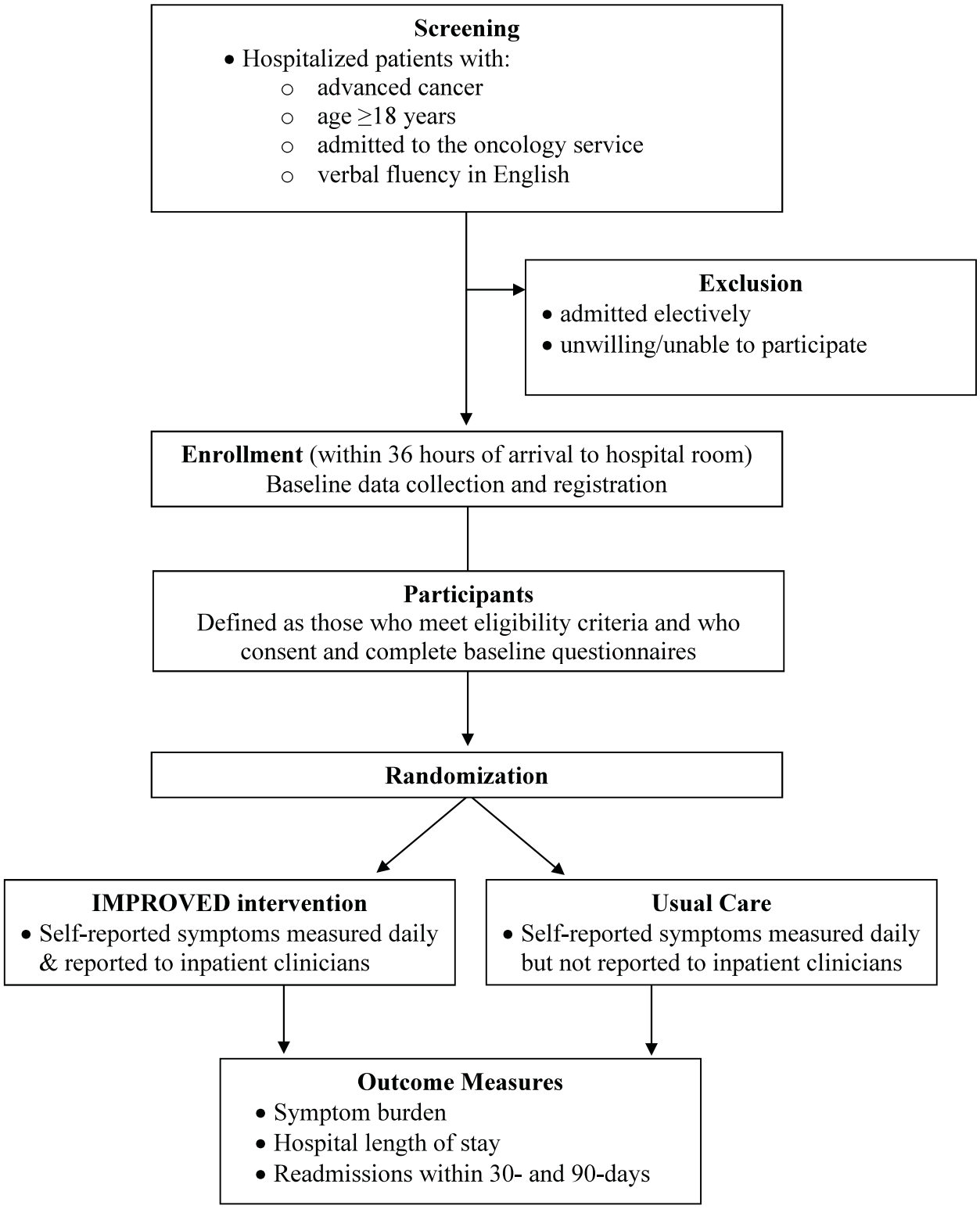
Section 1: Protocol Schema



Section 2: Body of Protocol

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1.0 INTRODUCTION

1.1 Overview.

This study addresses the challenge of symptom management for hospitalized patients with cancer.[1-9] Patients with cancer may experience a considerable symptom burden, often requiring hospitalizations for symptom management.[1-7] Patients' symptoms may also contribute to prolonged hospital stays and readmissions.[8,9] Notably, patients' symptoms represent a modifiable risk factor that, if properly managed, can improve care delivery and decrease unnecessary hospitalizations. Therefore, we will test an electronic symptom monitoring intervention, "Improving Management of Patient-Reported Outcomes Via Electronic Data (IMPROVED)," versus usual care in hospitalized patients with cancer.

The goals of the proposed study are: (1) to determine the effect of IMPROVED on symptom burden in hospitalized patients with advanced cancer; and (2) to assess the efficacy of IMPROVED on hospital length of stay and readmissions. Notably, IMPROVED consists of patients self-reporting their symptom burden using validated symptom assessment tools with delivery of their symptom burden to the clinicians (nurses, nurse practitioners [NPs], and physicians) caring for them each day of their admission. We will conduct a randomized controlled trial (RCT) (n=450) to determine the effect of IMPROVED versus usual care in hospitalized patients with cancer. By integrating symptom monitoring into the inpatient care for patients with cancer, we propose a novel intervention to improve these patients' symptom management and decrease their use of health care services.

1.2 Background and Rationale.

Patients with incurable cancer experience a substantial symptom burden.

Patients with incurable cancer often report considerable physical and psychological symptoms.[1-3] Symptoms such as pain, dyspnea, fatigue, and nausea lead to poor QOL and patients with these symptoms are more likely to report high rates of depression and anxiety, particularly later in the disease trajectory.[10] While much of the existing literature on symptom prevalence and severity reflects data from studies involving ambulatory cancer patients, little work has focused on the symptoms of patients with cancer in the inpatient setting.[3,11-13] Therefore, a critical need exists for studies to address the symptom burden of hospitalized patients with cancer.

Patients' symptom burden likely contributes to use of health care services.

