

Vanderbilt Personalized Palliative Care

The Creation of Models for Palliative Assessments to Support Severe Illness (COMPASS) investigation: testing early and ongoing implementation of palliative care for incurable non-malignant diseases

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1.0 Background

Terminology and General Benefits

Palliative care (PC) is specialized medical care focused on providing patients with relief from the symptoms, pain, and stress of serious or life-limiting illness, regardless of diagnosis, by anticipating, preventing, and treating suffering. The goal is to improve quality of life for both the patient and the patient's family. Palliative care is appropriate at any age and at any stage in a serious illness. It is intended to be provided together with curative treatment, and includes intensive focus on symptom and pain management, psychosocial support, and assistance in advance care planning.¹

In some studies, palliative care integration has been shown to improve patient quality of life (QOL), sleep quality, and spiritual well-being; reduce depressive symptoms, healthcare costs and utilization, and aggressive interventions at the end of life; increase participation in advance care directives, and even increase lifespan.^{2,3} A recent phase 3 randomized controlled PC trial in lung cancer patients showed that although fewer patients in the early palliative care intervention arm received aggressive end-of-life care (33% vs 54%), median survival was longer compared to patients who received standard of care alone (11.6 months vs 8.9 months).² Greater use of palliative care may also decrease end of life care costs in Medicare patients, particularly important to the national health care system⁴ as 30% of Medicare resources are expended on the 5% of beneficiaries who die each year.⁵ In an analysis of more than 5000 patients from 8 hospitals, PC involvement was associated with a cost savings of \$1,696 per admission for patients who survived hospitalization and \$4,908 per admission for patients who did not survive hospitalization.⁵ However, there are a paucity of PC efficacy data from randomized controlled trials.

A meta-analysis of palliative care trials found 22 randomized controlled studies with 14 of these interventions being of palliative intent and only 8 utilizing a specialized palliative care intervention. Overall, participants receiving palliative care showed improvements in QOL (5 out of the 7 trials which examined QOL as a primary outcome), increased satisfaction with care (7 out of the 10 trials which examined patient and caregiver satisfaction with care), and improved *coping* with physical symptoms (two trials that examined perceived symptom distress), with mixed findings in physical and psychological symptom improvement. These mixed findings may be due to methodological issues including small sample sizes, contamination of the control group, recruitment bias, and inadequate statistical power.⁶ There is a need for methodologically sound, randomized controlled trials examining specialized PC interventions, and in particular, there is a need to explore benefits of PC in patient populations with non-malignant, high mortality disease states such as cirrhosis, congestive heart failure, and emphysema.

Palliative Care for Hepatic Patients

Chronic liver disease and cirrhosis is the 12th leading cause of death in the United States.⁷ Patients with End Stage Liver Disease (ESLD), a progressive illness synonymous with decompensated cirrhosis, advanced liver disease, and liver failure⁸, face many complications and a variety of health symptoms including the development of ascites, variceal hemorrhage, hepatic encephalopathy, hepatocellular carcinoma, cognitive decline, fatigue, pruritus, malnutrition, pain, and renal impairment.^{9,10} Many cirrhotic patients face financial, emotional, and social problems relating to the stigma of liver disease,¹⁰ and QOL is often decreased due to physical and psychological symptoms.⁸ For patients with decompensated cirrhosis, liver transplantation is the only cure. 15,027 candidates were registered on the waiting list for liver transplant in the US as of December 31, 2013.¹¹ As hope for a transplant and cure is foremost in the mind of these patients, it is not surprising that palliative care opportunities may be overlooked. However, many patients are not candidates for transplantation, and those on the waitlist may never undergo transplantation or may have considerable wait time. In 2013 1,767 patients died while on the waiting list and 1,223 patients were removed due to being too ill to undergo transplant. Of the 5,921 patients who received a liver

transplant, 53.2% were on the waitlist for 3 months or longer and 21.1% for more than 1 year prior to transplant.¹¹ Even for those who undergo successful transplant, the symptom burden of cirrhosis warrants intervention.

In one retrospective study of 102 adult patients at a university hospital site who were either removed from the waiting list for liver transplant or were declined transplant, patients experienced significant symptoms including pain (65% of patients), nausea (58%), lack of appetite (49%), dyspnea (48%), anxiety (36%), and depression (10%). However, only 11% of patients were referred for palliative care, and only 28% had do-not-resuscitate (DNR) status in their chart.¹² Palliative care is often disregarded until hope of liver transplantation is lost, which may be in the last week or two of life. We hypothesize that offering both PC and disease-directed therapies simultaneously at the time of presentation to an inpatient hepatology service will delay or reduce hospital readmissions while maintaining or improving quantitative and qualitative measures of quality of life and end of life care.¹³

There is potential benefit to introducing palliative care earlier in the course of illness for patients with chronic liver disease. For some patients with cirrhosis, palliative care has been shown to improve physical and emotional symptoms. In a recent observational study, Baumann et al found that for patients with ESLD on the waiting list for liver transplant, an early PC intervention counteracted the progression of worsening symptoms and significantly improved pruritus, appetite, anxiety, depression, fatigue, and well-being.¹⁴

In addition to quality of life, hospital utilization for hepatic patients is of particular concern. Hospital admission rates and the economic burden of treating these patients have continued to rise.¹⁵ In a study of 402 patients with decompensated cirrhosis who were admitted to hospital, 78% of patients had at least one readmission, with 14% of these patients readmitted within 1 week after discharge at a mean cost of \$25,898 per readmission. Another 37% of these patients were readmitted within 1 month after discharge at a mean cost of \$20,581 per admission. Of these, 22% were determined to be possibly preventable admissions.¹⁶

Palliative Care interventions have been shown to reduce hospital utilization for some liver transplant service patients. Lamba et al conducted a prospective observational study comparing outcomes before and after structured palliative care program integration in the surgical intensive care unit for liver transplant service patients. After program implementation, goals of care discussions during physician rounds increased significantly (from 2% to 39% of patient-days), and the mean length of stay in the SICU decreased by 3 days for patients who died and by 4 days for patients who survived. Although mortality rates were similar pre- and post- program implementation, DNR status significantly increased in those who died from 52% pre-implementation to 81% post-implementation. DNR status was also instituted earlier, decreasing from 38 days after admission to 19 days after admission.¹⁷ Palliative care, once understood and integrated, has the potential to improve clinical outcomes, improve patient's quality of life, and reduce cost. But *when* to integrate the services, *how* to integrate services, and *for which* patients, is not well established.

