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# Randomised Clinical Trial: Palliative Long-term Abdominal Drains Versus Large Volume Paracentesis In Refractory Ascites Due to Cirrhosis

## Short title: REDUCe Study

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## Abstract

**Background:** Palliative care remains suboptimal in end-stage liver disease.

**Aims:** To inform a definitive study, we assessed palliative long-term abdominal drains in end-stage liver disease to determine recruitment, attrition, safety/ potential effectiveness, questionnaires/interview uptake/completion and make a preliminary cost comparison.

**Methods:** A 12-week feasibility non-blinded randomised controlled trial comparing large volume paracentesis vs. long-term abdominal drains in refractory ascites due to end-stage liver disease with fortnightly home visits for clinical/questionnaire-based assessments. Study success criteria were attrition not >50%, <10% long-term abdominal drain removal due to complications, long-term abdominal drain group to spend < 50% ascites-related study time in hospital vs. large volume paracentesis group and 80% questionnaire/ interview uptake/completion.

**Results:** Of 59 eligible patients, 36 (61%) were randomised, 17 to long-term abdominal drain and 19 to large volume paracentesis. Following randomisation, median number (IQR) of hospital ascitic drains, (long-term abdominal drain vs. large volume paracentesis group) were 0 (0,1) vs. 4 (3,7); week-12 serum albumin (g/L) and serum creatinine ( $\mu\text{mol/L}$ ) were 29 (26.5,32.5) vs. 30 (25,35) and 104.5 (81,115.5) vs.127 (63,158) respectively. Total attrition was 42% (long-term abdominal drain group 47%, large volume paracentesis group 37%). Median (IQR) fortnightly community/hospital/social care ascites-related costs and percentage study time in hospital were lower in the long-term abdominal drain group, £329 (253,580) vs. £843 (603, 1060) and 0% (0,0.74) vs. 2.75% (2.35,3.84) respectively. Self-limiting cellulitis/leakage occurred in 41% (7/17) in the long-term abdominal drain vs. 11% (2/19) in the large volume paracentesis group; peritonitis incidence was 6% (1/17) vs.

11% (2/19) respectively. Questionnaires/interview uptake/completion were  $\geq 80\%$ , interviews indicating that **long-term abdominal drains** could transform the care pathway.

**Conclusions:** The REDUCe study demonstrates feasibility with preliminary evidence of **long-term abdominal drain** acceptability/effectiveness/safety and reduction in health resource utilisation.

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**Key words:** **Liver** cirrhosis, quality of life, **economics**, **palliative care**

## Introduction

Liver related deaths in England have increased by more than 250% since 1971, and now constitute the fourth commonest cause of premature death (1). Development of ascites is an important milestone in the natural history of cirrhosis, 20% presenting with ascites dying within the first year of the diagnosis (2). **Refractory ascites**, defined by intolerance or unresponsiveness to diuretics (3), is a useful prognostic indicator as median transplant-free survival is about six months (3-4). Liver transplantation is however only possible in a minority with **refractory ascites** (3,5).

Based on reported exclusion criteria, a substantial number with **refractory ascites** are not candidates for trans jugular intrahepatic portosystemic shunts (TIPSS) and or the **automated low flow ascites pump** (3). The most common management for **refractory ascites remains** repeated hospitalisation for large volume paracentesis (LVP) (3). A British study (2013-2015) indicated that of the 45,000 cirrhosis related deaths, about a third required LVP in the last year of their life with overall healthcare costs being over £21,000 per person (6).

Long-term abdominal drains (LTAD) are tunnelled drains inserted in hospital under local anaesthetic, with community nurses/informal caregivers draining small amounts (1-2 litres) of ascitic fluid at home, up to three times a week (7-9). A **National Institute for Health and Care Excellence technology** guidance in malignant ascites reported that LTAD were clinically effective, had low complication rates and compared with inpatient LVP, resulted in cost savings of £679/patient at the cost of 23.5 additional community nurse visits (8). Nationally, > 3500 LTAD (including PleurX™ and Rocket® drains) are inserted annually for malignant ascites (Richard Varey, Rocket Medical, personal communication). LTAD are not routinely used in

**refractory ascites** due to **end-stage liver disease** (ESLD), mainly due to infection risk, specifically peritonitis (3).

Most patients (~ 75%) with ascites due to **ESLD** die in hospital (6) compared to 40% with advanced cancer (10). Despite potential benefits (11-12), less than a third of patients with ESLD are referred to palliative care services, which is often introduced late in the disease trajectory (13-14). To advance palliative care in ESLD, evidence is needed about effective interventions. To inform a definitive randomised controlled trial (RCT) including outcome measures, we conducted a feasibility study (**REpeated Drainage in Untreatable ascites- REDUCe** study). Our overarching aim was to improve palliative management of **refractory ascites** in ESLD.

### **Patients and methods**

The study design for this three-year (Sept 2015-Sept 2018) feasibility parallel RCT comparing LTAD vs. LVP has been previously described (15). The study was conducted across five hospital and corresponding community sites in England.

**Refractory ascites** was defined as ascites that could not be treated or early recurrence, which could not be prevented due to non-response to sodium restriction, diuretics and or development of diuretic induced complications that precluded use of an effective dose (3). Our inclusion criteria were ascites that recurred rapidly after LVP, requiring one or more LVPs/month (participants undergoing a minimum of two LVPs prior to recruitment), age  $\geq$  18 years, **Child Pugh Score**  $\geq$  9 (unless felt to be palliative despite lower CPS) and capacity to give informed consent. Study exclusion criteria were loculated or chylous ascites, presence of  $>$  grade 1 hepatic encephalopathy, evidence of active infection including **spontaneous bacterial peritonitis** during screening (**supplementary fig 1**) and eligibility for liver transplantation. Screening for infection

included urine dipstick and culture, blood culture and ascitic tap for **polymorphonuclear** count and culture (**supplementary fig 1**). Potential participants could be rescreened for the study once the infection had been successfully treated. To avoid potential conflict of interest, transplant eligibility was determined at local **multidisciplinary meetings** (with discussion/review by a transplant centre if appropriate), and not by the research teams.

### **Patient identification and Consent**

Patients were identified by Medical and Gastroenterology teams during the acute hospital admission or from those attending ascites day units. Once deemed to be transplant ineligible, a research team member provided a patient information sheet that included details of the LTAD insertion and after care process. Two-three days later, if willing, written informed consent was received from participants, and caregivers (if present). In the event that capacity for decision-making regarding trial participation was lost during study conduct, the participant's nominated personal consultee (e.g. family member), and if unavailable, the participant's medical consultant were approached. Ethical approval for the study was granted by the National Research Ethics Committee South Central - Hampshire A (REC ref 15/SC/0257).

### **Randomisation**

Patients fulfilling inclusion criteria were randomised (non-blinded) 1:1 to either Group 1: LTAD or Group 2: LVP using a web based system hosted by King's **Clinical Trials Unit**. The allocations were revealed upon registering a participant and requesting their allocation and made by minimising, with a random element, on centre, **Child Pugh Score** and gender.

## **Interventions**

### **Group 1: LTAD**

Rocket<sup>®</sup> (Rocket Medical, Watford, UK) LTAD insertion was performed in hospital as a day procedure under local anaesthetic using ultrasound guidance as previously described (15). Participants (and caregivers if present), community nursing teams, and primary care physicians were provided guidance on LTAD use (Rocket Medical provided additional support as needed). The community nurses visited the participants in their place of residence two-three times/week, draining 1-2 litres of ascitic fluid at each visit. No **human albumin solution** was **administered**.

