensive ptosis of the breast. Prior to consenting, patients will be informed that cancer treatment outcomes using RNSM have not been evaluated by the FDA and this is an ‘off label’ use of the device. Eligible patients will be informed of the purpose, procedures, and potential risks of the study. Patients will be eligible for inclusion in the study if they meet all the following inclusion

criteria and excluded from participation in the study if they meet any of the following exclusion criteria (Table 1).

Table 1. Inclusion and exclusion criteria

Inclusion criteria:	Exclusion criteria:

• adults: age ≥ 18 years
• surgical candidates, per standard of care for: open nipple sparing resection and reconstruction for following indications:
  ○ for risk reduction mastectomy
  ○ treatment of ductal carcinoma in-situ or clinically node negative cT1-T3 breast cancer
• surgical candidates for open NSM, per standard of care, with regards to patient anatomic factors and tumor location
• patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	• pregnant
	• patients with:
	  ○ inflammatory breast cancer skin involvement with tumor pre-operative diagnosis (clinical, radiological or pathologic) of nipple-areola complex involvement with tumor
	  ○ grade 3 ptosis of nipple
	  ○ bra cup size greater than C cup
	• current use of nicotine (ie. cigarette smoking, vaping, use of nicotine containing gum or transdermal patches or use of other forms of nicotine)
	• patients that are high risk for anesthesia, defined by the American Society of Anesthesiologists Scale ASA, grade 4 or higher
	• patients that do not have the ability to give informed consent
	• prisoner status at surgical clinic visit
	• previous thoracic radiation history

Sample Size

The number of cases to enroll in the pilot study has been set to twelve based on a previous study investigating the learning curve of RNSM.[18] The previous study of 39 cases found that docking time, robot console time, and overall operative time decreased on the 13th case, thus concluding that 12 cases were needed to decrease the operative time.

Subject withdrawal

Patients will be free to withdraw from the study at any point without consequence. Additionally, subjects may be withdrawn if during surgery the PI determines the patient requires surgery in the conventional manner and a pivot to this standard care surgery is immediately undertaken. For this initial trial, no patients will be replaced after their surgery for non-compliance to follow-up in The Ohio State University Wexner Medical Center breast oncological clinic.

TRIAL PROCEDURES

Surgery and biospecimen collection

Standard of care preoperative workup will be followed prior to surgery. RNSM will be performed using the da Vinci Robotic Surgical System, a software-controlled, electro-mechanical system designed for surgeons to perform minimally invasive surgery. The breast specimen will be removed via gentle manual extraction through the anterior axillary incision using the "waving flag technique" (move the gland back and forth and up and down gently until it is removed). For specimen extraction, no devices such as the morcellator will be used. To assure en bloc removal of the specimen, if it is not feasible to remove the entire gland as a single piece, the incision will be extended to assure removal of the intact specimen. The specimen will be labeled, as per standard of practice, with sutures and right/left orientation by the surgeon. All relevant data pertaining to the surgical procedure will be collected and breast specimens will be oriented for pathologic evaluation through the institution usual specimen processing protocol.

Post-operative phase

Per the usual standard of care, the patient will follow up in the breast surgical oncology clinic around post-operative day 14, day 30, 6 months, and 1 year. Photographs and study-related assessments will be obtained and completed at each of the previously stated time points. All images will be taken in a fashion that minimizes subject identification, such as exclusion of the head and neck region, any identifiers removed including tattoos, birthmarks, etc. At 6 weeks, a review of the patient's records will also occur to capture any re-operations/readmissions from a safety perspective. An implant exchange surgery will be performed around 3-6 months after expansion is complete or later if chemotherapy is required or the patient desires to wait.

Stopping Criteria

The study will be stopped if a) en bloc removal of the breast specimen is not achieved during the RNSM surgery, or b) the specimen is incorrectly labeled or oriented for pathologic evaluation. Specimen labeling with sutures is a part of standard practice and is performed by the investigator-surgeon. Any occurrence of the aforementioned events will trigger a temporary suspension of further enrollment into the study until additional evaluation utilizing the Corrective And Preventive Action (CAPA) process has been completed. Should the study be stopped, all regulating bodies (e.g. FDA, data safety monitoring committee) will be notified.

Data collection and management

The Ohio State Comprehensive Cancer Center clinical trial office research informatics services will be used as a central location for data processing and management, following standard operating procedures for the collection, storage, and analysis of electronic case report forms (eCRF). Data obtained from the patient's electronic medical record and surveys will be stored on a secure drive on university password protected computers, and/or entered into a secure username/password protected database, using OnCore as the electronic data capture tool. Data will be accessible only to the research personnel approved for this study.

STUDY OBJECTIVES AND OUTCOMES

The primary objectives are to generate preliminary data on the safety and complications from RNSM. En bloc resection and removal of the breast specimen will be assessed as a primary endpoint. We will also investigate the total duration of the operation, the frequency of conversion

to open technique, the length of hospitalization, and post-operative complications. Reported complications after RNSM include nipple areolar complex necrosis, mastectomy flap necrosis, temporary skin blistering, hematoma, seroma, infection, loss of implant from infection, delayed axillary wound healing, transient brachial plexus neurapraxia, and transient neurapraxia due to intraoperative patient positioning. Safety will be assessed by monitoring for all adverse events/serious adverse events, re-operations, and readmissions. Mastectomy and NAC necrosis will be assessed using a validated scoring system called the SKIN score.[19] To assess outcome, routine follow-up visits will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months. Patients will complete the study related assessments within the 12 months of completion of operation. Patients will continue standard of care follow-up for surveillance at minimum of 5 years after surgery.

Beyond this, we aim to define the benefits and challenges of RNSM from the surgeon's perspective. Additional endpoints include NMSQ and SURG-TLX validated surveys to determine surgeon musculoskeletal fatigue. To assess patient satisfaction with the breast after surgery and sensation recovery after surgery, BREAST-Q and NAC modules for patient reported outcomes and satisfaction, and Semmes-Weinstein monofilament skin testing will be used. An exploratory endpoint is technical familiarity, which will be measured through operative robot console time.

As part of standard of care, patients will follow up with the plastic and reconstructive surgery clinic on an annual basis for surveillance of long term known implant-related adverse events including but not limited to the following: capsular contraction, implant rupture and deflation, breast implant associated-anaplastic large cell lymphoma, asymmetry, chest wall deformity, extrusion, infection, malposition/displacement, seroma, skin rash, wrinkling/rippling of implant, and unsatisfactory shape/size.

Safety assessments

For this study, an adverse effect/event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs. All observed or subject-described adverse effects/events—serious or non-serious—and abnormal test findings, regardless of suspected causal relationship to the investigational device or other procedures, will be assessed beginning on the day of surgery and at every follow-up visit thereafter. As part of standard of care, patients will follow up with the plastic and reconstructive surgery clinic on an annual basis for surveillance of long term known implant-related AEs. AEs or abnormal test findings felt to be associated with the investigational device or, if applicable, other study procedures will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator. To ensure patient safety, all adverse events will be recorded, evaluated, and reported to FDA and IRB as required for all patient visits including long term follow-up.

Statistical Analysis Plan

This is a single-arm pilot study for feasibility and safety. Mainly descriptive analysis will be used to report the findings. Patient demographics, pathologic data, perioperative data, complication rate, mastectomy skin flap and nipple areolar complex necrosis, monofilament testing and patient reported outcomes will be reported. Patient reported outcomes will be evaluated by specific domains and compared to previously reported results in the literature.[18] In addition, to compare the previously reported results in the literature with this study, one

sample proportion test will be performed to compare the mastectomy flap complication proportion, conversion to open NSM proportion. One sample Wilcoxon signed-rank test will be used to assess the duration of surgery and length of hospital stay. For the analyses, statistical significance is set at two sided $\alpha<0.05$.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not directly involved in the development of the protocol design. However, our group discussed the study protocol with our local patient advocate prior to developing the trial design. We plan to actively engage with our patient advocates for future dissemination strategies and translation of the study findings to a larger multicenter trial.

ETHICS AND DISSEMINATION

The trial will be conducted in accordance with Good Clinical Practices (GCP). The protocol was reviewed and approved by the U.S. Food and Drug Administration (FDA) using the Investigational Device Exemption (IDE) mechanism (reference number G200096). The trial was registered with clinicaltrials.gov (NCT04537312) and the investigational plan was approved by The Ohio State University Institutional Review Board (IRB) 2020C0094 (8/18/2020). Any amendments to the trial protocol will be submitted to the IRB for approval.

The results of the study will be reported at appropriate scientific conferences. We plan to publish the trial results in a scientific, peer-reviewed journal. A full de-identified individual patient dataset of the trial will be made available after trial completion and publication upon request to the corresponding author.