Resistance and Conceptual Barriers

Even with its reported benefits, palliative care remains misunderstood and underutilized. Seventy percent of Americans describe themselves as “not at all knowledgeable” about palliative care.¹⁸ A majority of barriers to PC reported by patients were described either as a lack of referral by the doctor or lack of awareness in general about options related to palliative care. Data from a national public opinion survey of 800 adults commissioned by the Center to Advance Palliative Care showed 70% of people surveyed were totally unfamiliar with the term “palliative care” and the availability of the types of services it provides.¹⁹ When compared to palliative care, ‘supportive care’ has been associated with better understanding, more favorable impressions, and higher future perceived need.¹ In addition to the lack of understanding among patients, many healthcare professionals consider palliative care to be synonymous with end-of-life care. Approximately half of MDs in one study believed the purpose of PC is inconsistent

with cure and only appropriate when cure is no longer the goal.²⁰ This is unfortunate, given palliative care has been shown to prolong survival³ and decrease distress.²¹

Initiation of palliative care discussions with patients may depend on diagnosis rather than prognosis. One study found physicians were more inclined to discuss end of life decisions with patients who had cancer or HIV than patients with cirrhosis even when the prognosis was the same. Data from a multi-site study of 317 patients showed that patients with HIV or lung cancer had documentation of DNR orders more frequently than patients with cirrhosis, even after controlling for hospital, functional and mental status, severity of illness, and survival prognosis. DNR orders were present for 52% of patients with HIV, 47% of patients with lung cancer, 16% of patients with cirrhosis and esophageal varices, and 4% of patients with congestive heart failure. Only 8 out of the 51 patients with cirrhosis had DNR orders documented, and patient preference for this was documented in only 1 out of the 8 cases.²² The illness trajectory of patients with liver disease may differ compared to other types of organ failure (e.g., patients may experience periods of symptom improvement dependent on treatment of liver disease, i.e. alcohol cessation, antivirals therapy, low-sodium diet); however, “prognostic paralysis” should not delay palliative care.¹⁰

2.0 Rationale and Specific Aims

We will conduct a randomized, controlled study to evaluate the effectiveness of a systematic comprehensive palliative care intervention on patient outcomes in hepatology patients with poor prognosis. Our specific aims are to:

- 1) **Assess the impact of systematic, comprehensive palliative care services compared to usual hepatic care on time to first hospital readmission within 1-year post randomization.**
- 2) **Assess the impact of systematic, comprehensive palliative care services compared to usual hepatic care on other hospital utilization variables (including days alive out of hospital within 6-months post randomization, total days in hospital and ICU within 1-year post randomization, number and cost of hospital admissions within 1-year post randomization, median length of stay per admission, number of transfers to hospice within 1-year post randomization, time to hospice placement, and survival).**
- 3) **Assess the impact of systematic, comprehensive palliative care services compared to usual hepatic care on quality of life.**
- 4) **Assess the impact of systematic, comprehensive palliative care services compared to usual hepatic care on patient satisfaction and caregiver stress and satisfaction.**
- 5) **Evaluate the fidelity of the palliative care intervention and assess the generalizability of implementing a large-scale Palliative Care program.**

3.0 Preliminary Data

The term ‘Palliative Care’ is not well understood. The current study team conducted a pilot survey of ResearchMatch²³ participants which shows 81% of surveyed patients with chronic disease have heard of the term “palliative care” but they have variability in understanding the definition (See **Figure 1**).

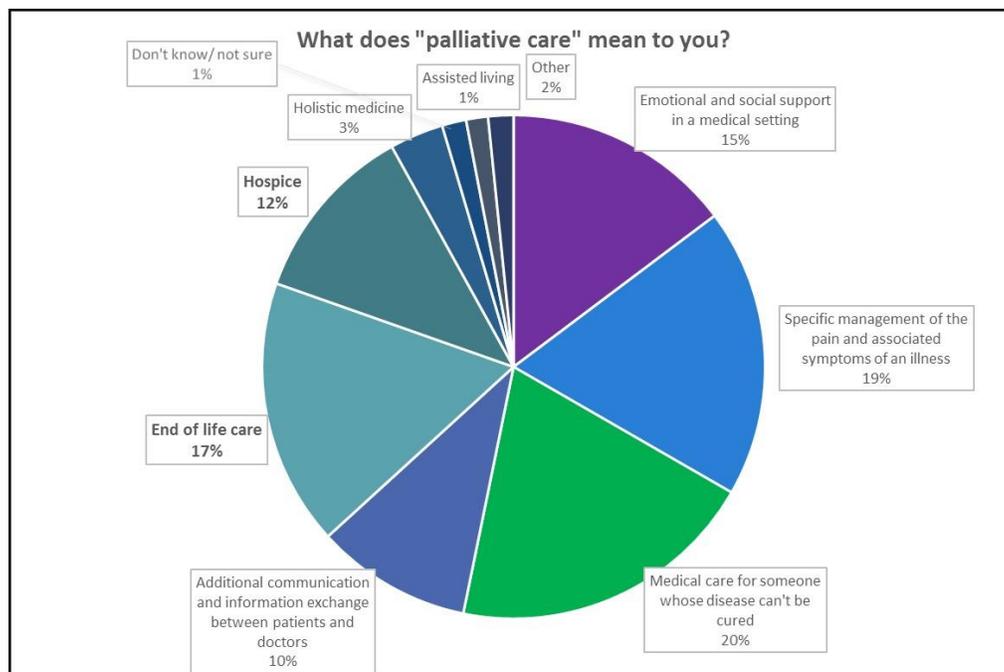


Figure 1. Response to pilot survey question, “What does palliative care mean to you?” Data collected from 572 participants via ResearchMatch.

Confusion surrounding the association of palliative care with hospice and active dying may prevent conversations from being initiated by patients or providers, thereby perpetuating the cycle of confusion. One potential concern with introducing palliative care earlier in the disease trajectory is the assumption that patients would prefer to avoid discussing end of life care or may feel as if their treatment team is “giving up.” However, when 444 patients with chronic disease were asked in a separate ResearchMatch survey “Would you want to know your prognosis if you had less than six months to live?” 97% of patients responded yes, and 100% of the 91 patients with liver disease responded yes. For the 91 patients with liver disease who were surveyed, the majority of patients responded they would prefer to hear this prognosis from a health professional rather than a loved one (see **Figure 2**).

