

## [Study Protocol] 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

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**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**

Short Title and Acronym: **REpeated Drainage Untreatable Cirrhosis (REDUCe)**

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## ABSTRACT

**Background:** UK deaths due to chronic liver diseases such as cirrhosis have quadrupled over the last 40 years, making this condition now the third most common cause of premature death. Most patients with advanced cirrhosis (end-stage liver disease, [ESLD]) develop ascites. This is often managed with diuretics, but if refractory then the fluid is drained from the peritoneal cavity every 10-14 days by large volume paracentesis (LVP), a procedure requiring hospital admissions. As the life expectancy of patients with ESLD and refractory ascites (if ineligible for liver transplantation) is on average  $\leq 6$  months, frequent hospital visits are inappropriate from a palliative perspective. One alternative is long-term abdominal drains (LTAD), used successfully in patients whose ascites is due to malignancy. Although inserted in hospital, these drains allow ascites management outside of a hospital setting. LTAD have not been formally evaluated in patients with refractory ascites due to ESLD.

**Methods:** Due to uncertainty about appropriate outcome measures and whether patients with ESLD would wish or be able to participate in a study, a feasibility randomised controlled trial (RCT) was designed. Patients were consulted on trial design. We plan to recruit 48 patients with refractory ascites and randomise them (1:1) to either a) LTAD or b) current standard of care (LVP) for 12 weeks. Outcomes of interest include acceptability of LTAD to patients, carers and healthcare professionals as well as recruitment and retention rates. Palliative care Outcome Scale (IPOS), the Short Form Liver Disease Quality of Life (SF-LDQOL), the EuroQoL (EQ-5D) and carer (Zarit Burden Interview [ZBI-12]) reported outcomes will also be assessed. Preliminary data on cost effectiveness will be collected and patients and healthcare professionals will be interviewed about their experience of the trial with a view to identifying barriers to recruitment.

**Discussion:** LTAD could potentially improve end-of-life care in patients with refractory ascites due to ESLD by improving symptom control, reducing hospital visits and enabling some self-management. Our trial is designed to see if such patients can be recruited, as well as informing the design of a subsequent definitive trial.

**Trial registration:** ISRCTN30697116, date assigned: 07/10/2015

**Keywords:** ASCITIC FLUID, END STAGE LIVER DISEASE, PARACENTESIS, PERMANENT INDWELLING PERITONEAL CATHETER, PALLIATIVE CARE, HEALTH RELATED QUALITY OF LIFE, QUALITY ADJUSTED LIFE YEARS, HEALTHCARE ECONOMICS

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## BACKGROUND

UK deaths due to chronic liver disease such as cirrhosis have quadrupled over the last 40 years, making this condition the third most common cause of premature death. [1] Ascites - an abnormal accumulation of fluid in the peritoneal cavity - is present in up to 90% of patients with advanced cirrhosis [2-3], resulting in frequent hospitalisations due to debilitating episodes of pain and breathlessness. In the early stages, this condition can be managed using diuretic therapy, but as the condition progresses (end-stage liver disease, [ESLD]) the ascites becomes unresponsive to medical treatment. In the absence of liver transplantation, a diagnosis of refractory ascites confers a median life expectancy of  $\leq 6$  months. [3-5]

End-of-life care in patients with ESLD and refractory ascites has not been a research priority. Over 70% of patients with ESLD die in hospital [6], a figure substantially – and in our view unacceptably - higher than that of 40% for patients with terminal cancer. [7] The most common palliative management for refractory ascites due to ESLD is large volume paracentesis (LVP), performed every 10-14 days. [3] This involves a costly 24-48 hour hospital admission, insertion of a temporary abdominal drain and removal of up to 15 L of ascitic fluid over 4-6 hours. There is simultaneous administration of intravenous 4.5% or 20% (w/v) human albumin solution, 8g -10g per 1L of ascitic fluid removed. [3] Consequently, patients often delay the hospital visits until their ascites is tense and painful [8], so reducing their quality of life (QOL). [9] Individuals with refractory ascites often have contraindications to alternative invasive procedures such as transjugular intrahepatic portosystemic shunt (TIPS) [10] and or the automated low flow ascites (ALFA) pump. [11]

In this feasibility randomised controlled trial (RCT) we will investigate the use of a simple and less invasive device, the long-term abdominal drain (LTAD), in patients with refractory ascites due to ESLD. This technique involves placing a tunnelled drain through the abdominal wall under local anaesthetic and with ultrasound guidance. Once the drain is in place, the patient's ascites can be drained in the patient's usual place of residence. Community nurses, or (where willing), carers can then remove smaller volumes (1-2 L) of

ascitic fluid in about 5-10 minutes, usually 2-3 times a week dependent on patient preference. These devices have been extensively utilised in patients whose ascites is due to advanced malignancy and have been shown to be both clinically and cost-effective, with low complication rates and improved quality of life (QOL). [12-14] In terms of palliative care in refractory ascites due to ESLD there may be additional benefits including the involvement of patients and carers in the management of this condition, reduced complications through the regular removal of smaller volumes of fluid, and, importantly, reduced stigma associated with hospital-based LVP (voiced to us as a concern by service users).

Given the relative success of these devices in patients with ascites due to malignancy there is a clear need for a RCT in ESLD and refractory ascites comparing palliative LTAD to current standard care (LVP), with end-of-life QOL and cost-effectiveness as major outcomes. LTAD have not been specifically assessed in patients with ESLD because of the potentially increased risks of bleeding (due to coagulopathy) [15] and infections, specifically spontaneous bacterial peritonitis. [16,17]

There are additional concerns related to this specific patient group. We do not know whether such individuals would be able or even willing to participate in a RCT, given their potentially higher prevalence of alcohol and substance misuse and other psychosocial issues. Similarly, there is uncertainty as to the most appropriate assessment tools and outcome measures. Finally, given the complex end of life care needs of this cohort, concerns remain to patients, carers and healthcare professionals (HCP) over a strategy that moves care away from the hospital to the community. To address these issues we have designed a feasibility study to inform the development of a subsequent definitive RCT.