ACKNOWLEDGEMENTS

We thank Sue Marting with her assistance with obtaining the FDA Investigational Device Exemption.

CONTRIBUTORS

The PI and first author of this paper (KP) initially designed the study protocol. Each co-author contributed to subsequent development of the protocol. KP wrote the initial draft of the manuscript. All authors approved the final version of this manuscript.

FUNDING

This work was supported by the Ohio State University 2019 Intramural Research Program IDEA Award (46050-502730) and the National Center for Advancing Translational Sciences (award number UL1TR001070). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institute of Health.

COMPETING INTERESTS STATEMENT

None declared.

REFERENCES

1. Galimberti V, Morigi C, Bagnardi V et al. Oncological Outcomes of Nipple-Sparing Mastectomy: A Single-Center Experience of 1989 Patients. *Ann Surg Oncol*

2018;25:3849-3857.doi: 10.1245/s10434-018-6759-0
2. Smith BL, Tang R, Rai U et al. Oncologic Safety of Nipple-Sparing Mastectomy in Women with Breast Cancer. *J Am Coll Surg* 2017;225:361-365. doi:10.1016/j.jamcollsurg.2017.06.013
3. Wei CH, Scott AM, Price AN et al. Psychosocial and Sexual Well-Being Following Nipple-Sparing Mastectomy and Reconstruction. *Breast J* 2016;22:10-17.doi: 10.1111/tbj.12542
4. Djohan R, Gage E, Gatherwright J et al. Patient satisfaction following nipple-sparing mastectomy and immediate breast reconstruction: an 8-year outcome study. *Plast Reconstr Surg* 2010;125:818-829.doi:10.1097/PRS.0b013e3181ccdaa4
5. Peled AW, Duralde E, Foster RD et al. Patient-reported outcomes and satisfaction after total skin- sparing mastectomy and immediate expander-implant reconstruction. *Ann Plast Surg* 2014;72(Suppl 1):S48- 52.doi:10.1097/SAP.0000000000000020
6. Yoon-Flannery K, DeStefano LM, De La Cruz LM et al. Quality of life and sexual well-being after nipple sparing mastectomy: A matched comparison of patients using the breast Q. *J Surg Oncol* 2018;118:238-242.doi:10.1002/jso.25107
7. Galimberti V, Vicini E, Corso G et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. *Breast* 2017;34(Suppl 1): S82-S84.doi:10.1016/j.breast.2017.06.034
8. Jackson RS, Sanders T, Park A et al. Prospective Study Comparing Surgeons' Pain and Fatigue Associated with Nipple-Sparing versus Skin-Sparing Mastectomy. *Ann Surg Oncol* 2017;24:3024-3031.doi:10.1245/s10434-017-5929-9
9. Park KU, Weiss A, Rosso K et al. Use of Mammographic Measurements to Predict Complications After Nipple-Sparing Mastectomy in BRCA Mutation Carriers. *Ann Surg Oncol* 2019;27:367-372.doi:10.1245/s10434-019-07704-1
10. Chirappapha P, Srichan P, Lertsithichai P et al. Nipple-Areola Complex Sensation after Nipple- sparing Mastectomy. *Plast Reconstr Surg Glob Open* 2018;6:e1716. doi:10.1097/GOX.0000000000001716
11. Hallowell N, Baylock B, Heiniger L et al. Looking different, feeling different: women's reactions to risk-reducing breast and ovarian surgery. *Fam Cancer* 2012;11:215-224. doi:10.1007/s10689-011-9504-4
12. Temple CLF, Ross DC, Kim S et al. Sensibility following Innervated Free TRAM Flap for Breast Reconstruction: Part II. Innervation Improves Patient-Rated Quality of Life. *Plast Reconstr Surg* 2009;124:1419-1425.doi:10.1097/PRS.0b013e3181b98963
13. Børsen-Koch M, Gunnarsson GL, Sørensen JA, Thomsen JB. Thermal injury in TAPIA breast reconstruction-thermal injury to thoracodorsal artery perforator flap. *Gland Surg* 2017;6:110-113.doi:10.21037/gs.2017.01.01
14. Park KU, Weiss A, Rosso K, Yi M, Hunt K, Kuerer H, Hanson SE, Candelaria R, Tevis S, Thompson A. Use of Mammographic Measurements to Predict Complications After Nipple-Sparing Mastectomy in BRCA Mutation Carriers. *Ann Surg Oncol* 2020;27:367-372.doi:10.1245/s10434-019-07704-1
15. Toesca A, Invento A, Massari G et al. Update on the Feasibility and Progress on Robotic Breast Surgery. Ann Surg Oncol 2019;26:3046-3051.doi:10.1245/s10434-019-07590-7
16. Park KU, Tozbikian GH, Ferry D, Tsung A, Chetta M, Schulz S, Skoracki R. Residual breast tissue after robot-assisted nipple sparing mastectomy. *Breast* 2020;55:25-29.doi: 10.1016/j.breast.2020.11.022

17. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, Buda A, Yan X, Shuzhong Y, Chetty N, Isla D, Tamura M, Zhu T, Robledo KP, Gebski V, Asher R, Behan V, Nicklin JL, Coleman RL, Obermair A. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *N Engl J Med* 2018;379:1895-1904.doi: 10.1056/NEJMoa1806395
18. Lai HW, Wang CC, Lai YC et al. The learning curve of robotic nipple sparing mastectomy for breast cancer: An analysis of consecutive 39 procedures with cumulative sum plot. *Eur J Surg Oncol* 2019;45:125-133.doi:10.1016/j.ejso.2018.09.021
19. Lemaine V, Hoskin TL, Farley DR, Grant CS, Boughey JC, Torstenson TA, Jacobson SR, Jakub JW, Degnim AC. Introducing the SKIN score: a validated scoring system to assess severity of mastectomy skin flap necrosis. *Ann Surg Oncol 2*015;22:2925-32.doi: 10.1245/s10434-015-4409-3

BMJ Open

Prospective Pilot Study Protocol Evaluating Safety and Feasibility of Robot-assisted Nipple Sparing Mastectomy (RNSM)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050173.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Jul-2021
Complete List of Authors:	Park, Ko Un; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Lee, Sandy; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Sarna, Angela; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Chetta, Matthew; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery Schulz, Steven; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery Agnese, Doreen; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Grignol, Valerie; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Carson, William; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Skoracki, Roman; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	Breast surgery < SURGERY, PLASTIC & RECONSTRUCTIVE SURGERY, Breast tumours < ONCOLOGY, ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Prospective Pilot Study Protocol Evaluating Safety and Feasibility of Robot-assisted Nipple Sparing Mastectomy (RNSM)

Authors: Ko Un Park MD[1], Sandy Lee BA[1], Angela Sarna BS[1], Matthew Chetta MD[2], Steven Schulz MD[2], Doreen Agnese MD[1], Valerie Grignol MD[1], William Carson MD[1], and Roman J Skoracki MD[2]

Author Affiliations:
1. Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center James Cancer Hospital, Columbus, OH
2. Department of Plastic and Reconstructive Surgery, The Ohio State University Wexner Medical Center James Cancer Hospital, Columbus, OH

Brief title: Robot-assisted Nipple Sparing Mastectomy

Financial and conflict of interest disclosure: The authors have no relevant financial disclosure. The authors declare that there are no competing interests.

Corresponding Author:
Ko Un Park, MD
Assistant Professor of Surgery
The Ohio State University Wexner Medical Center
The James Cancer Hospital
410 W 10th Ave, N908 Doan Hall
Columbus, Ohio 43210
Tel: 614-293-6708
Fax: 614-293-3465
Koun.park@osumc.edu

Requests for reprints should be addressed to:
Ko Un Park
410 W 10th Ave, N908 Doan Hall
Columbus, Ohio 43210
Tel: 614-293-6708

Word Count: 2630

ABSTRACT

Introduction

Nipple sparing mastectomy (NSM) can be performed for treatment of breast cancer and risk reduction, but total mammary glandular excision in NSM can be technically challenging. Minimally invasive robot assisted NSM (RNSM) has the potential to improve the ergonomic challenges of open NSM. Recent studies in RNSM demonstrate the feasibility and safety of the procedure but this technique is still novel in the United States.

Methods and analysis

This is a single arm prospective pilot study to determine safety, efficacy, and potential risks of RNSM. Up to 12 RNSM will be performed to assess the safety and feasibility of the procedure. Routine follow-up visits and study assessments will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months. The primary outcome is to assess feasibility of removing the breast gland en bloc using the RNSM technique. To assess safety, postoperative complication information will be collected. Secondary outcomes include defining benefits and challenges of RNSM for both surgeons and patients utilizing surveys, as well as defining the breast and nipple areolar complex (NAC) sensation recovery following RNSM. Mainly descriptive analysis will be used to report the findings.

