Ambulatory Cancer Care Electronic Symptom Self-Reporting for Surgical Patients

PROTOCOL FACE PAGE FOR
MSK NON THERAPEUTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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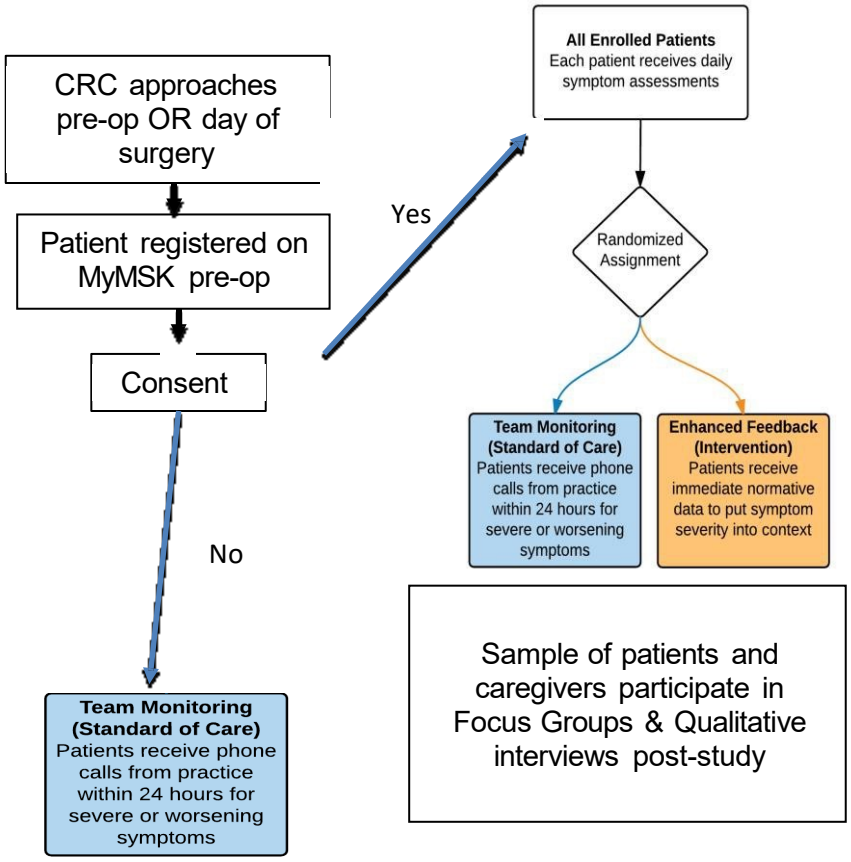
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Patients undergoing ambulatory cancer surgery at Josie Robertson Surgery Center (JRSC) at MSKCC will be eligible to participate in a randomized controlled trial comparing two different methods of symptom monitoring while recovering from ambulatory surgery. The study will evaluate the differences in patient-centered outcomes and experiences between Team Monitoring (symptom monitoring by the clinical team, with nursing outreach if symptoms exceed normal limits) and Enhanced Feedback (real-time feedback to patients about expected symptom severity, with nursing outreach if indicated) in response to the patients' daily symptom reporting.

A total of 2,750 adult patients and 1,375 caregivers will be recruited for this study at the JRSC. All potential participants will be informed of their rights as a volunteer in a research study. Patient disease types will include breast, urologic, gynecologic, and head and neck cancers, as well as benign diseases. Randomization will take place through the Clinical Research Database (CRDB). Patients will complete a symptom assessment (Recovery Tracker) for the first 10 days after surgery. Over the following 20 days, patients can tailor the survey to their needs by choosing when they complete the survey. Between days 11-30, patients can report symptoms on any day. By leaving the survey open after day 10, patients who develop new or worsening symptoms will have the ability to report these symptoms electronically whenever they wish. Conversely, patients not experiencing any symptoms will not be burdened by additional surveys. Outcomes will be measured for up to 60 days and will include patient anxiety, patient engagement, caregiver burden, urgent care visits, detection of adverse events, and nursing interventions.

The proposed study will not evaluate any investigational agents or methods that are not considered standard of care for this patient population. Therefore, there are minimal risks to the patient population. In both groups, if a patient reports severe symptoms, they are instructed to immediately contact their physician's office or seek medical attention, as is the current standard of care. Alternatives to participation in this study include the standard of care, which includes completing the Recovery Tracker (the Team Monitoring arm of the study), or not completing any surveys at all.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

We will perform a prospective, two-armed, randomized controlled trial of postoperative daily symptom reporting among patients undergoing ambulatory cancer surgery, to determine which of two approaches to management of patient-reported symptom data is most effective from a patient and caregiver perspective: (1) symptom monitoring by the clinical team, with nursing outreach if symptoms exceed normal limits **(Team Monitoring)**, or (2) feedback to patients about expected symptom severity, with patient-activated care as needed **(Enhanced Feedback)**. For symptom self-reporting, we will use a 20-question survey that includes 11 items from a validated instrument, the Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE[1]), three additional surgical symptom questions, and two questions about seeking urgent care or a doctor. The information provided to patients in the **Enhanced Feedback** group will be procedure-specific and based on continuously updated PRO-CTCAE data from previous patients who have completed PRO-CTCAE data. **We hypothesize that Enhanced Feedback about expected symptom severity will be more effective than Team Monitoring in improving patient-centered outcomes (SA1) and the patient/caregiver experience (SA2)**.

Specific Aim 1 (SA1): To compare the effectiveness of **Team Monitoring** and **Enhanced Feedback** with regard to patient-centered outcomes, including:

SA1a – urgent care, emergency department visits, and readmissions up to 30 days
SA1b – symptom-triggered interventions.

Specific Aim 2 (SA2): To compare the impact of **Team Monitoring** and **Enhanced Feedback** on the health care experience of patients and their caregivers, including:

SA2a – patient engagement
SA2b – patient anxiety
SA2c – caregiver burden

3.0 BACKGROUND AND RATIONALE

More than 1.5 million people were diagnosed with cancer in the US in 2015[2]; most underwent surgery as a component of their treatment. With health care cost constraints and recent technical innovations, increasing numbers of these surgeries are performed as ambulatory procedures.[3] This new model of short-stay surgery adds new complexities to the delivery of high-quality, patient-centered care. Although there are many advantages to shorter hospital stays, there is also an increased burden on patients and their caregivers. Postoperative symptoms, such as pain and nausea, are common[4] and represent a major source of morbidity[5] and distress for patients. After discharge, patients may have difficulty distinguishing normal and expected symptoms from potentially dangerous ones.[6] This may lead to unnecessary worry and health care use for normal symptoms, or worse, to unnecessary suffering and serious adverse events, when worrisome symptoms are unrecognized and neglected.

There is abundant evidence that patient self-reporting of symptoms improves quality of care,[7-9] and thus patients are increasingly being asked to provide this information[10] as a component of routine clinical care. A key knowledge gap in patient-centered care, however, is that we don't know the most effective way to monitor and manage such data.[11] To address this gap, we will conduct a randomized clinical trial among a diverse patient population, using an established informatics platform and well-validated symptom assessment questions developed by the National Cancer Institute PRO-CTCAE. We will compare two approaches, each of which has demonstrated effectiveness: (1) Team Monitoring—symptom monitoring by the clinical team, with nursing outreach if symptoms exceed normal limits, and (2) Enhanced Feedback—real-time feedback to patients about expected symptom severity, with patient-activated care as needed. The information provided to patients in the Enhanced Feedback group will be procedure specific and based on continuously updated PRO-CTCAE data from previous patients. We hypothesize that Enhanced Feedback about expected symptom severity will be more effective than Team Monitoring because patients will feel greater self-efficacy and engagement in their care. We will evaluate the following outcomes: Aim 1— urgent care and emergency department visits and symptom-triggered interventions; Aim 2—patient engagement, patient anxiety, and caregiver burden (Aim 2), as measured by validated patient-reported outcomes (PROs) measures and qualitative interviews.

