Refractory ascites in end stage liver disease focussing on the use of long term drains in a palliative setting

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Abstract

Background: The burden of end stage liver disease (ESLD) in England is high. Ascites is the commonest complication of ESLD, refractory ascites (RA) carries a limited prognosis, and the majority of patients are ineligible for liver transplantation. Standard management is large volume paracentesis (LVP), providing intermittent symptom relief, and is usually a palliative intervention. Long term abdominal drains (LTAD) are used in malignant ascites but evidence in ESLD is limited.

Aims: To characterise and describe local RA management with LVP, and current evidence on LTADs. To establish the feasibility of undertaking a research study in this patient group and report the methods and results of the REDUCe study.

Methods: REDUCe was a mixed methods feasibility RCT comparing LVP with LTAD, in those with ESLD and RA, running between September 2015-September 2018. Eligibility for liver transplantation was an exclusion. Clinical, health related quality of life assessments and qualitative interviews were undertaken.

Results: Nearly 40% undergoing an LVP developed RA, ≤15% were accepted for liver transplant and ≤45% highlighted as having palliative disease. Current data on LTAD in ESLD and RA are lacking. REDUCe study success criteria were achieved, 36 patients were randomised, attrition was 42%, uptake of questionnaires/interviews was ≥80% and those in the LTAD group spent ≤50% ascites related study time in hospital compared with the LVP group. No complications mandated LTAD removal and no LTAD related safety concerns were seen.

Conclusion: We demonstrated that research can be successfully undertaken in a palliative ESLD cohort. Initial results suggest LTAD are an alternative for managing RA and are an acceptable strategy for patients and healthcare staff. Definitive answers on safety and efficacy need to be established in a full scale trial.

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Acronyms and definitions

AE	Adverse Event
AHCR	Ambulatory and Home Care Record
AKI	Acute Kidney Injury
ALFApump®	Automated Low Flow pump
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BSMS	Brighton and Sussex Medical School
BSCTU	Brighton and Sussex Clinical Trials Unit
BSUH	Brighton and Sussex University Hospitals NHS Trust
BP	Bacterial Peritonitis
CDLQ	Chronic Liver Disease Questionnaire
CI	Confidence Interval
CLD	Chronic Liver Disease
CRF	Case Report Form
CRP	C Reactive Protein
CTIMP	Clinical Trial of an Investigational Medicinal Product
EASL	European Association for the Study of the Liver
eGFR	estimated Glomerular Filtration Rate
EoLC	End of Life Care
EQ-5D-5L	5-level EQ-5D tool
ESLD	End Stage Liver Disease
FBC	Full Blood Count

FFP	Fresh Frozen Plasma
GA	General Anaesthetic
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GP	General Practitioner
HAS	Human Albumin Solution
Hb	Haemoglobin
HCC	Hepatocellular Carcinoma
HDAS	Healthcare Databases Advanced Search
HE	Hepatic Encephalopathy
HRS	Hepatorenal Syndrome
ID	Identification
INR	International Normalised Ratio
IPCT	Integrated Primary Care Team
IPOS	Integrated Palliative care Outcome Scale
IQR	Interquartile Range
IV	Intravenous
KCTU	Kings Clinical Trials Unit
LT	Liver Transplantation
LTAD	Long Term Abdominal Drain
LVP	Large Volume Paracentesis
MC&S	Microscopy, culture and sensitivity
MDM	Multidisciplinary Meeting
MDT	Multidisciplinary Team
MELD	Model for End Stage Liver Disease

MeSH	Medical Subject Headings
NAFLD	Non Alcoholic Fatty Liver Disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NOS	Newcastle Ottawa Scale
PD	Peritoneal Dialysis
PIPC	Permanent Indwelling Peritoneal Catheters
PIS	Participant Information Sheet
PRH	Princess Royal Hospital
PRISMA	Preferred Reporting Items for Systematic reviews and Meta Analyses
QALY	Quality Adjusted Life Years
QOL	Quality of Life
RA	Refractory Ascites
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSCH	Royal Sussex County Hospital
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBP	Spontaneous Bacterial Peritonitis
SD	Standard Deviation
SF-LDQOL	Short Form Liver Disease Quality Of Life questionnaire
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TIPS	Transjugular Intrahepatic Portosystemic Shunt

TMG	Trial Management Group
tPA	Tissue Plasminogen Activator
UK	United Kingdom
UKELD	United Kingdom Model for End Stage Liver Disease
WBC	White Blood Cell count
WHO	World Health Organisation
ZBI-12	Zarit Caregiver Burden Interview Short Form

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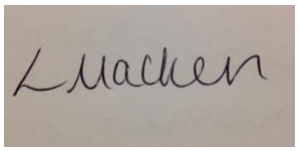
Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed: 

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Chapter 1 - Introduction

1.1 Background

The liver is an immensely important organ, although, in health, it goes largely unnoticed on a day to day basis whilst performing it's multitude of jobs. The scale and rate of growth of liver disease in recent decades in the United Kingdom (UK) is therefore staggering.[1]

1.2 Chapter aims

This chapter aims to outline the essential roles of the liver, the complications of chronic liver disease (CLD), as well as the implications of liver disease, both on the individual, and on wider society. To understand how much the liver does, and it's vital role in maintaining our health, is essential in comprehending it's role in the development of CLD and the resulting sequalae.

1.3 Context

The liver is the largest solid organ in the body, and performs many vital metabolic and homeostatic functions, allowing our bodies to function.[2–4] However in the UK, liver disease is a significant public health issue and in the year 2020 was the second leading cause of working lives lost in England, having overtaken ischaemic heart disease and accidental poisoning.[5]

1.4 Structure and function

1.4.1 Anatomy

Anatomically the liver is situated on the right side of the body, tucked within the right lower section of the ribcage, and protruding just out from underneath it, at the upper portion of the abdomen.[2,6]

It is functionally divided into two lobes, right and left, by the middle hepatic vein.[2,3] The external division of the right and left lobe is marked on the front of the liver by the falciform ligament, which attaches the liver to the anterior abdominal wall.[2,7] The right lobe is larger and contains the caudate and quadrate lobes.[2,3] The base of the falciform ligament contains a remnant of the vestigial umbilical vein, and in the setting of cirrhosis, this vein recanalises as a result of portal hypertension.[2,7]

The liver is further subdivided into a total of eight sectors by divisions of the right, middle and left hepatic veins.[3] Each lobe has its own arterial and venous supply and its own biliary drainage, described as the pedicle.[3,8] All the lobes perform the same functions and there are no areas of specialisation.[2]

Hepatic blood supply

The liver is unusual in that it receives it's blood supply from two sources, the hepatic artery, carrying oxygenated blood and supplying 20-25% of total blood flow, and the portal vein, which supplies the majority of hepatic blood flow, 75-80%.[2,3,7] The hepatic artery is a branch of the coeliac axis, which arises from the abdominal aorta.[6] The portal vein carries venous blood from the gastrointestinal tract to the liver.[2,7] Blood vessels and other structures converge at a region of the liver called the hilus (portal hepatis).[6]

The Portal circulation

Venous blood from the gastrointestinal tract drains into the superior and inferior mesenteric veins; these two vessels are then joined by the splenic vein and together they form the portal vein.[2,7] The portal vein divides to form the right and left branches, supplying about half of the liver each.[2]

On entering the liver, branches of the portal vein supply blood to all sectors, which then drain into the hepatic sinusoids via the portal tracts.[2,3,7] Hepatic sinusoids are small vascular channels which are essentially lined by liver cells, hepatocytes, as well as by specialised phagocytic cells derived from circulating blood monocytes (a type of white blood cell), called Kupffer cells.[2,9] Hepatic stellate cells are found between the hepatocytes and the sinusoids in the space of Disse; they store vitamin A (retinol) and their long dendritic cytoplasmic processes are important in intercellular communication and detection of cytokines.[3,9,10] Stellate cells regulate sinusoidal tone and blood flow, and also produce hepatocyte and vascular endothelial growth factors.[10]

Hepatic venous blood flow

Blood leaves the hepatic sinusoids, entering the central vein of the liver lobules, which are the functional units of the liver and are hexagonal in shape, and drains into branches of the hepatic veins.[2,4,6,7,9] There are three hepatic veins which exit the liver and drain into the inferior vena cava, just inferior to the diaphragm, which brings blood back towards the heart.[2–4]

1.4.2 The functions of the liver

The liver is the main organ of metabolism and energy production, and all of the biochemical functions of the liver are undertaken by the epithelial parenchymal cell, the hepatocyte.[2,3,9]

Hepatocytes are highly metabolically active and their cytoplasm contains many organelles as well as a large number of mitochondria.[9]

The portal venous blood contains and transports all of the products of digestion absorbed from the gastrointestinal tract to the liver, where they are processed, before being either released back into the hepatic veins or stored in the liver for later usage.[2]

Bile synthesis and secretion

Bile is produced in the liver and is transported in bile ducts to be stored in the gallbladder, and eventually excreted into the duodenum.[9] Here it mixes with ingested food, neutralising acid from the stomach, and bile salts, which are synthesised in hepatocytes from cholesterol, emulsify fats, which facilitates lipid digestion.[3,9]

Bilirubin is the breakdown product of the haem component of haemoglobin within mature red blood cells; haem is broken down by the spleen.[3,9] The bilirubin is initially unconjugated and is not water soluble, it is transported by albumin to the liver, where it is conjugated, becoming water soluble, to allow active secretion into the bile canaliculi, and then excretion into the duodenum within bile.[3,6,9]

Protein metabolism

Protein synthesis

The liver synthesises all circulating proteins in the blood, apart from the gamma globulins, immunoglobulins, which are produced by plasma cells, derived from lymphocytes.[3,4] Albumin, constituting the majority of plasma proteins, 60%, functions both to maintain intravascular oncotic pressure, as well as to transport water insoluble compounds including bilirubin, hormones, fatty acids and drugs.[3,4,6] Protein clotting factors in the blood, transporter and acute phase proteins, such as transferrin, which carries iron, and C-reactive protein are also produced.[3,6] Excess

amino acids are removed from the circulation, both having been absorbed from the gastrointestinal tract, as well as from muscle breakdown, regulated by the liver, by controlling the rate of protein synthesis, gluconeogenesis and transamination.[3]

Protein degradation

Amino acids are broken down in the liver to produce ammonia, this is then converted to urea, which is water soluble and relatively harmless.[3,6] Urea is then transported in blood and excreted by the kidneys.[9]

Carbohydrate metabolism

Glucose homeostasis and maintenance of stable blood sugar levels is another important role of the liver.[3,4] Hepatocytes remove excess circulating glucose from the bloodstream and store it as glycogen.[3,6] If circulating blood glucose levels drop, hepatocytes break down glycogen reserves to release glucose into the bloodstream in a process called gluconeogenesis.[3,4,6] The liver therefore acts as a buffer system to regulate blood sugar levels.[4] Lipids and amino acids can also be converted into glucose in the liver by gluconeogenesis, to be used as energy.[3,4,9] Carbohydrate metabolism is regulated by the hormones insulin and glucagon.[6]

Lipid metabolism

The liver has a major role in the regulation of circulating blood levels of lipids: triglycerides, fatty acids and cholesterol.[4,6] It metabolises lipoproteins, which are protein-lipid complexes formed to transport insoluble fats within the plasma; most cholesterol is also synthesised in the liver, rather than being from dietary sources.[3,6]

Iron homeostasis

Hepatocytes secrete the peptide hormone hepcidin, which is the main regulator of iron homeostasis in the body.[11] Expression of the hormone is stimulated by an increase in circulating iron levels in the blood; hepcidin subsequently then blocks the

transfer of iron into plasma.[11] This is achieved by inhibiting both dietary uptake from the cells lining the gut, enterocytes, as well as the release of iron from macrophages and hepatocytes.[11]

Storage

The fat soluble vitamins A, D, E and K, as well as vitamin B12, which is water soluble, are absorbed from the bloodstream and stored in the liver.[6,9] Lipids, in the form of triglycerides, and glycogen are also stored to be used in gluconeogenesis and for energy.[4,9] Trace elements, such as iron, are stored to be used in other metabolic processes and cell proliferation.[4,9] Iron is stored in the liver in the form of ferritin and is used in the formation of new red blood cells.[4,6]

Detoxification

Breakdown of toxins

Toxic substances such as alcohol and drugs are broken down, or conjugated, by the liver to convert them into other metabolites to facilitate their excretion, either in the bile, or in the urine.[3,9]

Hormone inactivation

Steroid hormones including oestrogen, progesterone and testosterone are also metabolised by the liver.[4]

Immune related function

Blood absorbed from the gut is screened by specialised macrophages within the hepatic sinusoids, Kupffer cells, to remove pathogens such as bacterial components and food antigens, as well as to phagocytise damaged or senescent red blood cells.[2,6,12] Kupffer cells are antigen presenting cells and also secrete interleukins, tumour necrosis factor, other cytokines, and chemokines which are involved in the immune response.[3,6,12]

1.5 Pathophysiology of liver disease

Although the liver is an extremely important organ in terms of metabolism and homeostasis, it has a large reserve capacity and huge regenerative potential whereby only severe hepatic disease leads to significant illness.[4,10,12,13] However, in causes of acute and chronic liver disease, where large numbers of hepatocytes are damaged, these capabilities are overwhelmed, its normal functions are disrupted without discrimination across domains, and liver transplantation (LT) is the only curative option.[4,9,13] In the setting of acute liver disease, if this process is severe and sudden in onset, the metabolic abnormalities also appear suddenly;[9] the most common underlying causes in Europe include acute viral hepatitis and drug induced liver injury.[14]

1.5.1 Chronic liver disease

In chronic liver disease (CLD), longstanding damage results in the initial inflammatory response becoming persistent, rather than transient, where the extracellular matrix continues to accumulate, resulting in fibrosis.[10,13]

In the United Kingdom (UK) the commonest causes of chronic liver disease are alcohol related liver disease (ARLD) and non-alcoholic fatty liver disease (NAFLD), which is related to the metabolic syndrome and obesity.[1,5] Worldwide, viral hepatitis, B and C, is historically the most common cause of CLD, however, targeted prevention (hepatitis B vaccination) and treatment of hepatitis C, are impacting on these trends.[15]

1.5.2 Liver fibrosis

In the presence of liver injury, hepatic stellate cells are activated and transdifferentiate into myofibroblasts which secrete extracellular matrix and

proinflammatory cytokines.[10,12,13] If the injury is ongoing, the functional hepatic parenchyma becomes progressively replaced with acellular connective tissue, predominantly collagen and elastin fibres.[13] This process of fibrosis development distorts the normal layout and stiffness of the tissues, and if damage is ongoing, progressive injury occurs, ultimately resulting in an advanced stage of fibrosis which is termed cirrhosis .[10,13,16]

Fibrosis in itself is not a static state, and can progress as well as regress.[17–19] However, once cirrhosis is established and there is development of clinically significant portal hypertension, reversal is no longer possible.[16]

1.5.3 Cirrhosis

Cirrhosis is an end result of parenchymal degeneration, regeneration and scarring, characterised by the formation of regenerative nodules of liver parenchyma which are surrounded by fibrotic septa.[7,16] Macroscopically, cirrhosis can be micronodular or macronodular, resulting from the formation of the regenerative nodules with surrounding areas of fibrosis.[7,9]

1.5.4 Clinical context

Cirrhosis is the end stage of chronic liver disease resulting from any initial aetiology; the natural history is that of an initial asymptomatic phase where no biological or physiological signs of liver disease are present.[20] This stage is termed clinically as compensated cirrhosis, and the Lancet report on liver disease in the UK in 2014 demonstrated that up to 75% of people with cirrhosis are not detected until they present to hospital with end stage liver disease (ESLD), where cirrhosis has become advanced and has decompensated.[1]

As the severity of cirrhosis progresses, the transition from compensated to decompensated cirrhosis occurs at a rate of 5%-7% per year, with increasing portal venous pressure and progressive liver function impairment.[9,20] Studies of the natural history of compensated cirrhosis have shown that at 10 years, just over half of patients will have developed features of decompensation, and when this occurs there is a significant negative impact on life expectancy in the absence of LT.[21] Clinical scores of the severity of cirrhosis are used to aid in prognostication, as higher severity scores confer poorer clinical and survival outcomes. The most widely used scores are the Child-Pugh score and Model for End Stage Liver Disease (MELD).[22,23]

1.6 Decompensated cirrhosis

In compensated cirrhosis, the portal pressure may be normal or may not have increased to the stage of developing clinically significant portal hypertension (CSPH).[20] However, with progression of disease stage, as portal pressures increase along with deterioration in liver function, the clinical features of decompensation develop.[7,9,20,24] The median survival in compensated cirrhosis is 12 years, however in decompensated cirrhosis, this drops to two years in the absence of the only curative option of undergoing LT.[20] As a result of this, when decompensation occurs, consideration should take place by clinicians, thinking ahead to the potential suitability for assessment for LT.[25]

The features of decompensated cirrhosis are:

- Ascites development
- Portal hypertensive bleeding
- Jaundice
- Hepatic encephalopathy

1.6.1 Portal hypertension

With advancing stages of cirrhosis, portal hypertension develops as a result of increasing liver stiffness and resistance to blood flow due to the distortion of the normal liver parenchyma, resulting in disruption of the sinusoidal connections between the portal venous system and the draining hepatic veins.[7,9] In addition to these structural effects, increased hepatic vascular tone also develops due to endothelial cell dysfunction.[26]

1.6.1.1 Ascites

The most common complication of decompensated cirrhosis, and that which is frequently the first to develop, is ascites.[20,21] In Europe and the United States of America, cirrhosis is the commonest cause of ascites, in up to 80% of cases, with other causes including malignancy and heart failure.[25,27] Ascites is the accumulation of fluid within the peritoneal cavity, and develops as a result of the interplay between two main key pathways, which are portal hypertension and the retention of sodium and water by the kidneys.[28] More recently, the influence of systemic inflammation is also thought to be playing a role in continued organ dysfunction.[29,30] With progressive stages of cirrhosis, and with the development of ascites, bacterial translocation starts to occur from the gastrointestinal tract.[29] This results in an elevation in circulating proinflammatory cytokines, increased splanchnic vasodilatation and resulting effective hypovolaemia.[29,30]

Pathophysiology

The peritoneal cavity is lined by a serous membrane, the peritoneum, and contains the liver, stomach, spleen, small intestine, and most of the large intestine.[6] The peritoneum continuously produces serous fluid which lubricates the peritoneal surfaces, however, at any one point only a tiny amount of fluid is present within the peritoneal cavity.[6] As sinusoidal pressures increase, intrahepatic resistance to blood

flow increases, vascular tone also increases, which is additive, and further exacerbates fluid accumulation.[26] Changes in vascular resistance also results in vasodilatation in the systemic circulation, mainly occurring in the splanchnic circulatory area supplying the abdominal gastrointestinal organs, and an effective resultant hypovolaemia, which in turn activates the renin-angiotensin-aldosterone and sympathetic nervous systems, causing sodium and fluid to be reabsorbed in the kidneys.[26,31,32]

Classification of severity of ascites

The volume of ascites which develops is variable and can range between that which is undetectable clinically (mild ascites), to large volume (severe) ascites.[25] Uncomplicated ascites is that in which there is no concurrent infection, spontaneous bacterial peritonitis (SBP), and that which is not associated with the development of hepatorenal syndrome (HRS).[33] SBP has a prevalence of 1.5%-3.5% in outpatients and up to 10% in patients admitted to hospital with asymptomatic ascites due to cirrhosis, and again confers a further reduction in life expectancy as another marker of progression of severity of liver disease.[34–37]

Grading of the severity of ascites:[25]

- Grade 1 mild – only detectable by radiological examination
- Grade 2 moderate – causing moderate abdominal distension
- Grade 3 severe – causing marked abdominal distension, which can also become tense and in addition to pain, can impair diaphragmatic functioning and therefore breathing

Management of ascites

In the earlier stages, and at smaller volumes, ascites can often be controlled by dietary modification of salt intake and medical therapy in the form of diuretics.[28] It is

also important to note that removal, if possible, of the underlying aetiology of the chronic liver disease can have a positive impact on reducing the progression of disease as well as on symptoms of decompensation.[25] With large volume ascites, and in more advanced stages however, ascites can become more difficult to manage and even become refractory to standard management.[33]

Refractory ascites

Refractory ascites is defined as that which cannot be mobilised by medical management or the early recurrence following therapeutic drainage, large volume paracentesis (LVP).[33,38] This is subdivided into two groups: diuretic resistant ascites, where there is no response to sodium restriction and diuretic usage; and diuretic intractable ascites, where diuretic related complications occur which prevent optimal doses of diuretics being used.[33] The median life expectancy once refractory ascites has developed is about six months, and should prompt consideration for assessment for LT, if felt to be clinically appropriate, as well as for an assessment of unmet supportive and palliative care needs.[37,39]

1.6.1.2 Portal hypertensive bleeding

Blood flow is shunted away from the liver, from the portal venous system, to the lower resistance systemic venous circulation via anastomotic channels.[7,9] These anastomotic channels are normally closed, however as portal pressure rises they open up, become distended, and are then termed varices.[9] The sites of portosystemic anastomoses where varices develop are: at the lower end of the oesophagus, the rectum, left renal vein, at the umbilicus, and surrounding the liver and spleen.[3,9] At the lower oesophagus and around the gastro-oesophageal junction, the varices run superficially, these are therefore the most frequent sites of portal hypertensive bleeding, which can be dramatic and in itself life threatening.[3,9]

1.6.1.3 Jaundice

Failure of the liver to excrete adequate bile into the gastrointestinal tract results in the hepatic retention of bile, termed cholestasis.[9] Components of bile enter the blood stream, causing elevation of the serum bilirubin levels, and a resulting yellow discolouration of plasma and tissues, which is detectable clinically as jaundice.[6,9]

1.6.1.4 Hepatic encephalopathy

The hepatocyte detoxification function is impaired with advancing stages of CLD, which results in increased circulating levels of toxins within the bloodstream.[9] Ammonia, which is produced by bacterial breakdown of peptides in the intestines, crosses the intestinal wall and enters the portal circulation.[4,6] The liver normally neutralises ammonia, converting it, by deamination, to a non-toxic compound, urea, for excretion by the kidneys.[4] Rises in the level of ammonia in the systemic blood circulation, functionally bypassing the liver, allows metabolites to pass directly to the brain causing progressive brain dysfunction, hepatic encephalopathy (HE), this results in multiple sequalae including: confusion,[40] an altered level of consciousness, and eventually coma and death.[6,9] Hepatic encephalopathy is graded in terms of severity and clinical symptoms and the gold standard classification system used is the West Haven Criteria.[40]

1.7 Liver disease in the UK

The first Lancet commissioned report on the crisis of liver disease in the UK was published in 2014; CLD constituted the third most common cause of premature death, and in the year 2020 was the second leading cause of working lives lost in England.[1,5] In the UK over the last 40 years, liver disease deaths have increased by 400%, and in people less than 65 years of age, have increased by almost five times.[1] The incidence of cirrhosis in the 10 years leading up to 2012 had increased

in the UK by 40%, and admissions to hospital due to CLD have also been increasing; the majority of cases having decompensated cirrhosis and ESLD at the time of index admission.[1]

1.8 End stage liver disease

Decompensated cirrhosis and end stage liver disease (ESLD) are synonymous terms which describe advanced cirrhosis where complications have developed. The trajectory of the disease process is fluctuant, as is seen in many other advanced chronic conditions, rather than linear, which is usually the case in advanced cancer.[20,41–44] This results in increasing contacts with hospital services and frequent admissions to hospital with significant symptoms such as pain and breathlessness, as well as repeated episodes of complications.[42,43,45,46]

1.8.1 Ascites

Since ascites is the most common complication of ESLD, affecting up to 90%,[20,27,35] symptoms relating to ascites are the most frequent experienced, with resultant impact being to cause physical and psychological distress, and reduction in quality of life.[43,46–48] The symptom prevalence of patients with ESLD is similar to those with other advanced chronic health conditions including advanced cancer.[46] The development of ascites is an important milestone in the natural history of cirrhosis, with 20% of people presenting with ascites dying within the first year of the diagnosis.[49] Refractory ascites develops in about 10% of cases and confers a further limited life expectancy of about 6 months.[27,50,51] Large volume paracentesis (LVP) is currently the standard of care in the management of large volume, and refractory ascites, although this only offers limited symptom relief, as the natural history of ascites due to ESLD is of continuous ongoing accumulation.[25,28,47] A recent UK study

published in 2018 indicated that of the 45,000 cirrhosis related deaths over the study period, about a third had required LVP in the last year of their life, with mean healthcare costs being over £21,000 per person in that final year.[52]

1.8.2 Current management of refractory ascites

LT is the only curative measure, however only a comparatively small proportion of patients are eligible for transplant assessment, and up to 40% of those proceeding to the stage of assessment are subsequently declined transplantation.[20,53–56] Reasons for ineligibility include ongoing alcohol use or substance misuse, which are absolute contraindications to transplantation, as well as comorbidity and frailty.[56] Cessation of alcohol use can also lead to regression of ascites and recompensation as a result of removal of the driver for worsened liver function.[55,56] Therefore it is common clinical practice to wait for a period of time once a person has been abstinent from alcohol to allow this process time to occur.[55,56] Those patients who have been listed for LT still require management of their ascites, as well as other symptoms, and a small number of cases, up to 20%, will not eventually proceed to LT due to being delisted due to a deterioration in health, or dying while waiting for a transplant.[53,54,56]

In the absence of the option of LT, and in the case of patients who have been listed for LT but who have not yet undergone surgery, there are a number of interventions which are currently used in the management of RA.[25,28] The most frequent procedure undertaken is intermittent LVP, which, in the majority of cases is undertaken with palliative intent.[57,58]

Large volume paracentesis

The current standard of care and treatment of choice for those with large volume, or grade three, ascites is LVP.[25,28] This is usually performed as a day case, and is an invasive procedure where a temporary drain is inserted directly into the peritoneal

cavity, passing through the skin and deeper tissues.[28,50] The aim of undertaking LVP is for symptomatic management of ascites, and it does not impact on the underlying disease process.[25]

LVP is a safe procedure, however requires repeated hospital attendances to insert the drains.[50] The frequency of drainage is guided by the symptoms of ascites experienced by patients, such as abdominal distension, can be undertaken as often as every two weeks, and in some cases even weekly.[28,50] The drains are inserted using a sterile technique, and with injection of local anaesthetic into the skin and subcutaneous tissues.[59] They are left in to drain for a maximum of up to six hours, or until a target volume of ascites has drained, not infrequently as much as ten litres or even occasionally larger volumes.[60] The arbitrary cut off of six hours duration of time for the LVP catheter to be left within the peritoneal cavity is underpinned by concerns over increased susceptibility to infections in cirrhosis.[61]

Infectious complications

Ascites due to cirrhosis can spontaneously develop a bacterial infection within it (spontaneous bacterial peritonitis, SBP), linked to bacterial translocation from the gastrointestinal tract,[62] this occurs in the absence of any interventional procedures, hence termed ‘spontaneous’. Rates of SBP are reported as being about 3.5% in asymptomatic outpatients, however the prevalence has been reported as being up to 19% overall.[34–36] Cirrhosis impacts on immunity and confers a higher susceptibility to bacterial infections due to cirrhosis associated immune dysfunction (CAID).[61] An LVP catheter is not designed for long term use, and represents a direct pathway from the skin to the peritoneal cavity, therefore has the potential to increase infection risk, and as a result it’s use is time limited.[63]

Haemodynamic complications

Due to the associated intra abdominal fluid volume shifts and impact on the splanchnic circulation during LVP, concurrent infusion of human albumin solution (HAS) is used to prevent post paracentesis circulatory dysfunction (PPCD).[60,64] The recommended volumes of HAS to be given is dependent on the volume drained, and current clinical practice guidelines advise eight grams of albumin per one Litre of ascites drained.[25]

1.8.3 Other strategies for ascites management

A number of other management strategies for ascites have been used, such as Transjugular Intrahepatic Portosystemic Shunts (TIPS) and the automated low flow (ALFApump®) pump, however, they are invasive procedures which could be considered unsuitable, or not appropriate, as palliative interventions.[20,25,65–67]

Transjugular Intrahepatic Portosystemic Shunts

The other main intervention currently used is the formation of an artificial shunt between the portal venous system and the systemic circulation, delivering blood to the inferior vena cava, called a transjugular intrahepatic portosystemic shunt (TIPS).[38] The shunt allows blood flow to bypass the liver allowing decompression of the portal system, therefore the aim being to reduce the portal pressures and resulting complications.[68] TIPS however is contraindicated in patients with high disease severity scores, MELD and Child Pugh, as well as pre existing HE and other comorbidities such as cardiac dysfunction.[25,69] This is due to the risk of recognised complications which include precipitating or worsening HE.[22,23,28,70] TIPS has been shown to improve the management of ascites in carefully selected groups with some

improvement in transplant free survival, however there is uncertainty over the impact upon quality of life (QOL).[25,28,38,69,70]

As an intervention to manage RA, TIPS may be contraindicated in patients eligible for LT due to the implications of technical challenges to surgery, and should be discussed with a transplant centre before being considered.[69] In those who are not eligible for LT, given this would be a palliative intervention, QOL and symptom management are the main aspects which should be taken into account, balancing these with potential side effects including the worsening of HE.[28,69] TIPS therefore may be a less appropriate option for palliation of symptoms in RA, given the contraindications for LT may be indistinguishable from those for TIPS, such as comorbidity or very advanced stage of liver disease.[28,56,69]

1.8.4 Less common interventions

Peritoneovenous shunts

Peritoneovenous shunts have been used in the management of RA, however are not in routine use currently due to their high complication rate, including that of infection and shunt occlusion.[71,72]

The ALFApump®

The ALFApump® is an implantable device which pumps ascites from the peritoneal cavity into the urinary bladder, and has been used in small numbers in the UK, including within randomised controlled trials (RCT).[65,66] It is not currently in use however due to high rates of complications being reported in the European multicentre RCT, including those of infections, renal dysfunction, and high rates of explantation of the devices, in up to 30%.[65,66,73,74] Recent guidance from the National Institute for Health and Care Excellence (NICE) on the ALFApump® advises use only with ‘special arrangements’ and in research settings.[75]

Long term abdominal drains

In the setting of the palliation of refractory malignant ascites, long term abdominal drains (LTAD) are currently an accepted strategy, having been assessed in the UK by the National Institute for Health and Care Excellence (NICE).[76] LTAD are specifically designed for long term use, and are tunnelled subcutaneously in the abdominal wall, under local anaesthetic and usually with ultrasound guidance.[77,78] The NICE technology guidance on malignant ascites reported that LTAD were clinically effective, had low complication rates and, compared with LVP, resulted in cost savings of £679 per patient at the cost of 23.5 additional community nurse visits.[76] Other potential benefits could be that LTAD may allow patients more autonomy over their ascites management, reduce frequent hospitalisations to allow more time of a limited life expectancy to be spent out of hospital and in their usual place of residence. There is also the potential that avoiding repeated LVP may reduce associated complications such as large fluid shifts, as only small amounts of fluid are removed at a time with LTADs. Finally, there may also be possible economic benefits to the National Health Service (NHS).[76]

Long term abdominal drains (LTAD) have been proposed as a potential strategy for managing ascites due to RA in ESLD, however there is currently limited data on their use in this context, with concerns remaining over safety, particularly surrounding infection risk and specifically peritonitis.[28,61] A review by NICE was in progress during 2022, and an interventional procedures document was expected to be finalised by the end of 2022 before guidance on their use was published.[79,80]

1.9 Palliative and end of life care

The terms palliative care and end of life care (EoLC) are not synonymous, although are often used interchangeably.[81] The World Health Organisation (WHO) defines

palliative care as an approach that improves the quality of life of patients and their families with any life threatening illness; and the NHS defines end of life care as the support received in the last months or years of life.[82,83]

Early palliative care interventions have been shown to improve the symptoms of those on the waiting list for LT assessment, however, those with ESLD rarely receive palliative care, despite services being available.[84–86] Palliative care in ESLD is frequently only instigated towards the end of life, in the last days or weeks, and only those with concurrent hepatocellular carcinoma (HCC) are more likely to have had a referral to palliative care services.[87,88]

The complexity of ESLD, along with patients often being of a younger age, the perceived stigma associated with cirrhosis, and other factors including ongoing substance misuse and addiction, means EoLC is more challenging, with minimal specialist palliative care provided in a hospice or community setting.[42,85,89]

1.10 Current trends in mortality in ESLD

More than two thirds of those in which liver disease is listed as a cause of death die in a hospital setting, which is in contrast to those with advanced cancer, where the number is about 40%, and in deaths from any cause, where the figure is about 50%.[42,89] Although this is not direct evidence of wishes of a preferred place of death, death in hospital is often used as a surrogate marker for this, as well as for the quality of care provided.[89,90]

It is also important to recognise that there are often other complicating factors involved in those with ESLD who die in hospital, most commonly sepsis and HRS.[89]

1.11 Summary

Liver disease is a large and growing problem in the UK, with the majority of cases presenting to hospital at an advanced stage with ESLD.[1] The commonest complication of ESLD is ascites, and management of this includes LVP.[28,52] In the setting of the development of refractory ascites, LVP is the current standard of care and, given the majority of patients with ESLD are not eligible for LT, this then is a palliative intervention.[28,47]

Repeated LVP requires regular hospital attendances for the insertion of temporary drains, however this strategy only improves symptoms temporarily, as the natural history of ascites is to continue to recur.[47]

This approach is also costly from a personal and NHS perspective, mandating a hospital day case attendance, as well as concurrent infusion of HAS.[52]

LTADs are currently used in malignant ascites as palliation of symptoms, but there is insufficient evidence of efficacy and safety in an ESLD population to advocate for their use as standard.[76,80]

1.12 Thesis aims

1.12.1 Primary aims

The primary aims are:

- To describe the methods used and results obtained from the feasibility randomised controlled trial (RCT) comparing palliative LTAD with LVP in patients with advanced cirrhosis and RA, **RE**peated **D**rainage **U**ntreatable **C**irrhosis (REDUCe).

The REDUCe study aims to explore the acceptability and feasibility to patients, carers and the NHS, of using LTAD as a strategy in managing RA.

The study was designed in accordance with phase two of the Medical Research Council (MRC) Complex Interventions Framework and the Method Of Researching End of life Care (MORECare) guidance.[91,92]

Specific objectives to explore are:

- Number of eligible patients
- Whether patients are willing to be randomised to LTAD, rather than receive usual care in hospital
- Attrition rates in both groups (to include attrition due to death, illness or at random)
- Complication rates in both groups
- Informal carers, if present, perceived burden with LTAD and LVP
- Properties of different outcome measures (including health resource utilisation and QOL instruments) to ascertain the most appropriate primary outcome for a full scale trial
- Acceptability of LTAD to patients, carers, and clinical staff using qualitative methods
- Resource implications of LTAD

1.12.2 Secondary aims

The secondary aims are:

- To explore local data on refractory ascites, and describe the natural history, including of large volume paracentesis use, and current local engagement with palliative care.

- To undertake a systematic review to describe the current available evidence of the use of long term abdominal drains in refractory ascites due to end stage liver disease.

Chapter 2 - Natural history of refractory ascites, including large volume paracentesis interventions, and engagement with palliative care

2.1 Introduction

The natural history of cirrhosis is initially that of a long phase termed ‘compensated cirrhosis’ which is the stage prior to the development of any complications, and is usually asymptomatic.[20] As a result, in the United Kingdom (UK), the majority of people with cirrhosis, 75%, are not detected until they have presented to hospital with a decompensation of their liver disease.[1]

The progression from compensated to decompensated cirrhosis occurs at a rate of between 5%-7% per year, and ten years after the diagnosis of compensated cirrhosis, just over half of cases will have developed a feature of decompensation.[20,21] Cirrhosis progresses to decompensated disease with the development of clinically significant portal hypertension (CSPH),[20] and as this develops, so do the resulting complications, including ascites and portal hypertensive bleeding, most frequently from varices.[93]

Advanced liver cirrhosis is the most common underling cause of ascites in the UK, with other less common causes including malignant ascites, and other organ failures such as heart and kidney.[25,38]

The development of ascites is the most frequent complication of cirrhosis. It is often the first complication to develop as a part of progressive liver disease, and therefore is the commonest feature of decompensated cirrhosis.[1,20,21] Once cirrhosis has decompensated with any of the clinical features of ascites, portal hypertensive bleeding, jaundice or hepatic encephalopathy (HE), the term end stage liver disease

(ESLD) is also often used interchangeably to describe this advanced stage of disease.[20,24] After presentation with ascites, the probability of progression to death at one year is as high as 20%.[49] It is important to note that the use of diuretics to control ascites is for the management of the resultant symptoms, such as abdominal distension, but does not impact on the underlying pathophysiology leading to its development, nor on survival rate.[25]

2.1.1 Medical management of ascites

The initial management of ascites is medical, with a no added salt dietary restriction and initially the use of aldosterone antagonist diuretics (Spironolactone), with dose titration to clinical effect.[28] Often the addition of a loop diuretic (Furosemide) is also used to augment diuresis, however maximal doses of both are rarely, if ever, achieved (Spironolactone maximum dose 400mg daily and Furosemide maximum dose 160mg daily)[28] as a result of side effects and adverse reactions which occur in up to 33%.[28] Well recognised side effects of diuretic use in ESLD include renal impairment, hyponatraemia, hyper and hypokalaemia and HE.[28] The development of any diuretic related complication requires a dose reduction, and even discontinuation of the drug if smaller doses are not tolerated.[28] Ascites can become refractory to medical treatment if patients are intolerant to diuretics, or if there is a lack of response to their initiation and dose escalation.[38] This situation occurs in about 10% of patients and is then termed refractory ascites (RA), as the ascites is recurrent and has become refractory to medical management.[33,50,94]

2.1.2 Refractory ascites

The development of RA is an important point in the natural history of decompensated cirrhosis and confers a significantly limited life expectancy.[51] RA has been shown to

hold a higher prognostic value than other regularly measured variables such as routine biochemical blood tests.[55] The median survival drops to six months in the context of RA without undergoing liver transplantation (LT), and therefore should prompt consideration by clinicians for whether or not patients who have developed RA would be eligible to be referred to undergo an assessment for suitability for transplantation, and/or a transjugular intrahepatic portosystemic shunt (TIPS) procedure.[25,39,51,55,94] The management of RA is symptomatic and does not impact on the underlying pathophysiology, or on survival, the only curative intervention that impacts on the underlying disease process of advanced cirrhosis is LT.[13,20,70]
The current standard management of refractory ascites is intermittent drainage of the ascites, a procedure called large volume paracentesis (LVP), where a temporary drain is inserted into the peritoneal cavity and the ascites drained for short term relief of ascites related symptoms.[28]

2.2 Study aims

The aims of this study were to characterise the group of patients undergoing LVP for ascites due to ESLD, at a large National Health Service (NHS) teaching hospital Trust in the Southeast of England. Specifically, to describe the natural history and outcomes of those who developed RA, including whether the RA group had any documentation regarding advance care planning, consideration for LT eligibility, and/or evidence of a palliative care team referral having been made. This could include discussions about treatment preferences, escalation and ceilings, as well as communication relayed in inpatient discharge summaries, or outpatient clinic letters regarding decisions relating to cardiopulmonary resuscitation (Do not attempt cardiopulmonary resuscitation orders, DNACPR).

2.3 Patients and methods

2.3.1 Methods overview

This was a retrospective cohort study of patients undergoing LVP at a large NHS teaching hospital Trust on the south coast of England, Brighton and Sussex University Hospitals NHS Trust (BSUH), which is now part of University Hospitals Sussex NHS Foundation Trust (UHS).

BSUH NHS Trust was formed by two acute hospitals, the Royal Sussex County Hospital and the Princess Royal Hospital, and as patients with decompensated cirrhosis present to and are under the care of both hospitals, LVPs occur on both sites.