Ethics and dissemination The RNSM protocol was reviewed and approved by the U.S. Food and Drug Administration (FDA) using the Investigational Device Exemption (IDE) mechanism (reference number G200096). In addition, the protocol was registered with clinicaltrials.gov (NCT04537312) and approved by The Ohio State University institutional review board (IRB), reference number 2020C0094 (8/18/2020). The results of this study will be distributed through peer-reviewed journals and presented at surgical conferences.

Trial registration number: NCT04537312

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first US investigator initiated trial assessing the safety and feasibility of RNSM.
- Patient reported outcome data including nipple sensation after surgery are collected.
- If RNSM proves to be safe and feasible, the results will form the basis for a subsequent multi-center trial measuring oncologic outcomes.
- The small sample size in this pilot study limit the comparison of RNSM outcomes to open NSM.

INTRODUCTION

Breast cancer is the most common solid tumor in women. With advances in breast reconstruction after mastectomy for the treatment of breast diseases including breast cancer, surgical techniques have evolved to preserve the skin flaps and nipple areolar complex (NAC) to give better aesthetic outcome without compromising oncologic outcome.[1, 2] Nipple sparing mastectomy (NSM) preserves the skin and nipple areolar complex for improved body image and patient satisfaction.[3-6] However, total mammary glandular excision for oncologic purposes in NSM can be technically challenging particularly due to small incision size in relation to the operative field and poor visualization of the dissection plane due to the curvature of the breast parenchyma and suboptimal illumination.[7] Surgeons experience greater physical symptoms such as neck and lower back pain, mental strain, and fatigue from performing NSM.[8] A more ergonomically sound technique with greater visualization is needed to improve surgeon ergonomics but also to improve the ease of the operation.

Open NSM results in variable rate of sensation in the nipple-areolar complex. In a study by Chirappapha et al, evaluation of 55 NSM for sensory recovery demonstrated 11 patients with partial sensation recovery in first 6 months.[9] Women undergoing risk reducing mastectomy with reconstruction report the breast feeling numb and lacking in sensation.[10] These changes in bodily sensations can have long-lasting quality of life repercussions and can actually cause harm as the skin acts as a functional protection against thermal injuries.[11, 12] Thus, understanding the sensation of the breast after RNSM from a patient-centered research perspective is important.

Additionally, traditional open NSM is associated with higher rates of mastectomy skin flap and nipple areolar complex necrosis if performed in larger breasted women.[13] While bra cup size is not a reliable marker for increased risk of complication, breast volume measured using the area visualized on mammogram can predict large volume associated with higher necrosis rate. For instance, 45% of patients with breast volume on mammogram of 675 cc or larger had mastectomy flap or nipple areolar complex necrosis.[13] The increased risk of skin flap necrosis complication in larger breast size may be related to increased traction and trauma on the skin flap for dissection of larger surface area. Currently, there is a need to develop innovative approach to NSM in women with larger breast size.

Minimally invasive robot assisted NSM (RNSM) has the potential to improve the safety and efficacy of NSM. Studies in RNSM demonstrate the feasibility and safety of performing a minimally invasive NSM using the da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA). Preliminary data from a randomized clinical study comparing 40 open to 40 robotic NSM cases indicate the safety of RNSM with regards to low perioperative complication rate and none of the patients had any mastectomy flap necrosis or loss of nipple due to complication.[14] Additionally, in a recent study comparing surgical outcomes between conventional open NSM and RNSM, the latter was associated with significantly lower rates of high-grade post-operative complications and nipple necrosis. [15] In a recent publication of the updated series by Toesca et al, between June 2014 and January 2019, 73 women underwent 94 RNSM with immediate implant-based breast reconstruction.[14] There were 39 patients with invasive breast cancer, 17 with ductal carcinoma in situ (DCIS), and 17 without cancer diagnosis but with BRCA mutation. The mean surgery time was 3 hours and 32 minutes. The most common complication after surgery was seroma (N=5) followed by eschar (N=4). The rates of infection and hematoma were low (N=2 each). Only 1 patient had necrosis after surgery. There was one patient in the series who had Stage IV disease at the time of surgery and died 4 months after surgery. Excluding this patient with metastatic disease, the disease-free survival rate was 100% with a median follow-up

was 19 months (range 3.1–44.8). Long term oncologic safety of RNSM will take time for data to mature.

To study the technical feasibility and safety of RNSM, we performed a series of cadaveric RNSM and assessed the mastectomy flap for presence of residual breast tissue.[16] We were able to demonstrate that RNSM is technically feasible. Residual breast tissue was only detectable in the NAC, and none was detectable in the mastectomy flap outside the NAC.

The technique of RNSM is still novel for U.S. surgeons and to date there are no published studies from US institutions because the use of the da Vinci surgical system is not FDA approved for use in breast surgery. This is partly due to the safety concerns expressed by the FDA, which stems from the inferior outcomes of minimally invasive surgery compared to open hysterectomy for cervical cancer.[17] In response to the safety concerns, our institution has received FDA approval of an Investigational Device Exemption (IDE) to initiate the RNSM clinical trial described here. This study aims to define the anatomic challenges and technical feasibility of RNSM and demonstrate its initial safety and efficacy profile. These data will inform a future, larger study of the procedure and help surgeons determine whether to consider the procedure for their practice.

METHODS AND ANALYSIS

Study design

This is a single arm prospective pilot study to determine safety, efficacy, and potential risks of Robotic Nipple Sparing Mastectomy (RNSM), funded by an Ohio State Intramural Research Program IDEA award and National Center for Advancing Translational Sciences award. All operations will occur at The Ohio State University James Comprehensive Cancer Center. Up to 20 subjects will be enrolled in order to perform 12 procedures of RNSM. This study will be performed in a single center, at The Ohio State University Wexner Medical Center James Comprehensive Cancer Center. All eligible interested patients must sign consent for enrollment into the robotic nipple sparing mastectomy clinical study. For patients undergoing sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) in the same operation, a separate small axillary incision will be made. This is similar to the approach taken in open NSM in our current practice. All axillary surgery will be performed in the traditional open manner.

Eligible patients will undergo RNSM as previously described.[16] Briefly, the anterior axillary incision will be used for dissection. The breast incision, measuring approximately 3cm, will be placed just lateral to the anterior axillary line. A subcutaneous dissection will be performed to create a working space. The single port system (GelPOINT Mini, Applied Medical, Rancho Santa Margarita, CA) combined with a small wound protector (Alexis Wound Protector, Applied Medical) will be inserted into the incision. By intussuscepting the wound protector with the single port system, we are able to move the fulcrum point of the robotic ports approximately 10cm from the incision and thus create a larger working space for the robotic arms. The three 8-mm-diameter robot ports will be inserted and secured into the GelSeal Cap connected to an insufflator to keep the pressure at 8 mm Hg. Once the robot is docked, subcutaneous dissection will be performed using the monopolar-curved scissors and bipolar grasping forceps for traction and exposure. Using similar technique the gland will be separated from the pectoralis major muscle. The specimen will be removed from the anterior axillary incision. All breast specimens will be evaluated by pathology through the institutional usual specimen processing protocol. To reconstruct the mound of the breast, plastic surgery will perform an immediate direct to implant-

based reconstruction or TE placement using the anterior axillary line incision following the standard technique.

Patients will be recovered in the postoperative phase following the usual standard of care. Routine follow-up visits and study assessments will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months, as well as standard of care follow-up for surveillance for a minimum of 5 years after surgery.

Study population and eligibility criteria

Patients who present to the breast surgical oncology clinic will be screened for eligibility for robot-assisted nipple sparing mastectomy (RNSM). These patients typically have small breasts (bra cup size B or smaller, less than 500 grams of breast tissue) and no extensive ptosis of the breast. The cohort for this pilot study is limited to smaller breasted women (traditional open NSM candidates) but will expand in future studies to larger breasted patients (greater than C cup). Prior to consenting, patients will be informed that cancer treatment outcomes using RNSM have not been evaluated by the FDA and this is an 'off label' use of the device. Eligible patients will be informed of the purpose, procedures, and potential risks of the study. Patients will be eligible for inclusion in the study if they meet all the following inclusion criteria and excluded from participation in the study if they meet any of the following exclusion criteria (Table 1). Interested eligible patients will be screened and consented by the clinical research coordinator.