Despite patients' preferences to avoid hospital admissions, patients with cancer often require hospitalizations for pain, fever, fatigue and nausea.[4-7] Additionally, patients' symptoms may impact their hospital length of stay and risk for readmissions.[8,9] Unfortunately, over half of incurable cancer patients are admitted to the hospital at least once during their last month of life, and nearly 10% experience a hospital readmission during this time.[14-21] Importantly, patients with incurable cancer often prefer to avoid time in the hospital, underscoring the need for efforts targeting modifiable risk factors (e.g. patients' symptoms) that contribute to prolonged hospital length of stay and readmissions.[14-17,22]

Hospital admissions are not only inconsistent with patients' preferences, but incur significant costs.[23] Rising health care costs represent a major challenge in the United States, affecting both patients and providers.[24,25] Notably, hospitalizations represent the largest component of health care spending for patients with cancer.[26] Both long hospital stays and readmissions cost the health system billions of dollars annually.[27-29] Thus, we need to develop interventions that align care with patient preferences and strive to decrease excessive use of health care services.

Patients' symptoms represent a modifiable risk factor that, if properly addressed, may both improve quality of care and decrease use of health care services.
While research suggests that patients' symptoms contribute to their need for hospital-level care, most of the efforts to address symptoms in patients with cancer are in the outpatient setting.[4-8,30-33] Importantly, these studies suggest that targeted interventions aimed at improving symptom management can improve patient outcomes.[32-34] A randomized trial of an intervention in which patients in the outpatient setting completed electronic self-reports of their symptoms, received tailored education, and had their symptoms delivered to their clinicians versus usual care demonstrated better symptom control for those who received the intervention.[33] More recently, a web-based patient-reported symptom monitoring intervention with automated reporting to clinicians for severe or worsening symptoms was compared to usual care in 766 patients.[32] Notably, patients who received the intervention reported better QOL and had fewer hospitalizations and emergency room visits. While these studies in the outpatient setting provide compelling evidence supporting the benefits of monitoring patients' symptoms, efforts to assess hospitalized cancer patients' symptom burden and deliver this data to their clinicians are lacking.

