BOLSTER: Building Out Lifelines for Safety, Trust, Empowerment and Renewal (NCT03367247)
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Dana-Farber Cancer Institute

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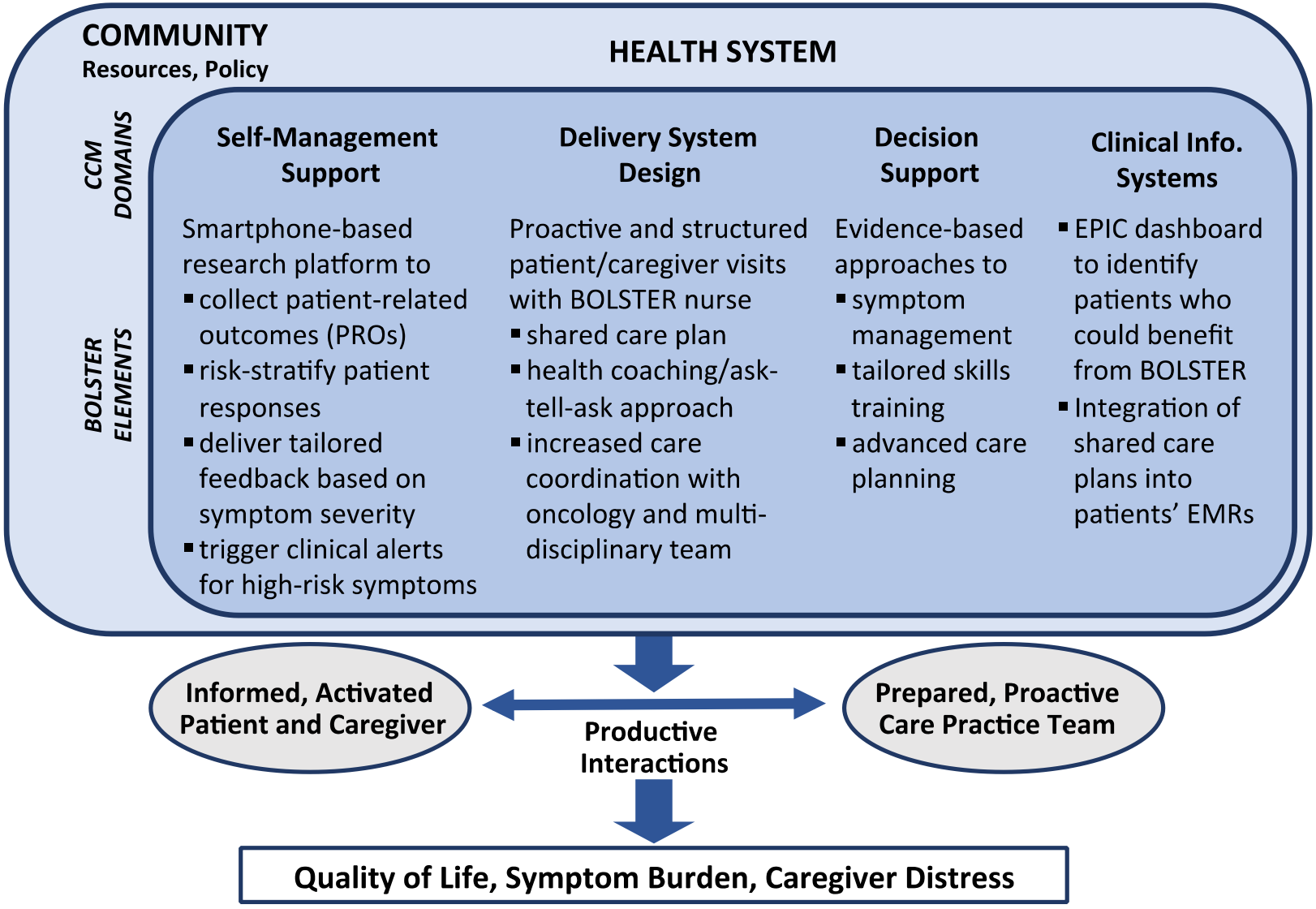


Figure adapted from Wagner et al, J of Alternative and Complementary Medicine, 2005

**SECTION 2: Body of Protocol**

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## 1.0 Introduction

*1.1 Overview*

Peritoneal carcinomatosis is a severe complication that affects many patients with advanced gynecologic and gastrointestinal cancers.[1-4] These cancers spread insidiously along the intestines, strangulating the bowel in a cement-like substance that blocks normal functioning. Bowel obstructions occasionally resolve with decompression, but most recur, subjecting patients to repeated emergency department visits and hospitalizations.[2] Management involves pain control and palliative surgeries; i.e. bowel resections, colostomies, or venting gastric tubes.[35,6] Peritoneal carcinomatosis (PC) also blocks the lymphatics, requiring frequent drainage of fluid. As the diseases advance, many patients accumulate tubes, lines, and drains, and family caregivers are expected to perform complex medical and nursing tasks with little or no preparation.[6-10] Caregivers of cancer patients with PC report high levels of distress and unmet needs for basic information about how to care for their loved ones.[11-15]

Despite frequent and distressing hospitalizations among advanced cancer patients, few researchers have tested palliative care interventions in cancer patients undergoing transitions in care.[16-19] Most have focused on ambulatory patients with common cancers (e.g., lung, breast).[20-28] In non-oncologic diseases, "high-touch" care management interventions have reduced hospital readmission rates and improved patient quality of life (QOL) by providing comprehensive support and care coordination across the inpatient-to-outpatient transition.[29-33] Compelling data from McCorkle et al. show that providing cancer patients with post-operative longitudinal nursing support (Standard Nursing Intervention Protocol, SNIP) improves patients' QOL and survival[26,34,35] while reducing hospitalizations[26] and caregiver distress.[36] We hypothesize that the use of a "high touch" intervention, focused on symptom management and skills training, will increase caregiver mastery—which, in turn, will improve patient outcomes[37-39] and attenuate caregiver distress.[40] We further expect that a longitudinal relationship with a clinician across care settings (e.g. hospital, home, clinic) will reduce care fragmentation, and provide a key therapeutic alliance to enhance patient and caregiver outcomes.[41-43]

The long-term goal of this research is to develop and implement effective and scalable palliative care interventions to improve advanced cancer patients' QOL, reduce burdensome hospital-based care, and decrease caregiver distress. The objective of this application is to determine the feasibility of BOLSTER (Building Out Lifelines for Safety, Trust, Empowerment, and Renewal)— applying key insights from Wagner's Chronic Care Model (CCM) and other evidence-based interventions (e.g., the SNIP, ENABLE II).[44] BOLSTER will provide patients and caregivers with multi-modal education and skills training (i.e. with a book, web site with educational materials and patient videos, and the nurse), multi-modal symptom management (i.e. with a smartphone app and nurse), longitudinal support across care settings, and advance care planning. We completed two single-arm pilot studies to examine the feasibility and acceptability of the BOLSTER program in patients with advanced gynecologic cancers (up to N=20) and their caregivers (up to N=20) receiving care at the Dana-Farber Cancer Institute. After establishing feasibility and acceptability, we propose a pilot RCT of BOLSTER vs. Enhanced Discharge Planning to finalize study procedures, determine approach-to-consent rate for randomization, and to estimate outcomes parameters to inform the design of a larger randomized controlled trial.

*1.2 Background and Rationale*

Peritoneal carcinomatosis causes tremendous suffering in patients with gynecologic (GYN) and gastrointestinal (GI) cancers. Many patients with advanced GYN and GI cancers develop peritoneal carcinomatosis (PC), a severe complication of late-stage disease, which causes bowel obstructions and fluid build-up in the abdomen and lungs. Some bowel obstructions resolve with decompression, but most recur, precipitating frequent emergency department (ED) visits, hospitalizations, and surgical procedures. Treatment includes medical management or surgery: bowel resections, ostomies, or venting gastric tubes (which often preclude eating).[1,2,4,6,10] Patients with malignant bowel obstructions live a median of 3-13 months, [9,45-48] and 20-50% experience major morbidities from procedures.[46,48] A palliative care intervention is desperately needed to reduce suffering, enhance decision-making and quality of life (QOL), and engage patients and families in advance care planning.

