UNIVERSITY OF SUSSEX

FULL/LONG TITLE OF THE STUDY

Palliative Long-term Abdominal Drains Versus Repeated Drainage in Untreatable Ascites Due to Advanced Cirrhosis: A Randomised Controlled Trial (REDUCe 2 Study)

SHORT STUDY TITLE / ACRONYM

REDUCe 2 Study (**RE**peated **D**rainage **U**ntreatable **C**irrhosis)

RESEARCH REFERENCE NUMBERS

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ISRCTN Number:	26993825
REC Ref Number	22/SC/0164 (protocol approved by South Central – Oxford C Research Ethics Committee)
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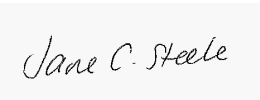
SIGNATURE PAGE

For and on behalf of the Study Sponsor:

Signature: Date: 19-May-26



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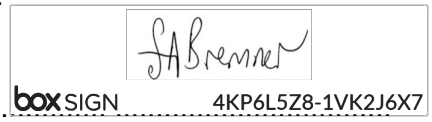
Signature: 

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PROTOCOL ACCEPTANCE FORM

REDUCe2 STUDY

Palliative Long-term Abdominal Drains Versus Repeated Drainage in Untreatable Ascites Due to Advanced Cirrhosis: A Randomised Controlled Trial (REDUCe 2 Study)

Chief Investigator: Prof Sumita Verma

Sponsor: University of Sussex

I agree to conduct the study in accordance with the current protocol, **Version 10.0 dated 14.05.2026**

……

Principal Investigator's Name (print)

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Principal Investigator's Signature Date

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Committees (if applicable)	**Trial Management Group (TMG)** This will comprise of members of the research team and the CI, Prof Verma, who will chair the meetings. The TMG will meet every month. **Trial Steering Committee (TSC)** This will comprise of the CI and Independent members to oversee the conduct and management of grant and the study. **Data Safety Monitoring Committee (DSMC)** This independent committee will review the safety, quality of the data, recruitment and overall management of the study and will provide recommendations to the TSC.

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1. **LIST OF ABBREVIATIONS**

AHCR	Ambulatory and Home Care Record
Ascites Q	Ascites Questionnaire
ALFA pump	Automated low flow ascites pump
BD	Becton, Dickinson and Company Ltd
BSCTU	Brighton and Sussex Clinical Trials Unit
BSMS	Brighton and Sussex Medical School
CRRS	Caregiver Roles and Responsibilities Scale
CI	Chief Investigator
CPS	Child Pugh Score
CLDQ	Chronic Liver Disease Quality of Life
CRN	Clinical Research Network
CTIMP	Controlled Trial of Investigational Medicinal Product
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic case report form
FFP	Fresh Frozen Plasma
GP	General Practitioner
GCP	Good Clinical Practice
HCP	Healthcare professional
HRQoL	Health related quality of life
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
IR	Interventional Radiology
LVP	Large Volume Paracentesis
LTAD	Long-term abdominal drains

MCID	Minimal clinically important difference
MNAR	Missing not at random
MELD	Model for endstage liver disease
MDM	Multidisciplinary meeting
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health and Care Research
NSAIDs	Non-steroidal anti-inflammatory drugs
PIS	Participant Information Sheet
PPI	Patient and public Involvement
PROMs	Patient reported outcome measures
PI	Principal Investigator
QALYS	Quality adjusted life years
RCT	Randomised Controlled Trial
R&D	Research & Development
REC	Research Ethics Committee
SFLDQoL	Short Form Liver Disease Quality of Life
SOP	Standard Operating Procedure
SHORE-C	Sussex Health Outcomes Research and Education in Cancer
TIPS	Transjugular intrahepatic portosystemic shunt
TMG	Trial Management Group
TSC	Trial Steering Committee
UKELD	United Kingdom endstage liver disease
UHS	University Hospitals Sussex NHS Foundation Trust

2. **STUDY SUMMARY**

Study Title	Palliative Long-term Abdominal Drains Versus Repeated Drainage in Untreatable Ascites Due to Advanced Cirrhosis: A Randomised Controlled Trial	
Internal ref. no. (or short title)	REDUCe 2 Study	
Clinical Phase, if relevant	NA	
Study Design	Intervention Group: Long-term abdominal drain (LTAD) Control Group: Large volume paracentesis (LVP)	
Study Participants	Patients with advanced cirrhosis and refractory ascites who are not candidates for liver transplantation and or transjugular intrahepatic portosystemic shunts	
Planned Sample Size	310	
Intervention duration	3 months	
Follow up duration	3 months	
Planned Study Period	60 months	
	Objectives	**Outcome Measures**
Primary	• To assess whether palliative LTADs result in better health related quality of life (HRQoL) compared to LVP in patients with refractory ascites due to advanced cirrhosis.	• Liver specific HRQoL assessed with the short form liver disease quality of life (SFLDQoL) questionnaire at the end of 3 months
Secondary	To assess impact of LTADs and LVP on • Infections (especially peritonitis) • Symptoms	• Cumulative peritonitis incidence in the LTAD and LVP groups • Symptoms in LVP and LTAD groups (assessed

		using Ascites Questionnaire-Ascites Q)
	• Caregiver workload	• Informal caregiver impact in LTAD and LVP groups (assessed using Caregiver Roles and Responsibilities Scale-CRRS)
	• Health resource utilization	• Health resource utilisation in LTAD and LVP groups (assessed using modified Ambulatory and Home Care Record (AHCR) for community service use; hospital records for hospital service use using an in-house designed questionnaire) Generic HRQoL and cost-utility analysis based on quality adjusted life years (QALYs) (assessed using EQ-5D-5L)
	And to explore • Perceptions of LTADs and LVP by patients, informal caregivers and healthcare professionals with qualitative interviews	• Patient, caregiver and health care professional perceptions/ perspectives of LTAD and LVP using qualitative methods

3. FUNDING AND SUPPORT IN KIND

FUNDER(S) **(Names and contact details of ALL organisations providing funding and/or support in kind for this study)**	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
Health Technology Assessment Project: National Institute for Health Research 133889 Hannah Sainsbury Research Manager (Monitoring) | Southampton NETSCC | NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) Alpha House, Enterprise Road, Southampton, SO16 7NS Phone: 02380595595 Email: hannah.sainsbury@nihr.ac.uk	Main funder. They will not be involved in data collection/analysis, manuscript write up and nor will they claim any intellectual property based on the trial
Rocket Medical Plc Imperial Way, Watford WD24 4XX Email: richardV@rocketmedical.com	Providing LTADs and drainage bags/bottles free of cost. They will not be involved in data collection/analysis, manuscript write up and nor will they claim any intellectual property based on the trial
Becton, Dickinson and Company Ltd (BD) 1 Becton Drive Franklin Lakes New Jersey 07417, USA Email: daniel.sime@bd.com	Providing LTADs and drainage bottles free of cost. They will not be involved in data collection/analysis, manuscript write up and nor will they claim any intellectual property based on the trial

4. ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor will ensure that

- The research has approval from a research ethics committee and regulatory and practical arrangements are in place before permitting the research to begin
- Roles and responsibilities of the various members of the research team is agreed and documented
- Adequate arrangements have been made for finance, risk/data management and insurance or indemnity

- Appropriate arrangements are in place for making information about the research publicly available before it starts, agreeing appropriate arrangements for making data and tissue accessible, with adequate consent and privacy safeguards,
- Appropriate procedures are in place and for reporting (progress reports, safety reports) and for monitoring
- There is a clear strategy for dissemination of research findings

5. ROLES AND RESPONSIBILITIES

5.1. Study Management Committees

Trial Management Group (TMG)

This will comprise of members of the research team and the CI, Prof Verma, who will chair the meetings. The TMG will meet every month to:

- Finalise trial related materials
- Oversee and co-ordinate the various aspects of the project, so that the research completes on time and on budget
- Assess study progress to ensure that recruitment is on target and on budget. If the anticipated recruitment is below that anticipated then strategies to improve this will be discussed
- Assess adherence to protocol

Trial Steering Committee (TSC)

This will comprise independent members (hepatologist (Chair), statistician, health economist, PPI member) and the CI Prof Verma. The TSC will provide overall supervision for the study on behalf of the study Sponsor and Funder. The TSC will consider recommendations from the Data and Safety Monitoring Committee (DSMC), including study progression. It will meet every six months.

Data Safety Monitoring Committee (DSMC)

This will be an independent committee and will comprise of an Independent Chair (hepatologist), independent statistician and an independent member (palliative care physician). Study data will be provided to the DSMC in accordance with the Terms of Reference for the Committee. The DSMC will meet approximately every six months to:

- Address any safety concerns
- Review any ethical issues raised
- Monitor adverse events

The DMSC will make recommendations to the TSC as appropriate.

6. **KEY WORDS**

Liver cirrhosis, community health nursing, palliative care, quality of life, refractory ascites, tunnelled abdominal drains

7. PARTICIPANT TIMELINE / STUDY FLOW CHART

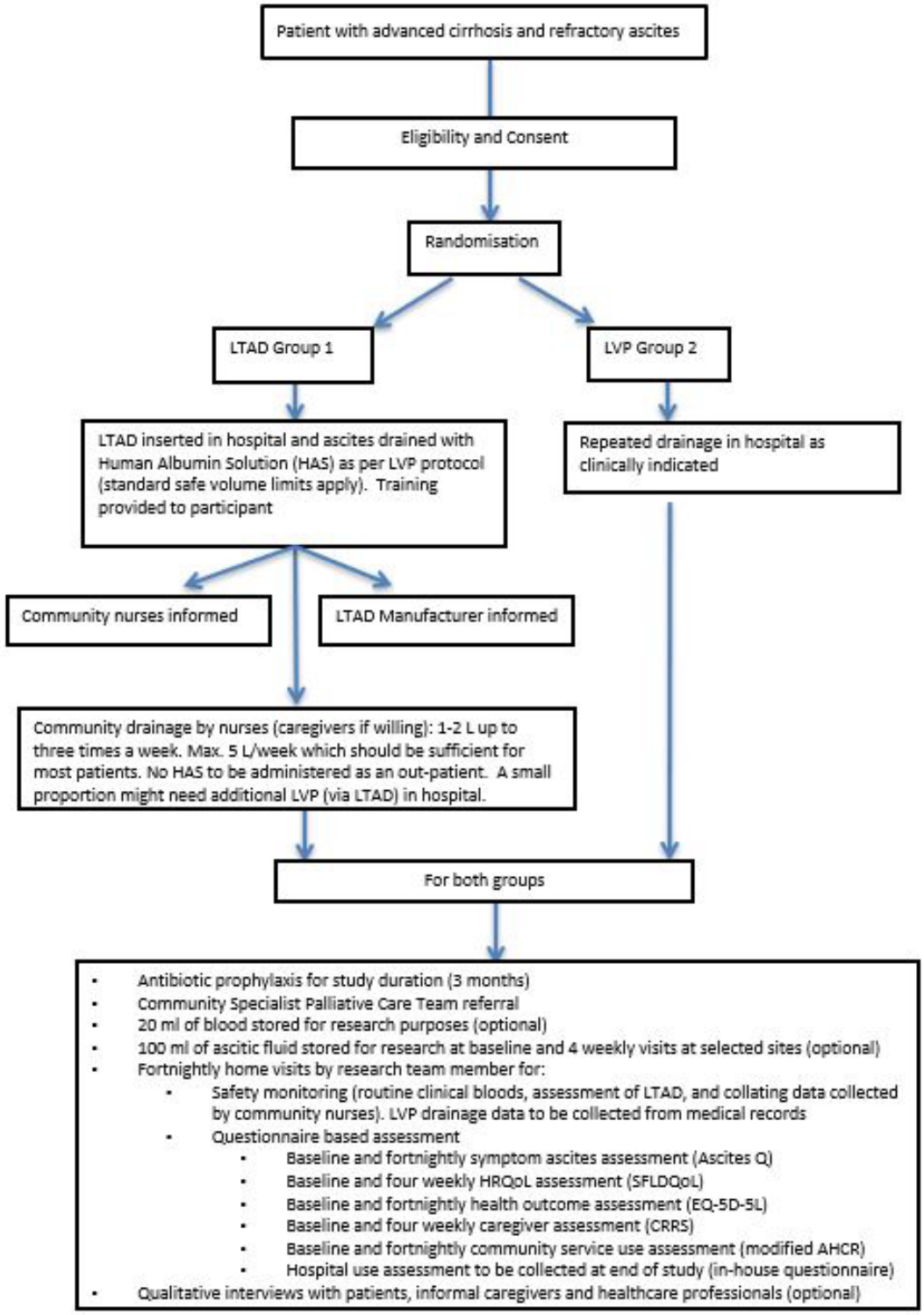


Figure 1. Participant Flow Chart

8. BACKGROUND AND RATIONALE

Ascites is the most frequent cirrhosis complication and also the most common complication requiring hospitalisation (1-2); up to a third of these patients can become unresponsive/ intolerant to medication. (3-4) This results in the debilitating condition called refractory ascites, associated with intense pain and breathlessness. As per the International Ascites Club Criteria, refractory ascites is defined as (i) diuretic-resistant ascites (ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment) and or (ii) diuretic-intractable ascites (ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic induced complications that preclude the use of an effective diuretic dosage). (5-6) In absence of a liver transplant, refractory ascites reduces average life expectancy to between 6-12 months. (3-4,7-8) However, most patients with advanced cirrhosis, including those with refractory ascites, are not candidates for liver transplantation, transjugular intrahepatic portosystemic shunt (TIPS) or the Automated Low Flow Ascites (ALFA) pump. (3-4, 7-10) Locally in Brighton, between 2013-2015, only 14% of patients with refractory ascites were listed/underwent fa liver transplant/underwent TIPS. (4)

The most common intervention for refractory ascites is hospitalisation every 10-14 days for palliative large volume paracentesis (LVP). This involves an abdominal drain insertion for up to six hours, removal of 5-15 litres of fluid and administration of intravenous human albumin solution. (9) A UK study indicated that from 2013-2015, of the 45,000 individuals dying from cirrhosis, a third required repeated LVP in their last year of life, costing the NHS > £21,000/ person. (11) During our Patient and Public Involvement (PPI) engagement, avoiding hospitalisation was seen as the overarching goal. Repeated hospital visits for LVPs were “unbearably painful” “devastating” and “traumatic” at a time when patients were coming to terms with the prospect of dying. Many also felt stigmatised in hospital.