## **METHODS**

### **Aim, design and setting of the study**

The aim of this study is to assess the feasibility of conducting a future RCT of the safety,

clinical-effectiveness and cost-effectiveness of refractory ascites management using LTAD against current standard of care (LVP) in patients with ESLD when liver transplant is not an option. This document is based on v6.0 of the protocol (13/10/2017). This multicentre trial has been designed in accordance with phase 2 of the Medical Research Council (MRC) Complex Interventions Framework [18] and the Method Of Researching End of Life Care guidance (MORECare). [19]

This feasibility RCT is being conducted both at a hospital (The Royal Sussex County Hospital [RSCH], Brighton, Sussex, UK and the Princess Royal Hospital [PRH], Hayward's Heath, Sussex, UK, both part of the Brighton and Sussex University Hospital [BSUH] National Health Service [NHS] Trust; Worthing Hospital, Worthing, Sussex, UK [Western Sussex NHS Foundation Trust], Plymouth Hospitals NHS Trust, Plymouth, UK, **Blackpool Victoria Hospital, Blackpool, UK [Blackpool Hospitals NHS Foundation Trust] and Southampton General Hospital, Southampton, UK [University Hospital Southampton NHS Foundation Trust]**) and a community setting (The Sussex Community Trust). Those randomised to LTAD will be followed up in the community. This three-year study is planned to run from Sept 2015 until Sept 2018.

### **Characteristics of participants**

Patients will be identified from acute medical units, outpatients and Gastroenterology and Hepatology wards. They will be approached for the study at the participating centres by the research team after having been identified by the local medical team as being potentially eligible.

### **Inclusion criteria**

1. Age  $\geq 18$  years, with no upper age limit.
2. Untreatable (refractory) ascites defined as:
  - a. Ascites that is unresponsive to fluid and sodium restriction and high dose diuretic treatment (spironolactone 400 mg/day and/or



furosemide 160 mg/day) and/or intolerance of diuretics [20, 21].

b. Ascites that recurs rapidly after LVP (requiring one or more LVP/month).

3. Child-Pugh Score [22] of  $\geq 9$  unless specifically decided by the medical team that they are to receive only palliative treatment.
4. Registered with a General Practitioner (GP) in the Community Trusts serving the participating centres.
5. Ability to speak, read and understand English.
6. Capacity to give written informed consent as assessed by using a Capacity to Consent Checklist (see additional files)

### **Exclusion criteria**

1. Loculated or chylous ascites.
2. Presence of > grade 1 hepatic encephalopathy (specified by West Haven Criteria. [23])
3. Evidence of active infection, which in the Investigator's opinion would preclude insertion of LTAD e.g. bacterial peritonitis. Such patients could be reconsidered for inclusion in the trial if infection has been successfully treated.
4. Eligible for liver transplantation, in the opinion of the Hepatology multi-disciplinary team (MDT) and according to national guidelines. [24]
5. Psychosocial issues which, in the medical team's opinion, would preclude engagement with the trial, such as posing a risk to the safety of oneself or the research team.

As this is a feasibility study we will not specifically exclude patients based on abnormal haemostasis measurements. Consistent with local practice, those individuals with platelet count of  $< 50 \times 10^9$  and/or an International Normalised Ratio (INR) of  $> 1.7$  will be given blood and/or clotting products prior to receiving LTAD or LVP.

Potential participants can be considered for inclusion in this trial even if they are currently participating in another research study, as long as their medical team are confident that participation in the current trial would be logistically feasible and not unduly onerous for the participants.

While we would prefer that potential carers/consultees are identified for each participant, their absence will not preclude study participation.

## **Consent**

Suitable participants will be identified by the usual medical teams. A research team member (to include Chief Investigator [CI], co-investigators, Principal Investigators [PI], Nurse and Research Fellow) will provide patient information sheets (PIS) to potential research participants **and give an explanation about the study including ascites management.**

Patients will be provided at least 48 hours to read the PIS. If willing, consent will be obtained in hospital by a research team member. If the research team is the usual medical team, to avoid any potential conflict of interest, potential participants will be discussed at the weekly liver multidisciplinary meeting (MDM). Capacity to give informed consent will be carefully assessed (see inclusion criteria). In the event that capacity is lost during the trial, the participant's nominated consultee will be approached to determine whether the participant should continue in the study. If a consultee has not been nominated or is unavailable then the participants usual medical consultant, (independent from the research team), will be consulted to decide whether it is in the participant's best interests to continue in the study.

## **Randomisation**

Patients who fulfil the inclusion and exclusion criteria and give written informed consent to participate in this trial will be randomised on a 1:1 basis to either Group 1: LTAD or Group 2: LVP (current standard of care). **The allocations will be made by minimising on 1) centre, 2) Child-Pugh Score and 3) gender. No stratification will be utilised.** Minimisation will

be implemented using an independent system hosted at Kings Clinical Trials Unit (KCTU). Patients will be enrolled by the research team member 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 outcome of allocation.

Patients will be followed up for 12 weeks. With the participants agreement we will inform their GP about their participation in the trial.

## **Interventions**

### **Group 1: LTAD**

There are two LTAD currently available in the UK: the PleurX™ (UK Medical Ltd, Basingstoke, UK [25] and the Rocket® (Rocket Medical, Watford, UK. [26] We have chosen to use the Rocket device (Figure 1) [26] primarily because our local clinicians and community nursing teams are already familiar with them. Rocket Medical already have an established training and support programme for local community nurses and care homes. In addition, our earlier experience [27] suggests that the Rocket devices are easier to insert than the PleurX™ devices, and require less expensive consumables that can currently be prescribed by community practitioners.

### **Procedure for insertion of LTAD**

Insertion of the LTAD will be performed in hospital in a side room, using bedside ultrasound guidance. Insertion will only be performed if, within the week leading up to planned LTAD insertion, haemostatic function (including INR and platelet count) has been checked and blood products administered as necessary. Where INR is > 1.7, patients will receive up to two volumes of fresh frozen plasma (FFP) transfused according to patient weight and INR,

immediately prior to drain insertion. Where the platelet count is  $\leq 50 \times 10^9$ , patients will be given one to two pools of platelets immediately prior to insertion of the drain.

To ensure consistency, it would be ideal that all LTAD are inserted at one site (RSCH), but if not possible due to patient preference or logistic issues they will be inserted at local sites, usually by an interventional radiologist.