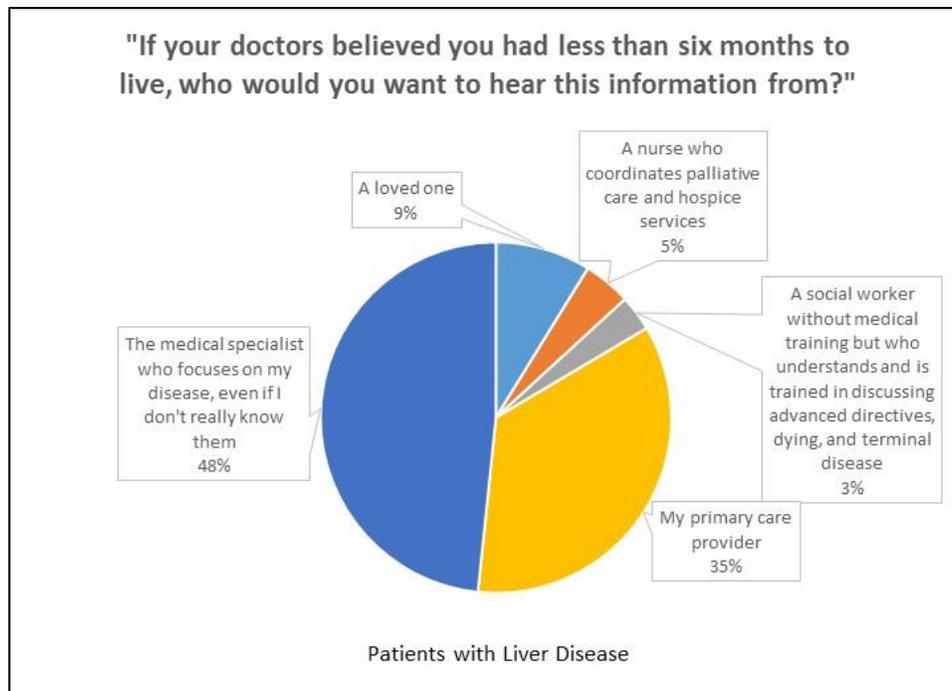


Figure 2. Response to survey question, “If your doctors believed you had less than six months to live, who would you want to hear this information from?” Data collected from 91 participants with liver disease via ResearchMatch.

4.0 Team and Study Personnel

While initial assessment, referral, and overall care are within the domain of the MD, mid-level provider support is essential. Lesperance et al showed that an educational program including palliative care training of mid-level providers (ARNPs, PAs, and LCSWs) successfully brings advanced directive discussions and palliative symptom assessment and management to outpatient oncology practices.²⁴ The current study will utilize mid-level providers including palliative care nurse practitioners and specialized nurses, and attempt to help answer the questions of when and how to integrate palliative care services.

Vanderbilt’s existing clinical Palliative Care Services team will be utilized for this study. This team has the expertise to provide patients and their families with services that attempt to help patients make the best possible medical decisions in the face of serious illness and to keep patients as comfortable and pain-free as possible. The team is comprised of the following (along with other physicians, nurse practitioners, nurses, and case managers):

- Mohana Karlekar, MD, FACP, Medical Director Palliative Care, Assistant Professor of Medicine, General Internal Medicine and Public Health
- Sara Martin, MD, Medical Director Outpatient Palliative Care, Assistant Professor of Medicine, General Internal Medicine and Public Health
- Sumathi Misra, MD, MPH, CMD, Assistant Professor of Medicine, General Internal Medicine and Public Health

The study team will be comprised of executive level project management, study coordinators, and consulting bio-statisticians who will be overseen by the study PI (Gordon Bernard, Associate Vice Chancellor for Research).

This study will be conducted in a focused inpatient hepatology environment. Participating medical hepatologists include:

- Joseph Awad, MD, Associate Professor of Medicine, VA Medical Center Transplant Service, Division of Gastroenterology, Hepatology, & Nutrition
- Chan Chung, MD, Assistant Professor of Medicine, Division of Gastroenterology, Hepatology, & Nutrition
- Roman Perri, MD, Assistant Professor of Medicine, Division of Gastroenterology, Hepatology, & Nutrition
- Michael Porayko, MD, Professor of Medicine, Division of Gastroenterology, Hepatology, & Nutrition
- Andrew Scanga, MD, Assistant Professor of Medicine, Division of Gastroenterology, Hepatology, & Nutrition
- Natasha Schneider, MD, Assistant Professor of Medicine, Division of Gastroenterology, Hepatology, & Nutrition

5.0 Participant Selection

Approximately 400 adult hepatology patients with poor prognosis (identified by the ‘surprise question’ see below) will be randomized to receive either usual hepatic care (control group, N=200) or usual hepatic care with comprehensive palliative care services (intervention group, N=200). Any Vanderbilt patient admitted to the primary inpatient service of one of the study hepatologists with limited life expectancy may be eligible for participation. We expect a participation rate of ~75% (based on the participation rate of a similar study conducted by Dr. Jennifer Temel²), and no more than 10% of patients excluded based on eligibility criteria. We are powered to detect a 13% difference in readmission rate between treatment arms with 400 participants, assuming equal mortality across arms (see section 8.0, Statistical Analyses). As this is an internally funded study, we will have flexibility to enroll patients past the the accrual goal of 24-months in order to enroll 400 participants if necessary.

Inclusion Criteria:

- Inpatient at Vanderbilt University Medical Center with advanced liver disease, whose treating hepatologist indicates a ‘No’ response to the question, “Would you be surprised if this patient died within 1 year?”

Exclusion Criteria:

- Age < 18 years
- Inability to give written informed consent (patient or surrogate decision-maker)
- Inability to respond to questions in English
- Treating hepatologist denies permission to enroll
- Receiving hepatology care at non-Vanderbilt sites (to ensure appropriate follow-up)

Recruitment

Potential patients will be identified within StarPanel using hepatology service codes and/or attending physician name. Patients’ electronic medical records will be manually reviewed by study personnel to confirm preliminary eligibility. Once preliminary eligibility is established, the treating hepatologist will receive a prompt via email with a REDCap survey link to respond to the question, “Would you be surprised if this patient died within 1 year?” The ‘surprise question’ has been used in a variety of patient populations for prognosis and to evaluate appropriateness for palliative care^{25,26} and has shown specificity (69.3%) and

sensitivity (83.6%) with a positive predictive value of 83.8% and negative predictive value of 69.0% when correlated to one-year mortality rate as applied by general practitioners in an oncology setting.²⁷ The REDCap survey will contain the patient's name and medical record number for physician reference (**Appendix A**). If the treating physician indicates a 'No' response, the patient will be considered for inclusion into the study. On the same survey, the hepatologist will confirm the patient may be approached for consent and randomization into the study. The study team will maintain a Pre-Screening Log within REDCap to track patients who are reviewed for eligibility.

Consent Procedures

Appropriate patients will be approached by a study coordinator (SC) on the inpatient unit. The SC will provide a verbal description of the study and will inform potential participants that participation is voluntary, and if they enroll, they may withdraw from the study at any time, for any reason, before it is completed. Study staff will access the REDCap survey containing the most recent IRB approved e-consent document via portable electronic device (iPad) or computer. Study staff will review the information with the participant, and give the subject ample time to ask questions and have their questions answered. Written informed consent will be documented on the e-consent document via a typed signature. If there are technical issues, difficulty accessing the e-consent electronically, or if the patient prefers, a paper consent form will be used.