The region is a pocket for high levels of liver disease, and in 2014/2015 as reported in the 2nd Atlas of variation in risk factors and healthcare for liver disease in England, published in 2017, the regional rates of admission to hospital at least once due to cirrhosis in those aged 18 years and older were 155 per 100,000 population, which was significantly higher than the average for the rest of England overall.[95]

The study period was from January 2013 until December 2015, the starting date was chosen as, prior to this, the pathways for undertaking day case episodes for LVP had not been well established, and drainage protocols were not well defined. After December 2015, a prospective feasibility randomised controlled trial (RCT), funded by the National Institute for Health Research (NIHR), opened and began recruitment at BSUH, Palliative Long Term Abdominal Drains versus Large Volume Paracentesis in Refractory Ascites Due to Cirrhosis (**RE**peated **D**rainage **U**ntreatable **C**irrhosis, the REDUCe Study (ISRCTN 30697116). The REDUCe study target recruitment cohort was patients with end stage liver disease (ESLD) and refractory ascites (RA) who were requiring recurrent LVPs. The study aimed to establish the feasibility of

running a large full scale RCT to investigate using long term abdominal drains (LTADs) as a strategy for managing RA in ESLD, rather than undergoing repeated LVPs, with the ultimate aim to understand if this strategy would be acceptable to the planned study population. The two study arms were; group one: insertion of a long term abdominal drain (LTAD or tunnelled permanent indwelling peritoneal catheter) in those patients who were not eligible for a liver transplant, and group two: standard of care, which is repeated LVP. Those who had been recruited to the study, and had been randomised to group one, the LTAD arm, had further drainage episodes which occurred in the community, undertaken by the integrated community nursing team Sussex Community Foundation Trust (SCFT). Therefore, the search for cases could not be continued beyond this date, due to trial recruitment impacting on the cohort, and altering the pool of patients attending hospital for LVP. It was decided that the end of the study search period, December 2015, would be when the RCT had started recruitment at BSUH.

The hospital coding system was searched for all coded hospital episodes at BSUH NHS Trust from the start of January 2013, to the end of December 2015, which had been allocated specific OPCS-4 clinical classification codes. The OPCS Classification of Interventions and Procedures (OPCS-4) is a Fundamental Information Standard which is revised periodically.[96] The OPCS-4 clinical classification codes used for the search were ‘T46.1’ & ‘T46.2’ ‘PARACENTESIS ABDOMINIS FOR ASCITES’ or ‘DRAINAGE OF ASCITES’.[96] The codes chosen for the search were to allow capture of episodes where patients had undergone ‘paracentesis’ or ‘ascitic tap’. The interventions and procedures code was chosen rather than the clinical ICD-10 International Classification of Diseases codes to allow

capture of all procedures which has been undertaken, rather than capturing all patients with liver disease, where LVP may not have actually taken place.

The codes chosen capture any undifferentiated episode, and therefore covered procedures which had occurred during both inpatient admissions and outpatient or day case attendances.

A list of hospital identification numbers (ID) was generated, these are identifiers for specific patients. Duplicate identification numbers, which represented recurrent episodes of drainage for the same patient, were removed.

In addition to coding searches to gather case episodes, the records for the medical ambulatory day case units at both hospitals during the same time period were searched for cases using the search terms “paracentesis”, “drainage” or “ascitic drain”. All episodes of patients who attended the medical day case units having been booked under any of the search terms were included in the list of hospital identification numbers.

Consecutive results of coding episodes identified where patients underwent paracentesis between January 2013 and December 2015 were examined. A retrospective review was undertaken of electronic clinical records, including hospital discharge letters summarising day case attendance procedures, inpatient hospital admissions, as well as outpatient clinical letters to GPs. Cases of those who had ascites in the context of ESLD were identified, and those who underwent LVP for ascites resulting from underlying aetiologies other than ESLD, such as malignant ascites and heart failure, were excluded. Electronic radiology and pathology results were also reviewed to establish the aetiology of ascites if this had not been clearly documented.

2.3.2 Inclusion and exclusion criteria

Inclusion criteria

- Undergone an LVP for ascites either as inpatient or as a day case/outpatient
- Underlying aetiology of ascites due to ESLD
- Development of RA (see study definitions section)

Exclusion criteria

- No evidence of having had an LVP
- Aetiology of ascites due to disease process other than ESLD
- Mis-coded as LVP in patients undergoing abdominal surgery

Individual patient electronic records were retrospectively analysed and the following data collected: numbers of patients identified overall who had undergone LVP, and underlying aetiology of ascites, with exclusion of non ESLD cases. In the ESLD group demographic data was collected, including underlying cause of chronic liver disease (CLD), numbers of LVPs overall undertaken, and whether these were performed as an elective day case on the medical day case unit, during an inpatient hospital admission, or in both settings.

Documentation of ongoing risk factors for the progression of liver disease such as alcohol and/or illicit drug use was recorded. Pathology results as well as liver disease severity scores (Child Pugh CP, Model for End Stage liver disease MELD, and the United Kingdom Model for End Stage Liver Disease UKELD) were collected and calculated from the source data.[22,23,51,97]

In those patients with ESLD, further characterisation was undertaken as to whether their ascites had become refractory to medical management, by recording episodes of LVPs undertaken. See study definition section below for how we defined RA for the purposes of the study.

2.3.3 Factors predictive of development of refractory ascites

Factors which may predict the development of RA, such as pathology results including markers of liver synthetic function and renal function, as well as liver disease severity scores, were recorded and analysed at first development of ascites as baseline. This was undertaken both in those who went on to develop RA and those who did not, and a comparison between the two groups was undertaken.

2.3.4 Complications of cirrhosis

The complications of CLD other than the development of ascites or RA recorded were: history of development of SBP, hepatocellular carcinoma (HCC) and previous alcoholic hepatitis. Data on other factors linked to ESLD such as HE or portal hypertensive bleeding were not recorded, as were outside of the aims and scope of this study.

2.3.5 Survival

The following were calculated as time from event to death in days: survival after first decompensating event of any kind, after first development of ascites, after first LVP, and after the development of RA, if it occurred. The time in days from the first decompensating event to the first LVP, as well as the overall total number of LVPs, was also calculated. In those who developed RA, the time from first decompensation of any kind, as well as from first LVP to the development of RA, was also calculated. All the survival data was calculated up until the point of the final data review date of 01/09/2016.

2.3.6 Liver transplantation

Evidence in clinical letters or electronic discharge summaries on whether eligibility for a liver transplant (LT) assessment had been considered or undertaken in all

those with ESLD was recorded, as well as reasons for this not having been pursued, if present. In those who had been assessed for LT, the outcomes relating to this were recorded.

2.3.7 Advance care planning and palliative care

In addition to eligibility for assessment for LT, other factors analysed were whether there was any identification in the electronic patient clinical letters, or electronic hospital discharge summaries to the patients GP, reporting that the patient's management from a liver perspective was now effectively of a palliative nature. This also included whether discussions regarding prognosis, advance care planning, including resuscitation status (DNACPR orders), had been documented in communications with the patients' GP, and if a referral to a specialist palliative care team had been made.

2.3.8 Study definitions

Cirrhosis: clinical description or diagnosis described in electronic documents, or report of an irregular or nodular liver margin on imaging if a formal diagnosis of cirrhosis had not been made in the electronic patient records.

End stage liver disease (ESLD): decompensated cirrhosis as a result of any aetiology and specifically in this study the inclusion criteria were patients with ESLD with ascites being their decompensating complication.

Refractory ascites: was defined as per the International Ascites Club definition,[38] as that which cannot be mobilised by medical management or the early recurrence following therapeutic drainage, large volume paracentesis (LVP).[33,38] For the purposes of inclusion into the study, having developed RA was defined as: patients with ESLD who had undergone ≥3 LVPs within a time period of six months.

Recidivism: was defined as any description in patients records, including outpatient clinic letters or discharge summaries, of ongoing alcohol consumption in any volume. This is also termed persistent alcohol misuse disorder.

Illicit drug use: defined as any description in patients records of ongoing illicit non prescription drug, or street drug use.

Palliative care: defined as documentation in patients electronic case records of a point in the trajectory of ESLD which was felt to be non curable by LT, either being too advanced, frail, or not meeting eligibility for LT due to other patient specific factors, or indication that a palliative stage of disease had been reached, or palliative care team referral or review during an inpatient hospital admission, or in the outpatient setting.

2.3.9 Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS®) Version: 28.0.1.0 (142) IBM®. Continuous data variables are presented as median and interquartile range (IQR, Q1-Q3), and categorical variables as total number and percentage (%). All reported *P* values are two tailed, normally distributed continuous variables were compared using the Independent Samples *t* Test, non normally distributed variables were compared using the Mann-Whitney U test and categorical variables were compared using the χ^2 test. A univariate analysis was performed to assess for predictors of the development of RA at first presentation with ascites. Variables were assessed for suitability for entering into a multivariate logistic regression and were felt to be suitable if the *P* value was <0.1.

2.3.10 Ethical review

The study was classified as part of a service evaluation and therefore did not require any formal ethical consideration or approval.

2.4 Results

2.4.1 Identification of study population

A search of the hospital coding system was undertaken for all events over the study time period, between January 2013 and December 2015, where the clinical procedural classification codes of ‘T46.1’ & ‘T46.2’ ‘PARACENTESIS ABDOMINIS FOR ASCITES’ or ‘DRAINAGE OF ASCITES’ had been allocated. A list of hospital ID numbers were generated from the search, ID numbers are specific to one individual patient.

After removal of duplicate entries of the same patient ID number, a total of 419 patients were coded as having undergone LVP over the search period. Electronic patient records were searched, and 11 patients were excluded due to having insufficient clinical information or data available to undertake further analysis, this included cases where usual care was under a different hospital but a procedure had been performed while out of area.

A further 91 patients were excluded as there was no evidence of them having undergone an LVP, the majority of these had had an ascitic tap, where around 20 millilitres of ascitic fluid is aspirated for analysis using a similar technique with a small hollow needle, however a drain is not inserted.

One patient was excluded due to having hepatic hydrothorax, which is a less common complication of ESLD, where ascites collects in the pleural cavity, often preferentially over the abdomen. If an intervention is required to manage respiratory

compromise secondary to ascites accumulation in the pleural cavity, this is with a chest drain rather than with LVP, and is carried out under respiratory protocols rather than LVP protocols.[25]

A total of 316 patients were identified as having undergone LVP and were therefore taken forward for further data analysis.

2.4.2 Aetiology of ascites

Clinical information on each patient was searched to identify cases of ESLD who had undergone LVP, and exclude other aetiologies of ascites. Over half of cases, 167 (167/316 52.8%) had malignant ascites, 131 (131/316 41.4%) had ESLD and 18 (18/316 5.6%) had ascites due to other causes. The other aetiologies were congestive cardiac failure in 14, intra abdominal sepsis in two, end stage renal failure in one, and one with a portal vein thrombus secondary to a JAK2 mutation. The JAK2 mutation is found in myeloproliferative disorders, and results in a prothrombotic tendency, which can lead to venous thromboembolism, especially of the splanchnic circulation, which can lead to non cirrhotic portal hypertension and ascites development rather than as a result of intrinsic CLD.[98]

End stage liver disease

Tables 2.1 and 2.2 show the demographic data for the RA and non RA groups respectively.

In the ESLD group the majority 92/131 70% were male, with a median age at the time of first LVP of 57 years (range 34-91). Alcohol related liver disease (ARLD) was the most common cause of CLD requiring LVP 83/131 (63.3%), this was followed by a combination of ARLD with non-alcoholic steatohepatitis (NASH) in 16/131 (12.2%), cryptogenic cirrhosis in 7/131 (5.3%), ARLD with chronic hepatitis C (HCV) 6/131 (4.5%), HCV alone in 4/131 (3%), autoimmune related diseases: primary biliary

cholangitis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) 4/131 (3%), and chronic hepatitis B (HBV) in 2/131 (1.5%).

2.4.3 Large volume paracentesis

Almost half of the LVP procedures were carried out during an inpatient admission 63/131 (48%), whereas a much smaller proportion of patients underwent LVP solely on the medical day case unit 12/131 (9.1%). The remainder of patients had LVPs performed during both inpatient hospital admissions as well as at an elective day case attendance for the procedure 56/131 (42.7%).

A total of 49 (49/131 37.4%) patients with ESLD who underwent LVP met study criteria for the development of RA, which was defined as having undergone ≥3 LVPs within a six month period.

2.4.4 Refractory ascites group

Demographics

Demographics in the RA group were similar to the main group, being predominantly male 34/49 (69.3%), with median age of the development of an episode of decompensation due to any cause, and development of RA of 55 years (IQR 22, range 33-85) and 56 years (IQR 20, range 35 to 86) respectively (Table 2.1).

Table 2.1 Demographics of those with ESLD who developed RA

Variable	**Data presented as number, % or median, IQR**	
Gender		
	34 male (69.3%), 15 female (30.7%)	
Aetiology of CLD		
	ARLD	28 (57.1%)
	ARLD/NASH	10 (20.4%)
	ARLD/HCV	4 (8.1%)

Variable	Data presented as number, % or median, IQR		
Aetiology of CLD			
	NASH	3 (6.1%)	
	HCV	3 (6.1%)	
	Cryptogenic	1 (2%)	
Decompensation			
Age at development of first decompensation of any type (years)	55 (22)		
Age at development of RA (years)	56 (20)		
Time from first decompensating event to RA development (days)	595 (948)		
Liver disease severity scores			
	Child Pugh	**MELD**	**UKELD**
Scores at first development of ascites	B 8 (3)	14.1 (7.5)	54.1 (6.6)
Scores at development of RA	B 9 (8)	15.8 (7)	56.5 (11.6)
Complications			
Developed SBP	12 (24.4%)		
Developed HCC	2 (4%)		
Developed alcoholic hepatitis	2 (4.1%)		
Liver transplantation			
Referred for LT assessment	18/49 (36.7%)		
Accepted for LT of those referred (either transplanted or on transplant waiting list)	7/18 (38.9%)		
Large volume paracentesis			
Age at first LVP (years)	55 (22)		
Time from first decompensating event to first LVP (days)	348 (975)		
Time from first LVP to development of RA (days)	102 (236)		
Number of LVPs overall	7 (9)		
Survival			
Survival from first decompensation to death (days)	861 (1288.5)		
Survival from first ascites to death (days)	500 (559.5)		
Survival from first LVP to death (days)	260 (428.5)		
Survival from development of RA to death (days)	179 (152.5)		
Follow up time from first decompensation to death or last data review (days)	1276 (1035)		
Advance care planning and palliative care			
Palliative/supportive care or DNACPR documentation	22 (44.9%)		
Palliative care team referral	16 (32.7%)		
Advance care or long term management plan	13 (26.5%)		

ESLD End Stage Liver Disease, RA refractory ascites, IQR interquartile range, CLD chronic liver disease, ARLD alcohol related liver disease, NASH non-alcoholic steatohepatitis, HCV chronic hepatitis C, LVP large volume paracentesis, SBP spontaneous bacterial peritonitis, HCC hepatocellular carcinoma, LT liver transplant, DNACPR do not attempt cardiopulmonary resuscitation

Aetiology of chronic liver disease

The most common aetiology of CLD was ARLD 28/49 (57.1%), others were ARLD with NASH in 10/49 (20.4%), ARLD with HCV 4/49 (8.1%), NASH 3/49 (6.1%), HCV 3/49 (6.1%), and one patient with cryptogenic cirrhosis developed RA.

Over half of cases had evidence of persistence of risk factors for progression of severity of liver disease 29/49 (59.2%), such as ongoing alcohol use and untreated chronic hepatitis C.

Liver disease severity scores

The liver disease severity scores in standard use are the Child Pugh, MELD and UKELD.[22,23,97] Scores were recorded at first development of ascites, and again at the development of RA, if it had developed, and were as follows: first development of ascites Child Pugh B8 (IQR 3), MELD 14.1 (7.5), UKELD 54.1 (6.6) and at development of RA Child Pugh B9 (IQR 8), MELD 15.8 (7), UKELD 56.5 (11.6).

Complications

In 12/49 (24.4%) patients with RA an episode of SBP had occurred, and 29/49 (59.2%) had been prescribed antibiotics as prophylaxis for SBP development.

Two patients had developed HCC 2/49 (4%) and two had previously had an episode of alcoholic hepatitis 2/49 (4%).

Liver transplant

A referral for LT assessment was made in 18/49 patients (36.7%), 16 of those underwent an assessment 16/18 (88.9%), one died before being assessed and the

second was not assessed as their liver disease severity scores did not meet assessment criteria, following this the patient then recompensated. Reasons for an LT referral not taking place despite the patient having RA were as follows: ongoing alcohol usage 12/49 (24.5%), age with co-morbidity 8/49 (16.3%), comorbidities 5/49 (10.2%), liver disease severity scores not meeting criteria in 3/49 (6.1%) and a reason was unable to be found in 3/49 (6.1%).

Of the 18 patients who were referred for LT assessment, seven were accepted for LT (7/18 38.9%) and six had been transplanted, the seventh patient was still on the transplant waiting list at the time of data acquisition.

Therefore overall in those who developed RA, seven (7/49 14.3%) were accepted for LT and had either been listed for transplant or already transplanted at the time the study took place.

Development of refractory ascites and drainage episodes

The median age at first LVP episode was 55 years (IQR 22) and median time in days from first decompensating event to first LVP was 348 days (975). Median time from first LVP to development of RA was 102 days (236) and median time in days to the development of RA from any first decompensating event was 595 days (IQR 948, range 34-2179).

The median number of LVP procedures which were undertaken in the RA group was seven (IQR 9, range 4 to 62), this is in comparison with the group who did not develop RA where the median number of LVP procedures was one (IQR one).

Survival

At the time of study data acquisition, 22 (22/49, 44.9%) patients who had developed RA were alive compared to 39 (39/82 47.6%) in the group who underwent LVP but did not develop RA. Median survival from first decompensation of any cause to death

was 861 days (1288.5). Follow up from time of first decompensation to death or final data review at the end of study follow up was 1276 days (1035). Median survival from the first development of ascites to death was 500 days (559.5). Median survival from first LVP to death was 260 days (428.5) and median survival from the development of RA to death was 179 days (152.5).

Advance care planning

In the refractory ascites group, 22/49 (44.9%) had evidence of a discussion regarding palliative care, supportive care or a DNACPR decision documented in their electronic patient records. Only 16/49 (32.7%) had a referral made to the palliative care team for supportive care and 13/49 (26.5%) had documentation pertaining to advance care planning or a long term management plan.

2.4.5 Non refractory ascites group

Demographics

Demographics in the non refractory ascites group reflected that of the whole LVP group and the RA group with 57/82 (69.5%) being male and the median age of decompensation due to any cause being 58 years (IQR 17.75, range 30 to 91) (Table 2.2).

Table 2.2 Demographics of those with ESLD and underwent LVP without RA development

Variable	**Data presented as number, % or median, IQR**	
Gender		
	57 male (69.5%), 25 female (30.5%)	
Aetiology of CLD		
	ARLD	54 (65.9%)
	NASH	7 (8.5%)
	ARLD/NASH	6 (7.3%)
	Cryptogenic	6 (7.3%)

Variable	Data presented as number, % or median, IQR		
Aetiology of CLD			
	PBC/PSC/AIH	4 (4.9%)	
	ARLD/HCV	2 (2.4%)	
	HCV	1 (1.2%)	
Decompensation			
Age at development of first decompensation of any type (years)	58 (17.75)		
Liver disease severity scores			
	Child Pugh	**MELD**	**UKELD**
Scores at first development of ascites	B 9 (3)	15.5 (8.5)	55.7 (7.8)
Complications			
Developed SBP	19 (23.2%)		
Developed HCC	5 (6.1%)		
Developed alcoholic hepatitis	3 (3.7%)		
Liver transplantation			
Referred for LT assessment	8/82 (9.8%)		
Accepted for LT of those referred (either transplanted or on transplant waiting list)	3/8 (37.5%)		
Large volume paracentesis			
Age at first LVP (years)	58.5 (18)		
Time from first decompensating event to first LVP (days)	128.5 (805.75)		
Number of LVPs overall	1 (1)		
Survival			
Survival from first decompensation to death (days)	579 (1333)		
Survival from first ascites to death (days)	374 (621)		
Survival from first LVP to death (days)	85 (411)		
Follow up time from first decompensation to death or last data review (days)	739.5 (1352.5)		
Advance care planning and palliative care			
Palliative/supportive care or DNACPR documentation	21 (25.6%)		
Palliative care team referral	14 (17.1%)		
Advance care or long term management plan	17 (20.7%)		

ESLD End Stage Liver Disease, RA refractory ascites, IQR interquartile range, CLD chronic liver disease, ARLD alcohol related liver disease, NASH non-alcoholic steatohepatitis, HCV chronic hepatitis C, LVP large volume paracentesis, SBP spontaneous bacterial peritonitis, HCC hepatocellular carcinoma, LT liver transplant, DNACPR do not attempt cardiopulmonary resuscitation

Aetiology of chronic liver disease

The commonest aetiology of CLD followed that as in the RA group, ARLD 54/82 (65.9%) with NASH being the second most common 7/82 (8.5%). ARLD/NASH in 6/82 (7.3%), cryptogenic cirrhosis 6/82 (7.3%), autoimmune related diseases: (PBC, PSC and AIH) 4/82 (4.9%), ARLD/HCV 2/82 (2.4%) and HCV 1/82 (1.2%).

In the non RA group, there was evidence of ongoing risk factors in 38/82 46.3%, 34/82 (41.5%) did not have identifiable ongoing risk factors and in 10/82 (12.2%) the presence of ongoing risk factors was unknown, as documentation of this information could not be found.

Liver disease severity scores

In the non RA group, scores were recorded at first development of ascites and were as follows: first development of ascites Child Pugh B9 (IQR 3), MELD 15.5 (8.5), UKELD 55.7 (7.8).

Complications

In 19/82 (23.2%) patients in the non RA group, an episode of SBP had occurred and 23/82 (28%) had been prescribed antibiotics as prophylaxis for SBP development. Five patients had developed HCC 5/82 (6.1%) and three had previously had an episode of alcoholic hepatitis 3/82 (3.7%).

Liver transplant in ESLD without RA

In the group who underwent LVP but who did not go on to develop RA, eight were referred for LT assessment (8/82, 9.8%). Of those who were referred for LT assessment, six underwent assessment, one died before undergoing an assessment and the further patient who was referred to a liver transplant centre for assessment during an inpatient hospital admission was declined for assessment due to ongoing

alcohol usage up to the time of hospital admission. Of those without RA who were assessed for LT, three (3/6, 50%) underwent transplantation, two were declined due to the presence of other comorbidities, and one further was declined due to liver disease severity scores not meeting minimum criteria for LT. Overall, of the eight patients who were referred for LT assessment, three 3/8 (37.5%) were accepted for transplant, or were on the LT waiting list at the time of data acquisition.

Drainage episodes

Median age at first LVP episode was 58.5 years (IQR 18, range 34 to 91 years) and median time in days from first decompensating event to first LVP was 128.5 days (806). In the non RA group, the median number of LVPs which were undertaken was 1 (IQR 1).

Survival

At the time of study data acquisition, 39 (39/82, 47.6%) patients in the non RA group were alive. Median survival from first decompensation of any cause to death was 579 days (1333). Follow up from time of first decompensation to death or final data review at the end of study follow up was 739.5 days (1352.5). Median survival from the first development of ascites to death was 374 days (621) and median survival from first LVP to death was 85 days (411).

Advance care planning

In the non refractory ascites group, 21/82 (25.6%) had evidence of a discussion regarding palliative care, supportive care or a DNACPR decision documented in their electronic patient records. Only 14/82 (17.1%) had a referral made to the palliative care team for supportive care and 17/82 (20.7%) had documentation evident of any advance care planning, or of a long term management plan.

2.4.6 Comparison between RA and non RA group

Patient characteristics between the RA and non RA groups were analysed for differences between the two groups (Table 2.3).

Table 2.3 Patient characteristics in refractory ascites and non refractory ascites groups, data presented as number, % or median, IQR

Variable	Non RA group	RA group	p value median
Age (years) at first decompensation	58 (17.75)	55 (22)	0.605
Female	25 (30.5%)	15 (30.7%)	0.988
Blood results at time of presentation with ascites			
Sodium (mmol/L)	134.5 (3)	135 (5)	0.645
Creatinine (μmol/L)	65.5 (41.75)	60 (47)	0.812
Bilirubin (μmol/L)	44.5 (84.25)	38 (50)	0.208
Albumin (g/L)	30 (6)	32 (4)	0.04
INR	1.4 (0.4)	1.3 (0.2)	0.712
Platelet count (10^9/L)	224 (99.5)	127 (81)	0.702
ALT (IU/L)	28 (39)	31.5 (30.75)	0.796
ALP (IU/L)	177 (109.75)	168 (105)	0.218
Scores at first presentation with ascites			
Child Pugh score	B 9 (3)	B 8 (3)	0.078
MELD Score	15.5 (8.5)	14.1 (7.5)	0.26
UKELD Score	55.7 (7.8)	54.1 (6.6)	0.282
Ongoing risk factors identified	38 (46.3%)	29 (59.2%)	0.487
Spontaneous bacterial peritonitis	19 (23.2%)	12 (24.4)	0.864
Hepatocellular carcinoma	5 (6.1%)	2 (4%)	0.62
Survival (days) from first decompensating event to death	579 (1333)	861 (1288.5)	0.27
Survival (days) from first development of ascites to death	374 (621)	500 (559.5)	0.11

Variable	Non RA group	RA group	p value median
Time (days) from first decompensating event to first LVP	128.5 (805.75)	348 (975)	0.6
Survival from first LVP to death (days)	85 (411)	260 (428.5)	0.007
% = percentage, IQR = interquartile range, RA = refractory ascites, CI = confidence interval, mmol = millimole, L = litre, μmol = micromole, g = grams, INR = international normalised ratio, ALT = alanine transaminase, ALP = alkaline phosphatase, IU = international units, LVP = large volume paracentesis			

There were no statistical differences in age at first decompensation of any type, nor in sex, between the two groups. Blood results were recorded at a baseline point, for this study this was at the first development of ascites in both groups, only serum albumin level reached statistical significance in terms of those who did go on to develop RA and those who did not, *p* =0.04. None of the liver disease severity scores calculated at the first development of ascites showed any statistical differences between the RA and non RA groups at baseline. Although at baseline, both the non RA and RA groups had evidence of persistent risk factors for liver disease progression, 38/82 (46.3%) and 29/49 (59.2%) respectively, there was no statistical difference between them. There was a statistically significant difference in survival from first LVP to death in the RA and non RA groups, showing survival was shorter in those who did not go on to develop RA *p* =0.007.

A univariate logistic regression was undertaken on the results reported, and serum albumin at first development of ascites was the only variable which reached statistical significance as predictive of the development of RA *p* = 0.043 (Table 2.4).

Table 2.4 Univariate analysis of patient characteristics in those who developed RA

Variable	Odds ratio	95% lower CI	95% upper CI	P value
Age (years) at first decompensation	0.993	0.966	1.02	0.602
Female	0.994	0.461	2.143	0.988
Blood results at time of presentation with ascites				
Sodium (mmol/L)	1.013	0.959	1.07	0.642
Creatinine (μmol/L)	1.0	0.993	1.007	0.918
Bilirubin (μmol/L)	0.997	0.993	1.001	0.19
Albumin (g/L)	1.082	1.002	1.169	0.043
INR	0.534	0.17	1.671	0.281
Platelet count (10^9/L)	0.999	0.994	1.003	0.593
ALT (IU/L)	0.996	0.985	1.006	0.394
ALP (IU/L)	0.999	0.996	1.002	0.368
Scores at first presentation with ascites				
Child Pugh score	0.831	0.675	1.022	0.08
MELD Score	0.964	0.903	1.028	0.261
UKELD Score	0.972	0.922	1.024	0.283
Ongoing risk factors identified	0.771	0.370	1.606	0.487
Spontaneous bacterial peritonitis	0.93	0.406	2.130	0.864
Hepatocellular carcinoma	1.526	0.285	8.183	0.622
Survival (days) from first decompensating event to death	1.0	1.0	1.001	0.412
Survival (days) from first development of ascites to death	1.0	0.999	1.001	0.387
Time (days) from first decompensating event to first LVP	1.0	0.999	1.001	0.956
Survival from first LVP to death (days)	1.001	1.0	1.002	0.151

% = percentage, IQR = interquartile range, RA = refractory ascites, CI = confidence interval, mmol = millimole, L = litre, μmol = micromole, g = grams, INR = international normalised ratio, ALT = alanine transaminase, ALP = alkaline phosphatase, IU = international units, LVP = large volume paracentesis

Given no further variables other than Child Pugh score, which is a composite score calculated from other variables described and therefore cannot be used as an independent variable alongside any of its individual components, met the criteria of $p < 0.1$ for entry into a multivariate logistic regression model, this was not performed.

2.5 Discussion

2.5.1 Key findings

Refractory ascites is reported in the literature as developing in 10% of those with cirrhosis and decompensation with ascites, however, a description of the natural history of RA in the context of large volume paracentesis is limited, specifically its development in those undergoing an initial LVP.[33,50,94]

A consecutive unselected cohort of patients undergoing LVP over a three year study period, January 2013 to December 2015, in a large teaching hospital in the Southeast of England has been characterised.

The findings have shown that close to 40% of the patients with end stage liver disease and ascites who underwent an LVP procedure subsequently went on to develop RA. Interestingly, although at baseline both groups had ongoing risk factors for liver disease progression, there was no statistical difference between those who went on to develop RA, and those who did not, and additionally, ongoing risk factors at baseline was not predictive of the development of RA on univariate logistic regression analysis p =0.487.

Of the patient characteristics at baseline, only the serum albumin level showed statical significance in terms of difference between those who went on to develop RA and those who did not. Liver disease severity scores at baseline development of ascites were not significantly different in the RA and non RA groups, and were not helpful in predicting the development of RA.

In those who developed RA, only a small proportion, 18 (36.7%) were referred for liver transplant assessment with seven (14.3%) accepted for LT at the time the study took place. The most frequent barrier which precluded referral for LT assessment in this group was alcohol recidivism.

2.5.2 Further important findings

Our data reflected the current literature reports of life expectancy of those who develop RA being a median of six months,[39,51,55,94] in the RA group the median survival from the development of RA to death was 179 days.

Interestingly, the survival data showed that those in the non RA group had overall worse survival from all measured time points: first decompensation episode, first development of ascites, as well as from first LVP. The differences however only reached statical significance in survival from first LVP to death. This unexpected finding could suggest that patients in the non RA group who underwent an LVP were more clinically unstable at the baseline development of ascites, and their ascites development may have been in the context of an acute event, possibly acute on chronic liver failure (ACLF).[99] Another explanation is that it may also be as a result of the identification of patients resulting in a sampling bias. This is by which all patients identified had advanced disease, given they had all required at least one LVP, however only those who survived long enough to have undergone three or more LVPs were then allocated to the RA group.

Although there is a well recognised limitation in life expectancy in the context of RA, less than half of those in the RA group, 44.9%, had evidence of a discussion regarding palliative care, supportive care or a DNACPR decision documented and even fewer, 26.5%, had any documentation pertaining to advance care planning. This is despite only a minority of patients in the RA group being eligible for LT and accepted on to the LT waiting list.

2.5.3 Current management of refractory ascites

LT is the only curative measure for RA, however, only a comparatively small proportion of patients are eligible for transplant assessment, and up to 40% of those proceeding to the stage of assessment are subsequently declined transplantation.[20,53–56] Those patients who have been listed for LT still require management of their ascites, and although there are a number of interventions which have been used in RA, LVP remains the mainstay of management.[25,28]

2.5.4 Palliative care in end stage liver disease and refractory ascites

If patients who have developed RA are deemed ineligible for LT, they are in effect in a palliative phase of their disease trajectory, with the most common palliative intervention for ascites being LVP.[28] In England, a significant number of LVPs are undertaken in patients with cirrhosis in their last year of life, both at planned hospital day case attendances and during emergency admissions.[52] This represents not only a symptom burden for individual patients, but also an associated personal and healthcare related financial burden.[52]

Patients with ESLD and RA have a significant symptom burden and palliative and symptom support is often focussed on managing ascites.[46,47,100] Due to the underlying pathophysiology of ascites development being unaltered, LVP typically

only results in short lived symptom relief of a few days, before the rapid re-accumulation of ascites results in the recurrence of symptoms.[47]

2.5.5 Impact of RA on prognosis and patient care

The development of RA is an important step where a patients' liver disease has become life limiting and should therefore be a trigger to clinicians for instigating discussions for 'parallel planning', where patients' understanding of their ESLD and preferences in care can be explored, alongside active management of decompensation.[37,81,85,95,101] Up to 90% of those who die from liver disease are admitted to hospital within the preceding year, often relating to ascites.[52,101] These episodes are opportunities for discussions regarding the unpredictable trajectory of ESLD, prognosis, preparing for uncertainty in disease progression, unmet supportive needs, and for advance care planning.[37,56,57,81,102] The onset of RA is one of the clinical indicators used in palliative care in identifying patients at risk of deteriorating and dying.[37] Gastroenterologists and hepatologists are traditionally less familiar with tackling discussions about prognosis, uncertainty in disease trajectory, and advance care planning, as often care in cirrhosis is focussed on interventions and geared towards LT.[85,86,102,103] However, since many patients are not eligible for LT and the burden of ESLD in the UK is increasing, there is a growing movement to improve palliative and supportive care in this group.[81,85,104,105] Early palliative care can improve symptom control,[84] however many opportunities to discuss advance care planning and palliative care are missed.[47,85,102,104] Patients with ESLD are often unaware that they are in a palliative phase of their disease, despite frequent hospital attendances and interactions with clinicians, and rarely receive a palliative care referral.[47,85,87,104]

2.5.6 Communication of advance care planning

Advice regarding good practice in clinical care is that once discussions regarding advance care planning have been undertaken, it is essential that General Practitioners (GP) are informed, to allow outcomes to be recorded and the GP palliative care register updated to better co-ordinate supportive care in the community.[85] Acute hospital attendances, both day cases and inpatient admissions, require communication with GPs via discharge summaries, which are now electronic, and are delivered to GPs electronically within 24 hours of completion.[106] This has improved the speed of information sharing, however, the quality of information conveyed is vitally important, and since the completion of discharge summaries usually falls to more junior clinicians, this can be more variable.[107,108]

2.5.7 Study data in clinical context

Since our data shows that less than 40% of those with ESLD and RA were felt eligible for LT assessment by their clinical team, and even fewer, less than 15%, were accepted for LT, that even in those listed for LT this represents a large burden of ongoing ascites management, the current standard of care being repeated LVP. It is surprising that although overall the disease trajectory of decompensated cirrhosis is often unpredictable, representing a challenge for clinicians in active management while balancing uncertainty and patient expectations, RA is well recognised as significant in terms of limitation of life expectancy, and yet our data shows that only a small number of patients had evidence of any sort of discussion regarding prognosis or advance care planning. It could be the case that those undergoing regular LVP in acute medical day case units do so without hepatology oversight and perhaps opportunities for these discussions are missed. Those undergoing LVPs solely on the acute medical day case unit however represented a

much smaller proportion of patients 12/131 (9.1%) than those who had LVPs during an inpatient admission and those who underwent the procedure both during the course of an inpatient admission as well as electively on the acute medical day case unit. This suggests then that despite inpatient admissions at the hospital Trust usually being under the care of the gastroenterology/hepatology team, that opportunities were still missed. There is evidence of physicians finding discussions regarding prognosis and advance care planning in ESLD challenging, despite being able to confidently recognise ESLD as a stage in the natural history of cirrhosis itself.[102,103] It could be that lack of experience or confidence in this aspect of patient care results in fewer potential opportunities for these discussions to be utilised.[102,105] It is not within the scope of this study to assess the impact of lack of discussions regarding prognosis and advance care planning on patient care, however earlier instigation of palliative care in those with ESLD awaiting LT has been shown to result in an improvement in symptom burden and mood.[84,105]

2.5.8 Study limitations

This was a retrospective electronic case records review, with cases identified using the clinical coding system. There are a number of areas where data may have been missed, such as case identification only relying on coding, which has its inherent problems of not always reliably capturing all cases, as well as miscoding others incorrectly.

As this was a review of electronic patient records, more data may have been available within paper records but inadequately recorded in communication with GPs, such as during completion of inpatient hospital admission clinical discharge summaries. Procedures and significant discussions, including those where it had been felt that a palliative stage of patients disease had been reached, and decisions

regarding resuscitation status, should always be communicated to patients GPs in a timely manner. This however relies mainly on the clinician completing the electronic records, and therefore there may have been missed opportunities in communication of these significant discussions with patients.

Some identified patients had no record of having undergone an LVP at all, and some had no clinical records, therefore these had to be excluded and it was unclear how they had received the procedural codes described.

Overall all attempts were made to review all electronic records relating to patients from all available sources, including pathology results of samples of ascites having been sent, therefore as many cases as possible were included and as much information as possible was collected in an effort to complete the dataset.

In terms of timepoint for data collection and analysis, it was felt that the initial development of ascites was an appropriate baseline timepoint with which to compare the patients who then either went on to develop RA, with those who did not. It could be suggested that other timepoints might have been appropriate, however this was felt to be a clear reproducible point in the progression from compensated to decompensated cirrhosis.

In terms of survival, the shorter survival in the non RA group may have been as a result of a sampling bias. Only patients who survived long enough to have undergone three or more LVPs were allocated to the RA group, however, in reality, all patients who have required an LVP are at an advanced stage of disease.

2.6 Conclusion

We have characterised an unselected consecutive cohort of patients coded as having undergone a large volume paracentesis over a three year period in a large NHS hospital Trust in England. The findings showed that in those with ESLD who

underwent LVP, almost 40% went on to develop refractory ascites, and only a minority of those were eligible for liver transplantation. Only baseline serum albumin was both significantly different in the two groups and also reached statistical significance in terms of predictors of those who went on to develop RA.

Those who developed RA underwent a median number of seven LVPs, but it was not unusual for this number to be much higher, with an IQR of nine, and highest recorded number of LVPs being 62, this is with an associated symptom burden for patients as well as healthcare, logistic, and financial burden. In those with RA, discussions regarding advance care planning and palliative care were limited and underutilised, and there is scope within optimising patient care to improve this.

Chapter 3 - Permanent Indwelling Peritoneal Catheters for the Palliative Management of Refractory Ascites in End Stage Liver Disease: A Systematic Review

3.1 Introduction

In the United Kingdom (UK) over the last 40 years, the incidence of chronic liver disease (CLD) and related mortality has increased dramatically.[1] The complexity of palliative and end of life care (EoLC) in end stage liver disease (ESLD) means the majority die in hospital,[42] with minimal specialist palliative care provided in a hospice or community setting.[109]

Ascites develops in most (approximately 90%) individuals with ESLD.[20,27] Refractory ascites (RA) either represents diuretic resistance (lack of response); or diuretic intolerant ascites (development of complications precluding further use).[27,38] Upon the development of RA, the median survival is only 6 months,[27] therefore mandating consideration of suitability and assessment for potential liver transplantation (LT). Only a minority with ESLD (1.3%-12%)[35,58,110] are eligible for consideration of LT assessment due to ongoing substance misuse, alcohol recidivism, comorbidities, psychosocial issues, advanced disease stage and in the context of a limited donor pool, actually proceed to undergo LT. [35,57,58,110,111] Additionally, such individuals are often also not deemed to be candidates for transjugular intrahepatic portosystemic shunt (TIPS) or the ALFApump® due to advanced disease stage.[65]

Individuals with RA who are not LT candidates are therefore considered to be in a palliative phase of their disease process. Since ascites is the most common complication in ESLD, palliation of symptoms is dominated by the management of RA. The most accepted palliative intervention is large volume paracentesis (LVP),

requiring repeated acute hospital attendance to medical day units or inpatient admission, and insertion of a temporary drain.[27] Other management strategies such as the automated low flow (ALFApump®)[65] pump and TIPS could be considered unsuitable or not appropriate as palliative interventions given the invasive nature of the procedures.[27]

RA development has a major impact on quality of life (QOL), resulting in a considerable symptom burden including abdominal distention, dyspnoea, and poor appetite.[47] RA management currently mandates frequent hospital attendances for LVP, although this only offers limited symptom relief, as the natural history of ascites due to ESLD is of continuous accumulation.

Permanent indwelling peritoneal catheters (PIPC) are currently a nationally accepted strategy in the palliation of recurrent malignant ascites.[76,78] Two PIPC are commercially available, PleurX™ and Rocket® Medical.[77,78] A National Institute for Health and Care Excellence (NICE) technology appraisal reported low device related infections (5.8%), 100% technical success, and improvements in symptom control.[76] There has been reluctance towards PIPC in an ESLD population due to concerns which are mainly surrounding infection risk and specifically peritonitis, due to the increased susceptibility to infection in ESLD due to cirrhosis associated immune dysfunction.[61] The systematic review presented in this chapter has been published in Liver International with publication details in the references.[112]

3.2 Aims

The aim of this systematic review is to identify and summarise the published available data on the use of PIPC in RA due to ESLD.