Refractory ascites is a reliable prognostic guide in advanced cirrhosis (3-4, 8) and should trigger a palliative care plan. However, only a minority of patients with advanced cirrhosis are referred to palliative care, often only in the last few days before death. (4, 12-15) Most continue to receive arduous hospital-based interventions which offer little to no benefit. (12-13,16) Not unsurprisingly, up to 75% of patients with advanced cirrhosis, including those with refractory ascites die in hospital (11,17), compared to 40% with advanced cancer. (18) Lack of evidence-based interventions is an important factor contributing to suboptimal palliative care in advanced cirrhosis.

8.1. Health Related Quality Of Life In Patients And Informal Caregivers With Cirrhosis

Health Related Quality Of Life (HRQoL) is a very important outcome from a patient perspective**.** HRQoL is more significantly impaired in patients with cirrhosis than in both healthy controls and those with non-cirrhotic chronic liver disease, the impairment increasing with worsening cirrhosis severity. (19-23) Ascites is the main driver of impaired HRQoL in patients with advanced cirrhosis patients. (21, 24-27) Patients associate ascites with disease progression, potentially further impacting HRQoL. (21) Poorer HRQoL in patients with cirrhosis

and ascites independently predicts both the 12-month mortality as well as unplanned hospitalisation. (27-28) Informal caregivers of patients with cirrhosis have high prevalence of caregiver burden with low HRQoL and high incidence of anxiety and depression, compared with the general population. (24, 29-30) Factors impacting HRQoL in caregivers include ongoing alcohol use in patients and presence of ascites and hepatic encephalopathy. (24,29-30) Better communication with patients and informal caregiver, coupled with earlier integration of palliative care in cirrhosis could help improve HRQoL. (31-32)

Palliative trials aimed at improving HRQoL need to use patient reported outcome measures (PROMs) that are responsive and validated in advanced cirrhosis patients. Generic PROMs have some advantages as the scoring of the different groups of patients can be compared other patient populations/healthy reference population. (33) However, the disease specific PROMs offer greater sensitivity and specificity and include the Short Form Liver Disease Quality of Life (SFLDQoL) PROM (34), the only validated PROM in advanced cirrhosis (see Table 1). Additional advantages of SFLDQoL include combination of both generic and disease specific domains and its ability to predict mortality, with an equal if not higher accuracy than the MELD score.(35)

Table 1. Short Form Liver Disease Quality of Life Questionnaire

Name of assessment tool (recall period)	**Details**	**Strengths**	**Limitations**	**How administered**
Short form Liver Disease Quality of Life (SF-LDQOL) (last four weeks)	- 25 item questionnaire. Comprising SF-36 and 36 liver specific items grouped into nine scales effect of liver disease, memory/concentration, sexual functioning/ problem, quality of social interaction, health distress, sleep, loneliness, hopelessness and stigma - Higher scores better HRQoL	- Disease specific - More responsive/sensitive than CLDQ in advanced cirrhosis - Thorough assessment as combined use of generic/ disease-specific tools - Could predict mortality - Available in other languages	- Limited use and limited published data	- Paper and pencil, self-administered - 15-20 mins to complete

(Table adapted from Bhanji R (36) and Younossi Z (37)

8.2. **Novel strategies for management of refractory ascites**

Potential role of long-term abdominal drains (LTADs)

LTAD are tunnelled drains which are inserted in the abdominal wall under local anaesthetic in hospital. Community nurses or informal caregivers (if willing), then drain small amounts (1-2 litres) of ascitic fluid at home, up to three times a week. LTADs have potential advantages over LVP as they could reduce hospitalisation, improve symptom control and HRQoL (38-41) and be cost effective to the NHS. (39) In ascites due to advanced abdominal malignancy there is evidence to support the use of palliative LTADs. (38-41) A systematic review (15 studies, 221

individuals) reported peritonitis (median 5.9%, range 2.5%-34%). (38) A National Institute for Health and Care Excellence (NICE) Medical Technology Guidance (nine studies, 180 individuals) reported device-related infections in 5.8% with an 80%-96% drain patency. Compared with inpatient LVP, LTADs resulted in cost savings of £679 per patient, though cost effectiveness was less apparent when compared with outpatient LVP. NICE concluded that LTADs were clinically effective, had low complication rates, could improve HRQoL, were less costly than inpatient LVP and should be considered in malignant refractory ascites. (39) A third systematic review (32 studies, 1,297 individuals) reported an infection rate of 4.4% with significant improvement in symptom control and HRQoL. (40)

8.3. **Long-term abdominal drain use in cirrhosis**

There have been national calls to improve palliative care in advanced cirrhosis. (42) However, LTADs are not routinely used in cirrhosis as firstly, those with cirrhosis can have a complex symptom burden and psychosocial issues like addiction, making community care potentially challenging. Secondly, unlike those with cancer, patients with cirrhosis are at higher risk of ascitic fluid infection (peritonitis) due to increased bacterial translocation, gut dysbiosis and immune dysfunction. (9) The concern is whether LTADs could further increase this infection risk. These issues were highlighted in our national survey of Gastroenterologists. (43)

A systematic review assessed LTADs in refractory ascites due to advanced cirrhosis (18 studies, all rated to be of poor quality, 176 patients). (44) Insertion success was 100% with no further ascites-related hospitalisations in 14/18 studies where data were provided. Peritonitis rates (12.7%) were more than two-fold higher than that reported in malignant ascites (5.9%) (38) Recent data comes from the REDUCe Study (45-46), comparing palliative LTADs vs. LVP in patients with refractory ascites due to advanced cirrhosis. This randomised controlled trial (RCT) was designed to determine feasibility, assessment tools, preliminary cost effectiveness and outcome measures for the main trial. Of the 59 eligible patients, 36 (61%) were randomised with 21 (58%) completing the 3-month study. Both groups received prophylactic antibiotics for the study duration. LTAD insertion was successful in all participants, only 2/15 (13%) requiring further hospitalisation specifically for ascites. Peritonitis incidence (LTAD vs. LVP) was 6% vs.11%, self-limiting cellulitis (none requiring hospitalisation) being 41% vs. 11% respectively. The LTAD group spent less ascites-related study time in hospital, the average fortnightly total costs being about 15% lower. Symptom and HRQoL scores, the latter assessed using SFLDQoL questionnaire (34), were highly variable in both groups, likely reflecting the small sample size. (46) A small qualitative sub study indicated LTAD acceptability by patients and nurses. (47) We achieved our study success criteria: attrition 42% (pre specified not >50%); LTAD complications requiring removal 0% (pre specified <10%); uptake/completion of questionnaires/interviews: $\geq$80% (pre specified 80%).

Recently published guidance by NICE (https://www.nice.org.uk/guidance/ipg746) recommended that due to lack of high quality safety and efficacy data, LTADs should only be used in cirrhosis with special arrangements such as research.

8.4. **Rationale**

Liver disease related deaths in England have increased by >250% since 1971. (48) In 2018, liver disease accounted for >10% of deaths in those aged 35-49 years, greater than deaths from suicide/heart disease/breast cancer. (49) Nationally, the COVID pandemic has resulted in a 20% increase in all cause alcohol-related deaths (mostly related to liver disease) in 2020. (50)

Studies confirm the escalating complex physical and emotional symptoms in advanced, often associated with addiction/social isolation and poor HRQoL. (16, 20-21, 23, 27-28) Debilitating pain and breathlessness, commonly observed with ascites are the most common symptoms in cirrhosis, reported by up to 88%. (23) Timely palliative care in cirrhosis can improve symptom control (51-52), address goals of care/advance care planning (53-55) and reduce hospitalisations (13,46,56) with costs savings of ~ £8000 per patient. (13) Better control of ascites symptoms by interventions such as LTADs, TIPS and ALFA pump can also improve HRQoL. (39-40, 57-60)

Unfortunately, unlike other advanced conditions, cirrhosis is not included in the James Lind Alliance research priorities. (61) The REDUCe 2 study addresses both this inequity in palliative care in advanced cirrhosis and the significant disparity between cirrhosis mortality and access to research (62) and is aligned with the Marie Curie palliative care triggers. (63) Further research into palliative LTADs in cirrhosis is endorsed by both UK and American cirrhosis guidelines. (64,65) The COVID pandemic further reinforces the need to transfer care to the community for this vulnerable cohort. Our PPI group have expressed consistent enthusiasm for this research describing it as “ground-breaking”, given that this is such a vulnerable population.

8.5. **Study Aim**

Our aim is to optimise palliative management in often vulnerable individuals with refractory ascites due to advanced cirrhosis, thereby resulting in better health-related quality of life (HRQoL).

8.6. **Assessment and Management of Risk**

Research involving vulnerable adults in research is essential to generate high quality evidence. (66) Factors considered when planning this research and strategies instituted are:

Emotional distress exacerbated by the demands of the research

Written participant informed consent, communication skills and consenting vulnerable adults training for clinicians and research staff. Participants will have the right to withdraw from the study at any time without prejudicing routine clinical care.

Burden of data collection on the patient

Research team members will collect data during home visits to minimise burden and support the process. Questionnaire data can be collected in a variety of formats to suit participant needs. Proxy scores will be allowed, i.e. informal caregivers and research team members can help patients to complete the questionnaires.

Gate-keeping by staff

Gatekeeping is when healthcare professionals (HCP) or other involved parties prevent eligible patients from entering a trial as a research subject. (67) Training and support will be offered to all staff involved in recruitment to address the issue of gatekeeping.

Communications skills training

Communication skills training will be provided and evaluated by researchers from SHORE-C with input from our PPI group. This training is important as during the feasibility study (46) reluctance of health care professionals to initiate timely end of life discussions contributed to recruitment challenges. The training will include a PowerPoint presentation during site initiation visits as well as four separate one-day workshops provided throughout the study duration. The PowerPoint presentation will include procedural information about completing study questionnaires and key information about talking to patients. Recruitment challenges including initiating discussions on palliative interventions and potential solutions will be discussed. A 'crib' sheet will be provided that includes highlights about the study, including those aspects clinicians may find difficult. The four separate workshops will include pre and post course evaluation forms along with scenarios to role-play and discuss. Several studies and systematic reviews demonstrate the potential effectiveness of these interventions with HCP on communication skills, increasing self-confidence in communicating key RCT concepts to patients, raise awareness of hidden challenges, and reducing some of the barriers associated with poor patient enrolment in clinical trials. (68-72)

9. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

9.1. Primary Objective

The primary objective is to assess whether palliative LTADs result in better health related quality of life (HRQoL) compared to LVP in patients with refractory ascites due to advanced cirrhosis.

9.2. Secondary Objectives

Secondary objectives are to assess impact of LTADs and LVP on

- Infections (especially peritonitis)
- Symptoms
- Caregiver workload
- Health resource utilization
- Generic HRQoL and QALYs
- Perceptions of LTADs and LVP by patients, informal caregivers and healthcare professionals with qualitative interviews.

9.3. Outcome measures/endpoints

Designing palliative interventional clinical trials in advanced cirrhosis is challenging, as generally accepted hard primary outcomes such as transplant-free survival or time to disease progression are inappropriate. Additionally, there remains uncertainty regarding appropriate assessment tools. Consequently, this already underserved cohort is grossly under-represented in research. Following our feasibility study (46), and PPI group and Health Technology Assessment (HTA) Committee feedback, HRQoL was deemed to be the most appropriate primary outcome. The international LiverHope consortium (73) have also recently recognised that HRQoL represents the primary clinical outcome of interest in a palliative advanced cirrhosis cohort and explicitly stressed the importance of including HRQoL in study design.

9.4. Primary endpoint/outcome

The primary outcome is liver specific HRQoL assessed at 3 months using the SFLDQoL questionnaire (34), the only HRQoL tool validated in advanced cirrhosis.