Family caregivers of cancer patients with PC are overwhelmed and underprepared**.** Caregiving for these patients is challenging because it is both intensive and extended. Family members spend >10 hours a day caring for their loved ones.[49] One of the most stressful periods is immediately after a hospitalization.[50] Patients are vulnerable,[51] medication errors are common,[52] and conditions require close monitoring by family.[53] Moreover, caregiver teaching is ad-hoc, provider-dependent, and often performed on the day of discharge.[50] There is no consensus on how to prepare and support caregivers.[50,54] More than 50% perform complex and skilled services at home—e.g., injecting medications, changing ostomies, and draining catheters—because visiting nurses cannot provide the frequency of care required.[53] Many learn through a process of trial and error, while at home alone.[53,55,56] Family caregivers report high levels of distress, feelings of helplessness, burden, and unmet needs for basic information on how to care for their loved ones.[13] Despite this, few interventions have targeted these caregivers to provide skills training, improve mastery,[37] or reduce distress.[12]

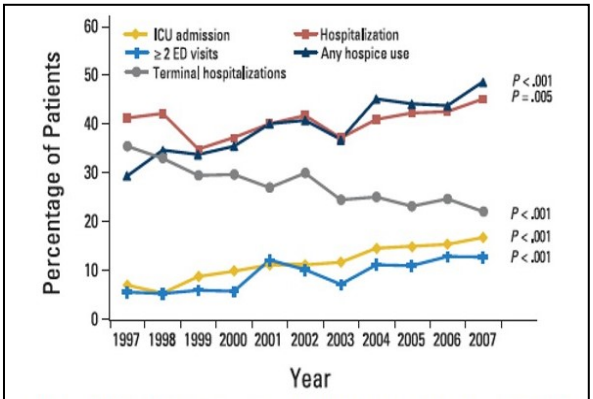



**Fig 1.** Adjusted yearly proportion of patients with ovarian cancer receiving medical care in last month of life.

Cancer patients with PC are at high risk of receiving fragmented end-of-life (EOL) care. Hospitalizations are common, costly, and distressing events for patients with advanced GYN and GI cancers. For example, we and others have found that nearly a third of patients with ovarian cancer are readmitted within ≤30 days of a hospital discharge, often for avoidable reasons.[57,58] In addition, patients with advanced ovarian cancer are at high risk for receiving intensive, hospital-based services (ED visits, hospitalizations) in the last month of life, despite increasing use of hospice (**Figure 1**). Nearly 70% of patients undergo a care transition within 30 days of death, and 20% occur in the last 3 days of life.[59] These findings suggest that additional supports are needed to allow ovarian cancer patients—and other patients with GYN and GI cancers complicated by PC--to receive EOL care at home, or in their preferred care setting.

***"No one showed us how to use the venting g-tube in the hospital—they said the visiting nurse would teach us. But she had never used one so we were stranded…." -- Quote from a caregiver***

Providing longitudinal symptom monitoring, support, and caregiver skills-training is an ideal strategy to improve patient QOL, while reducing care fragmentation and caregiver distress. One of the strengths of the BOLSTER (Building Out Lifelines for Safety, Trust, Empowerment, and

Renewal) model is that it combines intensive symptom monitoring and management, caregiver skills training, and support in the context of an acute crisis. This model involves teaching caregivers key problem-solving skills to more effectively manage patients' complex needs, which we expect will both improve caregiver mastery and reduce feelings of helplessness. Caregiver mastery, in turn, has been shown to improve patient outcomes, while attenuating caregiver distress.[37-39,40,62] We further expect that a longitudinal clinical relationship with a clinician will reduce care fragmentation and provide a key therapeutic alliance to improve patient and caregiver outcomes.[41-43]

If successful, BOLSTER has the potential to alleviate suffering for patients suffering from advanced GYN and GI cancers complicated by PC each year.[60-62] Moreover, because PC affects between 10-15% of all cancer patients, we expect that BOLSTER could be translated into other cancer types, potentially improving care for many more. Furthermore, since BOLSTER uses scalable strategies, we expect that it can be easily adopted into oncology practices if proven effective.

## 2.0 Objectives

**Phase I: (Single-arm study with up to 20 hospitalized or recently hospitalized ovarian cancer patients and their informal caregivers run-in)**

Primary Objective: Conduct a single-arm study to assess the feasibility and acceptability of the BOLSTER intervention.

- Hypothesis: The BOLSTER intervention will be feasible in hospitalized or recently hospitalized ovarian cancer patients and their caregivers. Feasibility will be defined as : 1) ≥50% enrollment among eligible participants (based upon prior RCTs);[63] 2) ≥70% fidelity to the intervention by the study nurse measured by: a) whether the BOLSTER encounters followed the planned intervention sessions (checklist of content in Table 2) and b) an analysis by the study team of 20% of recorded BOLSTER encounters for key content and overall quality, consistent with best practice and recommendations from the NIH Behavior Change Consortium.
- Hypothesis: The BOLSTER program will be acceptable in hospitalized or recently hospitalized ovarian cancer patients and their caregivers, defined as: 1) ≥70% of participants "agree" or "strongly agree" that they "would recommend BOLSTER to other patients with cancer and their family members."

Secondary Objective: Assess the perceived efficacy of the BOLSTER intervention and estimate outcomes parameters for this population.

- Hypothesis: Patients, caregivers and clinicians will perceive the BOLSTER program to be efficacious, measured with a 6-item questionnaire administered to patients, caregivers, and oncology clinicians at the 4-week assessment.[64]

**Phase II: 2-arm RCT with 60 hospitalized or recently hospitalized patients with gynecologic or gastrointestinal cancers and PC and their caregivers (30 dyads in each arm)**

Objectives:

- To determine the feasibility and acceptability of randomizing patients and family caregivers to enhanced discharge planning (EDP) or BOLSTER.
- To estimate outcome parameters (estimated by means, standard deviations, and proportions of 4-week measures) of future primary (days outside of a facility) and

secondary (self-efficacy, quality of life, mental health, health care utilization, and survival) outcomes to inform the design of a larger multi-center RCT

Hypotheses:

- Hypothesis 1: >50% of approached patients and family caregivers will agree to randomization to EDP vs. BOLSTER.
- Hypothesis 2: Participants randomized to BOLSTER will use fewer acute hospital-based services i.e. emergency department visits and hospital admissions—at 4-week follow-up, compared to EDP.
- Hypothesis 3: Participants randomized to BOLSTER will report higher self-efficacy (overall and skills-based self-efficacy) compared with EDP at 4-week follow-up, compared to EDP.
- Hypothesis 4: Participants randomized to BOLSTER will report higher QOL, as measured by the FACT-G at 4 weeks, compared with EDP.
- Hypothesis 5: Caregivers of participants randomized to BOLSTER will report lower caregiver burden at 4-week follow-up, compared with caregivers of participants randomized to EDP

## 3.0 Research Subject Selection

*3.1 Eligibility Criteria*

3.11 Patient eligibility criteria. Inclusion criteria for patients include: (1) adults (≥18 years old); (2) GYN or GI cancers receiving anti-neoplastic therapy; (3) hospitalized, recently hospitalized (i.e. within the first 2 visits after a hospitalization), or recent outpatient placement of tube, line, or drain (e.g. PleurX catheter); (4) plan to receive ongoing care at DFCI; (5) willingness to be recorded for the study (for monitoring of study fidelity); and (6) have complex care needs (e.g. an ostomy, ileostomy, a gastric tube, percutaneous nephrostomy tubes, a PleurX catheter, or need for total parenteral nutrition) due to PC.

3.12 Caregiver eligibility criteria. Inclusion criteria: (1) adults (≥18 years old); (2) family member or friend of an eligible patient; and (3) willingness to be recorded for the study (for monitoring of study fidelity); and (4) willingness to participate in study visits.

*3.2 Exclusion Criteria*

3.21 Patient exclusion criteria: (1) Unable to read and respond to questions in English; (2) cognitive impairment; (3) unable to complete the baseline interview; (4) plan for immediate hospice referral

3.22 Caregiver exclusion criteria: (1) Unable to read and respond to questions in English, (2) cognitive impairment or (3) unable to complete the baseline interview.

*3.3 Note on eligibility*

Patients will be excluded from enrolling in the study if they are cognitively impaired or have a plan for immediate hospice referral during the time of study enrollment. However, if a patient decides to transition to hospice after enrolling in the study and still wishes to remain on the study, or if a patient develops cognitive impairment during the study, patients and their caregiver will be permitted to remain on study.

Additionally, if a patient cannot identify a caregiver to participate in the study with them, they will not be excluded from participation. When the BOLSTER intervention was designed, the research team was concerned that patients with complex care needs would not be able to participate without their caregivers. However, after performing two pre-pilots, we have realized that this assumption was incorrect. In fact, only a few of the participating caregivers have been present for most of the sessions with the study nurse (largely due to competing demands of their own). Thus, patients who are discharged home but do not have a caregiver or feel that their caregiver would not be interested in participating will be eligible to participate in this study. If a patient cannot identify a caregiver, or is uncomfortable asking them to participate, the study team will document the reason but still enroll interested patients.

In the first pre-pilot of BOLSTER, more than 50% of potentially eligible patients enrolled in hospice or died prior to our approaching them. Similarly, nearly 50% of patients enrolled in the 10-week intervention enrolled in hospice or died participating in the 12-week intervention. Among those who did participate, several noted that they wished that this intervention had existed when they were first diagnosed during debriefing interviews. Thus, we have modified the protocol significantly, including the eligibility criteria, to tailor it to this population while also expanding the eligibility criteria to be responsive to participants' comments. In the revised protocol, we have expanded the eligibility criteria to include women who are hospitalized with ovarian cancer and complex care needs at any point in the disease trajectory, rather than limiting the study population to women hospitalized with recurrent ovarian cancer. We have also expanded recruitment to the outpatient setting immediately following a hospitalization in response to participant feedback that participants were sometimes too overwhelmed to enroll in a study during hospitalization.

