ENHANCED RECOVERY AFTER SURGERY IN AUTOLOGOUS BREAST RECONSTRUCTION: A PILOT RANDOMIZED CONTROLLED TRIAL

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements of the Degree of Master of Science

McMaster University

MASTER OF SCIENCE (2020)

Hamilton, Ontario (Health Research Methodology)

TITLE: Enhanced Recovery After Surgery in Autologous Breast Reconstruction (ERAS-ABR): A Pilot Randomized Controlled Trial

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NUMBER OF PAGES: 73

LAY ABSTRACT

Many women with breast cancer need surgical removal of their breast. Reconstructing the breast after such surgery improves patient quality of life. The breast can be reconstructed using implants or tissue from another part of the patient's body such as the abdomen. Patients undergoing breast reconstruction using their abdominal tissue experience longer recovery and use more pain medications compared to reconstruction using implants. We would like to test if a new approach to surgical care can improve recovery for patients having breast reconstruction using their abdominal tissue. As a first step, we would conduct a small pilot study to test if patients are willing to participate in this research, and if this approach can be delivered by the healthcare team. The results of this study will help decide if a larger study should be organized to test if we can improve recovery for patients having breast reconstruction using abdominal tissue.

150/150 words

ABSTRACT

Background: Enhanced recovery after surgery (ERAS) is an approach to perioperative care shown to shorten hospital length of stay (LoS) and decrease opioid use after colorectal surgery. There is increasing interest in applying ERAS to breast reconstruction, but the supporting evidence is limited. In this pilot study we evaluated the feasibility of conducting a randomized controlled trial (RCT) comparing ERAS to standard perioperative care among patients undergoing abdominal-based autologous breast reconstruction (AABR) for breast cancer.

Methods: We conducted a parallel two-arm pilot RCT of adult patients undergoing AABR between November 2019 and April 2020. Patients were randomly assigned to ERAS or standard perioperative care. Feasibility outcomes included patient rates of eligibility, recruitment, retention, and adherence to study protocol. The primary clinical outcome was median hospital length of stay. Secondary clinical outcomes included in-hospital opioid use, adverse events at 30-days, and quality of life questionnaires including BREAST-Q and EQ-5D-5L at 30-days.

Results: Of 22 screened patients, 21 (95.4%) were eligible for the study and 20 patients (95.2% of eligible) consented to study enrollment. Two patients did not undergo surgery due to COVID-19 related cancellations. Among the 18 randomized patients (90%) 10 received the study intervention and 8 received

standard care. All patients undergoing surgery completed the trial with 30-day follow-up. There was 85.8% adherence to study protocol items in the ERAS group. The ERAS group had a slightly shorter median hospital length of stay (ERAS 4 days, IQR 3-5; Standard care 4.5 days, IQR 3.25-5.75) and lower mean total oral morphine equivalent consumed (ERAS 82.3mg, SD 66.5; Standard care 408.1mg, SD 368.6).

Conclusions: This pilot study supports the feasibility of a larger RCT evaluating effectiveness of ERAS, as demonstrated by high rates of patient recruitment, study completion, and adherence to study protocols. Effectiveness outcomes also encourage a larger RCT.

Clinical Trial Registration: NCT04306003

298/300 words

ACKNOWLEDGEMENTS

I would like to thank my primary supervisor, Dr. Marko Simunovic, and the thesis committee: Dr. Sophocles Voineskos and Dr. Achilleas Thoma, for their support throughout the program. They are true role-models of the surgeon-scientist that I will continue to strive to become during my career.

I have immense gratitude to Dr. Ronen Avram and Dr. Clive Kearon for supporting my application to the Clinician Investigator Program. Similarly, I could not have come this far without having Dr. Sophocles Voineskos and Dr. Christopher Coroneos pave the path as stellar examples of the Clinician Investigator Program.

Additional thanks to Dr. Ronen Avram, Dr. Mark McRae, Dr. Christopher Coroneos, Dr. Sophocles Voineskos, Dr. Cynthia Horner, and Dr. Melanie Havers for their input and participation in the pilot study with such enthusiasm. Emily Dunn also deserves special recognition for her help during the study.

Finally, thank you to my fiance Cecily Bos whose endless support means the world to me.

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Abdominal-based autologous breast reconstruction: AABR

ASA: American Society of Anesthesiologist Classification

BRCA: BReast CAncer gene

DCIS: Ductal carcinoma in-situ

DIEP: Deep inferior epigastric perforator

ERAS: Enhanced Recovery After Surgery

IDC: Invasive ductal carcinoma

ILC: Invasive lobular carcinoma

MID: Minimally important difference

NSAID: Non-steroidal anti-inflammatory drug

OME: Oral morphine equivalent

PCA: Patient-controlled analgesia

PO: Per os (oral route)

POD: Postoperative day

PONV: Postoperative nausea and vomiting

RCT: Randomized controlled trial

DECLARATION OF ACADEMIC ACHIEVEMENT

I am primarily responsible for the development of the research question, study design, data collection, statistical analysis, and manuscript.

CHAPTER 1: INTRODUCTION

1.0 Background

Over 27,000 Canadian women are diagnosed with breast cancer every year.[1] While the 5-year survival of breast cancer has improved to 87% in Canada, nearly 1 in 3 patients undergo mastectomy which is associated with a negative impact in quality of life.[2,3] Specifically, mastectomy can result in morbidity to a patient's physical, psychosocial and sexual well-being.[4,5] The adverse effects of mastectomy on patient quality of life can be improved by breast reconstruction.[6–9] Despite these benefits, fewer than 1 in 6 Canadian women undergo breast reconstruction due to a multitude of factors such as public awareness, attitudes of referring physicians toward reconstruction, and geographic access to care.[10–13] Potential contributing factors may be the cost and resources needed to provide breast reconstruction. Interventions that can improve the efficiency of surgical care for patients undergoing breast reconstruction should expand access for Canadian women who would benefit from reconstructive procedures.

Breast reconstruction can be classified into alloplastic (implant-based) and autologous (tissue-based) reconstruction. While alloplastic reconstruction is the most common form of breast reconstruction in North America, autologous reconstruction using the patient's own tissue confers superior long-term satisfaction and quality of life.[14–16] The gold standard of abdominal-based autologous reconstruction (AABR) is

the deep inferior epigastric perforator (DIEP) flap which uses the patients' abdominal tissue to reconstruct the breast using microvascular techniques while preserving the abdominal musculature. AABR is surgically more complex than the alloplastic approach, involving surgery at the breasts, abdominal donor site, and reattachment of the abdominal tissue to blood vessels in the chest using microsurgical techniques. Patients undergoing AABR have a greater length of hospital stay and increased use of opioid analgesics when compared to those who undergo alloplastic surgery. According to the Canadian Institute for Health Information, the average hospital cost for a patient undergoing breast reconstruction is $3,715 per day.[17] For any surgical procedure, reducing postsurgical length of hospital stay and other associated costs (e.g. lower use of opioids) would be of value in the resource-constrained Canadian healthcare system.[18,19]

1.1 Enhanced Recovery After Surgery

Enhanced Recovery After Surgery (ERAS) is a multimodal approach to perioperative care intended to expedite and improve the quality of recovery after surgery.[20] ERAS requires modifications to patient management along the entire continuum of surgical care including instructions in the preoperative clinic, therapies in the surgical bay, operating room, post-operative recovery unit, and the ward.[21] Thus, ERAS requires a multidisciplinary approach involving surgeons, anesthesiologists, nurses, and other allied health professionals. ERAS represents the current standard of care in colorectal surgery and has been shown to reduce hospital

length of stay and postsurgical opioid use.[21–23] A meta-analysis of 16 randomized controlled trials (RCT) comparing ERAS to standard recovery in patients undergoing colorectal surgery demonstrated a reduction of 2.28 days (95% CI, 1.47 to 3.09) in hospital length of stay.[22] Despite substantial interest in applying the ERAS model in other surgical settings, there is limited high-quality evidence supporting its use in non-colorectal surgery.[24–28]

An ERAS guideline for perioperative care of alloplastic and autologous breast reconstruction patients has been published by the ERAS Society.[29] For this guideline, an international expert panel of physicians considering the quality and results of available evidence developed recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.[30] The guideline provides 18 recommendations encompassing preoperative planning and patient optimization, minimization of preoperative fasting, postoperative nausea and vomiting prophylaxis, multimodal opioid-sparing analgesia strategies, postoperative nutrition, early mobilization, and supportive care. All individual ERAS items received strong recommendations, with the majority of items supported by moderate to high level evidence and balanced by low risk of harm.[29]

However, there is weak evidence to support that ERAS as a bundle of interventions improves clinical outcomes in breast reconstruction. A recent meta-analysis of five observational studies on ERAS for patients undergoing AABR found that ERAS reduced mean hospital length of stay by 1.58 days (95%CI, 1.18 to 1.99,

I^2=65%) and mean opioid consumption by 248.13mg (95%CI, 108.32 to 387.95, I^2=69%) of oral morphine equivalent (OME) without an increase in complications.[31] Although the authors of the meta-analysis did not conduct a formal GRADE assessment, the certainty of evidence for these results would be low due to significant heterogeneity and the risk of bias associated with observational studies. In contrast to the multitude of RCTs that have investigated ERAS in colorectal surgery, there are no RCTs that have tested the effectiveness of ERAS in breast reconstruction.

Notwithstanding the existing guideline and gradual institutionalization of ERAS, there is an absence of high-quality evidence that ERAS as a package of interventions improves clinical outcomes of patients undergoing autologous breast reconstruction. A properly designed and executed RCT investigating the effectiveness of ERAS in breast reconstruction on key outcomes such as hospital length of stay and opioid use would contribute much needed evidence in this area.

1.2 Role of Pilot Trials

Randomized controlled trials investigating the effectiveness of interventions such as ERAS can be expensive, resource intense, and take many years to execute.[32] For example, trials testing the effectiveness of ERAS in colorectal surgery have an average sample size of 148 patients (range, 28 to 598), with the length of accrual ranging from 1 year to greater than 4 years.[22,33–36] Given the resource commitment

required to conduct RCTs, stakeholders recommend the use of pilot trials to evaluate feasibility prior to committing considerable resources to a full randomized trial. Research funding agencies increasingly request pilot data demonstrating feasibility of a study proposal and offer specific funding applications for conducting pilot studies.[37]

The terminology of feasibility and pilot studies, sometimes also described as vanguard studies, is not used consistently in the research community and often reflect a wide variety of research investigations that test the methods and procedures to be used in a larger study.[38] To address this issue, the framework proposed by Eldridge et al. define feasibility studies as the overarching concept for three distinct types of study.[39] *Randomized pilot studies* are smaller scale versions of an RCT that closely reflect the overall design of the future definitive trial. *Non-randomized pilot studies* similarly evaluate the design and processes of a future study but without the randomization of participants. *Feasibility studies that are not pilot studies* answer a specific question about some element of a future trial without active implementation of the study intervention (e.g. a survey of patients' willingness to be randomized in a trial comparing surgical interventions).