Impact on the health of individuals and populations

Ambulatory surgery is increasingly common, and it places new burdens on patients and caregivers. Enabled by technical innovations in surgery and anesthesiology, and driven by pressures to reduce costs, ambulatory procedures account for increasing proportion of surgeries.[3] In the US in 2015, patients underwent approximately 50 million short-stay (23-

hour) or ambulatory surgery procedures.[12] Although this approach may help to contain health care costs, it places new burdens on patients and caregivers. Patients no longer have the physical and psychological support of 24-hour care by nurses and allied professionals, nor do they receive daily visits by their surgeon. Instead, they are expected to manage the recovery process largely at home, with access to their clinical team only when they perceive that a complication may be occurring. In addition, their caregivers are asked to provide support without the benefit of knowledge or clear expectations about what symptoms are normal during postoperative recovery. Focus group and survey data from our institution suggest that caregivers experience tremendous burden, which significantly affects the primary caregiver's health, psychological well-being, and schedule.

Cancer patients undergoing surgery are especially vulnerable to this new model of care. The lifetime risk of developing cancer is approximately 40%,[11] and most patients undergo surgery as part of their treatment.[13] Major procedures, such as mastectomies, prostatectomies, and hysterectomies, are now being performed as ambulatory procedures, and patients often leave the surgical center while still experiencing symptoms.[5] Patients undergoing cancer surgery are particularly at risk in this new model of care, as they are often preoperatively compromised both physically and psychologically by their diagnoses and neoadjuvant treatments.[14,15] From a psychological perspective, these patients and their caregivers are often still struggling to adjust to a new cancer diagnosis at the time of surgery; they may thus feel heightened anxiety, which may overwhelm coping skills.

Potential benefits and relevance for patients

Patients experience postoperative symptoms at home but may not be able to distinguish expected from worrisome symptoms. Following ambulatory cancer surgery, symptoms are very common and are a source of considerable patient distress. Patients are expected to self-interpret symptoms and distinguish expected postoperative symptoms from those of concern—which is especially difficult when patients and caregivers have no way to know what is normal and expected. There is strong evidence that physicians may underestimate patient symptoms, and patients are often reluctant to report them.[6,16-19] This may lead to unnecessary suffering and serious adverse events when worrisome symptoms are unrecognized and neglected. Symptom self-reporting can improve safety by identifying problems that might have otherwise been unrecognized and can facilitate more efficient care before complications progress. Symptom self-reporting with feedback about expected symptom severity may also decrease anxiety and inefficient health care use.

Gaps in evidence and national interest

Our study addresses a high-priority knowledge gap. We do not yet know what is the most effective method to monitor and manage patient symptom data after ambulatory cancer surgery. Monitoring of symptoms, with outreach by the clinical team when severity exceeds the expected range, may identify problems at an earlier stage, to avoid or minimize adverse events, but it is resource intensive.[11,20,21] Alternatively, providing patients with feedback about expected symptom severity and allowing them to activate care as needed may allow for the identification of adverse events before they progress, while also decreasing patient anxiety and unplanned care, such as unnecessary visits to the

emergency department. In addition, patient focus groups have reported to us that feedback about expected symptoms increases patient engagement in their care and gives them a sense of empowerment.

A systematic review of randomized controlled trials that evaluated electronic reporting of symptoms confirmed that this is a major limitation in our knowledge. Although progress has been made to better understand how symptom data might be best incorporated into clinical care among nonsurgical ambulatory patients, little work has been done among patients having surgery. Notably, none of the 32 randomized controlled trials identified in this review evaluated symptom assessment in surgical patients. Furthermore, dual PIs Pusic and Temple organized an Agency for Healthcare Research and Quality–funded conference on PROs in surgery in January 2015. This meeting, cohosted by the American College of Surgeons, engaged a broad group of surgeons, patient advocates, quality of life researchers, and health informatics experts. At this meeting, a Delphi survey was conducted, which identified optimal evaluation and reporting of patient-reported symptoms for clinical care as a top research priority.[22] Our study thus provides a unique opportunity to address a critical evidence gap of utmost importance to patients and the surgical stakeholder community.

Our study addresses an evidence gap that is directly in line with the aims of the Institute of Medicine.[23-25] By determining which of these two approaches to monitoring and managing surgical patients' symptoms is the most effective, we will promote care that is timely, equitable, efficient, and coordinated. We may also improve patient safety and outcomes. Through earlier detection of worrisome symptoms, we can prevent serious adverse events. By communicating normative data on symptom burden to patients, reassuring them when they are on track and encouraging them to seek appropriate resources if problems develop, we can foster effective, patient-centered care.

The potential of this study to be adopted into clinical practice and improve delivery of care

Collection of PRO data in routine care is rapidly expanding, with data being collected in many different clinical scenarios and used in many different ways. We don't, however, know how to optimally use this information to maximally improve patient care. We hypothesize here that unnecessary emergency department visits and serious adverse events can be reduced if patients are provided with feedback about expected symptom severity and that this will be more effective than standard PRO monitoring by the clinical team. If we are correct, Enhanced Feedback, with its resulting patient-activated care, could easily be adopted by other facilities and could benefit large numbers of patients undergoing cancer and noncancer surgery alike, in both large- and small-volume centers. A system that features feedback based on normative data would be less costly than clinical team monitoring and would require less infrastructure and personnel for monitoring and follow-up phone calls. These savings—along with reduced complications, readmissions, and emergency department visits and improved outcomes and patient experience—would offset upfront costs for information technology infrastructure and implementation. We thus anticipate that our findings will be rapidly adopted in a variety of ambulatory surgery environments, including smaller centers

that do not have the personnel resources necessary to provide intensive monitoring of patient symptoms.

Although symptoms may differ by condition and treatment, the key lessons learned in our study will support the implementation of wider strategies for population health management for any treatment with burdensome side effects or symptoms. We expect that these tools will be highly relevant in designing coordinated care models that target improved health care value, such as the Oncology Care Model and the Perioperative Surgical Home. Thus, we believe that the knowledge gained here will be highly generalizable and will have a broad impact on surgical care overall.

There is abundant and broad evidence that routine collection of PROs and symptoms improves quality of care.[7-10] Such studies have confirmed that PRO data can improve communication with the clinical team, symptom control, quality of life, and patient satisfaction. As an example, study consultants Basch and Dueck reported on a large randomized trial that compared routine collection of PROs with usual care during chemotherapy.[11] In this study, nurses received and responded to email alerts when symptoms exceeded expected values or were noted to be worsening. Among patients who received the PROs intervention, quality of life improved (34% v 18%), and these patients were less likely to be seen in the emergency department (34% v 41%; P = 0.02) or hospitalized (45% v 49%; P = 0.08). This study and others provide a substantial foundation for the design of our study and the selection of our outcome measures. PROs measurement is rapidly becoming a standard of care, and our study represents an essential step to ensuring that patient-reported data is optimally integrated into health care systems to provide the greatest benefit to surgical patients and caregivers.