In the second pre-pilot of BOLSTER, each of the patients we approached agreed to participate, the intervention was well received, and none of the participants died during the study period. However, we were repeatedly approached by health care providers with requests to enroll patients with complex care needs (e.g. PleurX catheters, new ostomies) resulting from PC secondary to endometrial or cervical cancers. Given that the symptoms and skills training needs of patients with endometrial and cervical cancers complicated by PC are nearly identical to those experienced by patients with ovarian cancer, we decided to expand our eligibility criteria. Similarly, during this second pilot, we learned that the Shared Care Plan is burdensome for some patients; thus, we will make it optional for the pilot RCT.

## 4.0 Research Subject Entry

### *4.1 Subject Recruitment and Enrollment*

We will enroll patients from the DFCI Gynecologic Oncology and Gastrointestinal Program. We have created an EPIC workbench that enables us to identify all patients with GYN and GI cancers who are hospitalized at the BWH based upon billing codes. Members of the study team will run this workbench daily to identify potentially eligible inpatients and contact the patient's primary oncologist to determine whether the patient may be an appropriate study candidate. If the outpatient oncology team agrees and the patient is an inpatient, the study team will also contact the inpatient team to confirm that the participant is an appropriate study candidate. If the patient has been discharged or the inpatient team does not feel that the patient is appropriate (e.g., the patient is overwhelmed, delirious or considering transition to hospice) then the patient will be approached at the next outpatient appointment with their outpatient oncology team. Finally, as a number of tubes, lines and drains are placed in the outpatient setting (e.g., in

interventional radiology), we will also consider outpatients with new complex care needs due to PC and advanced GI and GYN cancers eligible.

Special Note on Minimizing Possibility of Coercion / Undue Influence

Because participants who enroll in BOLSTER may participate in informed consent while they are hospitalized, it is crucial to minimize the possibility of coercion or undue influence. We have developed a three-step screening and enrollment process to address this risk.

First, upon identification of a potential participant, the study team will contact the patient's outpatient oncologist to confirm eligibility and ensure that the patient and/or her caregiver are not too emotionally distressed to approach for participation. If the patients' oncologist suggests that the patient or caregiver may be too distressed to participate, the study team will not approach them.

Second, study staff will give potentially eligible participants a one-page information sheet (Appendix N: Study Info Sheet) about BOLSTER during the hospitalization and briefly explain the study. Study staff will explain that if the patient is interested, they can learn more about the study via the informed consent process. Patients and caregivers will be given ample time to consider whether they want to participate in the study. Patients who do not express interest upon receiving the one-page information sheet will not be approached again about participating in the study. Only patients/caregivers who express interest in learning more will even enter the informed consent process.

Third, study staff will provide the informed consent process, reviewing the consent form with potential participants in detail, answering any questions participants may have, and encouraging them to take their time in making a decision to sign consent. Study staff will reiterate that participation in the study is voluntary and will not affect the care that the patient receives whether they decide to participate in the research study or not. The study staff will also highlight that the patient and/or caregiver can withdraw from the study at any time without affecting the patient's medical care or relationships with the patient's care team. Additionally, study staff will provide each potential participant with both their contact information and the contact information of the PI in case the prospective participant has any additional questions or concerns to discuss.

We will follow a similar approach for patients who were recently hospitalized and will be introduced to the study in the outpatient setting. If the patient is approved to approach for enrollment, the study staff will coordinate with the oncology provider to meet with the patient to discuss the study at the time of their next clinic visit.

Every attempt will be made to approach patients in-person, but if this is not possible, the study team is permitted to implement remote recruiting procedures. Participants who are recruited remotely will be provided with a recruitment letter after obtaining permission from the patient’s oncology provider, outlining additional details about the study, such as the procedures and time commitment involved (Appendix AI). Recruitment letters can be sent via mail or email. If the oncology provider deems the patient ineligible or too distressed to participate in a research study at this time, the patient will not be approached for inclusion. If remote recruiting procedures are utilized, study staff will coordinate with the oncology provider and patient to find a time that is convenient for the patient.

4.3 Screening and Recruitment

Prior to obtaining informed consent, study staff will review the electronic medical records of patients in the gynecologic and gastrointestinal oncology groups to identify patients who meet eligibility criteria. These patients’ medical records will only be reviewed to confirm this protected health information (PHI), and it will only be shared with gynecologic and

gastrointestinal oncology providers in the context of patients' eligibility for the study. PHI will not be shared with anyone outside of the study team and patients' oncology providers. All emails will be sent within the Partners firewall. A HIPAA waiver requesting permission to review the PHI of these select patients prior to consent during screening and recruitment has been submitted to justify this process.

Please see the sections above for further details about the screening and recruitment process and special precautions taken to minimize the possibility of coercion.

4.4 Informed Consent

Informed consent will be obtained by the PI, study nurse, or research coordinator. The informed consent form will contain a section dedicated to explaining what constitutes PHI and how this information will be protected as confidential per HIPAA guidelines. The consent form will also provide contact information for both the Principal Investigator (PI) as well as the Office for the Protection of Research Subjects. All informed consent processes will adhere to the policies set forth by the Institutional Review Board. Signed informed consent forms will be stored in a locked file cabinet to maintain the privacy of all study participants.

If a patient or her caregiver decides she is not interested in the study when discussing with the RA or study nurse, the study team member will thank them for considering, and reassure the patient and caregiver that the process will have no impact on the patient's medical care. No further interactions will occur with patients and caregivers who either decline or prove ineligible for the study.

Remote consenting will be permitted if a patient is unable to be approached in-person. With permission from the patient's oncology provider, study staff will send the potential participant a recruitment letter to provide them with more information about the study, and to allow them to opt out of being contacted (Appendix AI). Recruitment letters can be sent via mail or email. Study staff will then follow up by phone with all potential participants who do not opt out of further contact and will send consent forms for review if they are interested in participating in the study. Consent forms will be sent either by mail or electronically through a secure and personalized link in REDCap. The consent forms will be IRB approved. During the consent discussion, study staff will emphasize that the study is voluntary, participants may withdraw from the study at any time, and that withdrawal of consent will not affect their medical treatment in any way. Consent discussions can be completed via phone or HIPAA-compliant Zoom.

As referenced in Section 3.3, if participants cannot identify a caregiver or if they are uncomfortable asking them to participate in the study (e.g., their caregiver is too overwhelmed or burdened) the study team will document the reason, but enroll interested participants who otherwise meet all other eligibility criteria.

4.5 Remote Consent for Caregivers of Consented Patients

In cases where patients' identified caregivers are not available in the hospital prior to discharge, are not present during an outpatient clinic visit or are not present during a HIPAA-compliant Zoom consent discussion, study staff will either provide consented patients with a letter describing the study to give their caregiver, or study staff will reach out to the participants' caregiver directly with the letter (Appendix AH). The letter may be sent via mail or email. A copy of the consent form will also be included with the letter. A staff member will contact the caregiver prior to the first visit or telehealth session. If the caregiver is interested in participating, they may opt-in and a staff member will guide them through the informed consent form and

baseline assessment and instruct them to sign and return the consent form. Consent forms will be sent either by mail or electronically through a secure and personalized link in REDCap. The staff member will not contact the caregiver beyond three unreturned phone calls.

*4.6 Subject Registration and Randomization*

A member of the study team will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. For this minimal risk protocol, registrations will occur retrospectively with the approval of the ODQ (as per DF/HCC SOP REGIST-101) because prospective OnCore registration would be disruptive to the study team workflow. An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Participants enrolled in the pilot RCT portion of the study will be randomized 1:1 to BOLSTER or Enhanced Discharge Planning using a computer-generated random allocation sequence with blocks of 4.

## 5.0 Study Design and Methods

*5.1 Design/Study Type*

Phase I: with a total sample size of up to 20 patient-caregiver dyads, we will assess whether BOLSTER is feasible and acceptable for further study. Other analyses of study outcomes will be descriptive in nature. Our analyses will provide preliminary estimates of safety outcomes, scale scores, missing data, and participant feedback.

Of note, there was a high mortality rate among patients enrolled to the first wave of the Phase I study, which was a 10-week intervention. Because of the high burden of symptoms and high mortality rate (3 out of 6 patients died before intervention completion), we have reduced the length of the intervention from 10 to 4 weeks; further tailored the intervention to be more focused upon the needs of this acutely-ill patient population and their family caregivers (e.g., we now include information on advance care planning); and we have added a post-mortem caregiver survey. We have also expanded the eligibility criteria to include women with ovarian cancer with complex care needs at any stage in the disease trajectory (removing the criterion that the disease is recurrent to be eligible). We did this based upon feedback from patients and their caregivers, who frequently expressed that they wished that they had had access to the intervention sooner.

Preliminary findings from the pre-pilot demonstrate that 70% of patients approached about the study agreed to participate and 80% of patients and caregivers “agreed” or “strongly agreed’ that they would recommend the BOLSTER program to other patients with cancer and their family. While the intervention was feasible and acceptable to patients and caregivers, we learned several key lessons that required significant protocol changes, including the need to:

1) Further tailor the intervention to the population. Given how acutely ill the study population was—50% of enrolled participants died within 3 months—we have streamlined the intervention so that it can be delivered in 4 weeks instead of 12 weeks. This was also in response to feedback from survivors who reported feeling as if they had learned the most in the first 4 weeks of the intervention and, while they enjoyed the additional support, were not sure that it was necessary. We have also revised the intervention content to explicitly address advance care planning. **Table 2** below includes summary of the content of each session of the 4-week intervention.

