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Randomised clinical trial: palliative long-term abdominal drains vs large-volume paracentesis in refractory ascites due to cirrhosis

Lucia Macken[1] | Stephen Bremner[1] | Heather Gage[2] | Morro Touray[2] | Peter Williams[2] | David Crook[1] | Louise Mason[1*] | Debbie Lambert[1] | Catherine J. Evans[1,3] | Max Cooper[1] | Jean Timeyin[1] | Shani Steer[1] | Mark Austin[1] | Nick Parnell[1] | Sam J. Thomson[4] | David Sheridan[5] | Mark Wright[6] | Peter Isaacs[7] | Ahmed Hashim[1] | Sumita Verma[1]

[1]Brighton, UK
[2]Guildford, UK
[3]London, UK
[4]Worthing, UK
[5]Plymouth, UK
[6]Southampton, UK
[7]Blackpool, UK

Correspondence
Sumita Verma, Brighton and Sussex Medical School, Main Teaching Building, Room 2.17, North South Road, Falmer, Brighton BN1 9PX, UK.
Email: s.verma@bsms.ac.uk

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Summary

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 nonblinded 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, the 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 group vs large-volume paracentesis group) were 0 (0-1) vs 4 (3-7); week 12 serum albumin (g/L) and serum creatinine (μmol/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 group vs 11% (2/19) in the large-volume

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Authors' complete affiliations are listed in Appendix section.

*Affiliation during conduct of the study.

paracentesis group; peritonitis incidence was 6% (1/17) vs 11% (2/19) respectively. Questionnaires/interview uptake/completion were ≥80%; interviews indicated 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.

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

1 | 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 6 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 of patients with refractory ascites are also not candidates for transjugular 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 L) of ascitic fluid at home, up to three times a week.[7-9] The National Institute for Health and Care Excellence technology guidance on 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 (**RE**peated **D**rainage in **U**ntreatable ascites (REDUCe) study). Our overarching aim was to improve palliative management of refractory ascites in ESLD.

2 | PATIENTS AND METHODS

The study design for this 3-year (September 2015-September 2018) feasibility parallel RCT comparing LTAD vs LVP has been previously described.[15] The study was conducted across five hospitals 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 nonresponse to sodium restriction, diuretics and or development of diuretic-induced complications that precluded the 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 ≥18 years, Child Pugh Score ≥9 (unless felt to be palliative despite lower CPS) and capacity to give informed consent. Study exclusion criteria were loculated or chylous ascites, the presence of >grade 1 hepatic encephalopathy, evidence of active infection including spontaneous bacterial peritonitis during screening (Figure S1) and eligibility for liver transplantation. Screening for infection included urine dipstick and culture, blood culture and ascitic tap for polymorphonuclear count and culture (Figure S1). 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.

2.1 | 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. After two to three days, if willing, a 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 (eg 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).

2.2 | Randomisation

Patients fulfilling inclusion criteria were randomised (nonblinded) 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.

2.2.1 | Interventions group 1: LTAD

Rocket® (Rocket Medical) 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 L of ascitic fluid at each visit. No human albumin solution was administered.

2.2.2 | 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 6 hours for ascites drainage and intravenous human albumin solution was administered (8-10 g/L of ascitic fluid removed).[3]

2.3 | 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 the 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 15 g/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 antibiotics to all LTAD and LVP participants (ciprofloxacin 500 mg once a day or equivalent) during the study duration.

Each participant was followed up for up to 12 weeks (Figure S1). Figure S2 shows participant timeline.

2.4 | 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]

2.5 | 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] (Figure S1). 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.

2.6 | 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 or serious adverse events. Reasons for transplant ineligibility were not formally recorded, although we would endeavour 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/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.

2.7 | 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 4 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 4 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 4 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). Figure S1 shows the assessment schedule.

3 | 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's study numbers. Although 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]

3.1 | 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 ± 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.

3.2 | 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 ± 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.

