RESEARCH PROTOCOL

Title: Introducing Palliative Care (PC) within the Treatment of End Stage Liver Disease (ESLD): A Cluster Randomized Controlled Trial.

Short Title: **PAL-LIVER Study** (PALliative Care for LIVER disease)

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CONFIDENTIAL

Reviewed and Approved by

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Site Investigator Protocol Signature Page

I have read and understand the protocol and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described. I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I am aware that this protocol must be approved by the Institutional Review Board or Ethics Committee. I agree to adhere strictly to the attached protocol. I agree that clinical data entered on case report forms by me and my staff will be supplied to the DCRI and may be utilized by the DCRI in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow DCRI monitors and auditors full access to all medical records at the research facility for subjects screened or randomized in the study. I agree to provide all subjects with informed consent forms, as required by government regulations and International Conference on Harmonization guidelines.

Version Date: 12-10-2024

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Printed Name of Site Investigator

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Signature of Site Investigator **Date**

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Printed Site Name

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ABBREVIATIONS

ASCO	American Society of Clinical Oncology
AUDIT	Alcohol Use Disorders Identification Test
BCLC	Barcelona Clinic Liver Cancer
CRF	Case Report Form
CTP	Child-Turcotte Pugh Score
DCC	Data Coordinating Center
DCRI	Duke Clinical Research Institute
DSMB	Data Safety and Monitoring Board
EMR	Electronic Medical Record
ER	Emergency Room
ESAS	Edmonton Symptom Assessment Scale
ESLD	End Stage Liver Disease
EWB	Emotional well being
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Hep	Functional Assessment of Cancer Therapy – Hepatobiliary
FAMCARE-P	Family Satisfaction with Care-Patient
FWB	Functional well being
HCC	Hepatocellular Cancer
HCS	Hepatobiliary cancer subscale
HCV	Hepatitis C
HIPAA	Health Insurance Portability and Accountability Act
HTE	Heterogeneity of Treatment Effect
ICC	Intraclass correlation coefficient
IRB	Institutional Review Board
LT	Liver transplant
MCID	Minimally clinically important difference
MELD	Model for End Stage Liver Disease
MI	Multiple imputations
MRN	Medical record number
NASH	Non-Alcoholic Steatohepatitis
NCCN	National Comprehensive Cancer Network
OPTN	Organ Procurement and Transplantation Network
PC	Palliative Care
PHQ-9	Personal Health Questionnaire
PROMIS-29	Patient Reported Outcomes Measurement Information System
PWB	Physical well being
QOL	Quality of Life
RAB	Research Advisory Board
RCT	Randomized controlled trial
SBP	Spontaneous Bacterial Peritonitis

SD	Standard deviation
SES	Social economic status
SFWB	Social and family well being
VA	Veterans Affairs
ZBI-12	Zarit Burden Interview

A. INTRODUCTION

1. Study Synopsis

Sponsor	Albert Einstein Healthcare Network
Protocol Title	Introducing Palliative Care (**PC**) within the Treatment of End Stage Liver Disease (ESLD): A Cluster Randomized Controlled Trial/ **PAL-Liver** study (Palliative Care for Liver Disease)
Diagnosis and Main Criterion for Inclusion	Patients with new onset or ongoing complications of End Stage Liver Disease including Hepatocellular Cancer (HCC), with or without a caregiver willing to participate.
Main Criterion for Exclusion	Model for End Stage Liver Disease Score (MELD)> 30, Expected life expectancy of less than 6 months, or anticipated time to transplant within three months of enrollment.
Primary Study Objective	To assess the comparative effectiveness of two Palliative Care Delivery models for patients with end stage liver disease on improving quality of life (QOL)
Two Comparative Models	**Model 1**: Consultative PC (i.e. consultation with a board-certified or board-eligible PC specialist provider) **Model 2**: Trained hepatologist-led PC intervention (i.e. hepatologist trained to deliver PC services)
Study Intervention Visits	All patients and caregivers participating in this study will receive palliative care intervention at an **initial visit, followed by 1, 2, and 3 months**. All study visits can occur in the outpatient (in person or remote/ phone) or inpatient setting.
Study Intervention Description	The intervention will comprise an approach to render palliative care, as taught to hepatologists through an on-line learning platform, and as delivered by PC providers as routine care. The elements of the intervention will follow a palliative care checklist (Table 1), to include: 1. Patient/caregiver understanding of diagnosis, illness and prognosis 2. Symptom assessment and management 3. Psychosocial assessment and management 4. Distress screening and management 5. Discussion of goals of care 6. Advanced directives The intervention is delivered over the course of initial, 1-, 2-, and 3-month visits, <u>each approximately one hour in duration</u>. The providers (PC provider or Hepatologist) will complete the PC checklist after each intervention visit to document what was discussed.
Primary Outcome	▶ Change in **quality of life from baseline to 3 months**, as assessed by FACT-Hep total score
Secondary Outcomes	Change from baseline to 3 months for: ▶ Overall quality of life (PROMIS-29, separate T scores) ▶ Symptom burden (modified ESAS, point score)

	▶ Depression severity (PHQ-9, total score) ▶ Distress (Distress Thermometer, total score) ▶ Satisfaction with care (FAMCARE-P, total score) ▶ Caregiver burden (ZBI-12, total score) ▶ Caregiver quality of life (PROMIS-29, separate T scores) ▶ Goal concordant care (Patient and Caregiver Questionnaire, total score) Healthcare utilization: ▶ Rate of unscheduled office visits within 1 year from the initial visit ▶ Proportion of patients with at least one scheduled or unscheduled hospital admission within 30 days from the initial visit ▶ Proportion of patients with at least one scheduled or unscheduled hospital admission within 90 days from the initial visit ▶ Rate of ER visits within 1 year from the initial visit
Exploratory Outcomes	Survival
Primary Hypothesis	Compared to consultative PC, ESLD patients receiving trained hepatologist-led PC will have higher QOL change scores at 3 months after baseline.
Study Design	This is a two-armed cluster randomized controlled trial (RCT). Randomization will take place at the level of clinical centers, and will be stratified by VA vs non-VA. Each arm will have initially 7 clinical centers. Additional centers will be added if needed and the study utilized 19 centers. Standardized protocols (including visit agenda) will be followed at each of the clinical centers to maintain intervention fidelity across sites.
Qualitative Methods	Semi structured interviews will be conducted with patients/caregivers and healthcare providers, to evaluate their experiences in the two PC models.
Duration of Study Participation	Each participating patient/caregiver dyad will participate for 3 months of study intervention, and 9 months of follow up for a total of 12-months of participation. Survival data will be collected for 12 months of participation. No study visits are mandated during the 9-month follow-up period.
Study Intervention Visits (for Both Model 1 and 2)	All patient-caregiver dyads will receive the intervention at the initial visit, and at 1, 2, and 3 months from the initial visit. Initial/ 1st visit will occur within 6 weeks after informed consent. Ascertainment of baseline assessments will occur within 1 week before the scheduled initial visit. Informed consent, baseline assessments and initial visit may occur on the same day, but must follow this sequence. 1, 2 and 3 month visits can occur within a window period of 1 week (before/after) of their respective times from the initial visit. All study visits can occur in person, or remotely (by phone or telehealth with the institutional secure platform). All caregiver visits can occur in person or by phone, as preferred by the caregivers. The initial caregiver visit can occur on the same day or within 1 week of patient's initial visit.

Data Collection for Study Visits (Month 1, 2 and 3)	All data collection (patients and caregivers) can occur by phone, paper forms or using online surveys. ESAS, DT and PHQ-9 are conducted before the study visit (within 1 week of visit), and all other assessments are conducted after the study visit (within 1 week after the study intervention visit)
Data Collection during Follow Up	Study follow up data collection will be conducted at 6, 9 and 12 months, by phone, paper or online, within 1 week/ 7 days (before/after) of the due date.
Number of Patient Caregiver dyads	936 patients with a caregiver when available (n=563) will be enrolled. We aim to recruit approximately an equal number of patients from each of the centers. The study will have power (83.2%) for the primary analysis to detect a minimally clinically important difference of 9 points in QOL change (baseline to 3 months) between the two randomized arms.
Number of Sites	19 Clinical Centers (8 VA and 11 non-VA Academic Centers).

2. Primary Hypothesis (superiority):

PAL-LIVER's primary hypothesis is that patients receiving PC via the trained hepatologist-led PC (Model 2) will demonstrate a greater change in QOL (FACT-Hep scores) from baseline to 3 months, compared to Consultative led PC (Model 1). The **primary outcome measure** will be change in QOL (FACT-Hep total score) from baseline to 3 months. **The study has 83.2% power (simulation based)based to detect a clinically important difference** in the primary outcome between the two randomized arms. A difference of a 9 point increase in FACT-hep scores is considered a minimally clinically important difference (**MCID**).[1] The scientific premise of the primary hypothesis is that hepatologist-delivered PC will build upon an existing therapeutic relationship and expert knowledge of hepatic disease, prognosis, and disease trajectory allowing them to better individualize, and integrate PC into general hepatology care.

2a. Non-Inferiority Hypothesis:

The above outlined superiority hypothesis will be assessed first and only if such superiority is not demonstrated then the non-inferiority (NI) analysis will be performed. The NI margin is pre-specified. We chose the NI margin DELTA = 4. With this NI margin there is 79.2% power (simulation based) assuming presence of half of the considered superiority effect (MCID).

3. Significance of the Study

Despite clear evidence that PC improves QOL and symptom burden in other serious illnesses, referral of ESLD patients to PC specialists is infrequent and delayed until the very end of life.[2] Furthermore, the receipt of PC is stigmatized due to the persistent but inaccurate associations of PC with end of life/hospice care.[3] Published research identifies some of the major barriers to PC utilization in the routine care for ESLD patients- inadequate access to PC providers, episodes of decompensation that occur with increased frequency over time, discomfort with end of life care discussions, and a preferential focus on life saving interventions.[4] There is no standard model for integrating PC services within a specialty practice like hepatology, where most of the care occurs for patients with ESLD. Although it may seem that PC providers are better prepared rather than a hepatologist to offer PC to seriously ill ESLD patients, there are three potential limitations to this approach. *First*, the PC providers may be overburdened to meet the demand of a whole new patient population, adding to the existing shortage of PC providers.[5] *Second*, adding another

specialist to the care of already complex patients may "unintentionally undermine existing therapeutic relationships".[6]*Third*, non-PC providers may defer symptom management to a PC provider, who may be less comfortable in some approaches, such as prescribing medications to treat the underlying liver disease. These reasons support the development of a sustainable model, involving formal PC training of hepatologists, equipping them with a baseline competency to render effective and expedient PC in the context of routine liver care.