Enrolling hospitalized patients with advanced cancer into a symptom monitoring intervention is feasible. We recently conducted a pilot study of IMPROVED versus usual care on a single oncology ward at MGH. From 10/26/16 to 6/18/17, we enrolled 150 of 185 patients approached (81.1% enrollment rate). Participants completed nearly 90% of potential symptom reports (753 of 842 total hospital days). We found that clinicians discussed the majority of symptom reports (60.4%) and immediately developed a plan during rounds to address their patients' symptoms over one-fifth of the time (20.8%). In addition, for this pilot study, we investigated the proportion of days that patients experienced improvements in their symptom burden. For this outcome, we determined the number of days patients reported that an improvement in their symptom burden and divided this by the number of days that they provided symptom reports. We found that the proportion of days with improvements in symptom burden (assessed by the ESAS physical composite score, which consists of symptoms of pain, fatigue, drowsiness, nausea, lack of appetite, shortness of breath, constipation, diarrhea[35]) within each group (intervention and control) was normally distributed with a mean difference of 0.091 and standard deviation 0.28.

We seek to conduct a randomized trial of an electronic symptom monitoring intervention, "Improving Management of Patient-Reported Outcomes Via Electronic Data (IMPROVED)." We will conduct a randomized trial (n=450) of IMPROVED versus usual care in hospitalized patients with advanced cancer. Specifically, IMPROVED consists of the following: (1) patients daily self-report their symptom burden using validated symptom assessment tools; and (2) their clinicians (nurses, NPs, and physicians) receive that information at morning rounds each day. Notably, the clinicians will receive reports detailing their patients' symptoms for each day of the hospital admission, including a graphic depiction of their patients' daily symptom trajectory, as well as symptoms that worsen by ≥2 points during the admission. By assessing hospitalized cancer patients' symptom burden and delivering this information to their clinicians, IMPROVED has the potential to enhance patient outcomes and prevent excess use of health care services.

2.0 OBJECTIVES

<u>Aim 1</u>: To determine the effect of IMPROVED on symptom burden in hospitalized patients with advanced cancer.

Hypothesis: Participants assigned to IMPROVED will report significantly decreased symptom severity over the course of hospitalization compared with those assigned to usual care.

Aim 2: To assess the efficacy of IMPROVED on hospital length of stay and readmissions in hospitalized patients with advanced cancer.

Hypothesis: Participants assigned to IMPROVED will have a shorter length of stay and lower risk for readmissions compared with those assigned to usual care.

Exploratory Objective 1: To identify potential moderators of the effect of IMPROVED on symptom burden and health care utilization (e.g. hospital length of stay and readmissions).

Exploratory Objective 2: To explore whether improvements in symptom burden mediate the benefit of IMPROVED on health care utilization (e.g. hospital length of stay and readmissions).

Exploratory Objective 3: To explore the effect of IMPROVED on patient satisfaction with care.

3.0 RESEARCH SUBJECT SELECTION

3.1 Study Subject Selection:

We will recruit 450 patients with advanced cancer, hospitalized at Massachusetts General Hospital (MGH).

Patient eligibility criteria:

Patient Inclusion Criteria	Patient Exclusion Criteria
1. Age 18 or older	1. Unwilling or unable to participate in the study
2. Diagnosed with advanced cancer (defined as receiving treatment with palliative intent as per chemotherapy order entry designation, oncology clinic notes, and/or trial consent forms, or not receiving chemotherapy but followed for incurable disease as per oncology clinic notes)	2. Admitted electively
3. Admitted to the oncology service at Massachusetts General Hospital	3. Participated during a previous admission
4. Verbal fluency in English	

We focused on patients with advanced cancers, as they experience high symptom burden, often resulting in hospitalizations. We limited our study to those with verbal fluency in English, as we do not have the funding or the staff availability to translate the study for non-English speaking patients. We will exclude patients who are readmitted who previously participated and therefore we will not allow patients to participate more than once.