9.5. Secondary endpoints/outcomes

- Cumulative peritonitis incidence in the LTAD and LVP groups
- Symptoms in LVP and LTAD groups assessed using the Ascites Q (74)
- Informal caregiver impact in LTAD and LVP groups assessed using the CRRS (75)
- Health resource utilisation in LTAD and LVP groups (modified AHCR (76-77) for community service use; hospital records for hospital service use using an inhouse designed questionnaire)
- Generic HRQoL and cost-utility analysis based on QALYs using EQ-5D-5L (78-79)
- Patient, caregiver and health care professional perceptions/perspectives of LTAD and LVP using qualitative methods

Table 2. Table of Endpoints / Outcomes

Objectives	**Outcome measure**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary		
To assess whether palliative LTADs result in better health related quality of life (HRQoL) compared to LVP in patients with refractory ascites due to advanced cirrhosis.	Liver specific HRQoL assessed at 3 months with the SFLDQoL questionnaire	To be assessed at baseline and four weekly
Secondary		
To assess impact of LTADs and LVP on:		
Infections (especially peritonitis)	Cumulative peritonitis incidence in the LTAD and LVP groups	To be assessed at 3 months
Symptoms	Symptoms in LVP and LTAD groups assessed using Ascites Q	To be assessed at baseline and fortnightly for 3 months
Caregiver workload	Informal caregiver impact in LTAD and LVP groups assessed using CRRS	To be assessed at baseline and four weekly for 3 months
Health resource utilization	Health resource utilisation in LTAD and LVP groups: community service use (modified AHCR) and hospital records for hospital service use (inhouse designed questionnaire) Generic HRQoL and cost-utility analysis based on QALYs using EQ-5D-5L	To be assessed at baseline and fortnightly, hospital service use at 3 months To be assessed at baseline and fortnightly

Explore perceptions of LTADs and LVP by patients, informal caregivers and healthcare professionals with qualitative interviews.	Patient, caregiver and health care professional perceptions/perspectives of LTAD and LVP using qualitative methods	Interviews (optional) to be conducted throughout the trial

10. STUDY DESIGN

This RCT will compare insertion of a palliative tunnelled long-term abdominal drain (LTAD) (Group 1 intervention) to standard of care (Group 2 large volume paracentesis (LVP) in the management of refractory ascites due to advanced cirrhosis.

This is a multi-centre, non-blinded parallel-group RCT with up to 3 months of follow up and will be conducted across 35 sites in England, Scotland and Wales. We aim to recruit 310 patients.

Thirty patients, 20 informal caregivers and 20 HCP will also be invited to give their perceptions/perspectives of LTAD and LVP using qualitative methods.

An 18-month internal pilot will assess recruitment and LTAD safety: 12 months recruitment, three months' follow up, one-month for analysis, two-months for a STOP/GO decision.

11. STUDY SETTING

National Health Service (NHS) Acute Hospitals and their corresponding Community Trusts to provide home care support to the participants with a LTAD (home drain). Sites will complete feasibility assessments to ensure they have the patient population and the resources available to conduct the study. The Clinical Research Networks (CRNs) and the British Association for Study of Liver Disease End of Life Specialist Interest Group will assist in the identification of sites.

12. PARTICIPANT ELIGIBILITY CRITERIA

12.1. **Inclusion criteria**

Male or Female

Age ≥18 years

Refractory ascites (with need for recurrent LVP) secondary to cirrhosis defined as per International Ascites Club criteria (5-6):

- *Diuretic-resistant ascites:* ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment (spironolactone 400 mg and furosemide 160 mg) and or
- *Diuretic-intractable ascites:* ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic induced complications that preclude the use of an effective diuretic dosage

Registered with a General Practitioner (GP) in the community Trusts served by the participating centres.

Capacity to give informed consent

12.2. **Exclusion criteria**

- Loculated and or chylous ascites
- Evidence of active infection that in the investigator's opinion would preclude insertion of LTAD (for example, bacterial peritonitis) – such patients would need to receive appropriate treatment and could then be reconsidered
- A candidate for liver transplantation and or TIPS
- Psychosocial issues which in the opinion of the medical team will preclude study participation
- Pregnancy – all women of childbearing age must have a negative pregnancy test
- Lacks capacity to give informed consent

Participants whose first language is not English can have materials translated so as not to exclude their participation. The translation of the patient PIS and consent form will be coordinated centrally by the CI.

Participants will not be excluded if they are already participating in another ongoing study, as long as their researchers are confident that participation in the current study will be logistically feasible and not too onerous for the participants. Approval for co-enrolment may be needed by on-going study Chief Investigator. Patients will also not be excluded from participation in the study in relation to their place of care/residence, for e.g. if they are in or move to a hospice/ care home. Study recruitment would remain unchanged with patient identification and consent undertaken in the hospital sites and follow-up data collection in usual place of residence (including care homes).

13. STUDY PROCEDURES

13.1. Schedule of Assessments

Table 3. Schedule of Assessments

	Screening	Telephone call	Baseline / W0 (7 +/- 3 days post screening)	W2 (+/- 3 days)	W4 (+/- 3 days)	W6 (+/- 3 days)	W8 (+/- 3 days)	W10 (+/- 3 days)	W12 (+/- 3 days)
Perform capacity check using capacity checklist. *England & Wales sites*: If patient loses capacity during study, approach Consultee *Scotland sites*: Capacity to be checked at start of study only.	X		X	X	X	X	X	X	X
Informed Consent (Informed consent can be given prior to the screening visit but must be confirmed at the screening visit)	X								
Demographics	X								
Medical History	X		X						
Routine clinical blood (Haemoglobin, white cell count, Platelets, APPT, INR/PT, Total Bilirubin, ALT/AST, Alkaline phosphatase, Total protein, Albumin, Sodium, Potassium, Urea, Creatinine, eGFR, C reactive protein)	X		X[1]	X	X	X	X	X	X

	Screening	Telephone call	Baseline / W0 (7 +/- 3 days post screening)	W2 (+/- 3 days)	W4 (+/- 3 days)	W6 (+/- 3 days)	W8 (+/- 3 days)	W10 (+/- 3 days)	W12 (+/- 3 days)
Pregnancy test if child bearing age	X								
Diagnostic ascitic tap (white cell count, neutrophil count and culture and total protein[2])	X[2]		X[1]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Eligibility check (inclusion/exclusion)	X		X						
Vital signs (Temperature, blood pressure and pulse) (Height and pre-drain weight at baseline only)	X		X	X	X	X	X	X	X
Liver disease scores (CPS/MELD/UKELD)	X		X	X	X	X	X	X	X
Liver disease assessment and history (includes hepatic encephalopathy, variceal bleeding, ascites and hepatocellular cancer	X		X	X	X	X	X	X	X
Alcohol and substance use assessment (self -reported)	X		X	X	X	X	X	X	X
Assessment of transport methods available to patient (in case the participant is to travel for LTAD insertion)	X								

	Screening	Telephone call	Baseline / W0 (7 +/- 3 days post screening)	W2 (+/- 3 days)	W4 (+/- 3 days)	W6 (+/- 3 days)	W8 (+/- 3 days)	W10 (+/- 3 days)	W12 (+/- 3 days)
Notification of Randomisation telephone call (If randomisation is done prior to baseline visit)		X							
Optional Research blood sample 20ml (10ml for serum, 10ml for whole blood. To be frozen at -80°C for analysis at end of study)			X						
Optional Research ascitic fluid samples 100ml (only in selected sites) (To be frozen at -80°C for analysis at the end of the study)			X		X[4]		X[4]		X[4]
Optional collection and storage of LTADs removed (To be frozen at -80°C for analysis at the end of the study)									X[5]
LTAD/LVP insertion[6]			X[6]						
Prophylactic antibiotics for both LTAD and LVP groups after discussing risks/benefits			X	X	X	X	X	X	X
Referral to palliative care for both LTAD and LVP groups			X						

	Screening	Telephone call	Baseline / W0 (7 +/- 3 days post screening)	W2 (+/- 3 days)	W4 (+/- 3 days)	W6 (+/- 3 days)	W8 (+/- 3 days)	W10 (+/- 3 days)	W12 (+/- 3 days)
LTAD (group 1) research team member to collect drainage data collated by community nurses, also assess LTAD and ask about abdominal pain			X	X	X	X	X	X	X
LVP (group 2) drainage assessment to be collected from medical records.			X	X	X	X	X	X	X
Adverse event review			X	X	X	X	X	X	X
Concomitant medication review			X	X	X	X	X	X	X
Ascites questionnaire (Ascites Q) completion (patient)			X	X	X	X	X	X	X
Liver specific HRQoL (SFLDQoL) questionnaire completion (patient)			X		X		X		X
Generic HRQoL (EQ5D-5L) questionnaire completion (patient)			X	X	X	X	X	X	X
Care giver questionnaire (CRRS) completion (caregiver)			X		X		X		X
Community service use (modified AHCR) questionnaire completion (patient)			X	X	X	X	X	X	X

	Screening	Telephone call	Baseline / W0 (7 +/- 3 days post screening)	W2 (+/- 3 days)	W4 (+/- 3 days)	W6 (+/- 3 days)	W8 (+/- 3 days)	W10 (+/- 3 days)	W12 (+/- 3 days)
Hospital service use in house designed questionnaire completion (research team member)									X
Optional qualitative interviews (patients, informal caregivers and healthcare professionals) will be conducted throughout the study. Only one interview per participant				X	X	X	X	X	X

[1] PT and or INR and platelet count and diagnostic ascitic tap need to be checked within 7 +/-3 days of LTAD insertion; Spontaneous bacterial peritonitis defined as ascitic white cell count > 500 cells/mm^3, and or neutrophil count > 250 cells/mm^3 and or a positive ascitic fluid culture. (64) NOTE: In those with a LTAD, peritonitis should only be diagnosed by an ascitic fluid sample taken via an ascitic tap and not via the LTAD.

[2] Ascitic fluid total protein to be checked at screening only

[3] To be done in LVP group at each drainage as is current standard of care, and LTAD patients only if suspicion for peritonitis. In those with LTAD and clinical suspicion for peritonitis, take ascitic fluid sample for analysis from both from LTAD and via a separate ascitic tap

[4] In the LTAD group, sequential ascitic fluid research samples will be collected via drain line extensions using aseptic technique. In the LVP group this will be done at the time of LVP closest to the indicated visit

[5] LTADs removed at any point during or after the trial follow-up period will be collected and stored for analysis at the end of the study.

[6] For LTAD only: Prior to LTAD insertion correct INR and platelet count as per local trust guidelines. If no local guidelines available use the following: if INR≥1.5 and platelet count <50x10^9 2 units of Fresh Frozen plasma and 1 -2 pools of platelets to be transfused prior to LTAD insertion

14. RECRUITMENT

14.1. Patient Identification

Potential participants will be identified by their existing medical team from acute medical units, LVP day units, outpatients and Gastroenterology/ Hepatology wards as potentially eligible. If patient is willing to hear more about the study they will then be approached by the research team. The research team will discuss the study in detail and provide the participant information sheet. The patient can then take their time to think about their participation and ask any questions they may have.

14.2. Consent

Participant consent

Potential research participants will be identified by the direct medical care teams at the participating sites and highlighted to the research teams. If the CI/PI is the usual consultant, then to avoid any potential conflict of interest these patients will be discussed either at multidisciplinary meetings (MDM) and/or referred to local transplant centres to ensure that liver transplant/TIPS is not an option. The participant information sheet (PIS) will be provided to the potential participant by a member of the research team and any questions addressed. After the participant has had time to read the PIS, the research team will meet up/call (dependent on patient preference) the potential participant/informal caregiver again and any further queries will be clarified. If the participant is willing then written informed consent will be received by the research team to participate in the main study. Participants may choose to take part in an optional interview and consent to an additional 20ml of blood being taken and stored for research purposes until the end of the study. At certain sites, they may also consent to 100ml of ascitic fluid being collected at baseline and every four weeks, and stored for research until the study ends. Additionally, at these sites, participants can consent to the storage, analysis, and eventual disposal of LTADs removed at any point during or after the trial follow-up period. Permission will also be received for participant contact details to be given to the qualitative researcher and if willing, the qualitative researcher will contact the patients directly.

A letter will be sent to the patient's GP informing them of their participation in this study.

Participants Who Lose Capacity During the Study

England and Wales
This is an end of life cohort with advanced liver disease. Such patients can be confused due to multiple reasons including hepatic encephalopathy. Capacity can fluctuate in this cohort. At each visit the participant's capacity will be checked using a capacity to consent checklist. If it is deemed that the participant lacks capacity then a Consultee will be approached. This can either be the participant's caregiver (personal Consultee) or if no caregiver is available, then the patient's independent medical consultant (nominated Consultee). The Consultee will be approached to advise whether participation in the trial is in the patient's best interest and provide written confirmation of this.

Scotland

In Scotland, once a patient gives consent then that remains valid for the remainder of the study. However, at the time of the initial consenting process, patients will be asked as to how they wish to proceed in case they lose capacity during the study. They can consent to either continue or withdraw from the study, and also whether their previously collected data can remain in the study.

Caregiver Consent

For all patients, potential informal caregivers (e.g., a friend or family member) will be identified if available. However, absence of a caregiver will not preclude participation in this trial. The informal caregiver will be approached with the patient's permission but both patient and caregiver do not need to take part together. Informal caregivers will be approached by the research team and an information sheet provided for participation in a questionnaire study assessing impact on caregivers. Written consent will be requested to participate in the questionnaire study. Informal caregivers will also have the opportunity to participate in an interview (optional). Permission will also be requested for caregiver contact details to be given to the qualitative researcher and if willing, the qualitative researcher will contact the caregiver directly to discuss further.

Healthcare professional (HCP) consent

HCPs (gastroenterologists, hepatologists, hospital and community nurses) will also be approached by the research team and given an information sheet to participate in an optional interview. Consent will be sought for their contact details to be passed on to the qualitative researcher, and if willing, they will be contacted directly by the qualitative researcher to discuss this further.

Screening Visit

Potential eligible patients will be invited to attend for an appointment. They will have the opportunity to ask questions about the study and written consent will be received. Routine bloods and assessments will be conducted in line with Table 3 Schedule of Assessments.