PC is an evolving subspecialty, focusing on patients' individual needs (including physical, psychosocial and spiritual).[7,8] PC has been shown to reduce healthcare costs, improve quality of care, and align goals of care between patients/families and their providers.[9] Specialized PC interventions in different settings have been shown to be an important element of care offered for serious illnesses like heart failure, advanced cancer, and multiple sclerosis.[10, 11, 12, 13, 14] Despite clear evidence that PC improves QOL and symptom burden in other serious illnesses, referral of ESLD patients to PC specialists is infrequent and often delayed until the very end of life.[15] Hence, the current proposal aims to build evidence in support of integration of PC into the routine care of ESLD patients who suffer from a high symptom burden, by comparing a **Consultative PC model to trained hepatologist-led PC delivery.**

4. Background and Rationale

End-Stage Liver Disease is the 12th leading cause of death in the US[16], the 7th leading cause of death in persons aged 25-64 years [17], and claims approximately 66,000 lives each year in the US. [18] The prevalence and mortality of ESLD have doubled from 2001 to 2013, with an expected peak in 2021.[19,20] This rise is primarily due to Hepatitis C, Non-Alcoholic Steatohepatitis (NASH), Alcohol Induced Liver Disease and Hepatocellular Cancer (HCC).[21] HCC is one of the few lethal cancers on the rise in the US, with an increase in incidence and mortality by 38% and 56%, respectively, from 2003-2012.[22] This disease burden translates into significant suffering, healthcare utilization, and loss of productivity, thereby making ESLD an important target for health services research.

ESLD is a chronic complex progressive illness that develops once the liver structure and function are disrupted due to inflammatory changes and scarring, the result of which is cirrhosis. It is commonly associated with functional and cognitive impairment, and often with comorbid mental and substance use disorders. These factors lead to significant deterioration in quality of life (QOL), with immense burden on caregivers. [23] ESLD patients, usually cared for by hepatologists, suffer physical discomfort and psychological stress due to the multi system effects of the disease. About a decade ago, the SUPPORT trial (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) showed that ESLD patients suffered similar pain as patients with lung and colorectal cancer.[24] Hospitalization rates due to ESLD and its complications have skyrocketed by 93% (due to hepatorenal syndrome), 62% (due to portal hypertension), and 190% due to Hepatitis C and its complications from 2004-05 to 2010-11.[25] Symptoms like fatigue, cachexia, abdominal pain, muscle wasting and disability lead to depression, the severity of which compounds patient suffering.[26] Furthermore, curative treatment, namely Liver Transplant (LT**)** is available only to a minority, leading to an urgent need for effective interventions which can potentially improve QOL, as well as reduce symptom burden and healthcare utilization.[27] Notably, proactive PC consultation has been shown to improve transplant rates.[28] Unfortunately, the limited availability of outpatient specialty PC services creates a gap in the care of ESLD patients and their caregivers.[29] The

current proposal will fill this critical gap through a comparative effectiveness study of two pragmatic models (as selected by our patients and caregivers):

Model 1: Consultative PC (i.e. direct access to board-certified or board-eligible PC provider), versus

Model 2: Trained Hepatologist- led PC intervention (i.e. a hepatologist will receive formal training to deliver PC services).

EVIDENCE TO SUPPORT THE MODELS OF COMPARISON:

A review of the evidence of outpatient non-hospice PC shows that outpatient PC improves QOL and clinical outcomes.[30] The majority of medical organizations (including the Institute of Medicine, World Health Organization, and National Quality Forum) recommend offering PC within routine care to all patients with serious illnesses. Our first comparator i.e. consultative PC (Model 1), has demonstrated efficacy in oncology [31,32], lung cancer[33] and heart failure.[34] A randomized controlled trial described by Temel, et. al. in patients with newly diagnosed metastatic non-small cell lung cancer demonstrated the benefits of early collaborative PC intervention in advanced cancer, showing better QOL, improved depression and a 2.7 month survival benefit.[35] A study done at Einstein Medical Center using collaborative PC for liver transplant patients showed significant improvement in symptom scores and reduction in depression.[36]

Our second comparator (Model 2) is based on the demonstrated improvement in confidence, knowledge and satisfaction of primary care providers in offering PC to their patients.[37] A randomized controlled trial demonstrated improved patient symptoms in the group receiving PC from primary care physicians trained in PC vs. those in the control (primary physicians not trained in PC).[38] Web based online training was effective in translating knowledge into real time patient care.[39]

B. STUDY METHODS

5. Study Design

5.1 Specific Aims

Primary Aim: To assess the comparative effectiveness of two PC delivery models for patients with ESLD in improving the disease specific quality of life from baseline to 3 months as assessed using FACT-Hep (Functional Assessment of Cancer Therapy- Hepatobiliary).

Secondary Aims:

1) To compare the effects of the two above-mentioned models of PC delivery (as a change from baseline to 3 months) on:

- Overall quality of Life, assessed using PROMIS-29 (Patient Reported Outcomes Measurement Information System)
- Patient's symptom burden, assessed using modified ESAS (Edmonton Symptom Assessment Scale),
- Patient's depression severity, as assessed by PHQ-9 (Personal Health Questionnaire)
- Patient distress, as assessed by Distress Thermometer (DT)

- Patient satisfaction with care, assessed using FAMCARE-P (Family Satisfaction with Care)
- Caregiver burden, assessed by Zarit Burden Interview (ZBI-12)
- Caregiver quality of life, assessed using PROMIS-29
- Goal concordant care measures assessed using advance directive and advance care planning documentation, a survey questionnaire and qualitative interviews with patients and caregivers.

2) To compare the effects of the two above models of PC delivery on:

- Healthcare utilization from the time of initial visit (rate of unscheduled office visits within 1 year, 30 and 90-day admission proportion, ER visit rate within 1 year)

3) Conduct semi structured interviews to explore and compare patient, caregiver, and provider experiences with the two models.

- Qualitative interviews of patients' and caregivers' experiences with receiving PC as a part of routine care provided by Hepatologists versus palliative care providers.
- Qualitative interviews of palliative care and hepatology providers' experiences and confidence with providing PC to ESLD population.

Exploratory Aim: To compare the effects of the two comparative models on survival over 1 year.

5.2 Study Overview

This is a five year, two-arm multicenter cluster-randomized controlled trial (RCT) to assess the effectiveness of two PC models for patients with ESLD. Year 1 is the planning phase. Enrollment begins in year 2 and continues through years 3-7. Year 8 aims for data analysis and dissemination of results.

The two comparative approaches are:

- Model 1: Consultative PC (i.e. PC offered by a board-certified or board-eligible PC provider)
- Model 2: Trained hepatologist led PC (i.e. PC offered by a trained hepatologist)

Randomization will occur at the level of clinical centers, by the Data Coordinating Center (DCC) at DCRI. All patients/providers within a clinical center will be randomized to the same intervention. Clinical centers will be randomized within two strata: VA centers and non-VA academic medical centers. Due to the differences in healthcare systems, and probably better access to PC providers in VA than in non-VA settings, we will be randomizing 4 of the VA centers to the consultative PC led arm and 3 to the hepatologist led arm. To maintain equal number of sites in each of the intervention models, we will be randomizing 4 of the non-VA centers to hepatologist led arm, and 3 to consultative PC led arm. This originally resulted in 7 centers in each of the 2 study arms. 5 new clinical centers have been added to the study in year 3, to expand the enrollment efforts. Given the lower enrollment in the Hepatologist led models, the new sites are randomized into 4 (hepatologist led) and 1 consultative led arm.

Eligible patients will receive the intervention model of care according to the center's random assignment. In both Models, patients will be identified and consented at the time of their routine hepatology clinical visit. Patient and caregivers can be consented separately (1 week window is allowed). The study coordinator will

schedule the initial/ 1st intervention visit within 6 weeks after informed consent. Baseline assessments will be collected by phone, online or on paper forms, within 1 week before the confirmed initial visit both by patients and caregivers. Informed consent, baseline assessments and initial visit may occur on the same day, but must follow this sequence. The initial intervention visit will be followed by 1, 2, and 3 month visits. All study visits can occur in person, or by phone or telehealth. ESAS, DT and PHQ-9 will be conducted before the 1, 2 and 3 month intervention visits; all other assessments (FACT-Hep, PROMIS-29, FAMCARE-P, ZB-12, GCC, AUDIT- when applicable) will be conducted after the respective intervention visits (other than initial visit). All the study providers will complete a PC checklist after each study intervention visit in both models of care. Follow up assessments will be conducted at 6, 9 and 12 months after the initial visit, by phone or online. No clinical intervention is mandated at these follow up time points. It is important to note that ESAS, PHQ-9 and DT will be given to providers in Model 2 (Hepatologist Led PC) only. Providing these data to PC providers as a part of study would represent a deviation of routine practice.

The primary outcome will be change in the QOL total score (assessed using FACT-Hep) from baseline to 3 months.