4 | 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 vs LVP participants. We aimed to interview 20 patients at diverse stages across the intervention, and 8 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]

5 | RESULTS

5.1 | Clinical outcomes

The study commenced in September 2015, recruitment running from November 2015 to June 2018 with 12 weeks of follow-up. During the study period, of the 78 participants approached, 19 did not fulfil eligibility criteria (CONSORT Figure 1A). Two were

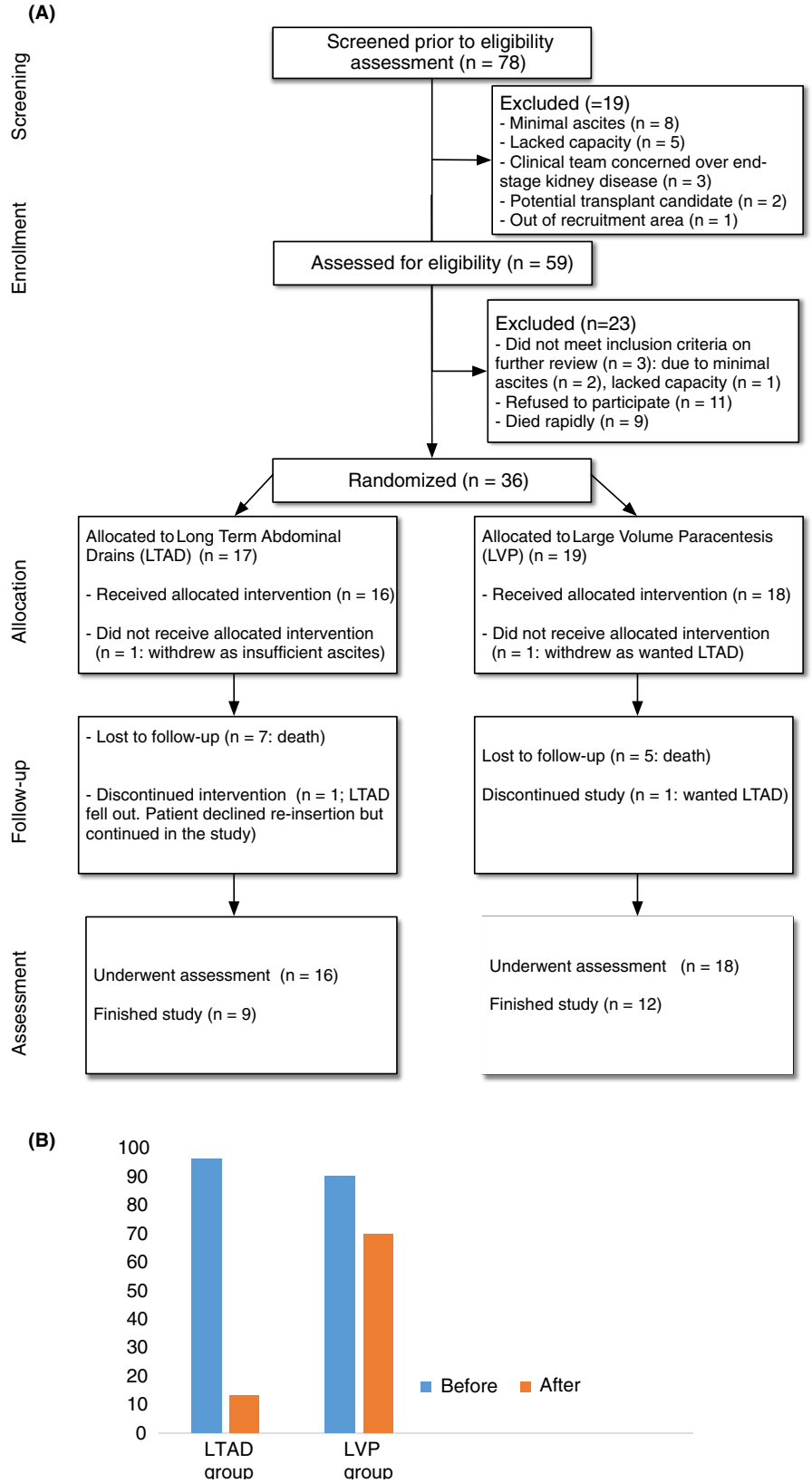

FIGURE 1 (A) CONSORT flow chart; (B) Total number of ascitic drains before and after randomisation in the long-term abdominal drain (LTAD) and large-volume paracentesis (LVP) groups; (C) Median (IQR) serum bilirubin (μmol/L) in the long-term abdominal drain (LTAD) and large-volume paracentesis (LVP) groups at each visit; (D) Median (IQR) serum albumin (g/L) in the long-term abdominal drain (LTAD) and large-volume paracentesis (LVP) groups at each visit; (E) Median (IQR) serum creatinine (μmol/L) in the long-term abdominal drain (LTAD) and large-volume paracentesis (LVP) groups at each visit . For figs 1C, 1D and 1E, number of patients with available data at each of the seven visits: LTAD 17, 17, 12, 13, 12, 12, 9; LVP 18, 18, 14, 15, 13, 11, 12.