15. THE RANDOMISATION SCHEME

Randomisation, set up by the Brighton and Sussex CTU (BSCTU) statistician on Sealed Envelope™, will be performed online by a research team member on a 1:1 basis to either LTAD or LVP (current standard of care), minimised on gender and liver prognostic scores (Child Pugh Score).

15.1. Allocation Sequence Generation

The random allocation of patients to treatments will be restricted by minimising on Child-Pugh Score (CPS) (<10 vs. ≥10) and gender (male/female) with an 80% probability of allocating to the arm, which minimises the imbalance. This will achieve near balance across interventions on disease severity and gender (the majority are expected to be male).

15.2. Allocation Concealment Mechanism

The allocation sequence will be generated dynamically, with a random element as described above. This way, the next allocation will only be generated and become known upon actioning a request from a member of the clinical research team.

15.3. Implementation

Randomisation will be implemented using Sealed Envelope™. Patients will be enrolled by the research team who will log into the web-based system, enter patient ID number, recruiting site, gender and Child-Pugh Score. The system will automatically generate a confirmation email informing the research team of the allocation, a copy being sent to the BSCTU.

15.4. Blinding

Due to the nature of the intervention, there can be no blinding in this trial except of the senior trial statistician who will be kept blinded until completion of the analysis. .

15.5. Notification of Randomisation

Randomisation can occur up to 10 days prior to the baseline visit. If it occurs prior to the baseline visit, the participants will be informed of their randomisation outcome via a telephone call from a member of the research team. In this call they will inform patients about which arm of the study they have been allocated to, and what to expect when they attend hospital for their baseline visit.

16. BASELINE VISIT

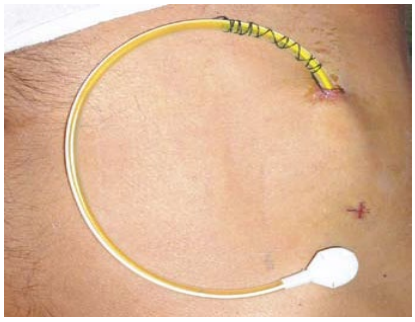
Assessments will be performed in accordance with Table 3. Insertion of the LTAD will occur at this visit.

16.1. Participants Randomised to the Long-Term Abdominal Drain (LTAD) (Group 1)

The two currently available LTADs in the UK, manufactured by either Rocket Medical or Becton, Dickinson and company (BD) will be used for this study (see Figure 2 Long-term abdominal drain in situ, courtesy of Rocket Medical plc). This will depend on stock availability

Figure 2. Long-term abdominal drain in situ

and site preference. Participants attending for LTAD placement will have their travel costs reimbursed.



LTAD Insertion

While at most sites, LTAD insertion will be performed by interventional radiology (IR), this is not essential. Individuals inserting LTADs outside of IR should undergo a period of supervised practice in IR and be assessed as competent to perform the procedure independently. Once a LTAD has been inserted the patient should undergo an LVP through the newly inserted drain to make subsequent community management of ascites easier. Draining in hospital with administration of human albumin solution (20%) on the day as per standard LVP protocol is recommended (9, 64). However, limits to the volume drained (6-8L) should be considered in high-risk patients (i.e. those with chronic kidney disease, previous history of hepatorenal syndrome or circulatory dysfunction). Do not perform another LVP over the next few days. Continue to drain in the community, 1-2 L up to three times a week. It must be ensured by the medical and research teams that appropriate transport is available for the participant to travel safely to the hospital if they are allocated to the LTAD arm.

Routine checking of haemostatic function is not recommended prior to LVP (9, 64). However, inserting a LTAD is a more invasive procedure as it involves tunnelling. Therefore, haemostatic function (INR and platelet count) will be checked within the preceding 7 +/- days of LTAD and corrected as per local trust guidance. In absence of local trust guidance please correct as below (see also Table 3)

INR < 1.5	no FFP will be administered
INR $\geq$ 1.5	2 units of FFP administered
Platelet count > $50x10^9$	no platelets transfused
Platelet count $\leq$ $50x10^9$	1-2 pools of platelets transfused

Technique of LTAD Insertion

The LTAD will be inserted with ultrasound guidance after informed consent has been received. Technique for insertion has been described previously. (45)

The insertion technique is a combination of tunnelled and Seldinger technique. After confirming the site for insertion with the help of ultrasound, local anaesthetic will be administered. A small incision is made where the catheter will enter the abdominal cavity. A Seldinger needle will be inserted through the incision into the peritoneal cavity and a guide wire is passed through the Seldinger needle which will then be removed.

A second incision will be made approximately 5cm away from the 1st, where the catheter will exit the tunnel.

The catheter will be tunnelled or threaded from the 2nd (exit site) incision to the 1st incision site with the tunneller, making sure the cuff is close to the 1st incision site.

The split sheath dilator will be then passed over the guide wire, the inner dilator and guide wire removed leaving the split sheath in situ.

The tunneller is removed from the catheter, which is then passed through the split sheath, separating the split sheath ensuring that all of the catheter is in the peritoneum.

The last of the split sheath is then removed.

The catheter is then adjusted along the tunnel, so the cuff moves towards the exit site. This will ensure that any possible kinks are removed from the catheter.

Avoiding the catheter, both incision sites will be sutured.

Use of Human Albumin Solution

Human Albumin Solution will not be administered to the LTAD group as outpatients.

Patients who remain symptomatic from ascites, despite drainage of 5L/week in the community should undergo supplementary LVP in hospital (via the LTAD) as required, with Human Albumin Solution replacement as per LVP protocol (9,64). In patients who recurrently require volumes higher than 5L drained off per week (e.g., 2 or more LVP in addition to 5L/week community drainage), higher volume community LTAD drainages can be considered on a **case-by-case basis**, in discussion with the named Principal Investigator/community teams

Ascitic fluid analysis

Routine ascitic fluid analysis in the LVP group will be performed at each drainage as is currently standard of care. In the LTAD group, routine ascitic fluid analysis will not be performed due to the likelihood of growing skin contaminants (80), the clinical significance of which remains uncertain. In those with a LTAD, ascitic fluid analysis will **ONLY** be performed if there is clinical suspicion for peritonitis: fever, abdominal pain, increased white cell count, worsening hepatic decompensation or renal function. In such instances the ascitic fluid sample will be taken for analysis from both the LTAD as

well as via a separate ascitic tap. Note the diagnostic criteria for peritonitis i.e. a neutrophil count > 250/mm^3, and or ascitic fluid white cell count >500/mm^3 and or if ascitic fluid culture is positive only applies to samples taken via a fresh ascitic tap, as parameters for samples taken from a LTAD remain uncertain. (9, 64) Peritonitis will be treated as per current guidelines. (9, 64) Development of peritonitis will not necessarily mandate LTAD removal. This needs to be decided on a **case-by-case basis** after discussion between site teams and the CI.

LTAD (Group 1) post drain insertion care (also see Figure 1)

- The research team will explain to the patient and informal caregivers how the LTAD will be used and provide them with the drainage kit, which will include at least two weeks supply of drainage bags/bottles. The Research teams will provide patients with the LTAD manufacturer information sheet and discharge letter, the latter also being sent to the GP and community nursing team. The discharge letter will state that patients have been discharged with a LTAD. LTAD manufacturer details are included in the discharge letter. An additional community nurse referral will be sent to the community teams with basic instructions on LTAD management.

- The research team will also contact the appropriate lead community nurse to update them. This will ensure that home visits can be organised by the community team to perform recurrent drainage and arrange necessary disposal of clinical waste. The research team will also inform the LTAD manufacturer so that they can organise additional bespoke training and support for participants/informal caregivers if needed and ensure supply of drainage bags/bottles.

- The patient and community teams will be provided with the contact number for the research team. Study sites will also be provided with written information describing LTAD management should they be admitted to hospital out of hours so that clinical teams are aware.

- The research team will provide clear instructions to the patient and community teams to ensure that the sutures are not removed too early. To optimise healing and minimise the risk of leakage the suture further away from the drain should not be removed before 7 days, while the one at the insertion site should not be removed before 14 days.

Community Management of LTAD

- The community nurses will visit patients at their usual residence, or in community centres to carry out ascites drainage as clinically indicated but drainage episodes should be limited to a maximum of three times a week. If additional training is required, the community nursing teams should contact the LTAD manufacturer as stated above. The amount to be drained will be dependent on clinical need, but would usually be 1-2L

at a time with a maximum of 5L/week. Each time drainage is performed it will be recorded by the community nurses in a drainage diary which will be kept in the patient's usual place of residence. This drainage diary data will be collected by the research team members during fortnightly home visits and entered into the electronic Case Report Form (eCRF) by a member of the research team.

- Additional drainage bags/bottles will be delivered to patients by the research team during the fortnightly home visits. The drainage bags/bottles will be disposed of in the usual way by the council as per standard arrangements in that region.

- The contact telephone number for the research team to be used **"in hours"** (9am-5pm) during week days will be provided to community teams. Out of hours, patients or community healthcare professionals should contact the out-of-hours GP service or the patients should attend Accident and Emergency (A&E) for emergency trial related problems.

- The community nurses will perform risk assessments during their home visits as per their usual practice and inform the research team of any concerns that have been identified as regards
    - Drain leakage or blockage
    - Cellulitis at the drain site
    - Abdominal pain not settling with usual analgesia i.e. suspicion of peritonitis
    - Anything else which in the opinion of the community nurse is directly related to the LTAD and requires hospitalisation

  Community nurses will train informal caregivers if they wish to perform drainage. Though caregivers can assist with drainage, the drainage diary will still be completed by the community nurses who will continue to visit the participants in the community. The feedback from our PPI group has been that caregivers are keen to be involved in home drainage as it is viewed to be much less onerous than hospital drainage.
- Drainage of about 5L/week may not be sufficient for a small percentage of patients. In such instances patients can be admitted for supplementary LVP in hospital. This can be done via the LTAD (using specific adaptors). HAS will be administered as per LVP protocol. There will no need to take routine ascitic fluid samples from the LTAD and or do a routine diagnostic ascitic tap, unless suspicion for peritonitis. If patients are requiring frequent admission to hospital for supplementary LVP, then higher volume community LTAD drainage can be considered **on a case-by-case basis**, after discussion with the site PI, CI and community teams

- If a participant dies, the LTAD will be left in situ as per the usual practice. The community nursing team who will also follow standard procedures with regards to informing the undertakers of the presence of the LTAD.

Integrated Working Between Hospital and Community Teams

The success to implementing LTAD will be integrated working between hospital Gastroenterology/Hepatology, the community nursing teams (both the ones doing the drainage and the palliative teams), GPs and the patients/informal caregivers. Funding will be made available for sites to arrange up to two meeting with community teams to ensure engagement and collaboration. It can be difficult for HCP involved in the care of any patient near the end of life, especially in a cohort when death usually occurs in hospital. Research teams should be available to debrief community staff if needed.

For a summary of post-drain care, see Figure 1. Participant Flow Chart. A community Study Procedures manual will also be made available to all study sites.

16.2. Insertion Of Large Volume Paracentesis Drain (LVP), Group 2

At baseline participants randomised to the LVP group will undergo insertion in-line with standard of care. LVP involves insertion of a temporary drain by the usual medical team, usually drainage of 5-10 litres of ascites and use of intravenous (IV) human albumin solution (about 10 gms of albumin per 1-2L of fluid drained) (9, 64). If the total volume of fluid to be removed is < 5 litres then there will be no need to administer IV albumin. During LVP patients have routine bloods done in line with Table 3 Schedule of Assessments. A sample of ascites is sent at LVP, as per usual standard of care for white cell and neutrophil cell count and culture

To mitigate against research home visits impacting HRQoL in group 2 and thus diluting effects between the two groups, a Study Procedures manual for the research home visits has been developed. The Study Procedures manual will promote standardisation of all the researcher visits to ensure they are limited to research tasks.

16.3. Antibiotic Use

There are no evidence-based guidelines on use of prophylactic antibiotics in setting of LTADs. NICE, European and BSG guidelines (9,64,81) recommend prophylactic antibiotics if total ascitic fluid protein is <15g/L. However, recent studies suggest that ascitic fluid protein may not predict peritonitis risk. (82-83) As already stated, peritonitis risk is more than two-fold higher when LTADs are inserted in patients with cirrhosis compared to those with malignant ascites. (38,44) Additionally, PPI feedback indicates that avoiding hospitalisation is the overarching goal for most patients. We would therefore recommend that all patients be offered prophylactic antibiotics as long as the LTAD remains in situ, especially if planned duration is for 3-months or longer. (80) Since this is a palliative cohort, the duration of antibiotic usage will in most patients be short-term in-keeping with overall life expectancy. Risk/benefits of prophylactic antibiotics should however be discussed with patients and their informal caregivers.

Both groups will:

- Receive ciprofloxacin 500 mg once a day (or an equivalent antibiotic depending on contraindications/local practice) for study duration
- Be referred to community palliative care and we will also record if the referral has been accepted and patient seen by the community palliative care teams
- Continue to receive all additional standard of care as clinically indicated. This includes symptomatic relief for pain (including use of opioids), shortness of breath, confusion (hepatic encephalopathy), jaundice and itching. Once deemed to have true refractory ascites there is little role for ongoing use of diuretics. (9, 64) As is current standard of care in patients with advanced cirrhosis, use of certain drugs (e.g. non-steroidal anti-inflammatory drugs (NSAIDS), aminoglyosides) will be avoided.

