Pragmatic Trial Investigating Surprise Question in End of Life (SeQuEL) Care and the Effect of Prompting Palliative Care Consultation on Provider Referral Rates and Subsequent Outcomes for Hospitalized Adults with Serious Illnesses: Master Protocol for a Pragmatic Platform Trial

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Study Protocol: Version 2.0 – 7/31/2024
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Primary Investigator: Mohana Karlekar, MD, FACP, FAAHPM

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Abbreviations:

BPA – Best Practice Advisor

ESLD – End-Stage Liver Disease

IRB – Institutional Review Board

PHI – Protected Health Information

PI – Principal Investigator

VUMC – Vanderbilt University Medical Center

1. Master Protocol Summary

Title	Master Protocol for Pragmatic Trials utilizing the Surprise Question and Evaluating the Effect of Prompting Palliative Care Consultation on Provider Referral Rates and Subsequent Outcomes for Hospitalized Adults with Advanced Illnesses.
Brief Summary	This Master Protocol describes the general design features of a platform trial evaluating the effect of prompting palliative care consultation on provider referral rates and outcomes for hospitalized adults with serious illnesses. The Master Protocol provides the background and overarching approach to all trials to be conducted on this platform. This includes rationale for the choice of primary outcomes based on stage, general inclusion and exclusion criteria, randomization, intervention, and blinding. The protocol also highlights expectations for final analyses, sample size considerations, safety reporting, and data collection. In addition, the Master Protocol describes general principles for trial operations and oversight. Appendices to the Master Protocol provide additional relevant information and identify patient populations with serious illness ("clinical domains") for whom the intervention will be evaluated, including additional eligibility criteria, sample size, and other features specific to the clinical domain.
Study Design	Single center, pragmatic, randomized platform trial
Study Population	Adults with serious illness admitted to the study hospital for whom the treating clinician would not be surprised if the patient died in the next 12 months.
Inclusion Criteria	• Patient is an adult (age ≥ 18 years). • Patient is admitted to the study hospital. • Patient meets criteria for serious illness in one or more clinical domains, as specified in the clinical domain Appendix. • Patient's treating physician, physician associate, or nurse practitioner answers "No" to a prompt in the electronic health record asking, "Would you be surprised if this patient died in the next 12 months?"
Exclusion Criteria	• Patient is known to have received any VUMC palliative care consultation during the prior 3 months and/or the current admission. • Patient is known to be a prisoner • Patient meets any additional exclusion criteria, as specified in the clinical domain appendices
Trial Groups	• Palliative Care Consultation Prompt Group – The patient's treating clinician will receive a prompt in the electronic health record encouraging the consideration of a Palliative Care consultation. • No Palliative Care Consultation Prompt Group – The patient's treating clinician will NOT receive a prompt in the electronic health record encouraging the consideration of a Palliative Care consultation.
Randomization	Eligible patients will be randomized to the Palliative Care Consultation Prompt Group or the No Palliative Care Consultation Prompt Group in a 1:1 ratio using the Epic coin toss tool in the electronic health record.

Primary Outcomes	Stage 1: Percentage of patients with palliative care consults placed within 48 hours after enrollment. Stage 2: Hospital-free days by day 90, defined as the number of calendar days between enrollment and day 90 in which the patient is alive and outside of an acute-care hospital.
Secondary Outcome	Survival to day 90
Exploratory Outcomes	• Total number of days in the hospital by day 90 • Total number of hospital admissions by day 90 • Intensive care unit admission by day 90 • Total number of days in the intensive care unit by day 90 • Referral to hospice by day 90 • Emergency Department visits
Process Outcomes	• Receipt of palliative care consultation • Time to receipt of palliative care consultation • Number of visits with palliative care team • Completion of advanced care planning upon admission as evidenced by POST form • Election of resuscitation status (Do Not Resuscitate (DNR) and/or Do Not Intubate (DNI))
Analyses	Stage 1: The primary outcome, percentage of patients with palliative care consults placed within 48 hours after enrollment, will be evaluated for an anticipated 10% of the total sample size. The following separations between groups, during Stage 1, would then determine trial progression to Stage 2. • > 50% group separation: the trial would move forward to Stage 2 without modification. • 15-50% group separation: the trial would move forward to Stage 2 with modification to the eligibility criteria, intervention, or other aspects of the study protocol. • < 15% group separation: the trial would not move forward to Stage 2. We are explicitly examining the separation between groups for the primary outcome at Stage 1 and have outlined the trial progression scenarios. It is anticipated that all patients will have the same data collected and will be included in the analyses for the primary, secondary, and exploratory outcomes. Stage 2: In the main analysis of the primary outcome, the number of hospital-free days by day 90 will be compared between patients in the two trial groups using a Wilcoxon rank-sum test. Secondary outcomes will be compared between groups using a Wilcoxon rank-sum test for continuous variables and Chi-square test for categorical variables.
Sample Size	Various Appendices will specify a sample size for the respective clinical domain. The number of patients enrolled in all the clinical domains under this Master Protocol is anticipated not to exceed 5,000 patients.

Expected Duration	Multiple patient populations can be actively enrolled concurrently for an anticipated 12 months. However, we expect a sequential initial operationalization.