Embedded within this cluster-RCT, we will conduct a ***qualitative study*** using semi-structured interviews to evaluate and compare patient, caregiver, and palliative care and hepatologist providers' experiences in the two PC models. The goal of the patient and caregiver interviews is to explore their experience of having exposure to palliative care delivered by different models. We will inquire about their overall experience and about their impressions about the timing, quality, and value-added of this approach in developing care consistent with the values and care preferences of patients and caregivers (Appendix K and L: Patient and Caregiver Interview Guides). 2-4 patient and caregiver dyads from each of the 19 sites (2*8-56 dyads and some solo patients/ caregivers*) will be interviewed. The main consent will include a statement for opting in or out for the interviews. If a patient agrees to opt in for interviews, their name will be included in the list for potential interview candidates. A patient/ caregiver can opt out from interviews at any time, and this does not exclude them from participation in the main study. A final number of interviews will be determined based on the team's assessment of whether theoretical saturation has been reached. [40]

The goal of the palliative care and hepatologist provider interviews will be to explore their perspectives on benefits and challenges of providing PC as well as their comfort level with providing palliative care to ESLD population within the context of this study. With hepatologists we will additionally explore their confidence with and attitudes about their enhanced palliative care skill set (e.g. symptom management, communication about goals of care and advance care planning, etc.) (Appendix M and N: Provider Interview Guides). For the purpose of this study all treating PC and hepatologists (approximately 30 providers) will be interviewed. The interviews will be digitally recorded, transcribed and analyzed with aid of NVivo qualitative software. The findings from the quantitative and qualitative studies will be integrated to identify a sustainable approach to integrate PC within routine care of ESLD. The interviews will last for approximately 30-40 minutes. Providers will be verbally consented for interviews, once the study enrollment period has completed or the last enrolled patient reaches 3-month end point. Further details on qualitative methods are in Section 10.

In addition to semi-structured interviews, each training module for hepatology training program has pre/post assessments (Appendix O) to assess the knowledge gained.

5.3 Specific Hypotheses

Primary Hypothesis: Stated above Section A.2. Superiority will be evaluated first and only if such superiority is not demonstrated then the non-inferiority (NI) analysis will be performed.

Secondary Hypotheses:
We hypothesize that Hepatologist led PC (Model 2) will be superior to Consultative PC (Model 1) for the change from baseline to 3 months for the following measures:

- Overall quality of life (PROMIS-29, separate T scores)
- Symptom burden (modified ESAS, point score)
- Depression severity (PHQ-9, total score)
- Distress (Distress Thermometer, total score)
- Satisfaction with care (FAMCARE-P, total score)
- Caregiver burden (ZBI-12, total score)
- Caregiver quality of life (PROMIS-29, separate T scores)
- Goal concordant care (Patient and Caregiver Questionnaire, total score)

We hypothesize that Hepatologist led PC will be superior to Consultative PC in having lesser:

- Proportion of patients with at least one scheduled or unscheduled hospital admission within 30 days from the initial visit
- Proportion of patients with at least one scheduled or unscheduled hospital admission within 90 days from the initial visit
- Rate of ER visits within 1 year from the initial visit
- Rate of unscheduled office visits within 1 year from the initial visit

Exploratory Hypothesis:

We hypothesize both models will have prolonged survival as compared to historical data.

Primary Outcome: Patient reported QOL (assessed using FACT-Hep total score) is the primary measure of this study. QOL will be assessed at the baseline visit and after the intervention visits at 1, 2 and 3 months. The primary outcome will be the change in QOL from baseline to the QOL assessment at 3 months. Further assessments will be conducted at 6, 9 and 12 months to assess sustainability of the interventions. The 1-month evaluation will allow assessing the immediate effects of the initial visit. The 3-month assessment will assess for the cumulative effects of all intervention visits (initial, 1, 2 and 3 month).

Secondary Outcomes:
The outcomes inset below will be assessed as a change from baseline to 3 months:

- Overall quality of life (PROMIS-29, separate T scores)
- Symptom burden (modified ESAS, point score)
- Depression severity (PHQ-9, total score)
- Distress (Distress Thermometer, total score)
- Satisfaction with care (FAMCARE-P, total score)
- Caregiver burden (ZBI-12, total score)
- Caregiver quality of life (PROMIS-29, separate T scores)
- Goal concordant care (Patient and Caregiver Questionnaire, total score)

Healthcare utilization:

- Proportion of patients with at least one scheduled or unscheduled hospital admissions within 30 days from the initial visit
- Proportion of patients with at least one scheduled or unscheduled hospital admissions within 90 days from the initial visit
- Rate of ER visits within 1 year from the initial visit
- Rate of unscheduled office visits within 1 year from the initial visit

Exploratory Outcome: Survival over 1 year

Qualitative Outcomes: Thematic qualitative description of patient, caregiver, and providers' experiences with the 2 models. In addition, knowledge gained by the hepatologists from the PC training program will be described.

5.4 Clinical Network

19 clinical centers (8 Veterans Administration (VA) systems and 11 non-VA Academic Medical Centers) will participate in this project (additional centers will be added if needed). The Organ Procurement and Transplantation Network (OPTN) has divided the US into 11 regions for organ allocation, and 8 of these 11 are included in the clinical network of the current trial.

All provide a range of inpatient and outpatient services and include teaching and research. Centers from both groups are distributed throughout the US, representing most major metropolitan areas, with many centers having penetration into suburban and rural communities. The participating clinical centers are committed to clinical research involving ESLD patients and have interest in PC. Each site has strong expertise in both hepatology and PC and a record of accomplishment in academic performance and clinical research productivity.

Each center has between 2 and 14 clinical hepatologists, 1 and 6 mid-level providers, and 1 and 15 PC providers. The centers see between 650 and 6000 ESLD patients annually, approximately one third or more of whom have decompensated ESLD at initial presentation. The wide distribution of centers affords a diverse patient population with respect to gender, race/ethnicity, and age. The randomization strategy has been introduced to all centers. All centers have received approval from local PC providers that it is acceptable for consultative services to be reduced during the period of study, if randomized to the trained hepatology led PC arm. Likewise, all centers have confirmed with their PC providers that their consultative services can be expanded as required if randomized to the consultative PC arm.

5.5 Study Population

Liver Disease can be conceptualized in two stages- compensated and decompensated. In the compensated phase, a patient may have no or only mild symptoms, and see their providers for routine regular checkups. But as the disease progresses into a decompensated state, there are multiple complications that can occur, accompanied by malfunction of multiple organs concurrently. The most common complications result from portal venous hypertension, a process whereby the main blood vessel leading to the liver (the portal vein) comes under increasing pressure due to the progressive scarring (fibrosis) of the liver. The organs that empty into the portal vein, including the intestine, spleen, and indirectly the kidneys, suffer greatly. The increased

pressure results in the leakage of fluid into the abdomen and legs and the development of new veins within the body which allow blood to escape the cleansing action of the liver. The consequence of this is retention of toxins that cause confusion and insomnia. These same newly formed veins predispose patients to life threatening gastrointestinal bleeding. The scarring of the liver causes it to lose its ability to manufacture proteins which, in turn, manifests as muscle wasting and a propensity for spontaneous bleeding and sometimes clotting. Finally, a scarred liver fails to replenish the body's energy stores, leading to fatigue that can become disabling, muscle cramping from lack of nutrients, and malnutrition. When any of these complications of ESLD occur, the liver disease is said to have entered into a state of decompensation; in general, decompensated patients have a reduced one-year survival, approximately 80% at one year for most complications.[41] Patients who have entered this state are the focus of this project. It is this population which is plagued with a high symptom burden, frequent hospitalizations and marked deterioration in QOL. [42]

We are also including patients with ESLD due to Hepatocellular Cancer (HCC). In general, patients with any stage of HCC often have symptoms such as fatigue, sad mood, sleep disturbance, pain, abdominal discomfort due to ascites, and confusion leading to progressive impairment in QOL.[43] BCLC (Barcelona Clinic Liver Cancer) staging is used clinically as a composite measure of the extent of tumor, liver function and physical status. All patients with BCLC stage 0, A, B and C are included in the study. Stage D (Terminal) is excluded as they have low survival rates and frequently are already on symptomatic treatment or palliative care. Since Cholangiocarcinoma has no standardized staging system, these patients will be excluded. Multifocal HCC with any CTP will also be included.

There are many causes of ESLD; the most common cause today is viral hepatitis C followed by metabolic syndrome, defined as the presence of obesity, hypertension, hyperlipidemia, and/or diabetes which leads to NASH.[44] Whatever the underlying cause of ESLD, the complications as described above are the same, and the onset of decompensated ESLD has the same dire prognostic implications. Ascites, the most common complication, is associated with at least 15% one-year mortality [45], hepatic encephalopathy at more than 50% one-year mortality,[46,47] variceal bleed at least 20% mortality at 6 weeks[48] and one form of hepatorenal syndrome a 50 % one year mortality. [49]

5.6 Inclusion/ Exclusion Criteria

Enrollment of DYAD

Patients willing to participate will be asked to select a caregiver (if present) to participate in the study. A caregiver is defined as someone who knows the patient well and is involved in their routine medical care. A caregiver must consent and be willing to attend the initial intervention visit along with the patient. Patient and caregiver consent can occur in person or remotely or by phone, as allowed by the site's institutional review board.

INCLUSION CRITERIA: Patients

1) Patient and Caregiver (if present) willing to provide informed consent (written or remote/phone)
2) Age >18 years old
3) Able to read/understand English
4) Any MELD <30 within 6 weeks of date of consent
5) Either of the following two clinical criteria:
    1. CTP Class B or C cirrhosis with one of the following (new or ongoing) within the prior 6 months from the date of consent:

1. Ascites (requiring diuretics)
2. Spontaneous Bacterial Peritonitis (SBP)
3. Hepatic Hydrothorax (requiring diuretics)
4. Variceal Bleed (with 1 or more recurrences)
5. Overt Hepatic Encephalopathy (requiring medications)
6. Type 2 Hepatorenal Syndrome

2. Hepatocellular Cancer (HCC) (with one of the following within the prior 6 months from the date of consent:
    1. Any BCLC (except Stage D) with CTP class B OR
    2. BCLC Stage C with CTP class A
    3. Multifocal HCC with any CTP.

EXCLUSION CRITERIA: Patients

1) Hepatologist-estimated life expectancy of less than 6 months
2) Prior Liver Transplant
3) Patients who, in the judgment of the investigator, are likely to undergo liver transplantation within 3 months of enrollment
4) Lacks capacity to provide informed consent, including those with stage 2 HE or higher at the time of consent
5) Patients who are already receiving, or who have received palliative care prior to study entry (within the past 3 months)

INCLUSION CRITERIA: Caregivers

1. Identified caregiver of ESLD patients
2. Age>18
3. Able to read/understand English
4. Providing direct care for at least >10 hours per week

EXCLUSION CRITERIA: Caregivers

1. Impaired cognitive function

Enrollment of Patient only (without caregiver)

We are allowing patients (who meet the study inclusion criteria as outlined above (2-5), without a caregiver to be enrolled, based on the following criteria: Patient reports he has no caregiver, or caregiver is unwilling, but the patient is interested to join the study.