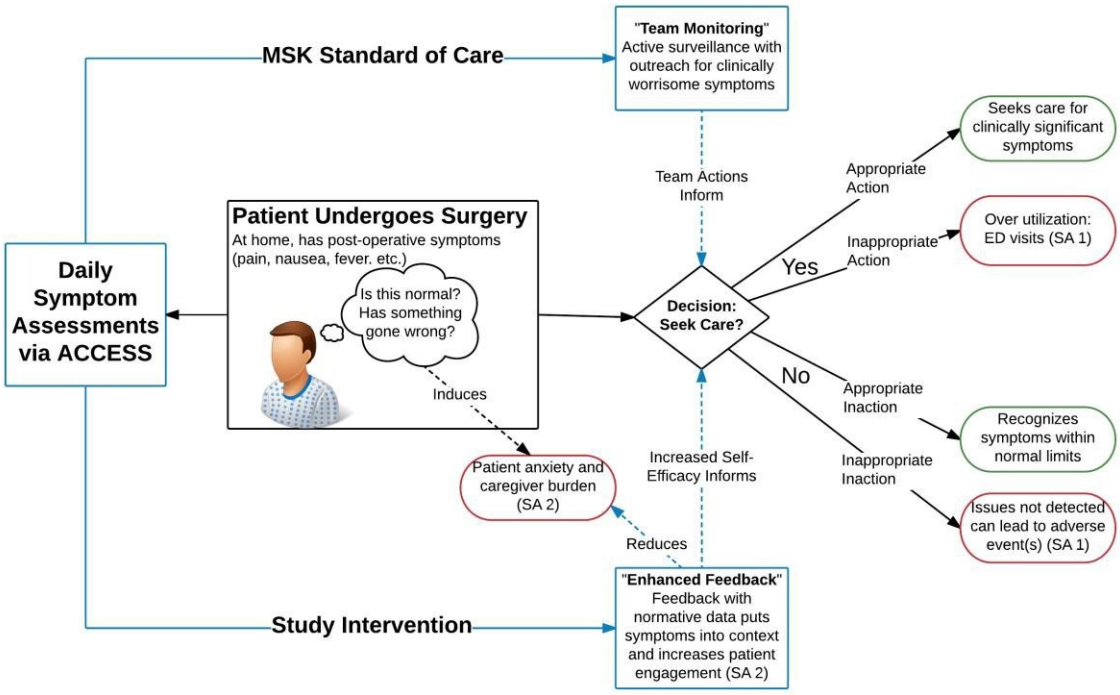
Our team has tremendous experience collecting and monitoring PROs data in routine clinical care. Using an informatics platform developed by our study team (Vickers, Stetson, Stein, Basch, Pusic, and Temple), patients complete validated PRO measures at regular postoperative intervals at MSKCC, and this information is used during clinical visits to improve patient-centered care. In the MSKCC Department of Surgery, more than 50,000 patients have completed such PRO assessments in routine clinical care. For example, on the MSKCC Breast Surgery Service, 8000 patients have participated, completing more than 22,000 BREAST-Q surveys (a PRO measure developed by study dual PI Pusic). Nurses use this information to monitor postoperative pain and physical function and to provide referrals for physical therapy and pain management as needed. On the Urology Service, more than 6,000 patients have participated, using validated urology-specific PRO instruments.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

Our study model is predicated on the hypothesis that daily symptom assessment with normative data (**Enhanced Feedback**) will increase patients' self-efficacy[26] and their confidence that they can manage their symptoms in the recovery period.[27] Without

information and risk awareness, patients may delay seeking care, with severe consequences, and/or they may experience unnecessary anxiety and fail to cope with their health conditions.[28] The normative data provided by the symptom monitoring modules in the patient portal will empower our patients, resulting in increased self-efficacy, and will help the patients to form realistic expectations, which has been shown to be a predictor of decreased symptoms and better physical function.[27,29] On the basis of this model, we predict that patients may avoid unnecessary emergency department visits by better understanding expected symptoms and by achieving more efficient and effective communication with their health care team. The aims our study and the outcomes measures selected reflect this model.



Methodological approach

The study is a parallel group trial, with 1:1 procedure-stratified randomization between the Team Monitoring and Enhanced Feedback arms. The two groups will differ by how their self-reported symptom information is handled: Enhanced Feedback (system displays the patient's self-reported symptom data alongside expected norms for that procedure, and patient initiates care escalation) vs. Team Monitoring (the patient completes self-reported symptom assessment as per standard care at MSKCC; the clinical team contacts the patient if symptoms are above expected levels or appear to be worsening). Note: When patients report severe symptoms in either group, the care team will receive an alert and patients will also be instructed to immediately contact the clinical team. (Alerts to the clinical team can only be monitored during business hours, so all patients must seek care after hours in the current standard care fashion.) Our study design follows CONSORT[30] and PCORI standards, including patient engagement, research methods, data integrity and

analysis (including stratification by surgical procedure), handling of missing data, and heterogeneity of treatment effect.

Primary outcome: The primary outcome for Aim 1, emergency department visits up to 30 days after ambulatory cancer surgery, is important to patients because emergency department visits are time-consuming and may increase anxiety and caregiver burden. It is relevant to health care systems and clinicians because such visits are inefficient and costly and may erode trust between the patient and provider.

Secondary outcomes:

SA1: We will evaluate symptom-triggered interventions (nursing follow-up calls, unplanned clinic visits and phone referral to clinic, pain management referrals, and adverse event detection) and rates of adverse events up to 30 days after ambulatory cancer surgery. We will also evaluate the number of readmissions up to 30 days. Adverse events will be defined according to the nomenclature established in the MSKCC Surgical Secondary Events Grading System.

SA2: We will evaluate patient engagement, patient anxiety, and caregiver burden with the experience of care using validated PROs measures and qualitative interviews.

- Patient engagement will be evaluated preoperatively and at 2 weeks and 2 months postoperatively using the Patient Activation Measure (description below).
- Patient anxiety will be measured on a daily basis for 10 days following surgery using three PRO-CTCAE Anxiety questions.
- Caregiver burden will be evaluated at 2 weeks and 2 months postoperatively among consenting caregivers using the Caregiver Reaction Assessment (description below). Each participating patient will be asked to identify a caregiver, who will then be invited to participate.
- Patient engagement and caregiver burden will also be evaluated using qualitative interviews, with a sample of each of the randomized cohorts, as described below.

4.3 Intervention

The intervention in our study will allow us to determine which approach to the management of patient-reported symptom data is most effective from a patient and caregiver perspective. In both groups, if a patient reports severe symptoms, they are instructed to immediately contact their physician's office or seek medical attention.

Cohort 1: Team Monitoring

Team Monitoring is the current standard of care for patients at JRSC. In this cohort, the electronic system will provide advanced informatics support for push notifications to the care team based on the severity of the symptoms reported. This platform promotes early detection and intervention. The care team is alerted when patients experience symptoms out of the expected range or if symptoms are worsening. Nurses receive secure message notifications and will contact the patient by phone depending on symptom severity. If a patient responds with a moderate-severe answer, the office team gets an alert and calls

the patient during business hours. Although nurses endeavor to call patients within 24 hours, this may not occur if symptoms are reported on weekends or holidays. If the patient reports very severe symptoms, they get a bold red alert instructing them to call the office (or call team after hours) immediately or seek medical attention. The actual response thresholds (i.e., when to give which alert) for each question are set individually and have been refined based on feedback from the office practice nurses. The workflow associated with Team Monitoring has been vetted by all teams at JRSC and has been operationalized for urology, breast, and gynecologic oncology patients.

Cohort 2: Enhanced Feedback

In this cohort, the electronic system will provide tailored normative data visualizations that offer context and education to patients regarding expected symptom severity. The information provided to patients in the Enhanced Feedback group will be procedure specific and based on continuously updated PRO-CTCAE data from previous patients. Patients are thus able to see their own recovery trajectory relative to that of patients who have undergone the same procedure. Care is patient-activated in that patients will use the information about expected symptoms to decide whether they should call the care team (e.g., if they are experiencing symptoms that are more severe or more prolonged than expected). If a patient reports severe symptoms, they are instructed to immediately contact their physician's office or seek medical attention. In addition, when patients in the Enhanced Feedback group report severe symptoms, the care team will receive an alert but as noted above, alerts to the clinical team can only be monitored during business hours, so all patients must seek care after hours in the current standard care fashion.