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

Participants randomised to LVP (3) (the current standard of care) were admitted to day units or hospital (as per local practice) as clinically indicated. A peritoneal drain was inserted for up to six hours for ascites drainage and intravenous **human albumin solution** administered (8g -10g per litre of ascitic fluid removed) (3).

### **Antibiotic prophylaxis**

There is no guidance on the use of prophylactic antibiotics in the setting of LTAD in ESLD. In fact, primary prophylaxis for spontaneous bacterial remains controversial and is the subject of ongoing studies (ASEPTIC, European Union Drug Regulating Authorities Clinical Trials Database Registration Number: 2019-000581-38). Both National Institute for Health and Care Excellence (16) and European Association for Study of Liver guidance (3) is to offer prophylactic antibiotics if total ascitic protein is 15g/L or less. However recent studies suggest that ascitic fluid protein may not predict peritonitis risk (17-18). Since refractory ascites indicates advanced liver



disease, we pragmatically offered all LTAD and LVP participants antibiotics (ciprofloxacin 500 mg once a day or equivalent), for the study duration.

Each participant was followed up for up to 12 weeks (supplementary fig 1).

Supplementary fig 2 shows participant timeline.

### **Study objectives**

Since this was feasibility RCT, there were no predefined primary or secondary outcome measures. Rather our objectives were to explore recruitment; attrition rates; safety and potential effectiveness of LTAD; uptake/completion of questionnaires/interviews; quality of life, symptom and caregiver workload. The resource implications of LTAD and LVP were explored and a preliminary comparison of costs conducted. The acceptability of LTAD to patients and clinical staff were assessed using qualitative methods (optional). Our study success criteria were attrition not > 50%; at least 80% uptake/completion of questionnaires/ interviews; those in the LTAD group to spend < 50% ascites-related study time in hospital compared to the LVP group; < 10% LTAD removal due to one or more of the following complications: failed insertion, peritonitis, bleeding and blockage (15).

### **Schedule of Assessments and analysis**

For both groups there were fortnightly home visits by a research team member for data collection and assessments as previously described (15) (supplementary fig 1).

Data were collected on paper case report forms and entered onto an electronic case report form within the Elsevier MACRO data capture system hosted by Kings Clinical Trials Unit.

## Clinical

Data collected included demographics, biochemistry, number of ascitic drains performed before and after randomisation, use of diuretics, comorbidity, assessment of LTAD insertion site, amount and frequency of LTAD and LVP drainage after randomisation and any adverse **events** or serious adverse **events**. Reasons for transplant ineligibility were not formally recorded, though we would endeavor to do this in any subsequent definitive study. Following discussion with our microbiology colleagues, we elected not to routinely culture the ascitic fluid from the LTAD due to the likelihood of growing skin contaminants. We took a pragmatic view to treat peritonitis if participants were symptomatic (fever, abdominal pain, hepatic decompensation, worsening renal function) and subsequent investigations revealed increased inflammatory markers,  $> 250/\text{mm}^3$  **polymorphonuclear** cells in the ascitic tap and or a positive ascitic fluid culture (3). Our service users also considered it ethically inappropriate to treat asymptomatic patients since this was an end of life cohort, major goals being symptom control and avoiding hospitalisation.

## Questionnaire based assessments

The rationales for instrument selection have been described previously (15).

- a. Symptoms assessed fortnightly using the Integrated Palliative Outcome Scale (IPOS) (19-21). The patient version has 17 items and scores from 0 (best) to 68 (worst). Besides a total score, the following subscale analyses were also performed as recommended in the recent validation study: physical symptoms, emotional symptoms and communication (21).
- b. Liver specific **health-related quality of life** assessed every four weeks using the Short Form Liver Disease Quality of Life (SFLDQoL) (22). This has 75 disease-targeted items transformed into the following 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 sex.

c. Generic **health-related quality of life** assessed every four weeks using EQ-5D-5L (23). This has a five item composite profile score (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), scored on a 5 point scale and converted to an index value range (-0.59 (worst) to 1(best)) and a 20 cm vertical **visual analogue scale** with range 0 (worst) to 100 (best).

d. Caregiver workload assessed every four weeks using Zarit Burden Interview (ZBI-12) (24-25). This has a 12 item composite scale completed by the caregiver with respect to negative feelings they experience in this role with 0 (never: best) to 48 (nearly always: worst).

**Supplementary fig 1** shows the assessment schedule

### **Resource use**

The main resource items were identified and collected at an individual patient level from two sources as described previously (15):

- Hospital use was extracted from participants' hospital records at the end of the study by research nurses in each site and transferred onto a bespoke proforma distinguishing drainage episodes as day case, inpatient or during a non-ascites related hospital admission.
- Community and home-based service use assessed fortnightly using a modified version of the Ambulatory and Home Care Record (AHCR) (26) which was administered to participants/caregivers by a research team member. The AHCR asks for the number of contacts in and out of the home covering primary, secondary and social care professionals or services, and informal caring input (unpaid by family or friends), recorded as hours per day (on

average). Although participants/caregivers were asked to report hospital use, the data from hospital records were found to be more complete and were used in preference during analysis.

The hospital and community databases were merged using the unique participant **study numbers**. Though data were collected on all service use both for hospital and community (liver and non-liver related), only ascites related service use was analysed further. When ascites drainage occurred during a hospital admission for a non-ascites related indication, the day case tariff for a drainage procedure was applied. This tariff differs from the inpatient ascites procedure cost which was used when patients were admitted to hospital solely for drainage. Resources used were converted to costs (British pounds 2018) using nationally validated unit costs (27) and **National Health Service** reference costs (28). Time spent by informal caregivers was valued using replacement cost methods and applying the tariff for community support workers (26).

### **Health economic analysis**

Since patients were in the study for different durations, and community data were gathered fortnightly (two-weekly), the data were standardised for fortnightly analysis.

Where data were missing, research members were contacted for clarification.

Resource use and costs for each main category are reported as mean  $\pm$  SD and median (range, IQR). The percentage study time spent in hospital for ascites drainage was calculated assuming 1 day for inpatient admissions solely for drainage and 0.5 days for day case procedures or if the patient had a drainage whilst in hospital for a non-ascites related indication.

### **Statistical analysis**

As this was a feasibility study, 12 participants in each group was considered to be an adequate sample size (29); however, assuming a 50% attrition (30), the sample size was increased to 24 participants in each group. Descriptive statistics were used to summarise and compare the quantitative outcome measures. Data were summarised by group, as frequencies and percentages, mean  $\pm$  SD or median (IQR) with 95% confidence intervals presented for the estimated difference in means between groups at end of follow up. Analysis was performed on available cases following the intention to treat principle.

### **Qualitative sub-study**

Detailed qualitative methods and results are being submitted for publication separately but are summarised here. A concurrent embedded qualitative study aimed to explore and contrast the experience, perceptions and care pathways of LTAD versus LVP participants. We aimed to interview 20 patients at diverse stages across the intervention, and eight **healthcare professionals** to assess similar areas as participant interviews but also focus on organisational/practical issues. All interviews were undertaken by telephone. Applied thematic analysis (31) supported by qualitative software (NVivo) (32) was used to extract overarching themes from interviews to capture participants' experiences and beliefs. These were considered in terms of a pathway approach towards accessing healthcare (33).