The Rocket® LTAD will be inserted using a combination of tunnelled and Seldinger technique as stated in the Rocket® information sheet. [26] After confirming the location of the insertion site using bedside ultrasound and skin preparation with Chloraprep™ (chlorhexidine gluconate and isopropyl alcohol), local anaesthetic (up to 10 ml 1% or 2% lidocaine) will be administered to the incision site and along the proposed tunnel tract. A small incision is made where the catheter will enter the abdominal cavity. The introducer needle will be inserted through the incision into the peritoneal cavity and a guide wire is passed through the needle, which will then be removed. A second incision (exit site) will be made approximately 5 cm medial from the first, where the catheter will exit the tunnel. The catheter will be tunnelled from exit site incision to the first incision site with the tunneller, making sure that the cuff is mid-way between the first and second incision sites. A split-sheath dilator will be then passed over the guide wire, and the inner dilator and guide wire removed leaving the split sheath *in situ*.

The tunneller is then removed from the catheter, which is then passed through the split sheath, separating the split sheath ensuring that all of the catheter is contained within the peritoneum. The last piece of the split-sheath is then removed. The catheter is then adjusted along the tunnel, so the cuff moves towards the exit site, ensuring that any kinks are removed from the catheter. Finally, both incision sites will be sutured (avoiding the catheter) and a dressing applied.

Participants will receive antibiotic prophylaxis (ciprofloxacin 500 mg/day) or an equivalent antibiotic (if contraindication to ciprofloxacin) or dependant on local practice.

We will provide guidance to the participant and carer (where present) on how to use the

LTAD, based on the information previously supplied in the PIS. Participants will also be given an information sheet provided by Rocket Medical. [26] Participants will be referred to their community nursing service. A Rocket Medical Discharge letter will be sent to their GP and the community nursing team. Rocket Medical will also be informed so that they can organise any further support/training for patients, carers, and community nurses. In addition, we will arrange for drainage bags to be delivered directly to the participant's usual place of residence on request by the community nurses.

The community nurses will visit the participants in their homes and either perform the drainage procedure themselves, or supervise the drainage of ascites. The frequency of these visits will depend on the participant's ascites-related symptoms, but work in ascites due to malignancy [28] indicates that two to three visits each week is most commonly required, with approximately 1-2 L of ascites being drained each time. It is recommended that drainage frequency not exceed 3 times per week. In the event that participants and/or carers wish to perform self-drainage, they will be trained to do so by the community nurse.

The Integrated Primary Care Team (IPCT) will closely monitor trial participants allocated to the LTAD arm. We expect that this will happen 2-3 times a week if the community nurses are performing ascitic fluid drainage.

For participants who live in a care home or move to a care home (with or without nursing), the follow-up procedure would be the same as for patients who live at home. In such cases we would seek approval from the care home managers. For those requiring hospice care, this would be a temporary stay since hospices do not generally provide long-term care.

Again, permission will be sought from the hospice team to visit the participants for follow up and only if such visits remain acceptable to the participants.

### **Group 2 Standard Care (LVP)**

Participants randomised to LVP [3], the current standard of care, will be admitted to hospital as either a self-referral or via their GP, whichever is current local practice. They will undergo

LVP as clinically indicated. LVP involves the insertion of a peritoneal drain for up to 6 hours, and removal up to 15 L of ascites. If the total volume of fluid to be removed is > 5 L, intravenous 4.5% or 20% (w/v) human albumin solution 8g -10g per 1L of ascitic fluid removed, will be administered. [3]

As with Group 1, participants will receive antibiotic prophylaxis (ciprofloxacin 500 mg once a day or an equivalent antibiotic (if any contraindication to ciprofloxacin) or dependent on local practice).

For both groups there will be fortnightly visits with a research team member for questionnaire based and clinical assessments as well as routine clinical blood samples (see below). We anticipate that these two weekly contacts will improve adherence to the protocol.

### **Clinical Follow up**

While participating in this trial, for no individual will routine clinical care be modified or denied whether in the community, primary care or hospital setting. This will include symptomatic relief for pain (including use of opioids), shortness of breath, confusion (hepatic encephalopathy), jaundice or itching. Use of diuretics will be permitted in both groups. As is the current standard of care in patients with ESLD, use of certain drugs (e.g. non-steroidal anti-inflammatory drugs, aminoglycosides) will be contraindicated. [3]

Palliative care needs and concerns will be reassessed at each visit for each participant using the integrated palliative outcome scale (IPOS) questionnaire [29] (see below). If a high level of specialist palliative care need is identified (as defined within a distress protocol standard operating procedure [SOP]), through the IPOS questionnaire, a research team mini MDM (either face-to-face or virtual) will be convened to agree the most appropriate way forward. As is usual clinical practice, referrals to a specialist service by the usual healthcare providers can also occur irrespective of any trial assessments or advice. If that occurs, **consistent with standard practice**, a referral is simultaneously made to a community (district) nurse, if not **already done for another reason**.

It may become necessary, after discussion with the CI and the Trial Management Group (TMG), to remove the LTAD. Reasons for this could include 1) patient request, 2) Serious Adverse Reaction (SAR) assessed by the CI as being directly related to the LTAD, 3) significant deviation from the study protocol with potential for harm (for example participant not allowing community nurses to enter residence to perform drainage).

The contact telephone numbers for key members of the research team will be provided to the participants. Out of hours, participants will be encouraged to contact their GP or attend the accident and emergency department of their local hospital, as **per** usual standard of care.

### **Outcome measures**

The objectives of this feasibility study therefore are to explore:

- Properties of different outcome measures (specifically health resource utilisation and QOL instruments) to ascertain the most appropriate primary outcome for the full trial and use the chosen primary outcome measure to inform sample size calculations from estimates of the standard deviations, for the full trial.
- Resource implications of LTAD compared to standard of care (LVP), including a preliminary assessment of cost-effectiveness to indicate whether a full trial is worthwhile
- The number of eligible patients
- The extent of HCP support in identifying possible participants
- Symptom burden in patients with ESLD and refractory ascites
- Informal carer/family perceived burden (if appropriate)
- Whether patients are willing to be randomised to LTAD, rather than LVP
- Acceptability of and adherence to home ascites drainage
- Attrition rates, including attrition due to death, illness or other causes
- Complication rates
- Willingness to participate in a qualitative interview (optional)

- Acceptability of LTAD to patients, carers and clinical staff using qualitative methods (optional)
- Acceptability of questionnaires

We will therefore collect data on a range of candidate primary outcome measures, including QOL and health resource utilisation. The primary outcome measure(s) for the definitive trial will be decided by the research team, including service users, on review of the final analysis of this feasibility study.