4.0 RESEARCH SUBJECT ENTRY

4.1 Study Research Subject Entry

Patient Recruitment. We will recruit patients hospitalized at MGH who are admitted to the oncology service. Trained study staff will identify all patients with a diagnosis of cancer admitted to the inpatient oncology service through the electronic medical record by querying the inpatient oncology patient census on a daily basis. To facilitate identification of potential participants and confirmation of

eligibility, study staff will review minimum necessary medical record data, including patients' electronic medical records, to collect information regarding their age, cancer diagnosis and treatment. The oncology team will be given a study handout [Appendix D] providing research staff information and a brief overview of the study being conducted. After familiarizing the oncology team with the study, we will ask the them if a patient would be suitable for the study prior to approaching potential study participants. Trained study staff will approach eligible patients within 36 hours of their admission. We will exclude any patient whose reason for admission is chemotherapy administration, as these patients would be expected to have a significantly different symptom profile. However, patients continuing on their outpatient regimen of oral chemotherapy (including cytotoxic chemotherapy and tyrosine kinase inhibitors) will be included. Additionally, we will exclude patients admitted electively for other reasons, including procedures and diagnostic work-up. We will exclude patients who are readmitted who previously participated and therefore we will not allow patients to participate more than once. Study staff will meet with eligible patients, introduce them to the study, and obtain consent in a private setting.

Patient Enrollment. After identifying patients for study participation, study staff will meet privately with the potential study participant in their hospital room. Trained study staff will obtain informed consent from eligible patients using a written consent form. The consent form will contain an introduction to the study, its purpose, rights as a patient, and study contact information. The consent will also contain text confirming the voluntary nature of the study, that the patients can refuse to answer any question, that they can withdraw from the study at any time, and that participation in the study is in no way related to their medical care. The consent form will also state that we will have access to their medical record as part of the research study. If the patient consents to enrollment in the study, trained study staff will provide baseline study measures at that time.

4.2 REGISTRATION AND RANDOMIZATION PROCEDURES

Randomization: Due to the need for randomization on weekend days, the research team will perform randomization procedures using computer generated randomization schema and assignments will be kept in concealed envelopes. We will complete the following registration procedures:
Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC SOP REGIST-101. When required by REGIST-101, registration must occur prior to the initiation of protocol-specific procedures or assessments.
Registration requires a signed informed consent document and a completed eligibility checklist according to DF/HCC SOP REGIST-104.
After randomization the research staff will inform the patients by phone or in person of their study arm assignment.

5.0 STUDY DESIGN & METHODS

5.1 Study Design.

The proposed project is a prospective randomized study evaluating the efficacy of a symptom monitoring intervention (IMPROVED) in hospitalized patients with cancer, randomized in a 1:1 fashion with stratification by cancer type.

5.2 Data Collection.

After patients have provided written, informed consent, we will ask them to complete the baseline study measures. We estimate that it will take patients under 5 minutes to complete the questionnaires. We will ask patients to be frank during the assessment, and will remind them that they may decline to answer any questions they choose. If any patient refuses or is unable to complete the symptom assessment on the tablet/computer, we will permit them to use paper versions. Patients who

consent for the study, but do not complete baseline questionnaires will not be registered or randomized and therefore will not count towards accrual numbers and will be replaced by eligible participants who consent and complete baseline questionnaires. We will collect patient-reported measures each day of patients' hospital admission.

5.3 Selection of study instruments.

Baseline sociodemographic factors (patient self-report) [Appendix A]:
To describe the study sample, we will ask participants to self-report their sociodemographic factors (e.g. race, ethnicity, household income, education, health insurance status, and marital status).