## **Results**

### **Clinical outcomes**

The study commenced in Sept 2015, recruitment **running** from Nov 2015 – Jun 2018 with 12 weeks of follow up. During the study period, of the 78 participants approached, 19 did not fulfil eligibility criteria (CONSORT **fig 1a**). **Two were**

initially regarded to be transplant ineligible at local multidisciplinary meetings but upon further review were deemed to be suitable for transplant assessment (fig 1a). Of the 59 eligible, we randomised 36 (61%), i.e. 75% of our target sample size (n=48). These 36 participants accounted for approximately 32% of those undergoing two or more LVPs at the recruiting sites. Of the eleven that declined to participate (fig 1a), five gave no reasons, three were not keen to be involved in research, one only wanted LTAD, one felt too unwell and one was unable to accept a limited life expectancy diagnosis. Nine out of 10 (90%) and 8/11 (73%) available caregivers in the LTAD and LVP groups respectively, were also successfully recruited.

The LTAD insertion was performed by LMa at two sites and by interventional radiologists at the remaining three sites. All LTAD were successfully inserted, though one individual accidentally pulled out the LTAD 24 hours after insertion. This participant declined to have it reinserted but was however willing to continue in the study.

Table 1 shows baseline demographic and clinical data. The prevalence of hepatic encephalopathy, alcohol aetiology for ESLD and body mass index were higher in the LTAD group (table 1). Of the 36 recruited, 35 had one or more absolute/relative contraindication for TIPSS as per European Association for Study of Liver guidelines (3), with one declining the procedure. Contraindications included serious co-morbidity (n=25, 69%), age > 70 years (n=13, 36%), prior hepatic encephalopathy (n=9, 26%), Child Pugh C disease (n=7, 20%), hepatocellular cancer (n=6, 18%) and serum creatinine >1.5ULN (n=6, 17%).

#### **Ascites drainage data**

Prior to randomisation, one participant has undergone two LVPs, the remainder undergoing three or more LVPs.

After randomisation, data on further ascites drainage were available for 30/36 (83%) participants (15 in each group) as one site did not return service use data. Comparing LTAD vs. LVP groups, median (IQR) follow up (days) was 82 (53, 90) vs. 86 (75, 92), median (IQR) amount of ascitic fluid (L) drained/week was 3.85 (2.85, 4.51) vs. 4.42 litres (3.00, 6.09) and median (IQR) number of visits per week for drainage was 1.9 (0.6, 2.5) vs. 0.33 (0.17, 0.5) respectively.

Fig 1b shows the total number of ascitic drains in both groups before and after randomisation. In 10/15 (67%) of the LTAD participants, the ascites drainage was successfully conducted by community nurses or caregivers outside of hospital. The remaining five LTAD participants (including the one whose LTAD was pulled out) required 13 further ascitic drains in hospital. This included five non-ascites related hospital admissions when drainage was performed, and a further eight admissions in an ascites day unit (one admitted overnight for solely drainage). In the 15 LVP participants after randomisation, there were a further 69 ascitic drains (64 in an ascites day unit including one admitted overnight and four non-ascites related hospital admissions when drainage was performed). The median (IQR) number of ascitic drains before and after randomisation in LTAD vs. LVP group were 5 (3, 8) vs. 5 (4, 7) and 0 (0, 1) vs. 4 (3, 7) respectively (fig 1b).

### **Biochemical data**

Data was available in  $\geq 92\%$  of participants at each visit except at week 10 in the LVP group (available in 85%). Baseline and week 12 serum albumin (g/L) (median, IQR), LTAD vs. LVP group were 33(33, 36) vs. 31(29, 34) and 29 (26.5, 32.5) vs. 30(25, 35) respectively. Week 2 serum albumin declined in the LTAD group to 29.5 (27.5,

31.5), but this remained stable at end of study. Baseline and week 12 serum creatinine ( $\mu\text{mol/L}$ ) (median, IQR), LTAD vs. LVP group was 109 (79, 141) vs. 113.5(89, 134) and 104.5 (81, 115.5) vs. 127 (63, 158) respectively. Figs 1c, 1d and 1e show the median (IQR) serum bilirubin ( $\mu\text{mol/L}$ ), albumin (g/L) and serum creatinine ( $\mu\text{mol/L}$ ) at each visit in both groups. Additional lab data (International Normalised Ratio) and liver prognostic scores (Child Pugh, United Kingdom End-stage Liver Disease, Model for End-stage Liver Disease) at each visit in both groups are shown in supplementary figs 3a, 3b, 3c and 3d respectively.

### **Attrition**

Overall attrition was 15/36 (42%), 95% CI (26, 59) - study withdrawal 3/15 (20%), 95% CI (4, 48) and death 12/15 (80%), 95% CI (52, 96) (seven in LTAD group and five in LVP group). Five out of the 12 deaths (42%) occurred within the first four weeks, three in LTAD and two in LVP group. Overall, 11/12 (92%) of the deaths were liver-related. Of the 12 deaths, eight (67%), 95% CI (35, 90) occurred outside of hospital (four in each group). Median survival (days) in those who died, LTAD vs. LVP was 53 (27, 70) vs. 61 days (26, 61) respectively. Overall 9/17 (53%) and 12/19 (63%) of the patients in the LTAD and LVP group respectively successfully completed the study. At the end of the study, all surviving LTAD participants elected to retain the drains.

### **Questionnaire-based assessments**

Table 2 shows data on EQ-5D-5L, IPOS (patient version) and ZBI-12 assessments and mean difference between the two groups at last follow up. Uptake of EQ-5D-5L at baseline and weeks 4, 8 and 12 was 97%, 86%, 85% and 95% respectively. IPOS (Patient) uptake at baseline and weeks 2, 4, 6, 8 and 12 was 97%, 94%, 89, 79%, 85%, 88% and 95% respectively. Almost all questions were successfully completed at each



visit (table 2), Median physical, emotional, communication and total IPOS scores remained consistent throughout the study period in both groups. The EQ-5D-5L index worsened in the LTAD group with some improvement in the LVP group, though the EQ-5D-5L **visual analogue scale** showed a trend towards improvement in the LTAD groups. Only 47% of the participants (17/36) had carers available to complete the ZBI-12 questionnaire. ZBI-12 scores remained stable in the LTAD group but there was an increasing trend (i.e. worsening carer burden) in the LVP group.

Table 3 shows data on **SFLDQoL** assessments and mean difference between the two groups at last follow up. Uptake of **SFLDQoL** at baseline, W4, W8 and W12 was 97%, 82%, 81% and 86% respectively. Again most questions were successfully completed at each visit except 4/25 questions (16%) related to sexual function. At baseline, LTAD group had higher scores (better **quality of life**) in all domains except loneliness. During follow up scores increased in most domains in the LVP group though reduced in the LTAD group (i.e. worsening **quality of life**).

### **Health economic outcomes**

Service use data were available for a total of 30/36 (83%) patients, 15 per group as one centre failed to return data. The comparison of the resource use and costs (standardised to a fortnightly rate) related to ascites drainage are shown in supplementary table 1 and table 4 respectively. Unit costs used are listed in the footnote to table 4. Community nurse usage and costs were higher in the LTAD vs. LVP group (median of £168 vs. £0). This is reflected in higher overall community costs (median of £232 vs. £11). LTAD participants also received higher median fortnightly social (£6 vs. £0) and informal care (£91 vs. £15) compared with the LVP group.

Of 82 hospital drainages, 13 were in LTAD (8 day cases) and 69 in LVP (64 day cases) group. Of the 10 inpatient drainages, 9 were during a non-ascites related-admission. The overall hospital costs were higher for the LVP vs. LTAD group (median £704 vs. £0).