2) Expand the eligibility criteria. As noted above, we will expand the eligibility criteria to include patients with ovarian cancer and complex care needs at any stage in the disease trajectory. Please see Section 3.3 for further details.
3) Increase the flexibility of recruitment and enrollment requirements. Recruiting from the inpatient setting proved very inefficient as 50% of potentially eligible participants enrolled in hospice or died before discharge. Moreover, several patients reported feeling "too overwhelmed" to enroll in a study as an inpatient. Thus, in the revised protocol, we have added an option to recruit patients in both the inpatient and outpatient settings (for the outpatient setting, we will mandate that participants are recruited within the first 2 visits after a hospitalization).
4) Change the smartphone platform (Beiwe) to another smartphone platform that we developed for monitoring patient-reported outcomes (PROs). Unfortunately, neither the study participants nor the interventionist felt that the Beiwe platform added value. In the interim, we developed another app that is more engaging and flexible because it collects PROs, includes a clinician dashboard that enables safer monitoring of PROs, and allows the interventionist to have contact with participants through the app and assign tailored content. This streamlines multiple components of the intervention, while enhancing safety for participants since the dashboard is significantly easier to manage.

As a result, we planned to re-pilot the revised BOLSTER intervention (Phase I) before proceeding with the Phase II RCT of 60 patient-caregiver dyads (30 in each arm). As noted above, in the second pre-pilot of BOLSTER (n=3), 3/3 patients approached agreed to participate, demonstrating feasibility, and the intervention was acceptable to all. However, we were repeatedly approached by health care providers with requests to enroll patients with complex care needs (e.g. PleurX catheters, new ostomies) resulting from PC secondary to other advanced GYN and GI cancers. Given that the symptoms and skills training needs of patients with GYN and GI cancers complicated by PC are nearly identical to those experienced by patients with ovarian cancer, we decided to expand our eligibility criteria, initially to all GYN cancers and now to include GI cancers as well. Similarly, during this second pilot, we learned that the Shared Care Plan is burdensome for some patients; thus, we will make it optional for the pilot RCT.

Given the additional pre-pilot run-in was feasible and acceptable, we will now initiate the Phase II RCT portion of BOLSTER as outlined below:

- Arm 1: BOLSTER
- Arm 2: Enhanced Discharge Planning (EDP)

We will exclude patients from all run-in phases from the final analysis since these patients will not undergo randomization. Our final analyses will provide preliminary estimates of feasibility, acceptability, safety outcomes, scale scores, missing data, and participant and physician feedback.

*5.2 Selection of Instruments*

The following updated measures will be used in the study interviews, study visits, and/or the smartphone application, including the Patient Baseline Interview (Appendix T), Caregiver Baseline Interview (Appendix U), Patient Post-Baseline Interview (Appendix V), Caregiver Post-Baseline Interview (Appendix W), Caregiver Post-Baseline Decedent Interview (Appendix AE), and Smartphone Symptom Survey (Appendix Y) to obtain basic descriptive statistics in

preparation for the larger RCT.

5.21 Patient Interviews

5.21a Patient Sociodemographic Information

Basic demographic information will be collected for all participants, including: age, marital status, race/ethnicity, education, religion, household structure, income, and employment. The questions will only take a few minutes to complete.

5.21b Global Health Status: EQ-5D-5L

The EQ-5D is a standardized measurement of health status that has been used in a wide range of health conditions and treatments, including cancer patient populations.[65] The EQ-5D-5L is the most recent 5-level version that has proven validity and reliability in a range of patient groups with chronic diseases[66] and cancer.[67] It is a 5-item questionnaire (measuring mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of perceived problems: 1) no problems, 2) slight problems, 3) moderate problems 4) severe problems, and 5) extreme problems. Patients check the statement level that best describes their current health status in each dimension, which are then scored to generate a patient's unique health state. In the EQ-VAS, patients report a single index value of how good or bad their current health state is on a visual scale that ranges from worst imaginable at zero to best imaginable at one hundred. The EQ-5D-5L can be administered with little to no guidance and takes only a few minutes to complete. Upon scoring, the EQ-5D produces a composite score between 0-1 (multiplied by 100 to generate a number between 0-100), which represents general health status, normalized for the US population.[68] Lower scores represent worse quality of life, and a change of ≥6 is clinically significant in US cancer populations.[69] The EQ-5D will be used in the patient baseline and post-baseline interviews.

5.21c Patient quality of life: FACT-G

Patients' quality of life (QoL) will be assessed with Functional Assessment of Cancer Therapy-General, which has demonstrated internal consistency, reliability and validity.[70] The measure is divided into four primary QoL domains: physical well-being (7-items), social/family well-being (7-items), emotional well-being (6-items), and functional well-being (7-items). Participants will rate each symptom over the past 7 days as: 0) Not at all; 1) A little bit; 2) Somewhat, 3) Quite a bit, and 4) Very much. Subscales can be analyzed separately or aggregated to produce a total score. FACT scores will be collected for patients during the baseline and post-baseline interviews.

5.21d. Patient Anxiety and Depressive symptoms

The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale,[71] measuring symptoms of anxiety and depression, which has been validated for screening for emotional distress in cancer patients[72] and their caregivers.[73] A score of ≥8 indicates significant symptoms of anxiety or depression with good sensitivity and specificity.[74] HADS will be assessed for both patients and caregivers during the baseline and post-baseline interviews.

5.21e Patient Self-Efficacy

Self-efficacy will be assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Self-efficacy for Managing Chronic Conditions item banks that comprise three domains: general self-efficacy, self-efficacy for managing symptoms, and self-

efficacy for medications and treatments. Each item is rated between 0 (not at all confident) to 4 (Very confident), and items are summed with higher scores indicating more self-efficacy. All measures have good internal consistency and cross-sectional validity with existing validated scales measuring self-efficacy and other PROMIS short forms.[75]

5.21.f Consumer Assessment of Health Care Providers and Systems (CAHPS)

This CAHPS Cancer Care Survey assesses patients' experiences with their overall cancer care, oncologist, symptom management and coordination of care. Each measure is rated between 0 (Never) and 3 (Always) with higher scores indicating better experiences of care. This survey has been widely used to assess cancer patients' experiences with clinicians and the health care system, from survivorship to the end-of-life.[76,77]

We will also measure whether patients received any training from health care providers for key skills (e.g. help changing bandages; caring for tubes, lines, and drains) and information about potential problems that they might encounter, how to reach the team to troubleshoot problems, whether they ever ran out of medical supplies, and their perceived difficulty with caring for themselves after a procedure. This will be measured using items from the Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium which assess whether participants' healthcare provider offered specific training or demonstrated how to perform medical tasks.

5.21g Treatment preferences, advance care planning

A simplified version of Fried's validated Willingness to Accept Life-Sustaining Treatment (WALT) technique[78] for eliciting patient treatment preferences will be used and related to goals of care. Participants will be asked to describe their preferences for comfort care measures (e.g., relieve pain and discomfort as much as possible) vs. aggressive treatment (extend life as much as possible) at the end of life.

To assess advance care planning, patients will be asked "Have you and your doctor discussed any particular wishes you have about the care you would want to receive if you were dying?" Responses will be coded as "yes" or "no."[79] Prognostic understanding, treatment preferences and advance care planning will be assessed in patients only during the baseline and post-baseline interviews.

5.21h Social Support Survey

The Social Support Survey instrument is a brief, multi-dimensional measure developed for patients in the Medical Outcomes Study, a two-year survey developed for patients with chronic conditions. The survey consists of four functional support scales (emotional/informational, tangible, affectionate, and positive social interaction); a composite, overall functional social support index can be calculated from the subscale items. Each subscale is reliable (Cronbach's alpha > 0.91) and stable over time.[80] The MOS Social Support will be administered to patients and caregivers during the baseline visits.

5.21i Brief COPE

We will be using a 15-item version of the Brief COPE, a measure developed to assess a broad range of coping responses.[81] The Brief COPE has been validated in several populations including breast cancer patients and community samples.[81] Subscales of the Brief COPE include use of emotional support, religion, and self-distraction, and individual subscales can be used independently. The Brief COPE will be administered to patients and caregivers during the baseline visits.

5.21j Cancer-related data and comorbidities

Cancer-related data (date of cancer diagnosis, stage, grade, treatments, hospitalizations, procedures, length of relationship with oncologist and hospitals where patient receives care) and information about comorbidities will be collected for patients via chart abstractions. Comorbidities will be collected for caregivers during the baseline interview.

## 5.22 BOLSTER Visits

5.22a Health Care Utilization

Patients and caregivers will be asked to self-report visits to their primary care doctors, oncologists, and other specialists during the time in which they are participating in the study using a validated medical event form (Appendix Q: Healthcare Utilization Tracker).[82,83] In addition, they will self-report radiographic imaging, emergency department visits, hospitalizations, and length of hospitalizations. The study staff will also review patients' medical charts to abstract information about healthcare utilization, including ED visits and hospitalizations.