3.3 Methods

A formal protocol was not written, as ethical approval was not required. The aim was 'to describe the current evidence available on the use of PIPC in RA due to ESLD'. This was broken down using the PICOS (participants, interventions, comparators, outcomes and study design) structure as described by PRISMA (Preferred Reporting Items for Systematic reviews and Meta Analyses).[113]

3.3.1 PICOS

Participants

Those with RA in the context of ESLD.

Intervention

The use of PIPC in the palliative management of recurrent ascites.

Comparisons

Not relevant as no known comparison studies.

Outcomes

This included:

- Numbers of participants with ESLD
- Reporting of adverse events (AE) and complications, particularly infection related
- The use of prophylactic antibiotics
- Details of where subsequent drainage was performed
- Duration PIPC remained in situ
- Specialist palliative care support provided
- Survival of participants following insertion of PIPC
- Quality of life measures
- Health economic considerations

Study design

Randomised controlled trials, prospective and retrospective cohort studies as well as case series and reports were included. Studies were not excluded if only reported as conference proceedings in view of the paucity of available data.

3.3.2 Search strategy

See appendix 1 for database systematic review search strategies.

A systematic electronic search was performed using the following databases: MEDLINE, EMBASE, CINAHL (The Cumulative Index to Nursing and Allied Health Literature) as well as Google Scholar and the Cochrane Database of Systematic Reviews. Platforms used to access the databases were the Healthcare Databases Advanced Search (HDAS) and OVID (research platform). The initial search was undertaken in December 2015 (Table 3.1 below shows the databases used and dates searches were performed).

Table 3.1 Databases used and dates searches performed

Databases	Date initial search performed	Date repeat search performed
Medline (HDAS) (1946 to date of search)	7.12.15	13.03.18
Medline (OVID) (1946 to date of search)	3.12.15	13.03.18
Embase (HDAS) (1974 to date of search)	4.12.15	13.03.18
Embase (OVID) (1974 to date of search)	7.12.15	13.03.18
CINAHL (HDAS) (1981 to date of search)	8.12.15	13.03.18
Cochrane library	8.12.15	13.03.18

The first search theme related to ascites, the second to palliative care, both were subsequently combined (Table 3.2). Search results were limited to English language publications. The initial search strategy was modified, following pilot searches, by removal of liver disease as a search theme, to capture studies without limiting participants to disease type. All levels of evidence were included as the current published evidence surrounding the theme is very limited, and wanting to ensure this was all captured.

Keywords and Medical Subject Headings (MeSH)

Medical Subject Headings (MeSH headings) and keyword search terms, itemised below, were constructed using results from pilot searches (Table 3.2).

Table 3.2 Keywords and Medical Subject Headings (MeSH)

Keywords
Ascit*, “refractory ascit*”, “resistant ascit*”, (refractory AND ascit*), (resistant AND ascit*), “ascitic drain*” (ascitic AND drain*), “diuretic intolerant ascit*”, paracentesis, “palliative medicine”, palliat*, “terminal care”, terminal*, “palliative care”, (palliative AND medicine), (palliative AND care), (terminal AND care), “end of life care”, (end AND of AND life AND care), (hospice AND care), hospice*
MeSH Terms
ASCITES, ASCITIC FLUID, PORTAL HYPERTENSION, TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT, PARACENTESIS, TERMINAL CARE, TERMINALLY ILL, PALLIATIVE CARE, PALLIATIVE MEDICINE, HOSPICE AND PALLIATIVE CARE NURSING, HOSPICE CARE, HOSPICES

References from database searches were exported into the Endnote™ web basic reference manager.

Hand searching of reference lists in relevant manuscripts meeting inclusion criteria was performed. Online portals for major journals including Hepatology (American Association for the Study of Liver Diseases journal) and the Journal of Hepatology (The European Association for the Study of the Liver journal) were searched for relevant publications and conference abstracts.

The search was updated on 13th March 2018 using the same methodology and search strategies. Articles were screened and reviewed using the original exclusion and inclusion criteria (Table 3.3).

3.3.3 Eligibility criteria

Table 3.3 below itemises the inclusion and exclusion criteria used to screen studies.

Table 3.3 Eligibility criteria

Inclusion criteria	**Exclusion criteria**
Adult participants (≥18 years of age)	Paediatric participants (<18 years of age)
PIPC for recurrent drainage of ascites secondary to liver disease	Animal studies
English language articles	Shunting devices (including peritoneovenous, TIPS) and ALFApump®
	Manuscripts reporting solely on malignant ascites and/or patients undergoing chemotherapy

3.3.4 Study selection

Lucia Macken (LM) and Ahmed Hashim (AH) took part in the initial study selection process. LM independently reviewed titles and abstracts of identified articles for relevance and screened all full text selected manuscripts, applying eligibility criteria. AH reviewed a selection of these independently.

3.3.5 Quality assessment

The Newcastle Ottawa Scale (NOS) was used as an objective tool to assess the quality of studies meeting inclusion criteria.[114] The NOS was developed to assess the quality of non randomised studies including case control and cohort studies.

3.3.6 Data extraction

LM designed a data extraction form which was applied to each of the selected studies by LM and AH independently. Data were extracted on study design, participants, complications, and outcomes. Results were compared for consistency with inconsistencies reviewed, where needed, by Professor Sumita Verma (SV).

3.3.7 Statistical analysis

Studies identified for full analysis were heterogeneous in design and reporting and had small sample sizes, therefore a descriptive approach was taken in terms of statistical analysis.

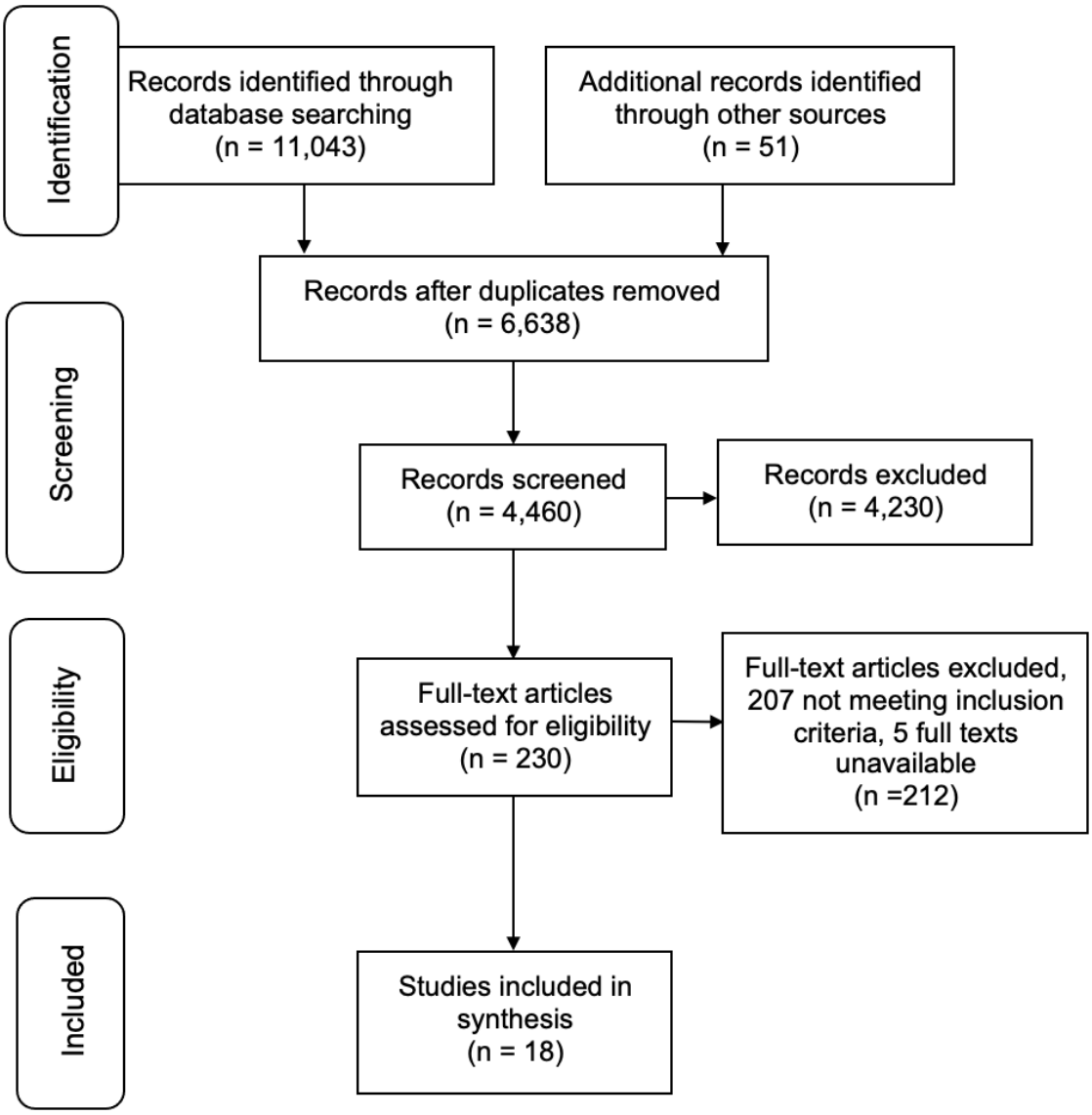
3.4 Results

The database search returned 11,043 results. An initial screen for duplicate results performed using Endnote™ resulted in 6634 duplicates being removed. On screening of titles of the remaining references, a further 4230 were removed on the basis of: duplications not initially detected by Endnote™, exclusion criteria and

relevance to the topic. Five full texts were unavailable in print or electronic format from other UK libraries, including the British Library and therefore excluded. It was however felt that this would not affect the overall results as the titles included shunt procedures n=2, malignant ovarian ascites and a review article. Full texts for the remaining 174 citations were put forward for full text review.

In addition to the updated database search, citations identified through hand searching of journals, conference abstracts, reference lists of relevant manuscripts, and those made known to the author were included, yielding a further 51 citations. In total, 225 studies were identified for full text review. A total of 18 studies met full inclusion criteria for final analysis, see figure 3.1, PRISMA flow diagram.

Figure 3.1 PRISMA flow diagram



3.4.1 Study characteristics

Studies included in the systematic review are summarised in table 3.4. Of the final 18 studies included, one was planned as a pilot randomised controlled trial of PIPC versus LVP but only recruited one patient into each arm.[115] Three were prospective[116–118] and seven retrospective cohort studies;[119–125] one retrospective

cohort study with matched controls;[126] five were case series;[127–131] one was a case report.[132] Of these, 12 studies were available as full manuscripts[115–118,120,121,123,125,126,129,131,132] and six as conference abstracts.[119,122,124,127,128,130]

Ten studies reported solely on RA due to cirrhosis;[115,118,119,121,124,127–129,131,132] of these, two were of cohorts which included both ascites and hepatic hydrothoracies.[119,124] These studies were not excluded due to the paucity of studies discovered, although those reporting solely on hepatic hydrothoracies were excluded due to this requiring a differing management strategy. The remaining eight studies described heterogeneous groups,[116,117,120,122,123,125,126,130] including ascites due to cirrhosis, malignancy, and other aetiologies with one reporting on both abdominal and pleural indwelling catheters.[116]

Due to the small numbers of published manuscripts, studies including participants with both CLD and non CLD aetiologies for ascites were not excluded from analysis. Only studies which did not include any participants with CLD as an underlying aetiology were excluded.

The heterogenicity of study design and reporting was a limitation for data extraction. Inconsistencies in the reporting of PIPC related complications and overall survival hampered direct comparison.

3.4.2 Patient characteristics

Across all studies, 176 patients with refractory abdominal ascites due to cirrhosis were described. Separate studies independently reported on between one to 33 patients from this group with RA due to cirrhosis. Cases of hepatic hydrothoracies which were described along with those of abdominal ascites in two studies,[119,124] have not been included in the final analyses.

Baseline liver disease severity scores were reported inconsistently, Model of End Stage Liver Disease (MELD)[23] mean score ranging from 10 to 22 and Child Pugh B or C across studies reporting both modalities;[119,121,124,126,129] Child Pugh (CP)[22] grade B or C in three studies solely reporting CP[117,122,131] and mean MELD scores of 17 and 19 respectively in the two studies solely reporting MELD.[118,125] The remaining eight studies did not record any severity scores.[115,116,120,123,127,128,130,132]

Table 3.4 at the end of the chapter summarises the studies.

3.4.3 Quality

Quality was assessed using the NOS, with thresholds converting NOS scores to the Agency for Healthcare Research and Quality standards of good, fair and poor.[114] All but one study scored six (maximum score of nine); the breakdown of the scores into the three domains (selection, comparability and outcome) scoring all studies as 'poor', since none scored points in the comparison domain. The one study which scored eight, was a well designed pilot randomised controlled trial of tunnelled peritoneal dialysis catheters versus LVP, however it could not be rated higher than 'fair' due to only two patients being enrolled, one to each arm, the outcomes therefore being significantly limited.[115]

3.4.4 Type of indwelling catheter

All studies included reported on permanent indwelling devices, comprising of permanent indwelling (tunnelled) peritoneal catheters in twelve studies (both PleurX™ and Rocket®),[118–124,126–129,132] permanent subcutaneous ports with intra abdominal catheters (three studies)[116,117,131] and permanent tunnelled peritoneal dialysis catheters (three studies).[115,125,130]

3.4.5 Procedural insertion and success

In all 18 studies there was a 100% technical success rate for insertion of catheters in patients with ESLD. Catheters were inserted by interventional radiologists in eight studies,[116,117,119,120,123,124,128,131] six of which stated insertion was performed under ultrasound guidance.[116–118,120,123,131] Three studies stated drainage catheters were inserted with ultrasound guidance but not by whom.[118,121,132] Catheters were inserted by interventional nephrologists in two studies,[115,125] one stating ultrasound and fluoroscopic guidance was used.[125] In a further two studies, catheters were inserted by consultant physicians/gastroenterologists under ultrasound guidance.[122,129] Two studies did not report on insertion methods;[118,127] one study reported catheters were inserted by trained physicians using X ray guidance,[126] and one drainage catheter was inserted surgically (Tenckhoff catheter)[130] (Table 3.4). There were no device related deaths reported.

3.4.6 Antibiotic prophylaxis

Nine studies used periprocedural antibiotics for initial insertion of indwelling catheters;[115–118,120,122,125,126,131] six of these did not use further ongoing long term prophylactic antibiotics,[115–117,120,125,131] whereas two used prophylaxis only in limited cases.[118,126] Cephalosporins were used for periprocedural prophylaxis in six studies,[116,117,120,122,126,131] with one study using Metronidazole in addition,[116] two studies using peritoneal dialysis catheters used either Cefazolin or Vancomycin,[115,125] and a further solely using Sulbactam/Ampicillin.[118] In one study, two patients with cirrhosis were commenced on long term antibiotic prophylaxis following development and successful treatment of bacterial peritonitis (BP).[122] In these two cases,[122] drainage catheters were not removed but were left in situ throughout. Four studies reported the use of long term antibiotic prophylaxis

(Ciprofloxacin or Norfloxacin);[118,126,127,129] in one of these, a case series, prophylaxis was only used in the final two patients after review of the initial five cases,[129] a second used prophylaxis if there was a history of prior spontaneous bacterial peritonitis (SBP) or other risk factors according to the European Association for the Study of the Liver (EASL) guidelines,[27,118] a third not defining in what population prophylactic antibiotics were used.[126] The remaining thirteen studies did not report on the use of prophylactic antibiotics (Table 3.4).[115–117,119–121,123–125,128,130–132]

3.4.7 Place of management of ascites subsequent to device insertion

In nine of the 18 studies, patients had subsequent ascites drainage exclusively in their homes either by community nurses, participants themselves, or their care givers.[115,118,120–122,125,128–130] Three studies reported ascites management in either a hospice or participants' home;[116,127,132] in a further two studies, ascites management was either in a hospital outpatient setting, including day case units, or the patients' home;[117,131] in one of these,[117] a small proportion (three of the total mixed cohort of 27) were also managed in hospital when admitted for unrelated medical conditions (Table 3.4). Four studies did not state the place of further ascites management (Table 3.4).[119,123,124,126] In none of the 14 studies which reported on the place of subsequent drainage following PIPC insertion was hospital admission required for further ascites management.

There was no documentation on LVP requirement prior to and following PIPC insertion in 13 studies;[115–117,119–121,125–128,130–132] two reported averages of 2.2 and 7 procedures respectively prior to PIPC insertion reducing to zero afterwards;[118,129] two studies reported no separate LVPs were required after PIPC insertion.[122,123] One study only reported that two of the patients required further inpatient hospital admission for full drainage with concurrent intravenous albumin infusion, however

this was a study in which both hepatic hydrothoracies were described along with those of abdominal ascites without any distinction made between cases.[124]

3.4.8 Specialist palliative care

Of the 18 studies, 12 commented on PIPC being performed as a palliative procedure[115–117,120,123,124,126–130,132] (Table 3.4). The remaining five used PIPC in both those who were and were not LT candidates.[118,119,121,122,131] Only three studies alluded to input from specialist palliative care services.[124,127,129]

3.4.9 Complications

Infectious and non infectious complications in patients with ESLD are summarised at the end of the chapter in table 3.5.

Device related infections

All but two studies reported on cases of bacterial peritonitis (BP) occurring in patients with ESLD,[123,126] however, other infectious complications were not reported separately in this group. Complications, other than BP, have been described in those with ESLD where it has been possible to do so.

In six of the studies there were no episodes of BP in patients with ESLD.[116,120,125,129,130,132] In our case series we reported organisms (*Pseudomonas aeruginosa* and *Corynebacterium striatum*) cultured from the PIPC in one case,[129] however the clinical significance of this was uncertain. Nine studies reported cases of BP in patients with ESLD,[117–119,121,122,124,127,128,131] of these, three defined BP, but only two studies stated that ascitic fluid samples were taken when clinically indicated,[124,131] rather than as part of routine sampling. One study reported two episodes of BP occurred despite Norfloxacin prophylaxis.[118] One study in which PleurX™ PIPC were used in both cases of abdominal ascites, as well as hepatic

hydrothoracies in ESLD, did report one case of BP but did not specify as to whether it was BP or bacterial empyema (within the thorax).[119] An additional case of *Escherichia coli* sepsis was reported, being described as a "catheter related infection", however no further information was offered.[119]

In one study with the highest prevalence of positive ascitic cultures (42%, n=14),[121] further clarification was sought from the authors, Reinglas et al, which confirmed that in addition to sampling ascitic fluid in symptomatic patients, ascitic fluid samples were also taken routinely during the follow up period. It was unclear if these samples were taken from the PIPC or directly from a new abdominal paracentesis sample. Organisms cultured were classified as typically associated with SBP in six patients (18%), and typical catheter associated organisms in 11 patients (33%).[121] Interpretation of routine ascitic fluid sampling in those with PIPC remains contentious due to the indwelling peritoneal catheter, therefore it is unclear if all were true cases of BP, or if they could represent colonisation of the catheter.

Rates of BP varied from 0% to 42% across individual studies, with an overall combined rate of 17% (29/166). Excluding the 11 patients in Reinglas et al with reported catheter related organisms,[121] the overall rate of BP was 12.7% (21 patients). However, if the Reinglas study was excluded as an outlier,[121] the overall rate of BP across the remaining 15 studies was 11% (15/133). Of these, four had the PIPC removed and subsequently received antibiotics as management for BP; eight were treated with concomitant antibiotics with the PIPC left in situ; one patient was palliated as was felt to have entered an end of life phase; in the remaining two, no subsequent management was described (Table 3.5).

Cellulitis at the catheter insertion site was reported in nine of 147 (6%) patients with ESLD.[118,121,124,129] Two studies with a mixed cohort of malignant and non malignant

ascites reported 11 cases of BP overall but did not differentiate between aetiology of ascites amongst those cases.[123,126] Four mixed cohort studies reported 11 patients with either cellulitis or “local infection”; without stating underlying aetiology of RA. These were therefore subsequently not included in the final analysis.[116,120,122,123]

Non infectious complications

Of the 142 patients with ESLD and PIPC, where complications have been reported separately in this group, minor transient hyponatraemia was reported in 16 (11%),[118] a small transient rise in creatinine in 12 (8%),[118] leakage of ascites at catheter exit sites was seen in 12 (8%),[117,121,127,131] catheter occlusion was reported in eight (6%),[118,121,128,131] elevated serum urea in three (2%),[121] accidental catheter displacement in two (1%),[121,127] other complications 3% (n=4) reported included acute kidney injury (AKI) n=1, haematoma n=1, hepatic encephalopathy (HE) n=1 and blood stained ascites post insertion n=1.[117,121,129,131] See table 3.5 for a list of non infectious complications.

The two bleeding complications (haematoma and blood stained ascites following catheter insertion), were reported to have both self resolved.[121,131] The three with elevated serum urea were managed by reducing the frequency of drainage episodes.[121] The case of AKI developed following leakage of ascites at an access port site, which likely then represented over drainage and reduced intravascular volume.[117] The patient with HE had no clear precipitating cause, however, of note, this was seen in the same patient in which *Pseudomonas aeruginosa* and *Corynebacterium striatum* were grown from the PIPC sampled ascitic fluid.[129] As has already been previously discussed, the clinical significance of this was uncertain as these could represent colonisation of the indwelling catheter itself rather than bacterial peritonitis. There were no other clinical features which indicated infection

and empirical antibiotic therapy did not lead to an improvement in symptoms, hence the authors felt therefore this was most likely to represent progression of ESLD rather than a complication of the PIPC.[129]

In the eight studies with mixed RA aetiology, non infectious complications were inconsistently reported, specifically in patients with cirrhosis, these are therefore included in table 3.5 where possible.[116,117,120,122,125,130] Complications reported without the aetiology of RA clarified consisted of 13 cases of ascites leakage at the catheter insertion site,[116,120,123] five reports of unspecified catheter malfunction,[120] five cases of occluded catheters, three of which were peritoneal ports where patency was restored after administration of tissue plasminogen activator (tPA);[116,123] four cases of accidental catheter displacement,[122,123] two episodes of groin pain,[123] one abdominal pain with BP excluded,[122] and one port failure due to undiagnosed loculated ascites prior to insertion of PIPC.[117]

3.4.10 Patient and PIPC survival post insertion

The heterogeneity of the studies, including mixed cohorts, limited reporting of patient and catheter related survival, and comparisons between them. Reported outcomes are shown in table 3.4. Overall patient survival was limited, as is expected to be seen in all aetiologies of RA. Where reported, median survival in patients with ESLD varied between 29 days to six months,[122,129] consistent with the reported median survival in RA due to ESLD.[27] Median PIPC survival in patients with ESLD, reported as ranging between six weeks to five months,[125,132] was in keeping with mean PleurX™ catheter survival in the NICE technology appraisal, where the ascites was due to an underlying malignant process.[76]

3.4.11 Quality of life assessments

One study, Monsky,[116] attempted to describe the impact of PIPC insertion on QOL. A modified questionnaire similar to the Chronic Liver Disease Questionnaire (CDLQ)[133] was utilised to make an assessment of this. Assessments were conducted following initial PIPC insertion. Home care and hospice nurses were also surveyed for perspectives on how care was affected by PIPC. Patients reported improvements in mobility and daily activities, however, there was no pre PIPC insertion questionnaire undertaken, which could have been useful to record for a comparison of symptoms to aid in assessing the impact of the PIPC insertion. Nursing staff were reported as stating the approach of a long term indwelling drainage catheter benefited QOL and also advocated for earlier placement of PIPC in patients' disease trajectory.[116]

No studies identified assessed health economic benefits of PIPC in ESLD.

3.5 Discussion

3.5.1 Key findings

The use of PIPC in the management of malignant ascites is well established.[76] However, in contrast, this is the first systematic review of PIPC in RA due to ESLD summarising current international literature. It is not surprising that of the 18 studies identified, all but 12 were retrospective case series and/or cohort studies,[119–129,132] the one randomised controlled trial (RCT) identified was well designed, however only enrolled one patient into each arm.[115] Of the total 176 patients with ESLD and RA who underwent PIPC insertion, technical success was 100%, rates of non infectious complications were generally low (<12%) and none life threatening. Rates of the most feared complication, that of BP (12.7%) were also not unacceptably high considering prophylactic long term antibiotics were only used in 21/169 patients

(12%).[118,126,127,129,134] It is unclear if all reported cases of BP were true BP, or were due to colonisation, however, these are still within those expected of rates of SBP in an ESLD population (up to 14% in more recent data, 15%-19% in older data).[34,35] In patients with kidney disease undergoing peritoneal dialysis (PD), PD peritonitis is a recognised and accepted complication for this group.[135] Current recommendations state that rates should not exceed 0.5 episodes per year.[135] However, this cannot be extrapolated to PIPC in ESLD as this is largely a palliative cohort focussing on symptom relief, as opposed to in PD where it represents active treatment of end stage renal disease and dialysis. This could explain why then, in some of the studies, development of BP did not mandate removal of the PIPC.[118,122,131]

3.5.2 Study limitations

While the initial data on safety and efficacy of PIPC in ESLD and RA are encouraging, they need to be interpreted with caution. This systematic review describes PIPC outcomes in ESLD from heterogeneous, poor quality studies with small sample sizes, using a variety of different indwelling catheters, which therefore makes direct comparison between each study impossible. Data provided on the severity of liver disease (Child Pugh, MELD), patient, and catheter related survival, prior history of spontaneous bacterial peritonitis (SBP), and use of prophylactic antibiotics were limited, and inconsistently reported. Prophylactic antibiotics were used in only three (12%) studies.[118,127,129] In the single study where QOL measures were recognised and discussed, interpretation of results were hampered by suboptimal design, by not having pre and post insertion assessments for comparison of the intervention.[116] Finally, none of the studies attempted to assess health economic outcomes of PIPC in ESLD and RA, which could potentially positively

impact the provision of healthcare and health systems in terms of ascites management and associated costs.

3.5.3 Burden of RA in ESLD

There is increasing burden from CLD deaths in the UK, which currently represents the third commonest cause of premature death.[1] Most individuals with ESLD develop ascites at some stage which, without subsequent liver transplantation, is associated with a limited life expectancy as it is an indicator of decompensation and progression of liver disease severity.[20,27] Ascites causes physical and psychological symptoms, which have a significant impact on QOL, both of patients, and also wider impacts on caregivers.[27,47] The development of RA confers a further limitation in life expectancy, its management in the majority of cases remains palliative, and the focus being on symptom management, as only a small proportion of patients successfully proceed to liver transplantation.[27,57]

3.5.4 Current management strategies in refractory ascites

LVP remains the commonest palliative intervention in RA, however it offers only limited improvement or relief of symptoms,[47] necessitates repeated hospitalisations, and can be associated with post paracentesis circulatory dysfunction (including hyponatraemia and renal impairment), HE, and rarely other complications.[60]

Other interventions for RA include invasive procedures such as peritoneovenous shunts, which are now virtually obsolete due to associated complications (shunt occlusion and infection), the ALFApump®, and TIPS.[27,65] TIPS is an invasive procedure, usually requiring a general anaesthetic (GA) for the procedure, and can result in HE as a result of blood shunting across the liver, without passing through the parenchyma and hepatocytes, resulting in ammonia shifts towards the brain.[20]

Meta analyses comparing TIPS with LVP reported TIPS to be more effective in reducing ascites recurrence, however, it was associated with a greater incidence of HE (prevalence 15%-61%), and with conflicting survival outcome data.[27] In one small retrospective study (n=10) which was reporting on palliative TIPS for RA +/- hepatic hydrothorax in ESLD, 50% of patients developed HE, of whom more than half subsequently died within three months.[67]

The ALFApump® (AP), another invasive procedure, requiring a GA for insertion, involves an implantable device pumping ascites from the peritoneal cavity into the bladder.[65] High complication rates have been reported in the initial European multicentre safety and efficacy study: HE and SBP 32.5%, and renal dysfunction 27.5%, other complications included bladder catheter dislodgement, pump failure, and pump pocket infections.[73] The European multicentre RCT comparing the ALFApump® (AP) with LVP reported significantly more occurrences of serious adverse events (SAEs) in the AP group (85.2% vs 45.2% p=0.002), including more than 50% of the AP group experiencing SAEs relating to renal dysfunction.[66] Recent studies have reported consistent findings, corroborating complication rates including those of infections (11%-56%),[74,136] renal dysfunction (21%-67%),[74,136,137] device issues including catheter occlusions (9%-33%),[74,136] and explantation of the device in up to 30% of cases.[74] Recent NICE guidance on the ALFApump® advises use only with 'special arrangements' and in research settings.[75]

TIPS and the ALFApump®, therefore, may be less appropriate as palliative interventions. Additionally, another aspect is that focussing on interventional procedures may be at the expense of whole patient centred care, delaying consideration of integrated holistic palliative care, which in itself could positively impact on symptom management and control. Focus on interventions could also

hinder instigation of discussions to establish patients' wishes with regards to future management, as well as advance care planning consideration.[86]

3.5.5 The use of permanent indwelling peritoneal catheters in the UK

With an increasing burden from CLD and lack of effective palliative options for RA, the absence of data on PIPC is notable.[57] PIPC are an accepted management strategy in malignant ascites, having undergone a NICE technology appraisal, concluding that PIPC were clinically effective, had low complication rates, could improve patient QOL, were less costly than repeated LVP, and should be used in recurrent malignant ascites.[76] A study using PleurX™ PIPC in malignant ascites reported improvement in dyspnoea within two weeks of PIPC insertion.[138] Other potential benefits include patient autonomy and transferring more care into the community setting, which would allow remaining life expectancy to be spent in patients' preferred place of residence, often within their homes.

3.5.6 Palliative care in end stage liver disease

Defining the final phase of illness in non malignant life limiting diseases can be challenging due to more fluctuations in disease trajectory compared than that which is seen in malignant disease. However, in ESLD, the development of RA is a valuable prognostic guide, with an associated median life expectancy of six months.[27,37] Despite this, and the fact that the majority of cases will be ineligible for LT, strategies for palliative management are not well defined or integrated into the current care models for patients with ESLD.[35,57,58] In addition to this, complex EoLC needs are often present concurrently and management remains mainly within secondary care, with more than 70% of patients with ESLD dying in a hospital setting. This is a crude marker of preferred place of death and contrasts with cancer

deaths where the opposite is seen.[42,85] In England, despite pockets of excellence,[139] little specialist palliative care related to ESLD is provided in hospices or the community, despite services being available.[42,109]

Only a small proportion (7.5%) of patients with cirrhosis receive an outpatient palliative care consultation regardless of symptoms or disease severity scores, and patients are referred late in their disease trajectory, with the only positive predictor of palliative care referral being concomitant hepatocellular carcinoma (HCC).[87] An early palliative care intervention in patients referred for LT assessment showed 50% of moderate to severe symptoms significantly improved following the intervention.[84]

Our local data in those with RA undergoing LVP showed that only 33% overall were referred to a specialist palliative care team despite a minority, 12%, being listed for, or undergoing LT.[58] A subsequent survey amongst UK medical consultants suggested potential contributors could include inadequate understanding of the fluctuating disease trajectory, and clinicians' own discomfort with the subject of palliative care in the context of ESLD.[103]

There have been calls to improve the quality of care for those living with, and dying from ESLD, with greater and timelier integration of palliative care.[109] This, as well as initial positive experiences of PIPC, prompted our group to obtain National Institute for Health Research (NIHR) funding for the prospective feasibility RCT comparing palliative PIPC (Rocket®) with LVP in ESLD (REDUCe Study, ISRCTN 30697116).[140,141] The mixed methods study protocol includes collection of clinical, qualitative, patient reported and health economic data to inform the development process for a potential future full size definite RCT.[140,141] With initial results being encouraging,[140] and although being a UK based trial, the implications could be wide reaching to an international level, with the ultimate aim being to improve EoLC and

contribute to the understanding of the palliative care needs of those with RA in the context of ESLD.

3.6 Conclusion

This systematic review has described the use and preliminary safety and efficacy data of PIPC in RA and ESLD. Though the prevalence of peritonitis was no higher than that seen in that of an ESLD population, the lack of well designed studies does impact on the pooled analysis. The results therefore underline the need for well designed RCT to assess the safety and efficacy of PIPC in RA in ESLD, including assessments of symptom burden, QOL, as well as health economics. This could potentially go a long way towards improving QOL, avoiding recurrent hospital attendances for drainage of ascites, as well as the complications and symptoms associated with undergoing recurrent LVP episodes.[27,47] Benefit has been demonstrated in working towards more integration of palliative care earlier in the disease trajectory of ESLD, which could include novel interventions such as PIPC.[84] The overall aim being to ensure that those with ESLD and RA, and therefore with a limited life expectancy, receive more equitable palliative and EoLC care, such as that which is seen in other advanced medical, non malignant but still life limiting, diseases.

Table 3.4 Summary of studies included in the systematic review

Author/ year (country)/ Design	Population/ drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Ahmed, 2018[115] **(Canada) Prospective – pilot single centre randomised controlled trial project report**	Cirrhosis; Peritoneal n=1 (1 patient in peritoneal dialysis catheter arm, 1 in standard care arm)	Tunnelled peritoneal dialysis catheters Interventional nephrologist	During insertion procedure only - Cefazolin or Vancomycin	Non-LT candidates; Palliative care not mentioned	Home (self-drainage by patient)	Reported the patient completed study follow up period of 6 months/ Not reported
Corrigan et al, 2018[124] **(UK) Retrospective cohort study (Conference poster**	Cirrhosis; Peritoneal and pleural n=24 (total 29 catheters in 28 patients with ascites and hepatic hydrothorax – not distinguished in abstract)	Unspecified tunnelled indwelling peritoneal catheter Interventional radiologists	None	Non-LT candidates 24 patients referred to palliative care	Not stated	6 and 12 month survival available on 24 patients; 50% and 25% respectively/ Not reported

Author/ year (country)/ Design	Population/ drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Hingwala et al, 2017[125] **(Canada) Retrospective cohort study**	Mixed; Peritoneal n=8	Tunnelled peritoneal dialysis catheters Interventional nephrologist under ultrasound and fluoroscopic guidance	During insertion procedure only - Cefazolin or Vancomycin	Not stated	Home (self-drainage by patient	Median catheter survival 146 days (interquartile range 33.5-1039 days)
Imler et al, 2012[119] **(USA) Retrospective cohort study (Conference poster)**	Cirrhosis; Peritoneal and pleural n=16 (26 total ascites and hepatic hydrothorax)	PleurX™ Interventional radiology database (insertion method not mentioned)	None	Patients on LT list as well as palliative. No mention of palliative care	Not stated	30 and 90 day mortality after device insertion: 30.8% and 61.5% respectively/ Not reported
Knight et al, 2017[123] **(USA) Retrospective cohort study**	Mixed; Peritoneal n=3	PleurX™ Interventional radiologists - ultrasound guidance	None	Palliative intent but no specific palliative care input mentioned	Not stated however stated no concomitant LVP required	Median survival from insertion to death 85 days

Author/ year (country)/ Design	Population and drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Kriese et al, 2013[127] (UK) Retrospective case series (Conference poster)	Cirrhosis; Peritoneal n=4	PleurX™ Not stated	Ciprofloxacin	Palliative intent but no specific palliative care input mentioned	Home/ hospice	Not reported/ Catheter in situ for a median of 30 days (20 – 50) before removal or death
Kundu et al, 2012[128] (USA) Retrospective case series (Conference poster)	Cirrhosis; Peritoneal n=12	Unspecified tunnelled indwelling peritoneal catheter Interventional radiologists	None	Non-LT candidates Palliative care not mentioned	Home (self-drainage by patient)	Not reported/ Median duration of catheter function 2 months
Lungren et al, 2013[120] (USA) Retrospective cohort study	Mixed; Peritoneal n=7	PleurX™ Interventional radiologists - ultrasound guidance	During insertion procedure only - Cefazolin or Clinamycin	No mention of palliative care other than some overall discharged to USA hospice care*	Home – patients or carers/hospice	Not reported/ Mean catheter survival 60 days (0-796 days), (11,903 cumulative catheter days)

Author/ year (country)/ Design	Population and drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Macken et al, 2016[129] **(UK) Retrospective case series**	Cirrhosis; Peritoneal n=7	Rocket® Ultrasound guidance, (gastroenterology) physicians	Ciprofloxacin/ Norfloxacin after review of first 5 cases	Non-LT candidates, reviewed by palliative care team	Home (district nurse)	median patient survival 29 days (8-219)/ Not reported
Monsky et al, 2009[116] **(USA) Prospective cohort study with QOL assessment**	Mixed; Peritoneal and pleural n=2 (further 1 with hepatic hydrothorax)	Peritoneal and pleural catheters with percutaneous access ports (Celsite DRAINAPORT) Interventional radiologists – ultrasound and fluoroscopic guidance	During insertion procedure only - Cefazolin and Metronidazole	No mention palliative care except USA hospice care*	Hospice/ home care nurses	Not reported/ Not reported

Author/ year (country)/ Design	Population and drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Po et al, 1996[130] (USA) Prospective case series (Conference poster)	Mixed; Peritoneal n=1	Peritoneal dialysis (Tenckhoff) catheter Surgical insertion	None	No mention palliative care input. "Terminally ill patients" suggests palliative intervention	Home, by patient	Mean duration of survival 6 months/ Not reported
Reinglas et al, 2016[121] (Canada) Retrospective cohort study	Cirrhosis; Peritoneal n=33	PleurX™ Tunnelled indwelling peritoneal catheter Ultrasound guidance. Not stated by whom	None	LT candidates and non-LT candidates Described as palliative management but not palliative care input	Home care nurses	Not reported/ Median duration 117.5 days

Author/ year (country)/ Design	Population and drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Reisfield et al, 2003[132] **(USA) Case report (total of 5 cases)**	Cirrhosis; Peritoneal n=5	PleurX™ Tunnelled indwelling peritoneal catheter Ultrasound guidance, not stated by whom	None	Non-LT candidates. USA hospice care* mentioned but not integrated palliative care	Hospice then at home, initially by hospice nurse then by patient and family member	Mean duration of catheters in situ was more than 6 weeks – all remained in situ until the time of death/ Mean duration more than 6 weeks
Riedel et al, 2018[126] **(Denmark) Retrospective cohort study with matched controls**	Mixed; Peritoneal n=7	PleurX™ Tunnelled indwelling peritoneal catheter Trained physicians, x-ray guided	Cefuroxime during insertion procedure Reported 16 patients received further prophylactic Ciprofloxacin but not which cohort	Non-LT candidates; Palliative care not mentioned	Not stated	Mean survival 200 days

Author/ year (country)/ Design	Population and drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Rosenblum et al, 2001[131] **(USA) Prospective case series**	Cirrhosis; Peritoneal n=9	Peritoneal catheter with access port (modified venous access ports) Interventional radiologists under ultrasound and fluoroscopic guidance	During insertion procedure only - Cefazolin	LT candidates and supportive care. No mention of palliative care input	Nurse in gastroenterology outpatient clinic and 2 in community by visiting nurse	Not reported/ Mean port patency was at least 255 days with a total of 1557 port days
Savin et al, 2005[117] **(USA) Prospective cohort study**	Mixed; Peritoneal n=4	Peritoneal catheter with access port (Port-a-cath peritoneal implantable access system) Interventional radiologists under ultrasound and fluoroscopic guidance	During insertion procedure only - Cefazolin	Palliative management. Palliative care input not mentioned	Hospital outpatients and as inpatient, as well as at home with visiting nurses	Not reported/ 1810 port days (in 27 patients in the total mixed cohort)

Author/ year (country)/ Design	Population and drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Semadeni et al, 2015[122] **(Switzerland) Retrospective cohort study (Conference poster)**	Mixed; Peritoneal n=9	PleurX™ Tunnelled indwelling peritoneal catheter Gastroenterology consultant under ultrasound guidance	During insertion procedure - Ceftriaxone. Two cases received prophylaxis with Norfloxacin and Ciprofloxacin, respectively after developed and treated for BP	LT candidates and non-LT candidates Palliative care not mentioned	Home (by patient)	Mean survival in patients with cirrhosis 192 days/ Mean catheter survival in patients with cirrhosis 111 days

Author/ year (country)/ Design	Population and drainage site/ Number (n) of cases with cirrhosis related ascites	Type of PIPC/ Place of insertion	Prophylactic antibiotics	Palliative or non-palliative	Place of further ascites management	Patient survival post PIPC insertion/ Duration PIPC remained in situ
Solbach et al, 2017[118] **(Germany) Prospective cohort study**	Cirrhosis; Peritoneal n=24	PleurX™ Tunnelled indwelling peritoneal catheter Ultrasound guidance. Not stated by whom	During insertion procedure Sulbactam/Ampicillin. Norfloxacin 15/24 63% - in prior history of SBP and defined risk factors as per EASL guidelines.[27]	LT candidates and non-LT candidates Palliative care not mentioned	Home (by patient)	16/24 67% remained in situ until death (mean 97.6+/-51.4 days). Five patients listed and underwent LT/ Mean indwelling catheter time 83.2+/-54.3 days

USA = United States of America, UK = United Kingdom, Mixed = malignant and cirrhotic ascites as well as ascites due to other causes, QOL = quality of life, LT = liver transplant, LVP = large volume paracentesis, BP = bacterial peritonitis, SBP = spontaneous bacterial peritonitis. *It is worth noting that in the USA that phrase “Hospice care” is usually interpreted as only being instituted late in disease (on average 14 days before death for all diseases). This differs from UK interpretation where “Hospice care” can be instituted synchronously with active/secondary care.

