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

Statistical Analysis Plan

5/3/24

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2024-05-22
Date

Introduction

Palliative care is specialized medical care focused on providing patients with relief from the symptoms, pain, and stress of serious illness, regardless of stage or prognosis, by anticipating, preventing, and treating suffering. 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. 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 to accomplish meaningful improvements.

In our pilot trial involving 63 patients hospitalized with End-Stage Liver Disease (ESLD), palliative care consultation appeared to increase the number of hospital-free days without affecting mortality, compared with usual care. Though preliminary, these findings support the need for further evaluation of prompting palliative care consultation for hospitalized patients with ESLD. In our pilot trial and other studies of serious illness, patients for whom consideration of palliative care consultation might be appropriate have been identified use the "Surprise Question", which asks the treating clinician "would you be surprised if this patient died in the next 12 months?" Despite its simplicity, this tool has been used extensively in prior palliative care studies.

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 relative to actual palliative care engagement which subsequently may impact hospital-free days among hospitalized patients with ESLD.

Population and design considerations

Study Population:

Adult patients with ESLD admitted to Vanderbilt University Medical Center (VUMC) 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'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?"
- Patient meets phenotype criteria for ESLD.

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

Exclusion criteria:

- Patient is known to have received any VUMC palliative care consultation during the prior 3 months and/or the current admission.
- Patient has received liver transplant.
- Patient is known to be a prisoner.

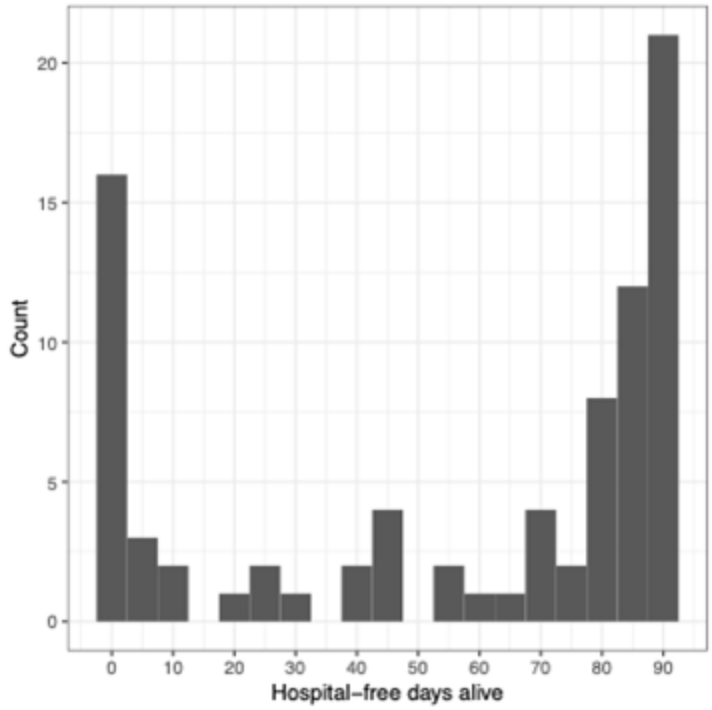
Study Design:
This is a single center, pragmatic randomized platform trial determining whether prompting consideration of palliative care consultation through the electronic health record increases both the number of palliative care consults placed and hospital-free days among hospitalized adults with ESLD.

Randomization:
A best practice advisor will algorithmically 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, "would you be surprised if this patient were to die in the next 12 months?" 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.

Sample Size Considerations:
The study will take a staged approach to ensure the trial protocol accomplishes separation between groups before assessing clinical outcomes.

Stage 1 is essentially a screening for Stage 2. An anticipated sample size for Stage 1 is approximately 10% of the total sample size for the trial (776 patients) or 78. The sample size estimations for the ESLD clinical domain were based on observational data obtained from hospitalized adults with ESLD at VUMC and Tennessee Hospital Associations hospitals.

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 ordinal logistic model for which the treatment effect can be summarized as a common odds ratio.



The minimal effect on the number of 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.

Interventions

a. Palliative Care Consultation Prompt Group: A clinical decision support tool in the electronic health record will inform the treating clinician to consider a palliative care consultation. 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. If the treating clinician feels that a palliative care consultation would not be indicated, then the clinical decision support will record a reason why a palliative care consultation is not indicated.

b. No Palliative Care Consultation Prompt Group: The patient's treating clinician will not receive a prompt in the electronic health record to consider a palliative care consultation.

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, irrespective of intervention assignment.

Endpoints

Primary Endpoint

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.

Secondary Endpoint(s)

There is one secondary outcome for this trial.

Survival to day 90. Defined as the number of calendar days in which the patient is alive between enrollment and day 90.

Exploratory Endpoint(s)

There are multiple prespecified exploratory outcomes for this trial.

Total number of days in the hospital by day 90. Defined as the number of calendar days in which the patient spends at VUMC or a THA hospital between enrollment and day 90. Days spent at home, at a rehabilitation facility, at a nursing facility, and at an inpatient hospice facility will not count towards this measure.

Total number of hospital admissions by day 90. Defined as the total number of admissions at VUMC or a THA hospital that occur for the patient between enrollment and day 90.

Intensive care unit admission by day 90. Defined as any intensive care unit admission that occurs at VUMC for the patient between enrollment and day 90.