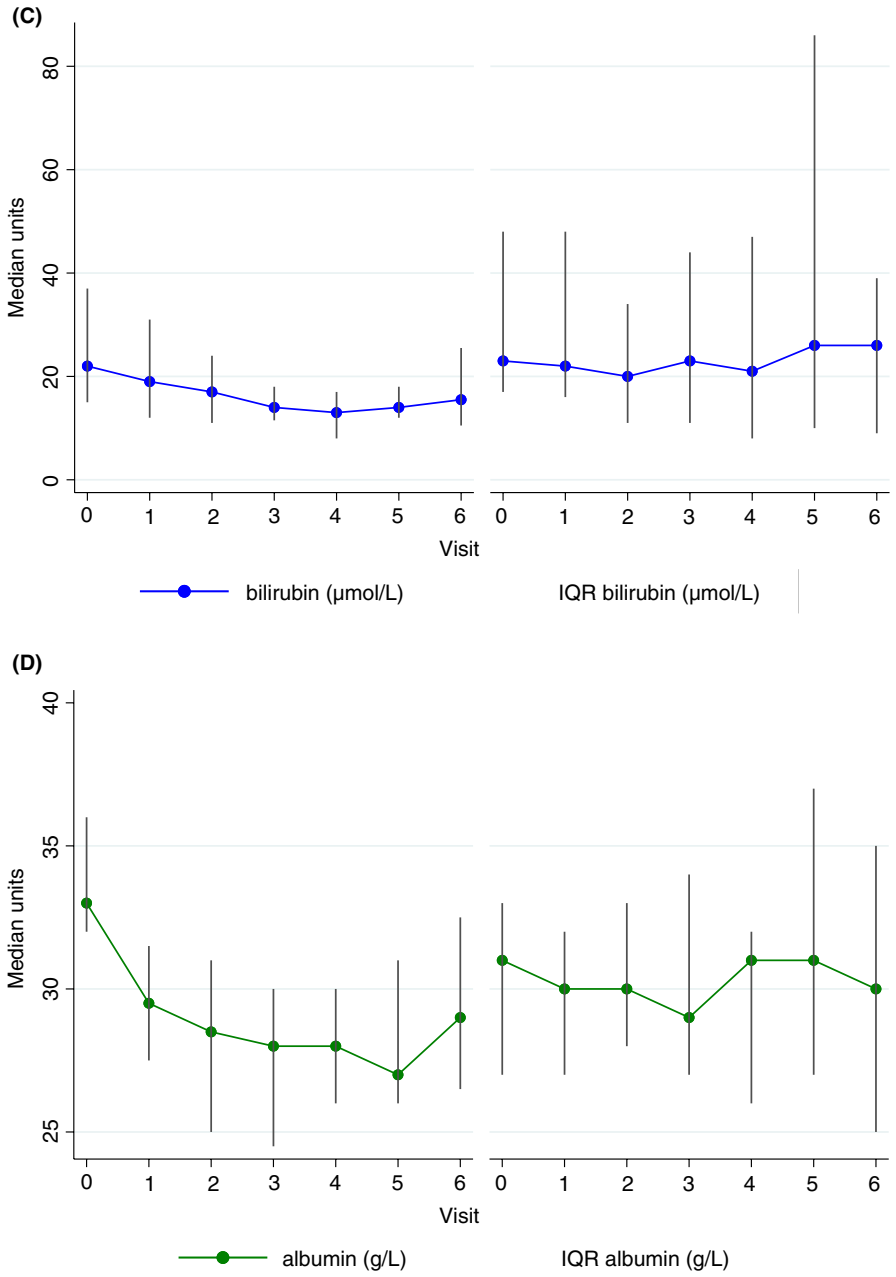

FIGURE 1 Continued

initially regarded to be transplant ineligible at local multidisciplinary meetings but upon further review were deemed to be suitable for transplant assessment (Figure 1A). Of the 59 eligible, we randomised 36 (61%), that is, 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 11 who declined to participate (Figure 1A), 5 gave no reasons, 3 were not keen to be involved in research, 1 only wanted LTAD, 1 felt too unwell and 1 was unable to accept a limited life expectancy diagnosis. Nine out of 10 (90%) and 8 out of 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 accidently 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

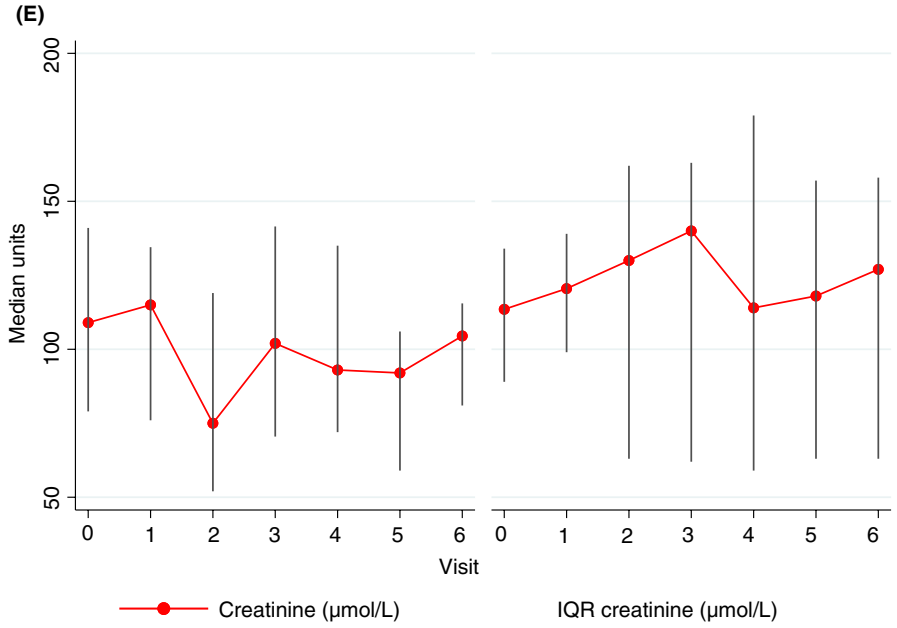

FIGURE 1 Continued

hepatic encephalopathy (n = 9, 26%), Child Pugh C disease (n = 7, 20%), hepatocellular cancer (n = 6, 18%) and serum creatinine >1.5 ULN (n = 6, 17%).

6 | 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 the 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 L (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. Figure 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 (Figure 1B).

7 | BIOCHEMICAL DATA

Data were available in ≥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) in the LTAD vs LVP groups 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 (μmol/L) (median, IQR) in the LTAD vs LVP groups were 109 (79-141) vs 113.5 (89-134) and 104.5 (81-115.5) vs 127 (63-158) respectively. Figure 1C-E show the median (IQR) serum bilirubin (μmol/L), albumin (g/L) and serum creatinine (μmol/L) at each visit in both groups. Additional laboratory 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 Figure S3A-D respectively.