Table 3.5 Infectious and non-infectious complications in patients with ESLD and PIPC

Author/ year (country)/ Number of cases (n)	Bacterial peritonitis	Cellulitis	Non-infectious complications
Ahmed 2018[115] **(Canada) n=1**	Not reported	Not reported	Not reported
Corrigan et al, 2018[124] **(UK) n=24**	3 (12.5%) received antibiotics after admission with abdominal pain, 2 having positive ascitic taps	3 (11%) with skin site erythema and positive skin swabs – not reported if received antibiotics Not reported if occurred in abdominal or pleural drains	3 leaking insertion sites (not reported if pleural or abdominal) 1 catheter blocked and subsequently removed
Hingwala et al, 2017[125] **(Canada) n=8**	None	None	None
Imler et al, 2012[119] **(USA) n=16**	1 (6%) – not specified if BP or spontaneous bacterial empyema	None	None
Kriese et al, 2013[127] **(UK) n=4**	1 (25%), non-fatal, catheter removed and replaced	None	1 (25%)accidental removal of catheter, 1 (25%) leakage of ascites at insertion site (same as patient as developed BP)
Kundu et al, 2012[128] **(USA) n=12**	2 (17%), catheters removed, treated with antibiotics	None	1 (8%) obstructed drain, re-sited

Author/ year (country)/ Number of cases (n)	Bacterial peritonitis	Cellulitis	Non-infectious complications
Lungren et al, 2013[120] **(USA) n=7**	None	3 (but included patients with mixed aetiology for RA and aetiology not specified)	5 “catheter malfunction” unspecified, 4 ascites leakage at incisional site (requiring suture placement) (but included patients with mixed aetiology for RA and aetiology not specified)
Macken et al, 2016[129] **(UK) n=7**	None	2 (29%) one treated with antibiotics, one drain removed and re-sited after treatment	HE of unclear cause
Monsky et al, 2009[116] **(USA) n=2**	None	3 (but included patients with mixed aetiology for RA and aetiology not specified)	3 temporary occlusions (patency restored using tPA infusion), 3 self-limiting ecchymosis, 1 leakage of ascites (but included patients with mixed aetiology for RA and aetiology not specified)
Po et al, 1996[130] **(USA) n=1**	None	None – none reported in mixed cohort	None – none reported in mixed cohort
Reinglas et al, 2016[121] **(Canada) n=33**	14 (42%) with positive routine peritoneal fluid cultures; 6 catheters removed, all patients successfully treated with antibiotics	3 treated with antibiotics – no mention if catheter removed	7 (21%) ascites leakage at PIPC site – 5 resolved, 1 PIPC removed, 1 further sutures around PIPC, 1 eventual PIPC removal due to persistent leakage. 3 (9%) rise in urea 3 (9%) PIPC occlusions (1 patency restored using tPA, 2 successful PIPC replacement) 1 (3%)accidental catheter displacement 1 (3%) haematoma, resolved

Author/ year (country)/ Number of cases (n)	Bacterial peritonitis	Cellulitis	Non-infectious complications
Reisfield et al, 2003[132] **(USA) n=5**	None	None	None
Rosenblum et al, 2001[131] **(USA) n=9**	3 (33%), 1 treated with intravenous antibiotics, 1 port removed, 1 palliated (no active treatment)	None	3 (33%) ascites leakage at PIPC site - patient subsequently developed BP 1 (11%) PIPC occlusion 1 (11%) blood stained ascites
Savin et al, 2005[117] **(USA) n=4**	1 (25%), management not reported mixed cohort but specified as being in ESLD patient	None – none reported in mixed cohort	1 (4% of total mixed cohort) leakage at site - in ESLD patient - same patient who developed BP 1 (4% of total mixed cohort) AKI – specified as being in ESLD patient 1 (4% of total mixed cohort) loculated ascites recognised after PIPC insertion
Semadeni et al, 2015[122] **(Switzerland) n=9**	2 (22%), treated with antibiotics, catheters remained in situ, subsequently started prophylactic antibiotics	2 “local infection” (but included patients with mixed aetiology for RA and aetiology not specified)	2 (4% of total mixed cohort) accidental catheter dislocation 1 intermittent abdominal pain with BP excluded (but included patients with mixed aetiology for RA and aetiology not specified)

Author/ year (country)/ Number of cases (n)	Bacterial peritonitis	Cellulitis	Non-infectious complications
Solbach et al, 2017[118] **(Germany) n=24**	2 (8%), treated successfully with antibiotics Developed despite Norfloxacin prophylaxis	1 (4%) – same patient developed BP	16 (67%) minor transient hyponatraemia at week 4 12 (50%) small transient increase in creatinine at week 12 2 (13%) PIPC occlusion – resolved with flushing 1 (4%) complete PIPC occlusion – further PIPC resited 1 abdominal pain with BP excluded – resolved with placement of shorter catheter

USA = United States of America, UK = United Kingdom, Mixed = malignant and cirrhotic ascites as well as ascites due to other causes, QOL = quality of life, SBP = spontaneous bacterial peritonitis, AKI = acute kidney injury, tPA = Tissue plasminogen activator

Chapter 4 - The REDUCe study: Methods for the multicentre feasibility randomised controlled trial - Palliative Long Term Abdominal Drains versus Large Volume Paracentesis in Refractory Ascites Due to Cirrhosis (REpeated Drainage Untreatable Cirrhosis)

4.1 Study aims

The aim of this study was to assess the feasibility of being able to conduct a future randomised controlled trial (RCT) of the safety, clinical effectiveness, and cost effectiveness of refractory ascites management, using a long term abdominal drain (LTAD) compared to the current standard of care, which is the use of repeated large volume paracentesis (LVP), in patients with ascites in the context of decompensated cirrhosis, when liver transplantation is not an option. The protocol for the study presented in this chapter has been published in the journal Trials, in accordance with protocols for randomised clinical trials, and details of the publication are in the references.[141]

4.2 Statement of contribution:

The original idea for the study was conceived by Professor Sumita Verma and Dr Louise Mason. Professor Catherine Evans and Professor Heather Gage advised on the palliative care and health economics aspects of study design, Dr Max Cooper led on the qualitative aspect of the study. As part of the Brighton and Sussex Clinical Trials Unit (BSCTU) Professor Stephen Bremner advised on and provided statistical analysis, and David Crook advised on trial protocol development.

In my role as the hepatology clinical trial research fellow I helped to finalise the study protocol, including all the study related procedures and wrote the study standard operating procedures. I was responsible for the day to day running of the trial, including co-chairing the trial management group to discuss study running and recruitment, and address any site related issues.

4.3 Study design

The study design was of a multicentre, feasibility RCT, which was conducted over a 36 month period from October 2015-September 2018. The initial timeline prior to study initiation was for a 24 month study, however a year's time extension was granted by the funding body (National Institute for Health Research, NIHR) as well as the overseeing research bodies, to facilitate targets in participant recruitment. The first site initiation visit was undertaken on 12th October 2015 at The Royal Sussex County Hospital. This thesis presents data from across the duration of the study to the close of the study.

4.4 Study Setting

The study was designed to operate across healthcare boundaries, following the patient journey, with initial recruitment of participants and study visits occurring within acute hospital National Health Service (NHS) Trusts and further study follow up in the Community NHS Trusts, or acute hospitals as necessary. Those randomised to the LTAD arm were planned to have study follow up visits in the community where possible. Patient participants were followed up for 12 weeks. With the participants' agreement their GPs were informed about their participation in the trial.

4.5 Participant identification

Participants were identified from acute medical inpatient and ambulatory units, gastroenterology/hepatology inpatient wards and outpatients departments at the participating sites. A list of potentially eligible patients was shared by the medical teams from the areas stated with the research team, and were those patients with cirrhosis decompensated with ascites who had undergone LVP. In the event that any member of the research team was also one of the usual medical team, to avoid conflicts of interest, potential participants were discussed at the weekly hepatology multidisciplinary meetings (MDM), with review by a liver transplant centre if appropriate, and not by the research team.

Sites were opened in a sequential fashion, the initial plans were to recruit participants from two acute hospital Trusts, Brighton and Sussex University Hospitals NHS Trust (BSUH) which has two hospital sites, The Royal Sussex County Hospital (RSCH) and The Princess Royal Hospital (PRH); and Worthing Hospital, which is part of Western Sussex Hospitals NHS Foundation Trust. The community NHS Trust which covers patients in both regions was Sussex Community NHS Trust. Further sites were opened during the course of the study, and at the close of the study there were five recruiting sites, these were the two initial sites, as well as Derriford Hospital (Plymouth), Southampton General Hospital, and Blackpool Victoria Hospital. The participants were approached by the research teams at the participating centres to review eligibility for inclusion into the study after having been identified by the medical team as potentially eligible candidates.

4.6 Ethical approval

Research Ethics Committee approval was obtained nationally from the National Research Ethics Committee South Central - Hampshire A (REC ref. 15/SC/0257).

The study was sponsored by Brighton and Sussex University Hospitals NHS Trust (BSUH) and received Research and Development approval from all five participating NHS Trust sites. The trial was conducted in accordance with the Declaration of Helsinki, the principles of Good Clinical Practice (GCP),[142] the Research Governance Framework, and through adherence to the Brighton and Sussex Clinical trials Unit and the King's Clinical Trials Unit (KCTU) standard operating procedures (SOPs). See appendix 2 for details of Research Ethics Committee approval.

4.7 Consent

Potential study candidates were identified at participating centres by their usual medical and gastroenterology teams. Participant information sheets (PIS) including details of LTAD insertion, how it is used, the aftercare process, and community nursing visits to their place of residence, were given to all potentially eligible study participants along with specific carer involvement PIS, if a carer was present and was willing to undertake the carer specific study questionnaires, by a member of the research team. At the same time point, potential participants were also given a PIS inviting them to be included in the concurrent embedded qualitative study. An initial study overview and explanation was given to potential participants at that point and at least 48 hours were given for potential participants to read the PIS. Capacity to give informed consent to be enrolled into the trial was carefully assessed, as per inclusion/exclusion criteria. Informed consent was received in the hospital setting by a member of the research team appropriately trained in receiving consent for the study, and signed on study consent forms at the screening visit, prior to any study specific procedures were undertaken. Consent could have been received prior to the screening visit, and if this was the case, it was recorded in the source documents

that the participant was still happy to proceed with the trial at the screening visit. See appendix 3 for patient participant information sheet (PIS) and consent form.

4.7.1 Withdrawal of consent or loss of capacity to give consent

As is standard research practice, participation in the study was voluntary, participants were free to withdraw from the study at any time, without giving a reason, and without this impacting on their routine clinical care. Recognised sequalae of end stage liver disease (ESLD) include the development of hepatic encephalopathy (HE),[40] variations in which can result in fluctuating cognitive function. In the event that capacity to give consent relating to continuing in the trial was lost during the duration of the trial, the participants' nominated consultee, who was identified by the participant at the time of giving consent to participate, was approached to determine whether the participant should continue in the trial. If a consultee was not available or nominated, the participants' usual medical consultant, independent from the research team, was approached to decide if it was felt to be in their best interests to continue in the trial or not.

4.8 Eligibility Criteria

4.8.1 Inclusion criteria

- Age ≥18 years, with no upper age limit
- Untreatable (refractory) ascites defined as:
    - Ascites that is unresponsive to fluid and sodium restriction and high dose diuretic treatment (Spironolactone 400mg per day and/or Furosemide 160mg per day) and/or intolerance of diuretics[33,38]

    - Ascites which reaccumulates rapidly after large volume paracentesis (LVP) (need for one or more LVP per month) and having had at least three LVPs prior to recruitment
- Child Pugh Score ≥9,[22] which signifies advanced liver disease, unless specifically decided by the medical team that they were to receive only palliative treatment. If the score is <9, the participant must have been considered to be in a palliative phase of their disease process by medical team, and not a candidate for a liver transplant for consideration for eligibility for the trial. This aimed to capture those patients who have refractory ascites but whose Child Pugh score did not fit into the initial criteria so as not to disadvantage that group of patients
- Registered with a general practitioner (GP) in the community NHS Trusts served by the participating centres, to enable appropriate follow up in the community both by the community nursing team and the GP
- Ability to speak, read and understand English. The reason for this being that the funding for the study was able to support documents in the English language only, therefore unable to extend to other groups
- Capacity to give informed consent to be included in the trial, as defined using the 'Capacity to Consent Checklist', see appendix 4.
- Consent received and consent form signed prior to any study specific procedures

4.8.2 Exclusion criteria

- Either loculated ascites, where the ascites is contained within discrete pockets within the peritoneal cavity, which would impede drainage; or chylous ascites, which can occur secondary to other causes than cirrhosis

- Presence of greater than grade one hepatic encephalopathy, defined by West Haven criteria, which could impact on potential participants capacity to give consent to be enrolled in the trial[40]
- Evidence of active infection that in the investigators' opinion would preclude insertion of the LTAD (for example, spontaneous bacterial peritonitis, [SBP]). Such patients would need to receive appropriate treatment and could then be reconsidered for inclusion within the trial if the infection had been successfully treated
- Eligible for liver transplantation, following discussion of the hepatology multidisciplinary team (MDT) and according to national guidelines[143]
- Psychosocial issues which, in the opinion of the medical team, would preclude study participation, such as posing a risk to their own safety or to that of the research team

4.9 Clotting parameters

This was a feasibility study, and therefore no specific cut off in abnormal laboratory clotting parameters was defined in terms of eligibility, as this would have been unnecessarily restrictive on inclusion into the trial. There are no established parameters which would preclude insertion of an LTAD, and standard laboratory clotting measurements do not reflect the balance of pro and anticoagulant factors at play in the context of liver disease.[28] However, as is current standard of care and consistent with local practice, those participants with a platelet count of $<50x10^9$ and/or an international normalised ratio (INR) of >1.7 would have received blood and/or clotting product support prior to LTAD and LVP insertion.

4.10 Participation in other research studies

Potential participants were not excluded if they were already participating in another ongoing study, as long as the researchers were confident that participation in the current study being described would have been logistically feasible and not too onerous for the participants.

4.11 Carer involvement

The trial team invited informal carers to take part in the trial and to participate in carer burden assessments, however, the absence of any carers did not preclude trial enrolment.

4.12 Randomisation

Patients who fulfilled the inclusion and exclusion criteria and gave written informed consent to participate in the trial were randomised, unblinded, using a web based system on a 1:1 basis to either Group one: LTAD or Group two: LVP (which is the current standard of care).[28] The allocations were made by minimising on three variables: centre, Child Pugh score, and gender.[22] No stratification was utilised. Minimisation was implemented using an independent system hosted by KCTU. Patients were enrolled by the research team member, who logged into the web based system, entering the patient ID number, recruiting site, gender, and Child Pugh score.[22] The system then automatically generated a confirmation email informing the research team of the outcome of allocation to one of the two different study groups.

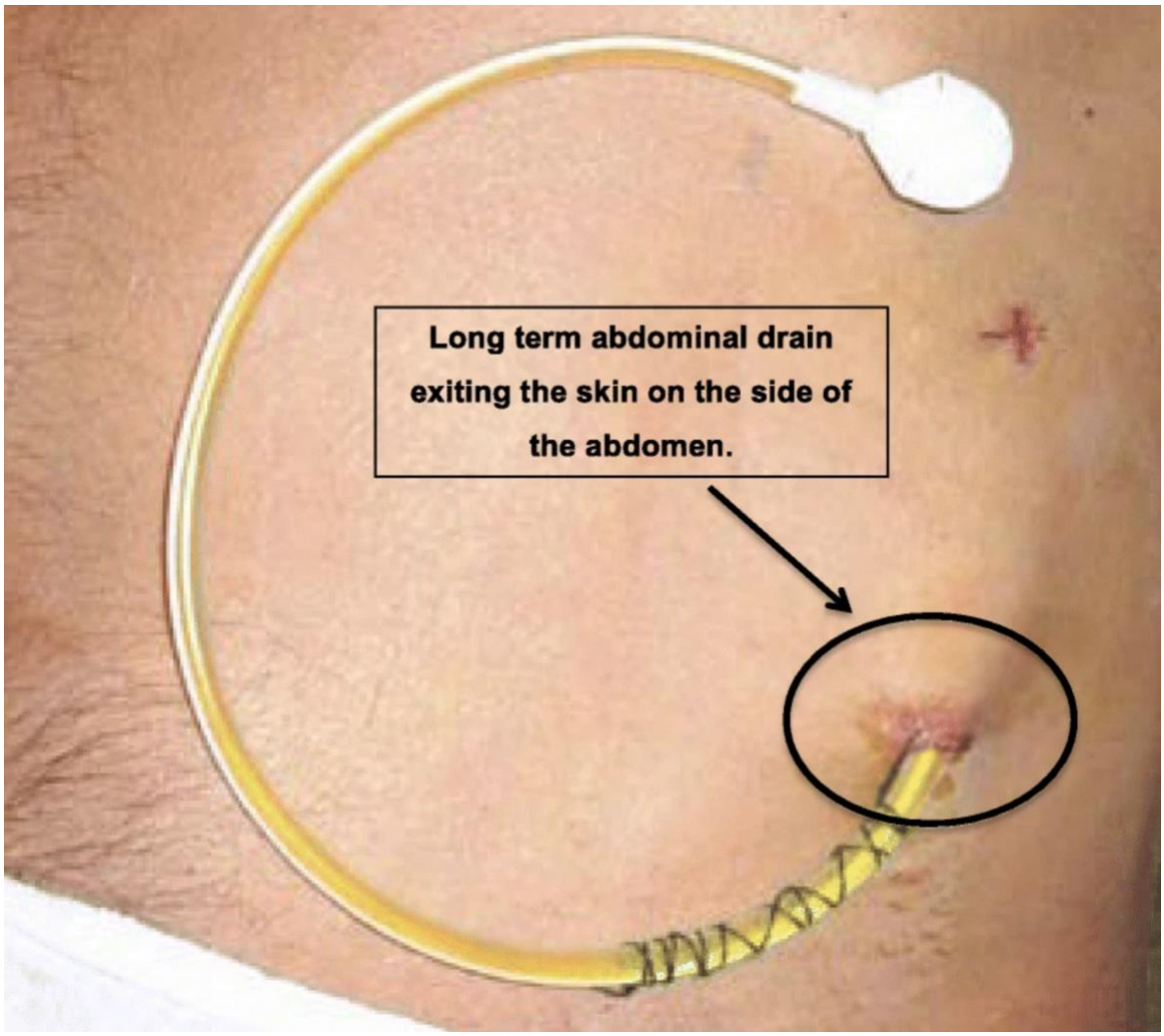
4.13 Intervention

This feasibility RCT compared insertion of a palliative tunnelled LTAD (Group one) to standard of care (LVP) (Group two) in the management of refractory ascites due to advanced cirrhosis.

4.13.1 Group one: Long term abdominal drains (LTAD)

Two LTAD are commercially available in the UK, from PleurX™ and Rocket® Medical.[77,78] There is extensive data on use of these drains for malignant ascites, including a National Institute for Health and Care Excellence (NICE) technology appraisal, which reported low device related infections (5.8%), 100% technical success, and improvements in symptom control using the PleurX™ catheter system.[76] We elected to use Rocket® rather than PleurX™ drains for a number of reasons, but importantly because they were the LTAD available locally to the two initially planned study sites in Sussex, and the local gastroenterology/hepatology team, as well as the community nursing teams, being already familiar with them. Earlier local experience had suggested that Rocket® devices were easier to insert than PleurX™ devices.[129] The Rocket Medical team already had an established training and support programme for the local community nursing teams as well as those in care homes. The required consumables were less expensive and could be prescribed by GPs on a community practitioner prescription form (FP10) which may positively support longer term use if the planned national definitive RCT were to prove successful. Figure 4.1 shows an image of an LTAD in situ.

Figure 4.1 Image of long term abdominal drain in situ



4.13.1.1 Procedure for long term abdominal drain (LTAD) insertion

Logistical considerations

To ensure consistency of the intervention being assessed, it was felt at the time of the two study sites being open in Sussex, that all LTADs should be inserted at one site, RSCH. Transport options were reviewed before the randomisation/baseline visit was undertaken, as part of the screening process, to ensure that appropriate transport was available for the participant in the event they were allocated to the

LTAD arm. Travel costs (taxi, petrol, or parking fees) were reimbursed as necessary for study visits. If insertion at RSCH was not possible due to patient preference or logistic issues, and as the further three study sites were opened, LTAD were inserted at the participating sites locally, usually by an interventional radiologist, depending on site experience. The research fellow initially inserted the drains with teaching and supervision from one of the co investigators for the first five drains, until competent to perform the procedure independently. The drains inserted at the two Sussex sites were done so by the research fellow as described. As the other sites were opened up, the geographical difference made it impossible for the insertion to be done by the research fellow, and therefore at those sites LTADs were inserted by interventional radiologists.

Insertion procedure

Informed consent for participation in the study was received before any study related procedures were undertaken. Insertion of the LTAD was performed in hospital in a side room, using bedside ultrasound guidance and under aseptic technique. Insertion was only performed if, within the week leading up to planned LTAD insertion, haemostatic function (including INR and platelet count) was checked, and blood products administered as necessary.

There are currently no accepted guidelines for giving clotting/blood products prior to undergoing LVP, product support is based on local standards of care, therefore based on an adaption to the current local standard of care, the following criteria was used for clotting product support during insertion of LTADs.[28] Where INR was >1.7, patients would receive up to two units of fresh frozen plasma (FFP), transfused according to patient weight and INR, immediately prior to drain insertion. If the

platelet count was ≤50x10^9, patients were planned to be given one to two pools of platelets, immediately prior to insertion of the drain.

- INR ≤1.7 no FFP to be administered
- INR >1.7 one or two units of FFP administered
- Platelet count >50x10^9 no platelets transfused
- Platelet count ≤50x10^9 one or two pools of platelets transfused

Rocket® LTAD insertion technique was undertaken using a combination of tunnelled and Seldinger techniques as stated in the Rocket® information sheet.[78,144] Sterile gowns, gloves and drapes were used to prepare the procedure area and the clinician performing the LTAD insertion. After confirming the location of the insertion site using bedside ultrasound and skin preparation with Chloraprep™ (chlorhexidine gluconate and isopropyl alcohol), a local anaesthetic (up to 10ml of 1% or 2% lidocaine) was administered at the incision site and along the proposed tunnel tract. A small incision was made where the catheter would enter the abdominal cavity. The introducer needle was inserted through the incision into the peritoneal cavity, and a guide wire passed through the needle, the needle was then removed. A second incision (exit site) was made approximately 5cm distal from the first, where the catheter was planned to exit the skin tunnel. The catheter was tunnelled from the exit site incision to the first incision site with the tunneller, making sure that the cuff was midway between the first and second incision sites. A split sheath dilator was then passed over the guide wire, and the inner dilator and guide wire removed, leaving the split sheath in situ.

The tunneller was then removed from the catheter, which was then passed through the split sheath, separating the split sheath and ensuring that all of the catheter was contained within the peritoneum. The last piece of the split sheath was then

removed. The catheter was then adjusted along the tunnel, so the cuff moves towards the exit site, but maintained well inside the skin tunnel, ensuring that any kinks were removed from the catheter. Finally, both incision sites were sutured (avoiding the catheter) and a dressing applied to the skin at the site of the procedure.

4.13.1.2 Post drain insertion care

Long term abdominal drain (LTAD) information

The research team provided guidance to the participant and carer, if present, on how the LTAD was to be used, the aftercare process, timing of visits by community nursing teams and further study procedures, based on the information already provided in the PIS. The participants were provided with an information sheet provided by Rocket Medical and a Rocket Medical Discharge letter which was sent to the relevant community nursing team and, with their consent, their GP.[78] The participants were referred to their community nursing service to organise regular visits for drainage sessions as well as for wound care and suture removal. As was current standard practice on insertion of an LTAD, Rocket Medical was also informed of the insertion, to allow them to contact the community nursing teams and organise tailored training and support as required. This would also allow consumables to be delivered directly to the participant, if appropriate, at the request of the community nurses.

Community nursing team referral

A referral was made to the relevant community nursing team, to plan visits to the participant's place of residence in order to undertake drainage of ascites two or three times a week at most, dependent on symptoms. Prior work in ascites due to malignancy indicated that two or three visits a week were most commonly required.[145,146] Clear guidance regarding LTAD care, suture removal, and drainage

guidance was given to community nursing teams and the contact details of the research team was also provided. Study visits were usually arranged to coincide with community nurse drainage visits to avoid lone community visits for the research team. See appendix 5 for all study standard operating procedures (SOPs) including the community SOP.

Drainage was usually undertaken by the community nursing teams, but if a willing and capable informal carer was identified by the nursing team to undertake drainage, they could train and supervise them in this. The Integrated Primary Care Team (IPCT) closely monitored trial participants allocated to the LTAD arm with frequency of the community nursing visits for drainage being dependent on the participants' ascites related symptoms, however this was initially planned to be two or three times per week. One or two Litres maximum (1-2L) was planned to be drained at each specific sitting, two or three times a week, not exceeding three times per week. The amount and frequency of drainage was recorded by the community nurses in LTAD drainage diaries and any observations in the community nursing files. The community nurses were familiar with this data collection as they routinely manage patients with LTAD due to malignancy related ascites in the community. The research team further trained and advised the community nurses and participants in LTAD study data collection to reduce the possibility of missing data.

4.13.2 Group two: Large Volume Paracentesis (LVP)

Participants randomised to group two, LVP, underwent LVP as per usual standard of care at each participating site.[27] This is usually performed as an acute hospital day case, where patients can either self refer, be referred by their GP, or alternatively from gastroenterology or hepatology outpatient clinic by their usual team. The referral process followed whichever was the local procedure, and drainage was

undertaken as per local standard of care, with participants undergoing LVP as was clinically indicated. LVP involves insertion of a temporary peritoneal drain by the usual medical team, for a maximum duration of six hours, with drainage of usually five to ten Litres of ascites and concomitant use of intravenous (IV) human albumin solution (HAS) (about eight to ten grammes of albumin per one to two Litres of fluid drained, usually as 100ml bottles of 20% HAS).[27] During LVP, patients have routine bloods done to include full blood count, clotting, liver, and renal function tests as well as a routine sample of ascites sent for microscopy, culture, and sensitivity (MC&S) at the time of drainage.

4.13.3 Both groups: one (LTAD) and two (LVP)

Antibiotic prophylaxis

As there is no current guidance on the use of antibiotic prophylaxis in the context of LTAD in ascites due to decompensated cirrhosis, a pragmatic approach was used.[27,28] This followed discussion with the BSUH local microbiology team and in conjunction with international guidance from The European Association for the Study of the Liver (EASL) and UK guidance from NICE where, based on a total ascitic protein value of 15g/L or less, primary antibiotic prophylaxis for SBP is offered.[27,147] The decision was that, given refractory ascites equates to advanced ESLD, if a participant was not already receiving antibiotic prophylaxis for secondary prevention of SBP, antibiotic prophylaxis was prescribed for all participants, (Ciprofloxacin 500 mg once per day) or an equivalent antibiotic (if there was a contraindication to Ciprofloxacin), dependent on local site practice. This was felt to be appropriate on review of the risk versus benefit balance, given concerns surrounding infection risk and specifically peritonitis, due to the increased susceptibility to infection in ESLD due to cirrhosis associated immune dysfunction.[61]

Study follow up and routine clinical care

Following enrolment into the study, randomisation, and initial study baseline visit, participants underwent study follow up visits with a research team member every other week for the duration of the study, in total 12 weeks, or in the event of attrition for whatever reason, to the final date of participation in the study. Study follow up visits were to undertake clinical and questionnaire based assessments as well as for routine clinical blood samples to be taken.

Group one were usually visited in their place of residence, unless a visit to the hospital setting was more acceptable to them; Group two usually underwent study visits in the hospital setting if this coincided with a visit for LVP, or in their current place of residence, whichever was both convenient for the participant and met planned study visit timelines.

Trial participants did not have any modifications to their routine clinical care, whether in the community or hospital setting. This included symptomatic relief for pain (including use of opioids), shortness of breath, confusion (HE), jaundice, or itching. Use of diuretics was permitted in both groups. As is the current standard of care in patients with ESLD, the use of certain drugs (e.g. non steroidal anti inflammatory drugs, aminoglycosides) was contraindicated.[27]

With participants' consent, their GPs were informed of their enrolment in the study.

Participants not living in their own home

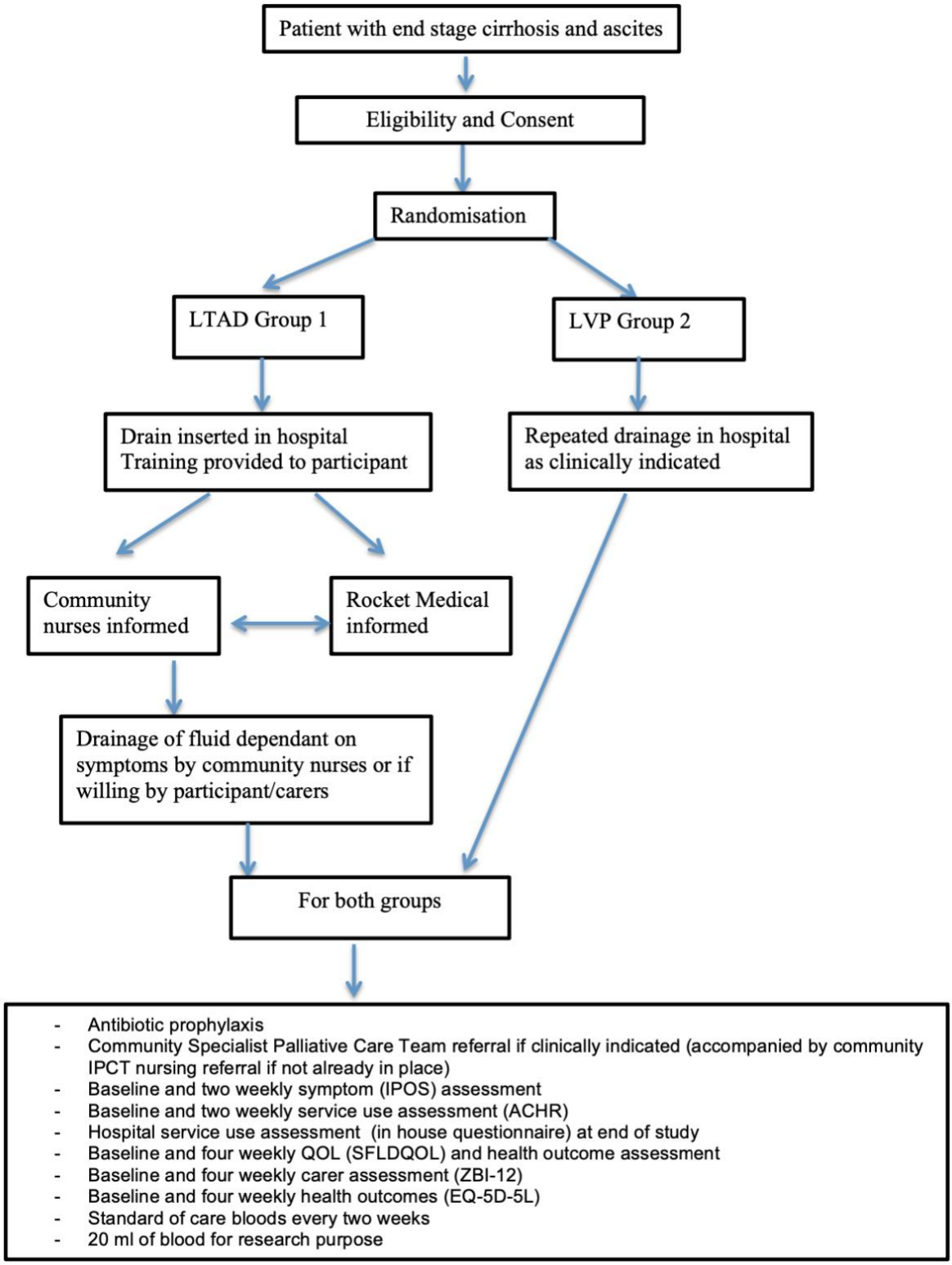
Patients were not excluded from participation in the study dependant on place of residence. Patient identification, receipt of consent and recruitment to the study was during a visit to the acute hospital setting and remained unchanged in terms of

planned follow up visits. For participants living in a care home or who moved to a care home (with or without nursing support), this was classed as their usual place of residence and the follow up procedure was the same as for those who lived at home. In such cases approval was sought from care home managers to undertake study visits. For those requiring a hospice stay, which would be short term, since hospices do not generally provide long term care, permission was sought from the hospice team to visit the participants for follow up, and only if such visits remained acceptable to the participants.

Palliative care assessment

Specialist palliative care needs were assessed utilising the Integrated Palliative care Outcome Scale (IPOS questionnaire).[148–150] A mini multidisciplinary meeting (MDM) (either face to face or virtual) agreed which participants were offered referral to a specialist palliative care service, this was dependent on identified need (reflecting usual clinical practice). If offered and accepted, the referral was arranged by the research team. Criteria was agreed so that if a high level of specialist palliative care need was identified through the IPOS questionnaire,[148–150] as defined within a distress protocol standard operating procedure (see appendix 5 for all SOPs), the research team proceeded with offering and arranging a specialist palliative care referral to the participant, without waiting for an MDM. As is usual clinical practice, if a specialist palliative care service referral was made to a community service, a community nurse (IPCT) referral was also made, if this had not already occurred previously for another reason. As is standard clinical practice, referrals to a specialist service by usual healthcare providers could also occur irrespective of any trial assessments or advice. Figure 4.2 shows the participant timeline.

Figure 4.2 Participant timeline



4.14 Study procedures and assessment schedule

The study procedures and assessment schedule can be seen in figure 4.3, 'SPIRIT schedule', which follows the SPIRIT 2013 recommendations for study protocol development in interventional trials.[151,152] SPIRIT supports adherence to the ethical principles mandated by the 2008 Declaration of Helsinki, and encompasses the protocol items recommended by the International Conference on Harmonisation Good Clinical Practice E6 guidance.[151,152]

Figure 4.3 Study procedures and assessment schedule

	Screening	Baseline	Followup 1	Followup 2	Followup 3	Followup 4	Followup 5	Followup 6
Timepoint (weeks)	-	t_0	t_2	t_4	t_6	t_8	t_{10}	t_{12}
Capacity check	✓	✓	✓	✓	✓	✓	✓	✓
Informed Consent[1]	✓							
Demographics	✓							
Medical History	✓	✓						
Eligibility according to inclusion/exclusion criteria	✓	✓						
Routine liver ultrasound[2]	✓							
Research blood sample for storage		✓[3]						
Liver screen blood tests[4]		✓						
Blood/urine culture, ascitic tap, urine dipstick [5]	✓	✓						
Randomisation[6]		✓						
Alcohol and substance misuse assessment	✓	✓	✓	✓	✓	✓	✓	✓
Liver disease scores	✓	✓	✓	✓	✓	✓	✓	✓
Routine haematology and biochemistry	✓	✓	✓	✓	✓	✓	✓	✓
Diagnostic paracentesis[7]	✓	✓	✓	✓	✓	✓	✓	✓
Liver disease assessment and history	✓	✓	✓	✓	✓	✓	✓	✓
Adverse event review		✓	✓	✓	✓	✓	✓	✓
Concomitant medication review		✓	✓	✓	✓	✓	✓	✓
Examination and vital signs[8]	✓	✓	✓	✓	✓	✓	✓	✓
LTAD insertion (or LVP)		✓						
Drainage assessment (both LTAD and LVP)		✓	✓	✓	✓	✓	✓	✓
Questionnaires: IPOS, AHCR		✓	✓	✓	✓	✓	✓	✓
Questionnaires: SF-LDQOL, EQ5D-5L, ZBI-12		✓		✓		✓		✓
Questionnaire: Hospital service use								✓
Qualitative interviews			←	Phase 1	→ ←	Phase 2	→	

Below is the accompanying legend for the assessment schedule (SPIRIT schedule figure 4.3).

1. Informed consent can be given prior to the screening visit, but must be confirmed at the screening visit.
2. Unless previous imaging (CT, MRI or ultrasound) is available within the previous six months.
3. 20 ml of blood will be taken at baseline for future ethically approved research, (10 ml saved as serum, and 10ml as whole blood as per laboratory SOP).
4. HBsAg, HCV antibody, HIV antibody, ANA (antinuclear antibody), AMA (Anti-mitochondrial antibodies), SMA (smooth muscle antibody), LKM (kidney microsomal antibody), serum ferritin, serum copper, serum caeruloplasmin, serum alpha one antitrypsin, fasting serum total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, total cholesterol:HDL ratio and low density lipoprotein (LDL) cholesterol (if not done in the previous three months).
5. If not performed within the last 48 hours or 14 days prior to baseline visit.
6. Randomisation can be done up to 14 days prior to the baseline visit.
7. If not performed within the last two days (screening visit) or seven days (baseline visit). For subsequent visits this will be done if clinically indicated (Group one: LTAD) or, in the case of Group two (LVP), at each visit.
8. Temperature, blood pressure and pulse; height and weight at baseline visit only.

4.14.1 Potential participant approach

Potential participants were approached by the research team after being identified by the usual medical teams; those expressing interest were given a PIS and were given at least 48 hours before being contacted in a pre agreed manner, usually via

telephone call, to allow them sufficient time to consider participation in the study. If willing to participate, a screening visit was arranged which was undertaken in the hospital setting.

4.14.2 Screening visit or rescreening visit

At the initial screening visit, capacity to give consent for trial participation was assessed, and written consent was received by the research team on the study consent form and recorded in the source documents. Willingness to continue in the study and capacity to give consent regarding this was checked at each subsequent study visit.

If a carer was present and was willing to participate in the study, their consent to be enrolled was also received at this point.

Once consent had been received for study enrolment, study specific procedures and data collection was undertaken following the study protocol to screen for eligibility, and was supported using case report forms (CRF). Data collected included inclusion/exclusion criteria assessment, demographics, liver disease specific history and severity scores, clinical examination, laboratory samples including standard of care bloods were taken at baseline and at all subsequent study visits: haematology and biochemistry for full blood count (FBC) which includes: haemoglobin (Hb), white blood cell count (WBC), platelets, clotting screen (including INR [international normalised ratio]), liver function tests which include: bilirubin, albumin, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), renal function which includes: creatinine, urea, sodium, potassium and estimated glomerular filtration rate (eGFR) as well as blood glucose and C reactive protein (CRP).

4.14.3 Baseline/Randomisation visit

Capacity checking (see appendix 4 ‘Capacity to Consent Checklist’) was undertaken at each study visit. Scheduled study visits were undertaken at baseline and then at every two weeks for a total of 12 weeks, which was the planned study follow up period if participants remained within the trial for the whole follow up duration.

The baseline visit included confirming eligibility to participate in the study, which required review of results from the screening visit; further data was then collected in the form of medical history, including concomitant medications review, non invasive liver screen, further routine laboratory samples including standard of care bloods, and 20mls of blood was taken for storage and study specific research.

A randomisation request was made and the participant informed of the outcome and allocation into study group.