Daily Patient-Reported Measures [Appendix B]

- **Symptoms:** We will use the self-administered Edmonton Symptom Assessment System-revised (ESAS-r) to measure symptoms, which has been previously validated in patients with advanced cancer.[35,36] The ESAS-r consists of ten items assessing pain, fatigue, drowsiness, nausea, anorexia, dyspnea, depression, anxiety, well-being, and a free-response item. Since constipation, diarrhea and insomnia are highly prevalent symptoms in advanced cancer,[37-40] we will include them as separate items in place of the free-response item. The ten items are scored on a scale of 0-10 (0 reflecting no reported presence of the symptom and 10 reflecting the worst possible severity of the symptom). We will instruct patients that items are to be rated based on the previous 24-hour period. We will compute composite ESAS physical, ESAS modifiable, and ESAS total symptom variables that include summated scores of patients' physical (pain, fatigue, drowsiness, nausea, appetite, dyspnea, constipation, diarrhea), modifiable (pain, drowsiness, nausea, shortness of dyspnea, depression, anxiety, constipation, diarrhea), and total symptoms (pain, fatigue, drowsiness, nausea, appetite, dyspnea, depression, anxiety, wellbeing, constipation, diarrhea). These ESAS-composite symptom scores have been utilized previously in the oncology setting.[35,41] To assess depression and anxiety symptoms in study patients, we will also use the PHQ-4.[42,43] The PHQ-4 is a valid, brief tool for detecting both anxiety and depressive symptoms. Although pain is included as a standard symptom assessed in hospital settings, MGH does not currently utilize the entire ESAS-r or the PHQ-4 as part of usual care.
- **Satisfaction with care:** In order to assess patient satisfaction with care, we will use these items from the previously validated FAMCARE-Patient (FAMCARE-P) scale[44,45]: "How satisfied are you with speed with which symptoms are treated?" "How satisfied are you with coordination of care?" The response scoring is on a 5-item Likert scale (very satisfied, satisfied, undecided, dissatisfied, and very dissatisfied).

Electronic medical record review:

- **Health care utilization**: We will review patients' electronic medical records (every 3 months until patient death) to obtain information about emergency department visits and hospitalizations.
- **Clinical factors**: We will also collect patients' clinical factors, such as their cancer history, treatment, comorbid conditions, medications, age and sex from their medical records.

The following table depicts the data to be collected and time points for the proposed data collection.

Data Collection	Baseline (within 12 hours of enrollment)	Daily
Patient Self-Report		
Sociodemographic factors	X	
Symptoms	X	X

5.3 Description of Intervention

Intervention: Patients randomized to IMPROVED will self-report their symptoms each day using a tablet computer. If any patient refuses or is unable to complete the symptom assessment on the computer, we will permit them to use paper versions. At morning rounds each day, the clinical team (nurses, NPs, and physicians) will view reports detailing their patients' symptom burden. Patients randomized to IMPROVED will have their symptoms presented to their inpatient oncology team, but we will not provide guidance about what actions to take in response to patients' symptoms. Patients randomized to IMPROVED will have their symptoms presented to the clinical team via both a print-out version of the symptom reports and a computer-based projection screen as they are being discussed. Trained study staff will insure that the symptom reports reach the clinical team before rounds each day. These detailed reports will contain patients' numeric symptom scores, as well as an alert whenever any specific symptom worsens by ≥2 points or reaches an absolute score ≥4. Additionally, we will provide clinicians with a graphic depiction of their patients' daily symptom trajectory for that admission.

Usual Care: Participants receiving usual care will also self-report their symptoms each day using tablet computers. However, these patients' clinicians will not receive their symptom reports. To ensure study interactions with the participant do not affect study results, we will train the study staff who obtain the daily symptom assessments to not comment on the patients' symptoms, and to explain to patients that they will need to report their symptoms to their clinicians as they usually would, at their own discretion.

5.4 Description of Study Process.

We will collect information from patients at baseline (within 12 hours of patient enrollment) and daily throughout their hospital admission.

5.43 Special Concerns.

The proposed study seeks to conduct a symptom monitoring intervention among individuals with cancer who are hospitalized and who may have multiple medical and psychosocial stressors that can occur on a daily basis. Efforts will be made to schedule study visits at times that are convenient to the participant, so as to reduce any burden.