17. ASSESSMENTS

Research team members will conduct fortnightly home visits for:

17.1. Safety Monitoring

This will include collection of routine clinical bloods, assessment of LTAD and collection of LTAD drainage data collated by community nurses (see community Study Procedures manual) for sample drainage diary). LVP drainage data will be collected from medical records.

17.2. Patient Related Outcome Measures (PROMs)

Questionnaires will be completed on paper as far as possible prompted by the fortnightly home visits by the research team members. Participants will however, also have the option to complete the questionnaires via phone. In those randomised to the LVP group, the questionnaires and fortnightly bloods could also be done in hospital if the LVP visit coincides with assessment visit (+/- 3 days). To further reduce patient and caregiver burden, research team members can assist the participants in completion of the questionnaires if needed and if specifically requested by the participant. If participants are too unwell, the questionnaires can be filled by proxy by the informal caregivers/research team members, both to reduce the patient burden as well as reduce risk of missing data. However, the aim will be to minimise proxy scores if possible. As far as possible informal caregiver questionnaire will be completed at the same time as patient questionnaires. If the caregiver is not available during the participant home visit, the questionnaires can be completed at a date and time which is convenient to them over the telephone.

Questionnaires to be used:

SFLDQoL: Liver specific HRQoL assessed at baseline and every four weeks (+/- 3 days). It incorporates a core quality of life assessment and disease-targeted items transformed into the following nine domains on a scale of 0-100 (higher score - better quality of life): distress, stigma, memory, symptoms, sleep, hopelessness, effect of liver disease, loneliness and sexual

function. (32) This is completed by the patient and takes 15-20 minutes to complete. Though there was a low completion rates in the feasibility study regarding sexual function questions, this data is important and will still be collected. The research teams will however ensure that questions on sexual function do not need to be answered, if patients feel uncomfortable or reluctant to answer them.

Ascites Q: Ascites symptoms assessed at baseline and fortnightly (+/- 3 days). It is validated in patients with ascites due to cirrhosis. It is a 11-item questionnaire (abdominal pain, fullness, loss of appetite, satiety, nausea, shortness of breath, back pain, mobility, fatigue, sleeping issues, size of abdomen). Each symptom is assessed with a frequency (6-point Likert scale "never" to "always") and discomfort (5-point Likert scale "not at all" to "a lot") question. A higher score indicates more symptoms. (74) This is completed by patients and takes 5-10 minutes to complete.

CRRS: Caregiver impact assessed at baseline and every four weeks (+/- 3 days). This tool measures the impact of caregiving on the other roles and responsibilities an individual has (finances, work, and social commitments), higher scores indicating better outcomes. The CRRS also captures any positive outcomes, such as benefit finding, that may come from caregiving. (75) This is completed by informal caregivers and takes 5-10 minutes to complete.

Modified AHCR: Primary, community and home-based health, social and voluntary service use will be assessed at baseline and fortnightly (+/- 3 days). The AHCR asks for the number of contacts in and out of the home with professionals or services, and informal caring input (unpaid by family or friends), recorded as hours per day (on average). It will be administered by research team member during home visits, ensuring low rates of missing information. (76-77) This is completed by the patient and takes about 10 minutes to complete.

In-house designed hospital use questionnaire: hospital use related to all ascites and non-ascites liver related treatment will be extracted at each site at the end of the study from patient hospital records and transferred onto a bespoke proforma distinguishing outpatient, A&E, day case and overnight stays. Will be completed by research team members at each site

EQ-5D-5L: Generic HRQoL assessed at baseline and fortnightly (+/- 3 days). It has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), rated on a 5-point Likert scale (1= no problems to 5= severe problems/ unable), to produce a health profile for use in the economic evaluation. It also comprises a 20 cm vertical Visual Analogue Scale (VAS) with range 0 (worst) to 100 (best). Health profile responses will be used to compute a utility index for estimation of QALYs. (78-79) This is completed by the patient and takes 5 minutes to complete.

18. CONCURRENT EMBEDDED QUALITATIVE STUDY

The aims of this qualitative study are to explore:

- Patient, informal caregiver and HCP, experience and acceptability of LVP and LTADs and factors that account for variability in experience and acceptability.
- "Real life" implementation of LTAD factors which may impact on embedding the intervention in standard practice.
- Relationship between trial outcomes (especially HRQoL and symptoms) and perceptions

We will undertake a series of semi structured interviews with patients (n=30, 15 per group), informal caregivers (n=20, 10 per group) and HCP (n=20). Sample sizes are informed by the principles of information power and saturation. (84) Patients with a range of demographics, socioeconomic status, and geographic location will be sampled to ensure diverse experiences are captured. Life expectancy in refractory ascites is limited, and we recognise that patient/caregiver beliefs and experiences may change across the period. We will therefore aim to recruit patients/informal caregivers who have been in the study for different durations but ensure that they have had at least one round of intervention, be that drainage in hospital or at home. A patient can still take part if their caregiver declines and vice versa. Similarly, we aim to capture a range of HCP views from those individuals involved in delivering the intervention (e.g. gastroenterologists, hepatologists, hospital and community nurses), at a range of different study sites. We hope this will give us a broad scope on intervention practices and views from teaching and district general hospitals. Interviews will start during the pilot phase and we will aim to recruit proportionate to overall recruitment i.e. we aim to complete 15% of participant interviews in the pilot, with the remaining 85% completed in the main trial. These interviews will help us ensure we capture a representative sample and will allow us to address any recruitment issues.

Topic guides for the interviews will be collaboratively developed with the PPI and clinical members of the research team. Interview themes will include an exploration of: experiences of recruitment, participation, LTAD/LVP and end of life care; beliefs about the role and value of LTAD in refractory ascites, practical steps and barriers involved in undertaking LTAD, and caregiver/HCP perspectives. Topic guides for patients and informal caregivers will mirror each other, using broad prompts to ask about HRQoL and the experience of LTAD/LVP (in line with the primary study objective), decision making at joining the study (aimed at the secondary objective of perceptions). Patients will be asked how their experiences could be improved while informal caregivers will be asked about any additional support they need. Participants will be given the opportunity to add in anything they feel is important to say. HCP will have a separate topic guide, focusing on the decision-making process for LTAD/LVP, perceived impact of the intervention, practical implications and implementation. Again, HCPs will be able to add any further comments or topics that they felt was missing during the interview. These topic guides are deliberately intended to be followed loosely, allowing researchers to follow the thread of conversation as led by the participant. Completed interviews will be reviewed across the study to amend the topic guide as necessary, incorporating any elements which seem to reoccur.

The interviews will be conducted by experienced SHORE-C researchers by phone or video link. It is estimated interviews will take between 15-45 minutes, dependent on how much or

how little a participant wants to say. To reduce participant burden, breaks will be allowed during the interviews and participants will be reminded that they can stop the interview at any time without giving a reason. Interviews will be digitally recorded, transcribed and analysed.

The research team member will provide patients and informal caregivers with information about the optional interview within their main information sheets. HCP will receive an information sheet solely about the interviews. All participating individuals have a unique consent for the interviews, separate to the main study. These will be audio-recorded but a paper copy will be provided so as to inform participants what they will be asked ahead of the interview. The qualitative researcher will contact participants, and after addressing any questions or concerns arrange a convenient time for the interview. The audio-recorded consents will be stored as an encrypted file, separate to the interview itself. Encrypted audio files of the interview will only be stored for as long as it takes to transcribe the interview and will be deleted after the transcripts are checked for accuracy.

19. PARTICIPANT WITHDRAWAL

Participants will be able to withdraw from the study at any time until the study has closed, without it affecting their future routine care. The reasons for withdrawal include, but are not limited to, the following:

- Patient death
- A request by a participant to withdraw from the study
- Serious adverse reaction
- Significant deviation from the study protocol, assessed on a case-by-case basis after discussion with the CI and TMG.

20. STORAGE AND ANALYSIS OF CLINICAL SAMPLES

Routine clinical bloods will be analysed on the day of collection. In addition, an optional 20 ml of blood will be collected (10 ml saved as serum, and 10ml as whole blood). In selected sites, with patient consent, an optional 100 ml of ascitic fluid will be collected at baseline and at the 4 weekly follow-up visits. Throughout the study, the research blood and ascitic fluid samples will be stored at sites, and subsequently sent at the end of the study to central labs where they will be analysed. Analysis into advanced cirrhosis will include but not be limited to bacterial DNA levels, microbiota analysis, lipopolysaccharide binding protein, tumour necrosis factor and interleukin 6. It may also include genetic testing if during the course of the study, new genetic biomarkers are identified. At the selected sites, removed drains (which would normally be discarded in clinical waste) will be stored at -80°C and transported to a central lab at the end of the study for analysis. Analysis will include presence and characteristics of biofilms on the removed catheters (external and luminal surface).

All research samples will be destroyed in accordance with the hospital procedures at the end of the study.

A lab manual will be provided to sites for the handling and storage of the research blood samples, ascitic fluid samples and removed drains at selected sites.

21. DEFINITION OF THE END OF STUDY

The study will end after the final follow-up data is collected after the 3-month Follow-Up visit, or death, or withdrawal of the last recruited participant.

22. SAFETY REPORTING

Table 4 Definitions of Safety Reporting Terms

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention.
Adverse Reaction (AR)	An untoward and unintended response in a participant to the intervention
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the Study treatments, based on the information provided.

22.1. **Assessing Relatedness of AE/SAEs**

AE/SAEs will primarily be assessed for relatedness to the study interventions at the site by the Principal Investigator, or an investigator delegated to do so. Unrelated events will include but are not limited to the following:

- Hepatic encephalopathy
- Gastrointestinal bleeding related to peptic ulceration, hypertensive portal gastropathy or varices
- Liver cancer and or its treatment
- Complications of gastroscopy (perforation, bleeding)
- Complications of drug treatment for cirrhosis (lactulose, beta blockers, terlipressin, antibiotics, diuretics)
- Death related to the liver disease- will include death from liver failure, multiorgan failure, hepatorenal syndrome, variceal bleeding and sepsis

Unrelated events will be recorded in the eCRF but not reported to BSCTU, Sponsor or the REC.

If an event is considered to be related to the study interventions then they will be classified as an Adverse Reaction (AR) or a Serious Adverse Reaction (SAR) and will be assessed for Expectedness, as below.

Any potential SARs are to be recorded on the eCRF *and* reported to the BSCTU via email to bsctusafety@bsms.ac.uk immediately when sites become aware of the event, and at least within 24 hours.

22.2. **Assessing Expectedness of AR/SARs**

This study involves a cohort with advanced cirrhosis with a high morbidity and mortality. Hence in this patient population worsening of existing conditions, hospitalisations and acute illnesses are to be expected.

Expected SAR will include the following (only <u>if they result in hospitalisation</u>):

- LTAD or LVP leakage or blockage
- Cellulitis
- Pain at site of insertion not controlled by analgesia
- Bacterial peritonitis
- Sepsis which in the opinion of the PI is directly related to LTAD or LVP
- Death (only if in the opinion of the researchers directly related to the LTAD or LVP)
- > 50%increase in serum creatinine from baseline
- Electrolyte imbalances with or without increase in serum creatinine
- Bleeding if directly related to LTAD or LVP
- Bowel perforation if directly related to LTAD and LVP

- Failed drainage and or drain displacement

22.3. **Suspected Unexpected SAR (SUSAR)**

Any events that in the opinion of the PI are directly related to the intervention and are not listed as expected are considered Suspected Unexpected Serious Adverse Reactions (SUSAR). All SUSARs that occur between participant consent and three months post insertion or death, whichever is earlier, will be recorded on the SAE form and emailed to BSCTU immediately (bsctusafety@bsms.ac.uk), at least within 24 hours of the research team becoming aware in accordance with the BSCTU Safety Reporting SOP. For each SUSAR, relevant information will be collected. All SUSARs will be followed up until resolved or a final outcome reached. The Research Ethics Committee (REC) will be notified of any SUSARs to the study intervention by the BSCTU within 15 days of the chief investigator becoming aware of the event, as per HRA guidance. Any urgent safety measures taken in response to any SUSARs will be reported immediately to the REC and Sponsor.

The CI will have direct and ultimate responsibility for reviewing all reported SARs and SUSARs and will ensure that BSCTU reports these appropriately according to the BSCTU SOP on Safety Reporting in Non-CTIMP studies.

Common terminology criteria for adverse events (CTCAE, version 4.03) will be used for assessing AE/SAEs.

22.4. **Potential Complications Of The Intervention**

Table 5 below summarises the complications seen in the LVP and LTAD group in the REDUCe feasibility study. (46) Rates of complications were similar in both groups except a higher incidence of self-limiting leakage and cellulitis in the LTAD group (none required hospitalisation.