Sample Size

The number of cases to enroll in the pilot study has been set to twelve based on a previous study investigating the learning curve of RNSM.[18] The previous study of 39 cases found that docking time, robot console time, and overall operative time decreased on the 13th case, thus concluding that 12 cases were needed to decrease the operative time.

Subject withdrawal

Patients will be free to withdraw from the study at any point without consequence. Additionally, subjects may be withdrawn if during surgery the PI determines the patient requires surgery in the conventional manner and a pivot to this standard care surgery is immediately undertaken. For this initial trial, no patients will be replaced after their surgery for non-compliance to follow-up in The Ohio State University Wexner Medical Center breast oncological clinic.

TRIAL PROCEDURES

Surgery and biospecimen collection

Standard of care preoperative workup will be followed prior to surgery. RNSM will be performed using the da Vinci Xi Robotic Surgical System, a software-controlled, electro-mechanical system designed for surgeons to perform minimally invasive surgery. The breast specimen will be removed via gentle manual extraction through the anterior axillary incision using the "waving flag technique" (move the gland back and forth and up and down gently until it is removed). For specimen extraction, no devices such as the morcellator will be used. To assure en bloc removal of the specimen, if it is not feasible to remove the entire gland as a single piece, the incision will be extended to assure removal of the intact specimen. The specimen will be labeled, as per standard of practice, with sutures and right/left orientation by the surgeon. All

relevant data pertaining to the surgical procedure will be collected and breast specimens will be oriented for pathologic evaluation through the institution usual specimen processing protocol. The entire robotic portion of the surgery will be recorded. Representative portions of the pre-docking and post-docking procedure will be videotaped as well.

Post-operative phase

Per the usual standard of care, the patient will follow up in the breast surgical oncology clinic around post-operative day 14, day 30, 6 months, and 1 year. Pre-operative and post-operative photographs and study-related assessments will be obtained and completed at each of the previously stated time points. All images will be taken in a fashion that minimizes subject identification, such as exclusion of the head and neck region, any identifiers removed including tattoos, birthmarks, etc. At 6 weeks, a review of the patient's records will also occur to capture any re-operations/readmissions from a safety perspective. An implant exchange surgery will be performed around 3-6 months after expansion is complete or later if chemotherapy is required or the patient desires to wait.

Stopping Criteria

The study will be stopped if a) en bloc removal of the breast specimen is not achieved during the RNSM surgery, or b) the specimen is incorrectly labeled or oriented for pathologic evaluation. Specimen labeling with sutures is a part of standard practice and is performed by the investigator-surgeon. Any occurrence of the aforementioned events will trigger a temporary suspension of further enrollment into the study until additional evaluation utilizing the Corrective And Preventive Action (CAPA) process has been completed. Should the study be stopped, all regulating bodies (e.g. FDA, data safety monitoring committee) will be notified.

Data collection and management

The Ohio State Comprehensive Cancer Center clinical trial office research informatics services will be used as a central location for data processing and management, following standard operating procedures for the collection, storage, and analysis of electronic case report forms (eCRF). Data obtained from the patient's electronic medical record and surveys will be stored on a secure drive on university password protected computers, and/or entered into a secure username/password protected database, using OnCore as the electronic data capture tool. Data will be accessible only to the research personnel approved for this study. As part of the FDA IDE study, additional data will be provided to the FDA.

STUDY OBJECTIVES AND OUTCOMES

The primary objectives are to generate preliminary data on the safety and complications from RNSM. En bloc resection and removal of the breast specimen will be assessed as a primary endpoint. We will also investigate the total duration of the operation, the frequency of conversion to open technique, the length of hospitalization, and post-operative complications. Reported complications after RNSM include nipple areolar complex necrosis, mastectomy flap necrosis, temporary skin blistering, hematoma, seroma, infection, loss of implant from infection, delayed axillary wound healing, transient brachial plexus neurapraxia, and transient neurapraxia due to intraoperative patient positioning. Safety will be assessed by monitoring for all adverse events/serious adverse events, re-operations, and readmissions. Mastectomy and NAC necrosis

will be assessed using a validated scoring system called the SKIN score.[19] To assess outcome, routine follow-up visits will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months. Patients will complete the study related assessments within the 12 months of completion of operation. Patients will continue standard of care follow-up for surveillance at minimum of 5 years after surgery.

Beyond this, we aim to define the benefits and challenges of RNSM from the surgeon's perspective. Additional endpoints include NMSQ and SURG-TLX validated surveys to determine surgeon musculoskeletal fatigue. To assess patient satisfaction with the breast after surgery and sensation recovery after surgery, BREAST-Q and NAC modules for patient reported outcomes and satisfaction, and Semmes-Weinstein monofilament skin testing will be used. An exploratory endpoint is technical familiarity, which will be measured through operative robot console time.

As part of standard of care, patients will follow up with the plastic and reconstructive surgery clinic on an annual basis for surveillance of long term known implant-related adverse events including but not limited to the following: capsular contraction, implant rupture and deflation, breast implant associated-anaplastic large cell lymphoma, asymmetry, chest wall deformity, extrusion, infection, malposition/displacement, seroma, skin rash, wrinkling/rippling of implant, and unsatisfactory shape/size.

The current study is a pilot study to demonstrate initial feasibility. Ultimately, these data will be used to inform a larger multi-center study in the future. Specific outcomes of interest in future studies include oncologic safety and cost-effectiveness of RNSM.

Safety assessments

For this study, an adverse effect/event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs. All observed or subject-described adverse effects/events—serious or non-serious—and abnormal test findings, regardless of suspected causal relationship to the investigational device or other procedures, will be assessed beginning on the day of surgery and at every follow-up visit thereafter. As part of standard of care, patients will follow up with the plastic and reconstructive surgery clinic on an annual basis for surveillance of long term known implant-related AEs. AEs or abnormal test findings felt to be associated with the investigational device or, if applicable, other study procedures will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator. To ensure patient safety, all adverse events will be recorded, evaluated, and reported to FDA and IRB as required for all patient visits including long term follow-up.

Statistical Analysis Plan

This is a single-arm pilot study for feasibility and safety. Mainly descriptive analysis will be used to report the findings. Patient demographics, pathologic data, perioperative data, complication rate, mastectomy skin flap and nipple areolar complex necrosis, monofilament testing and patient reported outcomes will be reported. Patient reported outcomes will be evaluated by specific domains and compared to previously reported results in the literature.[5] In addition, to compare the previously reported results in the literature with this study, one sample proportion test will be performed to compare the mastectomy flap complication proportion, conversion to open NSM proportion. One sample Wilcoxon signed-rank test will be used to assess the duration of surgery and length of hospital stay. For the analyses, statistical significance

is set at two sided $\alpha<0.05$.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not directly involved in the development of the protocol design. However, our group discussed the study protocol with our local patient advocate prior to developing the trial design. We plan to actively engage with our patient advocates for future dissemination strategies and translation of the study findings to a larger multicenter trial.

ETHICS AND DISSEMINATION

The trial will be conducted in accordance with Good Clinical Practices (GCP). The protocol was reviewed and approved by the U.S. Food and Drug Administration (FDA) using the Investigational Device Exemption (IDE) mechanism (reference number G200096). The trial was registered with clinicaltrials.gov (NCT04537312) and the investigational plan was approved by The Ohio State University Institutional Review Board (IRB) 2020C0094 (8/18/2020). Any amendments to the trial protocol will be submitted to the IRB for approval.

The results of the study will be reported at appropriate scientific conferences. We plan to publish the trial results in a scientific, peer-reviewed journal. A full de-identified individual patient dataset of the trial will be made available after trial completion and publication upon request to the corresponding author.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:	Exclusion criteria:

• adults: age ≥ 18 years
• surgical candidates, per standard of care for: open nipple sparing resection and reconstruction for following indications:
  ○ for risk reduction mastectomy
  ○ treatment of ductal carcinoma in-situ or clinically node negative cT1-T3 breast cancer
• surgical candidates for open NSM, per standard of care, with regards to patient anatomic factors and tumor location
• patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	• pregnant
	• patients with:
	  ○ inflammatory breast cancer skin involvement with tumor pre-operative diagnosis (clinical, radiological or pathologic) of nipple-areola complex involvement with tumor
	  ○ grade 3 ptosis of nipple
	  ○ bra cup size greater than C cup
	• current use of nicotine (ie. cigarette smoking, vaping, use of nicotine containing gum or transdermal patches or use of other forms of nicotine)
	• patients that are high risk for anesthesia, defined by the American Society of Anesthesiologists Scale ASA, grade 4 or higher
	• patients that do not have the ability to give informed consent
	• prisoner status at surgical clinic visit
	• previous thoracic radiation history

CONTRIBUTORS

The first author of this paper (KP) initially designed the study protocol. KP, AS, and RS contributed to initial planning of the trial. AS, RS, MC and SS contributed to initial preliminary data collection. Each co-author (KP, SL, AS, MC, SS, DA, VG, WC, and RS) contributed to subsequent development of the protocol. KP and SL wrote the initial draft of the manuscript. All authors (KP, SL, AS, MC, SS, DA, VG, WC, RS) approved the final version of this manuscript.