### **Study success criteria will include**

- a. Percentage of study period time in hospital for LTAD group is < 50% of that for the LVP group (where the study period time is the number of days from date of LTAD insertion to the end of the study period or the patient's death (whichever is earliest); time spent in hospital is the number of bed days used)
- b. Attrition rate is not > 50%
- c. There is <10% overall rate of LTAD removal due to one or more of the following complications: peritonitis, failed insertion, bleeding and blockage
- d. 80% of questionnaires and qualitative interviews completed by each patient.

### **Data collection**

Data will be collected on an electronic Case Report Form (eCRF), using the MACRO electronic data capture system provided by KCTU and hosted on the KCL server. The system is compliant with Good Clinical Practice (GCP), with a full audit trail and formal database lock functionality.

Figure 2 shows participant timeline/study flow chart



## **Schedule of Assessments (Figure 2 and SPIRIT Figure 3)**

The research team member will visit participants at home every two weeks for questionnaire based and clinical assessments (see below) as well as collection of routine clinical blood samples. The amount and frequency of drainage and other pertinent observations will be recorded by community nurses in a formal study diary, as is the case when LTAD is used in patients with ascites due to malignancy. The research team member will train and advise the community nurses and participants on data collection to reduce the possibility of missing data.

### **Questionnaire-based assessments**

The questionnaire-based assessments will be performed by the research team member and depending on patient preference, done either face to face at the patient's home or via phone (within three days of the research team member visit). The research team member will follow guidance in the lone worker policy when conducting home/usual place of care visits.

We have selected questionnaires validated with our population group (e.g. palliative care patients, and those with ESLD). Some, like the Integrated Palliative care Outcomes Scale (IPOS) [29] (see below), are short, relatively brief to complete and have a proxy version if a patient loses capacity during the study. As this is a feasibility study we will explore the acceptability of the measures used. We will pilot the patient questionnaires comprising the proposed measures with the first 8 patients to explore and assess patient fatigue and time taken for completion. We will review the pilot findings and amend the patient questionnaire schedule if indicated, submitting the required Research Ethics Committee (REC) amendment for all proposed changes. The research team member will 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 carers, both to reduce the participant burden as well as risk of missing data. Additionally, those patients

allocated to the LVP group, if the hospital visits coincides with questionnaire assessments, the assessments can be done at that point in hospital.

### **Symptom distress and concerns**

The IPOS [29-31] combines the Palliative care Outcome Scale (POS) and POS-S (symptoms). It is a measure frequently used in palliative care research and clinical practice [29-33]. These are validated for clinical practice, audit and research and can be used in any setting. POS-S captures physical symptom specific information, and, “other” symptoms specific to liver disease/ascites can be added e.g. abdominal bloating. A SOP will be implemented when clinical and/or risk of harm issues are identified to ensure timely assessment by their usual healthcare providers and/or referral to a specialist palliative service depending on needs identified.

A staff version of IPOS will be used in case participants are unable to complete the questionnaire. IPOS will be assessed at baseline and two weekly and takes less than 10 minutes to complete (a total of 10 questions).

### **Quality of Life (QOL)**

QOL will be assessed using the Short Form Liver Disease Quality of Life (SF-LDQOL) [34-35], a reliable and valid measure of health related QOL in patients with advanced liver disease awaiting transplant, incorporating a core QOL assessment and disease targeted items. As specific QOL assessment tools are lacking in cirrhosis, the SF-LDQOL is the most appropriate option and was selected after service user involvement. The original SF-LDQOL questionnaire has 43 questions though questions from 26 onwards are for the purposes of validating the questionnaire and not specific to the SF-LDQOL itself. [34-35] The authors have provided a scoring algorithm that includes only the first 25 questions, therefore only **these** will be used. This questionnaire takes about 15 minutes to complete and will be assessed at baseline and four weekly.

**Health economics outcome**

There are opposing views on use of EQ-5D as a composite measure of Quality-Adjusted Life Years (QALYs) in palliative care [19]. However, it is the most widely used indicator and until valid alternatives are available, we have elected to assess EQ-5D-5L, [36] (at baseline and four weekly) in this feasibility study for its utility as an outcome. The EQ-5D-5L has six questions and will take about 5 minutes to complete.

**Impact on carers**

For those willing to participate, the Zarit Burden Interview (ZBI-12) [37-38] will be employed at baseline and four weekly. This measures family/informal carer appraisal of the impact of caregiving. It has 12 items, is easy to administer and can be used in the hospital or community setting, taking about 10 minutes to complete.

**Service use assessment**

For each arm of the feasibility study, a comprehensive patient level database of services used will be collated, including all inpatient, outpatient, emergency, primary, community, social and voluntary services, equipment and supplies and assistance from family/informal carers. For community and home based services, a modified version of the ambulatory and home care record (AHCR) [39] will be used and administered by the research team member at baseline and two weekly. The carers will assist with this especially if the participant is too unwell. The AHCR, a standardised and comprehensive framework and tool, measures resources used within the end-of-life context from a societal perspective. This approach gives equal consideration to costs borne by the health system as well as those costs borne by care recipients and informal caregivers, such as family members and friends. It will take about 20 minutes to complete. Self-reported data will be verified and supplemented (e.g. for supplies) with reference to nursing records. Data on all hospital use will be gathered from

hospital records at the end of the study using a purposefully designed in-house proforma. Service use will be converted to costs using national sources [40] and NHS reference costs. Informal care will be valued using replacement cost methods, and applying the tariff for community support workers.

A feasibility study gives us the opportunity to test out candidate patient reported outcome measures with the intention of only taking the most useful measures through to any definitive study. Survey fatigue was always a concern for the research team and our service users and the issue also arose during the Ethical Committee review process. Therefore we had a safety check to reassess survey fatigue after the first eight patients were recruited. We have found no evidence of any problems so far; indeed some patients restate their willingness to complete the questionnaires.

### **Qualitative interviews**

Qualitative data will be collected as part of a concurrent embedded strategy. [41] 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, and practical steps and barriers involved in undertaking LTAD.