Table 5. Potential long-term abdominal drain and large volume-related complications observed in the REDUCe feasibility trial

Complication	**Recommended management**	**Incidence observed in the REDUCe trial**	
		LTAD	**LVP**
Leakage and cellulitis	Leakage usually self-limiting, if persists may need an extra suture. Continue ascites drainage via LTAD Cellulitis usually results due to leakage and is again self-limiting. If persist may need a short course of antibiotics. Very rarely LTAD needs to be removed and can be re-sited	Leakage/cellulitis 41%	Leakage/cellulitis 11%

Suspected peritonitis	Do a diagnostic tap for cell count and culture from peritoneum as well as taking sample from LTAD. Treat as per usual peritonitis guidelines. Decision to remove LTAD must be made on a case-by- case basis after discussion with patient/caregiver Routine sampling of ascitic fluid from LTAD and or routine blood tests in asymptomatic patients is not recommended.	6%	11%
Elevation in serum creatinine	Manage as clinically indicated	Serum creatinine (µmol/L) (median, IQR) Baseline: 109 (79-141) Week12: 104.5 (81-115.5)	Serum creatinine (µmol/L) (median, IQR) Baseline: 113.5 (89-134) Week 12: 127 (63-158)
LTAD blockage	Can be unblocked with flushing. If not admit to hospital and discuss need for replacement	0%	NA
LTAD displacement	Admit to hospital if necessary and discuss need for replacement	6%	NA
Bleeding	Usually self-limiting	0%	5%
Unable to manage ascites symptoms despite draining 1-2L three times a week from LTAD	Will need LVP in hospital - drain ascitic fluid via LTAD using adaptor with human albumin solution as per standard LVP protocols	13%	NA

Strategies to reduce complications related to the intervention (LTAD)

Haemostatic function and ascitic fluid analysis (to exclude infection) to be done within seven +/- 3 days of LTAD insertion

- To reduce leakage/cellulitis ensure that
  - An LVP is performed via the LTAD on the day of insertion in hospital using human albumin solution
  - Incisions are of appropriate size (may require a suture if too large)
  - The tunnelled portion of the LTAD is not under undue tension

LTAD to be inserted by experienced clinicians under ultrasound guidance in hospital

Ensure good communication between hospital and community teams

Fortnightly home visits for safety monitoring

Study sites will be provided written information about LTAD management in case there is an out of hours hospital admission

22.5. **Participant Safety Monitoring**

At each site an experienced research team member will visit **ALL** patients at home **fortnightly** for safety monitoring and questionnaire-based assessments. This will include assessment of abdominal pain, vital signs, LTAD and collection of routine clinical bloods (FBC, INR, renal/ hepatic profile and CRP). The research team member will collect ascites drainage data recorded by community nurses at each site. Please see SAFETY REPORTING (section 22) for adverse event reporting.

The research team member will follow guidance in the lone worker policy when conducting home/usual place of care visits.

23. STATISTICS AND DATA ANALYSIS

23.1. **Sample size calculation**

Following on from the HTA Committee and PPI feedback and the International LIverHope Consortium's recommendations (73), we have selected HRQoL as our primary outcome.

The minimal clinically important difference (MCID) is the mean change in HRQoL scores for patients reporting a minimal yet perceptible change in health between the baseline and follow-up assessments. (85) In the ongoing LiverPal Study (one of the largest palliative trial in the United States (86), an MCID of 9 points on the FACT-Hep questionnaire was used; and in a study assessing LTADs in cirrhosis (87), an MCID of 10 points was chosen (SF-36 questionnaire). While these studies show the use of the MCID to inform sample size in palliative trials, neither of the tools selected are validated in advanced cirrhosis. As we will be using the SFLDQoL, a sensitive and validated questionnaire in advanced cirrhosis (34), we have selected a MCID of 8 points.

In our feasibility REDUCe study (46), the pooled baseline mean across SFLDQoL domains (excluding sex function) was 56.4 (SD=26.1). With 93 participants in each group for the analysis, we will have 90% power for 5% significance to detect an adjusted difference in mean SFLDQoL scores of 8 points between the LTAD and LVP groups at the end of 3-months (effect size 0.31). This effect size falls within Cohen's recommended cut offs for small (0.20) to moderate (0.50) effect size. (88) We will assume a correlation between baseline and the 3 follow-up measurements of 0.48 which is the lower bound of the 95% Confidence Interval for the correlation (point estimate 0.77) (from REDUCe study data). (46) With an expected 40% attrition (REDUCe study) (46), we will recruit 310 participants in total for the trial.

The MCID is the minimal change between baseline and follow up for an individual that is considered clinically important. (85) However, as this is a RCT, we want to detect a difference in means between the LTAD and the LVP groups of 8 points at end of the 3-month follow-up. Randomisation should ensure that the difference in means between the groups is zero at baseline so, by end of the follow up, the difference in means we expect to see between the groups is 8 points. As described above, we have determined our MCID through standardisation against existing literature, as far as is possible. Furthermore, through embedding a parallel qualitative study we will be able to iteratively triangulate qualitative and quantitative data – ensuring the clinical significance of our primary outcome is validated. Finally, our data will contribute to the evolution of fully validated PROMs in advanced cirrhosis cohorts, enabling robust and high-quality trials of other potential interventions.

23.2. **Internal pilot**

An 18-month internal pilot will assess recruitment and LTAD safety: 12 months recruitment, three months follow up, one-month for analysis, two-months for a STOP/GO decision. We will recruit 48 patients to allow estimation of recruitment rate & retention with a margin of error of 15% assuming 60% retention. With an expected rate of one patient recruited per site every 4 months, this could be achieved with 24 sites (2 sites opened each month) over 12-months' recruitment. During the final follow up, analysis & STOP/GO decision period of the internal pilot, recruitment (n=36) would continue in the pilot sites in preparation for the main trial.

23.2.1. **Progression criteria for stop/go**

RED: end trial; AMBER: explore methods for increasing recruitment/improving LTAD safety and with permission of funder proceed with protocol revisions; GREEN: continue to main phase of trial.

Table 6. Progression Criteria for Pilot Stop/Go

	RED	**AMBER**	**GREEN** *
Pilot recruitment/total study recruitment target by end of study month 21	<10%	10-20%	>20%
Mean recruitment rate/site/month (based on data to end of study month 21)	<0.2	0.2-0.3	>0.3
Number of sites opened by end of study month 18	≤19	20-23	≥24
Total number of patients recruited by study month 18	<37	37-47	>47
Proportion of those recruited by study month 18 retained to end of follow up*	<50%	50%-60%	>60%

Percentage of LTADs removed due to peritonitis by end of study month 21*	>15%	10%-15%	<10%
Proportion completing SFLDQoL questionnaire (except questions on sexual function) in those retained at time point, by end of month 18* Baseline Week 4 Week 8 Week 12	 <91% <85% <80% <75%	 91%-95% 85%-90% 80%-85% 75%-80%	 >95% >90% >85% >80%
Checklist for LTAD insertion and post procedure monitoring % completed	<75%	75%-85%	>85%

* Based on feasibility study data (46), and systematic review (44)

Assuming a successful pilot, we will then open an additional 11 sites over the next 5 months, recruiting the remaining 226 patients from a total of 35 sites over 26 months of the main trial (on average about six patients/site). This is consistent with our feasibility study recruitment (36 patients recruited across five sites over 30 months). The first eight sites, which will be open the longest, will recruit 11 patients on average; the final seven, 6 on average, over a total recruitment period of 44 months.

23.3. **Analysis of pilot data**

At the end of the internal pilot, data will be analysed descriptively to assess whether or not to proceed with the remainder of the trial as is, with modifications or to stop at that point. The DSMC will make a recommendation to the TSC who will inform the Sponsor and Funder.

23.4. **Statistical Plan and Analysis**

All analyses will be performed in Stata version 17.0 (89) or later. A detailed statistical analysis plan (SAP) will be written up prior to data analysis.

Summary of baseline data and flow of patients

Participant flow will be depicted according to the CONSORT 2010 Statement. (90) Baseline data will be summarised by trial group, normally distributed variables described by their means/standard deviations, skewed continuous variables by their medians/interquartile ranges and categorical variables by their frequencies/percentages. Scoring rules for the study instruments will be detailed in the full statistical analysis plan.

Primary outcome analysis

The primary outcome will be analysed, following intention-to-treat principles, using a linear mixed effects model with fixed effects for time point (2 dummy variables), gender, continuous Child Pugh score, randomisation group, randomisation group by time point interaction and adjusting for SFLDQoL score at baseline, and with a random effect for participant to handle the correlation between repeated measurements. The model will be fitted using restricted maximum likelihood estimation. We will report the estimated treatment differences between LTAD and LVP groups at weeks 4, 8 and 12, their 95% confidence intervals and p values.

Secondary outcome analysis

Secondary outcomes will be analysed using mixed effects regression models appropriate to outcome type, adjusting for baseline measure of outcome, in addition to the fixed and random effects as detailed for the primary outcome analysis.

Subgroup analyses

Analysis will be stratified to include, but not limited to, liver prognostic scores, survival, development of peritonitis, ascitic fluid albumin level and presence of informal caregivers.

Participant population

All data collected on all randomised participants will be analysed in the arm to which they were randomised.

23.5. **Procedure(s) to account for missing or spurious data**

In accordance with MORECare guidance on palliative trials (66), we will summarise attrition in each group as due to mortality, illness and withdrawal. We will assume missing quantitative data to be missing not at random (MNAR) unless there is evidence to the contrary and test results using a range of plausible values. (91-94) If we find evidence of differential attrition, we will, in sensitivity analyses, explore MNAR scenarios by first multiply imputing missing outcomes and then add/subtract (as appropriate) constants from the scores in the most impacted arm and re-estimate the treatment effect. In a systematic review and meta-analysis of 108 palliative trials, there was no evidence of differential attrition related to mortality (95) and we would expect the same in our trial.

Whilst attrition in the feasibility trial (46) was greater in the LTAD arm than in the LVP arm, estimates were imprecise due to the small sample size. The estimated difference in attrition proportions between the two arms was 10.3%, 95% CI (-21.8%, 42.4%). Potential reasons for differential attrition include the contrasting nature of the interventions - participants may prefer to be allocated to LTAD over LVP. Differential attrition may also be due to potential LTAD/LVP related complications. However, our PPI group have stated that the disappointment of being randomised to LVP would be mitigated by the fact that all participants would receive close follow up and fortnightly home visits. Also, irrespective of which arm they were randomised to,

participants could take altruistic pride in the fact that they were contributing to the improvement of palliative care for future generations. We will aim to avoid differential attrition. However, if we find evidence of differential attrition, we will, in sensitivity analyses, explore MNAR scenarios e.g. by first multiply imputing missing outcomes and then add/subtract (as appropriate) constants from the scores in the most impacted arm and re-estimate the treatment effect.

23.6. **Other Statistical Considerations.**

A full statistical analysis plan will be agreed prior to final analysis. Any deviation from this plan will be fully documented in the final trial report.

24. ECONOMIC EVALUATION

The health economics analysis will adopt a health and social care perspective. Whole system costs for LTAD and LVP will be compared to assess if use of community services for drainage (which is primarily community nursing input), is resource saving, compared to hospital drainage. A probabilistic cost-effectiveness analysis will be conducted using repeated measures of EQ-5D-5L. Data on service use provided by primary, community, social and voluntary organisations, and informal caring, will be gathered during fortnightly home visits for participants in both groups by the research team members. Hospital service use will be obtained from records at the end of the study by the research team members. Further details on data collection are provided in the section above on questionnaire-based assessments. Hospital service use will include all ascites and non ascites related liver service use (including ascites drainage and resources as a result of potential LTAD/LVP complications). The hospital and community service use databases will be merged using the unique patient IDs. Resources used will be converted to costs (British pounds 2021) using nationally validated unit costs (96) and NHS reference costs. (97) Time spent by informal caregivers will be valued using replacement cost methods and applying the tariff for community support workers. (96) Since patients will be in the study for different durations, the data will be standardised for fortnightly analysis if necessary, for meaningful comparisons.

Our feasibility study demonstrated that collection of EQ-5D-5L data were possible (46) and this information will be used to compute utility values by applying the UK social tariff. QALYS per patient will be calculated using the area under the curve approach. Use of QALYs in palliative care remains controversial, due to problems with conceptualising quality of life, restrictions in life years gained and valuation of time. However, QALYs are widely used and until alternative measures are available, it is reasonable that their use should continue (66,98). Resource use and costs for each main category will be reported as mean, standard deviation and median (range, IQR). EQ-5D-5L utilities will be reported at each follow up time point as mean and standard deviation. Differences in costs and QALYs will be estimated using mixed effects linear models, in line with the statistical approach to other outcomes (QALYs adjusted for baseline utility) and used to compute cost per QALYs of LTAD vs. LVP. Uncertainty will be

characterised using probabilistic unit costs and non-parametric bootstrapping with replacement techniques to characterise uncertainty in estimation processes.

25. QUALITATIVE DATA ANALYSIS

Thematic analysis supported by qualitative software (NVivo) (99) will be used to extract overarching themes from the interviews. Interviews will be analyzed separately for the three groups of participants (patients, informal caregivers and HCP) to develop themes. After analysis, these will be compared across participant group to explore any overlap or discrepancies. Utilising the process of triangulation (100), the findings of the qualitative arm will be used to position the quantitative results, particularly in the context of HRQoL.

26. DATA MANAGEMENT

26.1. Data Collection Tools And Source Document Identification

CRF worksheets will be provided that may be used as source documents for some data (e.g. vital signs, questionnaires, alcohol/drug use, etc.) and maintained for recording data for each subject enrolled in the study. Data reported in the CRF derived from other source documents should be consistent with the source documents or the reasons for the discrepancies should be explained. Data that will be recorded in the patient notes includes:

- Informed consent process and a copy of the signed consent form
- Participants eligibility)
- Description of adverse events and actions taken (causality assessed by PI or delegated individual
- A copy of the PIS
- A research sticker should be placed on the front of the notes.
- Medical history and concomitant medications
- Missed / late visits with reasons
- Deviations from the protocol with reasons
- If the participant/informal caregivers withdraws from the study, this should be entered along with reason for withdrawal
- Any other issues pertinent to the study.