All six study assessment questionnaires were administered at baseline and then at differing time points in order to minimise the questionnaire burden for participants. IPOS,[148–150] assessing symptoms in relation to palliative care needs, as well as the modified Ambulatory and Home Care Record (AHCR) of hospital and community service use and a Hospital Service Use questionnaire (see appendix 6 for Hospital Service Use proforma), were administered at the baseline visit and then at each subsequent study visit.[153]

The remaining three questionnaires were administered at baseline and then at alternating visits, which was therefore at intervals of four weeks. These questionnaires were capturing data on quality of life (QOL) as well as burden on informal care givers. The Short Form Liver Disease Quality Of Life questionnaire (SF-LDQOL),[154,155] and health outcome assessment (5-level EQ-5D version [EQ-5D-5L] which is a tool to describe and value health.[156] In clinical trials the EQ-5D-5L

instrument can be used to measure treatment effects by measuring health status at different points in time. The carer assessment was undertaken using the Zarit Caregiver Burden Interview Short Form (ZBI-12).[157,158]

An invitation to participate in the qualitative interviews was made at baseline, since the participant had already received the qualitative interviews PIS when initially approached. If they were willing to participate in this embedded study, consent was received from them to pass on their most appropriate contact details to the qualitative interviewer, and the manner in which they were happy to be contacted by them. The consent to take part in the qualitative interviews was received by the qualitative interviewer at the time they made contact with the main study participant. The contact telephone number for the research team was provided to the participants on a contact number card. Out of hours, participants were encouraged to contact their GP or attend the accident and emergency department of their local hospital, whichever was most appropriate and the usual standard of care. If there was a community nurse related request, participants were encouraged to contact their specific community nursing team.

Community nursing teams were also given the contact details of the research team and a community related SOP (see appendix 5) was written to support study related community care.

4.14.4 Subsequent study visits

Subsequent study visits were undertaken every two weeks, either in the participants home, during a planned hospital attendance, in order to reduce the burden of hospital visits on the participant, or in the event that the participant was receiving care in a hospice or care home setting, within that setting, after agreement had been sought from the hospice or care home management team.

Capacity checking and willingness to continue to continue with participation in the study was undertaken at each study visit and recorded in the source documents. Review of any adverse events (AE), medication review, and other social history plus liver disease specific questions and assessment were undertaken. Standard of care bloods were taken to include renal function, liver function, and full blood count.
The amount and frequency of drainage and other routine observations were recorded by community nurses in a formal study diary, as is done in the context of LTAD use in ascites due to malignancy. The research team trained the community nurses on drainage data collection to reduce the occurrence of missing data. Drainage information was collected from drainage diaries in those in Group one (LTAD), and those in Group two (LVP) if they had undergone an LVP, details of the drainage and routine ascitic tap results were recorded in the CRF.

4.14.5 Questionnaire based assessments

The questionnaire based assessments were undertaken by the research team and, depending on patient preference, were performed either face to face, or via telephone (within 3 days of the study visit). Lone worker policy guidance was followed when conducting visits in participants homes/usual places of care but overall, visits were conducted in conjunction with a community nurse, during their planned visit, which facilitated drainage data collection as well as community nurse support and guidance, or in conjunction with a second member of the research team, in order to avoid lone working.
The questionnaires that were selected were those which have been validated within the study population group (e.g. those with ESLD and in those receiving palliative care). Some, like the IPOS (see the following section),[148] are short, relatively brief to complete and have a proxy version if a patient loses the ability or capacity to be able

to complete the questionnaire during the study follow up schedule. As this was a feasibility study, we explored the acceptability of the measures used and the Trial Management Group (TMG) reviewed the burden of questionnaires on participants after the initial eight recruits; no change to the protocol was made as questionnaire completion was well tolerated. The research team member assisted participants in completion of the questionnaires if needed and if specifically requested by the participant. If participants were too unwell to complete the questionnaires themselves, they were completed by proxy by carers, to reduce both the participant burden as well as the risk of missing data.

4.14.5.1 Symptom distress and concerns

The IPOS combines the Palliative care Outcome Scale (POS) and POS-S (POS with symptom list).[148–150,159,160] These are measures frequently used in palliative care research and clinical practice. They are validated for clinical practice, audit and research and can be used in any setting. The POS-S captures physical symptom specific information, and “other” symptoms specific to liver disease/ascites can be added, e.g. abdominal bloating. A distress protocol SOP (see appendix 5 for all SOPs) was implemented when clinical and/or risk of harm issues were identified by the research team, to ensure timely assessment by participants’ usual healthcare providers and/or referral to a specialist palliative service, depending on the need identified.

The IPOS questionnaire consists of a total of ten questions and takes less than ten minutes to complete.[148–150,159,160]

4.14.5.2 Quality of life

Liver disease specific quality of life (QOL) was assessed using the Short Form Liver Disease Quality Of Life questionnaire (SF-LDQOL), a validated measure of health related QOL in patients with advanced liver disease awaiting transplant,

incorporating a core QOL assessment and disease targeted items.[154,155] Specific and validated QOL assessment tools are lacking in cirrhosis and it was felt the SF-LDQOL was the most appropriate option, following involvement from service users. A scoring algorithm was used which included only the first 25 questions; the remainder of the questionnaire are for questionnaire validation, therefore, only these first 25 questions were used. The questionnaire takes about 15 minutes to complete.[154,155]

4.14.5.3 Generic quality of life

There are opposing views on the use of the EuroQol 5 dimensions (EQ-5D) as a composite measure of Quality Adjusted Life Years (QALYs) in palliative care,[92] however, QALY is still the most widely used indicator. We elected to use the 5-level version (EQ-5D-5L) in this feasibility study, as it can be used in isolation as a generic quality of life assessment tool, without calculating QALYs, as well as to monitor changes over time. We wanted to assess the utility of the tool as a potential outcome measure and for the possibility of its use to calculate QALYs in a full size study.[156] The EQ-5D-5L has six questions and takes about five minutes to complete.

4.14.5.4 Impact on carers

If carers were present and willing to participate in the carer specific questionnaires, the Zarit Caregiver Burden Interview Short Form (ZBI-12) was used.[157,158] This tool measures family/informal carer appraisal of the impact on themselves of caregiving. It has 12 statements which carers are asked to grade their agreement with at five levels starting at ‘never’ and ranging to ‘nearly always’ and it takes about ten minutes to complete.

4.14.5.5 Service use assessments and health economic measures

Comprehensive patient level service use was collected, including all inpatient, outpatient, emergency, primary, community, social and voluntary services, equipment and supplies, as well as assistance from family and/or informal carers. For community and home based services, a modified version of the Ambulatory and Home Care Record (AHCR) of hospital and community service use was administered by the research team.[153] Carers were able to assist with this, especially if the participant was too unwell to be able to recall care related interactions. The AHCR is a standardised and comprehensive framework and tool, measuring resources used within the end of life context from a societal perspective.[153] This gives equal consideration to costs borne by the health system as well as those costs borne by care recipients and informal caregivers, such as family members and friends. It takes about 20 minutes to complete.[153] Self reported data was verified, where possible, and supplemented (such as in the case of supplies used) with reference to nursing records.

Data on all hospital use was gathered from hospital records at the end of the study using a purposefully designed in house proforma, the Hospital Service Use questionnaire (see appendix 6). Service use was converted to costs using national sources and National Health Service (NHS) reference costs.[161] Informal care was valued using replacement cost methods and applying the tariff for community support workers.

4.14.6 Qualitative interviews

Qualitative data was also collected from study participants, as well as from community and hospital nurses, as part of a concurrent embedded study.[162] A total of 28 optional interviews (with 20 participants and eight clinical key informants) were

undertaken by a qualitative researcher. Clinicians and research participants were identified and recruited by the research team member. Interviews were conducted over the telephone.

4.14.6.1 Statement of contribution:

The qualitative interview PIS was given to potential study participants prior to screening visits. At the time of enrolment into the main study, participants were also invited to take part in the qualitative aspect. If willing, the research team received consent to pass their contact details and information on to the qualitative researchers.

4.14.6.2 Qualitative researcher aspects

The qualitative researcher contacted participants, received consent to take part in the qualitative interview embedded study, including from any carer requested by the participant to be present during the interview, then arranged a convenient time to undertake the interview themselves.

4.14.6.3 Qualitative interview data collection and analysis

Interview themes included an exploration of the experiences of recruitment, participation, undergoing LTAD or LVP, and the provision of end of life care. Beliefs about the role and value of the LTAD in refractory ascites, and practical steps and barriers involved in using the LTAD were explored.

As life expectancy in refractory ascites due to ESLD is very limited, with a median of six months,[27,37] the qualitative interview methodology sought to explore a wide range of patient experiences, recognising that participant beliefs and experiences may have changed across this period. Interviews therefore were divided into two phases:

Phase one (weeks 0–8) 12 patients (six from each arm), four clinical staff

Phase two (weeks 9–12) eight patients (four from each arm), four clinical staff

Interviews with key clinical staff followed the same aims of participant interviews and were anonymous (key informants were also asked to withhold participant identities to ensure participant confidentiality).

Since the interviews were undertaken via telephone, consent was received verbally and recording started before telephone consent was received, so that the verbal consent could be recorded as a separate file from the interview. Interview data was transcribed by the qualitative interviewer and the audio version deleted. The anonymised transcription of the interview (including the verbal consent) was stored (labelled with patient study number).

To reduce participant burden, breaks were allowed during the interviews if requested by the participants, and interviews lasted between 20 and 60 minutes. Figure 4.3 shows the SPIRIT diagram for study visits.

4.14.7 Feasibility study outcome measures and success criteria

The objectives of this feasibility study were to explore a number of aspects of undertaking research in a group with ESLD, who are in a palliative phase of their disease trajectory, with the longer term aim for the information gained to be able to be utilised in informing the design of a full scale study.

We therefore aimed to collect data on a range of possible primary outcome measures, including QOL and health resource utilisation.

Outcome measures:

- Properties of different outcome measures (specifically health resource utilisation and QOL instruments) to aid in ascertaining the most appropriate primary outcome for a full scale trial, and use the chosen primary outcome measure to inform sample size calculations from estimates of the standard deviations, for a full trial

- Resource implications of the LTAD compared to standard of care (LVP), including a preliminary assessment of cost effectiveness
- The number of eligible patients
- The extent of healthcare professional support in identifying possible participants
- Symptom burden in patients with ESLD and refractory ascites
- Informal carer/family perceived burden (if appropriate)
- Whether patients are willing to be randomised to LTAD, rather than LVP
- Acceptability of and adherence to drainage of ascites in a usual place of residence setting
- Attrition rates, including attrition due to death, illness, or other causes
- Complication rates, including peritonitis
- Willingness to participate in a qualitative interview (optional)
- Acceptability of the LTAD to patients, carers, and clinical staff using qualitative methods (optional)
- Acceptability of questionnaire assessments and questionnaire burden

Study success criteria

The study success will be based on the following criteria:

- The percentage of study period time in hospital for the LTAD group is <50% of that for the LVP group (where the study period time is the number of days from the date of LTAD insertion, to the end of the study period, or the patient's death, whichever is earliest; time spent in hospital is the number of bed days used)
- The attrition rate is not >50%

- There is <10% overall rate of LTAD removal due to one or more of the following complications: peritonitis, failed insertion, bleeding, and blockage
- Each participant completed 80% of the questionnaires and qualitative interviews

4.14.8 Safety monitoring

The Common Terminology Criteria for Adverse Events (AEs) was used when assessing AE and serious adverse events (SAEs).[163] All AEs and SAEs were recorded in the source data and reported on the electronic CRF. Only those SAEs that in the opinion of the Chief Investigator were related to the study intervention (LTAD) were reported in an expedited manner to the Brighton and Sussex Clinical Trials Unit (BSCTU).

The study population is a group with a background level of high morbidity and mortality rates and as part of the natural history of their ESLD are expected to have further decompensations and liver related complications.[27,28,34,40,61,134] Therefore worsening of existing conditions, hospitalisations, acute illnesses, and deaths linked to their underlying liver disease were expected. These events were recorded in the electronic CRF but were not reported to the BSCTU or the Research Ethics Committee (REC).

Expected/unexpected unrelated AEs/SAEs will include but not be limited to:

- Hepatic encephalopathy
- Gastrointestinal bleeding related to peptic ulceration, hypertensive portal gastropathy or varices
- Liver cancer and/or its treatment
- Complications of gastroscopy (perforation, bleeding)

- Complications of LVP (circulatory and or electrolyte disturbances, bleeding, bowel perforation, failed drainage)
- Complications of drug treatment for cirrhosis (lactulose, beta blockers, terlipressin, antibiotics, diuretics)
- Death related to liver disease: which includes death from liver failure, multiorgan failure, variceal bleeding, and sepsis

Expected serious adverse reactions (SARs)

If in the Chief Investigator's opinion a SAR was considered to be directly related to the LTAD and was an expected SAR, then this was recorded on the electronic CRF and reported to the BSCTU immediately following the Safety Reporting SOP (see appendix 5). Expected SARs included the following (but only if they resulted in hospitalisation):

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

Suspected unexpected serious adverse reactions (SUSARs)

This category included all SARs that in the opinion of the Chief Investigator were directly related to the intervention and were not listed as a known (expected) SAR.

All SUSARs occurring between insertion of the LTAD and within three months following the insertion, or death, whichever was earlier, were recorded on the electronic CRF and emailed/faxed to the BSCTU immediately, within 24 hours of the research team becoming aware of the event, in accordance with the BSCTU Safety Reporting SOP. The REC were notified of any SUSAR related to the study intervention by the BSCTU.

The Chief Investigator had direct and ultimate responsibility for reviewing all reported SARs and SUSARs and ensured that the BSCTU reported these appropriately according to the BSUH SOP on Safety Reporting in Non Clinical Trial of an Investigational Medicinal Product (CTIMP) studies.

4.14.9 Data analysis

4.14.9.1 Statistical considerations

Sample size

Guidelines for feasibility studies suggest that analysing at least 12 participants in each arm of a study will provide an adequate sample size to achieve the study objectives.[164] However, since the study population is a cohort with a limited life expectancy and prognosis, it was felt that attrition was likely to be high; and due to the advanced disease stage of the participants, we assumed a 50% attrition. The sample size therefore was increased to 24 participants in each arm – which meant a total recruitment target of 48 participants overall. It was felt that this sample size was adequate to inform the research methods for a larger definitive RCT.

Recruitment rate

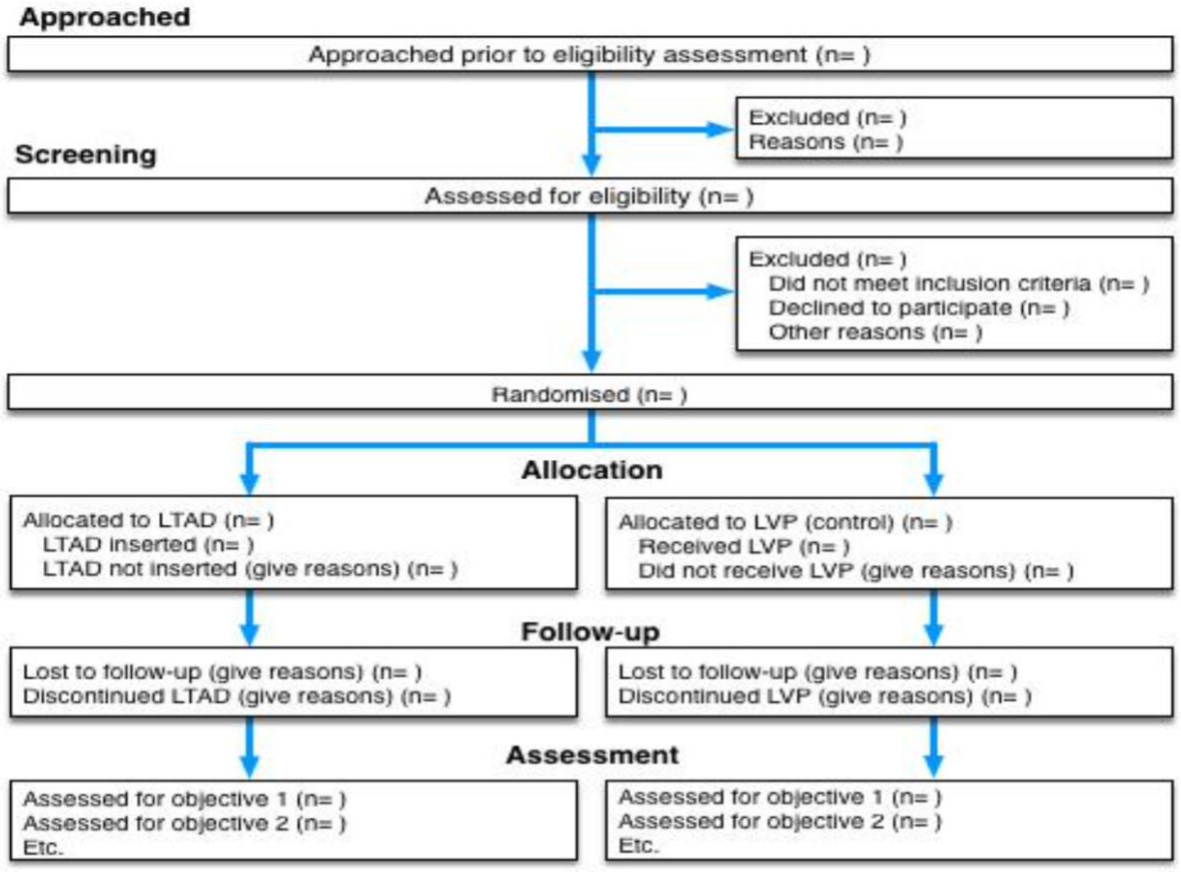
Recruitment rate was evaluated in terms of the proportion of eligible patients who gave informed consent. Attrition at all stages was recorded and particular interest was taken in cases of unwillingness to participate or receive the LTAD or inability to

manage the LTAD, as this was felt to be an indication of overall acceptability to patients of this ascites management method.

Data analysis

Data was analysed on available cases in the groups to which they were randomised. The flow of patients through the trial is depicted in the Consolidated Standards of Reporting Trials (CONSORT) diagram. The planed CONSORT diagram for the study is shown below in figure 4.4).[165] Data was analysed in a blinded manner, however, the research team members collecting information from the participants were aware of their allocation group, firstly since it is impossible to blind the intervention of LTAD or LVP insertion, but also since a high level of oversight was necessary to ensure that there were no safety events in the LTAD group.

Figure 4.4 CONSORT diagram for the study



4.14.9.2 Statistical analysis

Descriptive analysis

Descriptive statistics were used to summarise and compare the quantitative outcome measures which included:

1. Complication rates: failed insertion, drain leakage or blockage, cellulitis, bleeding, pain at site of insertion not controlled by analgesia, peritonitis, sepsis, and death (the latter two only if directly related to the LTAD)
2. Symptoms: IPOS, QOL (SF-LDQOL, EQ-5D-5L)[148,154–156]
3. Carer burden for each arm[157,158]

Means and standard deviations were determined for normally distributed outcomes, and medians and interquartile ranges for skewed outcomes at different time points, and at the end of the study. Analyses used all available cases following intention to treat principles. Calculation of 95% confidence intervals for parameter estimates was undertaken as appropriate.

Health economics data analysis

The economic analysis adopted the perspectives of the health and social care systems, and analysis was undertaken by health economists; a summary of the analysis plan is described below.

The feasibility study aims were in identifying the main resource items for which comprehensive data collection would be most appropriate, and to capture the required data elements as part of a full size trial. This was achieved by using the patient level database assembled from participant self reported, hospital, and community nursing records.

The interactions between the management of ascites and use of other palliative care services were explored. In particular, numbers of community nurse visits in both groups were monitored, so that the extra visits required for the management of the LTAD, compared to normal care, were identified. Data from this was then used to calculate the group mean total costs of services used in ascites management, and costs were compared between both groups, LTAD and LVP. This had been a source of uncertainty in an earlier study of PleurX™ in malignant ascites.[76]

The properties of the main clinical outcomes (IPOS, SF-LDQOL, EQ-5D-5L),[148,154–156] and the number of hospital days taken for ascites management, were investigated to assess their value as measures of effectiveness to be able to inform a future definitive trial and facilitate decisions on choice of a primary outcome measure. Data on QALYs from EQ-5D-5L were planned to be investigated for potential use in an economic evaluation in a full size study.[156] A preliminary cost effectiveness analysis was undertaken to determine the potential advantages of an LTAD approach to ascites management, with the aim to support the plan for the future development of a full size trial.[166] A sensitivity analysis was performed by varying the key cost drivers, such as the number of inpatient days and the cost of bed days.

Qualitative data analysis

Qualitative data analysis was undertaken by the qualitative researchers; a summary of the analysis plan is described below.

If purposive sampling was not feasible, the proportion of participants choosing to participate in qualitative interviews was noted.

Thematic analysis supported by qualitative software (NVivo) was used to extract overarching themes from the interviews undertaken to capture participants'

experiences, in both groups, of being part of the study, as well as their beliefs.[167] Utilising the process of triangulation, the findings of the qualitative arm were used to inform the quantitative results, particularly in the context of QOL and experience of end of life care provision.[168]

4.14.10 Ancillary and post trial care and follow up

All research participants continued to receive routine medical care as clinically indicated, whether that be in the community, primary care, or hospital setting. While participating in this trial, no individual had their routine clinical care modified or denied.

Group one: LTAD

For reasons of safety and clinical overview, situations where removal of the LTAD may become necessary were described, and in those circumstances, removal could be undertaken, after discussion with the Chief Investigator and the TMG.

These were defined as:

1. at patient request
2. In the event of a serious adverse reaction (SAR) assessed by the Chief Investigator as being directly related to the LTAD
3. In the event of a significant deviation from the study protocol with the potential for harm to occur (for example the participant not allowing community nurses to enter a residence to perform drainage)

In the event of a participant death during the study

If a participant in Group one (LTAD) died while the LTAD was still in situ, there was no need for the drain to be removed, and no alterations to standard management of indwelling plastic devices following death were required.

End of study follow up in both groups one and two

At the end of the trial, if they were still alive, participants continued to be assessed by their usual medical team, as per standard of care. This included undergoing LVP as clinically indicated if they were in the LVP group, as well as routine review in the gastroenterology/hepatology outpatient clinic. Those who were allocated to the LTAD arm were given the option to continue with the LTAD under the care of their usual consultant gastroenterologist/hepatologist, and with ongoing community nursing team support.

Chapter 5 - REDUCe study results: Study procedures, recruitment, demographics, and clinical outcomes

5.1 Introduction

A national study of healthcare use in patients with cirrhosis and ascites in England from 2013 to 2015 found that a third had required a large volume paracentesis (LVP) in their last year of life.[52] In acute hospitals across the country, it has become more common for LVPs to be undertaken as planned procedures on medical day case units.[52,95] While this reduces the healthcare burden and cost, compared with an acute hospital inpatient admission, it does still require patients to attend hospital on a regular basis for the procedure to be performed.[52]

Without liver transplantation, the median life expectancy of those with refractory ascites (RA), in the context of cirrhosis, is six months.[39,51,55,94] This was replicated in our local data on RA reported in chapter 2, as well as finding that nearly 40% of patients with cirrhosis who underwent an LVP, went on to develop RA, and of those, less than 15% were accepted for liver transplantation, consistent with national figures.[56] In the majority of patients with RA, LVPs are therefore essentially symptom management and undertaken as palliative procedures.[13,20,70]

There has been growing interest in the potential for using long term abdominal drains (LTADs) as an alternative to LVP, however, as we reported in chapter 3, evidence for their use in this population is lacking. LTAD are the current standard of care in malignant ascites, allowing ascites drainage episodes to be undertaken in patients' usual place of residence, which may improve quality of life in a palliative cohort, and carry a healthcare cost saving.[76,169]

Palliative care in patients with end stage liver disease (ESLD) is lacking, and given the stigma experienced of those with cirrhosis, this is a disenfranchised cohort.[1,41,104,170,171] There is a high symptom burden experienced, and patients are often, if at all, referred for palliative and supportive care late in their disease trajectory.[46,86,172–175] To support advancements in palliative care in ESLD, good quality research and evidence is needed on effective interventions, to include patient perspectives, quality of life, and impact on healthcare services[92,173].

The REDUCe study (**RE**peated **D**rainage **U**ntreatable **C**irrhosis) was designed following MORECare guidance on evaluating complex interventions in palliative care, with the overarching aim to improve the palliative management of refractory ascites in ESLD.[41,92,104,170]

The clinical and quantitative results for the REDUCe study presented in this chapter, as well as in chapter 6, have been published in Alimentary Pharmacology and Therapeutics, and details of the publication are in the references.[176]

5.2 Chapter aims

This chapter aims to report on the main study procedures, recruitment, demographics, and clinical outcomes from the REDUCe Study: Palliative Long Term Abdominal Drains versus Large Volume Paracentesis in Refractory Ascites Due to Cirrhosis - **RE**peated **D**rainage **U**ntreatable **C**irrhosis (ISRCTN 30697116).

5.3 Statement of contribution:

Statistical analysis of study procedures and clinical data was undertaken by Professor Stephen Bremner at the Brighton and Sussex Clinical Trials Unit (BSCTU).

5.4 Methods

5.4.1 Overview

A detailed description of the study design and methodology has been provided in chapter 4, and the participant reported outcomes are reported in chapter 6. This was a three year feasibility randomised controlled trial (RCT), which ran from September 2015 to September 2018, in a cohort of patients with end stage liver disease (ESLD) and refractory ascites (RA). The study compared the use of long term abdominal drains (LTAD) with the current standard of care, large volume paracentesis (LVP), for the management of RA using a mixed methods approach.

5.4.2 Study setting and population

This was a multicentre RCT running in England, and study sites crossed healthcare boundaries, from hospitals into the community, in order to map the patient journey and investigate the patient experience. The initial planned timeline during the study design phase was for a 24 month study, with recruitment from two study sites. However, the study was granted a one year extension, with the addition of further sites, by the funding body (National Institute for Health Research, NIHR) as well as the overseeing research bodies. This was granted as it was felt to be an important study to meet its defined success criteria on, given its focus on improving palliative care in a growing and disenfranchised cohort. The extension was given in order to facilitate the participant recruitment target, as initial recruitment rates were lower than expected, this improved after lessons learned were taken on board and implemented, and further study sites were opened. At the end of the study therefore, there were five sites with study procedures being conducted across acute hospitals and into corresponding community sites.

5.4.3 Definition of refractory ascites

Refractory ascites (RA) was defined according to international practice guidelines, as ascites that could not be treated, or early recurrence of ascites, which could not be satisfactorily prevented by medical therapy.[25] This represents either non response to sodium restriction and diuretics, and/or the development of diuretic induced complications which preclude the use of an effective diuretic dose.[25,28]

5.4.4 Inclusion criteria

The cohort of patients we wanted to investigate the intervention in was those with ESLD and refractory ascites (RA), specifically ascites recurring rapidly after LVP, and requiring one or more LVP procedures to be undertaken per month. Participants had to have undergone a minimum of two LVPs prior to screening for study eligibility, and ideally three prior to recruitment. The rationale for this was that it is not uncommon for patients with ESLD to require an ascitic drain during an acute episode of decompensation, however, this situation can be reversable, and does not mean that their ascites has become truly refractory.[25,56] It may represent a transient deterioration in severity of liver disease, but can sometimes either improve to small volume ascites, not requiring drainage, or recompensate, where the ascites resolves completely.[25,56] Since our target cohort was those who had RA requiring recurrent ascitic drainage, and not those with an acute decompensating episode with a reversible component, we identified potentially eligible patients, and allowed their drainage requirement to evolve for a clearer picture before proceeding.

The other inclusion criteria were: patient age ≥18 years, Child Pugh Score ≥9, unless the patient was felt to be in a palliative stage of their liver disease despite having a lower Child Pugh Score.[22,25] The final aspect of the inclusion criteria was that

patients needed to be assessed to have the capacity to give informed consent in order to be enrolled into the study.

5.4.5 Exclusion criteria

Study exclusion criteria were: loculated ascites, which would prevent adequate drainage by an LTAD, or chylous ascites, which could represent ascites due to an alternative cause, or be more prone to causing drain occlusion. The presence of greater than grade one hepatic encephalopathy (HE) was an exclusion, as would impact on patients' capacity to consider and weigh up the decision to give consent to be enrolled into the study, i.e. could mean that study consent was not valid.[40]

A further important exclusion was evidence of active infection in the potential participant, including spontaneous bacterial peritonitis, during the screening period (see chapter 4, figure 4.3 for study assessment schedule). Screening for infection included recording the results of a urine dipstick test and sending a urine sample to be cultured in the hospital laboratory. Blood samples were sent for culture, and an ascitic tap was taken and was analysed in the hospital laboratory, as standard, for polymorphonuclear count, and then cultured (chapter 4, figure 4.3). If an active infection was found or suspected, it was managed as per appropriate local clinical infection guidelines, and the patient could then be rescreened for study eligibility once the infection had been successfully treated.

Suitability for a transjugular intrahepatic portosystemic shunt (TIPS) was a further exclusion, as consideration for TIPS is currently part of the standard algorithm in the management of RA.[25,28] This is despite few patients with RA being suitable for TIPS, since a number of factors seen in decompensated cirrhosis are contraindications for TIPS in the context of RA, specifically, pre existing HE, and advanced Child Pugh or Model of End Stage Liver Disease (MELD) scores.[22,23,69]

Finally, eligibility for liver transplantation (LT) was an absolute exclusion factor as if it was felt that a potential participant was eligible, referral for LT assessment without delay is the most appropriate management strategy.[56] To avoid any potential conflicts of interest, transplant eligibility was determined at local multidisciplinary meetings, including discussion with, and/or review by the regional transplant centre if deemed appropriate, and not by the research team.

5.4.6 Patient identification and consent

The research teams were alerted to patients after being identified by their usual medical and gastroenterology clinical teams during an acute hospital admission, or from those attending medical day case units for standard ascites drainage procedures, LVPs. Research teams initially clarified that patients identified were deemed, by their usual clinical team, ineligible for liver transplantation and a TIPS procedure. Once confirmed, a member of the research team provided patients with a patient information sheet (PIS) which included details of the research study, information regarding LTAD insertion, and the after care process. Research teams also confirmed the method with which patients preferred to be contacted to further discuss the study. After a predefined amount of time for patients to consider taking part in the study, this was a minimum of 48 hours, but was usually followed up within 72 hours, patients were contacted again. If patients were willing to proceed with consideration of being part of the study, written informed consent was received from potential participants and caregivers, if present, and usually during the same sitting. At this point consent for details to be passed to qualitative researchers for participants to be contacted to take part in qualitative interviews was also received, if patient participants were willing.

During the consent process, patients were asked to nominate a personal consultee for the research team to approach as necessary, to consider whether or not they ought to continue in the research study, and with the study procedures, in the event that their capacity to give consent to do so had diminished. In the event that capacity for decision making regarding trial participation was lost during the study follow up period, the participant's nominated consultee, usually a family member but if none were given, or if they were unavailable, the participant's usual medical consultant was approached.

No study procedures were undertaken before the potential study participants had given written and informed consent to take part.

5.4.7 Ethical approval

Research Ethics Committee approval for the study was obtained nationally from the National Research Ethics Committee South Central - Hampshire A (REC ref. 15/SC/0257). The study was sponsored by Brighton and Sussex University Hospitals NHS Trust (BSUH) and received Research and Development approval from all five participating NHS Trust sites.

5.4.8 Randomisation

Once patients had given consent to be enrolled in the study, the screening visit and screening specific procedures were performed. The details of the study screening procedure are itemised in chapter 4, and main study procedures are summarised in the assessment schedule shown in figure 4.3, the participant timeline is shown in chapter 4, figure 4.2. Once participants had undergone screening, those fulfilling eligibility criteria, and who had no excluding factors, were randomised. The randomisation procedure is detailed in chapter 4, and was non blinded.

Randomisation was on a 1:1 basis to either group one: LTAD or group two: LVP using a web based system, which was hosted by King's Clinical Trials Unit (KCTU). After registering a participant using their unique study number, and requesting randomisation, the allocations were made by minimising, with a random element, on study centre, Child Pugh Score, and gender. An automatic email was generated confirming the randomisation, and informing the research team of the outcome of allocation to one of the two different study groups.

5.4.9 Intervention

Group one: Long term abdominal drain (LTAD)

Insertion of the Rocket® (Rocket Medical) LTAD was performed in hospital as a day case procedure, and using standard sterile techniques, ultrasound guidance, and local anaesthetic. A detailed description of the insertion procedure is given in chapter 4. Following insertion, participants were given a Rocket Medical standard information booklet and the next steps reiterated to them and their caregivers, if present. As is standard practice after a Rocket® long term drain is inserted, for example for malignant ascites or pleural conditions, Rocket Medical were informed of the insertion having taken place, using their standard communication sheet via fax. This was to allow the Rocket Medical team to support community nursing teams with drainage, or to provide further training if needed. Community nursing teams and participants' general practitioners (GPs) were sent information regarding the participants enrolment into the study, contact details of the research team, and guidance on LTAD use. Details for requesting further drainage bag supplies were also provided in the event that participants were alive at the end of the study follow up period, and elected to keep the LTAD drain in situ. Drainage bags and equipment

to be used by community nurses were supplied by the research team for the duration of the study follow up period.

Community nurses visited the participants in their usual place of residence two or three times per week, directed by the research team, and drained one to two Litres of ascitic fluid using the LTAD drainage bag system at each visit. No human albumin solution was administered in the community for drainage episodes. The maximum number of times per week which drainage was performed by community nurses was three, with a maximum volume of two Litres drained at each of those visits. This was as directed by the research team. If symptoms of ascites could not be controlled with that frequency and volume of drainage, a participant specific plan was decided on by the research team after discussion with the trial Chief Investigator.

Group two: Large Volume Paracentesis (LVP) - current standard of care

Participants randomised to the LVP group, which is the current standard of care,[25] followed the usual ascites pathway at their local hospital. The frequency of LVP procedures to be performed is clinically guided by patients' symptoms of ascites, and is undertaken via an admission to a medical day case unit, or inpatient admission to the acute hospital, but whichever was local standard practice.[52] A short term peritoneal drain was inserted by the usual medical team for up to six hours for ascites drainage, and intravenous human albumin solution was administered as per current international guidelines (eight to ten grammes per Litre of ascitic fluid removed).[25]

5.4.10 Antibiotic prophylaxis

It is standard care to offer long term prophylactic antibiotics in the case of patients with ESLD who have developed, and been treated for, spontaneous bacterial peritonitis (SBP).[25] There is no guidance on the use of prophylactic antibiotics in the

setting of LTAD in ESLD, and antibiotics for primary prophylaxis for SBP in ascites due to ESLD remains a controversial area, which the currently recruiting multicentre RCT ASEPTIC (Primary **A**ntibiotic prophylaxis using Co-trimoxazole to prevent **S**pontan**E**ous bacterial **P**eritoni**TI**s in **C**irrhosis)[177] evaluating Co-trimoxazole against placebo, is hoping to answer.

The UK based National Institute for Health and Care Excellence (NICE),[147] and the European Association for Study of the Liver (EASL)[25] international guidance both include offering prophylactic antibiotics to patients if their total ascitic protein is measured to be 15 g/L or less. The rationale behind this is that those with a lower ascitic protein are felt to be at higher risk of developing SBP,[25] however, more recent studies suggest that ascitic fluid protein may not be predictive of SBP risk.[178,179]

We felt that pragmatically, since the development of RA reflects advanced liver disease, and we were introducing an LTAD into a usually sterile environment in those in the LTAD group, that all participants in both the LTAD and LVP groups should be given prophylactic antibiotics for the duration of the study for comparability, if they were not already receiving them for standard SBP prophylaxis. The antibiotic used in the study was the same as for secondary SBP prophylaxis used in the UK, which is most commonly Ciprofloxacin 500mg once a day.[28] In the event of a different antibiotic being used in local hospital antibiotic guidance, or if there were patient related contraindications to Ciprofloxacin, an equivalent antibiotic was used.

5.4.11 Study aims

The aims and objectives of the RCT were not predefined as primary or secondary outcome measures, as this was a feasibility study. Our aims therefore were to explore the feasibility of undertaking a mixed methods study in this cohort of patients

with ESLD and RA who were in a palliative phase of their disease. The areas we wanted to explore included recruitment and attrition rates, bearing in mind the high mortality in this group.[51] We collected data on safety and potential effectiveness of the use of LTAD as a strategy to manage RA, although the study was not powered to detect statistical differences. We measured the uptake and completion of questionnaire based assessments and interviews, this included data on symptoms, quality of life, and informal caregiver burden. The health resource implications of using LTAD, compared with LVP as standard care, were explored, and a preliminary comparison of health economic costs was conducted by health economists. The acceptability of LTAD in managing ascites was assessed by undertaking optional qualitative interviews, to run as an embedded qualitative study, with patient participants, as well as healthcare professional clinical staff.

The results of the participant reported outcomes, including questionnaire based assessments, health economic analysis, and outcomes from qualitative interviews are described in chapter 6.

5.4.12 Study success criteria

We defined study success criteria as follows, and further details are given in chapters 4 and 6.

- Attrition due to any cause not more than 50%
- At least 80% uptake and completion of questionnaires and or interviews
- For those in the LTAD group to spend <50% ascites related study time in hospital compared to those in the LVP group
- For removal of LTAD to occur in <10% with causes for removal being possibly due to any one or combination of the following complications: failed insertion, peritonitis, bleeding, and blockage.

5.4.13 Schedule of assessments and analysis

Following randomisation and baseline visits, study visits occurred every other week in both the LTAD and LVP group and were undertaken by a member of the research team. In the LTAD group this was usually able to be undertaken at the patient participants' place of residence, in conjunction with community nurse visits, in order to strengthen links with, and support the community nurses. For participants in the LVP group, study visits were aimed to be undertaken during a hospital visit for an LVP procedure, in order to reduce the burden of participation in the study. Where this was not possible, such as if LVP visits did not coincide with the study timeline, study visits were then undertaken in participants' usual place of residence.

At the study visits, study data was collected, including routine blood samples, questionnaire based assessments, and ascites drainage related data. The study schedule is described in chapter 4, and summarised in figure 4.3. Data were collected on paper case report forms (CRF) and entered onto an electronic case report form within the Elsevier MACRO data capture system hosted by KCTU. Each participant was continued in study follow up for up to 12 weeks, or to the point of attrition, whichever occurred first (figure 4.3). Figure 4.2 shows the participant timeline. At the end of the 12 weeks, if participants in the LTAD were alive, they could choose to keep the LTAD in situ, in which case the community nurse visits would continue as had been undertaken throughout the study follow up, with oversight from the patients' usual gastroenterologist or hepatologist. Participants in the LVP group would continue with their usual hospital visits for LVP unaltered.

5.4.14 Clinical assessments

Clinical data collected included participant demographics and comorbidities, as well as acknowledgement of ineligibility for liver transplantation. The reasons for

transplant ineligibility were not formally recorded in CRFs, although if a subsequent study was undertaken, this would be included in the study design.

Medication use, including use of diuretics, was recorded at baseline and throughout subsequent study visits. Routine blood samples for biochemistry and haematology, were taken at each study visit in order to monitor for any safety concerns in the LTAD group, but also to compare the two groups.

The number of LVPs which participants had undergone before randomisation was recorded, as was the amount and frequency of all subsequent LTAD and LVP drainage episodes.

An assessment of the LTAD insertion site was made by community nurses at each drainage visit, as well as by the member of the research team undertaking study visits.

Any adverse or serious adverse events (AE, SAE) were also recorded and escalated to the Chief Investigator and clinical trials unit as necessary, details of defined reasons why this may have been necessary are reported in chapter 4.

Following discussion with local clinical microbiology colleagues during the study development phase, we elected not to routinely culture ascitic fluid samples from the LTAD. There was felt to be a significant likelihood of growing skin contaminants, and the results would be difficult to interpret, as well as recognition that colonisation of indwelling catheters can occur, but may not be of clinical significance, and especially not in a palliative cohort.[180] We took a pragmatic view to treat peritonitis if participants displayed any related clinical features or were symptomatic, following EASL guidance for diagnosis of SBP.[25] This included features such as fever, abdominal pain, further hepatic decompensation, worsening renal function, and with subsequent investigations revealing increased inflammatory markers, and greater

than 250/mm^3 polymorphonuclear cells in the ascitic tap, and/or a positive ascitic fluid culture. During consultation with service users in the study design phase, they also felt it was not ethically appropriate to treat asymptomatic patient participants. This was due to the study being undertaken in a cohort who are palliative, and likely to be receiving end of life care, with the major goals described by service users as being improved symptom control, and avoiding hospitalisation.