The patient's surrogate decision-maker will also be approached to provide consent for the study. The same process for obtaining written informed consent from the patient applies to the surrogate decision maker. He/she will indicate consent to allow the patient to participate via typed signature on the surrogate e-consent form or handwritten signature on the paper surrogate consent form. If the surrogate decision-maker is not present on the unit, the SC will contact the surrogate by telephone, describe the study, and will send an email containing the REDCap survey web link to the e-consent form. The email will also contain contact information (email and phone) of a member of the key study personnel for surrogate decision-makers to contact with questions prior to signing the e-consent. The SC will verbally review the study and e-consent form, and the surrogate decision-maker will sign the e-consent prior to enrollment.

If the patient does not have the capacity to give written informed consent due to his/her current health state, the surrogate will provide written informed consent prior to the patient's enrollment in the study. The patient will be re-evaluated periodically for the capacity to give consent. The SC will confirm with the treating hepatologist if the patient is capable of providing written informed consent while inpatient. If the patient is found capable, the study coordinator will obtain written informed consent from the patient. If the patient is found to be capable, but is discharged prior to providing written informed consent, the study coordinator will contact the patient by telephone. The patient will sign the e-consent form in a similar manner as the surrogate decision-maker e-consent procedures described above. If the patient does not have access to a computer, and the patient provides verbal permission, a paper informed consent form for the patient to sign and return, a blank copy for the patient to keep, and a stamped addressed envelope to return the signed copy will be mailed to the patient. If the patient is found capable and declines participation, the patient and surrogate will be immediately terminated from the study. Study staff will print a copy of the signed document, and give to participant at time of study visit. Should a participant choose to receive a link to the consent document in lieu of a hard copy (or if they sign electronically from a remote location), they will receive a link to a ROCKET site containing the consent form appropriate to the version date that they signed. Signed consent documents will NOT be housed electronically on ROCKET. No research procedures will be performed until after consent has been provided.

After written informed consent is provided by the patient or surrogate, baseline measures will be completed, and patients will then be randomized (stratified by treating hepatologist) to the control or intervention arm using validated computer programs (**see Figure 3**). If the surrogate decision-maker provided consent for

the patient, patients will be randomized, but baseline measures will be completed by the patient after providing written informed consent. A panel within the EMR containing all enrolled patients and the arm assignment will be created and shared with the PC team.

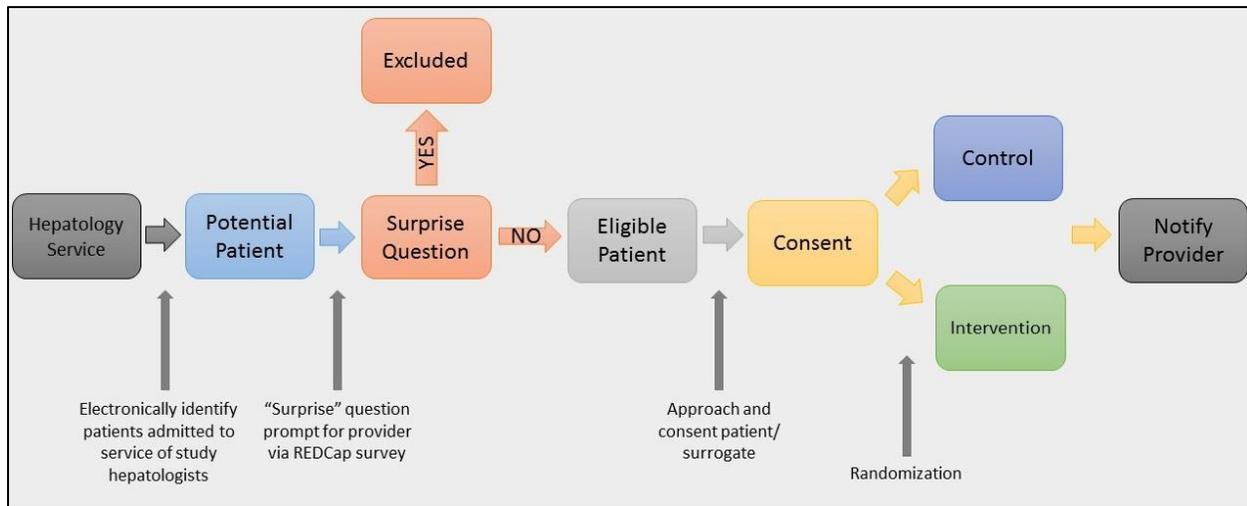


Figure 3. Approach for Study Participant Selection

Caregiver Participation

Patients will be asked to identify a primary caregiver to participate in the study. The identified caregiver may be the surrogate decision-maker. If the patient does not have a surrogate or if the patient prefers to name a different individual as the caregiver, he/she will be asked to identify a family member or close friend who is familiar with the patient's diagnoses and treatment, has daily or near daily contact with the patient in a variety of settings (home, hospital, etc.), and is someone the patient feels comfortable answering survey questions about his/her care. Written informed consent by the study participant for caregiver participation will be documented by separate signature on the main informed consent form. If the patient declines to name a caregiver or does not want the surrogate decision-maker to participate in this capacity, the patient will *not* be excluded from the study. The SC will approach the caregiver to explain the purpose of the study and the caregiver's role. If the caregiver agrees to participate, the SC will obtain the caregiver's written informed consent via the separate Caregiver e-consent or paper consent form in the same manner as described above. If the caregiver is not present on the hospital unit, the patient will be asked to provide contact information for the caregiver. The SC will contact the caregiver via telephone to obtain consent, in a similar manner as the procedures described above.

Caregiver participation includes the collection of demographic (**Appendix B**) and outcome data via a stress survey and satisfaction of care survey at specified time points (see Table 2).

6.0 Intervention

We will conduct a randomized, controlled study to evaluate the impact of systematic, comprehensive palliative care services vs. usual hepatic care. After providing written informed consent, patients will complete baseline measures including demographic (**Appendix C**), mood, and quality of life questionnaires on the inpatient unit. Patients will be randomized to either the control (usual hepatic care) or the intervention arm (usual hepatic care with comprehensive palliative care services). Patients who are randomly assigned to usual care will not be scheduled to meet with the palliative care service unless a meeting is requested by the patient, the family, or the treating physician.