Each visit should be documented - noting whether the participant is still happy to participate, and whether there are any new adverse events or concomitant medications.

A list of documents that will be used as source will be specified for each site prior to starting the study. All source documents and laboratory reports will be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Laboratory reports

should be signed and dated (or confirmation added to the notes) as reviewed by a clinician within an appropriate time frame.

26.2. **Data Handling and Record Keeping**

The research team member at each site will collect data on an electronic CRF (eCRF), using the MACRO™ electronic data capture system which will be provided by BSCTU. The system is compliant with Good Clinical Practice (GCP), with a full audit trail and formal database lock functionality. A participant identification number will be used.

Validation of the MACRO eCRF, security of the data, and data backups will follow BSCTU SOPs and will be included in a data management plan.

Data entered will be checked by the Data Manager in accordance with the Data Management Plan and queries raised to the clinical sites via MACRO™ when appropriate. Research team member at each site will be responsible for the entry of data into the eCRF. Patient data will be entered using study number only and no patient identifiable data will be seen by the data management team.

Patient and caregiver questionnaires will be entered via a webpage set up and managed by SHORE-C. The participant can enter this directly, with support from a research team member, or on paper with data to then be entered by the research team member. All paper copies to be sent to SHORE-C for quality control. The questionnaires will be entered using the same participant identification number as used in the MACRO eCRF.

26.3. **Access to Data**

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections - in line with participant consent

26.4. **Archiving**

Archiving will be authorised by the Sponsor following submission of the end of study report. All essential documents will be archived for a minimum of 5 years after completion of the study and can then be destroyed unless notified otherwise by the Sponsor. The research data will be stored for 10 years after the study has ended.

26.5. **Data Protection and Patient Confidentiality**

All investigators and study site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

In line with Sponsor policy and the 2018 Data Protection Act, any data collected as part of this trial will be kept strictly confidential. All study data will either be held on secure university and

hospital computers or in a secure and locked location at BSCTU. Initially patient identifiers will be utilised (name, address, date of birth, hospital no, telephone no) during randomisation, but after that all research participants will be allocated a unique study number that will be recorded on all other data collection forms. Patient consent will be requested to collect relevant data for the study including consent for data to be reviewed by relevant research team members, members of the direct clinical team, by the sponsor for monitoring/auditing purposes and by relevant regulatory authorities. Only those individuals directly involved with the research will have access to the study data. Any personal data will be kept securely and separately to the study data, and only accessible by the research team.

If central monitoring of source documents is needed by the BSCTU, only the research participants unique study number will be used, and all other identifiers removed.

The CI will be the custodian for the data.

27. MONITORING, AUDIT AND INSPECTION

Procedures for monitoring, audit and inspection:

A Trial Monitoring Plan will be developed by the BSCTU and agreed by the TMG based on the trial risk assessment. The Plan will be signed off by the Sponsor prior to recruitment of the first participant.

The plan may include items such as:

- Whether there is a requirement for on-site-monitoring
- The procedures and anticipated frequency for monitoring.
- The processes to review regarding participant enrolment, consent, eligibility, and allocation to trial arms; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection
- Monitoring by exploration of the trial dataset
- Any obligations that will be expected of sites to assist the sponsor in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally
- Whether the monitoring tasks may change over the duration of the study, e.g. monitoring might be initially conducted across all sites, and subsequently conducted using a risk-based approach that focuses, for example, on sites that have the highest enrolment rates, large numbers of withdrawals, or atypical (lower high) numbers of reported adverse events.
- Regular reports and updates to be provided to the Sponsor, as outlined in the Risk Assessment and as agreed with Sponsor.

28. ETHICAL AND REGULATORY CONSIDERATIONS

Before the study starts, approval will be sought from a Research Ethics Committee (REC) who will review the study protocol, informed consent forms and other participant facing and relevant documents. Substantial amendments that required review by the REC will not be implemented until the REC grants a favourable opinion. All correspondence with the REC will be retained in the Study Master File/Investigator Site File. It is the CI's responsibility to produce the annual reports as required. The CI will notify the REC of the end of the Study. If the Study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC Ending your project - Health Research Authority (hra.nhs.uk) and Sponsor.

29. PUBLIC AND PATIENT INVOLVEMENT

The Public and Patient Involvement (PPI) group have been involved since the feasibility trial and have helped shape the research methodology, outcome measures and assessment tools. PPI members Shani Steer, Tom Gaskin and Joan Bedlington are co applicants on the grant application and will be part of the TMG. Shani Steer and Joan Bedlington have extensive research experience including working on NIHR funded research projects. Our service users will provide input throughout the trial. Bespoke training will be provided to the PPI.

30. FINANCIAL AND OTHER COMPETING INTERESTS

Medical device companies will provide the LTAD for this definitive trial free of cost. They have not and will not be involved in development of study protocol, data collection and analysis and manuscript write up. They will not be claiming an Intellectual Property based on this trial. The other investigators have no conflict of interest as related to this study.

31. AMENDMENTS

The need for protocol amendments will be discussed by the TMG. Amendment proposals will be submitted to the Sponsor for approval and for determination of whether the amendment is substantial or non-substantial. Substantial amendments will be submitted to the Health Research Authority (HRA) for review. Once a favourable opinion has been given, the BSCTU will be responsible for notifying local sites of the amendment and ensuring the PI/CI is aware

when implementation can occur. For each amendment a risk impact assessment will be performed to determine whether participants need to be informed and requested to re-consent to the study. If re-consenting is required, then the sponsor will specify the timelines required for this.

32. POST STUDY CARE

All research participants will continue to receive routine medical care as clinically indicated whether in the community, primary care or hospital setting. While participating in this trial, for no individual will routine clinical care be modified or denied. At the end of the trial, all participants will continue to be assessed by their usual medical care team. Those allocated to the LTAD arm will have the option, if they so wish, to continue with the LTAD under supervision of their usual Gastroenterologist/Hepatologist. If they elect to retain the LTADs, drainage bags/bottles will be provided by their GPs. If they elect to have the LTAD removed this will be done in hospital under local anaesthetic and they will revert back to hospital drainage. Those in the control arm (LVP group) will also continue as such. However, if LTAD is deemed to be beneficial, each site will have the option to offer it to the control group outside of a trial setting at the discretion of their Gastroenterologist/Hepatologist.

33. ACCESS TO THE FINAL STUDY DATASET

Only members of the direct study team will have access to the final dataset. Any requests for data will need to be approved by the Chief Investigator

34. DISSEMINIATION POLICY

On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared and submitted to both the REC Committee and the NIHR, the latter being published.

Conference presentations (to include service user-facing events) will take place at British/ American/ European Hepatology and Palliative Medicine meetings.

The study will be published in peer reviewed publications in high impact factor journals (Hepatology, Journal of Hepatology and Palliative Medicine).

Policy brief publication for policy makers and Commissioners to inform potential future national guidelines will be prepared. The CI is the senior author of the recent national ascites guidelines (64) which, informed by the feasibility study (48), have recommended national trials assessing LTAD in advanced cirrhosis. Our definitive trial therefore, is also likely to influence

future national, international and NICE guidelines. LTADs in cirrhosis is currently undergoing NICE assessment (https://www.nice.org.uk/guidance/indevelopment/gid-ipg10194).

A lay summary of key study results (written with PPI input), will be provided to all study sites to disseminate to patients and informal caregivers. Further dissemination will occur by patient bodies (Hepatitis C/British Liver Trust and LIVErNORTH) via their respective website/ newsletters.

Service guidelines and resources will be developed for hospitals, community and palliative care services.

Study protocol and full study report will be made available on the ISRCTN registry. The CI is responsible for updating all registries.

Anonymised participant level dataset, and statistical code for generating the results can be made available upon written request to the Sponsor.

35. AUTHORSHIP ELIGIBILITY GUIDELINES

Authorship credit will be provided to those individuals that have made a significant contribution to the trial concept, design, data acquisition, interpretation and analysis, drafting the manuscript including intellectual content and critical revisions. Therefore, the CI, co-PIs, BSCTU members and site PIs recruiting 11 or more patients will be eligible for authorship credit. However, collaborators should not independently publish data of individuals that they have recruited for the study. No data will be released prior to first presentation and or publication without the explicit knowledge and consent of the CI. After discussion at TMG, it may be deemed appropriate to present interim results at local, national and international meetings and conferences.

36. COVID-19 CONTINGENCY MANAGEMENT

Home visits will be conducted with full personal protective equipment (PPE) and following current national guidance. If home visits become difficult, they will be shortened to only include routine clinical bloods and LTAD assessment with the questionnaire-based assessments being performed via telephone.

37. REFERENCES

1. Ginés P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatol.1987;7:122-8.
2. Lucena MI, Andrade RJ, Tognoni G et al; Spanish Collaborative Study Group On Therapeutic Management In Liver Disease. Multicenter hospital study on prescribing patterns for prophylaxis and treatment of complications of cirrhosis. Eur J Clin Pharmacol. 2002;58:435-40.
3. Salerno F, Borroni G, Moser P, et al. Survival and prognostic factors of cirrhotic patients with ascites: a study of 134 outpatients. Am J Gastroenterol. 1993;88:514–519.
4. Macken L, Hashim A, Potts J et al. Care of patients with end stage liver disease and refractory ascites remains suboptimal: need for earlier input from palliative care. Gut 2017;66:A161.
5. Moore KP, Wong F, Gines P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatol 2003;38:258–266.
6. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club.Hepatol.1996;23:164–176.
7. Moreau R, Delègue P, Pessione F, et al. Clinical characteristics and outcome of patients with cirrhosis and refractory ascites. Clinical characteristics and outcome of patients with cirrhosis and refractory ascites. Liver Int. 2004;24:457-64.
8. Medici V, Rossaro L, Wegelin JA, et al. The utility of the Model for End-Stage Liver Disease Score - A reliable guide for liver transplant candidacy and, for select patients, simultaneous hospice referral. Liver Transpl. 2008;14:1100-1106.
9. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. European Association for the Study of the Liver. J Hepatol 2018;69:406-460.
10. Subcutaneous automated low-flow pump implantation for refractory ascites caused by cirrhosis Interventional procedures guidance [IPG631] Published date: November 2018. Accessed at nice.org.uk.
11. Hudson B, Round J, Georgeson B, et al. Cirrhosis with ascites in the last year of life: a nationwide analysis of factors shaping costs, health-care use, and place of death in England. Lancet Gastroenterol Hepatol. 2018;3:95-103.
12. Poonja Z, Brisebois A, van Zanten SV, et al. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. Clin Gastroenterol Hepatol. 2014;12:692-8.
13. Patel AA, Walling AM, Ricks-Oddie J, et al. Palliative care and health care utilization for patients with end-stage liver disease at the end of life. Clin Gastroenterol Hepatol. 2017;15:1612-1619.
14. Holden JH, Shamseddeen H, Johnson AW, et al. Palliative Care and Hospice Referrals in Patients with Decompensated Cirrhosis: What Factors Are Important? J Palliat Med. 2020; 23:1066-1075.
15. Kathpalia P, Smith A, Lai JC. Underutilization of palliative care services in the liver transplant population. World J Transplant. 2016;6:594-598.
16. Hudson B, Hunt V, Waylen A, et al. The incompatibility of healthcare services and end-of-life needs in advanced liver disease: A qualitative interview study of patients and bereaved carers. Palliat Med 2018;32:908-918.
17. Peng JK, Higginson IJ, Gao W. Place of death and factors associated with hospital death in patients who have died from liver disease in England: a national population-based study. Lancet Gastroenterol Hepatol. 2019;4:52-62.
18. End of life care CCG profile. Cause of death and place of death. 2015. Accessed at http://www.endoflifecareintelligence.org.uk/ profiles/CCGs/Place and Cause of Death/atlas.html
19. Afendy A, Kallman JB, Stepanova, et al. Predictors of health-related quality of life in patients with chronic liver disease. Aliment Pharmacol Ther 2009;30:469-76.