The JRSC Recovery Tracker Platform

As the current standard of care, patients undergoing surgery at JRSC are asked to report on 11 items from a validated instrument, the Patient Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE[1]), three additional surgical symptom questions, and two questions about seeking urgent care or a doctor during the first 10 days after surgery. Over the following 20 days, patients can tailor the survey to their needs by choosing when they complete the survey. Between days 11-30, patients can report symptoms on any day. By leaving the survey open after day 10, patients who develop new or worsening symptoms will have the ability to report these symptoms electronically whenever they wish. Conversely, patients not experiencing any symptoms will not be burdened by additional surveys. This system is currently being further refined within the JRSC PRO Workgroup.

Invitations to complete questionnaires are triggered automatically on the basis of visit and operative schedules and sent via secure message to patients through the Patient Portal. The interface is built with a responsive design, so participants have the option of using the system via computers, tablets, or smart phones. Questionnaires are available in both English and Spanish. Nurses receive secure message notifications when patients' symptoms exceed expected values or worsen and will contact the patient by phone within 24 hours, depending on symptom severity. Patient symptom responses integrate directly into our electronic health record in two ways: (1) into nursing documentation templates

for point-of-care verification and (2) into the electronic health record reports after review of the data by the care team.

The PRO-CTCAE symptom questions

The JRSC platform is based on the PRO-CTCAE symptom questions. In cancer clinical trials, adverse events are collected and reported using the National Cancer Institute's CTCAE. To improve precision and patient-centeredness in the capture of symptomatic adverse events, the NCI funded a team of investigators led by Dr. Basch to develop a library of PRO items to supplement the CTCAE, called the PRO-CTCAE.[1] Of the 790 adverse events in the CTCAE, 78 were identified as amenable to patient self-report. For each of these adverse events, PRO items were created reflecting the attributes of presence, frequency, severity, interference with usual or daily activities, and/or amount. One to three attributes were selected for any given adverse event, depending on the nature of that particular adverse event. In total, 124 individual items represent the 78 symptomatic adverse events in the PRO-CTCAE item library. Each item includes a plain-language term for the adverse event, the attribute of interest, and the standard recall period of "the past 7 days" (in the current study, we plan to use a 1-day recall period since patients are asked to report daily). Cognitive interviews previously determined a high level of patient understanding and meaningfulness of the items,[31] and a national multisite validation study led by Dr. Dueck showed that items were valid, reliable, and sensitive to change.[32] Additional development work by the team of Drs. Basch and Dueck included testing administration mode equivalence,[33] relationship among various recall periods,[34] and a Spanish translation.[35] PRO-CTCAE items were selected for the symptom monitoring system and are now a component of routine clinical care for MSKCC patients undergoing surgery at JRSC. Eleven PRO-CTCAE items, plus 9 additional questions that were specifically targeted to capture important post-operative problems, evaluate the symptoms of patients recovering from ambulatory surgery in the MyMSK Patient Portal. Patients, nurses, surgeons, and anesthesiologists participated in the selection of these items. The items assess symptoms such as pain, nausea, fatigue, constipation, vomiting, fever, chills, dyspnea, swelling, discharge, and redness.

Study outcomes

	Aims	Measure	Data Source(s)	Assessment Time Point
Patient-Centered Outcomes	**SA1**			
Emergency Department Visits	SA1a	UCC visit at MSKCC	MSK institutional database	Up to 30 days after surgery
	SA1a	Emergency department visit outside MSKCC	Patient self-reporting via Patient Portal and corroborating phone call to patient by study team; MSK institutional database	Up to 30 days after surgery
Readmissions	SA1a	Readmission to MSK	MSK institutional database	Up to 30 days after surgery
	SA1a	Admission outside MSK	Patient self-reporting via Patient Portal and corroborating phone call to patient by study team; MSK institutional database	Up to 30 days after surgery
Symptom-Triggered Interventions	SA1b	Nurse calls due to alerts	Documented in EMR via clinical information system	Up to 30 days after surgery
	SA1b	Unplanned clinic visits and phone referral to clinic	Documented in EMR	Up to 30 days after surgery

	SA1b	Pain management referrals	Documented in EMR	Up to 30 days after surgery
	SA1b	Adverse event detection	EMR and MSKCC Surgical Secondary Events Database	Up to 30 days after surgery
Patient and Caregiver Health Care Experience	**SA2**			
Patient Engagement	SA2a	The Patient Activation Measure[36]	Patient self-report	Preoperatively (day of consent-POD1), 2 weeks (+7/-3 days), 60 (+/- 14) days after surgery
	SA2a	Qualitative data	Semistructured patient interviews	30 (+/- 10) days after surgery
Patient Anxiety	SA2b	PRO-CTCAE Anxiety Items	Patient self-report via symptom monitoring module in the Patient Portal	Daily for 10 days after surgery
Caregiver Burden	SA2c	Caregiver Reaction Assessment[49]	Caregiver self-report	2 weeks (+7/-3 days), 60 (+/- 14) days after surgery
	SA2c	Qualitative data	Semistructured caregiver interviews	30 (+/- 10) days after surgery

Patient-centered outcomes

We will evaluate the frequency of urgent care center (UCC) visits, readmissions and symptom-triggered interventions (pain management referrals, nursing calls) through triggers generated from the informatics platform as well as through thorough chart extraction by the clinical research coordinator (CRC) for 30 days after surgery.

Patient and caregiver health care experience

The Patient Activation Measure. The Patient Activation Measure[36] is a validated PRO measure developed to evaluate the engagement of patients in their care. The development process included conceptual definition and item generation through patient focus groups, literature review, and expert panel consensus. Psychometric evaluation of the scales was performed using Rasch psychometric methods, and further validation was completed in a large national sample. This measure includes items querying patients about their confidence (self-efficacy) and knowledge to take action specific to their health.[36] Items include *"I am confident I can tell when I need to get medical care"* and *"I am confident I can take actions that will prevent or minimize symptoms or problems."* This PRO measure was selected because it evaluates a key concept of interest in our study, was rigorously developed with qualitative and quantitative methods, and has strong psychometric properties. PAM yields only a total score that will be used in the analysis.

The Caregiver Reaction Assessment. The Caregiver Reaction Assessment is a validated instrument designed to assess the impact of caregiving on disrupted schedules, self-esteem, and financial and health problems.[37] The Caregiver Reaction Assessment assesses specific aspects of the caregiving situation, including both negative and positive dimensions of caregiving reactions. The Caregiver Reaction Assessment (CRA) consists of 5 subscales, 4 of which are negative and 1 positive. The negative subscales have higher scores indicating higher level of burden, rated from 1 (strongly disagree) to 5 (strongly agree). The four negative subscales are: Impact on

Schedule (5 items), Impact on Health (4 items), Lack of Family Support (5 items) and Impact on Finances (3 items). The positive subscale, Caregiver's Self Esteem (7 items), has lower scores indicating higher levels of burden rated from 1 to (strongly disagree) to 5 (strongly agree).

Five dimensions of caregiver reactions were identified through exploratory factor analysis: the impact of caregiving on disrupted schedules, financial problems, lack of family support, health problems, and self-esteem. Reliability analyses show that standardized Cronbach's alphas vary between 0.62 and 0.83 for the separate subscales, indicating sufficient internal consistencies and that construct validity is supported. This measure was selected because it is well-targeted to our outcomes of interest and was developed among partners of patients with cancer.[38]

The PRO-CTCAE Anxiety Items. The PRO-CTCAE Anxiety scale consists of three items scored 0–4, for a full-scale range of 0–12 (see pages 11 and 12 for PRO-CTCAE development and validation). These include: "How often do you feel anxiety?" "What was the severity of your anxiety at its worst?" and "How much did anxiety interfere with your usual or daily activities?"