7.1 | 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) (7 in LTAD group and 5 in LVP group). Five out of the 12 deaths (42%) occurred within the first 4 weeks, three in LTAD and two in LVP group. Overall, 11/12 (92%) of the deaths were liver related. Of the 12 deaths, 8 (67%), 95% CI (35-90), occurred outside of hospital (4 in each group). Median survival (days) in those who died in the LTAD vs LVP groups 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

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

	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^2)	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 >33 μmol/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 (10^9/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: nonalcoholic fatty liver disease		7/17 (41%)			7/19 (37%)	
Aetiology: other[a]		3/17 (18%)			6/18 (33%)	
Follow-up (days)[b]		82 (52-90)			85 (64-92)	

Note: Some had more than one aetiology for ESLD.

[a]Aetiology other LTAD group: cryptogenic n = 1, haemochromatosis n = 1, nodular regenerating hyperplasia + alcohol n = 1; Aetiology other LVP group: cryptogenic n = 2, alpha 1 antitrypsin deficiency n = 2, Primary biliary cholangitis n = 1, nodular regenerating hyperplasia + alcohol n = 1.

[b]Due to delayed research visits (participant on holiday, nonavailability 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 that than stipulated in the protocol

groups successfully completed the study. At the end of the study, all surviving LTAD participants elected to retain the drains.

7.2 | 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%, and 86%, 85% and 95% respectively. IPOS (patient) uptake at baseline and weeks 2, 4, 6, 8, 10 and 12 was 97%, 94%, 89, 79, 85, 88 and 95% respectively. Almost all questions were successfully completed at each visit (Table 2). 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. The median physical, emotional, communication and total IPOS scores remained consistent throughout the study period in both 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 (ie 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, and weeks 4, 8, and 12 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, the 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 although reduced in the LTAD group (ie worsening quality of life).

8 | 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 Tables S1 and Table 4 respectively. Unit costs used are listed in Table 4 footnote. Community nurse usage and costs were higher in the LTAD vs LVP groups (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 the LTAD (8 day cases) and 69 in LVP (64 day cases) groups. Of the 10 inpatient drainages, 9 were during a non-ascites-related admission. The overall hospital costs were higher for the LVP vs LTAD groups (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).

9 | ADVERSE 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 groups 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 groups respectively, difference −5%, 95% CI (−24, 14). There were no LTAD-related serious adverse events, none being removed after insertion due to complications.

10 | QUALITATIVE OUTCOMES

Of the 21 patients approached, 19 (90%) were willing to participate of whom 5 died rapidly. Therefore, 14 patients (6 allocated LTAD and 8 LVP) and 8 nurses (6 community and 2 hospital) were interviewed; all the 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.

11 | DISCUSSION

The REDUCe study demonstrates the feasibility to proceed to a full trial with no LTAD-related safety concerns, acceptability of

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) groups by time point

	Long-term abdominal drain (LTAD) (n = 17)					Large-volume paracentesis LVP (n = 19)						
	n/N	Mean	SD	Median	IQR	n/N	Mean	SD	Median	IQR	Mean difference	95% CI
EQ-5D-5L												
EQ-5D-5L Index												
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 to 0.22)
EQ-5D-5L VAS												
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 to 30.4)
Zarit Carer												
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 to 11.1)
IPOS-Physical												
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 to 5.6)
Week 14												
IPOS-Emotional												
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 to 5.4)
IPOS-Communication												
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 to 2.7)
IPOS-patient (total)												
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		

(Continues)

TABLE 2 (Continued)

	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		
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 to 3.1)

Note: n/N, number of patients completing questionnaires/number alive at each visit. Increasing EQ-5D-5L scores indicate better health outcome. Increasing IPOS and ZB1-12 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.