Pilot studies are most often used to evaluate *process measures* (or feasibility outcomes) such as recruitment rate, participant retention, and protocol adherence which are key to the success of the main study.[38] Other reasons to conduct pilot studies include estimating the required resources for the study, determining potential

issues with management of day-to-day study operations, as well as evaluating treatment safety, the treatment effect, and its variance.[38] Pilot studies should *a priori* state criteria for success which will be used to support feasibility of a subsequent larger RCT. Provided that the sampling frame and study methodology remain the same, patient data from a pilot study can be combined into the main RCT.[38]

The importance of pilot trials can be highlighted in a recently published multicentre randomized controlled trial conducted by the Chest Wall Injury Society.[40] The NON-FLAIL study was an RCT comparing surgical stabilization and non-operative management of patients with non-flail rib fractures across 12 academic trauma centres in the United States over the course of 18 months.[40] Eligibility criteria were fairly stringent and only 110 of 848 screened patients (13%) were eligible for the study. More significantly, only 23 eligible patients (21%) consented to randomization and the study ultimately failed to recruit the intended sample size of 74 patients. Had the investigators evaluated rates of eligibility and recruitment in a pilot trial, they may have modified eligibility criteria and other design elements to ensure a successful trial with the available funding and time constraints, or decided that the trial was not feasible and resources could have been placed elsewhere.

There is a clear need for an RCT testing the effectiveness of ERAS in AABR. A *randomized pilot study* would help demonstrate the feasibility of such a trial (e.g., valid estimates of participant eligibility, recruitment rate, retention rate, and

adherence to study protocols), would inform study design, and help justify study funding.

1.3 Study Objectives

We conducted a randomized pilot study comparing ERAS to conventional perioperative care for patients undergoing AABR. Our primary objective was to assess feasibility outcomes. Specifically, the study evaluated rates of patient eligibility, recruitment, retention, adherence to the ERAS protocol in the intervention arm. The primary clinical outcome was hospital length of stay; secondary clinical outcomes included in-hospital opioid use, condition-specific patient-reported outcomes, general health-related quality of life, and 30-day adverse events. The design and conduct of the proposed pilot study mirrored the expected methodology of a definitive trial testing effectiveness of ERAS in AARB, including randomization, delivery of interventions, and measurement of clinical outcomes.[39] Therefore, it may be appropriate to include patients and their results in this pilot trial into such a future RCT. The reporting of this study adheres to the CONSORT checklist for pilot studies (Appendix 3).[41]

CHAPTER 2: STUDY METHODOLOGY & PROCEDURES

2.0 Trial Design

A parallel two-arm pilot RCT was conducted to assess the feasibility of a larger effectiveness trial comparing ERAS versus standard perioperative care for patients undergoing AABR. Patients scheduled for AABR at two academic centres in Hamilton, Ontario (Juravinski Hospital and St. Joseph's Healthcare Hamilton Charlton Campus) between November 2019 and April 2020 (6 months) were screened for eligibility either during clinic visits with participating surgeons or prior to the preoperative clinic visit. Eligible and consenting patients were randomized using a centralized online service (Sealed Envelope Ltd)[42] with 1:1 allocation to ERAS (experimental) or standard perioperative care (control). Baseline demographics and patient-reported outcomes were documented at the time of randomization. Patients were followed for 30-days postoperatively for final collection of feasibility, clinical, and patient-reported outcomes.

2.1 Patient Population

Broad inclusion criteria were used to reflect the pragmatic nature of the study. The population was defined as adult women undergoing post-mastectomy AABR meeting the following inclusion criteria:

2.1.1 Inclusion Criteria

a. Women of age 18 years or older

b. Able to understand and communicate in English

c. Diagnosis of breast cancer or BRCA genetic abnormality

d. Undergoing (or previously undergone) unilateral or bilateral mastectomy

e. Scheduled for immediate or delayed AABR

Patients seeking AABR following a previous failed or unsatisfactory alloplastic or autologous reconstruction were considered as secondary reconstructions and still eligible to participate in the study.

2.1.2 Exclusion criteria

As ERAS specifically focuses on early patient mobility and includes medications which may be contraindicated in pregnancy, patients with the following factors were excluded:

a. Non-ambulatory or impaired mobility at baseline

b. Pregnant

c. Unable to provide informed consent or complete patient-reported outcome questionnaires

2.2 Study Setting

The trial was conducted at Juravinski Hospital (Hamilton Health Sciences) and St. Joseph's Healthcare Hamilton Charlton Campus. Both sites provide tertiary

level reconstructive surgery with AABR. The randomization, data management, statistical analysis, and oversight of the trial was performed at Juravinski Hospital.

2.3 Screening & Enrollment

All consecutive patients scheduled to undergo AABR were identified either at clinic visits with participating surgeons or through the operating room schedule managed by the surgeons' administrative assistants. These patients were screened for eligibility and those meeting criteria were invited to participate in the study. Patients already scheduled for surgery were approached via telephone by a member within the circle of care to obtain permission to be contacted by the study coordinator to discuss the study.

Patients expressing interest in participating in the study met with the study coordinator at the preoperative clinic appointment two to four weeks prior to scheduled surgery. A second screening was conducted to ensure that eligibility had not changed prior to obtaining signatures for the consent form and completing baseline demographic data and patient-reported outcomes (see **2.5.2 Clinical Outcomes**).

2.4 Trial Interventions

2.4.1 Experimental Group

The intervention in the experimental arm was a ERAS protocol based on the consensus ERAS Society recommendations for breast reconstruction[29], ERAS regimens from previous observational studies[43–46], availability of local resources, and consultation with local plastic surgeons, anesthesiologists, nurses and physiotherapists. We implemented interventions to target eight of the 18 recommendations made by the ERAS Society including: 1) *perioperative fasting*; 2) *preoperative carbohydrate loading*; 3) *preoperative & intraoperative multimodal analgesia*; 4) *postoperative nausea and vomiting (PONV) prophylaxis*; 5) *hypothermia prevention*; 6) *postoperative multimodal analgesia*; 7) *early feeding*; and 8) *early mobilization*. These ERAS items were selected as they could be implemented with discrete interventions which were measurable, required minimal study resources, were judged to have a likely impact on study clinical outcomes.

Five ERAS recommendations were not explicitly included in the study protocol since they were already standard of care at our institution including: 1) *perforator flap planning*; 2) *venous thromboembolism prophylaxis*; 3) *antimicrobial prophylaxis*; 4) *clinical postoperative flap monitoring*; and 5) *postoperative wound management*. The remaining five ERAS recommendations were not implemented due to limitations in study resources, challenges with standardization and objective

measurement, as well as likely weak relevance to clinical outcomes of interest. We expand on our reasoning for the latter five recommendations in Table 1,

Table 1. Unimplemented ERAS Recommendations

ERAS Recommendation	Rationale
Preoperative Education	There were insufficient resources with respect to study personnel and clinic time to provide patients with additional formal study preoperative education and counseling. All patients received preoperative education as per their discussion with respective surgeons.
Preadmission Optimization • *Smoking cessation* • *BMI under 30*	All patients undergoing AABR were encouraged to abstain from smoking. The guideline also recommends a BMI of under 30. However, not all participating surgeons had a strict criteria regarding BMI and routinely operate on patients of higher BMI which is reflective of the patient population at our institution (mean BMI 32.1, SD 5.3).
Standard Anesthetic Protocol • *Total intravenous anesthesia (TIVA)*	The ERAS protocol was developed with input from local anesthesiologists at each study site. It was challenging to enforce use of TIVA due to different preferences of anesthesiologists and the high turnover of different staff for each AABR case.
Euvolemic Fluid Resuscitation	Goal-directed fluid resuscitation would require invasive hemodynamic monitoring which would not be required for all patients. Furthermore, implementation was also challenged by the difficulty of objectively measuring successful euvolemia.
Post-discharge Home Support & Physiotherapy	There were insufficient resources to provide post-discharge home support for patients in the study. Furthermore, post-discharge recommendations would not impact the clinical outcomes of interest (hospital length of stay, in-hospital opioid use) which related to inpatient care.

The eight ERAS recommendations were broken down to 19 intervention items across three phases of care: preoperative (5 items), intraoperative (4 items), and postoperative (10 items).

I) Preoperative Phase (5 ERAS Items)

Recommendations: *Perioperative fasting & Preoperative Carbohydrate Loading*

Patients were permitted to consume solids until midnight before the evening of surgery and fluids up to 3 hours before surgery. To further minimize the catabolic effects of prolonged fasting, patients were instructed to consume a clear carbohydrate rich drink (e.g. apple juice, cranberry cocktail, sports beverage) before midnight and 3 hours prior to surgery. The final decision regarding NPO instructions was determined by the clinical judgment of the anesthesiologist at the preoperative clinic visit (e.g. patients with risk factors for gastroparesis may be excluded from preoperative carbohydrate loading).

> **Item 1:** Patients were instructed to consume a carbohydrate rich drink (3 glasses, 800mL) before midnight of surgery.

> **Item 2:** Patients were instructed to consume a carbohydrate rich drink (1.5 glasses, 400mL) 3 hours before surgery.

Recommendation: *Preoperative & Intraoperative Multimodal Analgesia*

Patients received the following medications with sips of clear fluid one hour prior to surgery.

Item 3: Acetaminophen 975mg per os (PO)

Item 4: Celecoxib 400mg PO

Recommendation: *Postoperative Nausea and Vomiting Prophylaxis*

Item 5: Dexamethasone 4-10mg IV administered before surgery

II) Intraoperative Phase (4 ERAS Items)

Recommendation: *Hypothermia Prevention*

Item 6: Use of forced-air warming units and core temperature monitoring

Recommendation: *Preoperative & Intraoperative Multimodal Analgesia*

Item 7: Chest wall intercostal nerve blocks with 0.25% bupivacaine

Item 8: Abdominal wall intercostal nerve blocks with 0.25% bupivacaine

Recommendation: *Postoperative Nausea and Vomiting (PONV) Prophylaxis*

Item 9: Ondansetron 4-8mg IV administered during emergence from anesthesia

III) Postoperative Phase (10 ERAS Items)

Recommendation: *Early Feeding*

Item 10: Patient allowed clear fluid diet on POD0.

Item 11: Patient advanced to regular diet on POD1.

Recommendation: *Postoperative Multimodal Analgesia*

Item 12: Acetaminophen 975mg PO every 6 hours POD1 to POD2, then administered as needed POD3 onward. Dose not to exceed 4g per day.

Item 13: Celecoxib 200mg PO every 12 hours POD1 to POD2, then administered as needed POD3 onward. Dose not to exceed 400mg per day.

Item 14: Patient controlled analgesia (PCA) pump not used.