FUNDING

This work was supported by the Ohio State University 2019 Intramural Research Program IDEA Award (46050-502730) and the National Center for Advancing Translational Sciences (award number UL1TR001070). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institute of Health.

COMPETING INTERESTS STATEMENT

None declared.

REFERENCES

1. Galimberti V, Morigi C, Bagnardi V et al. Oncological Outcomes of Nipple-Sparing Mastectomy: A Single-Center Experience of 1989 Patients. Ann Surg Oncol 2018;25:3849-3857.doi: 10.1245/s10434-018-6759-0
2. Smith BL, Tang R, Rai U et al. Oncologic Safety of Nipple-Sparing Mastectomy in Women with Breast Cancer. J Am Coll Surg 2017;225:361-365. doi:10.1016/j.jamcollsurg.2017.06.013
3. Wei CH, Scott AM, Price AN et al. Psychosocial and Sexual Well-Being Following Nipple-Sparing Mastectomy and Reconstruction. Breast J 2016;22:10-17.doi: 10.1111/tbj.12542
4. Djohan R, Gage E, Gatherwright J et al. Patient satisfaction following nipple-sparing mastectomy and immediate breast reconstruction: an 8-year outcome study. Plast Reconstr Surg 2010;125:818-829.doi:10.1097/PRS.0b013e3181ccdaa4
5. Peled AW, Duralde E, Foster RD et al. Patient-reported outcomes and satisfaction after total skin- sparing mastectomy and immediate expander-implant reconstruction. Ann Plast Surg 2014;72(Suppl 1):S48- 52.doi:10.1097/SAP.0000000000000020
6. Yoon-Flannery K, DeStefano LM, De La Cruz LM et al. Quality of life and sexual well-being after nipple sp[Toesca, 2019 #14]aring mastectomy: A matched comparison of patients using the breast Q. J Surg Oncol 2018;118:238-242.doi:10.1002/jso.25107
7. Galimberti V, Vicini E, Corso G et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. Breast 2017;34(Suppl 1): S82-S84.doi:10.1016/j.breast.2017.06.034
8. Jackson RS, Sanders T, Park A et al. Prospective Study Comparing Surgeons' Pain and Fatigue Associated with Nipple-Sparing versus Skin-Sparing Mastectomy. Ann Surg Oncol 2017;24:3024-3031.doi:10.1245/s10434-017-5929-9
9. Chirappapha P, Srichan P, Lertsithichai P et al. Nipple-Areola Complex Sensation after Nipple- sparing Mastectomy. Plast Reconstr Surg Glob Open 2018;6:e1716. doi:10.1097/GOX.0000000000001716

10. Hallowell N, Baylock B, Heiniger L et al. Looking different, feeling different: women's reactions to risk-reducing breast and ovarian surgery. Fam Cancer 2012;11:215-224. doi:10.1007/s10689-011-9504-4
11. Temple CLF, Ross DC, Kim S et al. Sensibility following Innervated Free TRAM Flap for Breast Reconstruction: Part II. Innervation Improves Patient-Rated Quality of Life. Plast Reconstr Surg 2009;124:1419-1425.doi:10.1097/PRS.0b013e3181b98963
12. Børsen-Koch M, Gunnarsson GL, Sørensen JA, Thomsen JB. Thermal injury in TAPIA breast reconstruction-thermal injury to thoracodorsal artery perforator flap. Gland Surg 2017;6:110-113.doi:10.21037/gs.2017.01.01
13. Park KU, Weiss A, Rosso K et al. Use of Mammographic Measurements to Predict Complications After Nipple-Sparing Mastectomy in BRCA Mutation Carriers. Ann Surg Oncol 2020;27:367-372.doi:10.1245/s10434-019-07704-1
14. Toesca A, Invento A, Massari G et al. Update on the Feasibility and Progress on Robotic Breast Surgery. Ann Surg Oncol 2019;26:3046-3051.doi:10.1245/s10434-019-07590-7
15. Lee J, Park HS, Lee H, et al. Post-Operative Complications and Nipple Necrosis Rates Between Conventional and Robotic Nipple-Sparing Mastectomy. Front Oncol 2021;10(2924).
16. Park KU, Tozbikian GH, Ferry D, Tsung A, Chetta M, Schulz S, Skoracki R. Residual breast tissue after robot-assisted nipple sparing mastectomy. Breast 2020;55:25-29.doi: 10.1016/j.breast.2020.11.022
17. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, Buda A, Yan X, Shuzhong Y, Chetty N, Isla D, Tamura M, Zhu T, Robledo KP, Gebski V, Asher R, Behan V, Nicklin JL, Coleman RL, Obermair A. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med 2018;379:1895-1904.doi: 10.1056/NEJMoa1806395
18. Lai HW, Wang CC, Lai YC et al. The learning curve of robotic nipple sparing mastectomy for breast cancer: An analysis of consecutive 39 procedures with cumulative sum plot. Eur J Surg Oncol 2019;45:125-133.doi:10.1016/j.ejso.2018.09.021
19. Lemaine V, Hoskin TL, Farley DR, Grant CS, Boughey JC, Torstenson TA, Jacobson SR, Jakub JW, Degnim AC. Introducing the SKIN score: a validated scoring system to assess severity of mastectomy skin flap necrosis. Ann Surg Oncol 2015;22:2925-32.doi: 10.1245/s10434-015-4409-3

ACKNOWLEDGEMENTS

We thank Sue Marting with her assistance with obtaining the FDA Investigational Device Exemption.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Location in Manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1 Line 1-2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2 Line 27
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1, 4, 5. 6, 8 (Table 1)
Protocol version	3	Date and version identifier	Page 1 Line 37-38
Funding	4	Sources and types of financial, material, and other support	Page 10 Line 31-33
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1 Line 4-12, Page 10 Line 26-28
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 10 Line 33-35
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3
	6b	Explanation for choice of comparators	Page 3, 4
Objectives	7	Specific objectives or hypotheses	Page 6, 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 4 Line 20
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 4 Line 23-25
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5 Line 8-19, Page 8 (Table 1)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 5, 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 6 Line 17-23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 5 Line 4-5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 4, 5

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 5, 6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 5 Line 22-25
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 5 Line 8-19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 6 Line 26-34
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 5 Line 4-5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 6 Line 26-34
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 7 Line 38-46
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 7 Line 38-46
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 6 Line 26-34
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 6 Line 17-23
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 6 Line 17-23, Page 7 Line 24-35
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 8 Line 10-15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 8 Line 10-15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 5 Line 18-19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 6 Line 311-33
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10 Line 38

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 6 Line 26-34, Page 8 Line 16-19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 8 Line 16-19
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 8 Line 16-19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 8 Line 16-19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Prospective Pilot Study Protocol Evaluating Safety and Feasibility of Robot-assisted Nipple Sparing Mastectomy (RNSM)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-050173.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Oct-2021
Complete List of Authors:	Park, Ko Un; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Lee, Sandy; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Sarna, Angela; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Chetta, Matthew; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery Schulz, Steven; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery Agnese, Doreen; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Grignol, Valerie; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Carson, William; The Ohio State University Wexner Medical Center Department of Surgery, Division of Surgical Oncology Skoracki, Roman; The Ohio State University Wexner Medical Center Department of Plastic and Reconstructive Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Oncology
Keywords:	Breast surgery < SURGERY, PLASTIC & RECONSTRUCTIVE SURGERY, Breast tumours < ONCOLOGY, ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Prospective Pilot Study Protocol Evaluating Safety and Feasibility of Robot-assisted Nipple Sparing Mastectomy (RNSM)

Authors: Ko Un Park MD[1], Sandy Lee BA[1], Angela Sarna BS[1], Matthew Chetta MD[2], Steven Schulz MD[2], Doreen Agnese MD[1], Valerie Grignol MD[1], William Carson MD[1], and Roman J Skoracki MD[2]

Author Affiliations:
1. Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center James Cancer Hospital, Columbus, OH
2. Department of Plastic and Reconstructive Surgery, The Ohio State University Wexner Medical Center James Cancer Hospital, Columbus, OH

Brief title: Robot-assisted Nipple Sparing Mastectomy

Financial and conflict of interest disclosure: The authors have no relevant financial disclosure. The authors declare that there are no competing interests.