2. Background

Palliative Care for Serious Illnesses

Palliative care is specialized medical care focused on providing patients with relief from the symptoms, pain, and stress of serious 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 may be provided together with curative treatment, and includes intensive focus on symptom and pain management, psychosocial and spiritual support, and assistance in advance care planning.[1-3]

In some studies, integration of palliative care has been shown to: improve patient quality of life, 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 increase lifespan.[4,5] A recent phase 3 randomized controlled palliative care 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).[4] Greater use of palliative care may also decrease end of life care costs in Medicare patients.[6] In an analysis of more than 5,000 patients from 8 hospitals, palliative care 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.[7] However, there is a paucity of palliative care effectiveness 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 quality of life (5 out of the 7 trials which examined quality of life 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.[8] In oncology settings, specialist palliative care interventions have demonstrated increased quality of life, decreased healthcare costs, and improved survival when initiated early in the course of cancer treatment.[4, 9-11] Trials in heart failure have shown similar promise for palliative care interventions.[12-15]

Despite the available evidence regarding the potential benefits of specialized palliative care across multiple serious illnesses, the incorporation of palliative care consultation into clinical practice in many settings is inconsistent and often too late in the clinical trajectory.[16,17] In an effort to introduce palliative care sooner and more consistently into patient's care pathways, we will explore an interruptive provider nudge to prompt palliative care consideration in key patient populations. This integrated approach will also help bridge the knowledge gap as to whether systematically prompting palliative care consultation can improve referral rates and outcomes for patients with serious illness.

The processes used to 1) identify hospitalized patients with serious illness, 2) query a provider about their status, and 3) prompt consideration of palliative care consultation are amenable to conduct through the electronic health record. Step 1 will employ phenotyping of clinical and admission characteristics readily extractable from the medical record. Step 2 will utilize the "Surprise Question" as a screening tool for identification of potentially unmet palliative care needs. In our pilot trial and other studies of serious illness, patients for whom consideration of palliative care consultation might be appropriate have used the "Surprise Question", which asks the treating clinician "would you be surprised if this patient died in the next 12 months?"[18-20] Step 3 will harness the capability to prompt a provider to consider appropriately indicated, complementary, supportive care that may be otherwise underutilized while managing the patient's immediate health crisis.

Given the preliminary evidence that specialist palliative care may improve the quality and quantity of time spent alive and outside of the hospital for patients with serious illness and the incomplete implementation of specialty palliative care in current clinical practice, we will evaluate the effect of prompting consideration of palliative care consultation in the electronic health record on provider referral rates to the palliative care service and hospital-free days among hospitalized patients with serious illness.

3. Aims and Hypotheses

The overarching goal of the Master Protocol is to investigate the effect of prompting consideration of palliative care consultation through a best practice alert on provider referral rates to the palliative care service and clinical outcomes for hospitalized adults with serious illness. In each clinical domain, we will test the hypothesis that prompting earlier palliative care consultation improves the engagement of the palliative care teams and clinical outcomes compared to not prompting consideration of palliative care consultation.

Primary Aim:
To determine whether prompting consideration of palliative care consultation through the electronic health record impacts the number of palliative consultations placed and hospital-free days among hospitalized adults with serious illness.

Primary Hypothesis:
Prompting consideration of palliative care consultation through the electronic health record will increase both the number of palliative care consults placed and hospital-free days among hospitalized adults with serious illness.

4. Study Design

Single center, pragmatic randomized platform trial.

5. Inclusion and Exclusion Criteria

Inclusion:

- Patient is an adult (age ≥ 18 years).
- Patient is admitted to the study hospital.
- Patient meets criteria for serious illness in clinical domain of interest, as specified in the clinical domain appendix.
- Patient's treating physician, physician associate, or nurse practitioner answers "No" to a prompt in the electronic health record asking, "Would you be surprised if this patient died in the next 12 months?"

Exclusion:

- Patient is known to have received any VUMC palliative care consultation during the prior 3 months and/or the current admission.
- Patient is known to be a prisoner.
- Patient meets any additional exclusion criteria, as specified in the clinical domain appendices.

6. Consent

Because this study of an alert in the electronic health record prompting clinicians to consider palliative care consultation for hospitalized adults with serious illness involves no more than incremental risk, could not practically be carried out without a waiver of the requirement for informed consent, and will not adversely affect the rights or welfare of the subjects, we will request that the trial be performed with waiver of the requirement for informed consent.

- Minimal risk of the research – For all patients in this study, the decision of whether to request a palliative care consultation will be made by the patient's treating clinician, as it would be in clinical care outside of the research. This study examines a clinical decision support tool in the electronic health record prompting the clinician to consider whether to request a palliative care consultation. A clinician decision support tool that collates clinically available information about the patient for the provider (i.e., the serious illness and the likelihood of death over the next 12 months) to prompt consideration of a palliative care consultation involves no more than minimal incremental risk compared to the providers' own synthesis of information within the clinical care outside of the research.
- Impracticability of conducting the research without a waiver of informed consent - This research could not be practicably conducted without a waiver of informed consent for two reasons. First, this study evaluates use of a clinical decision support tool that continuously and automatically screens hospitalized adults for serious illness and prompts clinicians in real-time to consider whether palliative care consultation would be beneficial for the patient. Obtaining written informed consent from patients before the clinical decision support tool identifies the patients as having serious illness and displays the prompt to their treating clinician would be logistically infeasible. Second, the study is designed to evaluate whether prompting of consideration of palliative care consultation affects outcomes. Obtaining informed consent for a study involving palliative care consultation would, in and of itself, prompt added consideration of palliative care consultation, thus biasing the results of the study and increasing the chances of missing a true effect from the intervention.