Based on these criteria and our screening activities, we project approximately 40% of patient population may be enrolled without a caregiver.

6. Study Intervention

PC Intervention visits (both Models): The PC intervention will be framed by a palliative care checklist (Table 1), based on ASCO (American Society of Clinical Oncology) Ambulatory Palliative Care Guidelines. [50,51] The key components of the PC intervention include: patients'/caregivers' understanding of diagnosis, illness and prognosis, symptom assessment, psychosocial assessment, distress screening and management, discussion of goals of care and advanced directives**. All the elements are suggested to be discussed per the visit agenda, although some can be discussed at any one of the four intervention visits or may repeat over many visits (i.e. initial, 1, 2 and 3 months) for both Models.** The providers (PC provider or Hepatologist) will complete this checklist after each intervention visit to document what was discussed at each study visit. The providers are encouraged to review the checklist before the intervention visits.

Palliative Care Checklist (Table 1):
To maintain uniformity across sites, we have standardized the content topic for each visit for both models as below (this is to ascertain that all data points can be compared across sites). Advanced directive discussion can be conducted at any of the four intervention visits, depending on the patient's readiness. Some elements such as symptom assessment and management plans may occur at multiple visits.

Table 1: Study Intervention (PC Checklist)

Elements to be Assessed PATIENT	Visit #1	1 mo.	2 mo.	3 mo.
ASSESSMENT				
1. Assess patient understanding of diagnosis, illness and prognosis	REQ	prn	prn	prn
2. Conduct Distress screening (**DT**) and assess adequacy of current management	REQ	REQ	REQ	REQ
3. Conduct symptom assessment (**ESAS**) and assess adequacy of management plan	REQ	REQ	REQ	REQ
4. Conduct a Psychosocial assessment and assess adequacy of management plan	REQ	prn	prn	prn
5. Conduct Depression screening (using **PHQ-9)** and determine current or future need for management plan	REQ	REQ	REQ	REQ
6. Assess Social Role (occupation, social role) and Family Support		REQ*	prn	prn
7. Assess Spiritual, Religious, Cultural Beliefs that impact illness		REQ*	prn	prn
8. Identify changes in liver conditions that trigger need for treatment decision-making and shifting goals	prn	prn	REQ	prn
9. Discuss Goals of Care		REQ*	prn	prn
10. Conduct Advance Care Planning (ACP_ assessment and presence of proxy decision maker, completion of Advanced Directives (CAN OCCUR AT ANY VISIT)		REQ*	prn	prn
PLANNING / RECOMMENDATIONS				
1. Identify care plan for future appointments	REQ	REQ	REQ	REQ
2. Document new prescriptions	REQ	REQ	REQ	REQ
3. Document Referrals: Social Work, Palliative Care, Nutrition, Physical/ occupational therapy, etc.	REQ	REQ	REQ	REQ
4. Document Goals of Care	REQ*	prn		
CAREGIVER				
1. Assess caregiver understanding of diagnosis, illness and prognosis	REQ	prn	prn	prn
2. Validate the normal feelings of stress, etc. associated with caregiving.	REQ*		prn	prn
3. Assess caregiver coping and material support resources		REQ	prn	prn
4. Assess caregiver burden, and document concerns	REQ	prn	prn	prn
5. Refer for support resource to alleviate caregiver burden, and/or document ways to relieve the burden, & self-care	REQ	prn	prn	prn
6. Assess for educational needs related to patient's condition: symptom triggers for doctor's attention, nutritional needs, understanding of complications, ACP		REQ	prn	prn
7. Discuss future care management and treatment options.	REQ*		prn	prn

REQ* = must be conducted within the first 2 visits

In general, the providers in both Models will conduct an assessment at each visit, and offer a recommendation for symptoms and distress management, discuss goals of care, and help with treatment decision making. In addition, as appropriate they will offer support, treatments, and review the hepatology treatment plan.

Psycho-educational and supportive counseling through providing information about the disease and ways to manage the disease will be offered. Other referrals like social work, community resources will be made as appropriate. If a palliative care consult is deemed necessary in the Hepatology led PC arm, a phone consultation with PC can be made, and the reason for PC consult and outcome of the PC consult will be documented in the clinical record and captured in the research case report form. A clinical note will be documented in EMRs after each study visit by the providers, per routine clinical care. During the time between study visits, the patients will have access to the providers by phone for any additional needs. These additional interactions are a part of the nature of PC services and may involve additional visits during this time. These follow ups may occur within a few days (e.g. patients with poorly controlled symptoms) to a month or more (patients who are symptom free but need resources for distress management). The visits are not scripted in either of the Models, allowing the providers freedom to address individual patient needs. These additional contacts will be tracked by the intervention team and documented in the research charts and case report forms. The study provider (PC providers or Hepatologists, who delivered the intervention) will be responsible for PC check list completion. The checklist (Patient and Caregiver, Table 1.1 and 1.2) will be based on Table 1. The completed checklists will be recorded into the Case Report Forms (CRF) and stored in research chart for future use at each study visit.

If an interim visit occurs close to study visit (within the windows defined in Table 2), data capture for outcomes assessment can be done by phone, paper form or online. This applies to either of the Models (1 and 2).

Table 1.1 PC Checklist Patient

PAL-LIVER PC CHECKLIST		
Please Circle: Visit 0, 1, 2, 3		Patient ID:
History of Present Illness	Yes	No
1) Assess patient's disease understanding		
2) Assess patient's prognosis understanding		
Comprehensive Assessment	Yes	No
1) Conduct Distress screening		
2) Assess adequacy of Distress management		
3) Conduct Symptom assessment		
4)a. Conduct Depression screening		
b. Conduct Psychological assessment, and assess adequacy of mx plan		
c. Discuss coping with life threatening illness		
5) Assess social role (occupation, social role) and Family Support		
6) Assess Spiritual, Religious, Cultural Beliefs that impact illness		
7) Identify changes in conditions that trigger need to reevaluate care goals		
8)a. Discuss current Goals of Care		
b. Discuss future Goals of Care (ex. values and preferences for life-sustaining and liver treatment)		
9) Advance Care Planning Discussion (with provider and/or family)		
A. Identify Health Care Proxy		
B. Complete Advance Directive/Living Will		
PLANNING / RECOMMENDATIONS		
Symptom Management (if applicable)		
PAIN	Yes	No
Patient education		
Medications (please circle)- Opiods, Non opiods, OTC analgesic, Other		
Non pharmacologic therapy (PT, Acupuncture, etc)		
Others (please specify)		
DEPRESSION		
Patient education		
Medications (please circle): SSRI, SNRI, Atypical, TCA, Other_____		
Non pharmacologic therapy (cognitive therapy, etc)		
Others (please specify)		
	Yes	No
1) Follow up appointments scheduled		
2) Referrals		
a) Counseling- Social Work, Chaplain		
b) Palliative Care		
c) Nutrition		
d) Physical / occupational therapy		
e) Others_ please specify		
3)Please document new prescriptions as a result of the intervention (PLEASE SPECIFY)		
Approximate Time spent (please circle) : <=20 min, 21-30 min, 31-40 min, 41-50 min, >51 min		

Table 1.2: PC Checklist Caregiver

PAL-LIVER PC CHECKLIST			
VISIT: Initial/0 1 2 3 (please circle) **In person Visit Phone Visit**			Caregiver ID:
Assess caregivers understanding of:		Yes	No
1)Liver Disease			
2)Prognosis			
3) Validate the normal feelings of stress, etc. associated with caregiving			
4) Assess caregiver coping and provide support resources			
5) Assess caregiver burden			
Caregiver education on			
a) Symptom triggers			
b) Nutrition			
c) Complications of liver disease			
d) Being the health proxy and partner in decision making			
PLANNING / RECOMMENDATIONS		Yes	No
1) Discuss care plan for future appointments			
2) Manage caregiver burden			
3)Referrals (please check all that apply)			
a) Counselling- Social Work, Chaplain			
b) Palliative Care			
c) Primary care			
d) Others_ please specify			
Approximate Time spent (please circle) : <=10 min, 11-20min, 21-30 min, 31-40 min, 41-50 min, >51 min			

Consultative PC (**Model 1**): Institutions randomized to this arm will be required to have a board-certified or board-eligible PC provider conduct an initial study visit within 6 weeks after informed consent. The PC provider includes a physician, physician assistant, or nurse practitioner performing clinical consults at their respective centers (reimbursed by insurance). The PC provider should be credentialed by his/her home institution to see patients and, if appropriate, bill for clinical services either independently, in the case of a physician, or under the supervision of a palliative care provider, in the case of an advanced practice provider. The PC model will include: PC study visits (initial, 1, 2, and 3 months), and completion of a PC checklist after each study visit (based on Table 1, 1.1 and 1.2, similar to Model 2). All visits can occur in person or by phone or virtual face to face using the institutional secure platform. All caregiver visits can occur in-person or by phone. Interim phone contact or visits will occur based on individual needs and will be documented within the patients' Electronic Medical Record (EMR). Visit documentation will be extracted from the EMR on a case report form by the research coordinator. Aside from following the visit agenda and completing the PC checklist, the PC interaction will not be pro-scripted, allowing each PC provider to establish his or her own rapport with the

patient, adhere to his or her own practice style, and make the care as pragmatic and generalizable as possible. The purpose of the visit agenda and checklist is to maintain intervention fidelity across different practices.

Hepatologist led PC **(Model 2**): The Hepatologist Led PC model will comprise:

1) Hepatologist training (through online training program), and
2) Study visits utilizing the same PC checklist as utilized in Model 1.

All study visits can occur in person or by phone or virtual face to face using the institutional secure platform, similar to Model 1. Initial visit will occur within 6 weeks (similar to Model 1) after informed consent. All caregiver visits can occur in-person or by phone. The providers will complete the same PC checklist, as in Model 1 after each visit, which will be retrieved by the coordinator for CRF data entry and stored in the patients' research records. The flexibility to offer phone/ in person visit will be left up to the provider's discretion and will be documented and recorded in the patient's EMRs. The research coordinator will add this information to the CRFs (similar to Model 1). The ESAS, PHQ-9 and DT will be given to providers in Model 2 (Hepatologist Led PC) only.