20. Bjornsson E, Verbaan, Oksanen A, et al. Health-related quality of life in patients with different stages of liver disease induced by hepatitis C. Scand J Gastroenterol. 2009;44:878-87.
21. Marchesini G, Bianchi G, Amodio P, et al. Factors associated with poor health-related quality of life of patients with cirrhosis. Gastroenterol. 2001a;120:170-178.
22. Younossi Z, Boparai N, Price LL, et al. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. Am J Gastroenterol. 2001;96:2199-205.
23. Peng JK, Hepgul N, Higginson IJ, et al. Symptom prevalence and quality of life of patients with end-stage liver disease: A systematic review and meta-analysis. Palliat Med 2019;33:24-36.
24. Hansen L, Chang MF, Lee CS, et al. Physical and Mental Quality of Life in Patients With End-Stage Liver Disease and Their Informal Caregivers. Clin Gastroenterol Hepatol. 2021;19:155-161.
25. Les I, Doval E, Flavia M, et al. Quality of life in cirrhosis is related to potentially treatable factors. Eur J Gastroenterol Hepatol. 2010;22:221-7.
26. Jara M, Bednarsch J, Malinowski M, et al. Predictors of quality of life in patients evaluated for liver transplantation. Clin Transplant. 2014;28:1331-8.
27. Kok B, Whitlock R, Ferguson T, et al. Health-Related Quality of Life: A Rapid Predictor of Hospitalization in Patients With Cirrhosis. Am J Gastroenterol. 2020;115:575-583.
28. Macdonald S, Jepsen P, Alrubaiy L, et al. Quality of life measures predict mortality in patients with cirrhosis and severe ascites. Aliment Pharmacol Ther. 2019;49:321-330.
29. Nagel M, Weidner V, Schulz S, et al. Continued alcohol consumption and hepatic encephalopathy determine quality of life and psychosocial burden of caregivers in patients with liver cirrhosis. Health Qual Life Outcomes. 2022;20:23.
30. Hareendran A, Devadas K, Sreesh S, et al. Quality of life, caregiver burden and mental health disorders in primary caregivers of patients with Cirrhosis. Liver Int. 2020;40:2939-2949.
31. Low J, Rhode G, Pittordou K, et al. Supportive and palliative care in people with cirrhosis: International systematic review of the perspective of patients, family members and health professionals. J Hepatol 2018;69:1260-1273.
32. Donlan J, Ufere NN, Indriolo T, et al. Patient and Caregiver Perspective on Palliative Care in End-Stage Liver Disease. Palliat Med. 2021;24:719-724.
33. Šumskienė J, Kupčinskas L, Šumskas L. Health-related quality of life measurement in chronic liver disease patients. Medicina (Kaunas). 2015;51:201-8.
34. Kanwal F, Spiegel BM, Hays RD, et al. Prospective validation of the short form liver disease quality of life instrument. Aliment Pharmacol Ther. 2008;28:1088-1101.
35. Kanwal F, Gralnek IM, Hays RD, et al. Health-related quality of life predicts mortality in patients with advanced chronic liver disease. Clin Gastroenterol Hepatol. 2009;7:793-9.
36. Bhanji RA, Carey EJ, Watt KD.A Review article: maximising quality of life while aspiring for quantity of life in end-stage liver disease. Aliment Pharmacol Ther. 2017;46:16-25.
37. Younossi Z, Henry L. Overall Health-Related Quality of Life in Patients With End-Stage Liver Disease. Clin Liv Dis. 2015;00.
38. Fleming ND, Alvarez-Secord A, Von Gruenigen V, et al. Indwelling catheters for the management of refractory malignant ascites: a systematic literature overview and retrospective chart review. J Pain Symptom Manage 2009;38:341–349.
39. White J, Carolan-Rees G. PleurX peritoneal catheter drainage system for vacuum-assisted drainage of treatment resistant, recurrent malignant ascites: a NICE Medical Technology Guidance. Appl Health Econ Health Policy 2012;10:299-308. Updated Feb 2018.
40. Stukan M. Drainage of malignant ascites: patient selection and perspectives. Cancer Management Res 2017;9:115-130.
41. Caldwell J, Edriss H, Nugent K. Chronic peritoneal indwelling catheters for the management of malignant and nonmalignant ascites. Proc (Bayl Univ Med Cent). 2018;31:297-302.

42. Kendrick E, GPwSI Older People and Chair End of Life Clinical Innovation Team, NHS North East. Getting it Right: Improving End of Live Care for People Living with Liver Disease. Feb 2013. Accessed at http://www.bsg.org.uk/clinical/commissioning-report/management-of-patients-with-chronic-liver-diseases.html.
43. Abbot J, Verma S, Saxsena A. Long term Abdominal Drain for Palliation in Advanced Liver Cirrhosis: a survey of risks& barriers. Gut. 2020;69:A7.
44. Macken L, Hashim A, Mason L, et al. Permanent indewelling peritoneal catheters for palliation of refractory ascites in end stage liver disease: A systematic review. Liver Int. 2019;39:1594-1607.
45. Macken L, Mason L, Evans C, et al. Palliative long-term abdominal drains versus repeated drainage in individuals with untreatable ascites due to advanced cirrhosis: study protocol for a feasibility randomised controlled trial. Trials. 2018;19:401.
46. Macken L, Bremner S, Gage H, et al. Randomised Clinical Trial: Palliative Long-term Abdominal Drains Versus Large Volume Paracentesis In Refractory Ascites Due to Cirrhosis. Aliment Pharmacol Ther. 2020;52:107-122.
47. Cooper M, Pollard A, Pandey A, et al. Palliative Long-term Abdominal Drains Versus Large Volume Paracentesis in Refractory Ascites due to Cirrhosis (REDUCe Study): Qualitative Outcomes. J Pain Symptom Manage. 2021;62:312-325.
48. Public Health England. The 2nd Atlas of variation in risk factors and healthcare for liver disease in England. Sept 2017. Accessed at https://fingertips.phe.org.uk/profile/atlas-of-variation
49. Office for National Statistics. Deaths registered in England and Wales 2018. 2019. Accessed at https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables
50. Quarterly alcohol-specific deaths in England and Wales: 2001-2009 registrations and quarter 1 (Jan to Mar) to Quarter 4 (Oct to Dec) 2020 provisional registrations. Accessed at https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/quarterlyalcoholspecificdeathsinenglandandwales/2001to2019registrationsandquarter1jantomartoquarter4octtodec2020provisionalregistrations
51. Baumann AJ, Wheeler DS, James M, et al. Benefit of early palliative care intervention in end stage liver disease patients awaiting liver transplantation. J Pain Symptom Manage 2015;50:882-886.
52. Kimbell B, Murray SA, Byrne H, et al. Palliative care for people with advanced liver disease: A feasibility trial of a supportive care liver nurse specialist. Palliat Med. 2018;32:919-929.
53. Ufere NN, O'Riordan DL, Bischoff KE, et al. Outcomes of Palliative Care Consultations for Hospitalized Patients With Liver Disease. J Pain Symptom Manage. 2019;58:766-773.
54. Brisebois A, Ismond KP, Carbonneau M, et al. Advance care planning (ACP) for specialists managing cirrhosis: A focus on patient-centered care. Hepatol. 2018;67:2025-2040.
55. Ufere NN, Robinson B, Donlan J, et al. Pilot Randomized Controlled Trial of and Advance Care Planning Video Decision Tool for Patients With Advanced Liver Disease. Clin Gastroenterol Hepatol. 2021 Oct 27
56. Shinall MC Jr, Karlekar M, Martin S, et al. COMPASS: A Pilot Trial of an Early Palliative Care Intervention for Patients With End-Stage Liver Disease. J Pain Symptom Manage. 2019;58:614-622.
57. Zhuang ZW, Teng GJ, Jeffery RF, et al. Long-term results and quality of life in patients treated with transjugular intrahepatic portosystemic shunts. Am J Roentgenol. 2002;179:1597-1603.
58. Wong F, Bendel E, Sniderman K, et al. Improvement in Quality of Life and Decrease in Large-Volume Paracentesis requirement With the Automated Low-Flow Ascites Pump. Liver Transpl. 2020;26:651-661.

59. Stepanova M, Nader F, Bureau C, et al. Patients with refractory ascites treated with alfapump(R) system have better health-related quality of life as compared to those treated with large volume paracentesis: the results of a multicenter randomized controlled study. Qual Life Res 2018; 27: 1513–1520.
60. van der Plas SM, Hansen BE, de Boer JB, et al. Generic and disease-specific health related quality of life in noncirrhotic, cirrhotic and transplanted liver patients: a cross-sectional study. BMC Gastroenterol. 2003;3:33.
61. James Lind Alliance Priority Alliance Partnership. Available at https://www.jla.nihr.ac.uk/priority-setting-partnerships/palliativeand-end-of-life-care/top-10-priorities/
62. NIHR 19/93 Liver disease commissioning brief Accessed at https://www.nihr.ac.uk/documents/1993-liver-disease-commissioning-brief/21532
63. Triggers for palliative care Marie Curie. Accessed at https://www.mariecurie.org.uk/globalassets/media/documents/policy/policy-publications/june-2015/triggers-for-palliative-care-executive-summary.pdf
64. Aithal GP, Palaniyappan N, China L, et al. British Society of Gastroenterology. Guidelines on the management of ascites in cirrhosis. Gut. 2021;70:9-29.
65. Rogal S, Hansen L, Patel A, et al. AASLD Practice Guidance: Palliative care and symptom-based management in decompensated cirrhosis. Hepatol. *Feb 1st* 2022
66. Higginson IJ, Evans CJ, Grande G, et al; MORECare. Evaluating complex interventions in end of life care: the MORECare statement on good practice generated by a synthesis of transparent expert consultations and systematic reviews. BMC Med. 2013;11:1-11
67. Kars MC, van Theil GJ, van der Graaf R, et al. A systematic review of reason for gatekeeping in palliative care research. Palliat Med. 2016;30:533-48
68. Wasp GT, Cullinan AM, Chamberlin MD, et al. Implementation and Impact of a Serious Illness Communication Training for Hematology-Oncology Fellows. J Cancer Educ. 2021;36:1325-32.
69. Lord L, Clark-Carter D, Grove A. The effectiveness of communication-skills training interventions in end-of-life noncancer care in acute hospital-based services: A systematic review. Palliat Support Care. 2016;14:433-44.
70. Townsend, D., Mills, N., Savović, J. et al. A systematic review of training programmes for recruiters to randomised controlled trials. Trials. 2015;16:432
71. Jenkins VA, Farewell D, Farewell V, et al. Teams Talking Trials: results of an RCT to improve the communication of cancer teams about treatment trials. Contemp Clin Trials. 2013; 35:43-51
72. Mills N, Gaunt D, Blazeby JM, et al. Training health professionals to recruit into challenging randomized controlled trials improved confidence: the development of the QuinteT randomized controlled trial recruitment training intervention. J Clinical Epidemiology. 2018; 95:34-44.
73. Solà E, Pose E, Campion D, Piano S, et al; LiverHope Consortium Investigators. Endpoints and design of clinical trials in patients with decompensated cirrhosis: Position paper of the LiverHope Consortium. J Hepatol. 2021;74:200-219.
74. Neijenhuis M, Gevers TJG, Atwell TD, et al. Development and Validation of a Patient-Reported Outcome Measurement for Symptom Assessment in Cirrhotic Ascites. Am J Gastroenterol. 2018;113:567-575.
75. Shilling V, Starkings R, Jenkins V, Cella D, et al. Development and validation of the caregiver roles and responsibilities scale in cancer patients. Qual Life Res 2019;28:1655-1668.
76. Guerriere DN, Coyte PC. The Ambulatory and Home Care Record: A Methodological Framework for Economic Analysis in End-of-Life Care. J Aging Res. 2011;2011:374237.
77. Chai H, Guerriere DN, Zagorski B, et al. The size, share, and predictors of publicly financed healthcare costs in the home setting over the palliative care trajectory: a prospective study. J Palliat Care. 2013;29:154-62.
78. EuroQoL group. Accessed at EQ-5D https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/

79. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15:708-15.
80. Reinglass J, Amjadi K, Petrcich B, et al. The palliative management of refractory cirrhotic ascites using the PleurX catheter. Can J Gastroenterol Hepatol. 2016
81. Harrison P, Hogan P, Floros L, et al. Guidance Development Group. Assessment and management of cirrhosis in people older than 16 years: summary of NICE guidance. BMJ. 2016;354:2850.
82. Terg R, Casciato P, Garbe C, et al. Proton pump inhibitor therapy does not increase the incidence of spontaneous bacterial peritonitis in cirrhosis: a multicenter prospective study. J Hepatol 2015;62:1056–1060.
83. Bruns T, Lutz P, Stallmach A, et al. Low ascitic fluid protein does not indicate an increased risk for spontaneous bacterial peritonitis in current cohorts. J Hepatol. 2015;63:527-8.
84. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qualitative Health Research. 2016;13:1753-1760.
85. Guyatt GH, Osoba D, Wu AW, et al. Methods to explain the clinical significance of health status measures. Mayo Clin Proc. 2002; 77: 371–383.
86. Verma M, Kosinski AS, Volk ML, et al. Introducing Palliative Care within the Treatment of End-Stage Liver Disease: The Study Protocol of a Cluster Randomized Controlled Trial. J Palliat Med. 2019;22:34-43.
87. Ahmed M. Peritoneal Dialysis Catheters for the Treatment of Refractory Ascites [Internet]. 2018. Available from: https://mspace.lib.umanitoba.ca/bitstream/handle/1993/33498/Ahmed_BSc%28Med%29Report.pdf?sequence=1&isAllowed=y
88. Cohen J. Statistical Power Analysis for Behavioral Sciences. Hillsdale, NH: Lawrence Erlbaum 1988.
89. StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.
90. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
91. White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ. 2011:342:d40.
92. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med. 2012;367:1355-60.
93. Morris TP, Kahan BC, White IR. Choosing sensitivity analyses for randomised trials: principles. BMC Med Res Methodol. 2014;14:11.
94. Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clin Trials, 2004;1:368-76.
95. Hussain JA et al. Missing data in randomized controlled trials testing palliative interventions pose a significant risk of bias and loss of power: a systematic review and meta-analyses. J Clin Epidemiol. 2016;74:57-65.
96. Curtis L and Burns A. Unit costs of health and social care 2020. Accessed at www.pssru.ac.uk
97. NHS England. 2019/20 National Schedule of Reference Costs. Accessed at https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/
98. Wichmann AB, Adang EM, Stalmeier PF, et al. The use of Quality-Adjusted Life Years in cost-effectiveness analyses in palliative care: Mapping the debate through an integrative review. Palliat Med. 2017;31:306-322.
99. NVivo qualitative data analysis software; QSR International Pty Ltd. Version 10, 2012O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ.2010;341:c4587100.
100. O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. BMJ.2010;341:c4587