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 ≥80%, those in the LTAD group spent ≤50% ascites-related study time in hospital vs the 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 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 were lower for LTAD vs LVP groups. 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 ($P < 0.001$), compared to those without liver disease.[36] Since collection of EQ-5D-5L data were feasible, quality adjusted life years could be calculated in a larger study. The 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 the use of quality adjusted life years should continue.[37,38]

Results from a recent national survey among Hepatologists/Gastroenterologists, indicate that although almost all were willing to consider LTAD in ESLD, the 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, although 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 nonhepatic 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.[37] 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 4 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

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) groups by time point

	LTAD (n = 17)					LVP (n = 19)						
	n/N	Mean	SD	Median	IQR	n/N	Mean	SD	Median	IQR	Mean difference	95% CI
Symptoms												
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 to 22.2)
Effect												
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 to 28.4)
Memory												
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 to 14.7)
Distress												
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 to 13.4)
Sleep												
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 to 18.3)
Loneliness												
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 to −13.9)
Hopelessness												
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 to 3.4)
Stigma												
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 to 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/a

Note: 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) groups

	Community/ LTAD n = 15					Hospital/ LVP n = 15				
Service	**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
All community health	225.2	149.1	232	24-660	109-266	106.5	245.8	11	0-921	0-85
Social care worker	76.6	123.1	6	0-376	0-122	22.1	66.4	0	0-251	0-0
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
Hospital total	128.2	227.8	0	0-704	0-188	723.7	289.2	704	173-1311	517-986
Informal care	759.9	984.5	91	0-2433	0-1370	685.1	1145.5	15	0-3402	0-1099
Overall cost with informal care	1189.8	937.9	909	174-2877	567-1631	1537.4	1193.8	1057	450-4462	844-1701
Overall cost (excluding informal care)	429.9	257.7	329	109-957	253-580	852.3	257.0	843	435-1311	603-1060

Note: 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.

and three (Figure S4). We aim to conduct a future definitive study, designed as a noninferiority 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, although 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.[46]

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

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 accidently pulled out (1)		Increasing bilirubin (1)	
		Fever (1)	
		Hospice admission (1)	
		Low energy/hypoglycaemia (2)	
		Umbilical hernia blister (1)	
		Anaemia/GI bleed (4)	

Abbreviations: GI, gastrointestinal; HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis.

collection, manuscript preparation nor will they claim any intellectual property based on this trial.

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AUTHORSHIP

Guarantor of the article: SV.

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.

All authors approved the final version of the manuscript.

ORCID

Sumita Verma https://orcid.org/0000-0001-7021-8409

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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APPENDIX

Authors's complete affiliations

Lucia Macken: Brighton and Sussex Medical School, Brighton, UK and Brighton and Sussex University Hospitals NHS Trust, Brighton, UK; Stephen Bremner: Brighton and Sussex Clinical Trials Unit, Brighton, UK; Heather Gage, Morro Touray and Peter Williams: University of Surrey, Guildford, UK; David Crook: Brighton and Sussex Clinical Trials Unit, Brighton, UK; Louise Mason: Brighton and Sussex University Hospitals NHS Trust, Brighton, UK; Debbie Lambert: Brighton and Sussex Clinical Trials Unit, Brighton, UK; Catherine J. Evans: Kings College, London, UK and Sussex Community NHS Foundation Trust, Brighton, UK; Max Cooper: Brighton and Sussex Medical School, Brighton, UK; Jean Timeyin: Brighton and Sussex Clinical Trials Unit, Brighton, UK; Shani Steer: Brighton and Sussex Clinical Trials Unit, Brighton, UK; Mark Austin: Brighton and Sussex University Hospitals NHS Trust, Brighton, UK; Nick Parnell: Brighton and Sussex University Hospitals NHS Trust, Brighton, UK; Sam J. Thomson: Western Sussex NHS Foundation Trust, Worthing, UK; David Sheridan: University of Plymouth and University Hospital Plymouth NHS Trust, Plymouth, UK; Mark Wright: Southampton Hospitals NHS Foundation Trust, Southampton, UK; Peter Isaacs: Blackpool Hospitals NHS Foundation Trust, Blackpool, UK; Ahmed Hashim and Sumita Verma: Brighton and Sussex Medical School, Brighton, UK and Brighton and Sussex University Hospitals NHS Trust, Brighton, UK.