- A waiver will not adversely affect the rights and welfare of patients – All patients enrolled in the study would be eligible for palliative care consultation in clinical care. For all patients in the study, the treating clinician will determine whether a palliative care consultation is indicated. In both arms of the study, the clinician will retain autonomy to provide the appropriate clinical care. All patients may request or decline a palliative care consultation at any time. No data are generated for this study beyond those generated as a part of clinical care. Thus, the rights and welfare of patients are not affected.

7. Study Sites, Enrollment, and Randomization

Recruitment Best Practice Advisories (BPAs) are one of the native Epic tools available to support research recruitment. Recruitment BPAs can be "silent", meaning they run in the background and perform automated actions without interrupting user workflow, or user-facing. Recruitment BPAs are built using pre-defined study inclusion/exclusion criteria, e.g., demographics, conditions, medications, lab results, etc. When a patient matches the pre-defined study inclusion/exclusion criteria, the BPA is triggered to alert predefined providers or staff who then further review the patient's chart for any additional screening. If the patient is eligible, the patient will automatically be enrolled in the trial (anticipated under a waiver of consent) and randomized. The outline of the BPA specific to this trial is described below.

The study will occur in the adult hospital at Vanderbilt University Medical Center. A best practice advisor will screen the electronic health record to identify patients who meet all inclusion criteria and no exclusion criteria. When a patient appears to meet the eligibility criteria, the best practice advisor will ask the treating clinician the Surprise Question. If the answer to the Surprise Question is "No", then the patient will be enrolled in the trial. Patients who are enrolled in the trial will be randomized in a 1:1 ratio to the 'Palliative Care Consultation Prompt Group' or the 'No Palliative Care Consultation Prompt Group' by the Epic coin toss. For patients deemed ineligible at the time of screening, they will be rescreened upon each eligible inpatient visit to VUMC. Enrolled patients will not be rescreened upon subsequent inpatient hospitalization. The process for screening, enrollment, and randomization is displayed in the figure below:

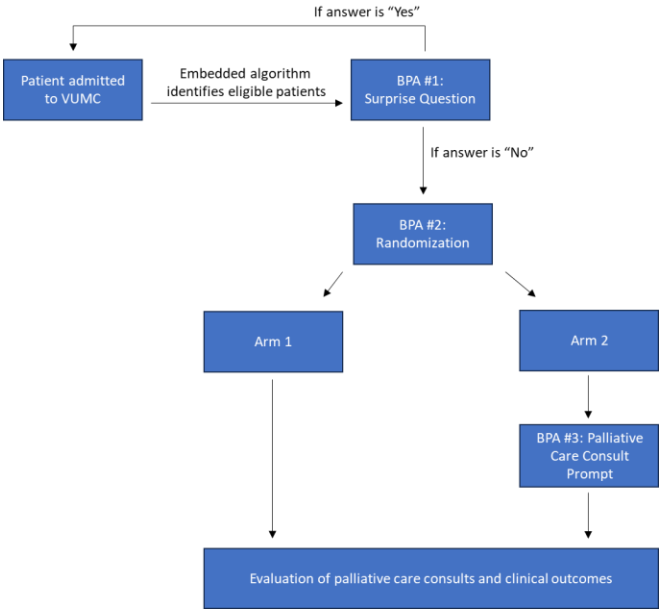

Figure 1. Flow Diagram outlining best practice advisor (BPA) logic and processing pathways.

8. Study Procedures

8.1 Palliative Care Consultation Prompt Group

When a patient is randomized to the Palliative Care Consultation Prompt Group, a clinical decision support tool in the electronic health record will inform the treating clinician of the patient's serious illness and the results of the Surprise Question and prompt the treating clinician to consider a palliative care consultation. The goal of this prompt is to encourage appropriate palliative care engagement. If the treating clinician feels a palliative care consultation would be indicated for the patient, the clinical decision support tool will facilitate the placement of a palliative care consultation by the treating clinician. As per usual care, the treating clinical team will then discuss elements of palliative care and the goals of the consult with the patient. The palliative care consultation will aim to provide best practices for supporting patients with serious illnesses, which is described in detail in the Appendix, Framework for Best Practices of (Inpatient) Palliative Care Consultation. If the treating clinician feels that a palliative care consultation would not be indicated, then the clinical decision support will record a reason for why a palliative care consultation is not indicated. A treating clinician can choose to place or discontinue a palliative care consultation at any time, retaining full autonomy to deliver the appropriate patient care. A patient may choose to request or decline a palliative care consultation at any time.

8.2 No Palliative Care Consultation Prompt Group

When a patient is randomized to the No Palliative Care Consultation Prompt Group, no prompt will occur. A treating clinician can choose to place or discontinue a palliative care consultation at any time. A patient may choose to request or decline a palliative care consultation at any time.