Qualitative patient and caregiver interviews will be conducted in a subsample of patients and their caregivers throughout the study. After study consent, patients and caregivers will be invited to volunteer for possible future in-depth, semistructured qualitative interviews (either individual or in group form). We will approach patients (and caregivers) numerous times throughout the course of the study until data saturation. We will select patients from both randomized cohorts and will seek to interview a heterogeneous patient sample (i.e., patients representing the full spectrum of established potential participants (patients and caregivers) for possible interviews in order to examine and evaluate both patient engagement and caregiver burden (SA2a, SA2c) throughout the study. We will ensure that we have a selection of volunteers that represent a range of procedure types and ages for all qualitative interviews.

The entire study team, including patient and caregiver partners and advocacy organization members will contribute to the development of the interview guide (see Appendices I and J). Dr. Jeanne Carter will conduct the interviews, which will be recorded and transcribed verbatim. The data will be coded using a line-by-line approach, where all concepts will be labeled by major and minor themes. Coding will take place as soon as possible after an interview so that findings can inform subsequent interviews in an iterative fashion. Codes (i.e., patient quotations) and their major and minor themes will be organized and analyzed using NVivo qualitative analysis software (QSR International). Patient characteristics (e.g., age, disease condition, procedure) will also be incorporated into the qualitative database to help identify groups that might experience the system differently (e.g., elderly patients or those with lower education levels). Interviews will continue until data saturation is reached (i.e., no new themes identified). On the basis of our team's previous experience with qualitative research studies, we anticipate reaching data saturation after approximately 30 patient and 30 caregiver interviews.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

All patients scheduled for ambulatory cancer surgery at JRSC will be eligible. For patients with disabilities that make it difficult to complete the electronic surveys (e.g., visual impairment, hand function problems), we will train caregivers to help with completion of the survey. The PRO-CTCAE questions have already been tested to ensure that they will be easily understood by patients with low literacy levels.

Additionally, patients will be asked to identify a caregiver to participate in a 2-week and 2-month follow-up questionnaire and possibly in a qualitative interview. Caregivers will be approached and consented to participate.

5.1 Subject Inclusion Criteria

- All patients >18 years of age who are scheduled for ambulatory cancer surgery at JRSC, and their caregivers, will be eligible for study participation.

5.2 Subject Exclusion Criteria

The following criteria apply to both patients and their caregivers:

- Inability to speak English
- Inability to access a computer, tablet, or mobile phone
- For patients: not interested in/unable to sign up for the MyMSK Patient Portal
- For caregivers: Unable to provide an email address
- Cognitive impairment that prohibits informed consent or understanding of the study protocol

6.1 RECRUITMENT PLAN

Patient Recruitment Plan

All patients who are scheduled for surgery at JRSC will receive IRB/PB-approved written educational materials that describe the study (see Appendices D and H) via the MyMSK Patient Portal, by email, or by a letter mailed to their home (see Appendices F and G). If a patient is not yet signed up for the MyMSK Patient Portal, the study team will also include a brief document that instructs patients how to register (see Appendix K).

Patients will be advised that they will be approached to participate in this study by phone prior to surgery, at their next clinic appointment, or in person on the day of their surgery. They will be encouraged to read through the information carefully and to also consider whether there is a caregiver in their life who can be approached to participate in the caregiver portion of the study. The materials will provide contact information for the CRC and the PI of the study in case patients have questions they would like addressed before the day of surgery. The CRC will then attempt to contact eligible patients by phone before surgery. Using an IRB-approved verbal consent script, the CRC will explain the study to

patients. Written consent will not be obtained; rather, the CRC will document the patient's verbal consent.

If the CRC is not able to contact the patient by email, Patient Portal, or phone prior to the day of surgery, she/he will approach the patient at one of their upcoming clinic appointments or when they arrive at JRSC for surgery. The CRC will describe the study in person, again using the IRB-approved verbal consent script. Patients will be approached on the day of their surgery in the waiting area, and the consent discussion will happen in a private consultation room on the third floor at JRSC. Patients will not be approached in the pre-operative area, and will be given as much time as needed to decide whether or not they will participate in the study.

Caregiver Recruitment Plan

Patients will be asked at the time of consent to identify a caregiver whom they would like to be actively involved in their recovery and may be interested in participating in the study. The CRC will obtain the caregivers' contact information from the patient.

Caregivers can be contacted in several ways:

1) If the caregiver is present in clinic with the patient, the CRC will approach the caregiver at that time.
2) If the patient suggests contacting the caregiver by email or phone, the CRC will proceed to contact the caregiver using the preferred method of contact provided by the patient.
    a. If personal email is preferred, the caregivers will be provided written education materials regarding the study via email (see Appendices E and H). Caregivers will be advised that they will be approached to participate in this study by phone prior to surgery or in person on the day of the patient's surgery. The materials will also provide contact information for the CRC and the PI for the study, in case caregivers have questions they would like addressed before the day of surgery.
    b. If phone is preferred, the CRC will call the caregiver and invite them to participate.
3) If no contact is made prior to surgery, or if the patient/caregiver requests to be approached on the day of surgery, the CRC will approach the caregiver on the day of surgery.

Given the extent to which caregivers are already integrated into the clinical experience at JRSC, we estimate that more than 50% of caregivers (n=1,375) will agree to participate in the study.

7.0 ASSESSMENT/EVALUATION PLAN

The Recovery Tracker will be completed by all patients for up to 30 days following their surgery. Patients will be sent the Patient Activation Measure (PAM) through the MyMSK Patient Portal (see Appendices A and H). In the event the electronic PAM survey is not available, a hardcopy version will be provided to the patient to complete.

Caregivers will be asked to provide their email and will be sent the Caregiver Reaction Questionnaire and a brief demographic questionnaire through REDCap (see Appendices B, C, and H). In the event the electronic survey is not available, a hardcopy questionnaire will be provided to the caregiver to complete.

	# of Items	Pre-Op (day of consent – POD1)	POD 1-10	POD14 (+7/-3 days)	POD30 (+/-10 days)	POD60 (+/- 14 days)
Patient						
Recovery Tracker (including PRO-CTCAE symptoms and anxiety items, and additional questions)	20		Daily		Available to complete if desired (POD11-30)	
Emergency Department Visits					X	
Readmission					X	
Adverse Events					X	
Patient Activation Measure	10	X		X		X
Patient Interviews					X	
Caregiver						
Caregiver Reaction Assessment	24			X		X
Caregiver Interviews					X	

8.0 TOXICITIES/SIDE EFFECTS

There are minimal risks to all subjects involved in any phase of the study. Patients who indicate excessive anxiety or distress will be offered a referral to an MSKCC psychiatry professional. If severe symptoms are reported, patients in both groups will be instructed to immediately contact their physician's office or seek medical attention and the clinical team be alerted.

9.0 PRIMARY OUTCOMES

The primary outcome for SA1, emergency department visits up to 30 days after ambulatory cancer surgery, is important to patients because emergency department visits are time-consuming and may increase anxiety and caregiver burden. It is relevant to health care systems and clinicians because such visits are inefficient and costly and may erode trust between the patient and provider.

10.0 CRITERIA FOR REMOVAL FROM STUDY

Participants will be considered off-study if they do not undergo an eligible procedure, their surgery is not performed at the Josie Robertson Surgery Center or they are not discharged within 48 hours of their surgery (POD2). All other participants will remain on study to be analyzed using an intent-to-treat approach.

11.0 BIOSTATISTICS

The data analysis plan corresponds to our Specific Aims as described on pages 9 and 10. All statistical analyses will be led by coinvestigator Dr. Andrew Vickers (who has been an investigator on more than 20 randomized trials and has written extensively on trial methodology) and study consultant Dr. Amylou Dueck (who contributed to the development and is experienced in analysis of the PRO-CTCAE items). The enrollment time frame for this protocol is three years.