5.4.15 Statistical analysis

The feasibility study was not powered for definitive statistics on safety and efficacy of LTAD use for managing RA in ESLD. This was a feasibility study and following the rule of thumb for pilot studies,[164] it was felt that 12 participants in each of the groups was an adequate sample size. However, following the MORECare guidance on evaluating complex interventions in palliative care,[92] a level of attrition was assumed at 50%, and therefore the sample size was increased to a target of 24 participants in each study group.[181]

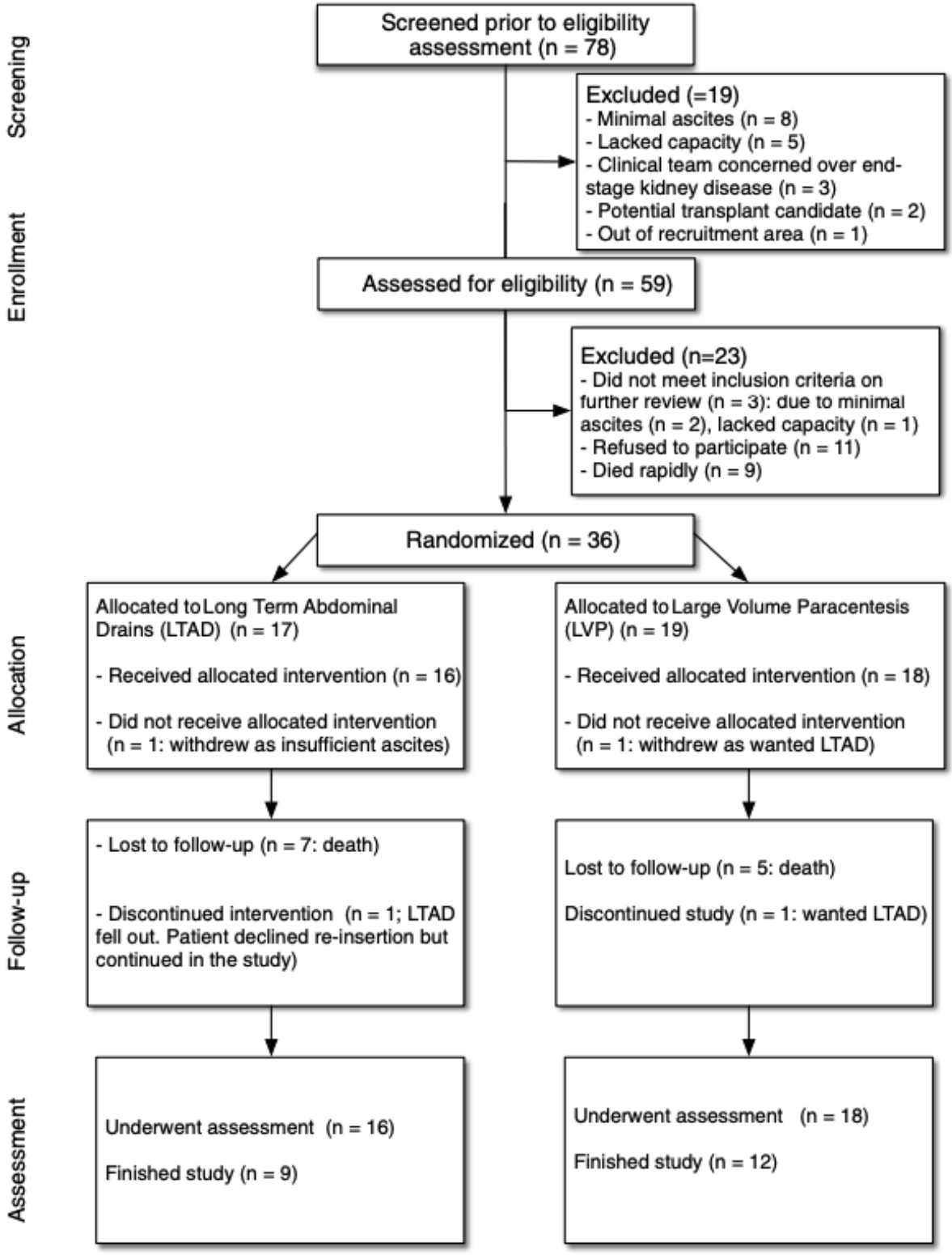
Given the small sample size, descriptive statistics were used to summarise and compare the quantitative outcome measures. Data were summarised, categorised into LTAD and LVP groups, and presented as frequencies and percentages, mean ± SD, or median IQR with 95% confidence intervals (CI) reported for the estimated difference in means between groups at the end of follow up. The analysis was performed, following the intention to treat principle, on those cases which were available.

5.5 Results

5.5.1 Study recruitment

The REDUCe study began in September 2015, with recruitment opening at the first site in November 2015. The study ran until September 2018, with the final patient participant recruited in June 2018, to allow for the 12 weeks of study follow up time. Across the study recruitment period, 78 potential participants were initially approached to discuss the RCT, however, 19 of those did not fulfil eligibility criteria to proceed further (CONSORT flow diagram figure 5.1). Two patients were initially regarded as not being eligible for liver transplantation when discussed by their usual clinicians at local multidisciplinary meetings, however, after further review, this decision was overturned, and they were deemed suitable to undergo a transplant assessment (Figure 5.1).

Figure 5.1 CONSORT flow diagram



There were 59 potential participants who were eligible, and of those, we randomised 36 (36/59 61%), this number equates to 75% of our original target recruitment sample size of 48, aiming for 24 patient participants in each study group. The 36 participants who were randomised represented almost a third (32%) of patients who had undergone two or more LVPs across all of the five recruiting centres. In terms of study group, 17 participants were randomised to group one, LTAD and 19 randomised to group two, LVP, continuation of standard care of RA management. There were 11 patients who declined to participate in the study, and, since recruitment to a research trial is optional for patients, and according to GCP principles,[142] patients were not asked for reasons for declining, but these were recorded if offered spontaneously by patients (Figure 5.1). No reasons for declining were given by five patients, three did not want to be involved in research, and one patient declined to participate as only wanted the LTAD. The patient who declined as only wanted to have the LTAD was not happy to be randomised, in case they were allocated to the LVP group, interestingly, this was despite already undergoing regular LVPs. One patient reported that they felt too unwell to be part of a research study, and the final patient to decline was unable to accept that they had a diagnosis consistent with a limited life expectancy.

In terms of care givers, 21 patients had available caregivers, however not all agreed to be recruited to take part in the carer burden questionnaire, ZBI-12. In terms of study group, nine out of ten (90%) in the LTAD group and eight out of eleven (73%) available caregivers in the LVP group were successfully recruited. Care giver burden results are further reported in chapter 6.

5.5.2 Clinical outcomes

Long term abdominal drain insertion

At the two main study sites, LTAD insertion was performed by the hepatology clinical research fellow, and at the other three sites, the insertion procedure was undertaken by interventional radiologists. The technical success rate for LTAD insertion was 100%, although one participant inadvertently pulled out the LTAD 24 hours following insertion. This study participant declined to have a further LTAD inserted, but was however willing to continue in the study and undergo study follow up visits, including questionnaire based assessments.

5.5.3 Demographics

Ages for patient participants were similar in both groups, median 66.3 (IQR 10.4) in the LTAD group and 67.9 (IQR 12) in the LVP group. Overall, the majority of participants were male 76% and 74%, and nearly all identified as white British 94% and 100%, in the LTAD and LVP groups respectively. Table 5.1 shows the baseline demographic and clinical data.

Table 5.1 Baseline demographic and clinical data in LTAD and LVP groups

Characteristic	Long Term Abdominal Drain group, LTAD n=17			Large Volume Paracentesis group, LVP n=19		
	n	Mean/ median (%)	SD/IQR	n	Mean/ median (%)	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%)	

Characteristic	Long Term Abdominal Drain group, LTAD n=17			Large Volume Paracentesis group, LVP n=19		
Ongoing alcohol/drug use	**n**	**Mean/ median (%)**	**SD/IQR**	**n**	**Mean/ median (%)**	**SD/IQR**
Aetiology of cirrhosis						
Aetiology: alcohol		12/17 (71%)			9/19 (47%)	
Aetiology: viral		1/17 (6%)			1/19 (5%)	
Aetiology: NAFLD		7/17 (41%)			7/19 (37%)	
Aetiology: other		3/17 (18%)			6/18 (33%)	
Laboratory results						
Bilirubin (μmol/L)	17	22	15-37	18	23	17-48
Bilirubin >33 μmol/L		6/17 (35%)			7/18 (39%)	
Albumin (g/L)	17	33	32-36	18	31	27-33
Albumin <35 g/L		12/17 (71%)			16/18 (89%)	
Serum creatinine (μmol/L)	17	109	79-141	18	113.5	89-135
Serum creatinine > upper limit of normal		9/17 (53%)			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
Liver disease severity scores						
Child Pugh Score	17			18		
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
Complications of cirrhosis						
Prior variceal bleed		2/16 (13%)			4/18 (22%)	
Prior SBP		1/15 (7%)			2/15 (13%)	
Prior HE		7/16 (44%)			2/18 (11%)	
HCC		3/16 (19%)			3/18 (17%)	
Follow up (days)		82 (52-90)			85 (64-92)	

Table footnotes

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

In terms of aetiology for the development of ESLD, alcohol was recorded in 71% in the LTAD group, but was lower in the LVP group, 47%. Non alcoholic fatty liver disease (NAFLD) was also a major aetiology recorded for ESLD development, 41% and 37% in the LTAD and LVP groups respectively, with mean body mass index (BMI) 28.4 (22.2-32.5) in the LTAD group and 24.6 (22.1-28.9) in the LVP group. It should be noted that some of the participants had more than one aetiology recorded for the development of ESLD. Ongoing alcohol and or illicit drug use was higher in the LTAD group (29%) compared to the LVP group (11%).

The majority of patient participants' severity of liver disease was scored as Child Pugh B, 82% in the LTAD group, and 72% in the LVP group, and the prevalence of hepatic encephalopathy (HE) was higher in the LTAD group, 44% compared to 11% in the LVP group.

Almost all of the 36 patients recruited (35/36 97%) had one or more absolute or relative contraindication to TIPS, according to current guidelines.[25,69] The one patient who did not have any contraindications declined to undergo a TIPS procedure for RA management. Contraindications to TIPS included serious comorbidity (n = 25, 69%), age >70 years (n = 13, 36%), prior HE (n = 9, 26%), Child Pugh C disease severity

(n = 7, 20%), hepatocellular cancer (HCC) (n = 6, 18%) and serum creatinine >1.5 times the upper limit of normal (n = 6, 17%).

5.5.4 Ascites drainage data

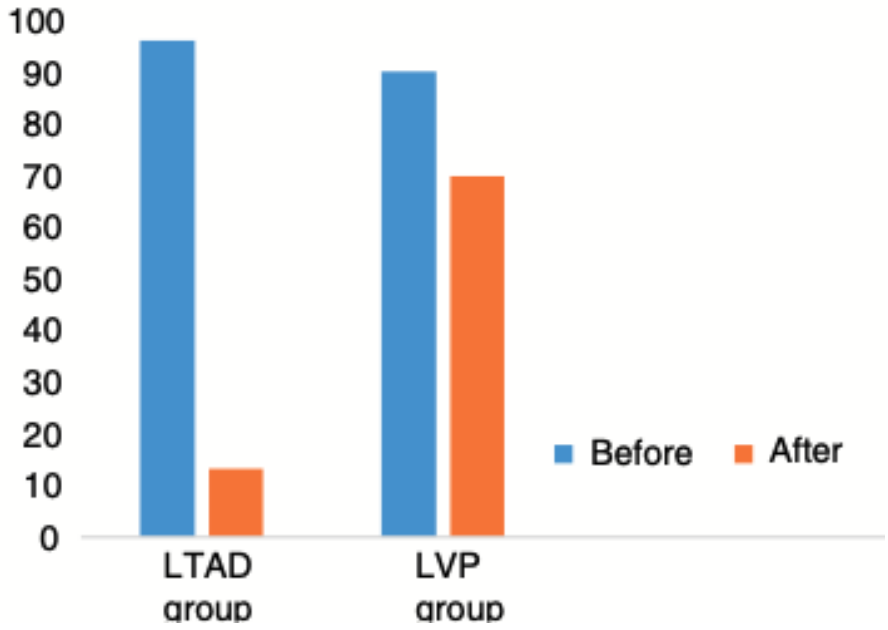
Prior to undergoing randomisation, one participant had undergone two LVP procedures, with the remainder of participants having undergone three or more LVP procedures.

Further ascites drainage data following study enrolment and randomisation was available for 30 of the 36 (83%) patient participants, this represented 15 participants in each group. The missing data was as a result of one study site not returning any ascites drainage data, nor any service use data, for the six participants who were recruited at that site. This was despite multiple requests for data to be returned.

Comparing the LTAD group with the LVP group, the median (IQR) volume of ascitic fluid which was drained per week in Litres (L) was 3.85L (2.85-4.51) versus 4.42L (3.00-6.09). The median (IQR) number of ascitic drainage episode visits undertaken per week was 1.9 (0.6-2.5) vs 0.33 (0.17-0.5) in the LTAD and LVP group respectively, with median (IQR) follow up, in days, 82 (53-90) in the LTAD group compared to 86 (75-92) in the LVP group.

The total number of ascitic drainage procedures undertaken in both the LTAD and LVP groups before and after undergoing randomisation is shown in figure 5.2. The median (IQR) number of ascitic drains before randomisation in the LTAD group compared to the LVP group were five (3-8) compared to five (4-7), and after randomisation in the LTAD group was 0 (0-1) compared to four (3-7) in the LVP group (Figure 5.2).

Figure 5.2 Total number of ascitic drains before and after randomisation in LTAD and LVP groups



LTAD group

After randomisation and insertion of the LTAD, 10/15 (67%) participants in the LTAD group, successfully had their subsequent ascites drainage episodes undertaken by community nurses, or caregivers, outside of the hospital setting. A further 13 ascitic drains were undertaken in the hospital setting in those five participants where this was not the case. The five participants in the LTAD group where drainage episodes occurred in hospital did include the one participant who had inadvertently pulled out the LTAD 24 hours after its insertion. The 13 hospital based drains comprised of five inpatient hospital admissions which were not ascites related, but however during which a drain was performed. The further eight drainage procedures were undertaken on medical day case units for the purpose of performing the procedure. In one of these eight drainage episodes, the participant ended up being admitted to hospital over night, solely to allow drainage to be performed.

LVP group

In the 15 participants in the standard of care, LVP, group where data were available, a total of 69 LVPs were undertaken following randomisation. The majority of further LVPs 64/69 (93%), following randomisation, occurring in the LVP group were performed on medical day case units, where participants present specifically for ascitic drainage. One LVP was performed during an overnight inpatient hospital admission, which occurred in order to allow an ascitic drain to be performed. Four LVPs were undertaken during the course of non ascites related inpatient hospital admissions.

5.5.5 Biochemical data

The majority of participants had data available at each study visit, ≥92%, this was except for at the week 10 study visit in the LVP group, where data were only available in 85%.

At the baseline and week 12 visits, the serum albumin level results, reported in g/L (median and IQR), in the LTAD vs LVP groups were 33g/L (33-36) vs 31g/L (29-34) at baseline and 29g/L (26.5-32.5) vs 30g/L (25-35) at week 12. At the week two study visit, the serum albumin level reduced to 29.5g/L (27.5-31.5) in the LTAD group, but this level then remained stable at the end of study follow up.

The serum creatinine level is reported in μmol/L (median, IQR), and at baseline was 109μmol/L (79-141) in the LTAD group and 113.5μmol/L (89-134) in the LVP group. At the week 12 study visit, levels in the LTAD group were similar to those at baseline, and compared to the LVP group were 104.5μmol/L (81- 115.5) and 127μmol/L (63-158) respectively.

Baseline median and IQR results for serum bilirubin (µmol/L), albumin (g/L), serum creatinine (µmol/L), and INR in both groups are shown in table 5.1 and are shown at each visit respectively in figures 5.3, 5.4, 5.5, 5.6. For figures 5.3 - 5.9 the numbers of patients with available data at each of the seven visits were as follows in each of the groups: LTAD 17, 17, 12, 13, 12, 12, 9; LVP 18, 18, 14, 15, 13, 11, 12.

Liver disease severity scores, Child Pugh, MELD and UKELD are shown at baseline in table 5.1 and at each study visit in each group in figures 5.7, 5.8, 5.9 respectively. In both groups the Child Pugh score remained consistent across all study visits. The MELD and UKELD scores in the LTAD group remained consistent across all study visits, however, in the LVP group at the week 12 visit, the MELD increased and conversely the UKELD reduced in the same group.

Figure 5.3 Median (IQR) serum bilirubin (µmol/L) in LTAD and LVP groups at each visit

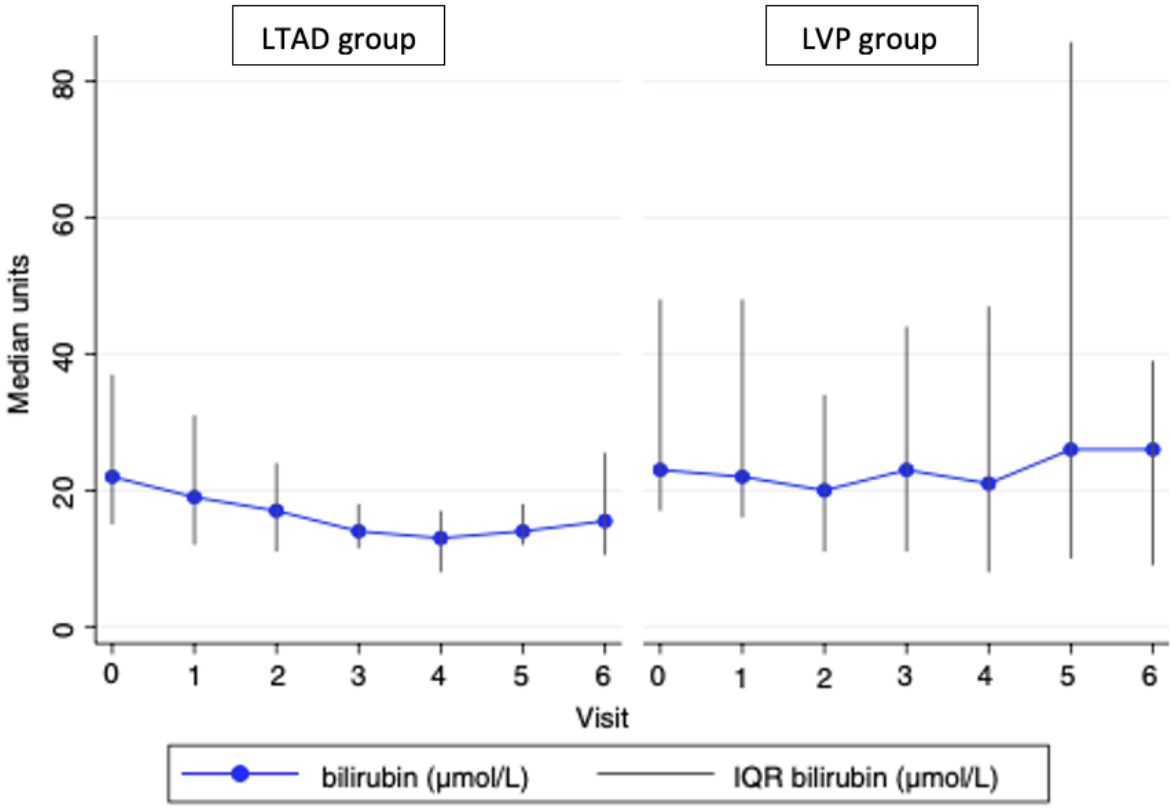


Figure 5.4 Median (IQR) serum albumin (g/L) in LTAD and LVP groups at each visit

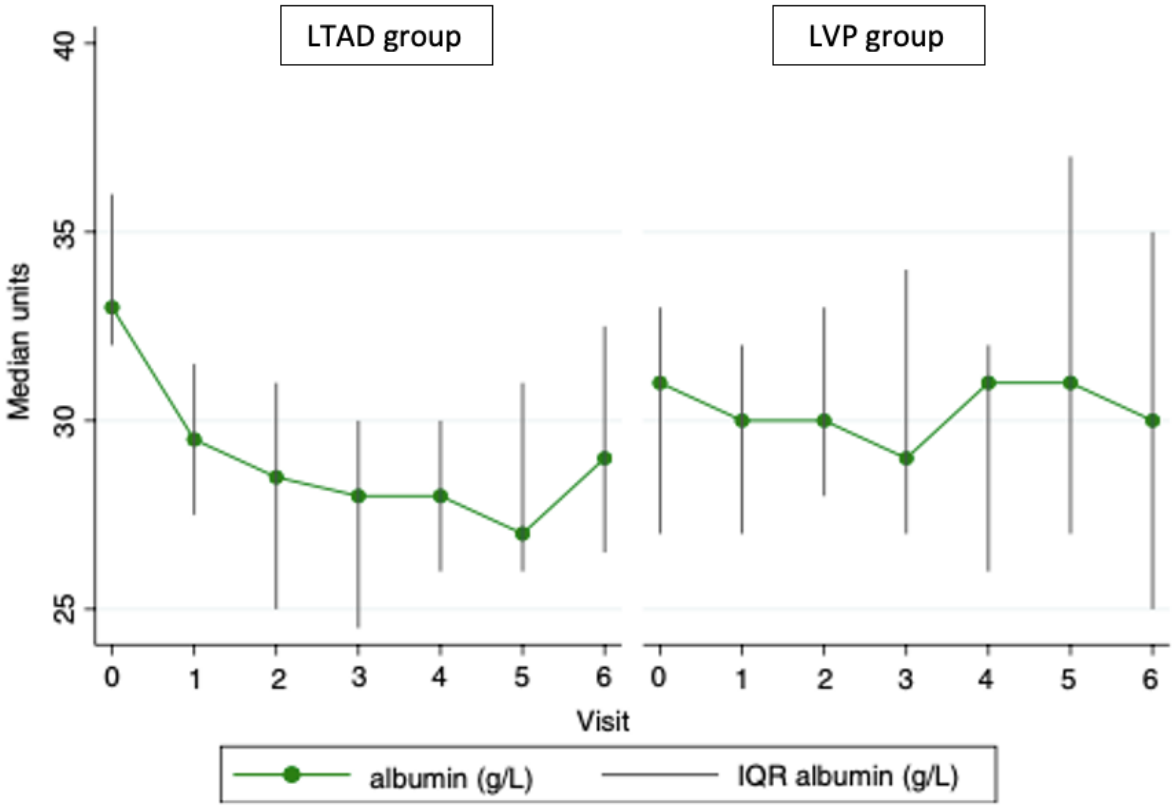


Figure 5.5 Median (IQR) serum creatinine (µmol/L) in LTAD and LVP groups at each visit

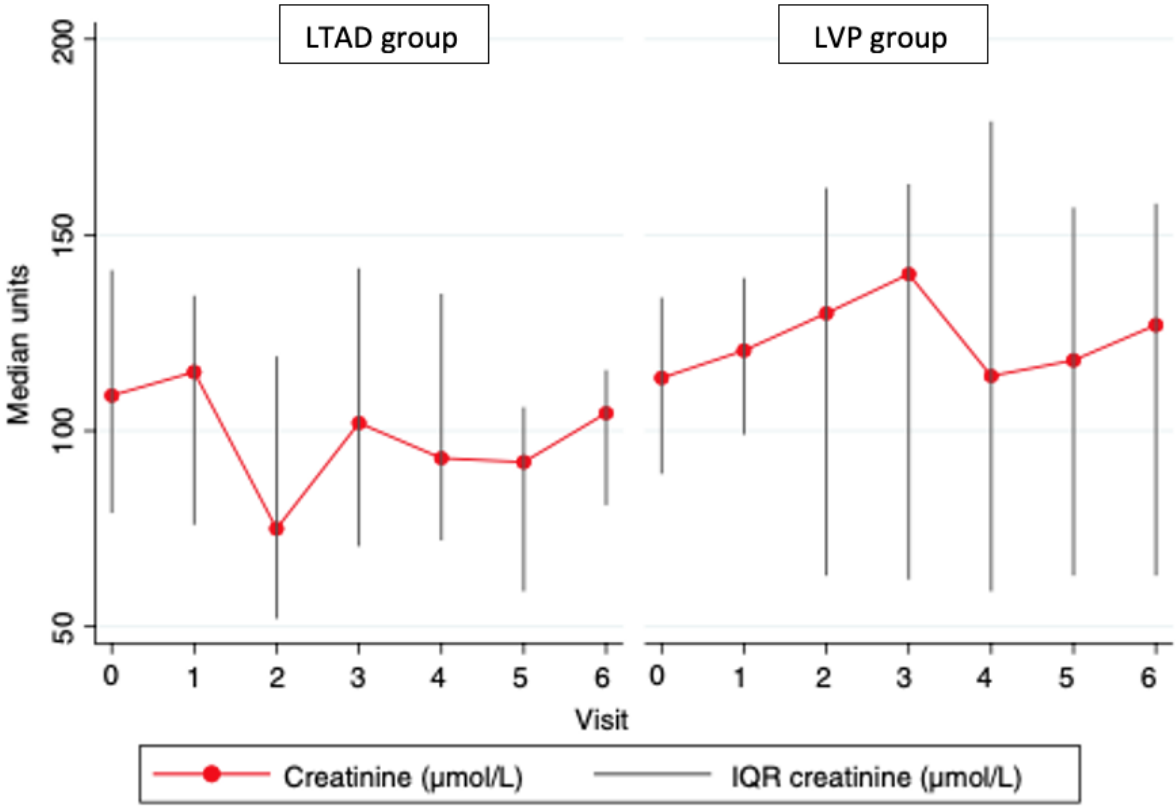


Figure 5.6 Median (IQR) INR in LTAD and LVP groups at each visit

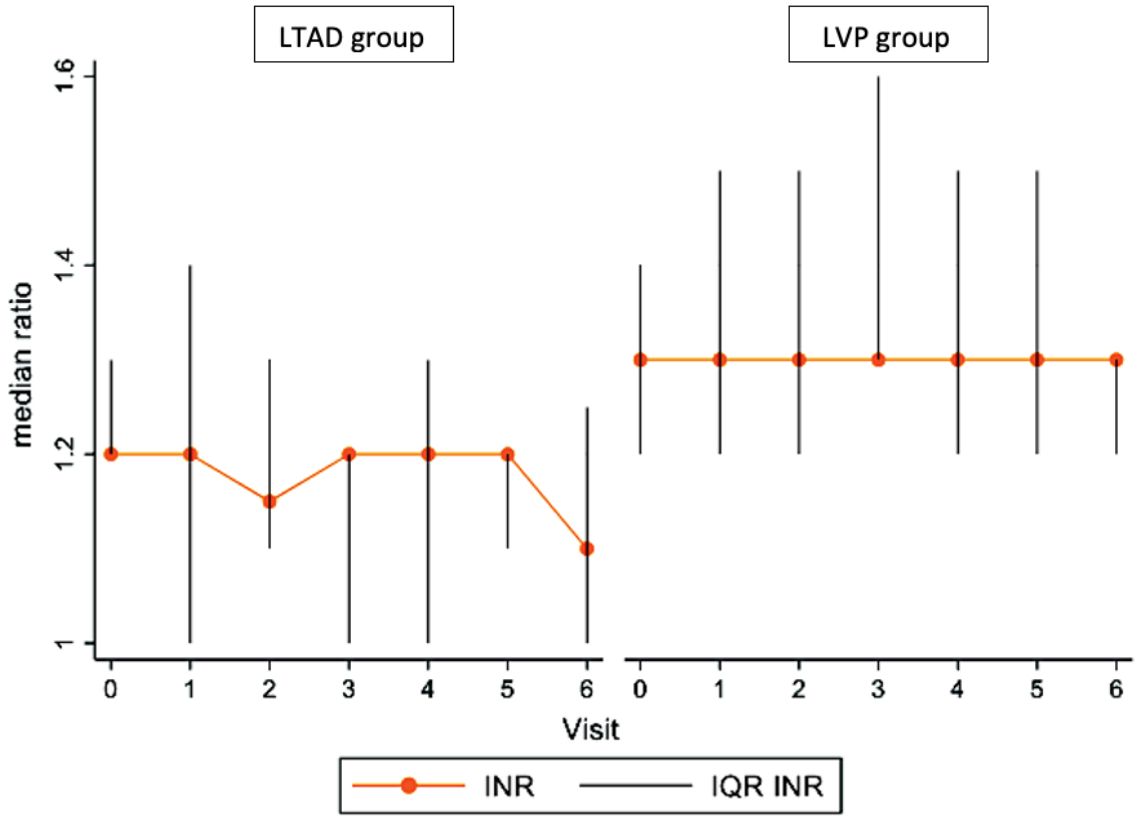


Figure 5.7 Mean (+/- SD) Child Pugh Score in LTAD and LVP groups at each visit

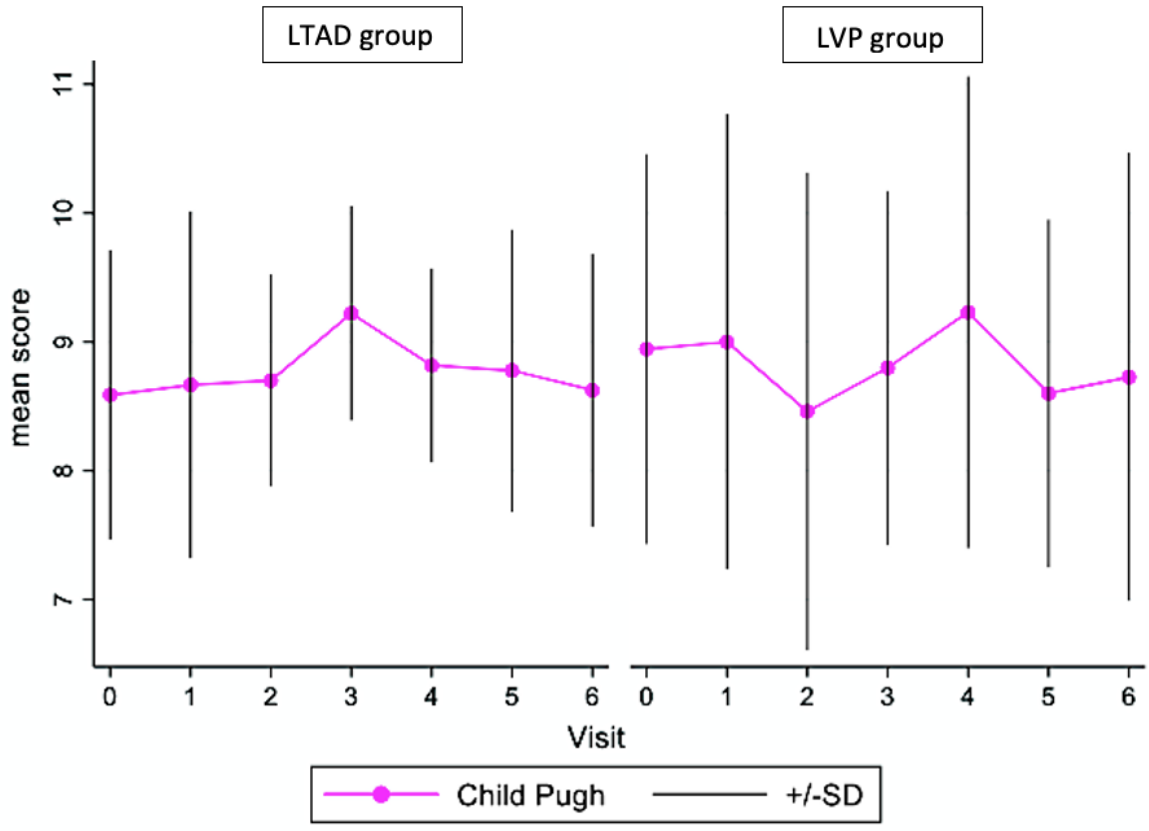


Figure 5.8 Mean (+/- SD) Model for End Stage Liver Disease (MELD) score in LTAD and LVP groups at each visit

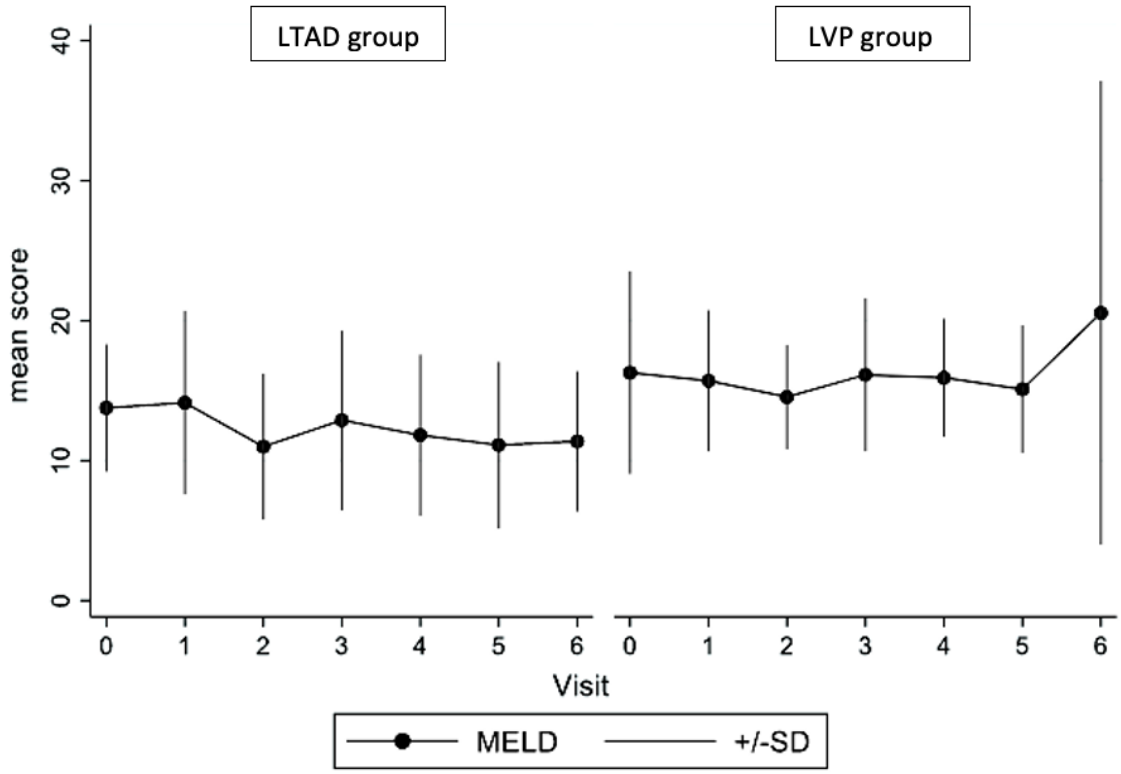
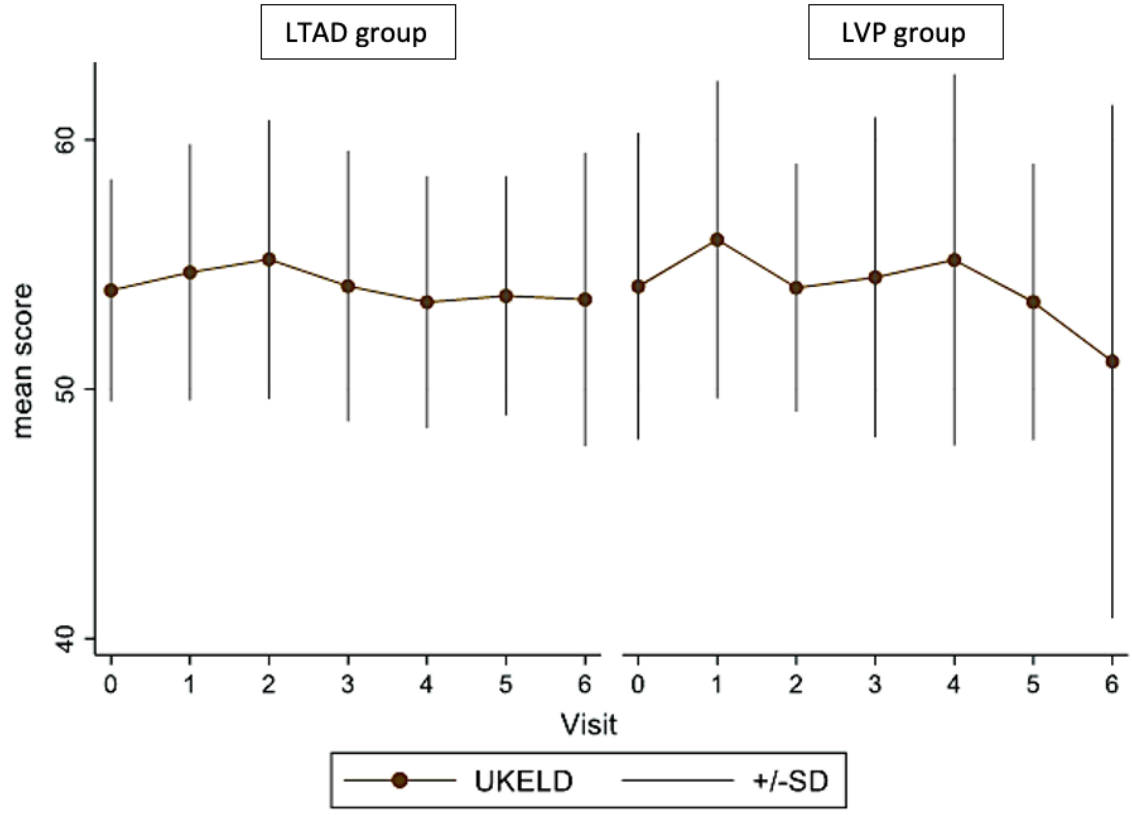


Figure 5.9 Mean (+/- SD) United Kingdom End Stage Liver Disease score (UKELD) in LTAD and LVP groups at each visit



5.5.6 Attrition

Overall attrition across the study was 15/36 (42%), with 95% confidence intervals (CI) being 26-59. The attrition data comprises withdrawal from the study in 3/15 (20%), 95% CI (4-48) and death 12/15 (80%), 95% CI (52-96). Seven participants in the LTAD group died compared with five who died in the LVP group. Five of the 12 (42%) overall deaths occurred within the first four weeks of the study follow up period, these comprised of three in the LTAD group, and two in the LVP group.

Most of the deaths which occurred during study follow up were liver related, 11 of the 12 (92%), and one was as a result of a stroke, where the participant was admitted to an acute hospital for specialist stroke management, and later died in a hospice. The majority of deaths occurred outside of a hospital setting, 8/12 (67%), 95% CI 35-90, this finding was distributed equally between both groups, with four participants dying outside of hospital in each.

The median survival in days in those who died during study follow up was 53 (27-70) in the LTAD group, compared with 61 days (26-61) in the LVP group. Over half of the participants in each group survived to successfully complete all of the study follow up visits, this was 9/17 (53%) in the LTAD group and 12/19 (63%) in the LVP group. At the end of the study follow up period, all those in the LTAD group who were still alive decided to keep the LTADs in situ to be used for further drainage episodes.

5.5.7 Adverse events and serious adverse events

Specific drainage related events are focussed on in the narrative here, and table 5.2 documents all the adverse events (AE) and serious adverse events (SAE) in both groups.

Table 5.2 Adverse events (AEs) and serious adverse events (SAEs) in LTAD and 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)	Falls (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 cultures (*Strep lutetiensis)* (1)	
Worsening renal function (4)		Worsening renal function (6)	
Cellulitis/leakage at drain site (7)		Bleeding/leakage after LVP (2)	
HE (3)		Hyponatraemia/ hypokalaemia (2)	
Worsening oedema/ breathlessness (2)		Hypotension (1)	
Drain accidently pulled out (1)		Increasing bilirubin (1)	
		Fever (1)	

Long term abdominal drain group (LTAD)		Large volume paracentesis group (LVP)	
Adverse event	**Serious adverse event**	**Adverse event**	**Serious adverse event**
		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.			

In the LTAD group, there were seven instances where participants experienced leakage or localised cellulitis following LTAD insertion, three with leakage, two with cellulitis and two with both leakage and cellulitis. In the LVP group there were two episodes of leakage, and/or bleeding following an LVP procedure. All events were recorded as being minor and self limiting, cellulitis was treated successfully with oral antibiotics, and no participant required hospitalisation as a result of any drainage related complication.

Renal function was documented as worsening in six participants in the LTAD group and in seven participants in the LVP group. The incidence of peritonitis in the LTAD group was 1/17 (6%) and in the LVP group was 2/19 (11%), with a mean difference of -5%, 95% CI (−24, 14).

Overall, there were no LTAD related SAEs and no LTAD related complications following insertion requiring the drain to be removed. The AEs experienced were successfully managed in the community and resolved, allowing ongoing community drainage episodes.

