Received: 21 January 2020 | First decision: 12 February 2020 | Accepted: 28 April 2020

DOI: 10.1111/apt.15802

AP&T Alimentary Pharmacology & Therapeutics WILEY

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

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Funding information
LMa is funded by the National Institute for Health Research and Kent Surrey and Sussex Deanery, AH by the Dunhill Medical Trust and Kent Surrey and Sussex Deanery and CJE by a HEE/NIHR Senior Clinical Lectureship. This manuscript presents independent research funded by the National Institute for Health Research under its Research for Patient Benefit Programme (Grant Reference Number PB-PG-0214-33068). The views expressed are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

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

The Handling Editor for this article was Dr Stephen Ryder, and it was accepted for publication after full peer-review.

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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

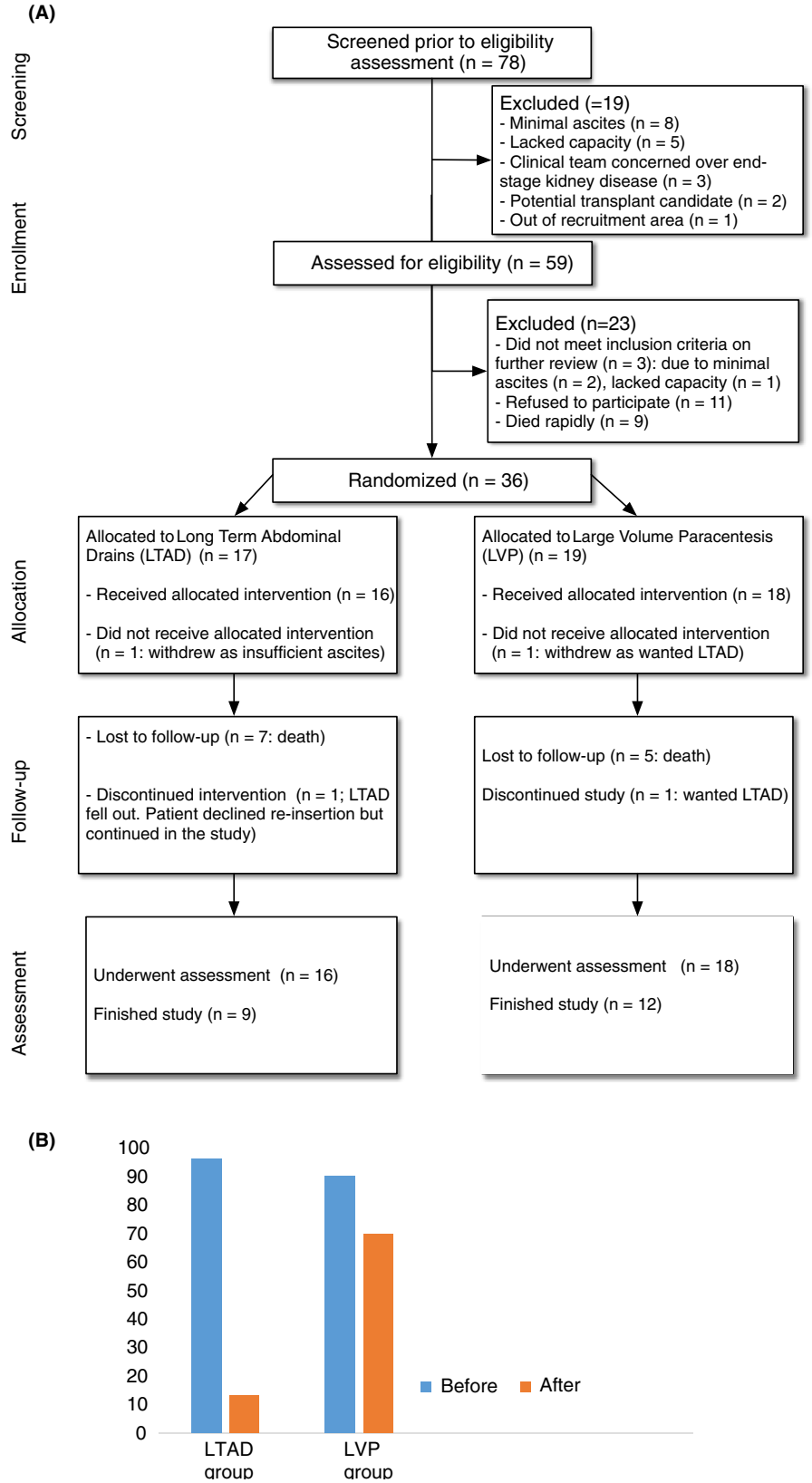

FIGURE 1 (A) CONSORT flow chart; (B) Total number of ascitic drains before and after randomisation in the long-term abdominal drain (LTAD) and large-volume paracentesis (LVP) groups; (C) Median (IQR) serum bilirubin (μmol/L) in the long-term abdominal drain (LTAD) and large-volume paracentesis (LVP) 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.

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.

ACKNOWLEDGEMENTS

We are indebted to the study participants and caregivers. We acknowledge the Clinical Investigation Research Unit Brighton, and study teams at each site (File S1). This study was supported by the United Kingdom Clinical Research Collaboration-registered King's Clinical Trials Unit at King's Health Partners, which is part funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Evaluation, Trials and Studies Coordinating Centre. 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

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.

Declaration of personal interests: SV research grants from the National Institute for Health Research and Dunhill Medical Trust and research grants/consultancy Gilead Sciences and Abbvie; LM employee of bluebird bio inc; DS: consultancy/ travel grants Intercept Pharmaceuticals, Norgine, Gilead Sciences; LMa, SB, HG, MT, PW, DC, DL, CJE, MC, JT, SS, MA, NP, ST, MW, PI, AH none.

Declaration of funding interest: This study was funded by the National Institute for Health Research.

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.

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SUPPORTING INFORMATION

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

How to cite this article: Macken L, Bremner S, Gage H, et al. Randomised clinical trial: palliative long-term abdominal drains vs large-volume paracentesis in refractory ascites due to cirrhosis. *Aliment Pharmacol Ther*. 2020;00:1–16. https://doi.org/10.1111/apt.15802

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