Patients randomized to the intervention arm will receive a binder (**Appendix D**) of patient materials including general information about palliative care services, the COMPASS study, and templates to document information if the patient wishes (names of medicine, upcoming appointments, important contact information, etc.). Intervention patients will also receive , contact information printed on a magnet (**Appendix F**), a wallet card (**Appendix G**), and a one-page handout (**Appendix H**). A VUMC palliative care physician or nurse practitioner will meet with the patient and appropriate surrogate, caregiver, family members, etc. after randomization to provide a verbal overview detailing palliative care services and to provide the comprehensive initial consult. Appropriate palliative care providers will provide follow-up in-person consults while the patient remains inpatient per usual palliative care services.

If the patient is discharged, follow-up consults will be provided by a palliative care nurse via telephone contact with the patient and/or surrogate, caregiver, or other individuals involved in the patient's care as appropriate. The nurse will assess the patient's physical and mental functioning, review medications and discharge instructions, review the patient's advance care plan and goals of care, respond to patient questions, and identify needs for additional care (procedures outlined in Table 1). The nurse will be provided a semi-structured telephone guide, informed in part by the Re-Engineered Discharge (RED) toolkit supported by Agency for Healthcare Research and Quality²⁸ (**Appendix I**). The initial telephone contact attempt will occur within 96 hours post-discharge. If initial call attempts are unsuccessful, the nurse will continue to contact the patient or other appropriate individuals up to 7 days post-discharge. If the patient and/or surrogate, caregiver, or other individual involved in the patient's care provides verbal permission for the team to send reminder texts or emails regarding the phone consults, and the nurse is unable to reach the individual by phone, the nurse may send text messages or emails. The text or email sent by the nurse will only serve to set up a time to complete the phone call. The nurse will not send sensitive health information via text or email. If unsuccessful after 7 days, the nurse will attempt contact again in 3 weeks (1 month after the scheduled contact). After the initial successful contact, telephone consultations will occur on a flexible schedule (e.g., weekly, bi-weekly, monthly) based on the needs and wishes of the patient, at a minimum frequency of once a month. Both the in-person inpatient consultations and the follow-up telephone contacts will be recorded using standard template forms via Starform in the patient's EMR (**Appendices J, K**).

During the telephone contact, if a palliative care nurse identifies a need for further care (e.g., referral to hospice, appointment with the outpatient palliative care office, appointment for symptom management, etc.), the nurse will engage the palliative care team and/or the Hepatology team as indicated. Nurses will relay all relevant information from the telephone contacts to the palliative care team and the treating hepatologists via StarPanel and other clinically appropriate communication channels. If the patient is readmitted to the hospital, the inpatient in-person follow-up and outpatient telephone follow-up schedule will restart. Patients will receive inpatient consultations and follow-up outpatient telephone consultations for one year after randomization to the intervention arm or until death.

After completion of the one-year intervention phase, patient participation will be complete. With the exception of the follow-up telephone contacts and patient-friendly materials, similar services are available to all patients per routine practices. There are no other investigational agents or processes being used for the intervention group of patients/providers. See **Figure 4** below for trial design.

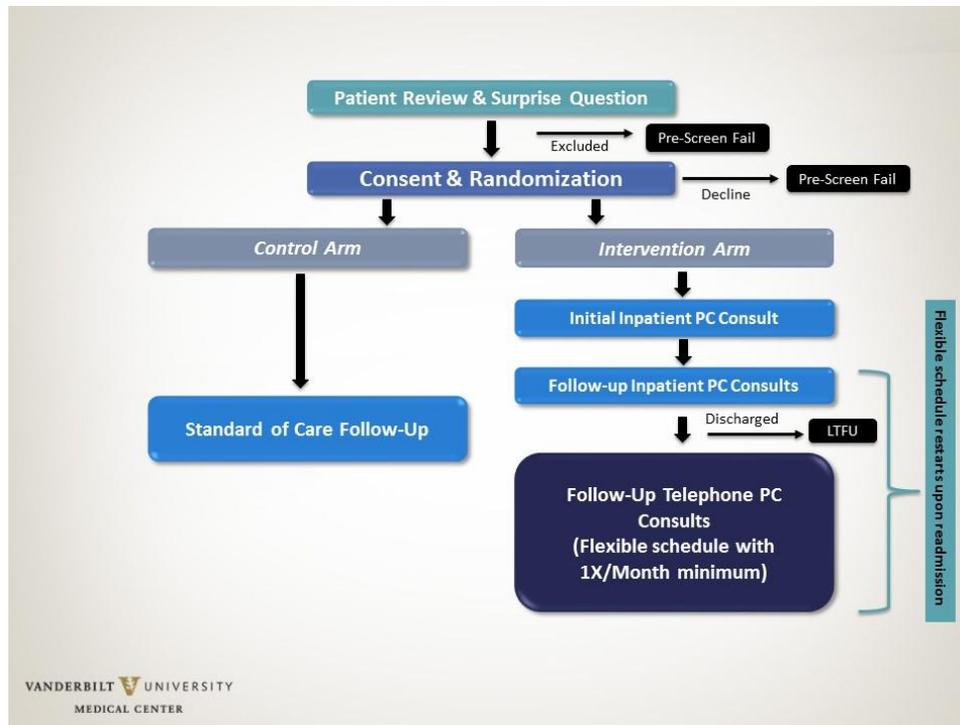


Figure 4. RCT Study Schema

The palliative care intervention is expected to include:

- Informational, patient friendly Palliative Care Binder, magnet, handout, wallet card
- Establishment of a palliative care plan
- Care coordination by palliative care team
- Early and regular ongoing engagement of palliative care physicians and nurse practitioners for inpatient consultations
- Telephone contacts conducted by trained palliative care nurses to review palliative care plan, assess changes in symptoms, identify patient needs and re-engage the palliative care team or Hepatology team as appropriate for referrals or appointments
- Communication by palliative care team to all providers and teams involved in patient's care
- Systematic collection of information, including identification of surrogate or health care proxy and advance care planning

Inpatient and telephone palliative care consults will consist of a systematic process utilizing standardized template forms and will include all of the components outlined in **Table 1**.