Twenty-eight optional interviews (20 participants and 8 clinical key informants) will be undertaken by a qualitative researcher, with additional support if needed. Clinicians and research participants will be identified and recruited via the research team member. Patient recruitment will seek to reach a maximum diversity sample of participants, i.e. interview participants with a wide range of demographic characteristics, with purposive sampling (if feasible), informed by the IPOS (given that the cohort are living with deteriorating health). The research team member will invite patients to participate in the qualitative interview study and will seek permission to pass contact details (normally telephone number) to qualitative researcher. The qualitative researcher will contact participants to arrange a convenient time for the interview. As life expectancy in refractory ascites due to ESLD is on average six

months, the qualitative interview methodology seeks to explore a wide range of patient experiences, recognising that participant beliefs and experiences may change across this period. Interviews will, therefore, be divided into two phases:

**Phase 1** (week 0-8): 12 patients (6 from each arm), 4 clinical staff

**Phase 2** (week 9-12): 8 patients (4 from each arm), 4 clinical staff

In the event of inability to recruit new participants for Phase 2 interviews, additional participants or repeat interviews will be sought during Phase 1. Interviews with key clinical staff will follow the same aims of patient interviews and will be anonymous (i.e. key Informants will be asked to withhold patient identities).

Interviews will take place at participants' homes or by phone according to participant preference and geographical location. Clinical staff will be interviewed at their place of work or at a mutually convenient venue. Consent will be taken from all participants, including any carer requested by the participant to be present. For telephone interviews, consent will be taken verbally and recording will be started before telephone consent is taken, so that the verbal consent can be recorded as a separate file from the interview. Signed consent forms will be kept for five years. Interview data will be transcribed and the audio version deleted. The anonymised transcription of the interview (including the verbal consent) will be stored (labelled with patient study number).

To reduce participant burden, breaks will be allowed during the interviews if requested by the participants and interviews will last between 20 and 60 minutes.

### **Safety Monitoring**

A monitoring plan will be put in place and adhered to for each research site (see additional files). Monitoring visits will be undertaken by the BSCTU on behalf of the Study Sponsor. The

study may be audited in line with the BSCTU or by the Sponsor requirements. Audits will be conducted by personnel independent from the research team.

Common terminology criteria for adverse events (AE) (CTCAE, version 4.03 [42]) will be used when assessing AE and serious adverse events (SAEs). As this is a feasibility study all AE and SAE will be recorded in the source data and reported on the electronic case record form (eCRF). Crucially, only those SAEs that in the opinion of the CI are related to the study intervention (LTAD) will be reported in an expedited manner to the Brighton and Sussex Clinical Trials Unit (BSCTU).

This feasibility RCT is investigating LTAD in a cohort with ESLD. By its very nature, this is a group with high morbidity and mortality. Hence in this patient population worsening of existing conditions, hospitalisations, acute illnesses and deaths are expected. These events will be recorded in the eCRF but not reported to BSCTU or the REC.

Expected/unexpected unrelated AE/SAE will include but not limited to:

- 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 LVP (circulatory and or electrolyte disturbances, bleeding, bowel perforation, failed drainage)
- 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, variceal bleeding and sepsis

### **Expected serious adverse reactions (SAR)**

If in the CI's opinion a SAR is considered directly related to the LTAD and is an expected SAR then this will be recorded on the eCRF and reported to the BSCTU immediately following the Safety Reporting SOP. Expected SAR will include the following (but only if they result in hospitalisation):

- Failure of LTAD insertion
- Drain leakage or blockage
- Cellulitis
- Bleeding
- Pain at site of insertion not controlled by analgesia
- Spontaneous bacterial peritonitis
- Sepsis which in the opinion of the CI is directly related to LTAD
- Death which in the opinion of the CI directly related to the LTAD

### **Suspected unexpected, serious adverse reactions (SUSAR)**

This will include all SARs that in the opinion of the CI are directly related to the intervention and are not listed as a known (expected) SAR. All SUSARs that occur between insertion of the LTAD and three months post insertion or death, whichever is earlier, will be recorded on the eCRF form and emailed/faxed to BSCTU immediately, at least within 24 hours of the research team becoming aware in accordance with the BSCTU Safety Reporting SOP. The Research Ethics Committee will be notified of any SUSAR to the study intervention by the BSCTU. For each SUSAR, all relevant information will be collected and they will be followed up until resolved or a final outcome reached.

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 BSUH SOP on Safety Reporting in Non-CTIMP studies.

## DATA ANALYSIS

### Statistical analysis

Guidelines for feasibility studies suggest that analysing 12 participants in each arm will provide an adequate sample size with which to achieve our objectives. [43] However, since this is a cohort with a poor prognosis, attrition is likely to be high. In our pilot study of seven patients [27], survival post insertion ranged from 6 to 96 days (though LTAD were inserted late in the disease trajectory). Due to the advanced disease stage of the participants we are assuming a 50% attrition. The sample size will therefore be increased to 24 participants in each arm, i.e. a total recruitment target of 48 participants. This sample size will be adequate to inform the research methods for a definitive phase 3 RCT.

Recruitment rate will be evaluated in terms of the proportion of eligible patients that provide informed consent. Attrition at all stages will be recorded, particularly due to unwillingness or inability to manage LTAD as this is an indication of acceptability. Data will be analysed on available cases in the groups to which they were randomised. We will present these data as a flow chart. The amount of missing data will be summarised for each variable but there will be no imputation. As this is a feasibility study, stopping rules will not be defined.

The flow of patients through the trial is depicted in the CONSORT diagram ([Figure 4](#)). [44]

Descriptive statistics will be used to summarise and compare the quantitative outcome measures to include a) complication rates :failed insertion, drain leakage or blockage, cellulitis, bleeding, pain at site of insertion not controlled by analgesia, peritonitis, sepsis and death (the latter two only if directly related to LTAD), b) symptoms: IPOS, QOL (SF-LDQOL, EQ-5D-5L) [29, 34-36] and c) carer burden [37-38] for each arm. Means and standard deviations will be determined for normally distributed outcomes and medians and interquartile ranges for skewed outcomes at the different time points and at the end of the study. Analyses will use all available cases following intention-to-treat principles. 95% confidence intervals will be calculated for parameter estimates as appropriate. Prior to the analysis of the data, a detailed statistical analysis plan will be written and signed off.



## Health economics data analysis

The economic analysis will adopt the perspectives of the health and social care systems.