Study Follow Ups: The patients and caregivers will complete the follow up assessments by phone, paper or online at 6, 9 and 12 months (from the initial visit). A window period of +/- 1 week (before/after) is allowed for these follow up assessments.

Early Termination: If a patient or caregiver chooses to terminate participation, he/she will complete an early termination visit. Assessments will be completed by phone, paper, or online. The ECOG score, concomitant medications, and AUDIT (if applicable) along with the final study intervention visit will only be completed if the patient's early termination visit occurs prior to the 3-month visit.

If a patient or caregiver withdraws and is unwilling to do the early termination visit, then their decision must be respected.

Distinct Clinical Scenarios:

Patient Death: In the event of a patient's death during the study intervention or follow up phase (12 months from initial visit), caregivers will be asked to complete the QOL questionnaire (PROMIS-29) as scheduled per their time point in the study (Table 1), and an after death interview (Appendix J: Kaiser Permanente End of Life Care Survey). The End-of-Life Care Survey will only be administered if the patient has provided consent to allow the caregiver to participate. These interviews will be done by the research coordinators at each respective site by phone. We will capture the place of death and any hospice utilization. It is consistent with PC practice to have one bereavement follow up call, and hence, it is suggested per local institution policies.

Inpatient admission: It is not uncommon for patients with advanced liver disease to be admitted to the hospital for management of decompensation events. In order to prevent unintended inpatient palliative care consultation, systems will be put in place to alert the local care providers of the patient's participation in this study, and to alert the local investigator. These systems will be site specific and include but may not be limited to the following:
1. Alert in the Electronic Medical Record that the patient is a participant in a Palliative Care Study and the local investigator or coordinator should be contacted.

2. The patient and caregiver will be provided with contact cards, available to share with other care-providers.
3. Caregivers will be asked to contact the coordinator or investigator in the event of visit to the Emergency Room or inpatient hospital stay.

Ad hoc Palliative Care Consultation: Hepatologists randomized to the hepatology led PC arm will have the opportunity to consult with a Palliative Care Provider. If such consultation is needed, a phone interaction will be encouraged. The ad hoc interaction between the hepatologist and the local Palliative Care Provider will be captured in the study CRF. Future intervention visits will continue, as per the schedule.

Hospice Transfer: In the event of a patient being admitted to home or inpatient hospice within 3 months from enrollment, the PC intervention will be stopped. However, data collection will continue as scheduled either in person during an office visit or over the phone, for both patients and caregivers until the 12 month follow up.

Patient Transplant: In the event of a patient undergoing liver transplantation prior to reaching the three month point, the PC intervention will be stopped. However, data collection will continue as scheduled, for both patients and caregivers until the 12-month follow-up.

Primary Analysis Population: Patients who undergo transplantation or hospice transfer prior to 3-month end point will not be included in the primary outcome analysis. Should they be transplanted or transferred to hospice after 3 months from enrollment, they will be included in the primary analysis.

Scheduled hospital admission: non-acute admission for any procedure or planned care.

Unscheduled office visits and hospital admissions (encounters). An unscheduled encounter will be defined as one which occurs for acute illness or complications for which care was never planned before.

Intervention fidelity will be assessed in both models through requiring completion of a PC checklist at the end of each study intervention visit. In addition, some of the clinical office notes for all study intervention visits (initial, months 1, 2, and 3) for randomly selected patients will be redacted for identifying information, and reviewed by members of the Executive Committee (EC). The research coordinator may be required to upload the redacted clinical office note into a secure password protected database. This review process will be scattered throughout the enrollment period.

7. Study procedures

This study provides support for a study coordinator at each clinical center. This person will function as a navigator as well as coordinator, to be sure that the providers in each Model have the materials needed to conduct the interaction with a patient/caregiver, that required study visits occur as per the study protocol, that providers in both study arms complete the PC checklist, and that the patients and caregivers complete the required study assessments per protocol.

Informed Consent: All participants (patients and caregivers) will provide informed consent (written or verbal) using procedures reviewed and approved by the Institutional Review Board (IRB). There will be a separate consent for patient and caregiver, and caregiver consent can be performed up to 1 week after the patient's consent.

Each subject will be contacted by research personnel in the clinical office or remotely and provided with an information packet including the informed consent document, and HIPAA authorization. Informed consent will be undertaken with the subject by a member of the study staff, and a copy of the consent form will be given to the patient and caregiver. Participants (patients and caregivers) will also be consented for possible participation in a qualitative interview at the time of the initial study consent. They will be informed at this time that if they opt in, they may be selected for a telephone interview regarding their experiences in the study. These interviews will occur within 3 months after their 3-month study visit, and will last approximately 30 minutes.
For providers (PC and Hepatologists) who participate in the qualitative interviews, we will obtain verbal consent via telephone and provide them with an information sheet with details about the qualitative component of the study. The principal investigators or key personnel will be available for any questions from the patients or caregivers regarding the study.

Enrollment Procedure:
In both the comparative models, patients will be identified and screened for participation in the study from their routine hepatology clinical care interactions or from the inpatient setting, through available medical records. Potentially eligible patients will be contacted to offer participation. The research coordinator will identify a caregiver from the patient and, if available, conduct an informed consent with both together or separately, depending on their individual preferences. If a caregiver is unwilling to participate, the patient will be given an opportunity to identify another caregiver who may be interested.

Once consented, an initial visit (for patient) is required to be scheduled within 6 weeks after informed consent in both comparative Models. Mode of visit will be collected in the research records.

Patient and caregiver initial visits can occur separately but should occur within 1 week window of each other. Once the initial visit is confirmed, all baseline assessments will occur by phone, on paper or online within 1 week before the scheduled initial visit. If a patient/caregiver missed the initial visit, and the initial visit is rescheduled after the 1 week of baseline assessments, these assessments will need to be repeated. PC study intervention will be offered at an initial visit, followed by 1, 2 and 3 months (from the initial visit). Up to 1 week window period (before/ after) is allowed for all the intervention study visits. .

De-identified clinical information will be collected from patients who decline participation, in order to understand potential bias in our study. A monthly screening log will be submitted from each site to capture this information. The information collected will include limited demographic information (age, gender, and ethnicity) and reason for declining to participate (e.g. frequent visits, travel, work, family issues, etc.).

Demographics will be collected at screening. All baseline assessments will be entered into the CRF (not later than 15 days after initial visit). The baseline assessments will include patient QOL, symptoms, depression, psychosocial functioning, patient satisfaction, caregiver burden and caregiver QOL using validated surveys (Table 2). In addition to the AUDIT-C, substance use and past alcohol use questions will be asked at baseline. Dependent upon the AUDIT-C score of the patient, these additional alcohol and substance use questions will be asked at the month 3 visit or early termination visit if conducted before the month 3 visit. Medical history will be collected at initial visit and at the month 3 visit or early termination visit if conducted before the month 3 visit. ESAS, DT and PHQ-9 will be conducted before the intervention visits (1, 2, and 3 month); all other instruments (FACT-Hep, FAMCARE-P, PROMIS-29, Goal Concordant care, Zarit Burden interview, AUDIT- if applicable) will be completed after these visits. The providers will complete the PC checklist after each study

intervention visit (initial, 1, 2 and 3 months). The ESAS, PHQ-9 and DT will be given to providers in Model 2 (Hepatologist Led PC) only. Providing these data to PC providers as part of the study would represent a deviation of routine practice.

Caregiver Assessments: Caregiver assessments for demographics, quality of life and burden will occur at the same time points as patients. Other than baseline, all caregiver instruments will be completed after the intervention visits (1, 2 and 3 month). All caregiver visits can occur in person or by phone. Mode of visit will be collected in the research records.

All data assessments (for both patients and caregivers) can occur on paper, online or by phone. Study coordinators are allowed to give paper copies of patients and caregiver questionnaires, for reference or completion (to be mailed back). The time window of 1 week is allowed for post visit questionnaires, and within 1 week for those to be completed before the study visits 1, 2 and 3 (i.e. ESAS, DT and PHQ-9)

Table 2: Schedule of Assessments

		Baseline*	Initial**	1 M	2M	3 M	6 M	9 M	12 M	Early Termination[1]
Informed Consent	**X**									
Inclusion/Exclusion Criteria	**X**									
Demographics (Patients & Caregivers)	**X**									
Medical History (Patients & Caregivers)			X			X				X^2
ECOG score (Patients)			X	X	X	X				X^2
Concomitant Medications (Patients)			X	X	X	X				X^2
Study Intervention (Patients & Caregivers)			**X**	**X**	**X**	**X**				X^2
FACT-Hep		X		X	X	X	X	X	X	X
ESAS		X		X	X	X	X	X	X	X
PHQ-9		X		X	X	X	X	X	X	X
Distress Thermometer		X		X	X	X	X	X	X	X
FAMCARE-P 13		X		X		X	X	X	X	X
PROMIS-29 (Patients & Caregivers)		X				X	X	X	X	X
MELD Labs (+/- 4 weeks for each time point) (Patients)		X^3				X	X	X	X	X
CTP score (Patients)		X				X	X	X	X	X
Goal Concordant Care questionnaire (Patients & Caregivers)		X				X	X	X	X	X
Caregiver Burden (Zarit Burden-12)		X		X		X	X	X	X	X
Patient/ Caregiver Interviews* **						X				
AUDIT-C and AUDIT** **		X				X				X^2
Healthcare Utilization		X	X	X	X	X	X	X	X	X

***Baseline assessments will occur by phone, online or on paper forms after informed consent, WITHIN 1 WEEK before the scheduled INITIAL VISIT. **Initial Visit must occur within 6 weeks after informed consent is provided.**

*****Patient/ Caregiver Interviews will occur within 3months after the 3 month intervention, and applies only to those who opt in at the time of consent, and are selected for interviews.**

1-, 2- and 3-month visit can occur within a window of +/- 1 week. All follow up visits (6, 9 and 12 month) can occur within a window of +/- 1 week (7 days). 1 month= 30 days
******AUDIT-C will be administered to all patients at baseline. If the AUDIT-C score is >=4 for men or >=3 for women, the full AUDIT assessment will be completed. Only patients who take the AUDIT at baseline are required to take the AUDIT at 3M.**
[1] An early termination visit will be completed if a patient or caregiver terminates participation in the study.
[2] Final Intervention visit, Medical History, ECOG score, Concomitant Medications, and AUDIT will only be included in the Early Termination visit if the visit occurs prior to the 3M visit.
[3] Baseline MELD can be within 6 weeks before the date of consent, but must be present prior to initial intervention visit. • All MELD Labs do not have to be drawn on the same day, but if drawn prior to Baseline they should be in the window for eligibility criteria (6 weeks before consent is provided). • If MELD labs are not available within 6 weeks, lab orders should be provided to patients on the day of consent and they should be instructed to get their blood drawn as soon as possible. Once the lab results are available, the patient's eligibility must be confirmed prior to their Initial Visit. If the labs are done a few days after consent, it would not be considered a protocol deviation. If the patient does not meet eligibility criteria, they will be considered a Screen Failure and hence not enrolled into the study. The patient can be re-screened at a later time if the PI determines the patient then meets criteria. At that point, the MELD labs would be redone and the patient re-consented.