5.22b Distress

The NCCN Distress Thermometer[84] is a single-item measure that assesses distress and problems that a patient may be experiencing. Patients will be asked to rate their distress in the past week on a scale of 1-10. The NCCN Distress Thermometer is both reliable and valid and is used widely to assess distress levels in cancer patients.[85-87] The distress thermometer will be used for patients at the beginning of each BOLSTER study visit

## 5.23 Smartphone App

5.23 PRO-CTCAE

The Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a patient-centered, standardized self-report measure that enables patients to report symptoms and AEs.[88-91]The PRO-CTCAE has demonstrated favorable validity, reliability, and responsiveness in a large heterogeneous United States sample of cancer patients undergoing treatment.[90] Ten PRO-CTCAE items that are salient to patients with advanced GI and GYN cancers will be collected, including: abdominal pain, nausea, vomiting, constipation, diarrhea, peripheral neuropathy, anxiety, depression, dizziness and fatigue.

The PRO-CTCAE items use conditional branching for AEs that contain multiple attributes. For example, if a participant reports a symptom, she is asked to quantify the severity and the extent to which the symptom interfered with her daily activities; if she does not report a symptom, these items are skipped. Participants will report their symptoms twice a week through the RMDY smartphone application, described in section 5.39.

## 5.24 Caregiver Interviews

5.24a Sociodemographic Information

Basic demographic information will be collected for all participants, including: age, marital status, race/ethnicity, education, religion, household structure, income, and employment. The questions will only take a few minutes to complete.

5.24.b Clinical Care tasks measure

This measure assesses all of the care that caregivers provide to patients, including Assistance with Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL) and Clinical Care tasks. Caregivers will be asked whether they have performed a series of tasks in the past two weeks, such as "help with a catheter, drain, or colostomy bag." Answers are "Yes," "No," and "Not needed." This measure was developed by a committee of nationally-recognized cancer-care providers, researchers, cancer survivors, and caregivers; refined during cognitive interviews; and used in a population-based study of cancer patients and their family caregivers.[92]

5.24.c Caregiver Preparedness Scale

The Caregiver Preparedness Scale includes four items on caregiver preparedness to care for a patient's physical and emotional needs, setting up services, and coping with the stress of caregiving. Each item is rated between 0 (not at all confident) and 4 (Extremely confident) and items are summed for a total score that can range from 0 to 16 with higher scores indicating feeling better prepared for the caregiving role.[93] In a prior large, population-based study of cancer caregivers, preparedness partially mediated the association of caregiver training on reported caregiver burden.[94]

5.24.d Caregiver Burden

The Caregiver Reaction Assessment is a multidimensional instrument designed to assess the reactions of family members caring for elderly patients with physical impairments, including cancer. The scale has three dimensions that had a high level of factorial invariance across a three-wave panel study and has been validated in cancer patients and family caregivers.[95]

5.24.e Caregiver health status

We will use the SF-12 health survey to elicit caregivers' views about their own health.[96] The SF-12 is a 12-item self-report survey that assesses health across physical and mental health domains. The SF-12 has been shown to have high internal consistency and validity.[96]

5.24.f Caregiver anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale,[71] measuring symptoms of anxiety and depression, which has been validated for screening for emotional distress in cancer patients[72] and their caregivers.[73] A score of ≥8 indicates significant symptoms of anxiety or depression with good sensitivity and specificity.[74] HADS will be assessed for both patients and caregivers during the baseline and post-baseline interviews.

5.25 Post-mortem Caregiver Interview

As noted in section 5.1 the first group of patients enrolled to BOLSTER (N=6 patients and N=6 caregivers) had a high-mortality rate. Thus, we have designed a brief post-mortem interview designed to briefly assess the primary outcomes of the study for caregivers of decedent patients. Specifically, we will ask caregivers where the patient died, about the patients' symptoms before death, the family caregivers' perceptions about the quality of care provided in the last month of life, and whether the patient received care that was congruent with her wishes.

These questions have been previously validated in a large, population-based cohort study of patients with colorectal and lung cancers.[97]

| **Table 1: Study measures and data collection by source and time** | | | | | |
|---|---|---|---|---|---|
| | **Time** | | | | |
| ***Study measures*** | ***Baseline*** | ***BOLSTER visits*** | ***RMDY App*** | ***4-weeks (Post-Baseline)*** | ***Abstractions*** |
| **Patients** | | | | | |
| **Sociodemographic data** | X | | | | |
| **Health Status (EQ-5D)** | X | | | X | |
| **Patient Quality of Life** | X | | | X | |
| **Anxiety and Depression** | X | | | X | |
| **Self-efficacy** | X | | | X | |
| **CAHPS** | X | | | X | |
| **Treatment preferences & goals** | X | | | X | |
| **Social Support** | X | | | | |
| **Brief COPE** | X | | | | |
| **Debriefing interview** | | | | X | |
| **Cancer data & comorbidities** | | | | | X |
| **Health care utilization** | | | | | X |
| **Distress** | | X | | | |
| **PRO-CTCAE*** | | | X | | |
| | | | | | |
| **Caregivers** | | | | | |
| **Sociodemographic data** | X | | | | |
| **Comorbidities** | X | | | | |
| **Social Support** | X | | | | |
| **Brief COPE** | X | | | | |
| **Debriefing interview** | | | | X | |
| **Clinical care tasks** | X | | | X | |
| **Caregiver preparedness** | X | | | X | |
| **Caregiver burden** | X | | | X | |
| **Health status (SF-12)** | X | | | X | |
| **Anxiety and Depression** | X | | | X | |
| | | | | | |
| **BOLSTER Nurse** | | | | | |
| **Recorded visits** | | X | | | |
| **Visit content, length, outcomes** | | X | | | |

*These items will be collected continuously throughout the study by the RMDY app. *5.39*

*5.3 Description of Intervention: BOLSTER*

5.31 Conceptual model

BOLSTER applies key insights from Wagner's Chronic Care Model (CCM)[44] and other evidence-based interventions (e.g., the SNIP, ENABLE II). To fill this gap in clinical care, self-management, and QOL for GYN and GI patients with complex care needs due to PC and caregivers, we developed BOLSTER – a BSN-trained nurse-delivered, multi-session intervention tailored to the needs of patients transitioning from hospital to home care. BOLSTER addresses each of the key Health System practice changes identified in the CCM, improving Self-Management Support, Delivery System Design, Decision Support, and Clinical Information Systems.