Power calculation

Sample size and power calculations were based on the primary outcome, the difference in emergency department visits without admission, between the Enhanced Feedback and Team Monitoring arms. On the basis of current MSKCC data, we expect for every 1,000 eligible patients treated surgically at JRSC, 69 patients will make emergency department isits. We also estimate that of these 69 patients, 28 will require readmission, and hence 41 will have visits the emergency department unnecessarily. The majority of such unnecessary visits are related to concerns about symptoms, which might be avoided if patients have a better understanding of expected symptom severity. Using a traditional alpha of 5% and an event rate of 4.1% in the control group, the power to detect different relative risk reductions is given below for a total sample size of 2,750 patients.

Relative Risk Reduction	Power
33%	45%
40%	64%
50%	85%
67%	96%

The primary analysis will compare, between groups, the proportion of patients with at least 1 emergency department visit without admission within 30 days (SA1a) of surgery by logistic regression with randomization strata as covariates. A difference between proportions will be calculated along with a 95% CI by applying the odds ratio from the regression to the event rate in the control group. A similar statistical approach will be taken for the proportion of patients referred to pain management and unplanned clinic visits (SA1b). For nursing follow-up calls (SA1b), phone referrals (SA1b) and rates of adverse events (SA1b), we will use both a binary approach (e.g., at least 1 nursing call vs. no nursing call) and analysis of count data using negative binomial regression with randomization strata as covariates. For all binary endpoints, an event will be counted only if it occurs within 30 days of surgery.

For the endpoints of patient engagement (SA2a) and caregiver burden (SA2c), we will use linear regression with randomization strata as covariates for each subscale separately. For all analyses, we will report an estimate of the difference between groups along with a 95% CI and a two-sided P value for the null hypothesis of no difference between groups. For the endpoint of patient anxiety (SA2b), as measured by the PRO-CTCAE, we will enter daily anxiety scores as a continuous outcome variable into a longitudinal mixed effects model with time, treatment, and treatment by time interaction as predictors and randomization strata as covariates. As all data are collected after randomization, both the treatment term and the treatment by time interaction term are valid indicators of a treatment effect. We hypothesize that initial anxiety will be similar between groups and will be related to immediate postoperative concerns. Subsequent anxiety may be related to emergent symptoms, whether they are considered worrying and how they are dealt with. Hence, we will treat the time by treatment interaction as the primary hypothesis for the purpose of establishing the treatment effect of enhanced feedback on patient anxiety.

In exploratory analysis, the mean of each PRO-CTCAE item (0–4 scale) will be compared between groups during the 10-day post-surgery daily reporting period using the same longitudinal mixed effects model described above for anxiety with time, treatment, and treatment by time interaction as predictors and randomization strata as covariates. All available data will be used in these models. This likelihood-based approach to the analysis of longitudinal PRO data provides valid estimates of intervention effects in the presence of ignorable missing data and is known to be robust to nonignorable missing data if covariates and previous values of the outcome explain much of the missingness.

Supplemental analysis will also employ longitudinal mixed ordinal logistic models to compare ordinal PRO-CTCAE scores between arms.

Data sources and data linkage plans

Many of the study endpoints will be obtained from MSKCC's institutional database. Endpoints such as MSKCC emergency department visits, nursing follow-up calls, clinic visits, and intrainstitutional referrals are automatically captured as part of electronic medical record (EMR)–enabled care management. Emergency department visits at outside institutions will be captured by a question on our daily symptom surveys and routine follow-up surveys. Responses to the follow up surveys will be captured electronically via MSK Engage. Patients describing an emergency department visit at an institution other than MSKCC are contacted by clinical staff for further details as a routine part of follow-up care. Adverse events are captured by the MSKCC Secondary Surgical Event database. Outside emergency department visits and admissions for patients participating in MSKCC's electronic health information exchange will also be utilized. Electronic health information exchange is carried out through organizations known as Health Information Exchanges (HIEs) or Regional Health Information Organizations (RHIOs). This data is captured within MSKCC's institutional database. Data for all patients who choose to opt out of the health information exchange program will not be used. To note: MSK may join additional HIEs or RHIOs in the future. Any available HIE or RHIO data for participating patients will be collected. PROs are obtained through MSKCC's symptom monitoring software, the same software used to implement symptom self-reporting. Covariates such as age, sex, and race are routinely captured in the MSKCC EMR. Comorbidities are captured by an MSKCC platform used to take the baseline medical history in all surgical patients potentially eligible for ambulatory cancer surgery. Caregivers' responses to the Caregiver Reaction Assessment questionnaires will be

collected via REDCap, a secure web application for building and managing online surveys and databases. In the event the REDCap survey is unavailable, a hardcopy form will be provided to caregivers to complete.

Sensitivity analyses to determine the impact of key assumptions and missing data

The primary threat to validity is a larger than expected number of emergency department visits to outside institutions and reporting that varies systematically between groups (e.g., if patients in the Enhanced Feedback group are less likely to report a visit to a non-MSKCC emergency department). We will conduct sensitivity analyses by first examining whether the proportion of visits to MSKCC vs. non-MSKCC sites varies between groups. We will then determine the number and distribution of unreported emergency department visits that would need to have occurred to change our conclusions (e.g., if we reject the null hypothesis in favor of the experimental arm, we will determine the number of excess unreported visits in the experimental arm that would result in a P value ≥ 0.05).

Approach to missing data for questionnaire items

Baseline characteristics between those with and those without missing data will also be compared to assess for bias. The rate of missing data is expected to be low. The main threat to data completion involves the caregiver and patient questionnaires obtained at 2 weeks and 2 months, respectively. In addition to automated electronic reminders, a research assistant will follow up with patients who have missing data. Patients from whom no data are obtained will be classified as "unable to contact," "too busy/uninterested," or "intervention related" (e.g., a patient who declines to complete the questionnaires because of an experience earlier in the trial). Patterns of missing data will be compared by treatment arm. In the unlikely event that the rate of missing data is more than 5%, we will impute missing data using multiple imputation by chained equations, with results combined using Rubin's rules. The principle assumption of such a method is that the data are "missing at random" or "missing completely at random." It seems at least possible that any missingness will be nonignorable on the grounds that a patient with a poor level of patient activation will be less likely to complete surveys. We will therefore repeat multiple imputation, except instead of missing activation measures being sampled from a distribution centered on the mean they will be sampled from the 25th and, alternatively, 10th percentiles. A similar approach will be taken for the caregiver measure, for comparable reasons.

Heterogeneity of treatment effect

It is possible that the effects of Enhanced Feedback vary predictably between patients. Although it is common to assess computer literacy as an effect modifier in trials of patient-facing software, we believe that this is inappropriate for the current proposal. This is because both groups will interface with the software, and the difference between the two groups is not highly software dependent. It does, however, seem plausible that patient willingness to make proactive decisions about their postoperative care in the light of data about expected symptoms would be mediated by age, educational status, and the type of procedure they undergo. We will therefore repeat all analyses including

interaction terms between allocation and age, education, and procedure. Educational status is obtained routinely at baseline for all MSKCC surgery patients and will be coded as a binary variable: education after high school/high school only. The models will be of the following form (with a linear case being shown for the sake of simplicity):

$$y=\beta 1\ Allocation + \beta 2\ Age + \beta 3\ Allocation \times Age + \beta(Randomization\ stratum) + c$$

Allocation is coded 1 for Enhanced Feedback and 0 otherwise; randomization stratum is a categorical variable. A similar model will be used for educational status and procedure type. We have no particular reason to believe that response to Enhanced Feedback would vary by race and ethnicity, but as a check to ensure that our approach does not inadvertently discriminate, we will conduct exploratory analyses of race and ethnicity using the structure of the model described above.