Breach of confidentiality is a concern in all studies with human subjects. Safeguards will be put in place to ensure that participant information is kept private and confidential. All data will be stored in locked cabinets located in the PI's office as well as password-protected computer files, accessible only to trained study staff. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept in a separate file under lock and key.

The MGH research team will meet on weekly basis throughout the study period and will discuss any issues or concerns that may arise regarding the study procedures. Should the protocol require modifications or amendments based on these meetings, the overall Principal Investigator will make the necessary changes and submit them to the DF/HCC IRB for approval.

5.44 Compensation.

Study participants and clinicians will not receive compensation for participating in this study or for completing questionnaires.

5.5 Adverse Reactions and Their Management.

5.51 Reporting Adverse or Unanticipated Events

We do not anticipate any adverse events related to participation in this study. Should patients or clinicians report any physical or psychological complications which are felt by either the patient or the

clinicians to be study-related this will be reported immediately to the IRB via standard adverse event reporting.

5.52 Anticipated Reactions

It is unlikely that participants will be at any risk for physical harm as a result of study participation. Participants may find some questionnaire items to be emotionally upsetting, and may experience some fatigue from completing assessments. Subjects may choose to discontinue their participation in the study at any time if they feel uncomfortable.

To safeguard participant information and confidentiality, all data will be stored in locked cabinets as well as password-protected computer files, accessible only to trained study staff. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept in a separate file under lock and key.

Patient data will be collected at each institution using REDCap. Participants will be identified on study forms and in the REDCap database by participant number only. To further prevent the loss of confidentiality, all electronic information stored on the main database within the MGH is password protected, and is protected by anti-virus software. Only study staff will have access to the study data on Shared file areas.

5.53 Reaction Management

If distressed patients request services for anxiety or depression, we will inform the inpatient team. The inpatient social worker for the oncology service will also be available to offer any further counseling, if needed.

6.0 STATISTICAL ANALYSIS

6.1 Study Endpoints

Primary endpoint: The primary endpoint is comparison of the average proportion of days with improved symptoms between study arms. For this outcome, we will determine the number of days patients reported an improvement in their symptom burden (symptom score decreased by ≥ 1 point) and divide this by the number of days that they provided symptom reports.

Secondary endpoints:

1) Compare the average proportion of days with worsened symptoms between study arms.
2) Compare change in patients' symptom scores from baseline to discharge (as per each ESAS symptom burden score measured continuously, the ESAS physical composite score, ESAS modifiable composite score, ESAS total symptom burden score, and the PHQ-4 scores) between study arms.
3) Compare hospital length of stay (measured continuously as days admitted to the hospital) between study arms.
4) Compare readmissions within 30 and 90 days of prior hospital discharge between study arms.
5) Explore potential moderators (e.g. sociodemographic and clinical factors, baseline symptom burden, overall length of stay) of the effect of IMPROVED on symptom burden and health care utilization (e.g. hospital length of stay and readmissions).
6) Explore whether improvements in symptom burden mediates the benefit of the intervention on health care utilization (e.g. hospital length of stay and readmissions).
7) Explore the effect of IMPROVED on patient satisfaction with care (e.g. FAMCARE survey items).

6.2 Sample Size

The primary outcome of our study is a comparison of the average proportion of days with improved symptoms between study arms. We chose this as our primary outcome because we found this to be sensitive to change in our pilot study, and this method for assessing change in symptom monitoring interventions has been employed in other studies.[46-48] In our pilot study, the proportion of days with improvements in symptom burden (ESAS physical symptoms) within each subject group was normally distributed with a mean difference of 0.091 (average proportion of days with improved symptoms in the intervention arm=0.683; average proportion of days with improved symptoms in the control arm=0.592) and standard deviation 0.28. If the true difference in the experimental and control means is 0.091, we will need to study 150 experimental subjects and 150 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. Based on our prior work, we estimate the rate of attrition to be 5%, and we will increase our sample size to 160 patients per arm to ensure adequate power. We plan to have a final evaluable sample of 320 patients who have two or more symptom reports completed. Thus, we plan to enroll 450 patients to ensure we have 320 patients who have two or more symptom reports completed. In our pilot study, which occurred on a single oncology ward at MGH, we enrolled approximately 20 patients per month. By including all patients admitted to the oncology service at MGH, we expect over 35 patients will meet eligibility per month. Thus, we are confident that we can feasibly enroll 450 patients to the proposed study within two years.