Using the patient-level database assembled from participant self-report and hospital and community nursing records, the feasibility study will identify the main resource items for which comprehensive data collection would be required in the main trial. Interactions between ascites management and other palliative care services will be explored. In particular, community nurse visits in both groups will be monitored so *extra* visits required for LTAD, compared to normal care, which was a major source of uncertainty in the earlier modelling study, can be identified. [13] The group mean total costs of services used in ascites management will be compared between LTAD and LVP.

The properties of the main clinical outcomes (IPOS, SF-LDQOL, EQ-5D-5L) [29,34-36] and the number of hospital days will be investigated to assess their value as measures of effectiveness for the definitive trial so that a primary outcome can be determined. Data on QALYs from EQ-5D-5L [36] will be investigated for possible use in the economic evaluation. A preliminary cost-effectiveness analysis will be undertaken to determine the likely advantage of conducting a full trial. [45] Sensitivity analysis will be performed by varying the key cost drivers, such as the number of inpatient days and the cost of bed days.

## Qualitative data analysis

If purposive sampling is not feasible, the proportion of participants choosing to participate in qualitative interviews will be noted. Interviews will be audio recorded and labelled using the same anonymous study number as the intervention component of this study. The same number will be used so that in the event of a participant reporting a serious concern about their condition or their care, the qualitative researcher can raise this with the patient's clinician. In this unlikely event, the researcher will inform the patient of the need to convey

this information to their clinician. The qualitative researcher will have access to the clinical study data of the individual if needed.

Thematic analysis supported by qualitative software (NVivo) [46] will be used to extract overarching themes from the interviews to capture patients' experiences and beliefs. Utilising the process of triangulation [47] the findings of the qualitative arm will be used to inform the quantitative results, particularly in the context of QOL and experience of end of life care provision.

Data will be analysed in a blinded manner. However, the research team members collecting information from the patients will always be aware of their allocation since a high level of scrutiny is necessary to ensure that there are no safety events in the LTAD group. Our service users were also insistent that participants not engage with multiple members of the research team, further excluding blinded data collection.

## **ANCILLARY AND POST-TRIAL CARE**

At the end of the trial, 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 care of their usual Consultant Gastroenterologist/Hepatologist.

## **COMMITTEES**

### **Trial Management Group (TMG)**

This will be constituted of the CI, all co-investigators and Principal Investigators (PIs), Research Fellow, trial manager, data manager and statistician and will be chaired by the CI (SV).

The TMG will meet every month to:

1. Finalise trial-related materials.
2. Oversee and co-ordinate the various aspects of the project, so that the research completes on time and on budget.

3. Assess study progress to ensure that recruitment is on target and on budget. If recruitment is below that anticipated then strategies to improve this will be discussed.
4. Assess adherence to protocol by reviewing protocol deviation logs.

### **Data Safety Monitoring Committee (DSMC)**

This will be an independent committee chaired by Professor Guruprasad Aithal, (Professor of Hepatology, Nottingham University NHS trust), with two other independent members, Professor Bobbie Farsides, (Chair of Medical Ethics at BSMS) and Professor Martin Llewelyn (Professor in Infectious Diseases, BSMS and Hon Consultant, BSUHT), as well as at least one Service User member. Study data report will be provided to the DSMC by the trial manager every 10-12 months for the first two years and then every 6 months for the last year, in accordance with the Terms of Reference for the Committee. The DSMC will meet as above to address any safety concerns, review any ethical issues raised and monitor adverse events. The DSMC will make recommendations to the TMG as appropriate, and has the power to stop the trial if necessary. The DSMC will be independent of the Study Sponsor. Details of IDMC Charter can be obtained from [trial.monitors@bsuh.nhs.uk](mailto:trial.monitors@bsuh.nhs.uk)

### **DISCUSSION**

The impetus for the REDUCe trial was driven by our concerns that patients with ESLD receive suboptimal end of life care compared to those with other terminal conditions. Most individuals with ESLD almost always die in hospital [6] while receiving end-of-life care even though in many cases palliative care provided within the community would be more appropriate and compassionate. Such an option is often not feasible due to the complex end of life needs of patients with ESLD (including LVP) and the fluctuating disease trajectory making it difficult to define when a palliative phase has been reached. [6,48] Most patients with ESLD develop ascites [2-3] and the management strategy in ESLD is thus often dictated by this specific symptom. Our own data suggests that approximately 40% of patients with

ascites requiring LVP can go on to develop refractory ascites [49]. This condition has a major impact on the QOL in ESLD, due to factors such as direct physical discomfort but also the need for recurrent hospitalisation for LVP. [3,50] We would argue that for many such individuals these recurrent hospitalisations impair their QOL. A more appropriate option would be to focus on holistic palliative care in the community, based on discussions on future wishes. [50-51] This will require a multidisciplinary approach to the disease, reflected in the composition of the REDUCe study team.

Consistent with the lack of research in this complex cohort of individuals and therefore not unexpectedly, recruitment to this trial has been challenging. We found that clinicians who were not part of the study team were often reluctant, particularly in younger patients, to diagnose ESLD and discuss the implications of a limited life expectancy and purely palliative management. In some instances prospective participants were only identified late and unfortunately died before they could make an informed decision about trial participation. The patients themselves are often vulnerable and (in their opinion) disenfranchised and stigmatised. Finally, setting up new sites for a study that spans both acute hospital and community settings, often without existing research collaborations, has been difficult and time consuming.

Conversely, we have already begun to note positive changes in attitudes, beliefs and practice of HCP locally and in the study sites. Simply by attempting to discuss the REDUCe trial we have seen a change in attitudes towards symptom control and QOL as well as timely referral to palliative care. There is also increasing recognition that patients should be able to be more involved in decisions about their end of life care. This trial has raised the local profile of these under-researched patients, with wider recognition of the need for MDT communication and collaboration. Specifically, many local hospitals now discuss all patients with ESLD at a weekly liver MDM so as to identify in a timely manner those that are entering the palliative phase of their disease. This has undoubtedly driven the improvement in

recruitment. The NIHR acknowledging this and the potential of this study to result in a paradigm shift in end of life care in ESLD have granted a funded extension for a year.

## **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-investigators, Research Fellow, members of the BSCTU and all **PIs at participating sites** will be eligible for authorship credit. However, as is current accepted practice, it will be unacceptable for PIs to 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.