ERAS patients were ordered hydromorphone 1 to 2mg PO every 6 hours as needed for breakthrough pain. Alternate opioids were permitted at the discretion of physicians providing care. Patient controlled anesthesia (PCA) pumps were avoided in the ERAS protocol to optimize pain control with oral medications and minimize use of intravenous lines which could restrict patient mobility.

Recommendation: *Early Mobilization*

Item 15: Patient assisted up to a chair on POD0.

Item 16: Removal of indwelling urinary catheter on POD1.

Item 17: Saline locking of intravenous lines on POD1.

Item 18: Assessment by ward physiotherapist on POD1.

Item 19: Patient ambulating on POD1.

The ERAS protocol was implemented into the perioperative care pathway through standardized study order sets for each phase of care. The preoperative package was updated to include a study information sheet on ERAS fasting guidelines and carbohydrate loading for the anesthesiologist and nursing staff evaluating the patient at the preoperative clinic. No specific training was required as the instructions for preoperative fasting and carbohydrate loading were the same as those implemented for patients undergoing colorectal surgery and thus already familiar to the perioperative staff. The preoperative orders were also updated to include multimodal analgesia administration one hour prior to surgery. Patients were also reviewed for potential contraindications to preoperative medications (i.e. Acetaminophen, Celecoxib) as part of baseline demographic data collection.

On the day of surgery, the patient chart was updated with a study information sheet to remind the surgical team on the intraoperative ERAS items. The resident physician in the operating room was also sent a reminder to complete the ERAS postoperative order sets. Additional orders and changes to ERAS items were permitted for individual patient indications (e.g. discontinuation of celecoxib due to allergy, cardiovascular, or renal disease).

We considered the inclusion of gabapentin and liposomal bupivacaine for our multimodal pain regimen as they have been used in some ERAS regimens.[43–46] However, gabapentin was excluded from the study protocol as it is not formally approved as an analgesic by Health Canada. The only indication that gabapentin is approved for is as an adjunct therapy for refractory epilepsy.[47] Similarly, liposomal bupivacaine is currently not approved for use in Canada.[48]

2.4.2 Control Group

Patients in the control group received standard perioperative care as determined by the existing practice and preference of surgeons and anesthesiologists for each study site. Preoperative and postoperative items were administered as ordered by the participating surgeon using pre-existing patient care order sets. As will be reviewed below, some parts of our intervention ERAS protocol were already being used by participating plastic surgeons, though not in a comprehensive or consistent fashion. This pragmatic approach to the control group reflects the heterogenous conditions in which a trial testing the effectiveness of ERAS would be performed in real clinical settings.

2.5 Outcomes

2.5.1 Feasibility Outcomes

The primary objective of this pilot study was to evaluate feasibility of an effectiveness RCT. Feasibility outcomes and criteria thresholds for pilot trial success included the following:

Eligibility: All patients scheduled for AABR at participating surgeon offices and sites were screened for study eligibility. We defined success as ≥**90%** of screened patients who were eligible for the study.

Recruitment: Patients who signed the informed consent form and successfully randomized to a study arm were considered fully recruited. We defined success as ≥**75%** of eligible patients recruited into the study.

Retention: The number of patients that reached the end of the trial with complete clinical outcome data, including BREAST-Q and EQ-5D-5L at 30-days, determined rate of patient retention. The sexual well-being domain of the BREAST-Q was excluded in considering completion of BREAST-Q as it permitted patients to skip the domain if they felt uncomfortable answering them. Reasons for study withdrawal were documented. We defined success as ≥**80%** of randomized patients who completed the study.

Adherence to ERAS: Adherence was measured by itemizing each ERAS interventions to calculate the proportion of ERAS items adhered to. There was a total of 19 ERAS items per patient divided into preoperative (5 items), intraoperative (4 items), and postoperative (10 items) phases of care. Clinical care data were audited through review of patient charts, physician orders, and medication administration records using standardized data collection forms. Reasons for protocol deviation were documented if available. We defined success as ≥**80%** overall adherence to ERAS interventions.

2.5.2 Clinical Outcomes

Primary Clinical Outcome

Hospital length of stay: The median hospital length of stay in days. Day of surgery was considered day zero.

Secondary Clinical Outcomes

In-hospital opioid consumption: The mean in-hospital opioid consumption was compared. We measured all sources of opioids administered in the postoperative period, from patient transfer to the Post Anesthesia Care Unit (PACU) to hospital discharge. Opioids given intraoperatively were not considered. Opioids were converted to its oral morphine equivalent (OME) in milligrams as the unit of measurement using an opioid equianalgesic table (Appendix 1). Outpatient opioid

use was not measured as ERAS does not influence discharge opioid prescribing practices.[49]

BREAST-Q Reconstruction Module: The Reconstruction Module of BREAST-Q is a validated condition-specific health-related quality of life instrument for patients undergoing breast reconstruction.[50,51] It measures six domains: psychosocial well-being, sexual well-being, breast satisfaction, abdomen satisfaction, chest wall physical well-being, abdomen physical well-being. BREAST-Q scores were obtained at baseline prior to surgery at the time of study enrollment and 30-days postoperatively. Questionnaires were reviewed to ensure completion of all questions; if a patient missed a question, they were asked to complete it in-person or via telephone. The change score from baseline for each instrument domain were compared at 30-days following surgery.

EQ-5D-5L: EQ-5D-5L is a multi-attribute utility instrument for measuring general health-related quality of life.[52] It measures five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, in addition to a visual analogue scale. Preoperative baseline data were obtained at study enrollment and 30-days postoperatively. Questionnaires were reviewed to ensure completion of all questions; if a patient missed a question, they were asked to complete it in-person or via telephone. Responses to the five domains and visual analogue scale were compared individually and as summarized health-state index values at 30-days following surgery.

30-day adverse events: Complications within 30-days of surgery were classified as *major* (complications requiring surgical intervention in the main operating room), *minor* (complications requiring medical management and/or local wound care on the ward), and *other resource utilization* (e.g. emergency room visits or hospital readmissions). Specific complications included: hematoma, arterial/venous flap failure, partial/complete flap necrosis, infection, and mastectomy skin necrosis.

Adverse event data was collected primarily via patient medical records. We specifically reviewed daily progress notes, discharge summaries, clinic dictations and visitation data (e.g. emergency room visits), as well as operative records if a patient required surgical management of a complication. Each patient was reviewed for adverse events at time of hospital discharge and at 30-days follow-up.

2.6 Frequency and Duration of Follow-up

The total duration of study follow-up was 30-days after surgery. The frequency of clinical follow-up was determined according to surgeon practice, but all surgeons agreed to 30-day follow-up (within a range of 25 to 35 days) to obtain final study data on patient-reported outcomes and adverse events. Patients who missed their 30-day follow-up appointment were contacted via telephone and provided the option to complete final data collection via telephone or an electronic survey administered via McMaster University's LimeSurvey.[53]

2.7 Randomization

All patients were randomized by the study coordinator at the preoperative clinic visit after obtaining consent and baseline data. A web-based randomization service (Sealed Envelope Ltd)[42] provided centralized patient-level randomization and maintained allocation concealment. Patients were randomized with 1:1 allocation to ERAS or standard care with variable permuted blocks (2 or 4) to improve study group balance given the small size of the pilot RCT.[54] Randomization was stratified by study site (Juravinski Hospital or St. Joseph's Healthcare Hamilton Charlton Campus) and timing of reconstruction (immediate or delayed). Patients were blinded to their study group allocation.

Differences in wait time between consultation and breast reconstruction depending on the indication of surgery were considered in deciding the timing of randomization. At our institution, patients undergoing delayed reconstruction after mastectomy may wait several months for surgery after consultation, whereas patients undergoing immediate reconstruction for active breast cancer may only wait weeks. We surmised that patients with significant wait-times prior to reconstruction would be at relatively high risk of post-randomization dropout and changes in baseline health unrelated to our study. We therefore randomized patients at the preoperative clinic visit once the surgery was officially scheduled (Figure 1).

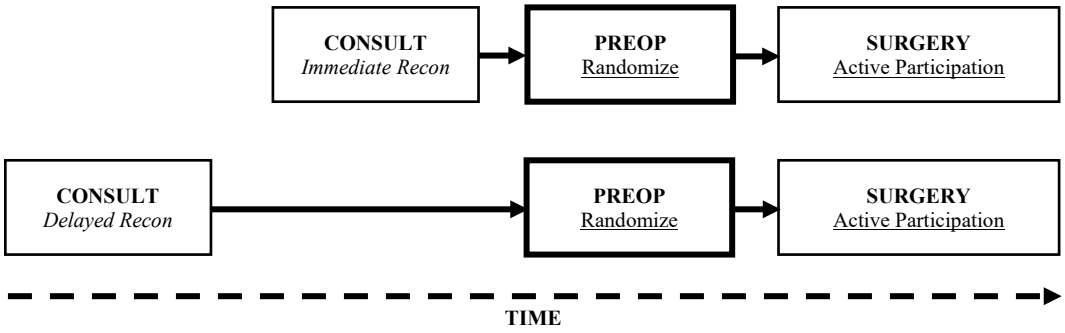

Figure 1. Patients were randomized at the preoperative clinic visit instead of at time of consultation to minimize variation in the time between randomization and active study participation.

2.5.1 Stratification

Based on a local 6-month review of breast reconstruction patients (n=27), the mean hospital length of stay of patients undergoing AABR was 4.0 days (SD 1.1). There was a difference in the mean length of stay between the study sites (Juravinski: 4.2 days, SD 1.2; St. Joseph's: 3.5 days, SD 0.5), which justified stratification by site. There was no important differences in mean length of stay for immediate (3.9 days, SD 1.1) versus delayed reconstruction (4.0 days, SD 1.0); or for unilateral (3.7 days, SD 0.8) versus bilateral reconstruction (4.0 days, SD 1.2). We thus did not justify stratification on timing of surgery (immediate versus delayed) based on length of stay but rather on anticipated differences in patient-reported outcomes (e.g. satisfaction with breasts).

2.8 Bias

2.8.1 Selection Bias

A web-based service (Sealed Envelope Ltd)[42] was used to generate the randomization sequence not accessible to study investigators to achieve allocation concealment. We used variable permuted block sizes (2 or 4) to improve balance between groups and mitigate study investigators being able to predict the next allocation based on a fixed block size. Consecutive recruitment of all eligible patients also minimized potential for selective sampling of patients. Stratification of randomization by study sites was used to improve balanced distribution of study patients from each hospital.

2.8.2 Blinding

We were not able to blind the clinical team due to the nature of ERAS as a complex multimodal intervention and limited study resources. This introduces a risk for performance bias. Even if the clinical team were not informed of the patient's study group, the use of study specific order sets would have made it apparent to which group the patient belonged. Treatment decisions specific to ERAS would need to be withheld to have a fully blinded clinical team. We theorized that lack of blinding could result in earlier discharge, potentially prematurely, for patients in the ERAS arm. Thus, we measured rates of hospital readmissions and emergency room visits to detect a potential signal indicative of performance bias.