6.3 Analysis Plan

Aim 1: To determine the effect of IMPROVED on symptom burden in hospitalized patients with advanced cancer.

We will analyze data from the RCT on an intent-to-treat basis. We will use data obtained via patient self-report and electronic medical record review to describe baseline sample characteristics. We will estimate the means, standard deviations (SDs), 95% CIs, medians and interquartile ranges for all continuous variables (e.g. symptom severity and length of stay).

We will first determine the proportion of days for each patient where they experienced symptom improvements (symptom score decreased by ≥ 1 point) and the proportion of days for each patient where they experienced symptom worsening (symptom score increased by ≥ 1 point). We will then compare differences in these outcomes between study arms using multiple linear regression, adjusted for baseline symptom burden and potential confounders that are imbalanced between groups (e.g. age and comorbidity). In addition, we will assess the significance of between-group differences for all symptoms and composite symptom burdens scores using multiple linear regression, ANCOVA and the two-sample t-test.

Aim 2: To assess the efficacy of IMPROVED on hospital length of stay and readmissions in hospitalized patients with advanced cancer.

We will assess the significance of between-group differences regarding health care utilization (length of stay and readmissions). We will compare mean differences in length of stay between study arms using t-tests and multiple linear regression, adjusted for potential confounders that are imbalanced between groups (e.g. age and comorbidity). While length of stay is not normally distributed, based on a sample size of 160 per group, the means will have a normal distribution although the variables themselves are not normally distributed (central limit theorem). We will also perform the Wilcoxon rank sum test to compare length of stay between the two groups and compare our results to those obtained using t-tests. Additionally, we will estimate 30- and 90-day readmission rates with CIs and compare

time to readmission within 30- and 90-days across study arms using Cox regression adjusting for potential confounders that are imbalanced between the groups.

***Exploratory Objective 1*: To identify potential moderators of the effect of IMPROVED on symptom burden and health care utilization (e.g. hospital length of stay and readmissions).**

To identify potential moderators (e.g. patients' sociodemographic factors, clinical characteristics, and patient-reported measures) of the effect of IMPROVED on continuous outcomes (e.g. symptom severity, hospital length of stay), we will examine the interaction between the moderator of interest and group assignment using linear regression models adjusting for baseline measures and potential confounders that are imbalanced between groups.

To identify potential moderators (e.g. patients' sociodemographic factors, clinical characteristics, and patient-reported measures) of the effect of IMPROVED on censored outcomes (e.g. time to readmission within 30- and 90-days), we will examine the interaction between the moderator of interest and group assignment using Cox regression models adjusting for baseline measures and potential confounders that are imbalanced between groups.

To identify potential moderators (e.g. patients' sociodemographic factors, clinical characteristics, and patient-reported measures) of the effect of IMPROVED on categorical outcomes (e.g. presence of moderate/severe symptoms), we will examine the interaction between the moderator of interest and group assignment using logistic regression models adjusting for baseline measures and potential confounders that are imbalanced between groups.

***Exploratory Objective 2*: To explore whether improvements in symptom burden mediate the benefit of IMPROVED on health care utilization (e.g. hospital length of stay and readmissions).**

We will conduct bootstrapped tests of mediation to determine whether group differences in health care utilization (e.g. hospital length of stay and readmissions) are mediated by improved symptom burden.

***Exploratory Objective 3*: To explore the effect of IMPROVED on patient satisfaction with care.**

We will also explore the effect of IMPROVED on patient satisfaction with the speed with which symptoms are treated and coordination of care (using FAMCARE survey items). We will compare differences in these outcomes between study arms using multiple linear regression.

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