5.6 Discussion

5.6.1 Key findings

We demonstrated successful recruitment to a complex, mixed methods interventional study in a cohort of patients with palliative ESLD. The study clinical success criteria were met. In terms of attrition, our aims were for less than 50%, and across the study our attrition for all reasons was 42%. None of the reported AEs or SAEs were linked to LTAD safety concerns, and none of the complications resulted in instances which mandated LTAD removal. Finally, hospital service use data showed that those participants in the LTAD group spent ≤50% ascites related study time in hospital compared to those in the LVP group.

The participant reported outcomes, including questionnaire based symptom and quality of life assessments, health economics, and a summary of results from the concurrent embedded qualitative study are reported in chapter 6.

5.6.2 Recruitment and demographics

Of the 59 patients who were eligible for recruitment into the study, we randomised 36 (36/59 61%). Although this was 75% of our target, therefore did not meet the original study recruitment aim, it did meet the sample size target for a feasibility study of 12 participants in each arm.[164] Three of the 11 patients who declined to take part reported not wanting to be part of research, and one patient was so in favour of having an LTAD that they did not accept that study inclusion would potentially mean being randomised to continue their current standard of care. We found that informal carers were willing to take part in the research process, with 17 of the 21 (81%) carers who were available giving consent to take part in the caregiver burden questionnaires.

Our experience of recruiting participants, particularly early on in the study, was that those who were potentially eligible for study inclusion were often referred late in their disease trajectory, with 15% dying prior to study inclusion. Initially, the study duration was due to run for 24 months, however, due to initial challenging recruitment rates, the study was granted a one year extension by the NIHR, to allow the study team to implement lessons learned in recruiting to this palliative intervention study. Prompted by initial experiences, we explored attitudes and beliefs towards advance care planning in ESLD amongst regional consultant physicians.[103] We found that although consultant physicians reported feeling confident in recognising ESLD, they felt less clear on aspects of prognosis and appropriate timing of the initiation of advance care planning and palliative care.[103] These findings were mirrored in results in a study from a tertiary liver referrals unit in London, where clinicians rarely discussed prognosis or future care preferences, lacking the skills and confidence to initiate these important conversations.[43]

Baseline demographics were similar in both groups, however, mean BMI in the LTAD group was 28.4 (22.2-32.5) compared with 24.6 (22.1-28.9) in the LVP group. The commonest aetiologies for the development of ESLD were alcohol and NAFLD. The LTAD group had a higher proportion of participants with alcohol recorded as the aetiological agent, 71% compared to the LVP group, 47%. Aetiology of ESLD was not a factor used in randomisation which is why the groups were unbalanced. Cirrhosis is the end point of any chronic liver disease and the sequalae of decompensation are the same, however, removal of potentially reversible agents can result in recompensation, therefore ongoing exposure will mask this possibility.[20,25,56] The LTAD group also had a higher recorded amount of participants with ongoing alcohol or illicit drug use, 29%, which may be a reflection of the higher proportion of

those with alcohol as the aetiological factor at baseline. A high number of participants in both groups remained on diuretics despite having RA, 71% prescribed Spironolactone in the LTAD group and 58% in the LVP group. It could be argued that diuretics could be reviewed for discontinuation after the development of RA. Although they may still provide some benefit in mitigating ascites, they should be reduced, or discontinued if they precipitate significant renal impairment or severe hyponatraemia, serum sodium <125mmol/L.[28]

The majority of participants were scored as having Child Pugh B disease, 82% and 72% in the LTAD and LVP groups respectively. A smaller number had Child Pugh C disease, 18% in the LTAD group and 22% in the LVP group. It was interesting therefore that a much higher number of participants in the LTAD had had a previous episode of HE recorded at baseline, 44% compared to 11% in the LVP group. The reasons for this are unclear, and again may be linked with a higher amount of ongoing exposure to alcohol and illicit drug use, which can precipitate episodes of acute on chronic liver failure (ACLF).[25,99]

5.6.3 Laboratory results

Laboratory results at baseline were similar except for serum creatinine and platelet count. Baseline serum creatinine was 109μmol/L (79-141) and 113.5μmol/L (89-135) in the LTAD and LVP groups respectively. Serum creatinine is a component of the MELD and UKELD calculations, however, despite creatinine differences, the two composite scores at baseline were similar. Week 12 creatinine values were similar to baseline scores in both groups, suggesting that despite the LTAD group not receiving human albumin solution (HAS) infusions with their community drainage episodes, this did not result in any compromise in renal function. In the LVP group at the week 12 study visit, the MELD score increased, and conversely the UKELD

score reduced. Given both scores reflect the severity of liver disease, and were measured in the same participants at the same study visits, the conflicting results are likely to be spurious.

The median serum albumin level in the LVP group was unchanged between baseline and week 12 visits. In the LTAD group however, we observed that the level initially reduced at the week two study visit, but then remained stable when measured at further study visits. This finding reflects that no HAS was given in the LTAD group during community nurse drainage episodes, and that the serum albumin results in the LVP group represented a supported albumin level.

Mean baseline platelet count was higher in the LTAD group $167x10^9$/L (103-193) compared to the LVP group of $124x10^9$/L (106-151). Platelet count of less than $150x10^9$/L is one of the markers for clinically significant portal hypertension and therefore it is surprising to find mean platelet counts higher than 150 in a cohort of patients with ESLD and RA.[93]

5.6.4 Ascites drainage data

The median volume of ascitic fluid drained per week in Litres was slightly more in the LVP group by just over 500mls, this may represent that symptoms could be controlled with smaller but more frequent drainage episodes in the community with LTAD. During LVP episodes, the volume drained is not as controllable as with an LTAD, as LVPs are under free drainage to a certain maximal volume, or time period. Finally, in the LTAD group, since the safety of their use in ESLD has not been confirmed, the study team placed a maximum drainage limit on participants in that group of no more than three episodes per week, with a maximum of two Litres drained at each episode. The median weekly drainage in the LTAD group was still well below this at 3.85L.

Prior to study enrolment, the median number of ascitic drains patients had undergone was similar in the two groups, both with a median of five drains. As expected, in the LTAD group, after randomisation and LTAD insertion, the median number of ascitic drainage visits was higher than in the LVP group, with 1.9 episodes per week compared with 0.33 per week respectively. The median number of LVPs after randomisation was zero in the LTAD group and four in the LVP group, which was expected, as the aims of using LTADs in RA are to transfer ascites management out of the hospital setting.

The majority of patients ascites related care, and drainage episodes following LTAD insertion were successfully undertaken outside of hospital. This however was not the case in five participants in the LTAD group (33%), including the one participant who had accidentally pulled out the LTAD and declined for a further to be inserted. The other four participants had drains undertaken either while an inpatient for a non ascites related reason, five drainage episodes, or because ascites symptoms in the community could not be managed adequately with the maximum drainage episodes mandated by the research study team for safety reasons. Excluding ascites drainage performed during a non ascites related hospital admission, and the participant where the LTAD was pulled out, only two LTAD participants required further hospital ascites drainage. In these two participants, their ascites related symptoms could not be adequately managed in the community with maximal drainage at each visit. It was decided by the clinical research team, that it would be a safer alternative for those participants to attend the medical day case unit, and the LTAD to be used with the accompanying adapter, to allow free drainage following the protocols and standard guidance for LVP, including HAS infusion.[25] This did mean however that no further invasive procedures were needed to be undertaken in those participants. This also

meant that in these participants, hospital day case drainage procedures were not limited by waiting for a clinician to perform the drainage procedure, as the LTAD can be used with the appropriate adaptor when necessary. In our systematic review on refractory ascites in ESLD, reported in chapter 3, no further hospital admissions were required for further drainage episodes in the 14 studies to report on this, following the insertion of permanent indwelling peritoneal catheters.

5.6.5 Attrition

As was expected to be seen in a study cohort with advanced disease, there were 12 deaths across both study groups, all except one being liver disease related. Five of the deaths, 42%, occurred within the first four weeks of the study follow up, which highlights the advanced stage of disease of the participants, but also the challenges in recruiting participants with a limited life expectancy, in an expedient time frame. The median survival in both groups in those who died in the study was around two months, and over half of the participants survived to complete all 12 weeks of study follow up visits. This is in keeping with median survival, once RA develops, of six months.[25]

The breakdown of deaths were of seven occurring in the LTAD group and five in the LVP group. Although there were more deaths overall in the LTAD group, the study numbers are too small to draw any inferences from this, and the sample size was not powered to do so.

An interesting finding is that the majority of deaths within the study occurred outside of a hospital setting, 67%, which differs from place of death seen with liver disease reported in an English population based study, where nationally this figure was 70%.[89]

This could represent the oversight of study participants, with focus on palliative and end of life care, from an experienced clinical research team where the benefits of earlier palliative care input are well recognised, including supporting participants' preferred place of death.

5.6.6 Adverse events and serious adverse events

There were no LTAD safety concerns, and we did not observe a higher incidence of peritonitis in the LTAD group, bearing in mind the sample size was not powered to give definitive evidence of this. The results we obtained are however consistent with rates of peritonitis we reported in the systemic review undertaken on current available evidence of permanent indwelling peritoneal catheters in RA, chapter 3, where peritonitis rates (12.7%) were not higher than those of background SBP rates which would be expected to be seen in ESLD.[25]

Infection is the most feared complication of using LTAD in this group, given the impaired immune function seen in cirrhosis, and SBP occurring in the absence of any interventions in patients with ascites and cirrhosis.[25,28,61,80] The current guidance from the National Institute for Health and Care Excellence (NICE) is that further evidence on the safety and efficacy of LTAD in ESLD are required.[80]

There were no LTAD SAEs, and the most common LTAD complication was leakage and or localised cellulitis in seven participants. All were successfully treated in the community, fully resolved, and did not require a hospital admission for management or mandated LTAD removal. Episodes of leakage were not unique to the LTAD group and were also seen in smaller numbers in the LVP group. This highlights that any interventional procedure is not without risk and must always be balanced in the context of risks and benefits to patients.

The leakage rates in the LTAD group were also felt to be part of the learning curve of the insertion procedure, which was undertaken at the two main study sites by the hepatology clinical research fellow. It is also worth noting that the mean BMI was higher in LTAD group, which may have impacted on the technical aspects of drain insertion, and post insertion leakage.

5.6.7 Challenges experienced and lessons learned

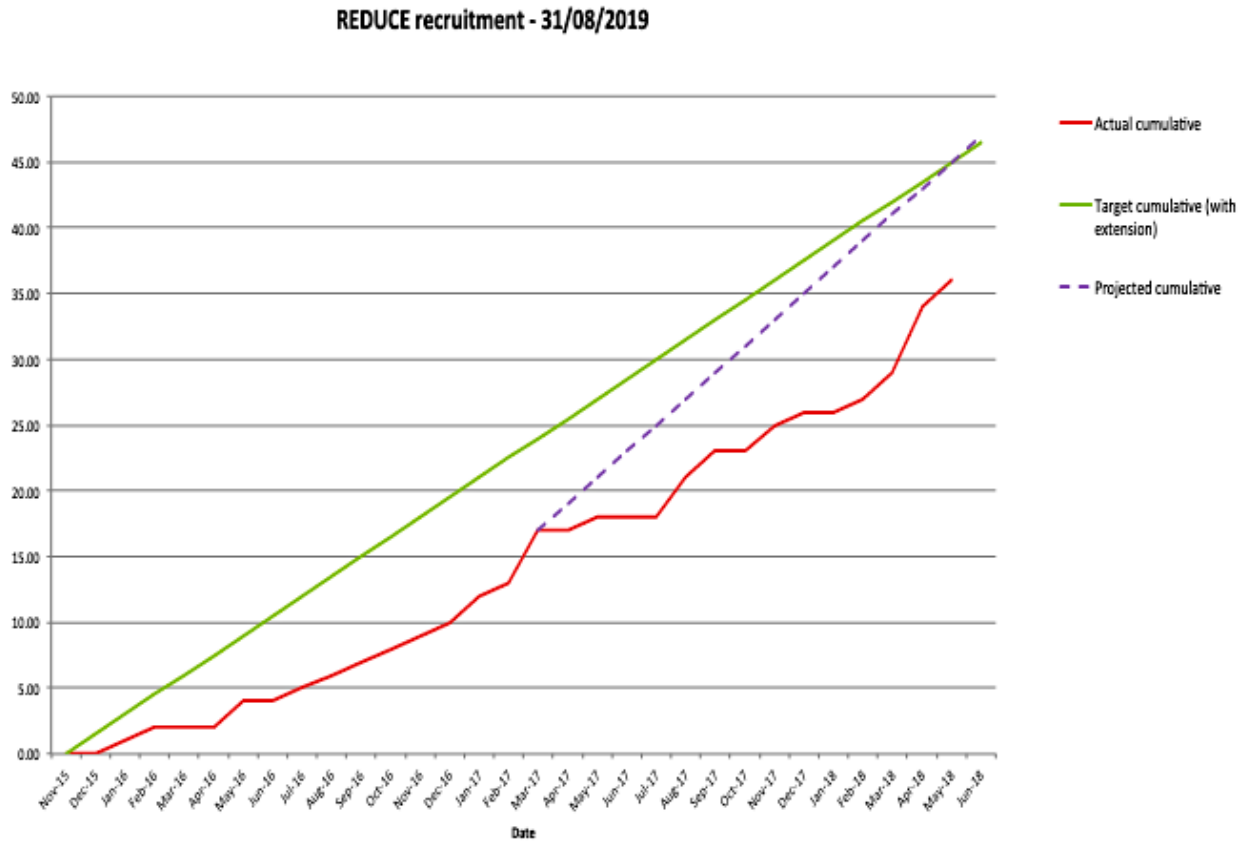
Challenges in undertaking clinical trials in a palliative setting have been recognised as contributing to a low overall reporting quality.[182] These include lack of clarity in identifying when the palliative phase of an illness has been reached, challenges in study recruitment, high levels of attrition, and uncertainty over appropriate assessment tools and outcome measures.[182] The REDUCe study design followed the MORECare guidance, which recommends a mixed methods approach, and recruiting patients who are likely to benefit most from the intervention.[92]

Our initial study recruitment was impacted by potentially eligible patients being referred to the research team late in their disease trajectory, with 15% dying before being able to proceed to inclusion. This prompted us to explore attitudes and beliefs surrounding palliative care and advance care planning in ESLD.[103] Lessons learned to improve recruitment included dedicated multidisciplinary meetings to aid earlier identification of ESLD, consideration of eligibility for liver transplant assessment, and if appropriate, for involvement of palliative care teams. We also found that patients and carers were often less prepared for conversations surrounding palliative care, sometimes as a result of inadequate prior discussions with their usual gastroenterologists or hepatologists, on the prognostic implications of ESLD and RA. This was reflected in potential participants declining to be included in the study, being unwilling to accept the diagnosis of a limited life expectancy, and findings in

qualitative interviews, reported in chapter 6, of some patient participants interpreting the LTADs as ongoing active treatment of their liver disease, rather than for the palliative management of ascites.

We found that engagement between community nurses supporting the intervention delivery and research staff at recruiting sites was key in successful community drainage and study data collection. The study extension allowed further sites to be opened to widen recruitment, and implementation of strategies described was reflected in an increase in recruitment rates between study years two and three, shown below in figure 5.10.

Figure 5.10 REDUCe study recruitment



5.6.8 Study limitations

Although our recruitment met the recommendations for pilot studies, being 12 participants in each arm, we did not meet our own study recruitment target.[164] This is despite being granted an extension to the study, opening new study sites to support recruitment, and implementing strategies in the lessons learned. The specific challenges experienced in recruitment to the study reflect those seen more widely in clinical trials in palliative care.[182,183]

More than half of the patient participants recruited, 56%, were from one study site, impacting on the generalisability of experiences.

The cases of self limiting leakage or localised cellulitis were higher in those in the LTAD group, however this may reflect insertion technique, and we would hope that with increasing experience in LTAD insertion methods this would reduce.

All participants in both groups were given primary SBP antibiotic prophylaxis, in the LVP group 13% of participants had prior SBP, and so were already receiving SBP prophylaxis, however, primary SBP prophylaxis in all cases is not standard care at present and incidence in the LVP group could have potentially been falsely low as a result. Our observed incidence of SBP in the LVP group, 2/19 (11%), was however in keeping with expected background rates of SBP in an ESLD population.[25]

5.7 Conclusion

The REDUCe study provides preliminary evidence of LTAD safety and effectiveness in refractory ascites due to ESLD, however further evaluation in a full size trial is needed to be able to give more definitive results.

We did not find higher rates of peritonitis in those with LTAD, although this cannot be extrapolated to more generalisable results, given this feasibility study was not powered to be able to answer this question. There were no safety concerns with

regards to LTADs, and despite not being given HAS supplementation, we did not see this have an impact on renal function. Serum albumin initially reduced in the LTAD group at week two, reflecting an unsupported level, and remained stable beyond this. The majority of participants had further ascites drainage episodes successfully performed outside of hospital, and at the end of the study follow up period, those in the LTAD group who were still alive, all chose to keep the LTADs in situ to continue their ascites management.

Trials focussed on improving palliative care in those with ESLD are a priority, and results from the REDUCe study could be used to inform future research design.

Chapter 6 - REDUCe study results: Participant reported outcomes, health economics and summary of qualitative outcomes

6.1 Introduction

The MORECare guidance on evaluating complex interventions in palliative care recommends using a mixed methods approach, and advises that offering patients and relatives the opportunity to be involved in meaningful research is ethically desirable.[92] Some of the challenges of conducting research surrounding palliative interventions includes the uncertainty of appropriate data collection tools, as well as the timing of studies along the patient journey, and high levels of attrition.[182]

We aimed to include data from patients, relatives and healthcare professionals in an effort to cover all aspects of the intervention pathway, as well as to assess the feasibility of using the designated data collection tools in this patient cohort.

Participant reported outcomes include questionnaire based assessments of symptoms experienced, as well as quality of life assessments. Health economic outcomes calculated using data collected from questionnaires is also reported, as well as a summary of results from the concurrent embedded qualitative study. The qualitative study has been published separately by the lead qualitative researchers, however the findings have been summarised in this chapter.[184]

The participant reported quantitative questionnaire results for the REDUCe study presented in this chapter have been published in Alimentary Pharmacology and Therapeutics, and details of the publication are in the references.[176]

6.2 Chapter aims

The aims of this chapter are to report on the participant reported outcome results from the REDUCe Study: Palliative Long Term Abdominal Drains versus Large Volume Paracentesis in Refractory Ascites Due to Cirrhosis - **RE**peated **D**rainage **U**ntreatable **C**irrhosis (ISRCTN 30697116).

6.3 Statement of contribution:

Statistical analysis of data relating to symptoms and quality of life was undertaken by Professor Stephen Bremner at the Brighton and Sussex Clinical Trials Unit (BSCTU), and the health economic data analysis was undertaken by the health economics team led by Professor Heather Gage at the University of Surrey.

The qualitative interview Participant Information Sheet (PIS) was given to potential study participants prior to study screening visits, and at the time of enrolment into the main study, participants were also invited to take part in the qualitative aspect. If willing, the research team received consent to share contact details and information with the qualitative researchers.

6.3.1 Qualitative researcher aspects

The qualitative researcher contacted participants, received consent to take part in the qualitative interview embedded study, and undertook the interviews themselves. Analysis of the qualitative interviews was undertaken by the qualitative researchers. An overview of the qualitative methods and results are given in this chapter and the full qualitative study is referenced.[184]

6.4 Methods

6.4.1 Overview

The rationales for selection of each specific questionnaire tool used have been described previously in chapter 4 and are summarised in this chapter. The questionnaires were undertaken during study visits in line with the study assessment schedule.

6.4.2 Questionnaire based assessments

6.4.2.1 Symptom distress and concerns

Symptoms were assessed on an alternate week basis using the Integrated Palliative Outcome Scale (IPOS).[148–150,185] The patient version consists of a total of 20 items integrated into ten questions, however only the 17 standardised items contribute to the overall IPOS total score.[185] The remaining items being free text to allow patients to self identify symptoms and concerns which are not covered in the standardised list.[148,185] The scoring of the standardised items is from 0 (best) to 68 (worst).[148,185] As well as calculating a total score, the following subscale analyses were also performed as recommended in the recent validation study: physical symptoms, emotional symptoms, and communication.[185]

6.4.2.2 Quality of life

Liver disease specific quality of life

Liver disease specific health related quality of life was assessed every four weeks during study visits using the Short Form Liver Disease Quality of Life questionnaire (SF-LDQOL).[155] The SF-LDQOL has 75 liver disease targeted items which are then transformed into the domains listed below on a scale of 0-100, with a higher score reflecting a better quality of life (QOL) reported. The domains are: distress, stigma, memory, symptoms, sleep, hopelessness, effect of liver disease, loneliness and sex.

Generic health related quality of life

Generic health related quality of life was assessed every four weeks during study visits using the EQ-5D-5L.[156] This has a five item composite profile score of mobility, self care, usual activities, pain/discomfort and anxiety/depression, scored on a five point scale, and converted to an index value range (−0.59 [worst] to 1 [best]) as well as a 20cm vertical visual analogue scale (VAS) with range 0 (worst) to 100 (best).[156] The EQ-5D-5L tool can also be used as a measure of Quality Adjusted Life Years (QALYs) in palliative care, although there are opposing views on its usage.[92] During the analysis of our study data, it was felt that calculation of QALYs would not be appropriate on such small numbers, however, this could be undertaken on a full scale study.

6.4.2.3 Impact on carers

If carers were present, had been willing, and gave consent to participate in the carer specific questionnaires, the caregiver workload was assessed using the Zarit Caregiver Burden Interview Short Form tool (ZBI-12).[157,158] The assessments were undertaken every four weeks during the study visits, and were usually administered to carers in the same sitting as the patient participant questionnaires. If carers expressed a wish to complete the questionnaires at a different time to the study visit with the patient participant, this was accommodated, whilst keeping within the study assessment schedule. The ZBI-12 tool has a 12 item composite scale completed by the caregiver, with respect to negative feelings they experience in their role as a caregiver, with zero equating to never, being the best score, to 48 equating to nearly always, being the worst score.[157,158] See figure 4.3 in chapter 4 which shows the study assessment schedule.

6.4.2.4 Health economics assessments

Service use assessments

The main resource usage items were identified and collected at an individual patient level from two sources, with the methods described previously in chapter 4.

Hospital service usage

Hospital usage was extracted from participants' hospital records at the end of the study period by the research teams at each participating study site, and transferred onto a bespoke, purposefully designed in house proforma, the Hospital Service Use questionnaire (see appendix 6). This data was often recorded concurrently alongside study visits, with hospital records re-reviewed at the end of the study follow up period, in order to minimise missing data. The Hospital Service Use questionnaire distinguished ascitic drainage episodes as occurring as part of an elective day case attendance, during an inpatient hospital admission, or during a non ascites related hospital admission.

Community and home based service use

Service usage in the community, including that accessed from within the home setting, was assessed fortnightly at each scheduled study visit, using a modified version of the Ambulatory and Home Care Record (AHCR).[153] The modified AHCR questionnaire was administered to participants by a member of the research team. Carers, if present and willing, were able to assist patient participants with completion of the AHCR in order to avoid missing data.

The AHCR uses prompt questions asking for the number of contacts made with services in and out of the home setting, and is designed to capture episodes covering primary, secondary, and social care professionals or services. The questionnaire design also captures episodes of informal care input, such as that

undertaken unpaid by family members or friends, this was recorded as average hours per day spent providing informal care.

Although participants and caregivers were asked to report hospital service use, the data extracted from participants' hospital records were found to be more complete, and therefore the decision was taken for this source to be used in preference during analysis.

The hospital and community databases were merged using the participants' unique study numbers. Data were collected across all healthcare boundaries and captured episodes of service use, both in a hospital, as well as in a community setting. This included capturing data for all episodes, both liver related and non liver related, however, only the 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 an ascitic drainage procedure was applied. Day case ascitic drainage incurs a different tariff from the inpatient ascites procedure cost, which was however used when patients were admitted to hospital solely for an ascitic drainage procedure. Resources used were converted to resource usage costs (in British Pounds Sterling 2018) using nationally validated unit costs,[161] and National Health Service reference costs.[186] Time spent caregiving by informal, unpaid, caregivers was translated into monetary value using replacement cost methods, and applying the tariff for community support workers who would otherwise provide a similar, but paid for service.[153]

6.4.3 Standardisations made for health economic analysis

Participants' survival during the study follow up period was variable and, as a result, participants were in the study for differing durations. Community data however were gathered every two weeks during study visits, as per the study assessment

schedule, and therefore the data were standardised for fortnightly analysis. Where there was missing data identified, members of the research team were contacted for further clarification in an attempt to complete datasets. Resource use and costs for each main category are reported as mean ± standard deviation (SD) and median, range, and interquartile range (IQR). The percentage of study time spent in hospital for ascites drainage was calculated assuming one full day for inpatient admissions solely for drainage, and half a day (0.5) for ascitic drainage undertaken as an elective day case procedure, the day case tariff was also applied to include situations where the patient had an ascitic drainage procedure performed whilst an inpatient in hospital for a non ascites related indication.

6.4.4 Statistical analysis

In terms of sample size, since this was a feasibility study, the pilot study rule of thumb was used, which states that 12 participants in each group are considered to be an adequate sample size as a starting point.[164] However, given the nature of the study population being at an advanced stage of disease with a high mortality,[27,51] therefore conferring a significant risk of participants not completing the intended study follow up time, a 50% attrition rate was assumed, as per guidance on research study design in palliative care.[92,181] To compensate for this, the sample size target for recruitment was increased to 24 participants in each group. The sample size was powered for a pilot study, and for feasibility for conducting a research study in this cohort of patients, with the longer term aim to inform a full scale study. The aim was not to provide definitive data on the safety and efficacy of the use of long term abdominal drains (LTADs) compared to the standard care of large volume paracentesis (LVP) in this setting, therefore, 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 and IQR with 95% confidence intervals (CI) presented for the estimated difference in means between groups at the end of follow up. An analysis was performed on the available cases following the intention to treat principle.

6.4.5 Qualitative study

Detailed qualitative methods and results have been published separately by the lead qualitative researcher, but are summarised here.[184]

The concurrently run, embedded qualitative study aimed to explore and contrast the experience, perceptions, and care pathways of participants in the two study groups, LTAD, the intervention group, and LVP, the standard of care group.

The recruitment aim for the qualitative study was for 20 patient participants to be interviewed at diverse stages across the study follow up period. In addition to patient participants, we also aimed to undertake interviews with eight healthcare professional participants, in order to assess similar areas as explored within patient participant interviews, but with additional focus on organisational and practical issues experienced by healthcare workers.

All interviews were undertaken by the qualitative researchers over the telephone. Analysis of the interviews was supported by qualitative software (NVivo).[187] Applied thematic analysis was used to extract overarching themes from interviews with both patient and healthcare professional participants' in order to capture the experiences of being part of the research study, of the ascitic drainage process, and of beliefs held.[188] These were considered with the aims of exploring the experience of accessing healthcare in terms of a pathway approach.[189]

6.5 Results

6.5.1 Recruitment

The REDUCe study commenced in September 2015, recruitment opened at the first study site in November 2015, and ran until June 2018, with 12 weeks of study follow up. Study recruitment has already been described in detail in chapter 5. The 36 (61% of potentially eligible) patients who were randomised equalled 75% of our target recruitment sample size of 48 overall, with a target of 24 participants in each study group. These 36 participants accounted for approximately 32% of all those who underwent two or more LVPs across all of the recruiting sites.

Of the participants who were recruited, 21 had available caregivers, 17 of those agreed, and gave consent to participate in the study, and were successfully recruited to undertake caregiver burden assessments. In terms of study groups, this represented nine out of ten (90%) available caregivers in the LTAD group, and eight out of 11 (73%) in the LVP group.

6.5.2 Questionnaire based assessments

6.5.2.1 Integrated Palliative Outcome Scale (IPOS)

Symptoms, distress and concerns were assessed on an alternate week basis using the IPOS tool, where higher scores indicate a larger symptom burden. Data from the patient version are presented, as our experience in the study was that the proxy staff version ended up being rarely used. Uptake of the IPOS (patient) questionnaire at baseline and at weeks 2, 4, 6, 8, 10 and 12 was 97%, 94%, 89%, 79%, 85%, 88% and 95% respectively, with almost all questions successfully completed at each visit, see table 6.1 at the end of the chapter. At baseline, the scores in the physical domain as well as the total IPOS score were higher in the LVP group, indicating a larger symptom burden. Median scores in all domains: physical, emotional,

communication, as well as total IPOS scores, remained broadly consistent throughout the study period in both the LTAD group and the LVP group. The mean difference in scores at last follow up in each domain were as follows: physical -1.3 (95% CI -8.1-5.6), emotional 1.6 (95% CI -1.4-5.4), communication 0.6 (95% CI -1.5-2.7) and total IPOS score -2.7 (95% CI -8.6-3.1).

6.5.2.2 Liver disease specific quality of life

The Short Form Liver Disease Quality of Life (SF-LDQOL) tool was used to assess liver disease specific quality of life every four weeks, where a higher score indicates a better quality of life reported. Uptake of the SF-LDQOL at baseline, and at weeks 4, 8, and 12 was 97%, 82%, 81% and 86% respectively, see table 6.2 at the end of the chapter. The majority of questions were successfully completed at each visit except the 4/25 questions (16%) which relate to sexual function. The experience of the research team was that patient participants in the study felt uncomfortable about answering these questions, including receiving some comments from them reporting that they felt too unwell to even consider sex.

Table 6.2 shows data on SF-LDQOL assessments broken down into each domain, as well as the mean difference between the two groups at last follow up. At baseline, compared to the LVP group, the LTAD group had higher scores (better quality of life) in all domains except for loneliness. During the follow up period, scores increased in most domains in the LVP group, however in the LTAD group, scores either reduced, representing worsening quality of life, or remained similar to baseline.

The domains with the greatest mean difference between the two groups at the last follow up were distress (mean difference -22.8, 95% CI -59-13.4), loneliness (mean difference -37.1, 95% CI -60.4 to -13.9), and hopelessness (mean difference -19.2, 95% CI -41.7-3.4).

6.5.2.3 Generic health related quality of life

The EQ-5D-5L tool was used to assess generic health related quality of life every four weeks, with the composite profile score converted to an Index value range (−0.59 [worst] to 1 [best]) reported alongside the Visual Analogue Scale (VAS) where a greater number indicates a higher quality of life. Table 6.3 at the end of the chapter shows descriptive data including the mean difference between the two groups at last follow up. Uptake of the EQ-5D-5L tool at baseline and at weeks 4, 8 and 12 was 97%, and 86%, 85% and 95% respectively. Again, almost all questions were successfully completed at each visit (Table 6.3). At baseline, the scores in both the Index and VAS areas were higher in the LTAD group than the LVP group. At the end of the study follow up, the Index score in both groups was similar, however the VAS score was higher in the LTAD group.

At the final study visit in the LTAD group interestingly, the EQ-5D-5L Index had worsened from baseline, however the VAS had improved. The LVP group showed a small improvement in the Index from baseline, however there was no change in the VAS. The mean difference between the two groups at the final study follow up was 0.02 (95% CI -0.18-0.22) in the EQ-5D-5L Index, and 10.6 (95% CI (-9.2-30.4) in the VAS.

6.5.2.4 Impact on carers

The Zarit Caregiver Burden Interview Short Form tool (ZBI-12), as an assessment of impact on carers, was undertaken every four weeks, with a higher score indicating a worse caregiver burden. Table 6.4 at the end of the chapter shows data on ZBI-12 assessments, and the mean difference between the two groups at last follow up. Almost all questions were successfully completed at each visit (Table 6.4). Only 47% of the participants (17/36) had carers available and willing to give consent to take part in the study and complete the ZBI-12 questionnaire. ZBI-12 scores remained

stable across study visits in the LTAD group, however, in the LVP group, the scores increased at successive study visits, indicating a worsening carer burden. The mean difference between the two groups at the last follow up was -2 (95% CI -15.1-11.1).

6.5.2.5 Health economic outcomes

Service use data were only available for a total of 30/36 (83%) patients, which was 15 per study group, as one study site unfortunately failed to return health economic related data. The comparison of the resource use and associated costs were standardised to a fortnightly rate, and were calculated only in relation to ascites drainage. Other non ascites related activity was not analysed any further as was outside the scope of the study. The data are shown at the end of the chapter in tables 6.5 and 6.6 respectively. Unit costs used are listed in the footnote for table 6.5. As could be expected, community nurse usage and costs were higher in the LTAD group compared to that in the LVP group, with median costs of £168 vs £0 respectively. This is reflected in the higher overall community cost in the LTAD group compared to the LVP group (median of £232 vs £11), as shown in table 6.5. Participants in the LTAD group also received higher median fortnightly social care and informal care compared with those in the LVP group, which was £6 vs £0 and £91 vs £15 respectively.

Of the 82 episodes of hospital drainages, 13/82 (15.9%) were in the LTAD group, of these, eight (8/13, 61.5%) were undertaken as day case procedures. In the LVP group, 69/82 (84.1%) episodes of hospital drainages occurred and 64/69 (92.8%) of these were undertaken as day case procedures. Of the ten inpatient drainages which occurred across both groups, nine were during a non ascites related hospital admission.

The overall hospital costs were higher for the LVP group compared to those in the LTAD group, median costs associated being £704 vs £0 respectively. Taken together, the median fortnightly community, social, and hospital costs were lower in the LTAD group compared to the LVP group (£329 vs £843). The difference between groups in terms of the overall total cost was less when informal care was included, offsetting the lower hospital costs in the LTAD group (£909 vs £1057). There was a notably high variability in the reporting of informal caring hours being undertaken, as can been seen demonstrated in table 6.6.

6.5.3 Qualitative interview outcomes

Of the 21 patient participants approached to participate in the embedded qualitative interview study, 19 (90%) were willing to take part, however, five of these died too rapidly to allow the qualitative interviewers time to proceed to obtaining consent and proceeding with an interview. Therefore, 14 patient participants, six from the LTAD group, and eight from the LVP group, as well as eight nurses, six community nurses and two hospital based nurses, were interviewed. All the interviews undertaken were completed.

Themes which emerged included the challenges of living with chronic ascites, recognising the need for drainage to be undertaken within a hospital setting, the logistics of organising hospital visits, and waiting to be discharged from hospital following a drainage episode having been completed.

Organisational barriers were perceived across the entire ascitic drainage pathway. There was recognition, however, that ascites drainage provided relief of symptoms, albeit temporarily.

In contrast to the standard ascitic drainage pathways undertaken in a hospital, usually day case setting, insertion of the 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 undertaken suggested that the continuity of care across the community and hospital healthcare boundaries were key to these positive experiences amongst participants in the LTAD group.

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

The community nursing staff reported that they found LTADs were manageable within their busy workloads. They nonetheless expressed concern that should LTAD be more widely adopted, additional community resources would be required to deliver the service.

Although patient participants were recognised by healthcare professionals as having a limited life expectancy, nurses reported during interviews that some participants appeared not to have fully taken in and understood this information, and sometimes interpreted the LTAD to be part of ongoing active treatment for their disease, rather than as part of palliative care.

6.6 Discussion

6.6.1 Key findings

We have demonstrated that a mixed methods, randomised controlled trial (RCT) in a cohort with advanced palliative liver disease is feasible to undertake. In terms of the patient reported outcomes and questionnaire based assessments, our study success criteria were achieved, as uptake, or completion of questionnaires and interviews was ≥80%. Health economic data demonstrated reduced health resource utilisation and costs, and those in the LTAD group spent ≤50% of ascites related study time in hospital compared to those in the LVP group.

The qualitative interviews demonstrated willingness of patients to be included in a research study, as well as acceptability of the LTAD as an intervention to manage refractory ascites (RA) in a community setting.

Both the LTAD and LVP groups reported a high symptom burden and poor quality of life both at the baseline assessments, and subsequently across all study visits. These findings are consistent with previously reported studies focussing on symptoms and health related quality of life in an end stage liver disease (ESLD) cohort,[46,190] and reflect the significant symptom burden experienced in this population.[46,47]

This feasibility study was not powered for further application of statistical inference, meaning that only descriptive statistics can be applied to the study results, and care given to apply caution to any suggested differences between groups.

6.6.2 Symptoms and quality of life

Interestingly, the baseline symptom and quality of life scores were reported as being better in the group randomised to LTAD in all domains across the IPOS, EQ-5D-5L

and the SF-LDQOL, except for in the loneliness domain. The median IPOS scores in both groups remained broadly consistent across further study visits, whereas in the SF-LDQOL, the LTAD group scores either reduced, representing worsening quality of life, or remained similar, this was in contrast to the LVP group, where scores increased in most domains.

The EQ-5D-5L Index at the final study follow up visit had worsened from baseline in the LTAD group, however the VAS had improved. The LVP group results showed a small improvement in the Index score from baseline, however there was no change in the VAS. At the end of the study follow up, the EQ-5D-5L Index score in both the LTAD and LVP groups was similar, however the VAS score was higher in the LTAD group.

In broad terms, we observed most quality of life (QOL) domains worsened in the LTAD cohort across the study follow up visits, although as already described, this does not provide as much granularity as a closer look at each tool individually. The sample size used was not intended to enable more definitive statistics, rather the aim was to inform a full size study. The questionnaire results overall differ from themes extracted from the qualitative interviews, which indicated LTAD acceptability to patient participants, as well as improved symptom control.

One consideration to take into account is, as per the study procedures schedule, the timing of the baseline questionnaires were undertaken at the same study visit as the randomisation outcome was revealed, or after randomisation had occurred. This factor could have influenced participants answers to the questionnaires undertaken at the baseline visit. The overriding preference of participants for allocation to the LTAD group, and the disappointment expressed during qualitative interviews at not being randomised to the LTAD group, could mean that baseline scores in both

groups may have also reflected their perceptions of their group allocations. Those randomised to the LTAD group could therefore have reported better baseline symptom and QOL scores, and those in the LVP conversely reported worse scores. Studies of using LTADs in malignant ascites also report inconsistent quality of life impact during questionnaire based assessments, and even incongruent supportive qualitative data as was also seen in our study.[76,169] These conflicting results could be explained by the absence of a validated ascites specific QOL questionnaire and the recurrent and incurable nature of refractory ascites.[169] A further aspect to take into account is that the patterns of symptoms reported may reflect those experienced in the advanced stages of any disease, and not just those symptoms commonly associated with ascites.[169] The IPOS scores reported in our study were similar to those reported in non hepatic malignancy.[148] It is also reasonable to suggest that the presence of an LTAD may have been a constant reminder of the incurable, palliative nature of participants' underlying disease.

6.6.3 Impact on carers

The carer burden scores recorded in the ZBI-12 tool showed worsening carer burden in the LVP group compared to those in the LTAD group, this could be a reflection of the increased community healthcare service contacts reported in the LTAD group, with resultant higher levels of support of caregivers. Interestingly, the ZBI-12 scores reported in our study were higher, representing a larger carer burden, than those seen in a study of caregiver burden in patients with cirrhosis with the complication of hepatic encephalopathy.[191] This may represent a previously under appreciated carer burden in those in whom ascites is the predominant feature. ZBI-12 scores were however similar to those seen in other advanced conditions, such as glioblastoma and heart failure.[192,193]

6.6.4 Health resource usage

Compared to the LVP group, community and social care costs were higher, and hospital costs were lower for the LTAD group, which is what was expected to be seen with this intervention. The overall median healthcare costs in the LTAD group were lower, however this difference between the two groups was less marked when the informal caring costs were included. The reported range in informal caring costs was notably wide as a result of the high variability in caring hours reported by informal carers. Given the small sample size, the reliability of this effect is therefore low, and must be interpreted with caution.

Standardisations made for health economic analysis, in terms of tariffs applied to calculate hospital use, could be less applicable in the context of the current high bed occupancy in the National Health Service, around 90% in the second quarter of 2022/2023.[194] It could be argued that one day for an acute hospital admission for an ascitic drainage episode is an ambitious target, given the inherent nature of delays of admission into an inpatient bed, and then of the procedure being performed with the inpatient clinical team balancing time pressures of managing other inpatients' care concurrently.

Excluding those where ascitic drainage was performed during a non ascites related hospital admission, and one individual whose LTAD was pulled out, only two participants in the LTAD group required further hospital ascites drainage. These results are in keeping with our systematic review on the palliative use of permanent indwelling peritoneal catheters for the management of refractory ascites in ESLD, which is reported in chapter 3, where in 14 of the 18 studies which provided data on drainage following the insertion of a long term drain, no further hospital admissions were required specifically for drainage of ascites. A reduction in hospital service use

and lowering the burden on acute hospitals is a current priority in the NHS, with the aim for more acute and emergency care to be delivered in a virtual outpatient setting, as set out in the NHS Long Term Plan in 2019.[195] The use of LTADs in transferring RA management into a community setting could be a tool with which to allow this target to be supported in patients with ESLD and RA.