The outcome assessor was likewise not blinded due to limited study resources and personnel which introduces a risk of detection bias. Patients were not informed of their study group allocation and therefore blinded to interventions. Due to limited study personnel, the outcome assessor was not blinded.

2.8.3 Contamination

Some degree of contamination was anticipated as some ERAS items (e.g. intraoperative body warmers) were likely already s part of standard care. The absence of physician blinding may also influence physician behaviour and result in contamination of ERAS items into the control group. The standardized data collection forms used in the intervention arm to detail use of all ERAS protocol items was also used in the control arm. This allowed us to evaluate potential contamination of ERAS items into the control arm, and such information would be important to the design and justification of a subsequent effectiveness study.

2.9 Sample Size

A convenience sample of 24 patients was chosen as the sample size of the pilot RCT. Based on a local 6-month retrospective chart review between September 2018 to February 2019, there were 27 patients that underwent AABR in Hamilton (19 at Juravinski Hospital and 8 at St. Joseph's Hospital Charlton Campus). Given the study hypothesis of 90% patients being eligible, an estimation of 24 recruited patients was considered realistic within the 6-month study duration.

Furthermore, a preliminary sample size for the full RCT was also estimated using the 6-month local data of breast reconstruction patients from Juravinski Hospital and St. Joseph's Healthcare Hamilton Charlton Campus. We used a non-parametric test (Wilcoxon-Mann-Whitney) as recommended for skewed variables such as hospital length of stay.[55] A mean length stay of 4.0 days (SD 1.1) was used as the representative control group based on the 6-month local chart review, and a mean length of stay of 3.0 days was estimated for the ERAS group using one hospital day as the minimally important difference. The variance for length of stay in the ERAS group was estimated by weighted pooling of standard deviations reported in previous observational studies (SD 1.75).[31] The sample size was calculated to be 74 (37 patients per group) using a two-tailed Wilcoxon-Mann-Whitney test, with an *alpha* of 0.05, and power of 80%. Based on this initial estimation, a sample of 24 patients for the pilot RCT represented 32.4% of the full trial sample size.

2.10 Statistical Analysis

We used descriptive statistics for feasibility and clinical outcomes. Patients were analyzed by their allocated group to follow the intention-to-treat principle. Inferential statistical analysis was not performed for clinical outcomes as this pilot study was not intended to measure clinical effectiveness. For the pilot study, we compared the change score from baseline for patient-reported outcomes such as BREAST-Q and EQ-5D-5L.

We planned that the statistical analysis for the main trial would use the Wilcoxon-Mann-Whitney test for the primary clinical outcome (*hospital length of stay*). Secondary clinical outcomes would be analyzed using a 2-sample t-test for *in-hospital opioid use* and analysis of covariance (ANCOVA) for postoperative *BREAST-Q* and *EQ-5D-5L* scores using baseline scores as the covariate. ANCOVA the preferred method of analysis compared to use of change scores which does not adequately address imbalance in baseline measurements.[56,57] Proportion data such as *30-day adverse events* would be analyzed with the Fisher's exact test.

2.11 Ethics

Institutional review board (IRB) approval was obtained before the start of recruitment. The Health Canada clinical trials office was consulted to ensure no study medications required a clinical trial application. The study was registered at clinicaltrials.gov (NCT04306003).

2.12 Funding

This pilot study was supported by grants from the RMA Scholarship Program, PSI Foundation, Canadian Institutes of Health Research, and Clinician Investigator Program at McMaster University.

CHAPTER 3: STUDY RESULTS

3.0 Patient Demographics

Patients scheduled for AABR were recruited from the offices of four plastic surgeons at the Juravinski Hospital (A.R. & C.J.C) and St. Joseph's Healthcare Charlton Campus (M.C. & S.V.) during a 6-month period between November 2019 and April 2020. Amongst all the participants, the mean age was 52.9 years (SD 6.9) with mean BMI of 32.1 (SD 5.3). All patients were either non-smokers or had quit prior to surgery (Table 2). The most common diagnosis for the entire study cohort was invasive ductal carcinoma (44.4%), followed by BRCA (27.8%) and invasive lobular carcinoma (22.2%).

A notable difference in patient demographic was the higher proportion of active cancer patients requiring therapeutic (vs prophylactic) mastectomy in the ERAS group (90%) compared to the standard care group (50%) (Table 3). Patients undergoing bilateral mastectomy for active cancer on one breast and prophylactic treatment on the other were considered to be receiving a therapeutic mastectomy. This distribution likely explains the difference in proportion of patients with preoperative radiation (ERAS 60% vs Standard care 25%) as there would be no role for neoadjuvant treatment in prophylactic mastectomy. There were no notable differences in the laterality or timing of reconstruction.

Table 2. Patient demographics and comorbidities

	ERAS	Standard Care
N	10	8
Age, mean years (SD)	51.6 (6.7)	54.5 (7.2)
BMI, mean (SD)	33.7 (6.3)	30.3 (3.3)
Smoking Status, N (%)		
Never	5 (50)	5 (62.5)
Past smoker	5 (50)	3 (37.5)
Current smoker	0	0
Diagnosis, N (%)		
BRCA	1 (10)	4 (50)
DCIS	1 (10)	0 (0)
IDC	6 (60)	2 (25)
ILC	2 (20)	2 (25)
ASA, N (%)		
II	2 (20)	2 (25)
III	8 (80)	6 (75)
Comorbidities		
Cardiovascular†	1 (10)	0 (0)
Gastrointestinal‡	0 (0)	0 (0)
Chronic kidney disease	0 (0)	0 (0)
Type II diabetes	0 (0)	1 (12.5)

ASA= American Society of Anesthesiologists Classification System;
DCIS=ductal carcinoma in situ; IDC=invasive ductal carcinoma; ILC=invasive lobular carcinoma
†History of angina, myocardial infarction, congestive heart failure, atrial fibrillation, transient ischemic attacks, or stroke
‡ History of gastrointestinal bleed, peptic ulcer, inflammatory bowel disease, or hepatic disease

Table 3. Summary of treatment variables

	ERAS	Standard Care
N	10	8
Study Site, N (%)		
Juravinski Hospital	6 (60)	6 (75)
St. Joseph's Healthcare	4 (40)	2 (25)
Laterality, N (%)		
Unilateral	4 (40)	4 (50)
Bilateral	6 (60)	4 (50)
Indication, N (%)		
Prophylactic	1 (10)	4 (50)
Therapeutic	9 (90)	4 (50)
Timing, N (%)		
Immediate	3 (30)	3 (37.5)
Delayed†	4 (40)	4 (50)
Secondary	2 (20)	1 (12.5)
Mixed‡	1 (10)	0 (0)
Preoperative Radiation, N (%)	6 (60)	2 (25)

†Defined as primary delayed reconstruction; Secondary reconstruction was defined as patients receiving AABR who had previously undergone alloplastic or autologous breast reconstruction

‡Patients undergoing bilateral reconstruction that is immediate for one breast and delayed for the other breast

3.1 Feasibility Outcomes

3.1.1 Eligibility

A total of 23 patients were scheduled for AABR at the two study sites during the 6-month study period (Figure 2). Of these patients, 22 (95.7%) were screened for eligibility during a clinic visit with the surgeon or by telephone. One patient missed study screening as the study coordinator was not aware the patient had been scheduled for reconstruction. All 22 screened patients were initially eligible at the time of screening, but one patient became ineligible as her surgical plan changed to immediate alloplastic reconstruction. In the end, 21 patients (95.4%) of 22 screened patients were eligible for the study.

3.1.2 Recruitment

Eligible patients met with the study coordinator at the preoperative clinic to sign consent, randomization, and collection of baseline study data. Of the 21 eligible patients, 20 patients (95.2%) were enrolled into the trial and randomized to study groups, yielding a mean recruitment rate of 3.3 patients per month. One eligible patient was excluded prior to randomization as her surgery was cancelled due to COVID-19. None of the eligible patients declined participation in the study.

3.1.3 Retention

Of the 20 patients recruited into the study, 11 patients were randomized to the ERAS group and nine patients were randomized to the standard care group. One patient in each study group had their reconstruction cancelled due to COVID-19 and thus excluded post-randomization but before receiving the assigned intervention. Overall, 18 patients (90% of randomized) proceeded with surgery and received study interventions (ERAS, n=10; Standard care, n=8). All 18 patients completed 30-day follow-up with complete data collection of feasibility and clinical outcomes. Data collection was completed in-person for 14 patients and electronically via LimeSurvey for four patients.