Reporting plan with assessments of internal and external validity

This is a randomized trial with good allocation concealment, and therefore selection bias can be discounted. Patients, however, will not be blinded. This is not an important issue for the primary endpoint, which is emergency department visits, as this is objectively measured and not susceptible to reporting bias. The question of performance bias in terms of differential patient behavior is complicated by the fact that the *aim* of the trial is to change behavior. Performance bias by clinicians is, however, a concern. For instance, it is plausible that a nurse speaking to a study patient by phone in the days after discharge might make differential recommendations about the necessity of an emergency department visit depending on patient assignment. However, this is an unlikely scenario given the context of nursing care at MSKCC. Nurses call large numbers of patients, both those eligible for the trial (ambulatory care surgery) and those ineligible (e.g., complex operations requiring an in-patient stay), and they are unlikely to know which patients are and are not on trial. Patients might potentially reveal allocation to nurses during the phone call (e.g., “I saw on the website that…”). But, again, as a large number of nurses will be dealing with a large volume of patient calls, it is unlikely that allocation will bias the advice given to a significant extent.

Regarding external validity, the system is currently in use by MSKCC patients, but it is possible that these patients (a referral population in a major urban center) may have higher computer literacy, health literacy, or numeracy than the general population. We recognize that usability barriers that might seem trivial to a highly technology-focused audience can sometimes seem insurmountable for patients facing stress due to illness or treatment or for patients who face preexisting hurdles in terms of computer literacy, health literacy, or numeracy.[39-41] As a result, we have built in a brief user-centered design stage supervised by coinvestigator Dr. Jessica Ancker to review the existing platform in a systematic fashion, elicit constructive feedback from representative users, and perform rapid-cycle modifications to ensure usability and utility for users. We anticipate that this intensive user-centered design project will successfully adapt the existing instrument.

12.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process, registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist will confirm whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

All participants will be registered through the Clinical Trial Management System. The completed signature page of the verbal script/RA, a completed Eligibility Checklist and other relevant documents will be uploaded via to CTMS.

12.3 Randomization

At the time of protocol consent, it will be explained to patients that they will be completing symptom self-reported questionnaires for up to 30 days after surgery (daily for postoperative days 1 to 10 and then at tailored time points) as a component of routine care, and they will be asked whether they are willing to be randomized to potentially receive additional information that may help them interpret the severity of their symptoms. Randomization will be implemented through CRDB, a fully secure, password-protected database that ensures full allocation concealment. It will be performed within 1 week of the patients' surgical visit. Randomization will be stratified by procedure and will be implemented by randomly permuted blocks of random length. The trial will not be blinded, as it relies on patient knowledge (i.e., how a patient's scores compare with other patients' scores) as a key part of the intervention.

Stratification will be based the following surgical procedure types:

- Gynecologic
  - Laparoscopic or robotic procedure
  - Laparotomy
  - Other
- Breast/Plastics
  - Mastectomy alone (with or without sentinel node and axillary node dissection)
  - Lumpectomy (with or without sentinel node and axillary node dissection)
  - Tissue expander placement
  - Other
- Urology
  - Prostatectomy laparoscopic or robotic
  - Partial or total nephrectomy- laparoscopic or robotic
  - Laparotomy
  - Other
- Head and Neck
  - Thyroidectomy
  - Other

13.1 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) and a Research Project Manager (RPM) will be assigned to the study. The responsibilities of the CRC and RPM include project compliance, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study, including patient demographic data, treatment variables, and survey responses will be recorded by the research team in a secure password-protected database.

Data collected for this study will be entered into and managed via a secure REDCap Database. REDCap, Research Electronic Data Capture, is an open source platform that allows for the collection of research data in a secure manner over a web based interface. Usage of the platform is contingent on an open source license. The platform was developed by Vanderbilt University which MSK has a standing agreement with to allow the usage of REDCap for academic/research purposes.

For this protocol, electronic data entry forms may be completed online by study staff. [If applicable], electronic participant responses will also be collected either by sending participants a direct link or having the participants fill out the electronic survey on site.

Data will be housed in the Memorial Sloan Kettering Cancer Center's (MSKCC) Jersey data center. REDCap has been approved by MSKCC's Information Security to store PHI. The MSKCC Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections to ensure data is protected. The server is backed up nightly in the event that disaster recovery would be necessary, and the system would need to be rolled back. Members of the Clinical Research Administration supporting the REDCap software will have access to REDCap projects for the purpose to ensuring the proper functioning of the database and the overall software system.

Permissions to the database for both internal and external users will be managed by the REDCap project manager or study staff. User access to the data is contingent on those a part of the study team and data sharing agreements in place with third party entities if applicable. Project managers are responsible for regularly auditing these permissions to ensure changes in staff are reflected appropriately.

REDCap has the ability maintain an audit trail of changes to the database providing a timestamp as well as the user making the update. In addition, a data resolution module offers the ability of opening and closing queries optionally requiring justification when data is being updated. Permission roles for data resolution are integrated in REDCap. Comprehensive system logs are also maintained of user activity and when changes to the database are made.

Source documentation will be available to support the computerized patient record. A minimal data set will be entered into CRDB.

13.0.1 Participating Sites Regulatory Document

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document, and each participating site will utilize that document. Participating sites that are consulting should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

The below describes the roles of each consultant named to the protocol:

Andrea Pusic, MD, Attending Surgeon in the Department of Surgery at Brigham and Women's Hospital, will serve as a Co-Principal Investigator on the IRB protocol. As a consultant to MSK, Dr. Pusic will have access to PHI (any identifiers relevant to study/participant management or analysis of study outcomes), and study data (i.e., participant disease and demographic characteristics and survey response data).

Larissa Temple, MD, Attending Surgeon in the Department of Surgery at University of Rochester will serve as an investigator on this protocol. As a consultant to MSK, Dr. Temple will have access to PHI (any identifiers relevant to study/participant management or analysis of study outcomes), and study data (i.e. participant disease and demographic characteristics and survey response data).

Jessica Anker, PhD is a consultant per the PCORI contract (IHS-1602-34355). Dr. Anker is an expert in the effects of health information technology on decisions and healthcare quality. She is an associate professor at Weill Cornell Medicine. In year one, she will supervise the user-centered design project. In years two and three, Dr. Anker will collaborate on any continued adaptations of the instrument suggested by analysis of the qualitative and quantitative data. Participant identifiers will not be shared, but she will have access to study data pertinent to her work in making the necessary instrument adaptations.

Amylou Dueck, PhD, is a consultant per the PCORI contract (IHS-1602-34355). Dr. Dueck has expertise in the design and analysis of cancer studies involving patient-reported outcomes. She contributed to the development and is experienced in the analysis of the PRO-CTCAE items used in the Recovery Tracker survey. Dr. Dueck will offer her professional expertise in patient-reported outcomes research and data analysis to help inform the study design, data collection and analyses, and future manuscripts for publication. She will assess the validity and reliability of the Recovery Tracker data. Participant identifiers will not be shared (all data will be de-identified and she will not have access to PHI), but she will have access to study data pertinent to her work in performing Recovery Tracker analyses.