9. Data Collection

All data on baseline characteristics, receipt of interventions, and outcomes will be extracted from the electronic health record, electronic data warehouse, or other publicly available sources (e.g., Tennessee Department of Health, Centers for Disease Control, Tennessee Hospital Association). The Research Derivative 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. The minimum necessary data containing patient or provider identities will be collected. All data will be uploaded into a password-protected computerized database maintained within a secure, web-based application for building and managing online databases (REDCap) or stored on secure servers with user-level access control.

10. Outcome Measures

10.1 Primary Outcome

Stage 1: The primary outcome will be the percentage of patients with palliative care consults placed within 48 hours after enrollment. This initial stage is designed to determine feasibility and separation between groups. We are explicitly examining the separation between groups for the primary outcome at Stage 1 and have outlined the trial progression scenarios. It is anticipated that all patients will have the same data collected and will be included in the analyses for the primary, secondary, and exploratory outcomes.

Stage 2: The primary outcome will be hospital-free days by day 90. Hospital-free days will be defined as the number of calendar days between enrollment and day 90 in which the patient is alive and outside of an acute-care hospital. Days spent at home, at a rehabilitation facility, at a nursing facility, and at an inpatient hospice facility will count as hospital-free. Hospital-free days has been recommended as a patient-centered outcome for trials among seriously ill patients.[21]

10.2 Secondary Outcomes

Secondary outcomes for this trial include the following:

- Survival to day 90

10.3 Exploratory Outcomes

Exploratory outcomes for this trial include the following:

- Total number of days in the hospital by day 90
- Total number of hospital admissions by day 90
- Intensive care unit admission by day 90
- Total number of days in the intensive care unit by day 90

- Referral to hospice by day 90
- Emergency Department visits

10.4 Process Outcomes

Process outcomes for this trial include the following:

- Receipt of palliative care consultation
- Time to receipt of palliative care consultation
- Number of visits with palliative care team
- Completion of advance care planning upon admission as evidenced by POST form
- Election of resuscitation status (Do Not Resuscitate (DNR) and/or Do Not Intubate (DNI))

11. Risks and Benefits

Potential Risks: In this study of a clinical decision support tool prompting a clinician to consider palliative care consultation, the treating clinician determines whether a palliative care consultation is indicated. Patients may request or decline a palliative care consultation at any point. There are no known risks associated with use of a clinical decision support tool prompting a clinician to consider whether palliative care consultation is indicated. The provider will retain the autonomy to decide the appropriate clinical care for their patient. The loss of confidentially associated with the use of clinically collected PHI is a potential risk. This risk is minimized by the collection and management of data in the secure, online database.

Potential Benefits: For some patients with serious illness, specialty palliative care has been shown to improve physical and emotional symptoms and decrease the time spent in the hospital. It is possible that a clinical decision support prompting consideration of palliative care consultation may increase the number and timeliness of appropriate referrals to the palliative care service and subsequently the number of days outside the hospital and improve physical and emotional symptoms for patients. The results of the trial may improve care for thousands of patients with serious illness across the United States each year.

12. Statistical Considerations

Power and Sample Size Considerations: The sample size and power calculation for each clinical domain will be specified in the corresponding Appendices. The cumulative sample size of all the clinical domains together is anticipated not to exceed 5,000 patients.

Statistical Analysis Plan: A statistical analysis plan for each clinical domain will be made publicly available before the conclusion of enrollment. General principles of the statistical analysis are outlined here. Stage 1 will evaluate the primary outcome, percentage of patients with palliative care consults placed within 48 hours after enrollment, for an anticipated 10% of the total sample size. This initial stage is designed to determine feasibility and separation between groups. The following separations between groups, during Stage 1, would then determine trial progression to Stage 2.

- > 50% group separation: the trial would move forward to Stage 2 without modification.
- 15-50% group separation: the trial would move forward to Stage 2 with modification to the

eligibility criteria, intervention, or other aspects of the study protocol.

- < 15% group separation: the trial would not move forward to Stage 2.

We are explicitly examining the separation between groups for the primary outcome at Stage 1 and have outlined the trial progression scenarios. It is anticipated that all patients will have the same data collected and will be included in the analyses for the primary, secondary, and exploratory outcomes.

Baseline demographic and clinical characteristics of the participants (i.e., age, sex, race, comorbidities, disease severity, 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. The main analysis will be an intention-to-treat comparison of the primary outcome between patients randomized to each of the two trial groups using a Wilcoxon rank-sum test. The main analysis of the secondary outcome will be an intention-to-treat comparison of the secondary outcome of survival to 90 days between the two trial groups using a Cox Proportional-Hazards model.

13. Privacy and Confidentiality

At no time during this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. As quickly as feasible, all data collected will be uploaded into a password-protected computerized database maintained within a secure, web-based application for building and managing online databases (REDCap) or stored on secure servers with user-level access control. All patients will be assigned a unique study number for use in the computerized database. At the time of publication all identifiers will be removed.

14. Follow up and Record Retention

Patients will be followed until complete data are available regarding clinical care and outcomes between enrollment and 90 days after enrollment. During the study and analyses, data will be stored in a secure, online database. At the time of publication, all identifiers will be removed and a fully deidentified dataset will be stored indefinitely to allow replication of the results.