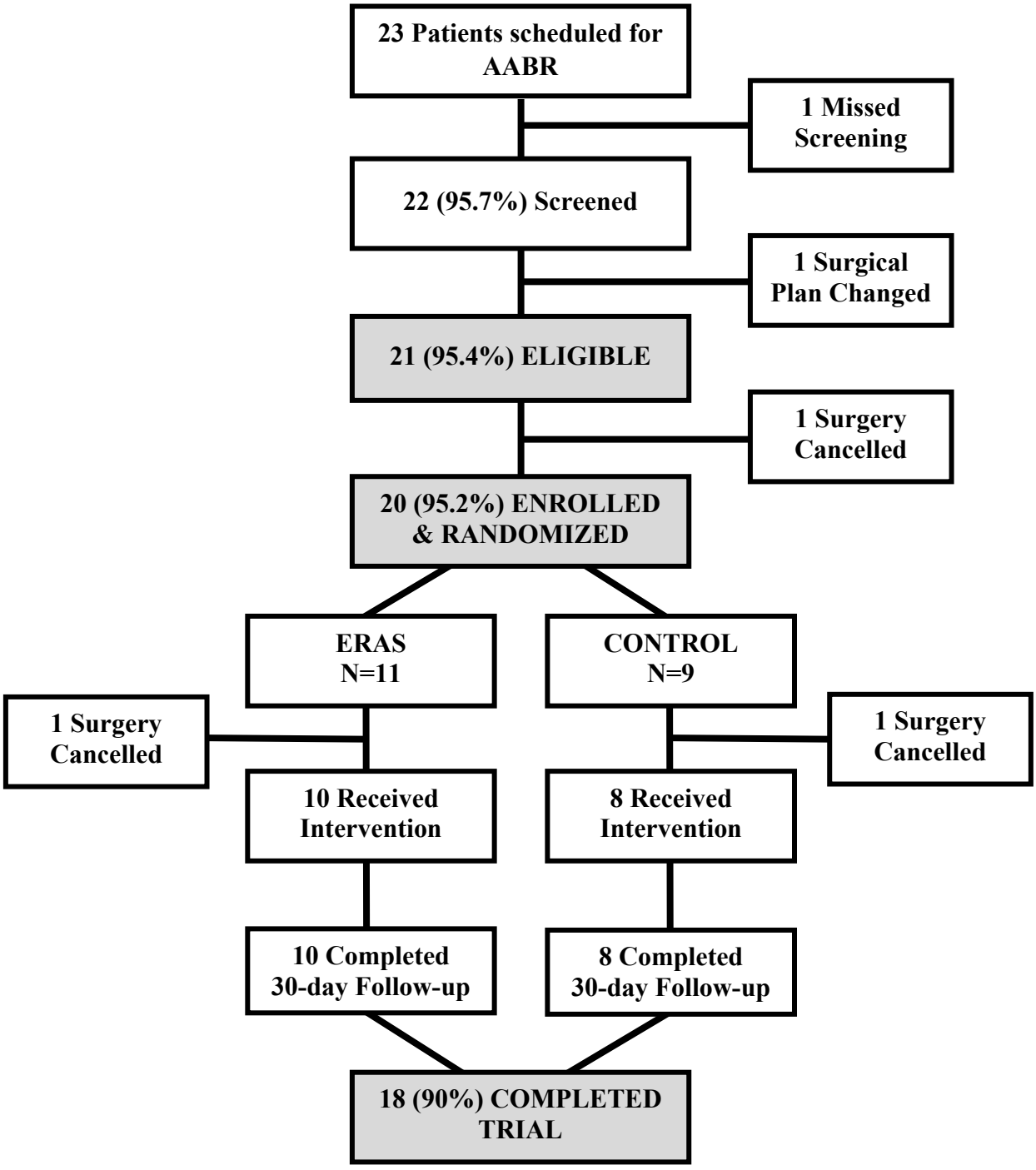

Figure 2. Flowchart of patient screening, enrollment, and retention

3.1.4 Adherence to ERAS Protocol

Overall, there was 85.8% protocol adherence to ERAS items in the ERAS group, with 7 of 10 patients achieving at least 80% adherence (Table 4). There was high adherence to preoperative (90%) and intraoperative (100%) ERAS items, with postoperative ERAS items demonstrating a lower adherence (78%). Among postoperative ERAS items, having the patient transferred to a chair on POD0 (50%) and receive physiotherapy assessment on POD1 (60%) had the lowest adherence.

3.2 Contamination

The ERAS adherence checklist was also used to monitor for contamination of ERAS interventions into the standard care group. There was overall 42.8% contamination of ERAS items with significant overlap of the four intraoperative items (97%), suggesting these interventions are already part of routine clinical care. Notably, there was significantly less contamination for the five preoperative items preoperative items (12.5%), with no control group patients receiving carbohydrate loading or multimodal analgesia prior to surgery. Although there was moderate contamination for the 10 postoperative items (36.3%), there were key differences for use of patient controlled-analgesia (PCA) pumps (ERAS 10% vs Standard care 87.5%), POD1 foley removal (ERAS 80% vs Standard care 12.5%), and ambulation on POD1 (ERAS 80% vs Standard care 0%). Patients in the ERAS group were

ambulating on average 1.2 days (SD 0.42, range 1 to 2) after surgery compared to 2.25 days (SD 0.46, range 1 to 3) after surgery for the standard care group.

Table 4. Adherence to ERAS protocol and contamination

	Compliant item (%)	
Protocol Item	ERAS (N=10)	Control (N=8)
1.1 Carbohydrate drink at midnight	8 (80)	0 (0)
1.2 Carbohydrate drink 3 hours prior to surgery	8 (80)	0 (0)
1.3 Acetaminophen 975mg given before surgery	10 (100)	0 (0)
1.4 Celecoxib 400mg given before surgery	8 (80)	0 (0)
1.5 Dexamethasone given before surgery	9 (90)	5 (62.5)
Maximum Total Preoperative Score†	50	40
Total Preoperative Score	45 (90)	5 (12.5)
2.1 Hypothermia prevention used‡	10 (100)	7 (100)
2.2 Nerve blocks: chest wall	10 (100)	8 (100)
2.3 Nerve blocks: abdomen	10 (100)	8 (100)
2.4 Ondansetron given before emergence	10 (100)	7 (87.5)
Maximum Total Intraoperative Score†	40	32
Total Intraoperative Score	40 (100)	31 (97)
3.1 POD0 clear fluids	8 (80)	2 (25)
3.2 POD0 up to chair evening of surgery	5 (50)	0 (0)
3.3 PCA not used	9 (90)	1 (12.5)
3.4 Routine oral acetaminophen	9 (90)	7 (87.5)
3.5 Routine oral NSAID	8 (80)	6 (75)
3.6 POD1 diet as tolerated	8 (80)	5 (62.5)
3.7 POD1 physiotherapy assessment	6 (60)	3 (37.5)
3.8 POD1 ambulating	8 (80)	0 (0)
3.9 POD1 saline lock	9 (90)	4 (50)
3.10 POD1 foley removed	8 (80)	1 (12.5)
Maximum Total Postoperative Score†	100	80
Total Postoperative Score	78 (78)	29 (36.3)
Overall Protocol Adherence	**85.8%**	**42.8%**

†Calculated by the number of adherence items multiplied by number of patients in each study group

‡This process measure was based on whether strategies for hypothermia prevention (e.g. forced-air warming units).

3.3 Primary Clinical Outcome

3.3.1 Hospital Length of Stay

We measured a small reduction in median length of hospital stay in the ERAS group (4 days, IQR 3-5) compared to the standard care group (4.5 days, IQR 3.25-5.75) (Table 5). The proportion of patients being discharged by POD4 was 70% in the ERAS group and 50% in the control group (Figure 3).

Table 5. Summary of in-hospital clinical outcomes

	ERAS Group	Control Group
N	10	8
Length of Stay (days), median (IQR)	4.0 (3.0-5.0)	4.5 (3.25-5.75)
Length of Stay (days), mean (SD)	4.0 (0.8)	4.6 (1.4)
In-hospital OME (mg), mean (SD)	82.3 (66.5)	408.1 (368.6)

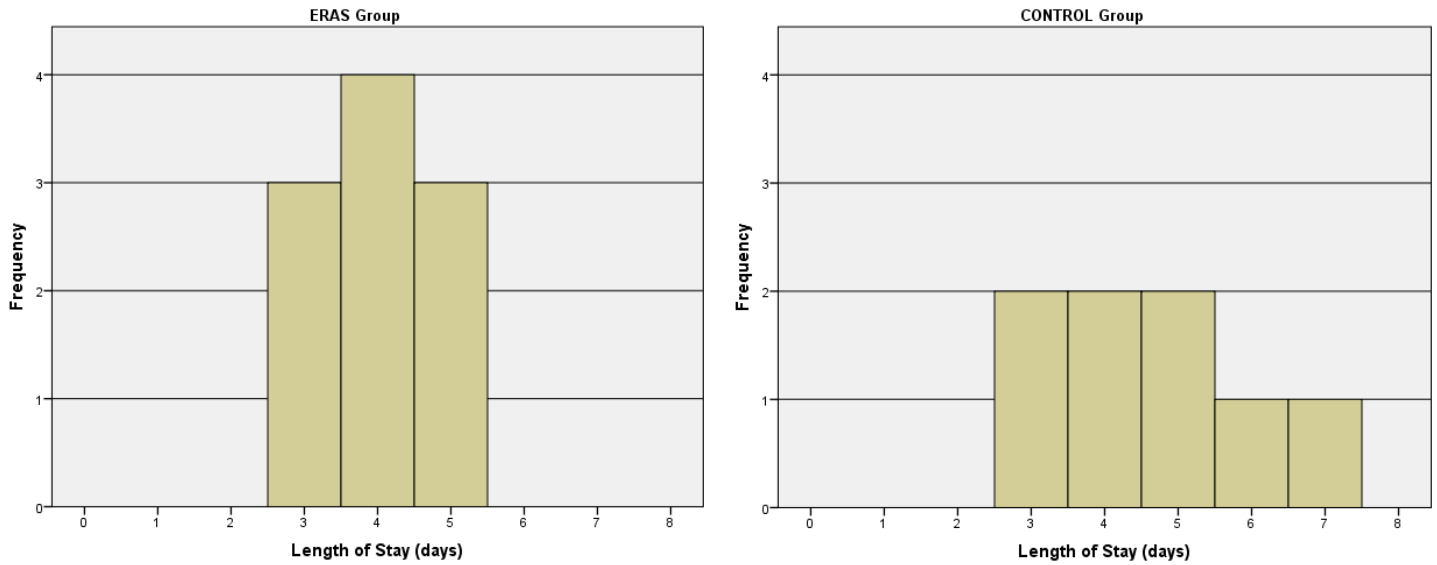

Figure 3. Histogram of length of stay in the ERAS group and Control (standard care) group

3.4 Secondary Clinical Outcomes

3.4.1 In-hospital Opioid Use

As presented in Table 5, there was a reduction in the mean total OME consumed in the ERAS group (82.3mg, SD 66.5) compared to the control group (408.1mg, SD 368.6).

3.4.2 BREAST-Q

Results on condition-specific quality of life across six domains measured using BREAST-Q are presented in Table 6. Four patients in the ERAS group declined to complete the sexual well-being domain of the BREAST-Q. Psychosocial well-being had changes which were discordant between the study arms, with improved well-being in the ERAS group (+11.6, SD 17.8) and decreased well-being in the control group (-6.1, SD 11.0). Sexual well-being similarly had discordant changes between groups, but the magnitude of the change was small. Patients in both study groups had similar improvements in satisfaction with their breasts (ERAS +32.5, SD 17.9; Control +28.0, SD 19.5) and abdomen (ERAS +5.4, SD 1.8; Control +4.0, SD 3.8), despite experiencing decreased physical well-being in both areas likely secondary to surgical recovery.

Table 6. Summary of patient-reported outcome scores on BREAST-Q

			Score, Mean (SD)		
BREAST-Q Domain	Study Group	N	Baseline	30d postop	Change Score
Psychosocial well-being	ERAS	10	57.2 (14.6)	68.8 (15.5)	11.6 (17.8)
	Control	8	63.1 (16.0)	57.0 (7.2)	-6.1 (11.0)
Sexual well-being	ERAS†	6	42.5 (19.4)	45.0 (17.1)	2.5 (11.2)
	Control	8	49.6 (14.8)	48.3 (13.7)	-1.4 (19.5)
Satisfaction with breasts	ERAS	10	36.5 (17.7)	69.0 (15.7)	32.5 (17.9)
	Control	8	44.0 (11.0)	72.0 (13.3)	28.0 (19.5)
Satisfaction with abdomen‡	ERAS	10	4.8 (2.1)	10.2 (1.6)	5.4 (1.8)
	Control	8	5.3 (2.1)	9.3 (2.8)	4.0 (3.8)
Physical well-being: Chest	ERAS	10	62.3 (31.8)	58.5 (26.6)	-3.8 (38.8)
	Control	8	76.0 (20.4)	58.5 (24.9)	-17.5 (25.8)
Physical well-being: Abdomen	ERAS	10	77.6 (23.3)	64.6 (16.3)	-13.0 (33.5)
	Control	8	77.0 (20.6)	58.1 (7.8)	-18.9 (20.9)

†Four patients declined to answer this domain

‡The baseline scale (1 to 4) was multiplied by 3 to be comparable with the postoperative scale (1 to 12)

3.4.3 EQ-5D-5L

General health-related quality of life was measured using EQ-5D-5L across five domains: mobility, self-care, activity, pain/discomfort, and anxiety/depression. The EQ-5D-5L domain scores were converted to a summary index using value sets derived from a general population in Canada.[58] Overall, patients in both groups experienced a decrease in health-related quality of life measured 30-days after surgery (Table 7). This was consistent with increased proportion of patients reporting problems with mobility, self-care, difficulty with usual activities, and pain/discomfort following surgery (Appendix 2).