Table 1

Palliative Care Intervention Procedures	Inpatient In-Person Consults	Outpatient Telephone Consults
Introduction to PC	X	
Introduction to concepts of Advance Directive, living will, healthcare agent	X	
Assess physical and mental functioning	X	X
Review and complete Advance Directives including: review of previously completed advance care directives, discussion/ completion of POST form, code status, and advance care directives (power of attorney, living will, or advance care plan)	X	X
Name surrogate	X	
Review medical history	X	
Review family history	X	
Review social history (marital status, tobacco use, smoking, alcohol use, drug use, occupation, children) and identify patient's barriers to healthcare access	X	
Dignity and Spirituality assessment (referral to chaplain where applicable)	X	X
Review medications and allergies	X	X
Review symptoms*	X	X
Explain medical condition/diagnosis in lay terms and discuss patient's understanding of prognosis	X	
Discuss questions to ask hepatologist	X	X
Discuss social/family support system	X	X
Develop Care Plan and Goals of Care in the context of the patients current medical condition	X	
Review Care Plan and Goals of Care in the context of the patients current medical condition	X	X
Direct/refer patient towards appropriate resources (e.g. hospice where applicable)	X	X
Record time spent with patient	X	X
Ensure family awareness as applicable	X	X
Communication of Care Plan and pertinent information back to Hepatology MD	X	X

*Symptoms include: lack of energy, lack of appetite, pain, dry mouth, weight loss, drowsiness, shortness of breath, constipation, diarrhea, difficulty sleeping, nausea, vomiting, fever, chills, sweats, sore throat, headaches, change in vision, polyuria, polydipsia, cold/heat intolerance, cough, hemoptysis, chest pain, palpitations, orthopnea, hematuria, renal stones, melena, anorexia, enlarged lymph nodes, bleeding, easy bruising, rhinitis, skin reactions, joint pain/swelling, weakness, myoclonus, sadness, agitation, anxiety, confusion, rash

Outcomes

Primary clinical endpoint:

- Time to first hospital readmission within 1-year post randomization

Secondary outcomes are expected to include:

- Days alive out of hospital within 6-months post randomization
- Total days in hospital within 1-year post randomization
- Total days in ICU within 1-year post randomization
- Number of hospital admissions within 1-year post randomization
- Cost of hospital admissions within 1-year post randomization
- Median length of stay per admission
- Number of transfers to hospice within 1-year post randomization
- Time to hospice
- Liver disease-specific health-related quality of life
- Generic measures of quality of life
- Patient mood
- Patient satisfaction with care
- Caregiver reported stress
- Caregiver reported satisfaction with patient care (including quality of death and dying, as applicable)
- Liver transplant status (deferred, listed, decline)
- MELD score
- Number of completed liver transplants
- Patient diagnoses and physical symptoms (e.g., presence of ascites, variceal bleeding, encephalopathy, delirium)
- Presence of Advance Directives (Goals of Care, Code Status, Surrogate decision-maker, etc.)
- Survival
- Staff satisfaction with intervention procedures

Process outcomes to measure intervention fidelity are expected to include:

- Number of responses to surprise question, number of 'No' responses to surprise question, number of patients with 'No' response to surprise question who are approved for enrollment
- Number of enrolled patients who receive the palliative care intervention
- Use of standardized forms by palliative care providers
- Clear documentation of a plan of care
- Concordance with goals of care (EMR derived, standardized, objective and measurable variables including DNR order non-adherence, aggressive treatment at end of life without expressed patient consent, CPR, mechanical ventilation, intubation, feeding tubes, re-admission, medications, etc.)
- Documented referrals/coordination with social workers or hospice when applicable
- Documented communication of Palliative Care Plan to patient's hepatology provider
- Completed Advance Directive, including designation of a Surrogate Decision Maker

7.0 Data collection

7.1 Primary Outcome Data

Primary outcome data (hospital admission and discharge dates) will be obtained for this study through retrospective chart review utilizing StarPanel and the Research Derivative (RD). The RD is a database of clinical and related data derived from the Medical Center's clinical systems and restructured for research. Data is repurposed from VU's enterprise data warehouse, which includes data from StarPanel, VPIMS, and

ORMIS (Operating Room Management Information System), EPIC, Medipac, and HEO among others. The medical record number and other person identifiers are preserved within the database. Data types include reimbursement codes, clinical notes and documentation, nursing records, medication data, laboratory data, encounter and visit data, among others. Output may include structured data points, such as ICD 9 codes or encounter dates, semi-structured data such as laboratory tests and results, or unstructured data such as physician progress reports. The database is maintained by the Office of Research Informatics under the direction of Paul Harris, Ph.D.

7.2 Secondary Outcome Data

Other patient level data will be obtained for this study through retrospective chart review utilizing StarPanel and the RD. Data to be collected include:

- Demographics (e.g., age, sex, race)
- Hospitalizations (date of admission, date of discharge, hospital unit), hospice referrals, and time to hospice placement
- Days alive outside of hospital
- Discharges to hospice
- Date of death (where applicable)
- Clinical interventions, procedures, and events (e.g., surgeries, resuscitation, intubation, ventilator use) extracted from the charts will inform our analyses as to whether initially established palliative care goals of care were met. Examples of met goals could include DNR and advanced care directives being met and whether aggressive treatment has been pursued at the end of life, against the documented wishes of the patient.
- Physical symptoms (e.g., ascites, variceal bleeding, encephalopathy, delirium)
- Liver transplant status (deferred, listed, decline), MELD score, and number of completed liver transplants

Additional secondary outcome data include change of health-related quality of life, as measured by the Chronic Liver Disease Questionnaire (CLDQ),²⁹ change in general quality of life, patient mood, and patient and caregiver satisfaction with care across the study period. Demographic information will also be collected at baseline for all participants and caregivers. Participating hepatology staff will complete a brief survey to provide feedback and gauge satisfaction with intervention procedures.

Questionnaire data will be captured electronically via online REDCap survey or via paper copy. All participants (patient and caregivers in both usual care and intervention arms) will complete outcome measures at the same frequency – at Baseline, 4 weeks, and at 3, 6, 9, and 12-months post randomization. Baseline measures will be completed using a provided computer tablet, or paper version if preferred, on the inpatient hospital unit. If participant discharges from hospital prior to completion of questionnaires, and at the subsequent time points, participants (caregivers and patients) will complete assessments over the telephone with the study coordinator administering the questionnaires and documenting participant response on the REDCap survey form, or participants will complete assessments at home by accessing the REDCap survey form online directly. If the patient or caregiver prefers to complete assessments online or is unable to be reached by telephone, the study coordinator will provide the participant with instructions to access the online survey via email reminder with the link to the survey. Study Coordinator will attempt to contact the participant for completion of assessments up to 7 days post scheduled time-point. If unsuccessful after 7 days or if the participant prefers, paper versions of the assessments for the participant (patient or caregiver) and a stamped addressed envelope to return the completed assessments will be mailed.

If the patient returns to hospital and is inpatient at a scheduled assessment time point, the SC will meet with the patient or caregiver in-person to complete the assessments on the hospital unit by using a provided computer tablet or paper versions. See **Table 2** for the schedule of outcome assessments. If the study

participant dies while active in the study, a one-time, one-item survey will be completed by the caregiver 3 months after the death of the participant to gauge quality of death and dying.