Taken together, the median fortnightly community, social and hospital costs were lower in the LTAD group (£329 vs. £843). The difference between groups on the overall total cost was less when informal care was included (£909 vs. £1057), as a result of the high variability in reporting of informal caring hours.

Median (IQR) percentage ascites-related study time spent in hospital was also lower in the LTAD group, **0%** (0, 0.74) vs. **2.75%** (2.35,3.84).

### **Adverse events and serious adverse events**

Table 5 shows the **adverse and serious adverse events** in both groups. Worsening renal function occurred in six and seven participants in the LTAD vs. LVP group respectively. There were seven participants with cellulitis/leakage post LTAD insertion (two with cellulitis, three with leakage and two with both cellulitis and leakage) and two with bleeding/leakage after LVP. All were minor and self-limiting with none requiring hospitalisation. Incidence of peritonitis was 1/17 (6%) vs. 2/19 (11%) in LTAD vs. LVP group respectively, difference -5%, 95% CI (-24, 14). There were no LTAD related **serious adverse events**, none **being** removed after insertion due to complications.

### **Qualitative outcomes**

Of the 21 patients approached, 19 (90%) were willing to participate of whom five died rapidly. Therefore 14 patients (six allocated LTAD and eight LVP) and eight nurses (six community and two hospital) were interviewed, all interviews being completed. Themes that emerged included challenges of living with chronic ascites, recognising the need for drainage in hospital, organising hospital visits and waiting for discharge post drainage. Organisational barriers were perceived across this entire pathway. There was recognition, however, that ascites drainage provided relief (albeit temporarily).

In contrast, LTAD appeared to transform this care pathway at all levels by mitigating practical challenges associated with navigating hospital services. Benefits beyond avoiding hospitalisation included improved symptom control and emotional support from regular home visits by community nurses. Interviews suggested that continuity of care across the community and hospital were key to these positive experiences by LTAD participants.

LTAD participants reported acceptability of the drain insertion process and aftercare. However, one patient and two nurses reported temporary leakage problems resulting in embarrassment and distress. More than half of the LVP group who gave an opinion (5/8 participants) expressed disappointment at not being included in the LTAD arm. They were however, still willing to be randomised to LVP.

Community nursing staff reported that LTAD were manageable within busy workloads. They nonetheless expressed concern that should LTAD be more widely adopted, additional resources would be required to deliver the service. Although patients had a limited life expectancy, nurses reported that some appeared not to have fully assimilated this information, and sometimes understood the LTAD to be part of ongoing active treatment rather than palliative care.

## Discussion

The REDUCe study demonstrates the feasibility to proceed to a full trial with no LTAD-related safety concerns, acceptability of intervention and assessment tools and reduced health resource utilisation and costs. Our study success criteria were achieved as attrition was 42%, uptake/completion of questionnaires/ interviews was  $\geq 80\%$ , those in the LTAD group spent  $\leq 50\%$  ascites-related study time in hospital vs. LVP group and no LTAD were removed due to complications. **Since the LTAD group did not routinely receive human albumin solution, serum albumin declined at week 2, but this then remained stable at the end of study.**

We have also shown **potential LTAD effectiveness in refractory ascites** due to ESLD that requires further evaluation in a definitive trial. Excluding those where ascites drainage was performed during a non-ascites-related hospital admission and the one individual whose LTAD was pulled out, only two LTAD participants required further hospital ascites drainage. In a recent systematic review **on refractory ascites in ESLD**, no further hospital admissions were required in 14/18 studies that reported drainage following LTAD insertion (34).

As expected, community and social care costs were higher, and hospital costs lower for LTAD vs. LVP group. Overall median LTAD costs were lower, although the group difference was less when informal caring costs were included, due to the high variability in informal caring hours reported by participants. Being research participants, individuals were closely monitored by staff who were aware of timely palliative care benefits. Consequently, about 70% of the deaths occurred outside hospital. In a real world setting cost saving could be greater as the majority with ESLD would be expected to die in hospital (6, 35). A recent study reported that patients with liver disease were twofold more likely to die in an institution with 15%

higher costs ( $p < .001$ ), compared to those without liver disease (36). Since collection of EQ-5D-5L data was feasible, **quality adjusted life years** could be calculated in a larger study. Use of **quality adjusted life years** in palliative care remains controversial, due to problems with conceptualising **quality of life**, restrictions in life years gained and valuation of time. However, they are widely used and until alternative measures are available, it is reasonable that use of **quality adjusted life years** should continue (37-38).

Results from a recent national survey amongst Hepatologists/ Gastroenterologists, indicate that though almost all were willing to consider LTAD in ESLD, main deterrents were infection risk (90%) and community management (57%) (Dr Sushma Saxsena, Consultant Hepatologist, personal communication). We did not observe a higher peritonitis incidence in the LTAD group, though this was a feasibility study without a post hoc analysis (39). Our results are however consistent with an earlier systematic review (32), where peritonitis rates (12.7%) were no higher than what would be expected in ESLD (3).

Consistent with earlier studies in ESLD (40-41), we found high symptom burden and poor **quality of life** in our cohort. Our observed IPOS scores were similar to those reported in non-hepatic malignancy (19). Our ZBI scores were in fact higher than those seen in patients with hepatic encephalopathy (42) but similar to other advanced conditions such as glioblastoma (43) and heart failure (44). While accepting that this feasibility study was not powered to detect statistical differences, we observed most **quality of life** domains to worsen in the LTAD cohort. This was despite interviews indicating LTAD acceptability and improved symptom control. LTAD studies in malignant ascites also report inconsistent **quality of life** improvement during questionnaire-based assessments despite supportive qualitative data (8-9). These

incongruous results could be explained by absence of a validated ascites **quality of life** questionnaire and the incurable nature of **refractory ascites**, the LTAD being a constant reminder of a palliative intervention (9). The ASQoL study is trying to develop and validate an ascites-specific QoL questionnaire (Rajiv Jalan personal communication).

Challenges in conducting clinical trials in a palliative setting include defining when the palliative phase of an illness has been reached, recruitment, high attrition, and uncertainty around appropriate assessment tools and outcome measures, contributing to a low overall reporting quality (45). MORECare guidance on evaluating complex interventions at the end of life recommends a mixed methods approach and recruiting patients who are likely to benefit most from the intervention, thus ensuring equipoise (46). In our study, participants were often referred late in the disease trajectory with 15% dying prior to study inclusion and a further 40% dying within four weeks of recruitment.

Lessons learnt to improve recruitment in future studies include **dedicated multidisciplinary meetings** to aid early identification of ESLD, not excluding those with hepatic encephalopathy and timely engagement between community nurses supporting the intervention delivery and research staff at recruiting sites. Additionally, ensuring appropriate funding for research home visits would enable prompt site set up and follow up data collection. Implementation of these strategies more than doubled our recruitment in years two and three (supplementary **fig 4**). We aim to conduct a future definitive study, designed as a non-inferiority trial for peritonitis incidence, with **quality of life** as one of the secondary outcomes. The sample size will be approximately 300, to be recruited from 40 sites nationally. **As in the feasibility study,**

all participants will receive prophylactic antibiotics for the study duration (ciprofloxacin 750 mg weekly).