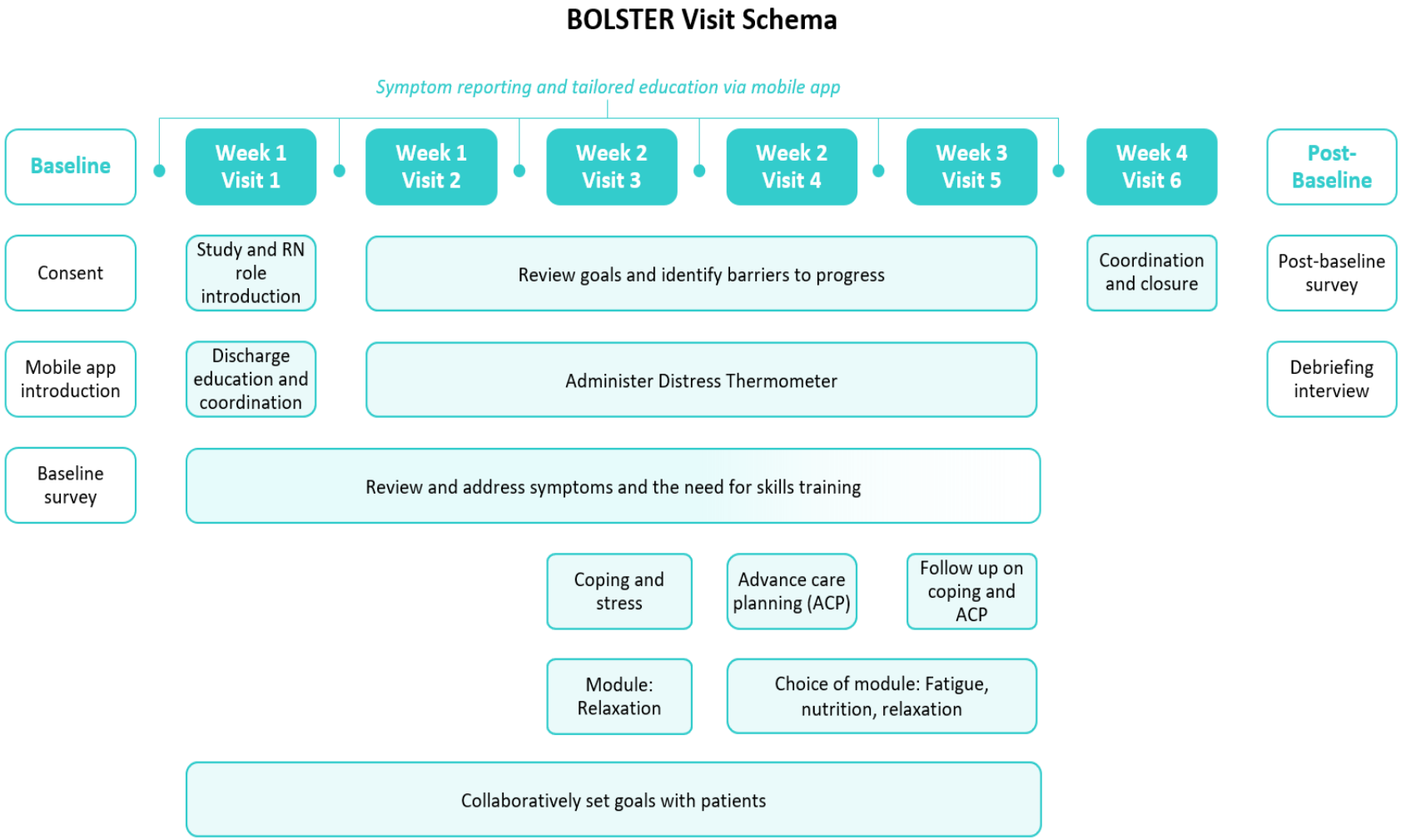
5.32 BOLSTER Intervention Time-Points

The intervention provides participants with longitudinal nursing support across care settings, a smartphone-based symptom management app, a print and web-based symptom management toolkit, and advance care planning to ensure that the patient receives care that is congruent with hi/her informed preferences. BOLSTER includes a total of 6 contacts with the study nurse over 4 weeks, and routine contact via a smartphone-based symptom app which queries patients about their symptoms using questions from the PRO-CTCAE, risk-stratifies their symptoms, and provides tailored symptom management advice.[88,91] For two weeks after study enrollment, when participants are in the acute phase of illness, the study nurse will contact the patient and caregiver twice weekly to assess patient symptoms, provide emotional support and ongoing education, engage in problem solving, and coordinate care. Subsequently, visits will taper to weekly.

5.33 BOLSTER Intervention by Session

The BOLSTER study nurse will conduct 6 study visits with the patient. Key content of the visits will be tailored to patient and caregiver needs as assessed by the BOLSTER study nurse: for example, one patient may prioritize symptom management while another may prefer to focus on psychosocial concerns. The BOLSTER nurse may provide other educational content outside the below chart and website materials tailored to patient and caregiver priorities as appropriate. An outline of suggested study content for the BOLSTER study nurse is below. Sample teaching materials include Appendices A-M, the Headspace App (Appendix AG), which is free for Dana-Farber patients to use, and additional mindfulness audio materials provided by the Dana-Farber Psychosocial Oncology Program.

Table 2: Sample BOLSTER Encounter Content



5.34 Hospital visits

During the first study visit, the patient and caregiver will create a Shared Care Plan (SCP) with the study nurse if they so choose. The SCP will include elements of an After-Hospital Care plan, or AHCP.[31] The AHCP, originally developed as part of the Re-Engineered Discharge program, is a patient-centered discharge summary that contains sections on future appointments, medication reconciliation, notes on patient-provider communication, and exercise and nutrition advice. Please see Appendix A for an example of the AHCP portion of the SCP.

If appropriate, the patient and caregiver will also receive a study summary sheet with relevant study timepoints and login information for clarity and organization (Appendix AD). This document may be updated as the study progresses. In addition, the study nurse will provide training and educational materials on an as-needed basis on symptom management, psychosocial concerns and caring for medical procedures that patients have received during the hospitalization.

Depending on feasibility and patient preference, a study nurse will either speak to patients via a HIPAA-compliant video conference software (i.e. Zoom) or speak to her by phone after discharge or after their outpatient visit to evaluate symptoms and distress level, provide medication and skills training, coordinate care, and assess the caregiver's ability to provide care. Patients hospitalized or recently hospitalized with a bowel obstruction will have an automatic nutrition referral, scheduled to coincide with their next clinic visit; patients with a score ≥7 on the National Comprehensive Cancer Center Network (NCCN) distress thermometer (indicating significant distress) will be assessed by the BOLSTER nurse to identify the patient's source of distress and receive a referral to the appropriate services based on their emotional health (i.e., social work or resource specialist), per current clinical guidelines.[98] If appropriate, the nurse may provide patients and caregivers with supportive tools, such as a pillbox for medication organization.

5.34a Telehealth Visits

The research team may conduct visits via telehealth video conferencing with patients and caregivers. The study team may provide appropriate equipment (e.g., video cameras or iPads) for patients whose equipment is not sufficient for the videoconference platform and contact patients and caregivers to help set up and troubleshoot the platform.

We will use Zoom for Healthcare, a HIPAA compliant telehealth platform that creates real-time and easy to use video communication solutions for the health care industry and enables secure, virtual healthcare delivery. The platform allows physicians, patients, and specialists to connect remotely across hospitals, clinics, homes, and geographically isolated areas to raise levels of patient care and improve the delivery of treatment. This technology integrates to allow clinicians and patients to connect at specific dates and times, allowing enhanced control around who has access to appointments and when they take place.

If technical problems occur with the telehealth technology during a patient's scheduled virtual visit, then the BOLSTER nurse may switch to calling the patient and conducting the visit via telephone. The BOLSTER nurse should notify the research team to address the technical issue prior to the patient's next study visit. The study team may also contact patients and caregivers via email, phone, or in-person to assist with technology set-up and troubleshooting.

5.35 Subsequent contacts

Patients and caregivers will have a choice between: (1) phone, (2) in person (before or after a scheduled oncology clinic visit), or (3) telehealth video conferencing. While the outline of sessions is structured as above (Table 2), the content of each session will be individually tailored

to patients' needs and personal priorities (determined by patient, caregiver, and nurse). For example, while all patients will receive symptom management, one patient may want information about intravenous nutrition, while another may prioritize spiritual concerns. The BOLSTER study nurse will provide targeted and tailored patient and caregiver educational materials based on patient and caregiver preference during these instructional sessions.

5.36 Monitoring and maintaining fidelity

In order to monitor and maintain intervention fidelity, the debriefing interviews and study sessions conducted between the BOLSTER nurses and patients/caregivers will be recorded.[102] Patients and caregivers will be informed about the recording in the study in the consent form and during the informed consent process, and will be encouraged to ask any questions they may have about the recording. Patients and caregivers who do not consent to being recorded during the study encounters and debriefing interview will be excluded from participating in the study. Before each study visit and debriefing interview, patients and caregivers will be asked to verbally give permission for recording of the encounter, and verbal permission will be documented. All recordings of study sessions and debriefing interviews will be stored in secure locations in restricted-access, locked filing cabinets on Dana 10 and 11, and in password-protected folders on Partners servers. Recordings will be tied only to a study ID number, and the only document linking the patient's study ID to identifiable information will be in a restricted-access, password-protected file stored securely on Dana-Farber servers. We will transcribe recordings of debriefing interviews (and if resources permit, recordings of study visits) for further analysis using a DFCI-approved, HIPAA-compliant transcription vendor. All patient identifiable information will be removed when the recordings are transcribed. Recordings will be destroyed when analyses are complete.

5.37 Data collection

Study staff will conduct patient and caregiver assessments at baseline and 4 weeks (post-baseline). Every effort will be made to conduct the assessments in person at a patient's regularly scheduled clinic visit; however, if this is not possible, assessments will be administered over the phone, mail, or email. If patients pass away before the end of the study, caregivers will be asked to complete the Caregiver Post-Baseline Decedent Interview (Appendix AE) instead of the Caregiver Post-Baseline Interview. All study documents and assessments completed by patients or caregivers will be stored in password-protected documents in a secure folder on Partners servers and access will be restricted to study staff only. Hard copies of assessments will be stored in a locked filing cabinet which will only be accessible to study staff. Data linked to anonymous study ID numbers will be entered and stored in the Harvard REDCap servers, and only designated research staff will have access to the data. The only study document linking anonymous study IDs to patients' identifying information will be stored in a password-protected file on a secure, restricted-access folder on Dana-Farber servers which only study team members have access to.

5.37a Clinician debriefing interviews

At the end of the study, the study staff will complete a semi-structured debriefing interview with oncology clinicians in GYN and GI Oncology who were involved with the study, to obtain feedback on improving the study and clinicians' experiences (Appendix AB.) The interviews are brief and are estimated to take under 10 minutes. The interviews will be recorded with clinician permission in order to ensure study fidelity, and the procedures for protecting the

recordings from improper use and disclosure will be identical to those procedures for patient and caregiver recordings as detailed elsewhere in the protocol.

5.38 RMDY app, and patient education materials

Throughout their enrollment in the study, patients and caregivers enrolled in the BOLSTER arm will have access to the RMDY smartphone application, which contains patient education materials tailored to the individual patients' symptoms and medical tasks. Patients will be able to access study pages that contain multimedia patient education materials that are personalized for the patient or caregiver within their apps.