Table 7. EQ-5D-5L Index Scores

		EQ-5D-5L Index Score, Mean (SD)		
Study Group	N	Baseline	30d postop	Change
ERAS	10	0.824 (0.105)	0.785 (0.160)	-0.039 (0.106)
Control	8	0.863 (0.052)	0.746 (0.138)	-0.112 (0.139)

3.4.4 Adverse Events

Adverse events at 30-days after surgery are presented in Table 8. For major complications, there was one case of partial flap necrosis managed with surgical debridement in both study groups, and one case of flap venous insufficiency requiring surgical exploration in the control group. Mastectomy skin necrosis requiring local wound care was seen in one patient in the ERAS group and two patients in the control group. One patient in the control group had partial dehiscence of the abdominal donor site requiring local wound care. Additionally, one patient in the control group experienced paroxysmal atrial fibrillation during in-hospital stay. With respect to other healthcare resource utilization, emergency department visits occurred in one ERAS patient due to a surgical drain issue (17 days post-discharge) and one ERAS patient due to upper respiratory tract infection symptoms (2 days post-discharge). In the control group, one patient visited the emergency department due to drainage from the surgical site (5 days post-discharge). No patients required readmission to hospital.

Table 8. Summary of 30-day adverse events

	ERAS Group, N (%)	Control Group, N (%)
N	10	8
Patients with at least one adverse event	4 (40)	5 (62.5)
Total Major Complication†	1 (10)	2 (25)
Hematoma	0 (0)	0 (0)
Flap exploration		
Arterial	0 (0)	0 (0)
Venous	0 (0)	1 (12.5)
Partial flap necrosis	1 (10)	1 (12.5)
Total Minor Complication‡	1 (10)	4 (50)
Infection	0 (0)	0 (0)
Mastectomy skin necrosis	1 (10)	2 (25)
Donor site dehiscence	0 (0)	1 (12.5)
Other		
Atrial fibrillation	0 (0)	1 (12.5)
Other Resource Utilization	2 (20)	1 (12.5)
ER Visits	2 (20)	1 (12.5)
Hospital readmission	0 (0)	0 (0)

†Complications requiring surgical management in the main operating room

‡Complications requiring medical management and/or local wound care

CHAPTER 4: DISCUSSION

4.0 Feasibility

The ERAS-ABR pilot study demonstrates the feasibility of a larger effectiveness RCT comparing ERAS and standard perioperative care in patients undergoing AABR at our institution. *A priori* feasibility targets for patient eligibility, recruitment, retention, and adherence were achieved. The fact that feasibility criteria were met despite the unanticipated impact of COVID-19 on the study further supports the feasibility of a larger RCT in a normalized post-pandemic setting.

The high proportion of eligibility was supported by the pragmatic approach adopted in defining the eligibility criteria which reflects the clinical diversity of patients undergoing reconstruction that may benefit from ERAS. As such, 21 of 22 (95.4%) screened patients were eligible for the study, achieving the goal that at least 90% of screened patients would satisfy the eligibility criteria. The one ineligible patient highlights the importance of confirming patient eligibility prior to randomization. The patient was initially scheduled for AABR but became ineligible upon re-evaluation at the preoperative clinic as the surgical plan had changed to alloplastic reconstruction.

The study enrolled 20 of 21 (95.2%) eligible patients, satisfying the goal of minimum recruitment of 75% of patients. Patient consent, collection of baseline data, and randomization all occurred during one encounter at the preoperative clinic visit

which eased the process of enrollment. We would likely have achieved 100% enrollment of all eligible patients had it not been for one patient whose surgery was cancelled due to COVID-19. As recruitment occurred over a 6-month study period (November 2019 to April 2020), we achieved an approximate recruitment rate of 3.3 patients per month. The recruitment rate was similar to our initial estimation of 3 patients per month based on 90% eligibility and 75% recruitment of 27 patients undergoing AABR between September 2018 and February 2019.

With respect to study retention, 18 of 20 (90%) randomized patients completed the study and satisfied the goal of 80% retention. There was complete data collection of clinical and patient-reported outcomes for these 18 patients. Selecting a few specific patient-reported outcomes with a relatively short 30-day follow-up period minimized study burden and reduced risk of incomplete data collection.[59] The majority of patients were able to attend 30-day follow-up with their plastic surgeon which allowed final data collection of patient-reported outcomes to be administered in person. In-person visits ensured that the trial coordinator was able to immediately confirm the completeness of questionnaires and address missing answers with the patient directly. Furthermore, the study had procedures in place to contact patients to complete the questionnaire in full or to obtain missing answers for specific questions via telephone or electronically. Due to limited in-person visits imposed by COVID-19, four patients successfully completed the 30-day questionnaires via LimeSurvey.

Two patients, one patient each from the ERAS group and standard care group, were excluded post-randomization as their reconstruction was cancelled due to COVID-19. As no surgery took place, the patients did not receive study interventions and had no outcomes measured. Intention-to-treat analysis would mandate that all included patients should be analyzed according to the group they were originally assigned which could be achieved via different approaches to handling missing data (e.g. complete case analysis, imputation).[60]

However, we adopted a different approach and excluded the two patients from the analysis. The justification for this decision was that the major concern with post-randomization exclusion is that it may bias the analysis if there is a relationship between treatment allocation and likelihood of exclusion.[61] In this case, the treatment allocation did not influence the likelihood of surgery being cancelled; all surgical patients were affected by the pandemic regardless of whether they were receiving ERAS or standard care. Furthermore, a balanced exclusion of one patient from each study arm also helped support this decision. Another perspective to consider is that the two patients were prematurely randomized into the trial as their eligibility was contingent on surgery.[61] Typically in surgical trials this may be mitigated by randomizing patients at time of surgery. For our study however, randomizing patients at the preoperative clinic was logistically the earliest point randomization could occur as preoperative ERAS items such as preoperative fasting and carbohydrate loading were determined by the anesthesiologist at this visit.

The overall adherence to study protocol items in the ERAS group was 85.8%, satisfying the goal of overall 80% adherence rate. Seven of ten ERAS patients achieved 80% or greater adherence to protocol items. The three patients below 80% adherence to ERAS protocol received the appropriate ERAS order sets but deviated from protocol due to individual patient factors precluding preoperative carbohydrate loading, contraindication to medications such as celecoxib, and delayed postoperative ambulation. As a comparison, a large prospective cohort study on ERAS adherence in colorectal cancer surgery conducted in Sweden demonstrated an overall adherence of 71% for 12 ERAS items.[62] Intraoperative ERAS items had perfect adherence, followed by preoperative items (90%) and postoperative items (78%). Although there was lower adherence to assisting patients to a chair on the evening of surgery (50%) or POD1 physiotherapy assessment (60%), the overall goal of early ambulation within the first 24-hours was achieved with 80% of ERAS patients ambulating on the first postoperative day compared to no patients in the control group.

4.1 Clinical Outcomes

We experienced no significant challenges with collecting data for clinical outcomes. Hospital length of stay and in-hospital opioid consumption were readily accessible through the patient chart and medication administration records. Study patients were also willing to complete questionnaires for patient-reported outcomes such as BREAST-Q and EQ-5D-5L. The clinical outcomes reported in this study

were measured as part of the conducting the randomized pilot trial. As these results are based on a small sample size that is wholly insufficient to make conclusions regarding the effectiveness of ERAS, clinical outcomes have been reported with descriptive statistic without the use of inferential statistics or p-values.

4.1.1 Hospital Length of Stay

There was a modest reduction of 0.6 days in LoS in the ERAS group (4.0 days, SD 0.8) versus the standard care group (4.6 days, SD 1.4) which is less than the minimally important difference of one hospital day. This is in contrast to larger reductions in the mean length of stay reported in a meta-analysis based on low quality evidence: 1.58 days (95%CI, 1.18 to 1.99).[31]

However, a notable difference is that the mean length of stay from the observational studies included in the meta-analysis was 4.92 days (SD 1.75) for the ERAS group and 6.95 days (SD 1.58) for the control group.[31] Patients receiving standard perioperative care in our study already had a shorter mean length of stay (4.6 days, SD 1.4) compared to both the control group (-2.3 days) and ERAS group (-0.32 days) from the meta-analysis. This highlights the risk of observational studies to overestimate treatment effects. Outcomes such as hospital length of stay are also likely to have a floor effect, a point at which its increasingly unlikely for a patient to be discharged sooner. There may be greater potential for benefit in shortening length of stay if the baseline length of stay is higher, with diminishing effects as length of

stay approaches the floor. Consequently, the potential for ERAS to reduce hospital length of stay in breast reconstruction should be considered in context of local length of stay measurements; there may be less benefit if the length of stay is already low.

4.1.2 In-hospital Opioid Use

There was an 80% reduction (OME 325.8mg) in in-hospital opioid consumption for the ERAS group (OME 82.3mg, SD 66.5) compared to the control group (OME 408.1, SD 368.6). This was similar to the magnitude of OME reduction reported in meta-analyses of ERAS in breast reconstruction: 248.13mg (95%CI, 387.95 to 108.32)[31] and 307.85mg (95%CI, 129.57 to 486.14).[63]

Patients in ERAS of our study were pre-emptively treated with a multimodal analgesia strategy (acetaminophen 975mg and celecoxib 400mg) one hour prior to surgery (90% adherence), while control patients received no preoperative analgesia (0% contamination). However, there was greater overlap in the postoperative pain control strategy. The postoperative ERAS protocol was composed of scheduled maximal dosing for non-opioids (acetaminophen 975mg PO q6h with maximum 4g in 24 hours; celecoxib 200mg PO q12h with maximum 400mg in 24 hours) and oral opioids as needed for breakthrough pain. In contrast, majority of patients in the control group were treated with a PCA pump which also included routine dosing of acetaminophen and ibuprofen as part of an existing order set, although ordered inconsistently and at lower doses. Nevertheless, 87.5% of patients received routine

acetaminophen and 75% received routine ibuprofen along with PCA in the control group.