## **DISSEMINATION PLAN**

Results of this study will be disseminated via local (Regional British Society of Gastroenterology), national (British Association for Study of Liver) and international (American Association for the Study of Liver Diseases and European Association for the Study of the Liver) meetings. Further dissemination will occur via palliative care conferences (UK Palliative Care Congress, European Association of Palliative Care World Congress, American Academy of Hospice and Palliative Medicine Annual Assembly) and regional research networks and end of life groups. We plan to publish our research in high **impact Hepatology** and Palliative Care journals. Our service user members will play a vital role in research dissemination. We also anticipate providing evidence to the National Institute for Health and Care Excellence (NICE).

## TRIAL STATUS

Now open, with 36 patients recruited as of May 2018. Funded extension obtained May 2017.

## PROTOCOL AMENDMENTS

The need for protocol amendments will be discussed by the TMG and submitted to Sponsor for determination of substantial/non-substantial amendment. 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 are aware when the implementation can occur.

## CONFIDENTIALITY

In line with BSUH trust policy and the 1998 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 during randomisation, but subsequently all research participants will be allocated a unique study number that will be recorded on all other data collection forms. Only those individuals directly involved with the research will have access to the study data.

## NON-STANDARD ABBREVIATIONS

|       |  |
|-------|--|
| AE    | Adverse event                            |
| AHCR  | Ambulatory and Home Care Record          |
| AMA   | Antimitochondrial antibody               |
| ANA   | Antinuclear antibody                     |
| ALFA  | Automated low flow ascites               |
| BSCTU | Brighton and Sussex Clinical Trials Unit |
| BSMS  | Brighton and Sussex Medical School       |
| BSUH  | Brighton and Sussex University Hospital  |

|       |  |
|-------|--|
| CI    | Chief Investigator                                     |
| CLD   | Chronic liver disease                                  |
| CTIMP | Clinical Trial of an Investigational Medicinal Product |
| ESLD  | End-stage liver disease                                |
| eCRF  | Electronic case record form                            |
| GP    | General Practitioner                                   |
| GCP   | Good Clinical Practice                                 |
| HCP   | Healthcare Professional                                |
| HRA   | Health Research Authority                              |
| HBsAg | Hepatitis B surface antigen                            |
| HCV   | Hepatitis C Virus                                      |
| HIV   | Human Immunodeficiency Virus                           |
| INR   | International Normalised Ratio                         |
| IPCT  | Integrated Primary Care Team                           |
| IPOS  | Integrated Palliative care Outcome Scale               |
| KCL   | Kings College London                                   |
| KCTU  | Kings College London Clinical Trials Unit              |
| LKM   | Liver kidney microsomal antibody                       |
| LTAD  | Long-term abdominal drain                              |
| LVP   | Large volume paracentesis                              |
| MDM   | Multidisciplinary meeting                              |
| MDT   | Multidisciplinary team                                 |
| MRC   | Medical Research Council                               |
| NHS   | National Health Service                                |
| NIHR  | National Institute of Health Research                  |
| PIS   | Patient information sheet                              |
| POS   | Palliative Outcome Score                               |

|          |   |
|----------|---|
| POS-S    | Palliative Outcome Score (Symptom list)       |
| PRH      | Princess Royal Hospital                       |
| PI       | Principal Investigator                        |
| QALYs    | Quality-Adjusted Life Years                   |
| QOL      | Quality Of Life                               |
| R&D      | Research & Development                        |
| REC      | Research Ethics Committee                     |
| RfPB     | Research for Patient Benefit                  |
| SAR      | Serious Adverse Reaction                      |
| SAE      | Serious Adverse Event                         |
| SF-LDQOL | Short Form Liver Disease Quality Of Life      |
| SMA      | Smooth muscle antibody                        |
| SOP      | Standard operating procedure                  |
| TIPS     | Transjugular intrahepatic portosystemic shunt |
| WSHFT    | West Sussex Hospital Foundation Trust         |
| ZBI-12   | Zarit Burden Interview                        |

## **DECLARATIONS**

### **Ethical Approval and Consent to participate**

Research Ethics Committee approval was obtained nationally from the National Research Ethics Committee South Central - Hampshire A, REC ref 15/SC/0257). All patients will sign an informed consent prior to participating in the study.

### **Consent for publication**

Rocket Medical hold patient consent for Figure 1



### **Availability of supporting data**

Supporting data including standard operating procedures, details of data management procedures and eCRFs can be obtained from [trial.monitors@bsuh.nhs.uk](mailto:trial.monitors@bsuh.nhs.uk). The datasets generated and/or analysed during the current study are available from the CI upon reasonable request.

### **Competing interests**

The authors declare that they have no competing interests. Rocket Medical have provided drains free of cost for the trial. They were however not involved in the study design, data collection and analysis or manuscript write up nor will they claim intellectual property.

### **Funding**

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### **Authors' contributions**

SV identified the research question, led on the development of the study protocol and provides clinical expertise in Hepatology. LMa helped design the study, and provides clinical expertise in palliative care, in particular the role of community professionals. LMac helped design the study, is responsible for the day-to-day running of the study including insertion of the LTAD and data collection. SV, LMa and LMac were major contributors in writing the manuscript. DC helped design the study and finalise the protocol. CE helped design the study and provides expertise in community-based palliative care as well as mixed methods trial methodology. HG and JJ helped design the study and provide expertise in health economics. MA has advised on the insertion of the LTAD within a hospital setting. NP has helped develop the recruitment strategy for patients. MC helped design the qualitative

aspects of the study. SS, an ex-service user, helped develop trial-related materials such as the PIS, information topic guides and service use questionnaire and has also contributed to the dissemination strategy. GE JB, JT and DL contributed towards the trial management and data management aspects of the project and had overall responsibility for the trial protocol. SB (Trial Statistician) developed the draft statistical analysis plan. All authors contributed to and approved the final published version of the trial protocol

## Acknowledgements

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### **INDEMNITY STATEMENT**

This RCT is being sponsored by BSUH and therefore NHS indemnity schemes will apply.

This is based on the sound and ethical principle that the NHS has a duty of care to all patients irrespective of whether they are taking part in research and therefore should remain liable for any negligent harm.