Our study did have limitations. It was a feasibility RCT with 56% of the participants recruited from a single site; hence, it lacks generalisability and external validity to support a national change in service delivery. Additionally, the incidence of self-limiting cellulitis/leakage was higher in the LTAD group, though with increasing expertise in LTAD insertion, this may reduce. Secondly, primary spontaneous bacterial peritonitis prophylaxis could have potentially resulted in a falsely low peritonitis incidence in the LVP group; however our observed incidence (11%) did not reflect that (3). Thirdly, health economic data were missing from one site (17% of participants) and the small sample resulted in substantial range in costs, hence data need be interpreted with caution. Finally, we recruited only 75% of our target sample size, consistent with an earlier palliative trial in ESLD (47).

In conclusion, the REDUCe study provides preliminary evidence of LTAD acceptability and safety in ESLD, with reduction in health resource utilisation, indicating feasibility to proceed to a definitive study. Trials focussed on improving palliative care in this growing disenfranchised cohort are a priority. The REDUCe study could help inform such future research.

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Rocket Medical (Imperial Way, Watford, Herts WD24 4XX) provided the LTAD free of cost for the trial. Rocket Medical were not involved in the study design, data collection, manuscript preparation, nor will they claim any intellectual property based on this trial.

### **Author contribution**

LMa recruitment, LTAD insertion, data collection; ST, DS, MW, PI, MA, NP, AH recruitment and data collection; HG, MT, PW health economics; DL database set up and data entry; SB statistical analysis; CJE mixed methods and community perspective; SS service user input; LM conceived original idea; SV conceived original idea and funding lead applicant. SV wrote the initial draft with input from LMa, LM, HG, SB, DC; all co-authors contributed to and approved the final manuscript draft. SV is the guarantor of the manuscript.



## Figure Legends

**Fig 1a.** CONSORT flow chart

**Fig 1b.** Total number of ascitic drains before and after randomisation in long-term abdominal drain (LTAD) and large volume paracentesis (LVP) group

**Fig 1c.** Median (IQR) serum bilirubin ( $\mu\text{mol/L}$ ) in the long-term abdominal drain (LTAD) and large volume paracentesis (LVP) group at each visit

**Fig 1d.** Median (IQR) serum albumin (g/L) in the long-term abdominal drain (LTAD) and large volume paracentesis (LVP) group at each visit

**Fig 1e.** Median (IQR) serum creatinine ( $\mu\text{mol/L}$ ) in the long-term abdominal drain (LTAD) and large volume paracentesis (LVP) group at each visit

## References

1. 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> Accessed 14<sup>th</sup> Aug 2019
2. Fleming KM, Aithal GP, Card TR, West J. The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study. *Aliment Pharmacol Ther.* 2010; 32: 1343-50.
3. EASL Practice Guidelines for the management of patients with decompensated cirrhosis. European Association for the Study of the Liver. *J Hepatol.* 2018; 69: 406-460.
4. Guardiola J, Barillas C, Viol X, Fernandez Esparrach, Ginès P, Ventura P, et al. External validation of a prognostic model for predicting survival of cirrhotic patients with refractory ascites. *Am J Gastroenterol.* 2002; 97: 2374–2378.
5. Medici V, Rossaro L, Wegelin JA, Kamboj A, Nakai J, Fisher K, 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.
6. Hudson B, Round J, Georgeson B, Pring A, Forbes K, McCune CA, 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.
7. Fleming ND, Alvarez-Secord A, Von Gruenigen V, Miller MJ, Abernethy AP. 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.
8. 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.
9. Stukan M. Drainage of malignant ascites: patient selection and perspectives. *Cancer Manag Res.* 2017; 9:115-130.
10. 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](http://www.endoflifecareintelligence.org.uk/profiles/CCGs/Place_and_Cause_of_Death/atlas.html). Accessed on 28<sup>th</sup> Oct 2019
11. Kimbell B, Murray SA, Byrne H, Baird A, Hayes PC, MacGilchrist A, 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.
12. Brisebois A, Ismond KP, Carbonneau M, Kowalczewski J, Tandon P. Advance care planning (ACP) for specialists managing cirrhosis: A focus on patient-centered care. *Hepatol.* 2018; 67: 2025-2040
13. Poonja Z, Brisebois A, van Zanten SV, Tandon P, Meeberg G, Karvellas CJ. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. *Clin Gastroenterol Hepatol.* 2014 ;12: 692-8.
14. Patel AA, Walling AM, Ricks-Oddie J, May FP, Saab S, Wenger N. 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.
15. Macken L, Mason L, Evans C, Gage H, Jordan J, Austin M, 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.
16. Harrison P, Hogan P, Floros L, Davies E; Guidance Development Group. Assessment and

management of cirrhosis in people older than 16 years: summary of NICE guidance. *BMJ*. 2016; 354: 2850

17. Terg R, Casciato P, Garbe C, Cartier M, Stieben T, Mendizabal M, 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.

18. Bruns T, Lutz P, Stallmach A, Nischalke HD. Low ascitic fluid protein does not indicate an increased risk for spontaneous bacterial peritonitis in current cohorts. *J Hepatol*. 2015;63: 527-8.

19. Hearn J, Higginson IJ. Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group. *Qual Health Care*. 1999; 8: 219-227.

20. Bausewein C, Le Grice C, Simon ST, Higginson IJ, on behalf of PRISMA. The use of two common palliative outcome measures in clinical care and research: A systematic review of POS and STAS. *Palliat Med*. 2011; 25: 304-313.

21. Murtagh FE, Ramsenthaler C, Firth A, Groeneveld EI, Lovell N, Simon ST, et al. A brief, patient- and proxy-reported outcome measure in advanced illness: Validity, reliability and responsiveness of the Integrated Palliative care Outcome Scale (IPOS). *Palliat Med*. 2019; 33: 1045-1057.

22. Kanwal F, Spiegel BM, Hays RD, Durazo F, Han SB, Saab S, et al. Prospective validation of the short form liver disease quality of life instrument. *Aliment Pharmacol Ther*. 2008; 28: 1088-1101.

23. EuroQoL group. EQ-5D <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/>  
Accessed 14<sup>th</sup> March 2020

24. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the Impaired Elderly: Correlates of Feelings of Burden. *Gerontologist*. 1980; 20: 649-655.

25. Higginson IJ, Gao W, Jackson D, Murray J, Harding R. Short-form Zarit Caregiver Burden Interviews were valid in advanced conditions. *J Clin Epidemiol*. 2010; 63: 535-542.

26. 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.

27. Curtis L and Burns A. Unit costs of health and social care 2013. Accessed at [www.pssru.ac.uk](http://www.pssru.ac.uk). Accessed April 2019.

28. NHS Improvement. 2017/18 National Schedule of Reference Costs. <https://improvement.nhs.uk/resources/reference-costs/#rc1718>  
Accessed 14<sup>th</sup> March 2020

29. Julious SA: Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005; 4: 287-291.

30. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. *Cancer*. 2013; 119: 1098-105

31. Guest G, MacQueen KM, Namey EE. *Applied Thematic Analysis* 2012 Sage: Thousand Oaks

32. NVivo qualitative data analysis software; QSR International Pty Ltd. Version 12, 2018)

33. Dixon-Woods M, Cavers D, Agarwal S, Annandale E, Arthur A, Harvey J et al. Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups. *BMC Med Res Methodol*. 2006; 6: 35