Despite most patients in both study groups receiving some form of multimodal analgesia, there was still substantially higher opioid use for patients in the control group. This is likely attributed to a combination of the preoperative analgesia received by patients in the ERAS group and the higher proportion of PCA use in the control group. A meta-analysis comparing PCA to non-patient controlled opioid analgesia found patients using PCA consumed higher amount of opioids.[64] While proper postoperative pain control is important, it should be balanced by its potential impact on patient mobility (e.g. sedation, dizziness) and oral intake (e.g. nausea, vomiting, constipation) which are also critical to early postoperative recovery.

The potential impact of analgesic co-interventions introduced by the clinical care team were also considered. Two patients (20%) in ERAS and three patients (37.5%) in the standard care group received diazepam as a muscle relaxant; and another two patients (25%) in the standard care group received gabapentin. It is difficult to interpret the impact of co-interventions as it may be related to opioid use in different ways—patients consumed less opioids due to the co-interventions or patients with higher pain, thus higher opioid need, were more likely to receive co-interventions.

4.1.3 BREAST-Q & EQ-5D-5L

The results of the BREAST-Q reconstructive module in the ERAS-ABR study were consistent with the Mastectomy Reconstruction Outcomes Consortium (MROC) study, which was a large multicentre prospective cohort study comparing patient-reported outcomes after alloplastic or autologous reconstruction.[16] Differences in baseline and postoperative scores were considered in context of the minimally important difference (MID) published for each domain of BREAST-Q (Table 9).[65] The MIDs were determined using a distribution-based approach using 0.2 standard deviations as the effect size and offer a starting point to interpret what changes in scores patients find important.

Table 9. Recommended MID estimate for BREAST-Q reconstruction module[65]

	Recommended MID Estimate
Satisfaction with breasts	4
Psychosocial well-being	4
Physical well-being (chest)	3
Sexual well-being	4

Patients in both ERAS and the control group experienced clinically meaningful improvements in breast satisfaction even at 30-days after surgery. In comparison with the MROC study, patients in the ERAS-ABR pilot had lower baseline scores (ERAS 36.5, SD 17.7; Control 44.0, SD 11.0; MROC 58.2, SD 20.2).[16] Despite baseline differences patients achieved similar breast satisfaction at

30-days compared to outcomes at 1-year in the MROC study (ERAS 69.0, SD 15.7; Control 72.0, SD 13.3; MROC 68.6, SD 17.0).[16]

Autologous reconstruction came at the cost of decreased physical well-being of the chest at 30-days in both study groups. Patients in the control group had a higher baseline score (76.0, SD 20.4) compared to the ERAS group (62.3, SD 31.8). These differences could be attributed to the higher proportion of ERAS patients (60%) having received chest-wall radiation compared to control patients (25%) given that the proportion of immediate and delayed reconstructions between the groups were quite similar. Patients in both groups reported similar chest physical well-being scores at 30-days (ERAS 58.5, SD 26.6; Control 58.5, SD 24.9). In contrast, patients in the MROC study reported decreased physical chest well-being at 1-year which was smaller than the MID (Baseline 76.8, SD 15.3; 1-year 74.9, SD 15.1).[16] The comparison of results suggest that patients are still undergoing recovery from surgery at 30-days, thus reporting decreased physical well-being, but return close to baseline by 1-year after surgery. Similar reductions in physical well-being of the abdomen was seen at 30-days for all patients. However, a notable difference to physical well-being of the chest is that a clinically important reduction in abdominal physical well-being was still observed at 1-year in the MROC study.[16]

Sexual well-being was essentially unaffected by breast reconstruction at 30-days, demonstrating slight changes that did not meet the MID. Similarly, there was

no change in sexual well-being meeting MID at 1-year in the MROC study, but there was a clinically important improvement at 2-years and beyond.[16]

There was a significant difference in baseline psychosocial well-being between ERAS (57.2, SD 14.6) and the control group (63.1, SD 16.0). Results at 30-days after surgery were also discordant, with ERAS patients experiencing increased well-being (68.8, SD 15.2; Change +11.6, SD 17.8) and control patients experiencing decreased well-being (57.0, SD 7.2; Change -6.1, SD 11.0). Both findings are likely explained by the higher proportion of patients with active cancer diagnoses in the ERAS group. The decreased baseline psychosocial well-being could be attributed to the negative impact of active breast cancer therapy (chemotherapy or radiation therapy) on patient quality of life.[66] Stratifying psychosocial well-being scores by cancer diagnosis corresponds to this trend, suggesting that patients with active cancer experience improvement in psychosocial well-being after reconstruction while patients with undergoing prophylactic treatment do not (Table 10).

Table 10. Psychosocial Well-Being by Cancer Diagnosis

		Score, Mean (SD)		
Cancer Diagnosis	N	Baseline	30d postop	Change Score
Active Cancer†	13	56.8 (15.4)	65.2 (15.2)	8.4 (17.9)
BRCA	5	67.8 (12.2)	59.4 (7.9)	-8.4 (7.2)

†Includes ductal carcinoma in situ, invasive ductal carcinoma, and invasive lobular carcinoma

Health-related quality of life measured by EQ-5D-5L similarly had a lower baseline index score for the ERAS group (0.824, SD 0.105) compared to the control group (0.863, SD 0.052). There was greater proportion of patients reporting problems for mobility, usual activities, self-care, and pain/discomfort 30-days after surgery which likely represent ongoing recovery which is consistent with the results for physical well-being of the chest (Appendix 2). This is reflected by the decreased summary index scores at 30-day follow-up.

4.1.4 Adverse Events

Although there was a proportional greater number of patients with both major and minor complications in the control group, these differences were based on a small number of events and should not be used to draw clinically meaningful conclusions. The data collection process for adverse events was achieved primarily through review of patient medical records without any issue. The inclusion of an exit interview with the patient at 30-days follow-up allowed us to determine if there were any unanticipated medical visits (e.g. emergency room, walk-in clinic) outside of the hospital system which would not be logged in the electronic medical record. This opportunity was also used to clarify the nature of the emergency room visits if the primary documentation was unclear.

4.2 Study Strengths

The ERAS-ABR pilot RCT is the first randomized study comparing ERAS to standard perioperative care in the breast reconstruction patient population. The current evidence for ERAS in breast reconstruction are all observational studies, with most being retrospective cohort studies with historical controls.[31,43–46] Secular trends such as overall improvements in perioperative care represent a potential confounder that may exaggerate the treatment of effect of ERAS, as well as diminish the generalizability to how contemporary surgical patients are managed compared to historical controls. Prospective implementation of ERAS with direct comparison to a control group within a consistent perioperative environment strengthens the validity of conclusions on the effectiveness of ERAS in the AABR patient population.

Furthermore, the development of a robust study protocol and procedure allowed screening of nearly all patients (95.7%) undergoing AABR at the study sites. We were successful in achieving high rates of patient recruitment, retention, and adherence to study protocol in a focused study timeline of 6 months. Although we had considered measuring other outcomes such as postoperative pain and quality of surgical recovery during inpatient stay, we decided to minimize study burden for patients while they are acutely recovering from surgery. Rather, we focused on a few important outcome measures that may have contributed to the completeness of data collection and high retention of participants at the end of the study.[59]

The use of a naturalistic control group dictated by existing surgeon preferences also reflects the heterogeneous conditions in which ERAS would be applied in a real-world setting. Individual surgeons have different approaches to perioperative care and the relative benefit of ERAS will depend on what its being compared to. Furthermore, we considered the ethical ramifications and potential bias which may be introduced by implementing a standardized perioperative protocol for the control group. A pragmatic real-world control group using pre-existing care order sets avoided the need to implement a control group protocol that may exaggerate the benefits of ERAS.

4.3 Study Limitations and Implications for the Main RCT

4.3.1 Patient Eligibility

The eligibility criteria in our pilot study demonstrated a high proportion of eligible participants. Nevertheless, the inclusion criteria is restricted to women with active breast cancer or a positive BRCA gene undergoing AABR. Women who undergoing AABR following mastectomy for high risk for breast cancer without BRCA (e.g. due to strong familial history) would not be eligible within the current inclusion criteria. Although no patients were excluded on this basis in our study, the eligibility criteria for the larger RCT will be expanded to include such patients to increase recruitment for the study.

4.3.2 Blinding

The lack of blinding was a significant limitation which increased the risk of bias in our study. As ERAS is a complex multimodal intervention that spans the entire perioperative care pathway, it was not possible to blind the clinical team of a patient's study allocation. It would not be difficult for a member of the clinical team to determine if a patient received preoperative pain medications and surmise the study allocation for that patient. Physician knowledge of the patients' study allocation could influence decisions regarding patient care resulting in performance bias. Potential consequences include patients in the ERAS group being discharged from hospital earlier than those in the control group. We surmised that some patients may be discharged prematurely which may be offset by increased visits to the emergency department or hospital readmission. Although there only was a small difference in ER visits (2 in ERAS group, and 1 in standard care group) and no hospital readmissions in either group in our pilot study, this would need to be measured further in the larger RCT.

With sufficient funding, having a blinded independent team that does not directly participate in patient care to adjudicate readiness for discharge would mitigate the effects of performance bias on the primary clinical outcome (hospital length of stay). A structured discharge criterion would be implemented to determine if a patient is medically ready for discharge (e.g. patient is able to eat and drink, pain is controlled by oral analgesics, capable of sufficient mobility for self-care, no

complications requiring hospital care).[67] There was minimal risk of performance bias from study patients as they were blinded to their study allocation.

The outcome assessor was also not blinded in our pilot trial due to limited study personnel. This introduces risk of detection bias, but we attempted to mitigate this through use of standardized data collection forms. Additionally, clinical outcomes such as hospital length of stay and opioid use had less risk for detection bias as these are objective outcomes that simply needed to be transcribed.[68] Mitigating detection bias for adverse events would require a blinded outcome adjudicator to assess the patient to ensure that complications are reported as objectively as possible.

4.3.3 Contamination

The absence of blinding also increased the risk of contamination in the control arm—that through the course of the trial the clinical team would introduce ERAS interventions into the standard care group. Using a surgeon-level or hospital-level cluster randomization trial design could mitigate the risk of contamination but at the cost of increased study complexity and the need for a larger sample size to account for cluster-level analyses.[69] To partially evaluate if cluster randomization would be necessary, the 19-item data collection form used to measure adherence to ERAS protocol also measured use of the relevant 19 ERAS items in the control arm.

The absence or presence of contamination, respectively, would justify the patient-level randomization in this pilot RCT or indicate the need for a cluster design.

Overall, there was 42.8% contamination of ERAS items into the standard care group, and the degree of contamination varied between phases of care. Preoperative items had 12.5% contamination from patients in the control group receiving PONV prophylaxis; no patients in the control group received carbohydrate loading or preoperative analgesia. Intraoperative ERAS items had near complete overlap with the control group (97%) which likely reflects that these interventions are part of standard care rather than influenced by the study.