15. Safety Monitoring and Adverse Events

15.1 Adverse Event Definitions

Adverse Event – An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any adverse event occurring during the research will be classified according to the following characteristics:

- **Seriousness** – An adverse event will be considered "serious" if it:
    - Results in death
    - Is life-threatening (defined as placing the patient at immediate risk of death)
    - Results in inpatient hospitalization or prolongation of existing hospitalization
    - Results in a persistent or significant disability or incapacity
    - Results in a congenital anomaly or birth defect or
    - Based upon appropriate medical judgment, may jeopardize the patient's health, and

may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- **Unexpectedness** – An adverse event will be considered "unexpected" if the nature, severity, or frequency is neither consistent with:
    - The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol; nor
    - The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

- **Relatedness** – The strength of the relationship of an adverse event to a study intervention or study procedure will be defined as follows:
    - Definitely Related: The adverse event follows (1) a reasonable, temporal sequence from a study procedure AND (2) cannot be explained by the known characteristics of the patient's clinical state or other therapies AND (3) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
    - Probably or Possibly Related: The adverse event meets some but not all of the above criteria for "Definitely Related".
    - Probably Not Related: The adverse event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
    - Definitely Not Related: The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
    - Uncertain Relationship: The adverse event does not fit in any of the above categories.

15.2 Monitoring for Adverse Events

The time interval during which patients will be monitored for the occurrence of adverse events begins at randomization and ends at the first of hospital discharge or 90 days. Adverse events occurring before randomization or after hospital discharge or 90 days will not be collected. The principal investigator will have primary responsibility for overseeing the monitoring, assessment, and reporting of adverse events. Study personnel will evaluate for the occurrence of adverse events by review of the electronic health record and by communication with treating clinicians. Study personnel will evaluate for the occurrence of adverse events by manual review of the electronic health record during initial data collection and during final data collection. Study personnel will also communicate regularly with the treating clinicians in the study environments to solicit information about any potential adverse events. If study personnel identify a potential adverse event, the principal investigator will be immediately notified. The principal investigator will assess the seriousness, unexpectedness, and relatedness of the potential adverse event. The principal investigator will determine whether the event qualifies for recording and reporting.

15.3 Recording and Reporting Adverse Events

The following types of adverse events will be recorded and reported:

- Adverse events that are Serious and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.
- Adverse events that are Unexpected and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.

Adverse events that do not meet the above criteria will not be recorded or reported. Adverse events that the principal investigator assesses to meet the above criteria will be recorded. The principal investigator will record an assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness. For any adverse event that is **serious AND unexpected**, and definitely related, probably or possibly related, or of uncertain relationship, the principal investigator will report the adverse event to the study support staff **within 24 hours** of becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the principal investigator will report the adverse event to the study support staff **within 72 hours** of becoming aware of the adverse event. The study support staff will coordinate with the principal investigator to obtain information about the adverse event regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness. The principal investigator will be responsible for making final determinations regarding seriousness and unexpectedness. The study support staff will facilitate final determinations regarding relatedness.

For adverse events that meet the above criteria for recording and reporting, study support staff will notify the IRB in accordance with the following reporting plan:

Characteristics of the Adverse Event	**Reporting Period**
Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibility related, or of uncertain relationship.	Report to the IRB within 7 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related, or of uncertain relationship.	Report to IRB within 15 days of notification of the event.
All other adverse events meeting criteria for recording and reporting.	Report to IRB during the annual continuing review.

15.4 Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of hospitalized patients with serious illness at high risk for death and other adverse outcomes due to their underlying serious illness, clinical outcomes, including death, will be systematically collected and analyzed for all patients. The primary, secondary, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or the principal investigator believe the event is Definitely Related or Probably or Possibly

Related to the study intervention or study procedures. This approach – considering death and other outcomes as clinical outcomes rather than adverse events and systemically collecting these clinical outcomes for analysis – is common in trials among patients with serious illness. This approach ensures comprehensive data on death and other outcomes for all patients, rather than relying on sporadic adverse event reporting to identify these important events. The following events are examples of study-specific clinical outcomes that would not be recorded and reported as adverse events unless treating clinicians or the principal investigator believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death
- Duration of ICU admission
- Duration of hospitalization

15.5 Unanticipated Problems involving Risks to Subjects or Others

The principal Investigator must also report Unanticipated Problems Involving Risks to Subjects or Others ("Unanticipated Problems"), regardless of severity, associated with study procedures **within 24 hours** of the principal investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol; and (b) the characteristics of the subject population being studied; AND
- Definitely Related or Probably or Possibly Related to participation in the research (as defined above in the section on characteristics of adverse events); AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If any study personnel become aware of an event that may represent an Unanticipated Problem, they will immediately contact the principal investigator. The principal investigator will assess whether the event represents an Unanticipated Problem by applying the criteria described above. If the principal investigator determines that the event represents an Unanticipated Problem, the principal investigator will record the Unanticipated Problem. The principal investigator will then communicate that an Unanticipated Problem has occurred to the supporting study team personnel **within 24 hours** of becoming aware of the Unanticipated Problem. The principal investigator or study personnel will report the Unanticipated Problem to the IRB within 15 days of becoming aware of the Unanticipated Problem.