Total number of days in the intensive care unit by day 90. Defined as the total number of calendar days in which the patient stays within an intensive care unit at VUMC between enrollment and day 90.

Referral to hospice by day 90. Defined as any patient referral to inpatient or outpatient hospice that occurs between enrollment and day 90.

Emergency Department visits. Defined as the total number of Emergency Department visits at VUMC or a THA hospital that occur for the patient between enrollment and day 90.

Process Endpoint(s)

There are multiple prespecified process outcomes for this trial.

Receipt of palliative care consultation. Defined as date/time in which the patient receives the VUMC inpatient palliative care consultation between enrollment and day 90.

Time to receipt of palliative care consultation. Defined as the amount of time (hours/days) from when the palliative care consultation is placed by the provider to when the patient receives the VUMC inpatient palliative care consultation.

Number of visits with palliative care team. Defined as the total number of visits in which the patient meets with the VUMC inpatient and outpatient palliative care team between enrollment and day 90.

Completion of advance care planning upon admission as evidenced by POST form. Defined as the date and time in which the patient has completed a POST form.

Election of resuscitation status (Do Not Resuscitate (DNR) and/or Do Not Intubate (DNI)). Defined as the date and time in which the patient has elected a Do Not Resuscitate and/or Do Not Intubate at VUMC between enrollment and day 90.

Analysis dataset
The analysis for the trial will use an intent-to-treat approach to answer the effectiveness question posed. That is, participants will be evaluated by treatment group as assigned regardless of what was delivered. All eligible participants will be included.

Statistical Approach
Our initial analysis will be descriptive in nature, summarizing information that characterizes the cohort and the outcomes. Then, we will proceed with inferential analysis to answer the main study question. Then, we will compare the secondary endpoints between study groups.

Descriptive Analysis
To characterize the study sample, baseline demographic and clinical data will be described overall and by group. Categorical variables will be described using frequencies and proportions, and continuous variables will be described using means and standard deviations, as well as medians and interquartile ranges. Missingness will be reported for each variable. Graphical summaries using extended box plots, violin plots, cumulative distribution plots, and/or histograms may be used to describe the data graphically. At a minimum, the following variables will be described at time of enrollment:

- Age (years)
- Sex (male, female, unknown)
- Race (African American, Asian/Pacific Islander, Caucasian, Multiple, Native American, Other, Unknown)
- Ethnicity (Hispanic, Non-Hispanic, Unknown)
- Comorbidities (Charlson or Elixhauser)
- MELD score

We will describe all of the outcome variables overall and grouped by study arm using the same approach as for the demographic data. Summary statistics and graphical representations may be displayed, and missingness will be reported for each variable.

No statistical comparisons between groups will be done for this descriptive analysis. Please note, showing descriptive statistics stratified by treatment groups that were randomized can be easily misinterpreted, as all apparent imbalances are by definition due to chance. Descriptive statistics of all-comers need to be emphasized in randomized studies.

Main Analysis
As indicated above, the Stage 1 outcome will evaluate the proportion 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. The main analysis of the primary outcomes will be intention to treat comparisons between patients randomized to each of the two trial groups. For the second stage primary analysis, the likelihood ratio test from the proportional odds ordinal logistic regression model will be used to compare groups on the number of hospital-free days alive. This is a generalization of the Wilcoxon two-sample test and will be adjusted for the pre-specified baseline covariates. If a baseline covariate is missing on 5 or fewer patients, it will be imputed using the grand median (mode if categorical). If any covariates are missing on more than 5 patients, multiple imputation will be used to impute sometimes-missing covariates, and the results from the separate completed-dataset analyses will be combined using Rubin's rule.

We do not expect missingness in the outcome variables.

The main analysis of the secondary outcome (survival to day 90) will be an intention-to-treat comparison between the two trial groups using a Cox Proportional-Hazards model.

There may be missingness in secondary or implementation outcomes. The cohort for which the outcome is available will be described, along with the results of the model evaluating treatment effects in this cohort. All model results will be summarized with point estimates and 95% confidence intervals (CIs), which will be emphasized over p-values when reporting the results for secondary and implementation outcomes. No adjustments for multiplicity will be made.

Additionally, a descriptive analysis of missingness tendencies is warranted. For example, logistic regression to predict the probability of missingness of an outcome measurement with predictors that include baseline variables and other outcomes that are never missing.

If there are missing outcomes, in rare cases, these may be imputed if they occur in less than 5% of cases. Proceed with caution and only upon consult with Lead Statistician of record.

Differential treatment effects
To determine whether effects of treatment on the primary endpoint depends on any of the baseline characteristics, we will test the interaction between the baseline characteristics and treatment effect in a proportional odds model. A secondary analysis (i.e., adjusted or subgroup analysis) will evaluate the interaction between treatment effect by baseline MELD score. The prespecified potential interacting factors are MELD score, the number of patient comorbidities, liver transplant candidacy, sex, race, ethnicity, and insurance status.

Summary
The results of this study will help to determine whether prompting consideration of palliative care consultation through the electronic health record increases palliative care engagement and subsequently the number of hospital-free days among hospitalized adults with ESLD. The analysis approach we describe is selected based on the trial's pragmatic nature and the intent to understand the effect of prompting consideration of palliative care consultation through a best practice alert on clinical outcomes for hospitalized adults with ESLD.