8. Study Instruments

Patients: It is estimated that all the study assessments will take approximately 30-35 minutes for patients, and 15-20 minutes for caregivers.

1) Quality of Life Assessment: FACT-Hep (Functional Assessment of Cancer Therapy- Hepatobiliary cancer) Appendix A - Fact-Hep has been utilized in several randomized and non-randomized clinical trials to assess the effectiveness of different treatments on the QOL of patients with ESLD. It has high internal consistency, with Cronbach-alpha of 0.94, good test-retest reliability (spearman correlation 0.91) and optimal convergent and discriminant validity.[52] This is a 45 item self-reported instrument, aimed to measure the QOL in patients with liver disease.[53] It comprises 27 questions from FACT-G (general), which assesses general well-being (physical, social, emotional and functional), and 18 items related to disease specific symptoms (pain, GI symptoms, anorexia, weight loss, jaundice), and its related treatment effects. The subscales of FACT-Hep include: 1) Physical well-being (PWB), 2) Social and family well-being (SFWB), 3) Emotional well-being (EWB), 4) Functional well-being (FWB), and 5) HCS- Hepatobiliary cancer subscale. The response options are on a Likert scale from 0 (not at all) to 4 (very much). The scores range from 0 to 160. Higher scores reflect better quality of life. The mean (SD) FACT-Hep score is 143 (20.6). The smallest clinically important difference is 9 points.[54,51] We received permission to utilize this tool from www.facit.org

2) PROMIS-29: (Patient Reported Outcomes Measurement Information System) Appendix B - PROMIS 29 assess the following domains: Physical Function, Fatigue, Sleep disturbance, Depression, Anxiety, Ability to participate in social roles, Pain Interference and Pain Intensity. The scores for each domain (except pain intensity) are reported as a T score (mean 50, SD=10) centered on the sample representative of 2000 US

general census[55]. The scoring system has been tested and validated in the general population[56, 57]. Higher scores mean more of a given domain (e.g. higher fatigue score means higher fatigue, higher physical function score means better physical function). We will utilize this instrument to assess the overall QOL of patients and caregivers, separately. For patients, it will add to the disease specific QOL assessed using FACT-Hep.

3) Patient Satisfaction: FAMCARE-P13 (Family Satisfaction with Cancer Care- Patient scale) Appendix E – This is a brief validated instrument used to assess patient satisfaction with outpatient palliative care interventions.[58] It measures the availability of care, symptom management, psychosocial care and information sharing including support for decision making.[59] It consists of 13 questions, with Likert scale response options with high reliability.

4) Goal Concordant Care questionnaire (for patients) Appendix G**:** Patients will be asked whether the care they received harmonized with what their values and preferences are, through a set of questions. Most responses are ranked on a Likert scale of 1-10 for them to completely agree (1) or disagree (10).

5) Qualitative Interviews (for patients) Appendix K: Standardized interview guides will be utilized for patient interviews. They will be asked about their overall experiences during the palliative care study visits in both models.

6) AUDIT-C and AUDIT (for patients): The Audit-C will be administered to all patients at baseline. Depending upon the AUDIT-C score (>=4 for men, >=3 for women), the entire AUDIT will be completed. The AUDIT assesses alcohol consumption, drinking behaviors, and alcohol related problems. If a patient completes the full AUDIT at baseline, he/she will be required to complete the AUDIT at the 3-month visit.

Intervention Toolkit (Available to Hepatologists – Model 2 - at each of the study intervention visits):

7) Symptom Burden: This will be assessed by using Modified ESAS (Edmonton Symptom Assessment Scale) Appendix C - This is a tool to measure the symptom severity in patients with any advanced disease, especially cancer.[60] This liver-specific ESAS will evaluate 13 symptoms (pain, fatigue/tired, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, muscle cramps, sexual dysfunction, sleep, itching/ pruritus) on a 10-point scale.[61] It has numerical visual scales with discrete checkboxes (range 0-10, where 0 is no symptom and 10 is the maximum). As ESAS has no time window required, we will specify the intensity of symptoms in the past 7 days as the assessment window. Individual symptom scores greater than 5 are considered moderate-to-severe.

8) PHQ-9 (Patient Health Questionnaire-9) Appendix D – This is one of the very commonly used tools to assess severity of depression in different settings, and has 9 questions taking about 5-10 minutes. [62] Each question is rated on a 4 point scale, with total score ranging from 0 to 27. Higher scores reflects greater severity of depression. Scores from 0-4 equates to no depression, 5-9 mild, 10-14 moderate, 15-19 mod severe and >20 reflects severe depression. [63] [64]

9) Psychological Distress: Distress Thermometer (DT) Appendix F – This is a brief valid instrument to assess the severity of psychosocial distress in patients with serious illnesses,[65] and helps initiate conversations about the wide range of difficulties, services and resources that may help address them.[66] DT has been utilized in patients with lung and breast cancer.[67] It measures the level of psychosocial distress on a scale of 0-10, where

10 is the maximum. In addition, it allows identification of the source of distress (practical, family, emotional, spiritual or physical).

Caregivers:

1) Caregiver Burden: Zarit Burden Interview- 12 (ZBI-12) Appendix H – This is a short, validated instrument extensively used for palliative care research in diverse populations. [68] It has high internal consistency, reliability and convergent validity to assess caregiver burden. It has high correlation [Rho (95% CI) 0.95 (0.92-0.96)] with the long form, and is less burdensome. The sensitivity and specificity is 92% and 94% with a cutoff score of 12.

2) Caregiver QOL will be assessed using PROMIS-29 (as described above) Appendix B.

3) Goal Concordant Care questionnaire (for caregivers) Appendix I: Caregivers will be asked whether the care their loved one received harmonized with what their values and preferences are, through a set of questions. Most responses are ranked on a Likert scale of 1-10.

4) End of Life Survey Appendix J: For patients who die during the 12 months of study, the caregivers will be approached to complete the Kaiser Permanente end of life survey. These questions will be completed within 3 months of death.

5) Qualitative Interviews (for caregivers) Appendix L: Standardized interview guides will be utilized for caregiver interviews. They will be asked about their overall experiences during the palliative care study visits in both models.

Qualitative Interviews (Providers) Appendix M, N: Qualitative Interviews will assess provider experiences in both Models of care.

9. Data Collection

All instruments mentioned in section 8 above (Patient and Caregiver) will be completed at different time points, as outlined in Table 2. Survival data will be collected throughout the 12-month study period. Patient screening data collection will include: demographics (age, gender, and race), education level, and employment status. Patient baseline data collection will include MELD scores and CTP score. Initial visit data collection will include duration of liver disease, Charlson comorbidity index, current medications (collected throughout intervention visits and early termination visit if conducted prior to month 3), and history of psychiatric disease. In addition, we will capture the primary liver disease diagnosis and associated complications.

Caregiver screening data collection sheet will include: demographics (age, gender, and race), education level, employment status, duration of caregiving, and relationship with patient. Caregiver initial visit data collection will include any preexisting medical illness.

Health care utilization will be assessed using EMRs and patient history at each of the study visits (to include hospitalizations, ER visits). Liver transplantation and new onset of liver disease complications will be assessed throughout the study duration.
Billing codes are collected for each study intervention visit in both Models.

Please see Table 2 for more details on schedule of assessments. Please note that ESAS, DT and PHQ-9 will be conducted before the 1-, 2- and 3-month intervention visits, while all other assessments will be conducted after these study visits.

10. Qualitative Interviews and Analysis Plan to Assess Patient, Caregiver and Provider experiences

Patient, Caregiver, and Providers' experience semi-structured interviews will be used to explore patient, caregiver, and clinical provider experiences with both interventions during this study.

To explore patient and caregiver experiences with the two models of care, the PC qualitative research team (led by Dr. Marie Bakitas, UAB Center for Palliative and Supportive Care) will conduct semi-structured interviews. We will use purposive sampling to interview a minimum of 7-8 patient-caregiver dyads from each clinical site from both arms within 3 months after they have completed their 3-month intervention visit. A final number will be determined based on the team's assessment of whether thematic saturation has been reached. We will aim to represent the perspectives of patients with various clinical etiologies of liver disease (alcohol, HCV, NASH, HCC, etc.) and also various demographic distributions (gender, race, SES). The interview guide consists of open-ended questions to explore the participants' understanding and impression of PC, and their experience with the intervention including provider, content delivered, convenience, acceptability, overall impression, and suggestions for improvement. Interviews will be conducted by trained interviewers over the telephone, recorded on an encrypted digital recorder and transcribed verbatim. Analysis will begin with the first interview and will be aided by NVivo qualitative data analysis software. We will code transcripts for themes and subthemes in an iterative process until thematic saturation is reached. We will construct a thematic matrix to compare the themes and subthemes across the two different models.

These interviews will occur throughout the study enrollment period (i.e. years 2, 3 and 4 of this five-year project).