Corresponding Author:
Ko Un Park, MD
Assistant Professor of Surgery
The Ohio State University Wexner Medical Center
The James Cancer Hospital
410 W 10th Ave, N908 Doan Hall
Columbus, Ohio 43210
Tel: 614-293-6708
Fax: 614-293-3465
Koun.park@osumc.edu

Requests for reprints should be addressed to:
Ko Un Park
410 W 10th Ave, N908 Doan Hall
Columbus, Ohio 43210
Tel: 614-293-6708

Word Count: 2977

ABSTRACT

Introduction

Nipple sparing mastectomy (NSM) can be performed for treatment of breast cancer and risk reduction, but total mammary glandular excision in NSM can be technically challenging. Minimally invasive robot assisted NSM (RNSM) has the potential to improve the ergonomic challenges of open NSM. Recent studies in RNSM demonstrate the feasibility and safety of the procedure but this technique is still novel in the United States.

Methods and analysis

This is a single arm prospective pilot study to determine safety, efficacy, and potential risks of RNSM. Up to 12 RNSM will be performed to assess the safety and feasibility of the procedure. Routine follow-up visits and study assessments will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months. The primary outcome is to assess feasibility of removing the breast gland en bloc using the RNSM technique. To assess safety, postoperative complication information will be collected. Secondary outcomes include defining benefits and challenges of RNSM for both surgeons and patients utilizing surveys, as well as defining the breast and nipple areolar complex (NAC) sensation recovery following RNSM. Mainly descriptive analysis will be used to report the findings.

Ethics and dissemination The RNSM protocol was reviewed and approved by the U.S. Food and Drug Administration (FDA) using the Investigational Device Exemption (IDE) mechanism (reference number G200096). In addition, the protocol was registered with clinicaltrials.gov (NCT04537312) and approved by The Ohio State University institutional review board (IRB), reference number 2020C0094 (8/18/2020). The results of this study will be distributed through peer-reviewed journals and presented at surgical conferences.

Trial registration number: NCT04537312

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first US investigator initiated trial assessing the safety and feasibility of RNSM.
- Patient reported outcome data including nipple sensation after surgery are collected.
- If RNSM proves to be safe and feasible, the results will form the basis for a subsequent multi-center trial measuring oncologic outcomes.
- The small sample size in this pilot study limit the comparison of RNSM outcomes to open NSM.

INTRODUCTION

Breast cancer is the most common solid tumor in women. With advances in breast reconstruction after mastectomy for the treatment of breast diseases including breast cancer, surgical techniques have evolved to preserve the skin flaps and nipple areolar complex (NAC) to give better aesthetic outcome without compromising oncologic outcome.[1, 2] Nipple sparing mastectomy (NSM) preserves the skin and nipple areolar complex for improved body image and patient satisfaction.[3-6] However, total mammary glandular excision for oncologic purposes in NSM can be technically challenging particularly due to small incision size in relation to the operative field and poor visualization of the dissection plane due to the curvature of the breast parenchyma and suboptimal illumination.[7] Surgeons experience greater physical symptoms such as neck and lower back pain, mental strain, and fatigue from performing NSM.[8] A more ergonomically sound technique with greater visualization is needed to improve surgeon ergonomics but also to improve the ease of the operation.

Open NSM results in variable rate of sensation in the nipple-areolar complex. In a study by Chirappapha et al, evaluation of 55 NSM for sensory recovery demonstrated 11 patients with partial sensation recovery in first 6 months.[9] Women undergoing risk reducing mastectomy with reconstruction report the breast feeling numb and lacking in sensation.[10] These changes in bodily sensations can have long-lasting quality of life repercussions and can actually cause harm as the skin acts as a functional protection against thermal injuries.[11, 12] Thus, understanding the sensation of the breast after RNSM from a patient-centered research perspective is important.

Additionally, traditional open NSM is associated with higher rates of mastectomy skin flap and nipple areolar complex necrosis if performed in larger breasted women.[13] While bra cup size is not a reliable marker for increased risk of complication, breast volume measured using the area visualized on mammogram can predict large volume associated with higher necrosis rate. For instance, 45% of patients with breast volume on mammogram of 675 cc or larger had mastectomy flap or nipple areolar complex necrosis.[13] The increased risk of skin flap necrosis complication in larger breast size may be related to increased traction and trauma on the skin flap for dissection of larger surface area. Currently, there is a need to develop innovative approach to NSM in women with larger breast size.

Minimally invasive robot assisted NSM (RNSM) has the potential to improve the safety and efficacy of NSM. Studies in RNSM demonstrate the feasibility and safety of performing a minimally invasive NSM using the da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA). Preliminary data from a randomized clinical study comparing 40 open to 40 robotic NSM cases indicate the safety of RNSM with regards to low perioperative complication rate and none of the patients had any mastectomy flap necrosis or loss of nipple due to complication.[14] Additionally, in a recent study comparing surgical outcomes between conventional open NSM and RNSM, the latter was associated with significantly lower rates of high-grade post-operative complications and nipple necrosis. [15] In a recent publication of the updated series by Toesca et al, between June 2014 and January 2019, 73 women underwent 94 RNSM with immediate implant-based breast reconstruction.[14] There were 39 patients with invasive breast cancer, 17 with ductal carcinoma in situ (DCIS), and 17 without cancer diagnosis but with BRCA mutation. The mean surgery time was 3 hours and 32 minutes. The most common complication after surgery was seroma (N=5) followed by eschar (N=4). The rates of infection and hematoma were low (N=2 each). Only 1 patient had necrosis after surgery. There was one patient in the series who had Stage IV disease at the time of surgery and died 4 months after surgery. Excluding this patient with metastatic disease, the disease-free survival rate was 100% with a median follow-up

was 19 months (range 3.1–44.8). Long term oncologic safety of RNSM will take time for data to mature.

To study the technical feasibility and safety of RNSM, we performed a series of cadaveric RNSM and assessed the mastectomy flap for presence of residual breast tissue.[16] We were able to demonstrate that RNSM is technically feasible. Residual breast tissue was only detectable in the NAC, and none was detectable in the mastectomy flap outside the NAC.

The technique of RNSM is still novel for U.S. surgeons and to date there are no published studies from US institutions because the use of the da Vinci surgical system is not FDA approved for use in breast surgery. This is partly due to the safety concerns expressed by the FDA, which stems from the inferior outcomes of minimally invasive surgery compared to open hysterectomy for cervical cancer.[17] In response to the safety concerns, our institution has received FDA approval of an Investigational Device Exemption (IDE) to initiate the RNSM clinical trial described here. This study aims to define the anatomic challenges and technical feasibility of RNSM and demonstrate its initial safety and efficacy profile. These data will inform a future, larger study of the procedure and help surgeons determine whether to consider the procedure for their practice.

METHODS AND ANALYSIS

Study design

This is a single arm prospective pilot study to determine safety, efficacy, and potential risks of Robotic Nipple Sparing Mastectomy (RNSM), funded by an Ohio State Intramural Research Program IDEA award and National Center for Advancing Translational Sciences award. The study start date is November 17, 2020. The estimated primary completion date is December 31, 2022 and estimated study completion date is December 31, 2023. All operations will occur at The Ohio State University James Comprehensive Cancer Center. Up to 20 subjects will be enrolled in order to perform 12 procedures of RNSM. This study will be performed in a single center, at The Ohio State University Wexner Medical Center James Comprehensive Cancer Center. All eligible interested patients must sign consent for enrollment into the robotic nipple sparing mastectomy clinical study. For patients undergoing sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) in the same operation, a separate small axillary incision will be made. This is similar to the approach taken in open NSM in our current practice. All axillary surgery will be performed in the traditional open manner.

Eligible patients will undergo RNSM as previously described.[16] Briefly, the anterior axillary incision will be used for dissection. The breast incision, measuring approximately 3cm, will be placed just lateral to the anterior axillary line. A subcutaneous dissection will be performed to create a working space. The single port system (GelPOINT Mini, Applied Medical, Rancho Santa Margarita, CA) combined with a small wound protector (Alexis Wound Protector, Applied Medical) will be inserted into the incision. By intussuscepting the wound protector with the single port system, we are able to move the fulcrum point of the robotic ports approximately 10cm from the incision and thus create a larger working space for the robotic arms. The three 8-mm-diameter robot ports will be inserted and secured into the GelSeal Cap connected to an insufflator to keep the pressure at 8 mm Hg. Once the robot is docked, subcutaneous dissection will be performed using the monopolar-curved scissors and bipolar grasping forceps for traction and exposure. Using similar technique the gland will be separated from the pectoralis major muscle. The specimen will be removed from the anterior axillary incision. All breast specimens will be evaluated by pathology through the institutional usual specimen processing protocol. To

reconstruct the mound of the breast, plastic surgery will perform an immediate direct to implant-based reconstruction or TE placement using the anterior axillary line incision following the standard technique.