16. References

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Appendix A: End-Stage Liver Disease

Clinical Domain Investigators: **End-Stage Liver Disease**

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1.0 End- Stage Liver Disease Protocol Summary

Clinical Domain	Patients with serious illness due to End-Stage Liver Disease (ESLD).
Study Design	As per Master Protocol.
Trial Groups	As per Master Protocol.
Domain-Specific Criteria	**Inclusion Criteria:** • Patient meets phenotype criteria for ESLD. **Exclusion Criteria:** • Patient has received liver transplant.
Risks	As per Master Protocol.
Benefits	As per Master Protocol.
Consent	As per Master Protocol.
Randomization	As per Master Protocol.
Domain-Specific Primary Outcome	As per Master Protocol.
Domain-Specific Secondary Outcomes	As per Master Protocol.
Domain-Specific Exploratory Outcomes	As per Master Protocol.
Domain-Specific Process Outcomes	As per Master Protocol.
Analysis	As per Master Protocol.
Domain-Specific Sample Size	An anticipated sample size for Stage 1 is approximately 10% of the total sample size for the trial (776 patients) or 78 patients, 39 per group. The estimated sample size for Stage 2 is 698 patients, 349 per group. Patients from Stage 1 will be incorporated and evaluated at Stage 2 resulting in a total sample size of 776 patients, 388 per group. The sample size estimations for the ESLD clinical domain were based on observational data obtained from hospitalized adults with ESLD at VUMC and THA hospitals.
Expected Duration	12 months anticipated

2.0 Background

Chronic liver disease and cirrhosis is the 12th leading cause of death in the United States.[1] Patients with End-Stage Liver Disease (ESLD), a progressive illness synonymous with decompensated cirrhosis, advanced liver disease, and liver failure[2], 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.[3,4] Many cirrhotic patients face financial, emotional, and social problems relating to the stigma of liver disease,[4] and quality of life is often decreased due to physical and psychological symptoms.[2] For patients with decompensated cirrhosis, liver transplantation is the only cure. More than 15,000 candidates were registered on the waiting list for liver transplant in the US as of December 31, 2013.[5] 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.[5] 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 status in their chart.[6] Another study considered all patients discussed by an institution's Liver Transplant Committee at a tertiary care academical medical center with a large liver transplantation program. Of 769 patients discussed, 135 were removed from transplant consideration; and only 27 of those 135 were referred to palliative care.[7] 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 prompting the consideration of palliative care services earlier and more consistently in context with disease-directed therapies will improve palliative care introduction into ESLD patient treatment plans subsequently yielding the hospital-free days in this population and will delay or reduce hospital readmissions while maintaining or improving quantitative and qualitative measures of quality of life and end of life care.[8]

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 palliative care intervention counteracted the progression of worsening symptoms and significantly improved pruritus, appetite, anxiety, depression, fatigue, and well-being.[9] Moreover, the introduction of palliative care within the care course of patients with decompensated cirrhosis is endorsed by an AASLD (American Association for the Study of Liver Diseases) practice guidance document.[10]

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.[11] 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.[12]

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 surgical intensive care unit 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, do-not-resuscitate status significantly increased in those who died from 52% pre-implementation to 81% post-implementation. Do-not-resuscitate status was also instituted earlier, decreasing from 38 days after admission to 19 days after admission.[13] 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.

ESLD has been recognized as a condition in which early palliative care may be beneficial.[9,13] Patients with ESLD have high rates of severe symptoms, high levels of healthcare utilization, and a low rate of advance care planning.[6,8] Moreover, for patients with decompensated cirrhosis, liver transplantation is the only cure. As of March 19, 2019, over 13,000 candidates were registered on the waiting list for liver transplant in the US.[14] Previous studies in ESLD patients have shown associations of palliative care interventions with improvements in symptom control, mood, and quality of life and reduction in healthcare utilization.[9,13] These results suggest that the many patients who are not candidates for transplantation and those on the waitlist who may have considerable wait time would likely benefit from specialist palliative care.

We previously designed and implemented a randomized, controlled trial of a specialist palliative care intervention for ESLD patients admitted as inpatients to our institution. An important component of eligibility related to the use of the Surprise Question, which was demonstrated to be a potentially useful screening tool in this population. Due to slower than expected enrollment, the trial was terminated before full enrollment. Despite the trial's early closure, early palliative care intervention increased time to readmission and hospital free days compared to usual care with no effect on mortality, though our study was underpowered for the latter endpoint. These encouraging outcomes in this small trial indicate a potential signal for the effectiveness of specialty palliative care impact on time to readmission and

days alive outside of the hospital in ESLD patients that should be investigated in further, fully powered studies.[15]

3.0 Aims and Hypotheses
As per Master Protocol.

4.0 Study Design
As per Master Protocol.

5.0 Condition-Specific additional Inclusion and Exclusion Criteria

Inclusion:

- As per Master Protocol
  AND
- Patient meets phenotype criteria for ESLD.

Exclusion:

- As per Master Protocol
  AND
- Patient has received liver transplant.