Table 2

Schedule of Assessments						
Instrument	Baseline	Month 1 (Wk 4)*	Month 3 (Wk 13)*	Month 6 (Wk 26)*	Month 9 (Wk 39)*	Month 12 (Wk 52)*
Study Participant						
Demographic survey	X					
CLDQ	X	X	X	X	X	X
EQ-5D-5L	X	X	X	X	X	X
PROMIS Depression 4a	X	X	X	X	X	X
PROMIS Anxiety 4a	X	X	X	X	X	X
Quality of End-of-Life Care: Patient Questionnaire**	X	X	X	X	X	X
Caregiver						
Demographic survey	X					
Quality of End-of-Life Care: Caregiver Questionnaire**	X	X	X	X	X	X
Kingston Caregiver Stress Scale (KCSS)	X	X	X	X	X	X
QODD-1***						X***

* Call window for completing assessments is within 7 days after time-point. After 7 days, paper versions will be mailed.

** Survey renamed "Satisfaction Questionnaire"

*** Completed once, 3 months post-death of participant

Outcome data will be collected via:

Quality of Life Instruments

The Chronic Liver Disease Questionnaire (CLDQ)²⁹ is a 29-item self-report questionnaire addressing domains specific to patients with liver disease including: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry. Items are scored on a Likert-type scale measuring frequency of symptoms within the timeframe of the 'last two weeks,' from 1 – All of the time to 7 – None of the time. Initially validated in adults with a variety of types and stages of liver disease, the CLDQ has shown the ability to detect differences between patients without cirrhosis, with early cirrhosis, and with advanced cirrhosis (based on Child's Pugh classification), has shown good concurrent validity when compared to clinical evidence of deterioration²⁹, and has the ability to detect significant improvement in health-related QOL between patients pre-liver transplant and post-transplant.³⁰ (**Appendix L**)

In addition to a liver disease-specific assessment, the EQ-5D-5L³¹ will be collected as a secondary outcome measurement. The EQ-5D-5L is a valid and reliable generic health survey questionnaire, with 5 items measuring dimensions of Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. The 5L version has 5 response categories ranging from absence of symptom to extreme experience of the symptom. The EQ-5D-5L has been evaluated in patients with chronic hepatic diseases and has shown good criterion-related and construct validity in liver transplant patients.³² Scalone et al. (2013) evaluated the 5L version compared to the 3L version in 1,088 adult patients with chronic hepatitis (HCV and HBV), cirrhosis, hepatic carcinoma, or a recent liver transplantation, finding the 5L version performed well with a reduction

in ceiling effect with a modest-low gain in discriminant validity and slightly higher convergent validity as compared to the 3L version.³³ (**Appendix M**)

Mood Instruments

We will use PROMIS adult short forms to assess mood in study participants, specifically depression (**Appendix N**) and anxiety (**Appendix O**). Patient Reported Outcomes Measurement Information System (PROMIS) is a system of highly reliable, validated, precise measures of patient-reported health status for physical, mental, and social well-being.³⁴ PROMIS' measures can be used as primary or secondary endpoints in clinical studies of the effectiveness of treatment. The domains of depression and anxiety are measured through four targeted questions each on a 5-point Likert scale. The four items are selected from a full item bank to yield an accurate estimate at a targeted range of the measured domain. Evaluation of construct validity has been accomplished through the specification and testing of hypotheses about the relationship between the PROMIS domain scores, actual clinical status, and other relevant variables. A variety of statistical techniques have been employed to evaluate these hypotheses including mixed-effects models, regression analysis, and structural equation models. Evaluation of construct validity is based on the relationship between the PROMIS scores and other health and clinical measures, and by evaluating known groups' validity.

Hospital Utilization

Days admitted as an inpatient will be compared between the usual care and intervention arm. Admission date, discharge date, and length of stay for inpatient hospitalizations and ICU admissions will be obtained from the Research Derivative. Associated costs and days alive outside of hospital will also be compared between arms.

Survival

Survival rates will be compared between the control and intervention arm one year after study enrollment.

Physical Symptoms

Disease trajectory including diagnoses and physical symptoms (e.g., ascites, variceal bleeding, encephalopathy) will be compared across arms.

Liver Transplant Status

Listing of liver transplant status (deferred, listed, declined), change in MELD score, and the number of completed liver transplants will be compared across arms.

Satisfaction Instruments

Quality of End-of-Life Care: Questionnaire for Patient, developed at the University of Washington was modified for the current study.³⁵ The original instrument is an 11-item self-report questionnaire designed for the patient to rate the clinician, doctor, or nurse practitioner on 11 elements measuring quality of care. Items are scored on a 10-point Likert-type scale with 0 = "Poor", 5 = "Very Good", and 10 = "Absolutely Perfect" with an option for Does Not Apply (NA). The study team has modified this original questionnaire to remove the "End-of-Life Care" title from the header (**Appendix P**).

Caregiver Instruments

The Quality of End-of-Life Care: Questionnaire for Patient was modified for use by the Caregiver. The study team modified questions to be applicable for caregiver rather than patient response. For example, altering item 2 from "Responsive to your emotional needs . . ." to "Responsive to the patient's emotional needs . . .". The study team has modified this original questionnaire to remove the "End-of-Life Care" title from the header (**Appendix Q**).

If patients die during study participation, caregivers will be asked to complete one questionnaire at 3-months post-death to gauge quality of end-of-life care. The Quality of Death and Dying (QODD-1) is a 1-item questionnaire that measures overall quality of dying with the question, “Overall, how would you rate the quality of your loved one’s dying?” Response options range from 0 – a “terrible” experience to 10 – an “almost perfect” experience. The QODD-1 has shown to correlate significantly with clinical variables associated with end-of-life care and palliative care.^{36,37} (**Appendix R**)

The Kingston Caregiver Stress Scale (KCSS)³⁸ will be used to measure caregiver stress. The KCSS is designed to measure stress experienced by lay caregivers, not institutional staff, and was designed to monitor change in an individual's stress over time. Ten items are grouped into three categories: care giving, family, and financial issues. (**Appendix S**)

Provider satisfaction

Study hepatologists will be surveyed once prior to research participant enrollment and again every 6 months after the first participant is enrolled until study close-out, to gauge level of satisfaction with the palliative care service. An important part of the feasibility of a large-scale palliative care program is provider satisfaction. The “ICU Provider Satisfaction Survey with the Palliative Care Program: Veterans Affairs of Ann Arbor” instrument is available online and has been modified for the current study by removing the ‘ICU’ reference and revising ‘pain’ to symptoms more relevant to the current population. (**Appendix T**)

7.3 Process Outcomes

Concordance with plan will be measured via EMR derived, standardized, objective and measurable variables including CPR, mechanical ventilation, intubation, feeding tubes, re-admission, medications, etc. Although each intervention encounter will ultimately be tailored to fit the individual’s specific needs, structured protocols will be in place to insure all participants receive consistent palliative care services and that those services are properly documented and recorded. All standard components of the clinical intervention listed above will be assessed and recorded by the palliative care and/or research staff. The palliative care provider will enter data elements into structured fields on a standardized palliative care Starform, and the research staff will enter relevant data elements into a REDCap database.