34. Macken L, Hashim A, Mason L, Verma S. Permanent indwelling peritoneal catheters for palliation of refractory ascites in end stage liver disease: A systematic review. *Liver Int.* 2019; 39: 1594-1607.
35. 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.
36. Kelly EM, James PD, Murthy S, Antonova L, Wong F, Shaw-Stiffel T, et al. Health Care Utilization and Costs for Patients With End-Stage Liver Disease Are Significantly Higher at the End of Life Compared to Those of Other Decedents. *Clin Gastroenterol Hepatol.* 2019; 17: 2339-2346.
37. Higginson IJ, Evans CJ, Grande G, Preston N, Morgan M, McCrone P, 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
38. Wichmann AB, Adang EM, Stalmeier PF, Kristanti S, Van den Block L, Vernooij-Dassen MJ, 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
39. Reinglas J, Amjadi K, Petreich B, Momoli F, Shaw-Stiffel T. The palliative management of refractory cirrhotic ascites using the PleurX catheter. *Can J Gastroenterol Hepatol.* 2016; 2016: 4680543.
40. Peng JK, Hepgul N, Higginson IJ, Gao W. 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.
41. Macdonald S, Jepsen P, Alrubaiy L, Watson H, Vilstrup H, Jalan R. Quality of life measures predict mortality in patients with cirrhosis and severe ascites. *Aliment Pharmacol Ther.* 2019; 49: 321-330.
42. Bajaj JS, Wade JB, Gibson DP, Heuman DM, Thacker LR, Sterling RK, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. *Am J Gastroenterol.* 2011; 106: 1646-53.
43. Seibl-Leven M, von Reeken C, Goldbrunner R, Grau S, Ruge MI, Galldiks N, et al. Clinical routine assessment of palliative care symptoms and concerns and caregiver burden in glioblastoma patients: an explorative field study. *J Neurooncol.* 2018; 138: 321-333.
44. McIlpatrick S, Doherty LC, Murphy M, Dixon L, Donnelly P, McDonald K, et al. 'The importance of planning for the future': Burden and unmet needs of caregivers' in advanced heart failure: A mixed methods study. *Palliat Med.* 2018; 32: 881-890.
45. Bouça-Machado R, Rosário M, Alarcão J, Correia-Guedes L, Abreu D, Ferreira JJ. Clinical trials in palliative care: a systematic review of their methodological characteristics and of the quality of their reporting. *BMC Palliat Care.* 2017; 16: 10.
46. Higginson IJ, Evans CJ, Grande G, Preston N, Morgan M, McCrone P, MORECare et al; 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: 111.
47. Shinall MC Jr, Karlekar M, Martin S, Gatto CL, Misra S, Chung CY, 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.

Table 1. Baseline demographic and clinical data in the long-term abdominal drain (LTAD) and large volume paracentesis (LVP)

	LTAD (n=17)			LVP (n=19)		
	n	mean/med (%)	SD/IQR	n	mean/med (%)	SD/IQR
Age (years)	17	66.3	10.4	19	67.9	12
Female		4/17 (24%)			5/19 (26%)	
White British		16/17 (94%)			19/19 (100%)	
BMI (kg/m <sup>2</sup> )	16	28.4	22.2, 32.5	15	24.6	22.1, 28.9
Serious comorbidity		11/17 (65%)			14/19 (74%)	
Prescribed Furosemide		5/17 (29%)			6/19 (32%)	
Prescribed Spironolactone		12/17 (71%)			11/19 (58%)	
Ongoing alcohol/drug use		5/17 (29%)			2/19 (11%)	
Child Pugh A		0/17 (0%)			1/18 (6%)	
Child Pugh B		14/17 (82%)			13/18 (72%)	
Child Pugh C		3/17 (18%)			4/18 (22%)	
MELD Score	17	13.8	4.5	18	16.3	7.3
UKELD Score	17	54	4.5	18	54.1	6.2
Bilirubin (µmol/L)	17	22	15, 37	18	23	17, 48
Bilirubin > 33µmol/L	17	6/17 (35%)		18	7/18 (39%)	
Albumin (g/L)	17	33	32, 36	18	31	27, 33
Albumin < 35 g/L	12	12/17 (71%)		16	16/18 (89%)	
Serum creatinine (µmol/L)	17	109	79, 141	18	113.5	89, 135
Serum creatinine > upper limit of normal.	17	9/17 (53%)		18	10/18 (56%)	
Sodium (mmol/L)	17	133	130, 138	18	133.5	129, 137
Sodium < 135 (mmol/L)		11/17 (65%)			11/18 (61%)	
INR	17	1.3	1.2, 1.5	18	1.3	1.2, 1.4
Platelet count (10 <sup>9</sup> /L)	17	167	103, 193	18	124	106, 151
Prior variceal bleed		2/16 (13%)			4/18 (22%)	
Prior spontaneous bacterial peritonitis		1/15 (7%)			2/15 (13%)	
Prior hepatic encephalopathy		7/16 (44%)			2/18 (11%)	
Hepatocellular cancer		3/16 (19%)			3/18 (17%)	
Aetiology:						
alcohol		12/17 (71%)			9/19 (47%)	
Aetiology: viral		1/17 (6%)			1/19 (5%)	
Aetiology: non alcoholic fatty liver disease		7/17 (41%)			7/19 (37%)	
Aetiology: other *		3/17 (18%)			6/18 (33%)	
Follow up (days)**		82 (52-90)			85 (64-92)	

Some had more than one aetiology for ESLD

Aetiology other LTAD: cryptogenic n =1, haemochromatosis n=1, nodular regenerating hyperplasia + alcohol n=1

Aetiology other LVP: cryptogenic n= 2, alpha 1 antitrypsin deficiency n= 2, Primary biliary cholangitis n= 1, nodular regenerating hyperplasia + alcohol n= 1

\*\*Due to delayed research visits (participant on holiday, non-availability of research staff), three participants, one in LTAD group (119 days) and two in LVP group (109 and 128 days) were in the study for longer than stipulated in the protocol

Table 2. Summary statistics for EQ-5D-5L, Integrated Patient Outcome Scale (IPOS) (Patient) and Zarit Burden Interview (ZBI-12) questionnaires in the long-term abdominal drain (LTAD) and large volume paracentesis (LVP) group by time point