5.1 ESLD Phenotyping Criteria
Patients will be considered to have met the "phenotype criteria" for ESLD if they meet BOTH of the following criteria:

1. Electronic health record contains one or more of the following ICD-10 codes for a diagnosis of a cause of end-stage liver disease within the last 5 years:
   - ICD10 B18.0-Chronic viral hepatitis B with delta-agent
   - ICD10 B18.1-Chronic viral hepatitis B without delta-agent
   - ICD10 B18.2-Chronic viral hepatitis C
   - ICD10 B18.8-Other chronic viral hepatitis
   - ICD10 B18.9-Chronic viral hepatitis, unspecified
   - ICD10 B19.10-Unspecified viral hepatitis B without hepatic coma
   - ICD10 B19.11-Unspecified viral hepatitis B with hepatic coma
   - ICD10 B19.20-Unspecified viral hepatitis C without hepatic coma
   - ICD10 B19.21-Unspecified viral hepatitis C with hepatic coma
   - ICD10 K70.0-Alcoholic fatty liver
   - ICD10 K70.2-Alcoholic fibrosis and sclerosis of liver
   - ICD10 K70.30-Alcoholic cirrhosis of liver without ascites
   - ICD10 K70.31-Alcoholic cirrhosis of liver with ascites
   - ICD10 K71.7-Toxic liver disease with fibrosis and cirrhosis of liver
   - ICD10 K73(group)-Chronic hepatitis, not elsewhere classified
   - ICD10 K74.0-Hepatic fibrosis

- ICD10 K74.1-Hepatic sclerosis
- ICD10 K74.2-Hepatic fibrosis with hepatic sclerosis
- ICD10 K74.3-Primary biliary cirrhosis
- ICD10 K74.4-Secondary biliary cirrhosis
- ICD10 K74.5-Biliary cirrhosis, unspecified
- ICD10 K74.60-Unspecified cirrhosis of liver
- ICD10 K74.69-Other cirrhosis of liver
- ICD10 K75.4-Autoimmune hepatitis
- ICD10 K75.89-Other specified inflammatory liver diseases
- ICD10 K75.9-Inflammatory liver disease, unspecified
- ICD10 K76(group)-Other diseases of liver
- ICD10 P78.81-Congential cirrhosis (of liver)

AND

2. Electronic health record contains one or more of the following complications of end-stage liver disease within the last 5 years:
    - ICD10 G93.40-Encephalopathy, unspecified
    - ICD10 G93.49-Other encephalopathy
    - ICD10 I85.0(group)-Esophageal varices
    - ICD10 I86.4-Gastric varices (this includes gastric varices with bleeding)
    - ICD10 K65.0-Generalized (acute) peritonitis
    - ICD10 K65.2-Spontaneous bacterial peritonitis
    - ICD10 K65.9-Peritonitis, unspecified
    - ICD10 K70.11-Alcoholic hepatitis with ascites
    - ICD10 K70.31-Alcoholic cirrhosis of liver with ascites
    - ICD10 K71.51-Toxic liver disease with chronic active hepatitis with ascites
    - ICD10 K72.90-Hepatic failure, unspecified without coma
    - ICD10 K72.91-Hepatic failure, unspecified with coma
    - ICD10 K76.7-Hepatorenal syndrome
    - ICD10 K76.82-Hepatic encephalopathy
    - ICD10 K92.2-Gastrointestinal hemorrhage, unspecified
    - ICD10 R18.8-Other ascites

5.2 Additional Demographics for the ESLD Clinical Domain

- MELD score

6.0 Consent

As per Master Protocol.

7.0 Study Sites, Enrollment, and Randomization

As per Master Protocol.

8.0 Study Procedures
As per Master Protocol.

8.1 Palliative Care Consultation Prompt Group
As per Master Protocol.

8.2 No Palliative Care Consultation Prompt Group
As per Master Protocol.

9.0 Data Collection
As per Master Protocol.

10.0 Outcome Measures
10.1 Primary Outcome
As per Master Protocol.

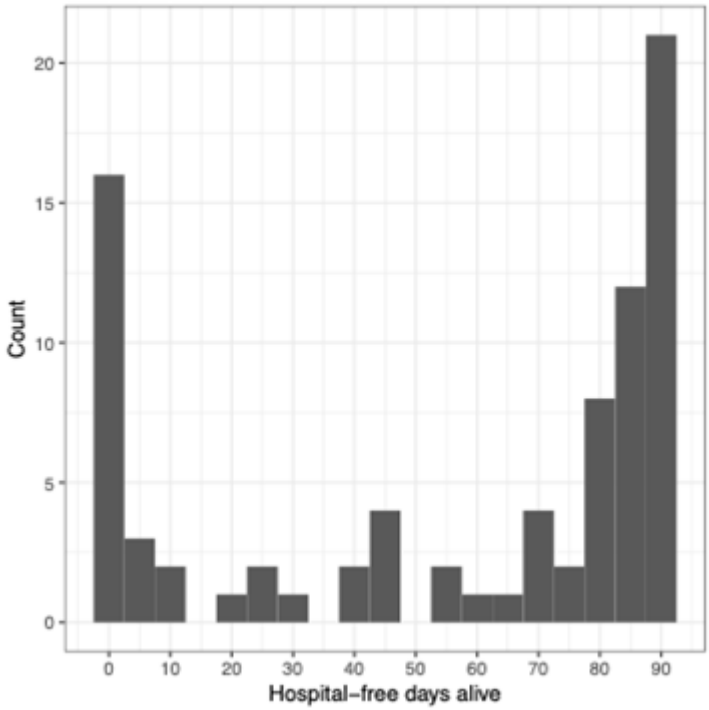
10.2 Secondary Outcomes
As per Master Protocol.