8.0 Statistical Analyses

Power Calculations

Power calculation was conducted on the primary outcome (time to first hospital readmission) using Cox proportional hazards model accounting for competing risk of death.³⁹ Assuming 50% 1-year mortality in both arms of the expected study cohort (‘surprise question’ inclusion which is comparable to a 50% 1-year mortality rate), with type I error of 0.05 and power of 80%, the minimum detectable hazard ratio (HR) under sample size N=400 was calculated given varying hospital readmission rate in the usual care arm ranging from 0.5 to 0.9. The corresponding rate reduction in the intervention arm (DR) and the relative rate reduction (RDR) were also provided. See **Table 3**. To assess clinical rationale of the power calculation, 1-year hospital readmission rate was assessed from pilot data obtained from a retrospective data pull via the Research Derivative. Admission to a study hepatologist during a 3-month window was required for cohort inclusion, and subsequent admission data (1-year post ‘qualifying admission’) was analyzed. Of the 151 patients included in the pilot data, 93 patients (62%) were readmitted within 1 year of the qualifying admission with a 1-year mortality rate of 35%. This pilot cohort (35% mortality rate) may be healthier than expected study cohort. However, due to competing risk of death, we are not sure whether the 1-year readmission rate of 62% from the pilot cohort is an overestimate or underestimate of the target population. Nonetheless, the proposed sample size provides sufficient power (80%) to detect rate reduction

of 13% when the hospital readmission rate in the usual care arm is between 50% and 70%, which is comparable with the pilot data.

Table 3

Various risk of readmission in the usual care arm (R), and the corresponding minimum detectable hazard ratio (HR) and the corresponding inverse HR (1/HR), difference of risk of readmission (DR) and relative difference of the first readmission (RDR) under sample sizes N = 400 with power 80% and type I error 0.05.

N = 400				
R	HR	1/HR	DR	RDR
50%	0.67	1.5	13%	0.26
60%	0.69	1.4	13%	0.22
70%	0.71	1.4	13%	0.18
80%	0.73	1.4	11%	0.14
90%	0.74	1.4	8.3%	0.092

Analyses Plan

Demographic and clinical characteristics of the participants such as age, gender, etc. will be compared between the control and the intervention arms using Wilcoxon rank-sum test for continuous variables and Pearson's Chi-square for categorical variables.

Aim 1: Time to first hospital readmission within 1-year post randomization will be compared across treatment assignment using Cox proportional hazards model, accounting for the competing risk of death and adjusting for relevant demographic and clinical characteristics. A less than 1 hazard ratio for the treatment group status implies reduced readmission rates in the intervention arm given equal mortality rates.

Aim 2: Days alive out of hospital within 6-months post randomization, total days in hospital and ICU within 1-year post randomization, number and cost of hospital admissions within 1-year post randomization, median length of stay per admission, number of transfers to hospice within 1-year post randomization, time to hospice placement after referral, survival, presence of advance directives within 1-year post randomization, presence of physical symptoms, transplant status listing (deferred, listed, declined), and number of completed liver transplants will be obtained via chart review and compared across treatment assignment using proportional odds model for ordinal outcomes, Cox proportional hazards model for time-to-event outcome and logistic regression for binary outcomes, adjusting for relevant demographic and clinical characteristics.

Aims 3 and 4: Both cross-sectional and longitudinal analysis will be conducted to compare between group differences in CLDQ. For the cross-sectional study, for each time point of data collection, linear regression with ordinary least square will be used with CLDQ as the dependent variable (DV) and treatment assignment (0 for control arm and 1 for the intervention arm) as the independent variable (IV) of interest adjusting for baseline CLDQ and potential confounding factors based on clinical and statistical considerations. A positive value of the regression parameter for treatment status indicates higher CLDQ in the intervention arm. For longitudinal analysis, linear mixed model will be adopted including follow-up time and the interaction between follow-up time and treatment group on top of the cross-sectional model. The interaction term is included to compare decreasing rate of CLDQ between groups with a positive value of the corresponding regression parameter indicating slower decline rate of CLDQ in the intervention arm.

The same series of analyses for the CLDQ will be conducted for the PROMIS (depression, anxiety), ED-5D-5L, the Quality of End-of-Life Care patient and caregiver questionnaires, and the KCSS. Histogram of baseline secondary outcomes will be used to evaluate ceiling/flooring effect and degree of skewedness. Appropriate transformation such as log transformation will be considered for highly skewed secondary outcomes to improve efficiency. A positive value of the main effect for intervention status in the cross-sectional analyses and a positive value of the interaction effect in the longitudinal analyses indicate favorable intervention effect.

Aim 5: Summary descriptive measures such as mean, quartiles and standard deviation for continuous variables and frequencies for categorical variables will be provided for process outcomes from participants in the intervention arm to evaluate fidelity of the proposed intervention and generalizability of implementing a large-scale intervention program. The following data will be collected for each arm: percentage of patients with answered surprise question (stratified by provider), percentage of patients with a 'No' response to the surprise question (stratified by provider), percentage of patients with 'No' response to the surprise question who were approved for study enrollment (stratified by provider), percentage of intervention patients who received initial PC inpatient consult, percentage of patients who received scheduled follow-up telephone contact, percentage of patients who attended an appointment for care after referral was obtained, percentage of patients with completed questionnaires at each time point, percentage of patients who received Palliative Care materials, and percentage of patients who received an inpatient PC consultation upon hospital readmission during the intervention phase will be calculated.

Interim Analysis

Interim analysis will be conducted when N=30 and N=150 participants are enrolled and followed for at least 6 months to evaluate whether the study is feasible, study procedures are conducted as intended, and that there is not significant patient dropout for mortality or other reasons.

8.0 Risks and Benefits and Means of Mitigating Risks

The benefits of this research are potentially quite large and the risks comparatively small. Specifically, this research may lead to a better understanding of the value of palliative care and its optimal timing for patients with life-threatening illnesses. It will also potentially yield important information about the impact of the time of such palliative care on the patients and their well-being. We believe the potential benefit to society of results of this study, if positive, may ultimately lead to different and improved clinical approaches to the care of such patients with life-threatening illnesses, most of whom could be considered to be at the end of life. The risks associated with this research relate to the potentially emotionally upsetting nature of some of the questions, including those related to estimating the likelihood of patients being cured of their life-threatening diseases and their likelihood of survival. Our preliminary data show that patients overwhelmingly want to know about this kind of information, but we will work to minimize risks to patients by forewarning them during the consent process about the potential emotional distress and refer patients to a trained social worker if necessary.

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