To explore clinical providers' experiences with the two models of care, we will interview all providers who participated in the study (assuming 3 providers per site we will interview the total sample of 42 providers). The interview guide will focus on their experience providing PC to the liver disease population, their evaluation and impression of the intervention including feasibility, acceptability, overall impression, and suggestions for improvement. Provider interviews will also be conducted by trained interviewers over the telephone, and analyzed in an iterative process as described above. We will construct a thematic matrix to compare the themes and subthemes across the two different models.

11. Statistical Plan

11.1 Sample size estimation

Patient reported quality of life, as measured by FACT-Hep total score, is the primary outcome measure in this study. Published estimates show the average performance on this measure for typical patients with ESLD is 143.0 points (SD 20.6) [54,1] and a difference of 9 points on this measure reflects a minimal clinically meaningful difference (MCID) in QOL. Originally, we planned to enroll 1260 patients but the trial sample size was modified to enrollment of 936 patients.

The primary outcome is change in QOL from baseline to 3 months post enrollment. An individual patient level data analysis will be considered with adjustment for clustering, i.e. adjustment for correlation of patients' outcomes within a cluster (site). This correlation is quantified by the intraclass correlation coefficient (ICC).

11.2 Statistical Power

Based on the final site-specific enrolled counts (total n=936) and corresponding evaluable patient counts (as of September 30, 2024), there is 83.2% power (simulation based) for a superiority test to detect the originally specified MCID=9, with two sided type I error equal to 0.05, and utilizing SD=19.1, ICC= 0.09. The superiority hypothesis will be assessed first and only if such superiority is not demonstrated then the non-inferiority (NI) analysis will be performed. The NI margin is pre-specified. We chose the NI margin DELTA = 4. With this NI margin there is 79.2% power (simulation based) assuming presence of half of the considered superiority effect (MCID). The power values will be slightly higher when 3 months follow-up is completed resulting in few more patients with evaluable primary endpoint.

11.3 Statistical Analysis Plan

General Approach Statistical analysis will be performed by the Data Coordinating Center (DCC) at the DCRI. Although the methodological approaches and operational details of the data analysis will be coordinated by the study biostatisticians, the major analyses of the study data will be highly collaborative, involving both statisticians and clinicians to ensure appropriate approaches and interpretation of the data. All major treatment comparisons between the randomized groups in this trial will be performed according to the principle of "**intention-to-treat**;" that is, subjects will be analyzed (and outcomes attributed) according to the treatment group to which patients were randomized, regardless of subsequent medical care or potential discontinuation of treatment. However, patients who undergo transplantation or hospice transfer prior to the 3-month end point will not be included in the primary outcome analysis. Statistical comparisons will be performed using two-sided significance tests. Additional perspective regarding the interpretation of the data will be provided through extensive use of confidence intervals and graphical displays. Analyses will be performed with the SAS version 9.4 and R statistical software.

Baseline Demographic and Clinical Assessments including relevant descriptors from the history and baseline examination will be summarized for the two arms of the study. Descriptive summaries of the distribution of continuous baseline variables will be presented in terms of means and percentiles (median, 25th and 75th percentiles), while discrete variables will be summarized in terms of frequencies and percentages. Since randomization is expected to produce balance at baseline between the two arms of the trial, statistical comparisons of treatment groups with respect to baseline characteristics will be more informal (no statistical tests will be used) and limited to selected variables and disease factors known to influence prognosis.

Analysis for the Primary Hypothesis and Outcome: To account for the cluster-based randomization we will utilize linear mixed model with treatment arm indicator (binary variable) as a fixed effect and center as the random effect, and change in QOL as outcome. We will also adjust for baseline QOL and the randomization strata variable (VHA vs. non-VHA). Binary variable TRT is coded as 1 for the hepatologist led PC and 0 for the Consultative PC. Rejection of the null hypothesis stating that coefficient for the treatment indicator TRT is zero will provide evidence for presence of the treatment effect. In addition to the statistical hypothesis testing, 95% confidence intervals descriptively summarizing the difference in outcome between the two treatment arms, as well as outcome in each randomized arm will be computed. We will report the observed ICC. The superiority

hypothesis will be assessed first and only if such superiority is not demonstrated then the non-inferiority (NI) analysis will be performed. Non-inferiority (with the pre-specified NI margin DELTA=4) will be claimed when L > - DELTA, where L is the lower limit of two-sided 95% confidence interval for the above- mentioned coefficient for the treatment indicator.

A *supplementary analysis* will involve multivariable analysis with covariate adjustment of the treatment effect performed with the mixed linear regression model as above but with inclusion of additional baseline covariates as fixed effects. The regression model will be evaluated with respect to functional form of continuous covariates and use splines if needed to accommodate non-linear effect of a covariate.

The secondary outcomes which are summarized by a score will be analyzed in fashion similar to the primary analysis described above. Survival will be summarized with Kaplan-Meier curves and Cox regression will be used for multivariable models, and will consider a shared-frailty model to account for center clustering.

For subgroup analyses, using multivariable models, a potentially differential impact of the intervention will be assessed across complementary subgroups by testing for interaction of the treatment variable with a subgrouping variable. In addition to tests we will present estimated treatment effects and the corresponding 95%CI for subgroup/subset treatment effects.

Palliative care knowledge gained by the hepatologists will be assessed by summarizing the responses to pre post assessment questionnaires in the training program.

Missing Data: Every effort will be made to minimize the extent of missing values by proactive strategies, inevitably we will need to deal with some missing value problems. To prevent and limit missing data other than due to patient's death or curative therapy prior to completion of the study we will perform data checks and consistency checks during the study and collaborate with sites to complete missing or incorrect data items. If less than 10% of subjects have missing data for a particular analysis, we will consider complete case analysis utilizing only non-missing data. However, if more missing data is present we will utilize multiple imputations (MI) to mitigate potential bias of the complete case analysis. We will utilize the recommendations of the National Research Council Panel on Handling Missing Data in Clinical Trials published by the National Academy of Sciences in 2010. [69]

Sensitivity Analyses: Due to severity of their disease patients will likely be compliant and motivated and thus we do not expect many patients with missing follow-up QOL at 3-month evaluation needed for the primary outcome. However, missingness of the primary outcome may still occur due to mortality or curative therapy prior to the 3 month follow-up QOL assessment. It is not likely this will bias treatment effect estimation because of randomization. As a simplest sensitivity analysis, we will consider assignment of the last reported QOL to those who died prior to 3-month QOL ascertainment and then compare two randomized arms. Similarly, we will consider the best observed QOL for those with curative therapy before 3 months.

See section 10 for the qualitative data analysis plan.

12. PCORI Methodology Standards

Table: PCORI Methodology Standards Met in the Research Protocol		
Standards for Formulating Research Questions	RQ-1	Identify gaps in evidence
	RQ-2	Develop a formal study protocol
	RQ-3	Identify specific populations and health decision(s) affected by the research
	RQ-4	Identify and assess participant subgroups
	RQ-5	Select appropriate interventions and comparators
	RQ-6	Measure outcomes that people representing the population of interest notice and care about
Standards Associated with Patient-Centeredness	PC-1	Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context
	PC-2	Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants
	PC-3	Use patient-reported outcomes when patients or people at risk of a condition are the best source of information for outcomes of interest
	PC-4	Support dissemination and implementation of study results
Standards for Data Integrity and Rigorous Analyses	IR-1	A priori, specify plans for data analysis that correspond to major aims
	IR-2	Assess data source adequacy
	IR-3	Describe data linkage plans, if applicable
	IR-4	Document validated scales and tests
	IR-5	Provide sufficient information in reports to allow for assessments of the study's internal and external validity
	IR-6	Masking should be used when feasible
Standards for Preventing and Handling Missing Data	MD-1	Describe in protocol methods to prevent and monitor missing data
	MD-2	Use validated statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness
	MD-3	Record and report all reasons for dropout and missing data, and account for all patients in reports
	MD-4	Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation
Standards for Heterogeneity of Treatment Effect (HTE)	HT-1	State the goals of HTE analyses, including hypotheses and the supporting evidence base
	HT-2	For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods
	HT-3	Report all prespecified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed
Standards on Research Designs Using Clusters	RC-1	Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or the individual level
	RC-2	Justify the choice of cluster randomization
	RC-3	Power and sample size estimates must use appropriate methods to account for the dependence of observations within clusters and the degrees of freedom available at the cluster level
	RC-4	Data analyses must account for the dependence of observations within clusters regardless of its magnitude
	RC-5	Stratified randomization should be used when feasible

13. Dissemination and Implementation Plan

Dissemination activities, tools, timing, and responsibilities: The first step in our dissemination and implementation process will be peer review. Our RAB stakeholders (patients, caregivers and advocacy organization), the leadership team, center PIs (VA and non-VA), with support from DCRI, will collaborate to analyze the study findings, and prepare papers for peer review, including national meetings and publication. Hepatology and Palliative Care specialty journals will be targeted, as well as health services journals, as our findings may also impact healthcare costs and utilization. The executive committee will oversee dissemination of information by organizing the investigators into writing committees for publication preparation and submission. The findings of this study will be coincident with an anticipated rise in the incidence of hepatocellular cancer, as well as morbidity and mortality attributed to ESLD, assuring great interest in our findings.
Patient newsletters, blogs and free lectures within our patient community will be the means of sharing information with study participants. The involvement of the patient advocacy group will facilitate dissemination to the liver disease community and policy makers, through their website and social media. The RAB members will be directly involved in writing and reviewing the details. With the assistance of the Global Liver Institute, we will create partnerships to disseminate information through various patient education, advocacy, and research organizations such as the American Cancer Society and the American Liver Foundation.

Contemporaneously, our rich network of hepatology providers within VHA and non-VHA sites will provide an opportunity to widely disseminate the findings throughout organizations such as the American Association for the Study of Liver Disease as well as the VHA HIV, Hepatitis & Related Conditions program. In fact, the former organization will incorporate the findings into practice guidelines through a formal proposal by the executive committee.