10.3 Exploratory Outcomes
As per Master Protocol.

10.4 Process Outcomes
As per Master Protocol.

11.0 Risks and Benefits
As per Master Protocol.

12.0 Statistical Considerations
Power and Sample Size Considerations: The number of hospital-free days can have a very asymmetric distribution with floor and ceiling effects and many tied values. This results in a scale that is best analyzed with a proportional odds model and treatment effect can be summarized as a common odds ratio.



The minimal effect on hospital-free days to avoid missing is judged to be 7 days. Assuming the distribution shown in the above histogram, this represents an odds-ratio-shifted distribution from the observed mean of 56 to 63 for an odds ratio of 1.5. Again, using the reference distribution above, to detect a difference of 7 days (odds ratio of 1.5) with 0.9 power would require 388 subjects per study group.

An anticipated sample size for Stage 1 is approximately 10% of the total sample size for the trial (776 patients) or 78 patients, 39 per group. The estimated sample size for Stage 2 is 776 patients, 388 per group. We are explicitly examining the separation between groups for the primary outcome at Stage 1 and have outlined the trial progression scenarios. It is anticipated that all patients will have the same data collected and will be included in the analyses for the primary, secondary, and exploratory outcomes. Stage 1 to Stage 2 trial progression will occur utilizing the same group separation framework described in the Master Protocol. The sample size estimations for the ESLD clinical domain were based on observational data obtained from hospitalized adults with ESLD at VUMC and THA hospitals.

13.0 Privacy and Confidentiality
As per Master Protocol.

14.0 Follow-up and Record Retention
As per Master Protocol.

15.0 Safety Monitoring and Adverse Events

As per Master Protocol.

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Appendix B: Framework for Best Practices of (Inpatient) Palliative Care Consultation

1. Definitions
    a. Palliative care is medical care that aims to alleviate suffering and improve the quality of life of patients with serious illness.[1]
    b. Primary Palliative Care: palliative care provided by a healthcare provider not specializing in palliative and hospice medicine (e.g., primary hepatologist).
    c. Specialty Palliative Care: palliative care provided through consultation by those trained and/or board certified in hospice and palliative medicine.[2,3]

2. Standard Consultation of Palliative Care Interdisciplinary Team.
    a. Interdisciplinary team (IDT): a team of palliative care specialists that includes but not limited to: physicians, advanced practitioners, nurses, social workers, and chaplains, dedicated to assessment of physical, psychological, social, spiritual, cultural, and ethical care plans of those with serious illness and at end of life.[4]
    b. Consultations will follow standard palliative care consultations conducted at VUMC, acknowledging the heterogeneity of real-world encounters and tailored to address individual/family/caregivers' needs. Palliative care specialists may address any or all of the following:

        i. Introduction/Education of palliative care field and its goals.
        ii. Assess and/or treat symptoms.
        iii. Identify patient surrogate and Advance Care Planning.
        iv. Engage patient and/or surrogate on:
            1. Understanding of serious illness and prognosis.
            2. Patient's values and goals of care.
            3. What is and is not an acceptable quality of life.
        v. Facilitate communication and explore possible treatment pathways based on available medical interventions in setting of above goals.
        vi. Implement goal-concordant treatment pathway.
        vii. Referral to post-acute support services as appropriate (e.g., hospice, outpatient palliative care, skilled nursing, OT/PT…).

3. End-Stage Liver Disease/SeQuEL Considerations
    Below are topics of consideration to guide Palliative Care consultations for patients hospitalized with ESLD:
    a. Indication, possibility, and requirements for transplant should be delineated as clearly as possible in order to allow for most effective discussion of treatment pathways.
    b. Eliciting patient (and/or surrogate) understanding of their liver disease (including treatment and/or prognosis) in the context of their lives and personal values/goals.
    c. Within context of elected goals/treatment pathway, procedural ESLD symptom management and discussions (e.g., transplant, ascites-TIPS/Indwelling catheters, variceal bleeding-EGD/TIPS/BTO) should be coordinated with, if not guided by, hepatology treatment team.

d. Within context of elected goals/treatment pathway, non-procedural symptom management and discussions (e.g., encephalopathy, pain, nausea, dyspnea, pruritus, muscle cramping, sleep disturbance, depression/anxiety etc.) may not require specific consultation with hepatology team other than coordination to ensure clear roles for effective teamwork and management; coordination and multidisciplinary discussion is always encouraged.
e. When feasible, family meetings and discussions should include patient-important stakeholders as well as members of primary medical stakeholders, in particular primary treatment team and hepatology consult team. Pre-meeting and debriefing should be components of family meeting protocol to ensure most effective communication.

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