Patients will be recovered in the postoperative phase following the usual standard of care. Routine follow-up visits and study assessments will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months, as well as standard of care follow-up for surveillance for a minimum of 5 years after surgery.

Study population and eligibility criteria

Patients who present to the breast surgical oncology clinic will be screened for eligibility for robot-assisted nipple sparing mastectomy (RNSM). These patients typically have small breasts (bra cup size B or smaller, less than 500 grams of breast tissue) and no extensive ptosis of the breast. The cohort for this pilot study is limited to smaller breasted women (traditional open NSM candidates) but will expand in future studies to larger breasted patients (greater than C cup). Prior to consenting, patients will be informed that cancer treatment outcomes using RNSM have not been evaluated by the FDA and this is an 'off label' use of the device. Eligible patients will be informed of the purpose, procedures, and potential risks of the study. Patients will be eligible for inclusion in the study if they meet all the following inclusion criteria and excluded from participation in the study if they meet any of the following exclusion criteria (Table 1). Interested eligible patients will be screened and consented by the clinical research coordinator.

Sample Size

The number of cases to enroll in the pilot study has been set to twelve based on a previous study investigating the learning curve of RNSM.[18] The previous study of 39 cases found that docking time, robot console time, and overall operative time decreased on the 13th case, thus concluding that 12 cases were needed to decrease the operative time.

Subject withdrawal

Patients will be free to withdraw from the study at any point without consequence. Additionally, subjects may be withdrawn if during surgery the PI determines the patient requires surgery in the conventional manner and a pivot to this standard care surgery is immediately undertaken. For this initial trial, no patients will be replaced after their surgery for non-compliance to follow-up in The Ohio State University Wexner Medical Center breast oncological clinic.

TRIAL PROCEDURES

Surgery and biospecimen collection

Standard of care preoperative workup will be followed prior to surgery. RNSM will be performed using the da Vinci Xi Robotic Surgical System, a software-controlled, electro-mechanical system designed for surgeons to perform minimally invasive surgery. The breast specimen will be removed via gentle manual extraction through the anterior axillary incision using the "waving flag technique" (move the gland back and forth and up and down gently until it is removed). For specimen extraction, no devices such as the morcellator will be used. To assure en bloc removal of the specimen, if it is not feasible to remove the entire gland as a single piece, the incision will be extended to assure removal of the intact specimen. The specimen will

be labeled, as per standard of practice, with sutures and right/left orientation by the surgeon. All relevant data pertaining to the surgical procedure will be collected and breast specimens will be oriented for pathologic evaluation through the institution usual specimen processing protocol. The entire robotic portion of the surgery will be recorded. Representative portions of the pre-docking and post-docking procedure will be videotaped as well.

Post-operative phase

Per the usual standard of care, the patient will follow up in the breast surgical oncology clinic around post-operative day 14, day 30, 6 months, and 1 year. Pre-operative and post-operative photographs and study-related assessments will be obtained and completed at each of the previously stated time points. All images will be taken in a fashion that minimizes subject identification, such as exclusion of the head and neck region, any identifiers removed including tattoos, birthmarks, etc. At 6 weeks, a review of the patient's records will also occur to capture any re-operations/readmissions from a safety perspective. An implant exchange surgery will be performed around 3-6 months after expansion is complete or later if chemotherapy is required or the patient desires to wait.

Stopping Criteria

The study will be stopped if a) en bloc removal of the breast specimen is not achieved during the RNSM surgery, or b) the specimen is incorrectly labeled or oriented for pathologic evaluation. Specimen labeling with sutures is a part of standard practice and is performed by the investigator-surgeon. Any occurrence of the aforementioned events will trigger a temporary suspension of further enrollment into the study until additional evaluation utilizing the Corrective And Preventive Action (CAPA) process has been completed. Should the study be stopped, all regulating bodies (e.g. FDA, data safety monitoring committee) will be notified.

Data collection and management

The Ohio State Comprehensive Cancer Center clinical trial office research informatics services will be used as a central location for data processing and management, following standard operating procedures for the collection, storage, and analysis of electronic case report forms (eCRF). Data obtained from the patient's electronic medical record and surveys will be stored on a secure drive on university password protected computers, and/or entered into a secure username/password protected database, using OnCore as the electronic data capture tool. Data will be accessible only to the research personnel approved for this study. As part of the FDA IDE study, additional data will be provided to the FDA.

STUDY OBJECTIVES AND OUTCOMES

The primary objectives are to generate preliminary data on the safety and complications from RNSM. En bloc resection and removal of the breast specimen will be assessed as a primary endpoint. We will also investigate the total duration of the operation, the frequency of conversion to open technique, the length of hospitalization, and post-operative complications. Reported complications after RNSM include nipple areolar complex necrosis, mastectomy flap necrosis, temporary skin blistering, hematoma, seroma, infection, loss of implant from infection, delayed axillary wound healing, transient brachial plexus neurapraxia, and transient neurapraxia due to intraoperative patient positioning. Safety will be assessed by monitoring for all adverse

events/serious adverse events, re-operations, and readmissions. Mastectomy and NAC necrosis will be assessed using a validated scoring system called the SKIN score.[19] To assess outcome, routine follow-up visits will occur at 14 days, 30 days, 6 weeks, 6 months, and 12 months. Patients will complete the study related assessments within the 12 months of completion of operation. Patients will continue standard of care follow-up for surveillance at minimum of 5 years after surgery.

Beyond this, we aim to define the benefits and challenges of RNSM from the surgeon's perspective. Additional endpoints include NMSQ and SURG-TLX validated surveys to determine surgeon musculoskeletal fatigue. To assess patient satisfaction with the breast after surgery and sensation recovery after surgery, BREAST-Q and NAC modules for patient reported outcomes and satisfaction, and Semmes-Weinstein monofilament skin testing will be used. An exploratory endpoint is technical familiarity, which will be measured through operative robot console time.

As part of standard of care, patients will follow up with the plastic and reconstructive surgery clinic on an annual basis for surveillance of long term known implant-related adverse events including but not limited to the following: capsular contraction, implant rupture and deflation, breast implant associated-anaplastic large cell lymphoma, asymmetry, chest wall deformity, extrusion, infection, malposition/displacement, seroma, skin rash, wrinkling/rippling of implant, and unsatisfactory shape/size.

The current study is a pilot study to demonstrate initial feasibility. Ultimately, these data will be used to inform a larger multi-center study in the future. Specific outcomes of interest in future studies include oncologic safety and cost-effectiveness of RNSM.

Safety assessments

For this study, an adverse effect/event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs. All observed or subject-described adverse effects/events—serious or non-serious—and abnormal test findings, regardless of suspected causal relationship to the investigational device or other procedures, will be assessed beginning on the day of surgery and at every follow-up visit thereafter. As part of standard of care, patients will follow up with the plastic and reconstructive surgery clinic on an annual basis for surveillance of long term known implant-related AEs. AEs or abnormal test findings felt to be associated with the investigational device or, if applicable, other study procedures will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator. To ensure patient safety, all adverse events will be recorded, evaluated, and reported to FDA and IRB as required for all patient visits including long term follow-up.

Statistical Analysis Plan

This is a single-arm pilot study for feasibility and safety. Mainly descriptive analysis will be used to report the findings. Patient demographics, pathologic data, perioperative data, complication rate, mastectomy skin flap and nipple areolar complex necrosis, monofilament testing and patient reported outcomes will be reported. Patient reported outcomes will be evaluated by specific domains and compared to previously reported results in the literature.[5] In addition, to compare the previously reported results in the literature with this study, one sample proportion test will be performed to compare the mastectomy flap complication proportion, conversion to open NSM proportion. One sample Wilcoxon signed-rank test will be used to

assess the duration of surgery and length of hospital stay. For the analyses, statistical significance is set at two sided $\alpha<0.05$.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not directly involved in the development of the protocol design. However, our group discussed the study protocol with our local patient advocate prior to developing the trial design. We plan to actively engage with our patient advocates for future dissemination strategies and translation of the study findings to a larger multicenter trial.

ETHICS AND DISSEMINATION

The trial will be conducted in accordance with Good Clinical Practices (GCP). The protocol was reviewed and approved by the U.S. Food and Drug Administration (FDA) using the Investigational Device Exemption (IDE) mechanism (reference number G200096). The trial was registered with clinicaltrials.gov (NCT04537312) and the investigational plan was approved by The Ohio State University Institutional Review Board (IRB) 2020C0094 (8/18/2020). Any amendments to the trial protocol will be submitted to the IRB for approval.