The postoperative phase of care had the most variation in contamination across ERAS items (36.3%). Key differences between ERAS and standard care were for use of PCA (ERAS 10% vs Standard care 87.5%), POD1 ambulation (ERAS 80% vs Standard care 0%), and POD1 foley removal (ERAS 80% vs Standard care 12.5%). As noted previously, the use of acetaminophen and NSAID in the control group was high in control group as these were bundled as part of an existing PCA order set.

The degree of contamination was also compared at two times points covering 3 months of the study period: November to January and February to April. The degree of contamination was not significantly different between the two time points (November to January: 44.75%; February to April: 41.0%), which suggests that the

degree of contamination is reflective of existing overlap of ERAS interventions in current standards of care, and not items introduced secondary to study involvement.

The issue of contamination will require adjustments in the design of the main RCT based on the cause of contamination. The presence of any contamination in the control arm will undermine our ability to isolate the treatment effect of ERAS interventions.[69,70] Despite the overall contamination of 42.8% in our study, this was largely inflated by 97% contamination of the four intraoperative ERAS items which likely represent current standard of care. Essentially, the contamination measured for the intraoperative items was caused by the design of the ERAS protocol (contamination due to design)—namely, the specific interventions we decided to include. Excluding the intraoperative ERAS items—like how other ERAS recommendations such as antimicrobial prophylaxis was purposefully excluded as they were recognized already as part of standard care—would have reduced contamination in the control arm down to 28.3%. This form of contamination due to design would not be resolved by cluster randomization but would require changes to the study intervention. On the other hand, contamination of ERAS items introduced intentionally by physicians aware of the patient's allocation (contamination due to lack of blinding) would be mitigated by a cluster design.

Proceeding with patient-level randomization will likely require increasing the power of the study with a higher sample size to detect a smaller treatment effect.[69] Alternatively, adopting a cluster randomization design would similarly require a

larger sample size and recruitment of additional clusters (i.e. hospital study sites). Considering all these factors demonstrate that the larger effectiveness RCT should use a cluster design to mitigate contamination of ERAS interventions into the control group. In particular, a step-wedge cluster design may be the optimal design choice as it is increasingly used for evaluation of complex interventions such as ERAS.[71] A key advantage of a step-wedge cluster design is that all clusters start with standard care (control) then transition to ERAS (intervention) in a staggered fashion. This can attract cluster units (i.e. hospital study sites) to participate in the study when receiving the intervention is guaranteed and allow comparisons within (each cluster has an internal control) and between clusters.[71,72] The step-wedge cluster design can also be more efficient, requiring less clusters and patients than traditional parallel cluster designs.[73,74]

4.3.4 Modifications to ERAS

The variable implementation of ERAS recommendations in different local institutional environments demonstrate there is no singular protocol that must be strictly followed to improve patient care. However, the key targets for ERAS interventions should be directed to achieve the general conditions for patient discharge: tolerating an oral diet, adequate pain control, and sufficient mobility for self-care. To that end, we feel that the absolute components of ERAS that should be implemented include PONV prophylaxis, multimodal analgesia, early feeding, and early mobilization. While care goals of removing the urinary foley catheter on POD1

is an important component to achieve early mobilization, the specific type (e.g. celecoxib or ibuprofen) or dosing of medications for pain control are likely less important. Furthermore, our pilot study established that the intraoperative ERAS interventions are already a routine part of standard perioperative care, and thus will be excluded from the ERAS protocol for the larger RCT. Setting the focus of ERAS on preoperative and postoperative interventions will streamline the intervention and reduce contamination due to design discussed previously.

Recruitment of additional clusters in a step-wedge design will also have an influence on what ERAS interventions are implemented. Considering that there are likely differences in the standard of care between institutions, the existing standard of care for each cluster will be reviewed to exclude ERAS interventions that are routinely being used to minimize contamination. Identifying ERAS interventions that could be implemented for a specified threshold of clusters will be critical in shaping the intervention protocol for the main RCT.

4.3.5 Generalizability of Feasibility Outcomes

The study was impacted by cancellation of breast reconstructions due to the COVID-19 pandemic. This resulted in three patients at different points in the trial becoming ineligible for the study, as well as decreasing the total number of patients that could be screened as future reconstructions were no longer being scheduled. Consequently, our pilot RCT completed at 6-months with 18 patients; the planned

sample size (n=24) for the pilot study was not reached. The implication of the smaller sample size is that the feasibility data may not be as generalizable for the larger trial. We attempted to evaluate the imprecision of feasibility outcomes by calculating 80% confidence interval *post-hoc* for feasibility outcome estimates (Table 11).[38]

Table 11. Confidence interval of feasibility outcome estimates

	Score, Mean (SD)		
Feasibility Outcome	Target	Result	80% Confidence Interval†
Eligibility	90%	95.4%	86.5 to 98.6%
Enrollment	75%	95.2%	85.3 to 98.6%
Retention	80%	90.0%	78.2 to 95.8%
Adherence	80%	86.0%	82.6 to 88.9%

†Calculated using Wilson interval

The confidence interval approach demonstrates that the lower bound of the confidence interval does fall below the *a priori* targets for patient eligibility and retention. However, one could argue that the differences between the lower bound feasibility outcome estimates and *a priori* targets are marginal, and that overall, the feasibility of a larger RCT is still supported by the results of this study.

4.3.6 Generalizability of the Effectiveness RCT

Given the present design of the pilot study, the generalizability of the effectiveness RCT will be limited to patients undergoing AABR at academic institutions. AABR is largely performed at academic centres due to the microsurgical

expertise and perioperative support required for this procedure. Although some community hospitals may provide AABR, differences in available resources such as a dedicated preoperative clinic and access to imaging for preoperative perforator planning may significantly change what ERAS interventions are required, or even possible to implement, which limits the generalizability of our study to less resourced non-academic settings.

4.3.7 Incorporating a Cost-Utility Analysis

The potential clinical benefits and cost-savings (i.e. decreased hospital length of stay) may be offset by increased costs of implementing ERAS. Prospective micro-costing to estimate the economic cost of ERAS from the third-party payer or societal perspective can be incorporated with health state values from EQ-5D-5L to perform a cost-utility analysis. Time-driven activity-based costing methods can be used to determine precise costs associated with requiring additional personnel weighted by time.[75] The incremental cost-effectiveness ratio (ICER) derived from the cost-utility analysis can be used to evaluate the relative value of ERAS compared to other health interventions, and justify future funding for implementation.

4.3.8 Clinical Data from the Pilot Study

Although the feasibility of the main RCT is supported by having achieve targets for feasibility outcomes, there are significant methodological changes

required for the larger effectiveness RCT. Therefore, the clinical data collected in this pilot study will not be combined into the larger trial.

4.4 Conclusion

In conclusion, the ERAS-ABR study has demonstrated the feasibility of conducting an effectiveness RCT comparing ERAS to standard perioperative care in patients undergoing AABR at our institution. This is supported by a broad eligibility criteria, high proportion of patient recruitment and study completion. Nevertheless, the full-scale RCT will benefit from adjustments study design to achieve improved blinding, reduce contamination through cluster randomization, and streamline ERAS items to focus on the novel interventions in the preoperative and postoperative phases of care.

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Appendix 1. Equianalgesic conversion table

	Equivalence to Oral Morphine 30mg[76]	Parenteral Equivalent[77]
Morphine	30mg	10mg
Hydromorphone	6mg	1.2mg
Oxycodone	20mg	-
Codeine	200mg	-

Appendix 2. Summary of EQ-5D-5L domains

	ERAS Group, N (%)		Control Group, N (%)	
EQ-5D Domain	Baseline	30d post-op	Baseline	30d post-op
Mobility				
Level 1	8 (80)	6 (60)	6 (75)	4 (50)
Level 2	1 (10)	2 (20)	2 (25)	4 (50)
Level 3	0 (0)	2 (20)	0 (0)	0 (0)
Level 4	1 (10)	0 (0)	0 (0)	0 (0)
Level 5	0 (0)	0 (0)	0 (0)	0 (0)
Self-Care				
Level 1	9 (90)	6 (60)	8 (100)	5 (62.5)
Level 2	1 (10)	2 (20)	0 (0)	3 (37.5)
Level 3	0 (0)	2 (20)	0 (0)	0 (0)
Level 4	0 (0)	0 (0)	0 (0)	0 (0)
Level 5	0 (0)	0 (0)	0 (0)	0 (0)
Usual Activities				
Level 1	7 (70)	3 (30)	8 (100)	0 (0)
Level 2	3 (30)	3 (30)	0 (0)	4 (50)
Level 3	0 (0)	4 (40)	0 (0)	2 (25)
Level 4	0 (0)	0 (0)	0 (0)	0 (0)
Level 5	0 (0)	0 (0)	0 (0)	2 (25)
Pain/Discomfort				
Level 1	4 (40)	1 (10)	3 (37.5)	0 (0)
Level 2	2 (20)	7 (70)	3 (37.5)	4 (50)
Level 3	4 (40)	2 (20)	2 (25)	4 (50)
Level 4	0 (0)	0 (0)	0 (0)	0 (0)
Level 5	0 (0)	0 (0)	0 (0)	0 (0)
Anxiety/Depression				
Level 1	2 (20)	4 (40)	2 (25)	3 (37.5)
Level 2	3 (30)	5 (50)	4 (50)	3 (37.5)
Level 3	5 (50)	0 (0)	2 (25)	2 (25)
Level 4	0 (0)	1 (10)	0 (0)	0 (0)
Level 5	0 (0)	0 (0)	0 (0)	0 (0)
	Mean (SD)		Mean (SD)	
VAS	72.3 (14.0)	79.8 (14.5)	76.6 (12.4)	76.3 (6.4)

Level 1=No problems; Level 2=Slight problems; Level 3=Moderate problems; Level 4=Severe problems; Level 5=Extreme problems/unable to do; VAS=visual analogue scale

Appendix 3: CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	ii
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	iv
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	1-6
	2b	Specific objectives or research questions for pilot trial	7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	8-9
	4b	Settings and locations where the data were collected	9-10
	4c	How participants were identified and consented	10
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	11-17
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	18-19
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	18-19
Sample size	7a	Rationale for numbers in the pilot trial	25
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	22
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	22-23
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	22-24
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	22

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	24-25
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	26
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	31-33
	13b	For each group, losses and exclusions after randomisation, together with reasons	31-33
Recruitment	14a	Dates defining the periods of recruitment and follow-up	28
	14b	Why the pilot trial ended or was stopped	28
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	29-30
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	31-33
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	31-33,60
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	39-40
	19a	If relevant, other important unintended consequences	39-40
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	53-61
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	59-60
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	41-44
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	53-61
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	27
Protocol	24	Where the pilot trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	27
	26	Ethical approval or approval by research review committee, confirmed with reference number	27