The RMDY app will contain information about how to manage medical procedures which patients with advanced ovarian cancer must often manage at home, including ostomies, venting gastric tubes, percutaneous nephrostomy tubes, and PleurX catheters. Working with a patient education specialist, the study team created instructional videos and pamphlets on managing the above medical procedures that are housed on the RMDY app. Instructional materials were developed and approved by a multidisciplinary team of clinical staff at Dana-Farber and Brigham and Women's Hospital, which ensures that the materials are both patient-centered and clinically accurate. The RMDY app also contains symptom advice from the symptom management toolkit developed by study consultants Dr. Barbara and Bill Given, and used successfully to manage symptoms in cancer patients in prior studies.[99] Materials that are provided to patients and caregivers during BOLSTER study sessions will also be available on the website or through the RMDY smartphone app, including clinically appropriate materials outside Table 2 that are tailored to patient and caregivers' individual needs and approved by clinical staff on the study (i.e. BOLSTER nurse or physicians on study.)

Additional Patient Education Materials (PREPARE for Your Care)

Given the high mortality rates we encountered in our first pre-pilot, we have added a module about advance care planning. During one of the BOLSTER study visits, the interventionist will ask participants about choosing a medical decision maker and introduce them to advanced directives using a free online toolkit called PREPARE for Your Care (https://prepareforyourcare.org). PREPARE for Your Care was developed by researchers at the University of California, San Francisco with the goal of making medical information easier for patients to understand so they can make informed medical decisions. The PREPARE website uses interactive modules and resources to help patients learn how to identify medical decision makers, talk to their doctors about the care that they want, and ensure that they receive goal-concordant medical care. Patients and caregivers will be able to access these resources at any time and the modules can be tailored to patient and caregiver needs as assessed by the BOLSTER study nurse.

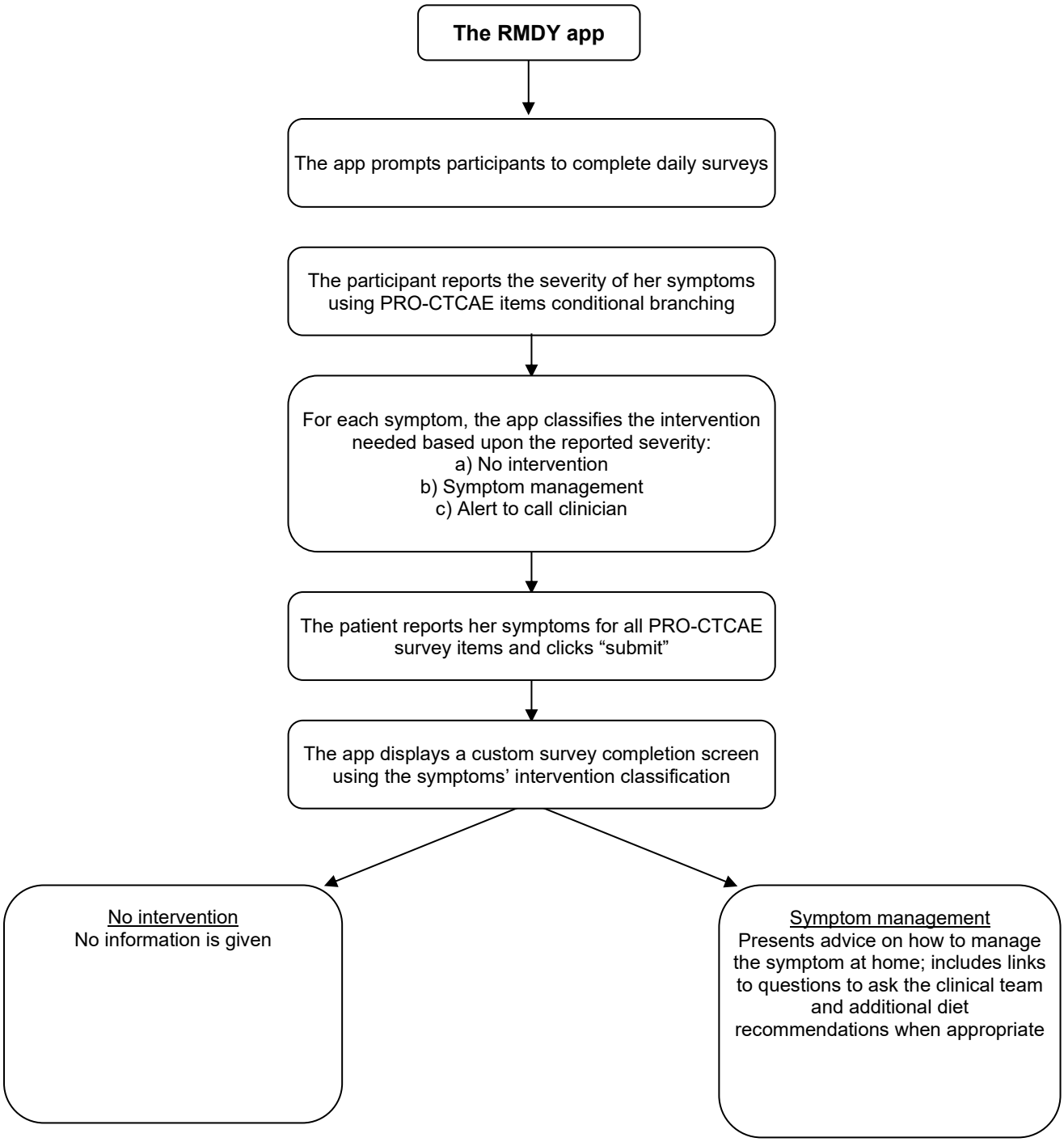
5.39 RMDY data collection

If patients have a smartphone or access to an iPad/tablet, they will have the opportunity to receive a smartphone application called RMDY and/or the SMART app, that collects information about their health and behaviors. In the first phase of the BOLSTER pre-pilot, we tested the use of a different smartphone-based research platform (Beiwe) in this patient population. Our goal was to use Beiwe to assess participant symptoms, provide nurse-led coaching, and offer tailored educational materials to participants. Unfortunately, we encountered some limitations in piloting this smartphone app: 1) the platform proved infeasible because it lacked a clinician dashboard and the ability to communicate directly with study participants by text 2) we were unable to send tailored educational materials through the platform 3) neither study participants nor the study intervention nurse felt it added value to the intervention.

As a result, we have created a new smartphone app in collaboration with RMDY Health, an established digital health provider, to provide the study nurse with a clinical dashboard to triage patients, allow the study nurse to text directly with participants, and provide easy access to more dynamic displays of educational materials. RMDY Health specializes in creating HIPAA-compliant, custom "white-label" digital health platforms catered to specific patient populations and for different clinical needs (i.e. interventions for medication management, weight loss, prevention, adherence, and lifestyle modification programs). The RMDY platform is comprised of three main components: 1) an app where patients can answer surveys and receive symptom management advice or information regarding managing medical tasks at home 2) a web-based clinician dashboard where staff can track patients' progress and symptoms, and communicate with patients, and 3) an administrative website where program content can be managed and generated. Through the RMDY app, the study nurse and research team will be able to better assess participant symptoms, provide nurse-led coaching, and offer tailored educational materials to participants. In addition, participants and the study nurse can communicate directly through the messaging feature of the smartphone app.

Please see the RMDY/SMART App Features and Screenshots Patient Guide (Appendix P) for descriptions of the app's features, including: log-in screen, symptom management advice, notifications, surveys, and general app navigation. Please note the RMDY app will only collect data from participants' survey responses. If a participant reports a severe symptom in their survey responses, they are notified to contact their clinician. Information regarding data collection and privacy measures for the RMDY/SMART app is located in RMDY/SMART App Data Privacy and Security (Appendix O).

**Table 3.** Symptom classification and response in the smartphone app intervention (patients only)



*5.4 Description of Intervention: Enhanced Discharge Planning (EDP)*

Patient-caregiver dyads randomized to the EDP arm will receive standard of care discharge planning, a single visit with the BOLSTER nurse, and educational relevant to their reason for hospitalization. Patients will be given the educational materials related to the complex care need that led to a hospitalization (e.g., patients hospitalized with a small bowel obstruction who received a gastric tube will receive the educational materials developed for gastric tubes). Patients and caregivers enrolled to the EDP arm will still complete surveys at baseline and post-baseline, but they will not receive any of the BOLSTER intervention components (e.g., smartphone app, additional telehealth visits with study nurse).

*5.5 Study Process*

Study procedures are outlined below:

5.51 Hospital or Outpatient Clinic Visit (Baseline Study Visit; Both arms):

- If a patient and caregiver agree to participate in the study, study staff will administer the baseline interview to patients and caregivers at a convenient time either remotely (via Zoom or phone) or prior to hospital discharge or during the patients' next scheduled outpatient clinic visit. Please note: if a caregiver is not present at the baseline study visit, they can be enrolled in the study remotely before the patient's first BOLSTER study visit. Additionally, if a patient cannot identify a caregiver or is uncomfortable asking them to participate, we will document the reason but still enroll interested participants who otherwise meet all other eligibility criteria.
- Study staff will also introduce the patient and caregiver (if present/participating) to the study technology (i.e., RMDY app, BOLSTER arm only) and assist them in the initial setup of the new technology.
- If patients opt to use the RMDY app, study staff will be available to help patients download, install, and run the RMDY app on their personal smartphones, as needed.
- (Estimated time to completion: 30 minutes)

5.52 Initial Telehealth Visit (BOLSTER arm only)

- The BOLSTER study nurse will contact the patient via telehealth or phone. Based on the patient and caregiver preference, caregiver attendance during BOLSTER study visits is optional.
- The study visit will include review of the patient's discharge medications; content training; skills training (if patient had a procedure in the hospital requiring outpatient medical management); and care coordination (appropriate referrals if necessary).
- The visit will be recorded to ensure study fidelity.
- Estimated time to completion: 1-2 hours

5.53 BOLSTER Educational Sessions 2-6 (BOLSTER arm only)

- The BOLSTER study nurse will conduct BOLSTER sessions 2-6 with patients and their caregivers (if the caregiver would like to join) via telehealth. BOLSTER sessions will be recorded to ensure protocol fidelity.
- Content of sessions 2-6 will be based on the content outlined above and tailored to patient and caregiver (if applicable) preferences. Patients and caregivers will be given copies of materials discussed in the sessions.