### **SPONSOR**

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Figure 1 Rocket Long-Term Abdominal Drain in situ [26]



Figure 2 Participant Timeline

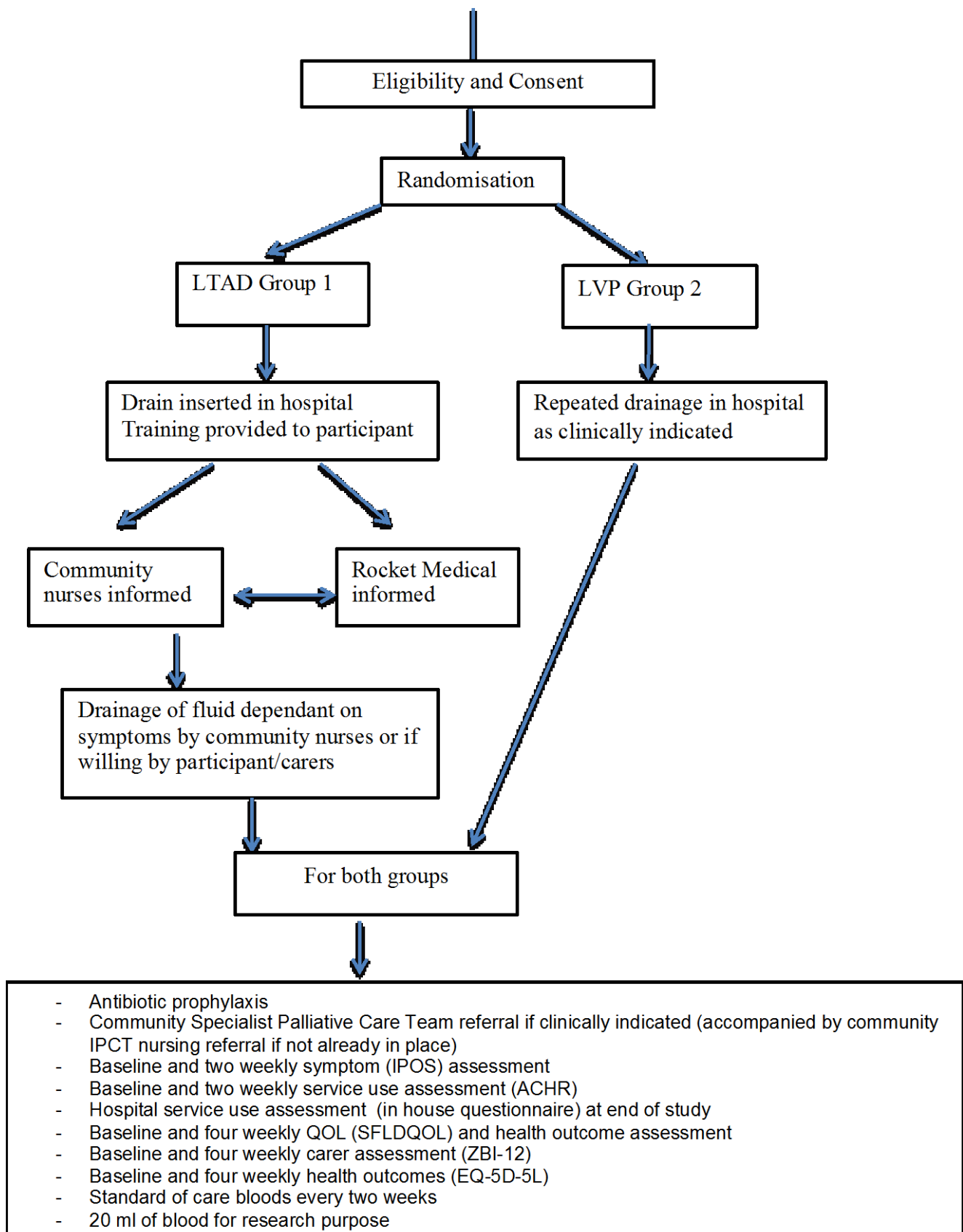


Figure 3 SPIRIT Figure 3

|  | Screening | Baseline       | Followup 1     | Followup 2     | Followup 3     | Followup 4     | Followup 5      | Followup 6      |
|--|-----------|----------------|----------------|----------------|----------------|----------------|-----------------|-----------------|
| Timepoint (weeks)  | -         | t <sub>0</sub> | t <sub>2</sub> | t <sub>4</sub> | t <sub>6</sub> | t <sub>8</sub> | t <sub>10</sub> | t <sub>12</sub> |
| Capacity check   | ✓         | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Informed Consent <sup>1</sup>                                | ✓         |                |                |                |                |                |                 |                 |
| Demographics   | ✓         |                |                |                |                |                |                 |                 |
| Medical History  | ✓         | ✓              |                |                |                |                |                 |                 |
| Eligibility according to inclusion/exclusion criteria        | ✓         | ✓              |                |                |                |                |                 |                 |
| Routine liver ultrasound <sup>2</sup>                        | ✓         |                |                |                |                |                |                 |                 |
| Research blood sample for storage                            |           | ✓ <sup>3</sup> |                |                |                |                |                 |                 |
| Liver screen blood tests <sup>4</sup>                        |           | ✓              |                |                |                |                |                 |                 |
| Blood and urine culture, urine dipstick testing <sup>5</sup> | ✓         | ✓              |                |                |                |                |                 |                 |
| Randomisation <sup>6</sup>                                   |           | ✓              |                |                |                |                |                 |                 |
| Alcohol and substance misuse assessment                      | ✓         | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Liver disease scores   | ✓         | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Routine haematology and biochemistry                         | ✓         | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Diagnostic paracentesis <sup>7</sup>                         | ✓         | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Liver disease assessment and history                         | ✓         | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Adverse event review   |           | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Concomitant medication review                                |           | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Examination and vital signs <sup>8</sup>                     | ✓         | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| LTAD insertion (or LVP)                                      |           | ✓              |                |                |                |                |                 |                 |
| Drainage assessment (both LTAD and LVP)                      |           | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Questionnaires: IPOS, AHCR                                   |           | ✓              | ✓              | ✓              | ✓              | ✓              | ✓               | ✓               |
| Questionnaires: SF-LDQOL, EQ5D-5L, ZBI-12                    |           | ✓              |                | ✓              |                | ✓              |                 | ✓               |
| Questionnaire: Hospital service use                          |           |                |                |                |                |                |                 | ✓               |
| Qualitative interviews                                       |           |                |                |                |                |                |                 |                 |

← Phase 1 → ← Phase 2 →

Figure 4 Consort Flow Chart