	Long-term abdominal drain (LTAD) (n=17)					Large volume paracentesis LVP (n=19)					Mean difference	95% CI
	n/N	mean	SD	Median	IQR	n/N	Mean	SD	Median	IQR		
<b>EQ-5D-5L</b>												
<i>EQ-5D-5L Index</i>												
Baseline	17/17	0.65	0.30	0.75	0.40	18/19	0.52	0.28	0.56	0.38		
Week 4	10/13	0.75	0.12	0.73	0.18	14/15	0.53	0.24	0.53	0.22		
Week 8	10/13	0.66	0.15	0.66	0.09	13/14	0.54	0.25	0.55	0.36		
Week 12	8/9	0.59	0.15	0.65	0.20	12/12	0.57	0.24	0.54	0.31	0.02	(-0.18, 0.22)
<i>EQ-5D-5L VAS</i>												
Baseline	17/17	57.6	26.7	55.0	30.0	18/19	54.1	23.4	52.5	45.0		
Week 4	10/13	51.5	32.7	50.0	55.0	14/15	56.9	22.4	57.5	38.0		
Week 8	10/13	67.5	20.3	67.5	30.0	13/14	55.8	18.8	50.0	35.0		
Week 12	8/9	66.3	28.1	67.5	45.0	12/12	55.7	20.8	52.5	23.5	10.6	(-9.2, 30.4)
<b>Zarit Carer</b>												
Baseline	9	17.9	9.4	14.0	6.0	8	14.6	8.4	17.0	12.5		
Week 4	5	20.8	8.6	18.0	8.0	6	14.8	8.1	13.5	9.0		
Week 8	5	20.6	10.5	22.0	17.0	3	20.0	11.1	18.0	22.0		
Week 12	3	18.0	11.5	17.0	23.0	5	20.0	3.7	19.0	3.0	-2.0	(-15.1, 11.1)
<b>IPOS-Physical</b>												
Baseline	17/17	10.6	7.2	11	12	18/19	15.6	5.8	16	10		
Week 2	16/17	8.9	5.2	8	7.5	18/18	14.1	6	14	9		
Week 4	11/13	10.7	6.1	11	9	14/15	14.1	6.1	13.5	7		
Week 5	11/13	11.4	5.5	11	5	12/15	11.7	5.4	10	7.5		
Week 6	10/13	11.9	4.1	12.5	5	13/14	13.8	5.8	14	7		
Week 10	10/12	10.3	5.2	9.5	4	12/13	12.2	7.2	12.5	12.5		
Week 12	8/9	14	6.4	14.5	9	12/12	15.3	7.6	14	14	-1.3	(-8.1, 5.6)
Week 14												
<b>IPOS-Emotional</b>												
Baseline	16/17	6.9	3.2	7.5	3	18/19	6.6	3.4	6	5		
Week 2	16/17	4.9	3.9	3.5	5	18/18	5.8	3.5	5.5	5		
Week 4	11/13	4.5	3.8	5	9	14/15	4.9	2.9	4.5	3		
Week 5	12/13	6.8	4.8	6.5	5.5	12/15	4.5	2.7	3.5	2.5		
Week 6	11/13	6.5	4.5	6	7	13/14	5.3	3.5	4	4		
Week 10	10/12	6.2	4.5	5.5	8	12/13	4.4	3.1	5	5.5		
Week 12	8/9	6.5	5.1	7.5	8.5	12/12	4.5	2	4	3	1.6	(-1.4, 5.4)
<b>IPOS-Communication</b>												
Baseline	17/17	2.4	2.9	1	5	18/19	2.4	2.6	2	4		
Week 2	16/17	2	2.2	1.5	4	17/18	2.8	2.8	3	4		

Week 4	11/13	1.7	2.7	1	3	14/15	2.1	2.4	1.5	4	
Week 5	11/13	2.9	2.7	2	3	12/15	1.9	2.2	2	1.5	
Week 6	11/13	2.9	2.2	3	3	13/14	2.2	2.6	1	4	
Week 10	10/12	1.8	2.1	1	2	12/13	2.3	2.3	2	3	
Week 12	8/9	2.4	2.4	2.5	3.5	12/12	1.8	2.1	1	2	0.6 (-1.5, 2.7)
<b>IPOS-Patient (Total)</b>											
Baseline	16/17	19.2	8.9	20.5	15.5	18/19	24.5	9.8	22.5	15	
Week 2	16/17	15.9	8.4	14	10.5	17/18	22.6	10.1	21	17	
Week 4	11/13	17	10.4	15	13	14/15	21	9.7	20	8	
Week 5	10/13	21.2	10.2	17	7	12/15	18.1	8.5	14.5	12.5	
Week 6	10/13	21.3	7.8	21	6	13/14	21.3	10.1	23	14	
Week 10	10/12	18.3	8.2	18.5	12	12/13	18.8	10.9	19	18	
Week 12	8/9	22.9	10.8	23	16.5	12/12	21.5	8.9	19.5	13	-2.7 (-8.6, 3.1)

n/N number of patients completing questionnaires /number alive at each visit.

Increasing EQ-5D-5L scores indicate better health outcome

Increasing IPOS and ZBI-12 scores indicate higher symptom and carer burden respectively

Uptake of ZBI-12 could not be calculated, as number of caregivers at each assessment visit was not consistently collected

Table 3. Summary statistics for the Short Form Liver Disease Quality of Life (SFLDQoL) questionnaire in the long-term abdominal drain (LTAD) and large volume paracentesis (LVP) group by time point

	LTAD (n=17)					LVP (n=19)					Mean difference	95% CI
	n/N	Mean	SD	Median	IQR	n/N	Mean	SD	Median	IQR		
<b>Symptoms</b>												
Baseline	17/17	64.5	19.8	70.0	26.7	18/19	49.8	23.1	45.0	36.7		
Week 4	9/13	65.6	30.1	83.3	36.7	14/15	52.1	20.1	55.0	23.3		
Week 8	10/13	58.6	21.4	56.7	26.7	13/14	48.7	18.9	50.0	20.0		
Week 12	8/9	54.6	21.2	45.0	36.7	10/12	53.3	20.7	58.3	36.7	1.3	(-19.7, 22.2)
<b>Effect</b>												
Baseline	15/17	58.9	23.5	50.0	41.7	17/19	50.5	24.2	50.0	33.3		
Week 4	9/13	57.9	25.7	50.0	41.7	14/15	60.4	24.3	64.6	16.7		
Week 8	9/13	57.4	10.6	58.3	16.7	12/14	60.8	22.9	54.2	39.6		
Week 12	8/9	61.5	27.8	62.5	45.8	10/12	60.4	26.7	54.2	54.2	1.0	(-26.3, 28.4)
<b>Memory</b>												
Baseline	17/17	74.6	23.3	75.0	37.5	18/19	67.0	27.9	68.8	56.3		
Week 4	9/13	81.3	26.0	100.0	31.3	14/15	68.9	25.1	75.0	43.8		
Week 8	10/13	71.3	24.0	71.9	50.0	13/14	65.4	26.3	68.8	37.5		
Week 12	8/9	64.8	28.7	68.8	46.9	10/12	74.4	19.9	81.3	37.5	-9.5	(-33.8, 14.7)
<b>Distress</b>												
Baseline	17/17	47.1	39.7	37.5	87.5	18/19	37.5	30.0	31.3	50.0		
Week 4	9/13	58.3	41.9	62.5	75.0	14/15	50.9	28.8	50.0	37.5		
Week 8	10/13	58.8	31.2	56.3	25.0	12/14	49.0	29.4	43.8	31.3		
Week 12	8/9	35.9	39.8	25.0	68.8	10/12	58.8	32.8	56.3	75.0	-22.8	(-59.0, 13.4)
<b>Sleep</b>												
Baseline	17/17	57.4	22.2	55.0	25.0	18/19	36.0	21.9	35.0	40.0		
Week 4	9/13	52.8	12.5	55.0	15.0	14/15	46.8	19.7	50.0	30.0		
Week 8	10/13	55.0	18.1	55.0	30.0	12/14	33.8	16.9	30.0	20.0		
Week 12	8/9	45.0	14.1	42.5	22.5	10/12	41.5	15.1	40.0	20.0	3.5	(-11.3, 18.3)
<b>Loneliness</b>												
Baseline	17/17	67.1	19.3	75.0	25.0	18/19	72.8	31.5	85.0	45.0		
Week 4	9/13	70.0	26.3	80.0	35.0	14/15	73.6	26.3	80.0	35.0		
Week 8	10/13	65.5	18.3	65.0	30.0	12/14	72.5	30.9	85.0	55.0		
Week 12	8/9	51.9	30.1	57.5	57.5	10/12	89.0	15.6	95.0	15.0	-37.1	(- 60.4, - 13.9)
<b>Hopelessness</b>												
Baseline	17/17	50.0	26.5	50.0	41.7	18/19	43.1	24.6	50.0	33.3		
Week 4	9/13	55.6	26.7	58.3	33.3	14/15	48.2	20.2	50.0	16.7		
Week 8	9/13	45.4	27.7	50.0	33.3	12/14	47.9	24.7	50.0	45.8		
Week 12	8/9	29.2	27.1	20.8	41.7	10/12	48.3	17.9	50.0	33.3	-19.2	(- 41.7, 3.4)
<b>Stigma</b>												
Baseline	17/17	66.4	28.7	62.5	50.0	18/19	61.8	24.2	62.5	37.5		
Week 4	9/13	54.9	25.5	56.3	31.3	14/15	68.3	24.1	75.0	37.5		
Week 8	9/13	63.9	30.3	68.8	50.0	12/14	70.8	25.2	78.1	46.9		
Week 12	8/9	60.9	28.1	59.4	37.5	10/12	64.4	24.3	62.5	43.8	-3.4	(- 29.6, 22.7)