14. Study limitations

This cluster RCT in the field of palliative care and Hepatology is a complex intervention with a pragmatic design. Our aim is to make PC part of routine clinical practice for ESLD patients, and equip the hepatologists with the knowledge and resources they may need to meet this aim. Participant heterogeneity and a minimum of exclusion criteria are allowed to a large extent. Caregivers are given flexibility to do the assessments over phone or in person, depending on their availability. Telehealth is now becoming a part of routine standard of care at VA healthcare systems and many non-VA settings; hence, we are including it as a mode of delivery of PC intervention. The technological platform may vary from site to site, but the overall concept of reducing travel, distance, time, access and space issues applies to all sites. We will capture which part of intervention was done using these platforms and look for any differences.

The barrier of time constraints during routine clinical practice is overcome by allowing the initial intervention visit to occur within a 6-week window, in both models of care. The expansion of work relative value units demonstrates the material benefits of the additional PC activities. The PC community may resist hepatology led PC, as it may be viewed as an infringement upon their scope of activities. However, given the shortage of PC providers, as well as the anticipated need in ESLD, and with the inclusion of PC providers in the conduct of this research, we anticipate building a bridge between the PC and hepatology communities by demonstrating that hepatology led PC will facilitate real world implementation of PC. Furthermore, the complexity of

disease and comorbid conditions in ESLD patients will make transferring PC to the liver subspecialist more palatable.
Patients may continue to perceive PC as end-of-life care. Through our research, we will assess the acceptability of both interventions, and thus allow us to understand the underpinnings of such a perception. One important consideration may be to propose renaming palliative care, *as supportive or comfort care*. In doing this on a larger scale, patients may abandon the concern of end-of-life care, given an association of the word palliative with terminal.

Potential Bias:

1. Selection bias: It is possible that an investigator may select patients to participate based on various factors that include, but may not be limited to the investigator's expectation that patients will participate and adhere to study procedures, the volume of patients being seen and time to screen/enroll during any given clinic session, availability of the investigator and/or coordinator to see patients, and even the volume of patients being seen in the office. Language barriers may also introduce some selection bias, as we will be enrolling only participants who are able to read/understand English. All patients referred to the site investigator staff will be eligible for participation.
   Mitigation Strategy: Our DCC will monitor enrollment on an ongoing basis, including rates of refusal, as a function of the total number of patients seen (by the investigator). We will also capture basic demographic information and clinical data of those who are screened to be eligible but refuse to participate. Significant differences between sites may indicate the presence of selection bias.

2. Information bias: The identification of patients who are appropriate for this trial depends upon having sufficient information available to make an accurate diagnosis of end stage liver disease and HCC. Furthermore, some centers may be more likely than others to qualify or disqualify a patient for liver transplantation.
   Mitigation Strategy:
   We will rely upon each hepatologist following conventional guidelines and teaching for diagnosis of ESLD, HCC (within conventional criteria based on standardized imaging criteria), and determination of a patient being a transplant candidate (based on conventional published guidelines).
   a. Non-differential bias which would push the results toward the null hypothesis – thus any significant findings would be very believable. The possibility for non-differential bias exists if all patients enrolled into the study have a preconceived notion that palliative care is useful or not, and this preconceived notion impacts their adherence to procedures and/or responses to assessments. Additionally, the conventional thinking about palliative care may change during the course of the study; for example, palliative care may become a more conventional approach in certain forms of liver disease, but this approach would apply equally to both arms of the study, at all sites.
   b. Differential bias. The "direction" of bias would be important. This is a real concern if some hepatologists (centers) have a preconceived notion of PC, either to use or under use. We would only know this by tracking patients who declined enrollment (or who the doctors did not enroll). For example, if one site in the hepatologist led PC model had a higher rate of declining to participate than others, and that site was sending the patients who declined participation to PCs more frequently than other sites in the same arm, we may have a differential bias.

Mitigation Strategy: To assess this, we will capture the rates and reasons for declining to participate at each site.

Potential Confounding:

1. Other variables that may affect our assessments include life events that we do not capture such as weddings, deaths of loved ones, and other stressful or joyful.
2. The patient may have other co-morbid conditions that impact the assessments; these include but are not limited to non-liver organ dysfunction. We will be capturing Charlson Comorbidity Index for all patients.

15. Human Subjects Protection

15.1 Human Subjects Involvement and Characteristics

IRB approval will be obtained prior to enrollment of patients and caregivers. Human research participants in this study are involved at two levels- the patient and caregiver research advisory board (RAB) members, and the other research participants. Both groups are involved throughout the length of the study. Since the members of RAB are the stakeholders, they are involved as investigators and will not be study participants at any time. The RAB members attend all the meetings related to formal protocol development and implementation in year 1, and future meetings discussing recruitment/ retention throughout the study.

All study participants complete study assessments at baseline, 1, 2, 3, 6, 9 and 12 months from their initial visit. In addition, we propose to conduct semi structured interviews by phone, with a purposive sample of participants during year 2, 3 and 4. At all points of contact we will maintain privacy by offering a closed office setting and reminding all members to maintain confidentiality. All participants will be more than 18 years of age, patients with a history of End Stage Liver Disease, along with caregivers of ESLD patients. They must be cognizant to understand the informed consent, and willing to participate in the study.

Informed consents will have an opt in option for qualitative interviews, and only those patients/ caregivers who agree will be considered for interviews. During the purposive sampling, UAB will select a few dyads from each site for an interview, and will call the individual Site Coordinator to get the name and phone number of that patient by phone. Interviews will follow the IRB approved qualitative interview guides, and will be audio recorded using a secure/encrypted audio recorder. Patient identifiers, digital files and transcripts will be kept in a secure, UAB server that is located behind the UAB firewalled network that is accessed from Dr. Bakitas' office. Dr. Bakitas' password protected computer is in a locked office that is located in the Office of Research and Scholarship in the School of Nursing. The office is only available through pass key. No paper copies of names will be kept. Audio recordings of interviews will remain at UAB, and saved in their own secured password protected shared drive, linked to only unique patient ID. Names and contact information will be destroyed after all interviews are completed. The audio recordings will be transcribed verbatim via a secure, UAB IRB approved transcription service. If names were used during the interviews they will be redacted from the transcripts. Digital files are transferred through a secure file transfer. Files are protected through multiple layers of encryption. Transcription polices strictly adhere to HIPAA, CITI and NIH requirements for handling sensitive, confidential data. These deidentified transcripts will be used for analysis. Results will be reported in aggregate.
Inclusion of Women and Minorities: We will include women and minorities in our study; and they will be offered the same degree of protection and rights as all others.

Inclusion of Children: No children will be included in this trial.

15.2 Sources of Materials

All the eligible patients will be identified through individual methods at each of the participating clinical centers, including a search algorithm using each institution's EMR system, or scheduling systems. All the demographic information will be captured in the form of a baseline survey. This survey will be marked with a unique patient ID and all the information captured from this point on will be captured with this unique ID. The key to match the unique ID with the patient MRN will be housed within a secured network in a password protected drive at each site. Only the site study personnel will have access to this.

We will conduct semi structured interviews with a purposive subset of patients and caregivers. Consent for interviews will be included in the main consent. All these interviews will be audio recorded and transcribed. The data will be kept in password protected shared drive, with all individual transcripts as password protected documents labeled with the unique ID. Providers will be consented verbally at the end of the enrollment period, and interviewed by the trained interviewers. These will also be audio recorded and transcribed for analysis.

15.3 Potential Risk

There is no medical risk to any participant and no sharing of protected health information in this project. It is completely up to the participants to agree to this study. Refusal of participation will not impact their health care in the office. All patients will be assigned a unique ID. There are minimal risks to participants related to their completion of study assessments. There may be some emotional distress as they complete the survey, but this will influence their engagement in their own care.

15.4 Protections against risk

There are no known risks to the study.

Confidentiality: An electronic copy of a 'master identifier' log will be kept on a password protected computer in the research office. This log will match patient to their anonymous study ID for the purposes of matching data. This study ID will be also linked to the audio-taped data (in the form of recordings of interviews) collected in this study. The audio recordings will be destroyed after analysis, and a de-identified hard copy data-sheet and a de-identified database (all linked only to study ID) are kept with the research team.

15.5 Potential benefits of the proposed research to human subjects and others

The potential benefits to individual participants and for the target population in general are much greater than any risk, especially for improvement in QOL, symptom management, reduced distress among patients and caregivers, improved access to palliative care, and reduced hospitalizations or ER visits. The proposed project is a comparative effectiveness study of two models of palliative care delivery: Consultative PC versus Trained Hepatologist led PC. The results will help improve the overall healthcare outcomes of ESLD patients.

15.6 Data Safety Monitoring Plan

A Data and Safety Monitoring Board (DSMB) is formed to monitor patient safety and to review performance of the study. It includes a Chair with relevant clinical and research expertise, senior statistician with prior DSMB experience, and additional three clinicians with expertise in the clinical area. A DSMB charter that outlines the operating guidelines for the committee and the procedures for periodic evaluations of study data has been developed and will be agreed upon at the initial meeting of the DSMB (prior to the start of patient enrollment). After the written operations plan for the DSMB has been finalized (and approved by PCORI), any changes to the plan will be documented in the minutes of the DSMB meetings. Depending upon the operational plan established by the DSMB, the regular report might include recruitment and retention rates, primary and secondary endpoints, and other information as requested by the committee Chair. It is anticipated that the DSMB will convene at approximately 6-month intervals via teleconferences to review the accumulating data and make recommendations regarding continuation of the study. There will be both an open and closed sessions for each DSMB meeting.

16. APPENDICES

Appendices listed below are compiled as a separate document.

Appendix A. FACT-Hep
Appendix B. PROMIS 29
Appendix C. ESAS
Appendix D. PHQ 9
Appendix E. FAMCARE-P13
Appendix F. Distress Thermometer
Appendix G. Goal Concordant Care (Patient)
Appendix H ZBI-12
Appendix I. Goal Concordant Care (Caregiver)
Appendix J. End of Life Survey
Appendix K. Qualitative Interview Script for Patients
Appendix L. Qualitative Interview Script for Caregivers
Appendix M. Qualitative Interview Script for Hepatology Providers
Appendix N. Qualitative Interview Script for Palliative Care Providers
Appendix O. Pre/post assessment questionnaires for Hepatologists undergoing the training program
Appendix P. Alcohol Use Disorders Identification Test-C (AUDIT-C)
Appendix Q. Alcohol Use Disorders Identification Test (AUDIT)

17. REFERENCES

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