Ethan Basch, MD, PhD is a consultant per the PCORIcontract (IHS-1602-34355). Dr. Basch is an expert in the development and evaluation of patient-reported outcomes systems. He will offer his professional expertise in patient-reported outcomes research to help inform the study design, recruitment efforts, study materials, and future manuscripts for publication. Participant identifiers will not be shared. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

Debra Paget is a stakeholder and consultant per the PCORI contract (IHS-1602-34355). She is a 17-year volunteer at the patient advocacy group, Support Connection, which provides emotional, educational, and social support ot women and families affected by breast and ovarian cancer. Ms. Paget is also an ovarian cancer survivor and has been a caregiver for two cancer patients. She will offer personal insight and constructive feedback on certain aspects of the study design, recruitment efforts, study materials, and future manuscripts for publication. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

Jaime Blanda is a stakeholder and patient partner consultant per the PCORI contract (IHS-1602-34355). As a former patient, she will offer personal insight and constructive feedback on certain aspects of the study design, recruitment efforts, study materials, and future manuscripts for publication. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

Paul Carter is a stakeholder and patient partner consultant per the PCORI contract (IHS-1602-34355). As a former patient, he will offer personal insight and constructive feedback on certain aspects of the study design, recruitment efforts, study materials, and future manuscripts for publication. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

Thomas Chiusano is a stakeholder and caregiver partner consultant per the PCORI contract (IHS-1602-34355). As a former patient, he will offer personal insight and constructive feedback on certain aspects of the study design, recruitment efforts, study materials, and future manuscripts for publication. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

James Guttridge is a stakeholder and patient partner consultant per the PCORI contract (IHS-1602-34355). As a former patient, he will offer personal insight and constructive feedback on certain aspects of the study design, recruitment efforts, study materials, and future manuscripts for publication. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

Christine Nippes, PA-C is a stakeholder and patient partner consultant per the PCORI contract (IHS-1602-34355). As a former patient, she will offer personal insight and constructive feedback on certain aspects of the study design, recruitment efforts, study materials, and future manuscripts for publication. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

Amy Malale is a stakeholder and patient partner consultant per the PCORI contract (IHS-1602-34355). As a former patient, she will offer personal insight and constructive feedback on certain aspects of the study design, recruitment efforts, study materials, and future manuscripts for publication. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

Magen Miranda is a stakeholder and patient partner consultant per the PCORI contract (IHS-1602-34355). As a former patient, she will offer personal insight and constructive feedback on certain aspects of the study design, recruitment efforts, study materials, and

future manuscripts for publication. De-identified data will be shared if it is necessary for the analysis of study outcomes and preparation of study manuscripts.

13.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracyof evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year, and more frequently if indicated.

Regular meetings will be held by the study team to discuss progress and to ensure that the study timeline is being followed. The data will be stored carefully in computer form, with several forms of backup. Data will be available immediately when a patient completes the surveys, which will allow for follow-up collection of missing or incorrect data.

13.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials,” which can be found at http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

14.1 PROTECTION OF HUMAN SUBJECTS

The following safeguards will be used with respect to protection of human subjects:

Recruitment and Informed Consent: All potential patients will be informed as to their rights as volunteers in a research study. The right to refuse or withdraw at any point during the study, without compromising medical and other care will be explained. Verbal consent will be obtained. The purpose of the study and potential risks and benefits associated with it will be stated. If patients or caregivers withdraw consent prior to completing the study, they will no longer be prompted to complete the Patient Activation Measure/Caregiver Reaction Assessments. They will only be sent the Recovery Tracker, which is sent to all patients are part of the standard of care at MSKCC.

Confidentiality Safeguards: Patients will be informed that information collected during their participation in this study is considered confidential. All data gathered will be kept in a secured location. Patients will be assigned code numbers, so that names will not be connected to any information. Confidentiality of each patient's data will be protected with utmost care with all questionnaire data identified solely by a code number. A list matching subject names and code numbers will be maintained on a separate sheet of paper kept in locked storage.

Sources of Materials: Patient information will be obtained from existing patient records. Patient responses to surveys will be the main source of research material. Some of the data being collected is already part of the standard care patients get after their surgery at JRSC. Any additional information will be collected for research purposes only and not used for any other purposes.

Potential Risks: There will be minimal risks to subjects involved in the study. If a patient reports severe symptoms, they are instructed to immediately contact their physician's office or seek medical attention. Patients may feel some anxiety or stress when they complete the daily surveys. They will be encouraged to contact the study coordinator, who will ensure that the patient is contacted by one of the surgeons involved in the study and given the opportunity to discuss any concerns that they might have.

Potential benefits of the proposed research to the subjects: There will not be any direct benefit to subjects involved in the study.

Financial Costs: There will not be any financial cost to patients.

14.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also

stated in the Research Authorization that their research data may be shared with other qualified researchers.

14.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Only SAEs specifically related to the protocol intervention (Recovery Tracker and PAM/CRA survey completion) will be reported. Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.
Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form

• If the SAE is an Unanticipated Problem Version Date: 12/21/2018 For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

15.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time.

The investigators are requesting to waive the documentation of informed consent for this study for the following reasons:

Patients

1. The research involves no more than minimal risk to the participants. The majority of the protocol is part of the standard care and evaluation that patients at JRSC receive. The only exception is that additional features of the system will be available to patients who are randomized to the Enhanced Feedback arm. They will receive additional information about expected symptoms after their surgery. In addition to symptom assessment, all patients will be asked to complete 1 survey at 3 different time points and possibly to participate in a 30–60-minute qualitative interview at a convenient time.

2. The waiver will not adversely affect the rights and welfare of the research participants, as they will willingly engage in the research. Even if they provide verbal consent, if they later decide not to participate, they do not have to complete the questionnaires. Participation will be entirely voluntary.

3. If deemed appropriate by the PI and granting organization, the patients will be provided with additional pertinent information after participation. We will be actively following these patients, so we will be able to contact them easily.

4. The research cannot be practicably carried out without this waiver. Patients would normally be consented to this protocol during a routine clinic visit to consent to their surgery. Patients are sent to JRSC by surgeons who have clinics at several locations in the city. It will be physically impossible for the CRC assigned to this study to consent all of the patients in this manner.

   We anticipate that the CRC will approach 30–40 patients per day at JRSC, and it is not feasible for this person to have a full consent discussion with each of the patients. We feel that our proposed solution of providing educational materials to the patients prior to their surgery date and having a member of the research team available to answer any questions that arise will allow us to take all necessary precautions to ensure the comfort and safety of the patients who will participate in this protocol.

5. The research is not regulated by the FDA.

Caregivers

1. The research involves no more than minimal risk to the participants. Caregivers will only be approached if they are identified by the patient. They will be asked to complete 1 survey at 3 different time points and possibly to participate in a 30–60-minute qualitative interview at a convenient time. The questionnaire and qualitative interview are not expected to have any serious psychological impact on the caregiver.

2. The waiver will not adversely affect the rights and welfare of the research participants, as they will willingly engage in the research. Even if caregivers provide verbal consent on the date of surgery, if they later decide not to participate, they do not have to complete the questionnaire when it is sent to them. Participation will be entirely voluntary.

3. If deemed appropriate by the PI and granting organization, the caregivers will be provided with additional pertinent information after participation.

4. The research cannot be practicably carried out without this waiver. For the same reason that this would not be feasible with patients, documenting consent for all caregivers would be extremely challenging, as we expect a high volume of caregivers (30–40 per day) to be approached for participation. Because the CRC will be approaching 30–40 patients and 30–40 caregivers, we feel it is clearly impractical to require documentation of consent for a study with sucha vast scope but that poses no more than minimal risk to any of the participants.

5. The research is not regulated by the FDA.

All participants must provide their consent to participate. This IRB/PB-approved consent script meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent script and the education materials provided to the patient will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information.

The member of the research team who has the consent discussion with the patient will sign the verbal form and have it scanned to the patient's medical record.

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17.0 APPENDICES

Appendix A: Patient Activation Measure (PAM) – Short Form
Appendix B: Caregiver Reaction Assessment (CRA)
Appendix C: Caregiver Demographic Questionnaire
Appendix D: Study Information_Patients
Appendix E: Study Information_Caregivers
Appendix F: Recruitment Letter_Patients
Appendix G: Recruitment Letter_PFACQ
Appendix H: Correspondence Templates
Appendix I: Qualitative Interview Script_Patients
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Verbal Consent_Patients
Verbal Consent_Caregivers