The results of the study will be reported at appropriate scientific conferences. We plan to publish the trial results in a scientific, peer-reviewed journal. A full de-identified individual patient dataset of the trial will be made available after trial completion and publication upon request to the corresponding author.

Table 1. Inclusion and exclusion criteria

Inclusion criteria:	Exclusion criteria:

• adults: age ≥ 18 years
• surgical candidates, per standard of care for: open nipple sparing resection and reconstruction for following indications:
  ○ for risk reduction mastectomy
  ○ treatment of ductal carcinoma in-situ or clinically node negative cT1-T3 breast cancer
• surgical candidates for open NSM, per standard of care, with regards to patient anatomic factors and tumor location
• patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
	• pregnant
	• patients with:
	  ○ inflammatory breast cancer skin involvement with tumor pre-operative diagnosis (clinical, radiological or pathologic) of nipple-areola complex involvement with tumor
	  ○ grade 3 ptosis of nipple
	  ○ bra cup size greater than C cup
	• Smokers with heavy current use of nicotine (defined as > 20 cigarettes/day)
	• patients that are high risk for anesthesia, defined by the American Society of Anesthesiologists Scale ASA, grade 4 or higher
	• patients that do not have the ability to give informed consent
	• prisoner status at surgical clinic visit

	• previous thoracic radiation history

CONTRIBUTORS

The first author of this paper (KP) initially designed the study protocol. KP, AS, and RS contributed to initial planning of the trial. AS, RS, MC and SS contributed to initial preliminary data collection. Each co-author (KP, SL, AS, MC, SS, DA, VG, WC, and RS) contributed to subsequent development of the protocol. KP and SL wrote the initial draft of the manuscript. All authors (KP, SL, AS, MC, SS, DA, VG, WC, RS) approved the final version of this manuscript.

FUNDING

This work was supported by the Ohio State University 2019 Intramural Research Program IDEA Award (46050-502730) and the National Center for Advancing Translational Sciences (award number UL1TR001070). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institute of Health.

COMPETING INTERESTS STATEMENT

None declared.

REFERENCES

1. Galimberti V, Morigi C, Bagnardi V et al. Oncological Outcomes of Nipple-Sparing Mastectomy: A Single-Center Experience of 1989 Patients. Ann Surg Oncol 2018;25:3849-3857.doi: 10.1245/s10434-018-6759-0
2. Smith BL, Tang R, Rai U et al. Oncologic Safety of Nipple-Sparing Mastectomy in Women with Breast Cancer. J Am Coll Surg 2017;225:361-365. doi:10.1016/j.jamcollsurg.2017.06.013
3. Wei CH, Scott AM, Price AN et al. Psychosocial and Sexual Well-Being Following Nipple-Sparing Mastectomy and Reconstruction. Breast J 2016;22:10-17.doi: 10.1111/tbj.12542
4. Djohan R, Gage E, Gatherwright J et al. Patient satisfaction following nipple-sparing mastectomy and immediate breast reconstruction: an 8-year outcome study. Plast Reconstr Surg 2010;125:818-829.doi:10.1097/PRS.0b013e3181ccdaa4
5. Peled AW, Duralde E, Foster RD et al. Patient-reported outcomes and satisfaction after total skin- sparing mastectomy and immediate expander-implant reconstruction. Ann Plast Surg 2014;72(Suppl 1):S48- 52.doi:10.1097/SAP.0000000000000020
6. Yoon-Flannery K, DeStefano LM, De La Cruz LM et al. Quality of life and sexual well-being after nipple sp[Toesca, 2019 #14]aring mastectomy: A matched comparison of patients using the breast Q. J Surg Oncol 2018;118:238-242.doi:10.1002/jso.25107
7. Galimberti V, Vicini E, Corso G et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. Breast 2017;34(Suppl 1): S82-S84.doi:10.1016/j.breast.2017.06.034
8. Jackson RS, Sanders T, Park A et al. Prospective Study Comparing Surgeons' Pain and Fatigue Associated with Nipple-Sparing versus Skin-Sparing Mastectomy. Ann Surg Oncol 2017;24:3024-3031.doi:10.1245/s10434-017-5929-9

9. Chirappapha P, Srichan P, Lertsithichai P et al. Nipple-Areola Complex Sensation after Nipple- sparing Mastectomy. Plast Reconstr Surg Glob Open 2018;6:e1716. doi:10.1097/GOX.0000000000001716
10. Hallowell N, Baylock B, Heiniger L et al. Looking different, feeling different: women's reactions to risk-reducing breast and ovarian surgery. Fam Cancer 2012;11:215-224. doi:10.1007/s10689-011-9504-4
11. Temple CLF, Ross DC, Kim S et al. Sensibility following Innervated Free TRAM Flap for Breast Reconstruction: Part II. Innervation Improves Patient-Rated Quality of Life. Plast Reconstr Surg 2009;124:1419-1425.doi:10.1097/PRS.0b013e3181b98963
12. Børsen-Koch M, Gunnarsson GL, Sørensen JA, Thomsen JB. Thermal injury in TAPIA breast reconstruction-thermal injury to thoracodorsal artery perforator flap. Gland Surg 2017;6:110-113.doi:10.21037/gs.2017.01.01
13. Park KU, Weiss A, Rosso K et al. Use of Mammographic Measurements to Predict Complications After Nipple-Sparing Mastectomy in BRCA Mutation Carriers. Ann Surg Oncol 2020;27:367-372.doi:10.1245/s10434-019-07704-1
14. Toesca A, Invento A, Massari G et al. Update on the Feasibility and Progress on Robotic Breast Surgery. Ann Surg Oncol 2019;26:3046-3051.doi:10.1245/s10434-019-07590-7
15. Lee J, Park HS, Lee H, et al. Post-Operative Complications and Nipple Necrosis Rates Between Conventional and Robotic Nipple-Sparing Mastectomy. Front Oncol 2021;10(2924).
16. Park KU, Tozbikian GH, Ferry D, Tsung A, Chetta M, Schulz S, Skoracki R. Residual breast tissue after robot-assisted nipple sparing mastectomy. Breast 2020;55:25-29.doi: 10.1016/j.breast.2020.11.022
17. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, Buda A, Yan X, Shuzhong Y, Chetty N, Isla D, Tamura M, Zhu T, Robledo KP, Gebski V, Asher R, Behan V, Nicklin JL, Coleman RL, Obermair A. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med 2018;379:1895-1904.doi: 10.1056/NEJMoa1806395
18. Lai HW, Wang CC, Lai YC et al. The learning curve of robotic nipple sparing mastectomy for breast cancer: An analysis of consecutive 39 procedures with cumulative sum plot. Eur J Surg Oncol 2019;45:125-133.doi:10.1016/j.ejso.2018.09.021
19. Lemaine V, Hoskin TL, Farley DR, Grant CS, Boughey JC, Torstenson TA, Jacobson SR, Jakub JW, Degnim AC. Introducing the SKIN score: a validated scoring system to assess severity of mastectomy skin flap necrosis. Ann Surg Oncol 2015;22:2925-32.doi: 10.1245/s10434-015-4409-3

ACKNOWLEDGEMENTS

We thank Sue Marting with her assistance with obtaining the FDA Investigational Device Exemption.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Location in Manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1 Line 1-2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2 Line 27
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1, 4, 5. 6, 8 (Table 1)
Protocol version	3	Date and version identifier	Page 1 Line 37-38
Funding	4	Sources and types of financial, material, and other support	Page 10 Line 31-33
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1 Line 4-12, Page 10 Line 26-28
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 10 Line 33-35
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3
	6b	Explanation for choice of comparators	Page 3, 4
Objectives	7	Specific objectives or hypotheses	Page 6, 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 4 Line 20
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 4 Line 23-25
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5 Line 8-19, Page 8 (Table 1)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 5, 6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 6 Line 17-23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 5 Line 4-5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 4, 5

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 5, 6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 5 Line 22-25
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 5 Line 8-19
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 6 Line 26-34
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 5 Line 4-5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 6 Line 26-34
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 7 Line 38-46
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 7 Line 38-46
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 6 Line 26-34
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 6 Line 17-23
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 6 Line 17-23, Page 7 Line 24-35
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 8 Line 10-15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page 8 Line 10-15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 5 Line 18-19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 6 Line 311-33
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 10 Line 38

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 6 Line 26-34, Page 8 Line 16-19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 8 Line 16-19
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 8 Line 16-19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 8 Line 16-19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.