**Sex**

Baseline	1/17	n/a	n/a	n/a	n/a	1/19	n/a	n/a	n/a	n/a	
Week 4	3/13	3.8	0.7	4.0	1.3	3/15	2.6	1.6	2.0	3.0	
Week 8	2/13	4.4	0.1	4.4	0.2	3/14	2.4	1.7	2.0	3.3	
Week 12	1/9	n/a	n/a	n/a	n/a	1/12	n/a	n/a	n/a	n/a	n/a

n/N number of patients completing questionnaires/ number alive at each visit  
 Increasing SFLDQoL scores indicate better QoL

**Table 4. Cost per fortnight (British pounds 2018) in the long-term abdominal drain (LTAD) and large volume paracentesis (LVP) group**

Service	Community / LTAD n=15					Hospital / LVP n=15				
	Mean	SD	Median	Range	IQR	Mean	SD	Median	Range	IQR
District nurse	1.8	6.8	0	0, 26	0,0	0.70	2.7	0	0, 11	0, 0
Community/ specialist nurse	160.1	79.1	168	0, 252	109, 224	24.3	57.5	0	0, 218	0, 31
Palliative care nurse	36.1	97.5	6	0, 385	0, 26	16	33.7	0	0, 131	0, 22
GP (home visits)	12.8	14.2	11	0, 37	0, 21	6.3	13	0	0, 37	0, 11
Allied health professional	9	15.2	0	0, 53	0, 18	34	127.8	0	0, 496	0, 0
Other health professional	5.3	18	0	0, 70	0, 0	25.2	96.3	0	0, 373	0, 0
<b>All community health</b>	<b>225.2</b>	<b>149.1</b>	<b>232</b>	<b>24, 660</b>	<b>109, 266</b>	<b>106.5</b>	<b>245.8</b>	<b>11</b>	<b>0, 921</b>	<b>0, 85</b>
<b>Social care worker</b>	<b>76.6</b>	<b>123.1</b>	<b>6</b>	<b>0, 376</b>	<b>0, 122</b>	<b>22.1</b>	<b>66.4</b>	<b>0</b>	<b>0, 251</b>	<b>0, 0</b>
Day case drainage	74.6	174.3	0	0, 557	0, 0	663.1	316.4	704	0, 1057	463, 986
Inpatient drainage	0	0	0	0, 0	0, 0	20.2	78.4	0	0, 303	0, 0
Admitted to hospital for non ascites reasons and had drainage	53.5	114.2	0	0, 333	0, 0	40.4	88.8	0	0, 291	0, 0
<b>Hospital total</b>	<b>128.2</b>	<b>227.8</b>	<b>0</b>	<b>0, 704</b>	<b>0, 188</b>	<b>723.7</b>	<b>289.2</b>	<b>704</b>	<b>173,1311</b>	<b>517, 986</b>
Informal care	759.9	984.5	91	0, 2433	0, 1370	685.1	1145.5	15	0, 3402	0, 1099
<b>Overall cost with informal care</b>	<b>1189.8</b>	<b>937.9</b>	<b>909</b>	<b>174, 2877</b>	<b>567, 1631</b>	<b>1537.4</b>	<b>1193.8</b>	<b>1057</b>	<b>450, 4462</b>	<b>844, 1701</b>
<b>Overall cost (excluding informal care)</b>	<b>429.9</b>	<b>257.7</b>	<b>329</b>	<b>109, 957</b>	<b>253, 580</b>	<b>852.3</b>	<b>257.0</b>	<b>843</b>	<b>435, 1311</b>	<b>603, 1060</b>

Unit costs from Curtis and Burns 2018 (27): District nurse, band 6, £37 per half hour patient related work, page 123; Community / specialist / palliative nurse, band 7, £43.50 per half hour patient related work, page 123; GP home visit £74 per visit, assumes twice the cost of a consultation in the GP surgery/ office @£37 for 9.22 minutes, page 127; Allied Health Professionals (AHP) (physiotherapist, occupational therapist, speech and language therapist, dietician), average of 4 professions, £35 per half hour, page 18; other health professionals, assumed as AHPs; social care worker, £13.50 per half hours visit, page 143, home care worker; informal care – as social care worker, £27 per hour. Hospital ascites drainage, from NHS Improvement Reference costs 2018 (28): Day case £915.60, currency code YF04A (DC), also used when drainage was performed during a hospital stay for a non-ascites related reason; in hospital single drainage £1300.47, currency code YF04A (NES). A&E, Outpatient use and tests not shown – no significant difference between groups.

Table 5. Adverse and serious adverse events in the long-term abdominal drain (LTAD) and large volume paracentesis (LVP) group

Long-term abdominal drain group (LTAD)		Large volume paracentesis group (LVP)	
Adverse event	Serious adverse event	Adverse event	Serious adverse event
Abdominal pain (5)	Fall (1)	Abdominal pain (4)	Abdominal pain (1)
Nausea/Vomiting/diarrhoea/constipation (7)	Hospital acquired pneumonia (1)	Nausea/Vomiting/diarrhoea/constipation (8)	Hospital admission after LVP (1)
Urinary tract infection (Klebsiella and E.coli) (2)	Hepatic hydrothorax (1)	Urinary tract infection (1)	Leg fracture (1)
Sacral/vaginal/penis pain/skin laceration (6)	SBP (1)	Sacral pain/skin laceration (9)	Hospital acquired pneumonia (1)
Lower Respiratory tract/chest infection (3)	Worsening renal function (2)	Lower Respiratory tract infection (1)	Hepatic hydrothorax (1)
Falls (6)	Hyperkalaemia (1)	Fall (4)	SBP (2)
Hoarse voice (1)	Worsening HE (1)	Mouth ulcers (2)	Worsening renal function (1)
Oesophageal candida (1)	Acute gastroenteritis (1)	Epistaxis (2)	Hyperkalaemia (1)
Pruritus (1)	Umbilical hernia leakage (1)	Pruritus (1)	Variceal bleed (2)
Hypotension 1	Stroke (1)	Increased ferritin (1)	Death (5)
Anaemia/GI bleed (2)	Death (7)	Cough/reflux (3)	
Hyperkalaemia (3)		Positive blood culture (S lutetiensis) (1)	
Worsening renal function (4)		Worsening renal function (6)	
Cellulitis /leakage at drain site (7)		Bleeding/leakage after LVP (2)	
HE (3)		Hyponatremia/hypokalaemia (2)	
Worsening oedema/ breathlessness (2)		Hypotension (1)	
Drain accidentally pulled out (1)		Increasing bilirubin (1)	
		Fever (1)	
		Hospice admission (1)	
		Low energy/hypoglycaemia (2)	
		Umbilical hernia blister (1)	
		Anaemia/GI bleed (4)	

HE hepatic encephalopathy, GI Gastrointestinal; SBP Spontaneous bacterial peritonitis