5.54 Post-Baseline Interview (Both arms)

- Study staff will administer the post-baseline interview to participants (both patients and caregivers) at approximately 4-weeks after their baseline visit. Every effort will be made to

administer these interviews in-person at a regularly scheduled clinic visit; however, if this is not possible, participants will complete interviews via video conference, email, or phone as close to the 4-week time interval as possible.

- Study staff will contact participants to complete their study surveys. After three unreturned voicemails, participants will not be contacted again for additional surveys.
- Estimated time to completion: 30 minutes

5.55 Debriefing Interview (Both arms)

- The study staff will conduct semi-structured debriefing interviews (Appendices R, S, and AB) with participants and clinicians following patients' and caregivers' completion of the 4-week post-baseline survey (either in-person, via video conference, or over the phone.). Debriefing interviews will be flexible as to incorporate questions raised by the pre-pilot study.
- Study staff will discuss the debriefing interviews to identify opportunities for protocol improvement.
- Estimated time to completion: 20 minutes

5.56 Health/Treatment Information (Both arms)

- The study staff will review patients' medical charts for healthcare utilization and treatment information (e.g. hospitalizations, ED visits, palliative care appointments, chemotherapy, comorbidities etc.) at the conclusion of the study.
- Patients and caregivers will complete the healthcare utilization tracker (Appendix Q) to report visits to their physicians, laboratory tests and radiographic imaging, and hospitalizations/ED visits during nurse visits.

5.57 Compensation (Both arms)

- Patients and caregivers participating in both study arms will each receive financial compensation for their completion of study interviews. Each participant will receive prepaid gift cards valued at $20 for the baseline interview and $30 for the 4-week post-baseline interview.

5.58 Note on study process

In developing BOLSTER and in the proposed work to finalize it, we use the well-supported adaptation framework, ADAPT-ITT.[100] Table 2 shows ADAPT-ITT steps and our corresponding prior work to develop and proposed research to refine BOLSTER for efficacy testing among ovarian cancer patients and their caregivers. We will leverage an 8-person Adaptation Workgroup of PFAC members, DFCI providers, and research team topical experts to evaluate the preliminary analysis of the study. We will present process evaluation and pilot test results to the Adaptation Workgroup and potentially additional patient advocates and clinicians. Based on their recommendations, the research team will produce a revised intervention draft, balancing adaptation with fidelity to the intervention and underlying theoretical framework. This will be presented to the Adaptation Workgroup again, resulting in a final version of the intervention manual, study procedures, and assessments for testing in the final analysis. The pre-test will also allow us to optimize training procedures for RCT study nurses.

5.59 Withdrawal of Subjects

If a participant is unable to complete the study intervention for any reason, the study staff may decide to remove the subject from the study. Subjects are notified during the informed consent process that they may contact the study team in writing to request withdrawal of their complete data from use. If a participant decides to withdraw from the study, research staff will

assure them that this will have no impact on their clinical care or relationship with their clinical oncology team.

*5.6 Adverse Reactions and Their Management*

5.61 Reporting Adverse or Unanticipated Events

Potential adverse events (AE) for this project are expected to be primarily non-medical in nature. Subjects may experience mild anxiety when answering interview questions about emotional issues or questions about coping challenges or difficulties related to discussing the subject matter. For the purpose of this study a Serious Adverse Event (SAE) is defined as an event that, as a direct result of the study, causes serious harm to the subject (e.g., hospitalization).

5.62 Anticipated Reactions & Reaction Management

Should participants become exceedingly upset, disoriented or fatigued or need to attend to matters of personal care during the interviews or study visits, study staff will ask the subject if they would like to take a break or reschedule the survey for another time. In the event that participants experience distress while completing interviews, we will follow standard procedures used in our behavioral health intervention studies for counseling and referral. The PI will be notified immediately, and participants will be provided with the pager numbers for both the study PI and the study psychiatrist included in the consent form. Dr. Ilana Braun, a DFCI psychiatrist, has agreed to serve as a psychiatrist on the study. Dr. Braun will evaluate any participants who are distressed for risk of imminent danger and refer them to appropriate services if they are needed.

**6.0 Statistical Analysis**

6.1 Primary Endpoints

*Primary Endpoints*

1) Feasibility of the BOLSTER intervention
2) Acceptability of the BOLSTER intervention

*Secondary Endpoints (exploratory to obtain descriptive statistics of scale scores and rates of missing data):*

1) Perceived efficacy
2) Additional patient outcomes, including: days at home (outside of hospital/facility), self-efficacy, quality of life, symptom burden, mental health, health care utilization, intensity of end-of-life care (hospitalization, ED visit, hospice), and overall survival (from study enrollment to death).
3) Additional caregiver outcomes, including: caregiver self-efficacy, health status, mental health, burden, and tasks.
4) Additional provider outcomes, including perceived impact on patient population.

*6.2 Sample Size and Statistical Power*

The primary objective of this study is to assess the feasibility and acceptability rates of the BOLSTER intervention. During the run-in phase, a convenience sample of up to 20 patient-caregiver dyads will be enrolled to the study. The table below summarizes precision with which we will be able to estimate confidence intervals for a variety of feasibility/acceptability rates.

| Feasibility/acceptability rate | Width of exact 90% CI |
|---|---|

| | |
|---|---|
| 50% | 40% |
| 60% | 39% |
| 70% | 37% |

For the RCT, enrolled participants will be randomized 1:1 to one of the two study arms (BOLSTER vs. enhanced discharge planning.) Randomization will use a 1:1 ratio using a computer-generated random allocation sequence with blocks of 4 in order to maintain balance between study arms over time. Study staff will generate group assignments in sequentially numbered and sealed opaque envelopes.

| Arm | Patients | Caregivers | Total participants (patients + CGs) |
|---|---|---|---|
| Arm 1: BOLSTER | 30 | 30 | 60 |
| Arm 2: EDP | 30 | 30 | 60 |
| Total | 60 | 60 | 120 |

*6.4 Analysis Plan*

Due to the limited sample size, statistical analysis will be descriptive in nature and will assess feasibility, acceptability, and perceived efficacy, as well as estimate outcomes parameters.

Feasibility: Feasibility will be defined as 1) ≥50% enrollment among eligible participants (based upon prior RCTs),[63] 2) ≥70% fidelity to the intervention by the study nurse measured by: a) whether the BOLSTER encounters followed the planned intervention sessions (checklist of content in Table 2) and b) an analysis by the principle investigator of 20% of recorded BOLSTER encounters for key content and overall quality, consistent with best practice and recommendations from the NIH Behavior Change Consortium.[101] We will also record eligibility, approach, interest, enrollment, reasons for non-participation, and attrition rates.

Acceptability: Acceptability will be defined as: ≥70% of participants "agree" or "strongly agree" that they "would recommend BOLSTER to other patients with cancer and their family members."

Perceived efficacy, measured with a 6-item questionnaire[64] administered to patients, caregivers, and oncology clinicians at the 4-week assessment, and additional patient/caregiver outcomes will be summarized using descriptive statistics (e.g. means, medians, standard deviations, and ranges for continuous variables; and proportions for categorical variables).

Intervention experience and refinement: Study personnel will also perform a qualitative analysis of semi-structured debriefing interviews with patients, caregivers, and providers to evaluate their experiences with the intervention for the purposes of further intervention refinement. For this analysis, study team members and an external collaborator from the University of Alabama will conduct a thematic analysis of the deidentified transcripts. A data use agreement will be in place prior to the transfer of any data to this external collaborator. Study members will first perform open coding and memoing to evaluate the transcripts, entering data into MAXQDA, a software package for qualitative data analysis. During the deductive phase of coding, transcripts will be independently coded by study members, and team members will meet to identify themes, summarize the data, and compare and discuss discrepancies with the goal of identifying emergent themes within and across participant types.[102, 103]

Study data will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Dana-Farber Cancer Institute.[104]

*6.5 Handling of Missing Data*

For both primary and secondary quality-of-life analyses, we will exclude from our analyses any patients and caregivers who do not complete the 4-week post-baseline questionnaires. If >10% of participants have missing data from the 4-week survey, we will perform sensitivity imputation analyses including: 1) no observations carried forward, 2) minimum observation values carried forward, 3) average observation values carried forward, and 4) last observation carried forward.

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## 8.0 Appendices

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