Given the palliative nature of the research study, participants were closely monitored by staff who were aware of the benefits of early palliative care intervention, and who were also able to identify when these may be appropriate in the context of each patient participant. This may have impacted the place of death in those participants who died during the study follow up period, as we found this to be outside of a hospital setting in about 70%. This is in contrast with place of death in those with ESLD across the whole of England, where the majority are found to die in hospital, 66.9% in a national population based study published in 2019.[89] A recent study reported that patients with ESLD were more likely to die in an institutional setting, and that associated end of life care costs were significantly higher compared to those without ESLD.[196] Our findings, showing a transformation in the place of death for those with ESLD, could mean a further healthcare related cost saving, in contrast with the pattern which is currently observed nationally.[52,89]

The EQ-5D-5L tool can also be used to calculate quality adjusted life years in economic evaluations of healthcare interventions, we found that collection of the data using the tool was feasible and could therefore be calculated in a larger powered study.[156] The use of quality adjusted life years is however controversial in palliative care, due to measuring this in a cohort with differing priorities, as well as treatments and outcomes being more complex.[92] Given that at present they continue to be a widely used measure, and in the absence of alternatives, it is reasonable to

consider this aspect of the EQ-5D-5L to be utilised and included in the design of a full scale RCT.[92,197]

6.6.5 Study limitations

The limitations included the majority of patients recruited to the multicentre feasibility RCT being from one study site, 56%, meaning generalisability at a national level is lacking. This therefore could have implications for study design for a full scale national RCT.

The sample size was low, in keeping with a feasibility study, and the descriptive statistics reported cannot be used in place of definitive results on the impact of the use of LTAD on symptoms and QOL in the context of RA in ESLD.

Health economic data were missing from one site (17% of participants), and the substantial range in costs reported in the context of a small sample size requires cautious interpretation of the results. Data were standardised for fortnightly analysis, although the duration of time spent during study follow up differed due to attrition, and as a result, may under or overestimate costs due to the small sample size. The high variability in the reporting of informal caring hours being undertaken may have impacted on the total costs calculated, and in subsequent studies it may be helpful for carers to be given guidance on the recording of time spent caregiving to aid with standardisation.

In terms of initial study recruitment aims, we only achieved 75% of the target sample size, despite being granted an extension from the funding and ethics bodies. This proportion of recruitment achieved against the overall target is consistent with a recently published study of an early palliative care intervention in ESLD.[183] The recruitment did still however meet the pilot study requirements of 12 participants in each arm.[164]

6.7 Conclusion

Mixed methods are an important part of evaluating interventions in patients with ESLD, as outcome measures are less well defined in this cohort of patients who are in a palliative phase of their disease.[92] We demonstrated the feasibility of undertaking research in this population of patients, as well as their willingness to be included in the research study. Patient reported outcomes, questionnaire based assessments, and qualitative interviews undertaken in the REDUCe study produced incongruent results, however did provide preliminary evidence of the acceptability of the use of LTADs in ESLD, as well as of the assessment tools used, and suggested a reduction in healthcare resource utilisation and costs.

The REDUCe study results could be used to inform the design of a full scale RCT, which would be powered to give more definitive data, and answer questions on safety, efficacy, impact on QOL and healthcare cost. Lessons learned in reporting methods could be applied to improve recruitment and uptake of assessment tools, with the aim to provide definitive evidence with which to improve ascites management in those with ESLD and RA.

Table 6.1 Summary statistics for Integrated Patient Outcome Scale (IPOS) (Patient) in LTAD and LVP groups by time point

Questionnaire	Long Term Abdominal Drain group, LTAD n=17					Large Volume Paracentesis group, LVP n=19						
	n/N	Mean	SD	Median	IQR	n/N	Mean	SD	Median	IQR	Mean difference	95% CI
IPOS												
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 6	11/13	11.4	5.5	11	5	12/15	11.7	5.4	10	7.5		
Week 8	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)
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 6	12/13	6.8	4.8	6.5	5.5	12/15	4.5	2.7	3.5	2.5		
Week 8	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)

Questionnaire	Long Term Abdominal Drain group, LTAD n=17					Large Volume Paracentesis group, LVP n=19						
IPOS-Communication	**n/N**	**Mean**	**SD**	**Median**	**IQR**	**n/N**	**Mean**	**SD**	**Median**	**IQR**	**Mean difference**	**95% CI**
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 6	11/13	2.9	2.7	2	3	12/15	1.9	2.2	2	1.5		
Week 8	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)
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		
Week 4	11/13	17	10.4	15	13	14/15	21	9.7	20	8		
Week 6	10/13	21.2	10.2	17	7	12/15	18.1	8.5	14.5	12.5		
Week 8	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)

Table 6.2 Summary statistics for the Short Form Liver Disease Quality of Life (SF-LDQOL) questionnaire in the LTAD and LVP groups by time point

Questionnaire	LTAD n=17					LVP n=19						
	n/N	Mean	SD	Median	IQR	n/N	Mean	SD	Median	IQR	Mean difference	95% CI
SF-LDQOL												
Symptoms												
Baseline	17/17	64.5	19.8	70	26.7	18/19	49.8	23.1	45	36.7		
Week 4	9/13	65.5	30.1	83.3	36.7	14/15	52.1	20.1	55	23.3		
Week 8	10/13	58.6	21.4	56.7	26.7	13/14	48.7	18.9	50	20		
Week 12	8/9	54.6	21.2	45	36.7	10/12	53.3	20.7	58.3	36.7	1.3	(-19.7-22.2)
Effect												
Baseline	15/17	58.9	23.5	50	41.7	17/19	50.5	24.2	50	33.3		
Week 4	9/13	57.9	25.7	50	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	(-26.3-28.4)
Memory												
Baseline	17/17	74.6	23.3	75	37.5	18/19	67	27.9	68.8	56.3		
Week 4	9/13	81.3	26	100	31.3	14/15	68.9	25.1	75	43.8		
Week 8	10/13	71.3	24	71.9	50	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)
Distress												
Baseline	17/17	47.1	39.7	37.5	87.5	18/19	37.5	30	31.3	50		
Week 4	9/13	58.3	41.9	62.5	75	14/15	50.9	28.8	50	37.5		
Week 8	10/13	58.8	31.2	56.3	25	12/14	49	29.4	43.8	31.3		
Week 12	8/9	35.9	39.8	25	68.8	10/12	58.8	32.8	56.3	75	-22.8	(-59-13.4)

Questionnaire	LTAD n=17					LVP n=19						
	n/N	Mean	SD	Median	IQR	n/N	Mean	SD	Median	IQR	Mean difference	95% CI
Sleep												
Baseline	17/17	57.4	22.2	55	25	18/19	36	21.9	35	40		
Week 4	9/13	52.8	12.5	55	15	14/15	46.8	19.7	50	30		
Week 8	10/13	55	18.1	55	30	12/14	33.8	16.9	30	20		
Week 12	8/9	45	14.1	42.5	22.5	10/12	41.5	15.1	40	20	3.5	(-11.3-18.3)
Loneliness												
Baseline	17/17	67.1	19.3	75	25	18/19	72.8	31.5	85	45		
Week 4	9/13	70	26.3	80	35	14/15	73.6	26.3	80	35		
Week 8	10/13	65.5	18.3	65	30	12/14	72.5	30.9	85	55		
Week 12	8/9	51.9	30.1	57.5	57.5	10/12	89	15.6	95	15	-37.1	(-60.4 to -13.9)
Hopelessness												
Baseline	17/17	50	26.5	50	41.7	18/19	43.1	24.6	50	33.3		
Week 4	9/13	55.6	26.7	58.3	33.3	14/15	48.2	20.2	50	16.7		
Week 8	9/13	45.4	27.7	50	33.3	12/14	47.9	24.7	50	45.8		
Week 12	8/9	29.2	27.1	20.8	41.7	10/12	48.3	17.9	50	33.3	-19.2	(-41.7-3.4)
Stigma												
Baseline	17/17	66.4	28.7	62.5	50	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	37.5		
Week 8	9/13	63.9	30.3	68.8	50	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	1.3	3/15	2.6	1.6	2	3		
Week 8	2/13	4.4	0.1	4.4	0.2	3/14	2.4	1.7	2	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

Table 6.3 Summary statistics for the EQ-5D-5L questionnaire in the LTAD and LVP groups by time point

Questionnaire	LTAD n=17					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	0.3	0.75	0.4	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	0.2	12/12	0.57	0.24	0.54	0.31	0.02	(-0.18-0.22)
EQ-5D-5L VAS												
Baseline	17/17	57.6	26.7	55	30	18/19	54.1	23.4	52.5	45		
Week 4	10/13	51.5	32.7	50	55	14/15	56.9	22.4	57.5	38		
Week 8	10/13	67.5	20.3	67.5	30	13/14	55.8	18.8	50	35		
Week 12	8/9	66.3	28.1	67.5	45	12/12	55.7	20.8	52.5	23.5	10.6	(-9.2-30.4)

Table 6.4 Summary statistics for Zarit Burden Interview (ZBI-12) questionnaire in the LTAD and LVP groups by time point

Questionnaire	LTAD					LVP						
	n	Mean	SD	Median	IQR	n	Mean	SD	Median	IQR	Mean difference	95% CI
Zarit Carer												
Baseline	9	17.9	9.4	14	6	8	14.6	8.4	17	12.5		
Week 4	5	20.8	8.6	18	8	6	14.8	8.1	13.5	9		
Week 8	5	20.6	10.5	22	17	3	20	11.1	18	22		
Week 12	3	18	11.5	17	23	5	20	3.7	19	3	-2	(-15.1-11.1)

Table 6.5 Cost per fortnight (British pounds 2018) in the LTAD and LVP groups

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	0.7	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 (excluding informal care)	429.9	257.7	329	109-957	253-580	852.3	257	843	435-1311	603-1060
Overall cost including informal care	**1189.8**	**937.9**	**909**	**174-2877**	**567-1631**	**1537.4**	**1193.8**	**1057**	**450-4462**	**844-1701**

Footnote for tables 6.1, 6.3 and 6.4:

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.

Footnote for table 6.2:

Note: n/N, number of patients completing questionnaires/ number alive at each visit; Increasing SF-LDQOL scores indicate better QOL.

Footnote for table 6.5:

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 201828: 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 6.6 Service use contacts per fortnight in the LTAD and LVP groups

Number of service use contacts/ events per fortnight*	Community / LTAD n=15				Hospital / LVP n=15			
	Mean	**SD**	**Median**	**Range**	**Mean**	**SD**	**Median**	**Range**
District nurse	0.05	0.18	0	0-0.71	0.02	0.07	0	0-0.29
Community / specialist nurse	3.68	1.82	3.86	0-5.8	0.56	1.32	0	0-5
Palliative care nurse	0.83	2.24	0.14	0-8.9	0.37	0.77	0	0-3
GP (home visits)	0.16	0.19	0.14	0-0.5	0.09	0.17	0	0-0.5
Allied health professional	0.26	0.43	0	0-1.5	0.97	3.65	0	0-14.17
Other health professional	0.15	0.51	0	0-15	0.72	2.75	0	0-10.67
All community health	**5.14**	**3.38**	**5.25**	**0.4-15**	**2.72**	**6.72**	**0.14**	**0-25.70**
Social care worker	5.65	9.13	0.17	0-27.8	1.62	4.92	0	0-18.6
Day case drainage	0.08	0.19	0	0-0.61	0.72	0.35	0.74	0-1.15
Inpatient drainage	0.00	0.00	0.00	0-0	0.02	0.06	0	0-0.23
Admitted to hospital for non ascites reason and had drainage	0.06	0.12	0	0-0.36	0.04	0.10	0	0-0.32
Informal care (hours)	6.57	8.49	0.80	0-24	5.21	7.51	0.14	0-24
*A&E, outpatient use and tests not shown – no significant difference between groups								

Chapter 7 - Conclusions and future directions

7.1 Introduction

In the UK, advanced cirrhosis and resulting decompensated, or end stage liver disease (ESLD), is a growing health problem, with many cases of advanced chronic liver disease remaining asymptomatic until presentation to an acute hospital with complications of cirrhosis and a decompensating event.[1,198] Ascites is most frequently the first complication of hepatic decompensation to develop, and is also the most commonly experienced complication of cirrhosis, affecting up to 90% of those with ESLD.[20,27] Interventions to manage ascites therefore, often dominate overall symptom management in ESLD.[46–48] Ascites is reported in the literature as becoming refractory to medical management, which begins with dietary sodium restriction and progresses to the use of diuretics, in 10% of cases.[50,94] However, this is in all cases of ESLD with ascites, and the natural history of RA development has not been well described specifically in those who undergo an initial short term drainage procedure, large volume paracentesis (LVP). The current standard of care in managing refractory ascites is symptom based, and in the absence of eligibility for liver transplantation (LT), which is the only curative option, this is with intermittent LVP.[28] Undergoing repeated LVPs necessitates recurrent hospital attendances, and the associated symptom burden for patients with RA is significant.[47] The financial cost for healthcare providers, where repeated hospital attendances are required, such as that in RA, is also significant, as well as resultant increased pressure on acute hospital services.[52] In addition to this, despite the high symptom burden experienced in ESLD, and the palliative nature of the management of those with ESLD and RA in the absence of LT, supportive and palliative care is

underutilised.[46,47,52,174,175] Alternative strategies for managing RA are being sought and there is a growing movement to improve supportive and palliative care in ESLD, with more focus from the national and international hepatology community.[28,81,105,171] Notably, the American Association for the Study of Liver Diseases (AASLD) published the first specific practice guidance on palliative care and symptom based management in decompensated cirrhosis in 2022, which reflects the start of a mindset shift amongst hepatologists, from focussing on LT, to considering integration of more holistic patient care.[171,199]

7.2 Overview of chapters

The work described in this thesis has aimed to characterise the current standard interventional management of refractory ascites in the context of end stage liver disease, and investigate possible variables which could identify any predictors of the development of RA. The next aspect was to undertake a systematic review and report on the current available evidence of the use of permanent indwelling peritoneal catheters as a strategy for the management of RA in ESLD. Finally, the methods and results from the feasibility randomised controlled trial (RCT): Palliative Long Term Abdominal Drains versus Large Volume Paracentesis in Refractory Ascites Due to Cirrhosis - **RE**peated **D**rainage **U**ntreatable **C**irrhosis, the REDUCe Study (ISRCTN 30697116) have been described and reported. The REDUCe study aims were to establish the feasibility of using a long term abdominal drain (LTAD) as a strategy for the palliative management of RA, when compared to the current standard of care. We aimed to explore whether using long term abdominal drains (LTADs) would be acceptable to patients and healthcare professionals, by transferring ascites management into the community setting. The longer term aims were for data from the feasibility study to inform a full scale mixed methods RCT,

including methods, data collection tools, primary outcome measures, and whether a study of this kind would be achievable to conduct in a group of patients with palliative, end stage disease and complex needs.

7.3 Summary of findings

We examined an unselected consecutive cohort of patients undergoing LVP procedures at a large NHS teaching hospital on the South Coast over a three year period, excluding those with conditions other than ESLD. We described the ESLD group in terms of aetiology of ESLD, baseline characteristics as well as factors relating to LVP, liver transplantation, and finally, in terms of advance care planning. We found that in the group of patients with ESLD who underwent an initial LVP, following their patient journey revealed that almost 40% went on to develop RA, requiring ≥3 LVPs. Other than the serum albumin level, there was no significant difference between the two groups at baseline in those who did not go on to develop RA and those who did, this being in terms of patient characteristics, aetiology and liver disease severity scores. The only baseline characteristic which was predictive of the development of RA was again the serum albumin level, reaching a level of statistical significance $p = 0.043$. Our findings regarding LT eligibility have been in keeping with known rates nationally,[56] of all patients with RA undergoing LVP in our data, this rate was less than 15%. The most common reason which precluded eligibility for liver transplant assessment was persistent alcohol use disorder. In terms of survival outcomes, there was a statistically significant difference between the RA and non RA groups in the time from first LVP to death, in our data the median survival was 260 days and 85 days respectively $p = 0.007$. This finding was surprising, as it might have been expected that the RA group would have a worse survival, however, it could perhaps reflect the timing of the recorded baseline data,

which was arbitrarily decided to be at the first development of ascites. This could have resulted in a sampling bias, and therefore those classified as having RA had to have survived long enough to have met the criteria of three of more LVPs, whereas the requirement for an LVP in itself represents an advanced disease state in all the patients identified. Those who did not go on to develop RA could have been in a more acute phase of their disease, with ascites development as part of acute on chronic liver failure (ACLF), whereas those who went on to develop RA could have been in a more stable progressive disease state.[99] The development of RA confers a limited life expectancy, this is reported in current literature as being a median of six months,[27] and our data is in keeping with this, with median survival from the development of RA to death of 179 days. Despite this, less than half, 44.9%, of patients in the RA group had any acknowledgement communicated to their general practitioners (GPs) that the focus of their care was now supportive, or palliative in nature, this also included discussions and decisions pertaining to cardiopulmonary resuscitation. In addition, a palliative care team referral had been made in only 26.5% of patients in the RA group, and evidence of advance care planning, or discussion of a long term management plan having been communicated to patients' GPs was found in just over a quarter, 26.5%. These results reflect the need for a more holistic view in managing patients with ESLD, as well as the challenges expressed by clinicians regarding predicting prognosis, and perhaps under confidence in communicating the inherent uncertainty in advanced liver disease,[43,102,103] where both improvement and deterioration can occur rapidly.[41,104] Even when LT is an option, or when on the transplant waiting list, not only do a proportion or patients die while awaiting a transplant,[56] but also, the ongoing burden of symptoms experienced is large, and all too often overlooked by clinicians.[46,89] This

is despite growing evidence that early palliative care in those on the transplant waiting list significantly improves symptoms and further, could be a source of support for caregivers.[84,171] Supportive and palliative care services are underutilised by patients with ESLD overall, and even when accessed, this is often typically limited to inpatient end of life care, rather than as part of advance care planning.[174,175]

We have presented the first systematic review of the use of long term abdominal drains in the management of ascites due to decompensated cirrhosis. Although there has been a reasonable volume of published evidence of the use of long term drains (LTAD) in the context of malignant ascites,[146] and endorsement of their use in this setting by the National Institute for Health and Care Excellence (NICE),[76] the same is not the case for ascites due to cirrhosis.[80] Management of refractory ascites has not significantly changed over the years and, although there are a few interventions which have been tried, and some, such as transjugular intrahepatic portosystemic shunts (TIPS) can be quite successful, these overall however are often not appropriate in the majority of patients who develop RA.[25,28] In the case of TIPS, in transplant eligible patients, TIPS must be discussed with the transplant centre and may not be appropriate, as can impact on the surgical aspects of transplantation.[56] In those patients who are not transplant eligible, the contraindications for TIPS share a high degree of commonality.[28,69]

Improvements in the management of RA is currently an unmet need in our patients with ESLD and RA. Our systematic review showed that the use of LTAD was of growing interest internationally as a potential option,[121,124] however it also demonstrated that much is as yet unanswered in terms of complication rates, effectiveness, and impact on patient quality of life (QOL), as well as health economic perspectives. Our systematic review was one of the peer reviewed publications used

to inform the supporting evidence review for the recently published NICE interventional procedures guidance [IPG746] on Tunnelled peritoneal drainage catheter insertion for refractory ascites in cirrhosis.[80] The guidance stated that 'Evidence on the efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.'[80] The NICE guidance also stated that they encouraged and supported further research to be undertaken on the use of LTAD in RA in cirrhosis, as there are unanswered questions remaining, before their use can be recommended as an alternative to the current standard of care.

7.4 The REDUCe study

7.4.1 REDUCe study overview

We reported the results of the feasibility RCT: Palliative Long Term Abdominal Drains versus Large Volume Paracentesis in Refractory Ascites Due to Cirrhosis (**RE**peated **D**rainage **U**ntreatable **C**irrhosis, the REDUCe Study). The REDUCe study is the first RCT undertaken in a cohort of patients with ESLD and RA, comparing the palliative use of LTAD with the current standard of care, LVP. The study used mixed data collection methods following the MORECare guidance on evaluating complex interventions in palliative care, where optimal data collection tools and outcome measures are often less clear.[92,182] The call to improve the quality of research undertaken in palliative and end of life care aims to improve the robustness of evidence based practice within this area of medicine.[92,182]

The aims of the study were to investigate the feasibility of undertaking an RCT in a cohort of patients with ESLD and RA, indicating an advanced disease stage, and in whom care was palliative in nature. Patients who were eligible for liver

transplantation or TIPS were excluded from study recruitment. We aimed to investigate the acceptability of using LTADs for the palliative management of RA, transferring care from within a hospital setting to the community, by assessing impact on patients, healthcare staff, and informal carers. The mixed methods approach included assessments of clinical outcomes, symptoms, quality of life, impact on informal carers, health economic aspects, and also included an embedded qualitative component. These tools were selected with the aim to capture the patient journey, as well as aspects of healthcare logistics and organisational factors. A qualitative component was included to allow patient and healthcare professionals experiences and beliefs to be explored, as nuances can be missed when using standardised tools, particularly of the patient experience. Inconsistencies have been reported between quantitative quality of life assessments and qualitative data in studies of the use of LTAD in malignant ascites.[76,169] Therefore it was felt that both methods should be included in the study to allow a richer overview of experiences. The study outcomes met our predefined success criteria, which covered all cause attrition of not more than 50%, uptake of questionnaires and interviews to be at least 80%, rates of mandatory LTAD removal of less than 10% and finally, for those in the LTAD group to spend less than 50% of ascites related study time in hospital compared to those in the LVP group.

7.4.2 REDUCe study recruitment

Study recruitment was 75% of our target, however, the proportion of those recruited compared to those who were eligible was 61%. A total of 17 participants were randomised to the LTAD group and 19 to continue with standard care, the LVP group. Challenges faced with recruitment included potential participants being referred to the research team late in their disease trajectory, late discussions

regarding prognosis between patients and their usual gastroenterologists and hepatologists, with resultant uncertainty as to suitability for liver transplantation. We also experienced that discussions regarding palliative care were overlooked, perhaps reflecting clinicians' lack of experience as to the suitability or timing of palliative care interventions.[103,171] The impact of this was reflected in lower than expected recruitment rates in the first year of the study, and 15% of patients who were potentially eligible for study recruitment dying before being able to proceed to study inclusion. This is also mirrored in our attrition data, where 42% of patient participants' deaths during the study occurred within the first four weeks of follow up. The study was granted an extension for a further year beyond the initially planned two years, by the NIHR funding body, to support recruitment, as it was recognised that REDUCe was an important study being undertaken in a disenfranchised population. We had identified areas which had hindered recruitment and sought to improve these by implementing the lessons learned. We developed an ESLD multidisciplinary meeting to allow patients to be identified earlier, also with the aim to improve their clinical care, including discussions of transplant suitability and eligibility for parallel planning in conjunction with ongoing active management based on the Bristol supportive care intervention tool.[174] Three further study sites were also opened to boost recruitment, and overall, our strategies were reflected in improved study recruitment in years two and three.

7.4.3 REDUCe study outcomes

The study outcomes are reported as descriptive statistics as, being a feasibility RCT, the aims were not to give definitive evidence of the safety and efficacy of using LTAD as a strategy in RA management.

Clinical outcomes did not demonstrate any safety concerns in the LTAD group, with stable renal function, and with regards to the serum albumin level, following the initial reduction at the week two visit, this then also remained stable. These variables are particularly relevant, given no human albumin solution (HAS) was infused to patient participants during community drainage episodes in the LTAD group. Current clinical guidance on the use of HAS states concurrent infusion during LVP is advised, and is a recognised indication for its use, however, using HAS as a replacement fluid is not required when draining less than five Litres of ascites.[25] In REDUCe, HAS was not used in the LTAD group, given our aim was for small volumes of ascites to be drained, but on a more regular basis, aiming for symptom management. The exception to this was in the two participants in whom ascites symptoms could not be managed solely with community based LTAD drainage. For study safety, we limited community drainage episodes to a maximum of two Litres of ascites to be drained at a maximum of three times per week. The two patients with LTADs who required further hospital based drainage had HAS infused, while the LTAD was used with an adaptor to allow it to be used as in LVP. There is currently some debate over the use of HAS outside of current defined indications in patients with ESLD.[200–202] It is important to recognise that in our study, which was aimed at improving palliative care in this group of patients, high importance was placed on reducing the burden of medical interventions and hospital attendances, to allow more focus on symptom management and supportive care.

There were no LTAD specific serious adverse events, and no instances where an LTAD complication required its removal. Infection is one of the most feared complications in patients with ESLD, given cirrhosis related immune dysfunction, and high mortality rates are seen in those with infection.[30,61,99] With the caveat of a small

sample size, we did not see higher rates of peritonitis in the LTAD group compared to what would be expected within background rates of spontaneous bacterial peritonitis in an ESLD population.[25] There were two episodes of localised cellulitis at the LTAD drain insertion site which were treated successfully with oral antibiotics, following which the cellulitis resolved.

Higher rates of leakage following LTAD insertion were seen compared to leakage post drainage in the LVP group. This may reflect insertion technique, and therefore hopefully reduce with increasing experience in LTAD insertion methods. Five participants experienced a degree of leakage following LTAD insertion, three with leakage and two with both leakage and cellulitis developing. In the LVP group there were two episodes experienced of leakage, and/or bleeding following an LVP procedure. All of these drain procedure related leakage events were minor, and self limiting, with either an additional suture applied, and/or dressing management, while the insertion tract healed. No participant required hospitalisation as a result of any of the reported drain related adverse events.

At the end of the study follow up period, those who were alive in the LTAD group all chose to keep their LTADs for further ascites management, and continued with community based drainage episodes.

The participant reported outcomes were chosen with the aim to capture all aspects of the patient journey and include informal carers, as well as healthcare professionals, to give a broad picture.

Reporting tools used included questionnaire based assessments of symptoms experienced and quality of life (QOL) assessments. Health economic outcomes were calculated, and an embedded qualitative study ran concurrently to capture the experiences of patient participants in both groups. Healthcare staff were also invited

to take part in qualitative interviews, which allowed further insight into organisational and practical aspects of care delivery.

We found there was a high symptom burden and poor quality of life in this group of patients, which is consistent with previous studies in ESLD.[46,190] Our symptom and QOL results broadly showed those randomised to the LTAD group reported a lower symptom burden and better QOL at baseline, prior to LTAD insertion, than those randomised to the LVP group. There is no clear reason why this should be the case, as no study interventions had taken place at this point, and could possibly represent participant bias after being made aware of the group allocation. The qualitative interviews reported a preference, by patient participants, for allocation to the LTAD group, and disappointment amongst those allocated to the LVP group when this had not occurred.

Although the study was not powered to show statistical differences, we observed that symptom and QOL outcomes worsened in most domains in the LTAD group. This is in contrast with results from the ZBI-12 tool, which showed that carer burden worsened for those caregivers of patient participants in the LVP group. We found the quantitative data were incongruous with that reported by patient participants in the qualitative interviews, which indicated LTAD acceptability, with improved control of symptoms.

In terms of care pathways, data from the qualitative interviews reported that insertion of the LTAD transformed the ascitic drainage pathway at all levels compared to the current standard of care. Challenges experienced in navigating hospital services were avoided, along with hospital attendances, and participants reported improved emotional support from regular home visits by community nurses.

Place of death, which is often used as a surrogate marker for quality of end of life care, given preferred place of death is usually not in a hospital setting, was transformed.[42,89,90] The current national figures of place of death in ESLD are of 70% dying within hospital,[89] our study results, however, found around 70% of those who died, did so outside of a hospital setting. This in itself demonstrates the impact of a clinical research team who have a palliative and supportive care focus, and who understand the benefits of early palliative interventions including discussions regarding advance care planning and preferred place of death.[81,102,105,171,174]

We showed reduced health resource utilisation and costs overall, including reduced burden on hospital services, with those in the LTAD group spending less ascites related study time in hospital.

7.5 Impact, final remarks and future directions

The body of this work has shown that although RA develops in less than half of those with ESLD who undergo an initial LVP, patients have a high burden of symptoms, face many challenges in following current ascites drainage pathways, and are often overlooked when it comes to parallel advance care planning or supportive care.

Our work has informed national guidance on the use of LTAD in cirrhosis and RA from NICE,[112] where it was felt that evidence on their efficacy is limited in quantity and quality, and support was given for further research into these unanswered questions.[80]

Results from REDUCe have shown potential LTAD effectiveness in refractory ascites due to ESLD, however, the feasibility study was not designed to be able to provide evidence to support a national change in service delivery. We have, however, demonstrated feasibility to proceed with a full scale mixed methods RCT, to provide

more definitive data on the safety and efficacy of LTAD use, with the aim to improve palliative care in this disenfranchised group of patients.

The REDUCe study team was recognised for our work, winning the Royal College of Physicians Excellence in Patient Care Awards: *Lancet* research award 2018.[203] Our work has also been presented at National (British Society of Gastroenterology, BSG 2019) and International (European Association for the Study of the Liver, EASL 2019) conferences, as well as the British Association for the Study of the Liver (BASL) End of Life, and Portal hypertension special interest groups (SIGs). As part of the BASL End of Life SIG we have also co written the BASL/BSG consensus document on the palliative use of LTAD in RA and cirrhosis.[204]

The aims to design a large national multicentre RCT have been realised in REDUCe2 (ISRCTN 26993852),[205] where data collection methods and tools have been streamlined, and funding included community follow up visits, to support site set up and data collection. The primary aims of REDUCe2 are to assess whether palliative LTADs improve patient QOL compared to standard care.[206] The secondary outcomes include assessing infection rates, symptoms, and resource utilisation.[206] The REDUCe2 study opened in September 2022 and is currently planned to close in September 2026.[205]

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Appendices

Appendix 1: Systematic review search strategies

CINAHL search history HDAS 8.12.15

Search Strategy:
1. CINAHL; exp LIVER FAILURE/ OR exp LIVER DISEASES, ALCOHOLIC/ OR exp LIVER DISEASES/ OR exp NONALCOHOLIC FATTY LIVER DISEASE/; 24421 results.
2. CINAHL; exp LIVER FAILURE/ OR exp ACUTE-ON-CHRONIC LIVER FAILURE/; 1352 results.
3. CINAHL; exp LIVER CIRRHOSIS, ALCOHOLIC/ OR exp LIVER CIRRHOSIS/ OR exp HYPERTENSION, PORTAL/; 2989 results.
4. CINAHL; exp LIVER DISEASES/; 24421 results.
5. CINAHL; exp HEPATITIS, CHRONIC/ OR exp HEPATITIS, ALCOHOLIC/; 2020 results.
6. CINAHL; exp CARCINOMA, HEPATOCELLULAR/; 1909 results.
7. CINAHL; exp LIVER NEOPLASMS/; 4131 results.
8. CINAHL; exp LIVER NEOPLASMS/; 4131 results.
9. CINAHL; exp HEPATIC VEIN THROMBOSIS/; 83 results.
10. CINAHL; exp SINUSOIDAL OBSTRUCTION SYNDROME/; 8 results.
11. CINAHL; "liver disease*".ti,ab; 3899 results.
12. CINAHL; (liver AND disease*).ti,ab; 6986 results.
13. CINAHL; "liver fibro*".ti,ab; 377 results.
14. CINAHL; (liver AND fibro*).ti,ab; 1112 results.
15. CINAHL; "hepatic disease*".ti,ab; 140 results.
16. CINAHL; (hepatic AND disease*).ti,ab; 2138 results.
17. CINAHL; "hepatic fibro*".ti,ab; 206 results.
18. CINAHL; (hepatic AND fibro*).ti,ab; 502 results.
19. CINAHL; "end stage liver disease*".ti,ab; 380 results.
20. CINAHL; (end AND stage AND liver AND disease*).ti,ab; 511 results.
21. CINAHL; cirrho*.ti,ab; 2946 results.
22. CINAHL; "liver cirrho*".ti,ab; 701 results.
23. CINAHL; (liver AND cirrho*).ti,ab; 1954 results.
24. CINAHL; "chronic liver disease*".ti,ab; 699 results.
25. CINAHL; (chronic AND liver AND disease*).ti,ab; 1875 results.
26. CINAHL; "chronic liver failure".ti,ab; 48 results.
27. CINAHL; "chronic liver failure".ti,ab; 48 results.
28. CINAHL; "chronic liver failure".ti,ab; 48 results.
29. CINAHL; 1 OR 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 27; 29104 results.
30. CINAHL; exp ASCITES/ OR exp PERITONEOVENOUS SHUNT/; 581 results.
31. CINAHL; exp HYPERTENSION, PORTAL/; 852 results.
32. CINAHL; ascit*.ti,ab; 886 results.
33. CINAHL; "refractory ascit*".ti,ab; 35 results.
34. CINAHL; "resistant ascit*".ti,ab; 1 results.
35. CINAHL; (refractory AND ascit*).ti,ab; 59 results.
36. CINAHL; (resistant AND ascit*).ti,ab; 19 results.
37. CINAHL; exp PARACENTESIS/; 642 results.
38. CINAHL; paracentesis.ti,ab; 146 results.
39. CINAHL; "ascitic drain*".ti,ab; 4 results.
40. CINAHL; (ascitic AND drain*).ti,ab; 9 results.

41. CINAHL; "diuretic intolerant ascit*".ti,ab; 0 results.
42. CINAHL; (diuretic AND intolerant AND ascit*).ti,ab; 0 results.
43. CINAHL; 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41; 2436 results.
44. CINAHL; exp TERMINAL CARE/ OR exp PALLIATIVE CARE/ OR exp HOSPICE CARE/ OR exp TERMINALLY ILL PATIENTS/; 44213 results.
45. CINAHL; exp HOSPICE PATIENTS/ OR exp HOSPICE AND PALLIATIVE NURSING/ OR exp HOSPICES/ OR exp HOSPICE CARE/; 11507 results.
46. CINAHL; "palliative medicine".ti,ab; 808 results.
47. CINAHL; pallit*.ti,ab; 3 results.
48. CINAHL; terminal*.ti,ab; 10002 results.
49. CINAHL; "palliative care".ti,ab; 14571 results.
50. CINAHL; (palliative AND medicine).ti,ab; 1708 results.
51. CINAHL; (palliative AND care).ti,ab; 15934 results.
52. CINAHL; "terminal care".ti,ab; 446 results.
53. CINAHL; (terminal AND care).ti,ab; 2150 results.
54. CINAHL; "end of life care".ti,ab; 5159 results.
55. CINAHL; (end AND of AND life AND care).ti,ab; 9565 results.
56. CINAHL; hospice*.ti,ab; 8519 results.
57. CINAHL; (hospice AND care).ti,ab; 5475 results.
58. CINAHL; 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56; 58894 results.
59. CINAHL; 42 AND 57; 98 results.
60. CINAHL; 58 [Limit to: (Language English)]; 97 results.

MEDLINE search history OVID 3.12.15

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 exp Liver Diseases/ (545006)
2 exp Liver Diseases, Alcoholic/ (14638)
3 exp Fatty Liver/ or exp Liver Cirrhosis, Alcoholic/ or exp Liver Cirrhosis/ (110583)
4 exp Non-alcoholic Fatty Liver Disease/ (7100)
5 exp Liver Failure/ or exp End Stage Liver Disease/ or exp Liver Diseases/ (545006)
6 Liver Cirrhosis, Biliary/ (8196)
7 exp liver diseases/ or exp cholestasis, intrahepatic/ or exp fatty liver/ or exp focal nodular hyperplasia/ or exp hepatic insufficiency/ or exp hepatic veno-occlusive disease/ or exp hepatitis/ or exp hypertension, portal/ or exp liver cirrhosis/ or exp liver diseases, alcoholic/ or exp adenoma, liver cell/ or exp carcinoma, hepatocellular/ (545006)
8 "liver disease*".mp. (142278)
9 (liver and disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (328219)
10 "liver fibro*".mp. (12615)
11 (liver and fibro*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (55058)
12 "hepatic disease*".mp. (4732)
13 (hepatic and disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (105214)
14 "hepatic fibro*".mp. (8051)

15 (hepatic and fibro*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (24052)
16 "end stage liver disease*".mp. (8293)
17 cirrho*.mp. (124247)
18 "liver cirrho*".mp. (95536)
19 (liver and cirrho*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (116824)
20 exp liver failure/ or exp end stage liver disease/ or exp acute-on-chronic liver failure/ (23118)
21 "chronic liver disease*".mp. (17543)
22 (chronic and liver and disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (67045)
23 "chronic liver failure*".mp. (1408)
24 (chronic and liver and failure).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (13208)
25 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (716775)
26 exp Ascites/ (16895)
27 exp Ascitic Fluid/ or exp Portasystemic Shunt, Transjugular Intrahepatic/ (16164)
28 ascit*.mp. (60195)
29 exp Peritoneovenous Shunt/ or exp Hypertension, Portal/ (27718)
30 "refractory ascit*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1038)
31 "resistant ascit*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (132)
32 (refractory and ascit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1573)
33 (resistant and ascit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1604)
34 paracentesis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4176)
35 exp Paracentesis/ (11284)
36 "ascitic drain*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (17)
37 (ascitic and drain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (546)
38 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (97593)
39 25 and 38 (42329)
40 exp Terminal Care/ or exp Palliative Care/ (91139)
41 exp Palliative Medicine/ (183)
42 exp Terminally Ill/ (6670)
43 palliat*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (86230)

44 "palliative care".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (58365)
45 terminal*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (520830)
46 "end of life care".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (8097)
47 (end and of and life and care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2428)
48 "terminal care".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (27037)
49 (palliative and medicine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5167)
50 (palliative and care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (61284)
51 (terminal and care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (32202)
52 exp Hospices/ (5153)
53 exp Hospice Care/ (6047)
54 (hospice and care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (11816)
55 hospice*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (15165)
56 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 (618088)
57 "diuretic intolerant ascit*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)
58 "diuretic intolerant ascites".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)
59 38 and 56 (1856)
60 limit 59 to english language (1526)

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MEDLINE search history HDAS 7.12.15

Search Strategy:
1. Medline; exp END STAGE LIVER DISEASE/ OR exp LIVER DISEASES/ OR exp LIVER DISEASES, ALCOHOLIC/ OR exp NON-ALCOHOLIC FATTY LIVER DISEASE/; 319839 results.
2. Medline; exp LIVER CIRRHOSIS/ OR exp LIVER CIRRHOSIS, ALCOHOLIC/ OR exp LIVER CIRRHOSIS, BILIARY/; 53063 results.
3. Medline; exp HYPERTENSION, PORTAL/; 14977 results.
4. Medline; exp HEPATITIS/ OR exp HEPATITIS, CHRONIC/; 99587 results.

5. Medline; exp LIVER NEOPLASMS/; 100617 results.
6. Medline; exp LIVER DISEASES, ALCOHOLIC/ OR exp NON-ALCOHOLIC FATTY LIVER DISEASE/; 17531 results.
7. Medline; exp ACUTE-ON-CHRONIC LIVER FAILURE/ OR exp LIVER FAILURE/; 15675 results.
8. Medline; exp CARCINOMA, HEPATOCELLULAR/; 50161 results.
9. Medline; exp HEPATIC VENO-OCCLUSIVE DISEASE/; 896 results.
10. Medline; "liver disease*".ti,ab; 76711 results.
11. Medline; (liver AND disease*).ti,ab; 156900 results.
12. Medline; "liver fibro*".ti,ab; 10633 results.
13. Medline; (liver AND fibro*).ti,ab; 32718 results.
14. Medline; "hepatic disease*".ti,ab; 4165 results.
15. Medline; (hepatic AND disease*).ti,ab; 54094 results.
16. Medline; "hepatic fibro*".ti,ab; 6594 results.
17. Medline; (hepatic AND fibro*).ti,ab; 17614 results.
18. Medline; "end stage liver disease*".ti,ab; 6648 results.
19. Medline; cirrho*.ti,ab; 84012 results.
20. Medline; "liver cirrho*".ti,ab; 23422 results.
21. Medline; (liver AND cirrho*).ti,ab; 59195 results.
22. Medline; "chronic liver disease*".ti,ab; 15972 results.
23. Medline; (chronic AND liver AND disease*).ti,ab; 39759 results.
24. Medline; "chronic liver failure".ti,ab; 1268 results.
25. Medline; (chronic AND liver AND failure).ti,ab; 7811 results.
26. Medline; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25; 463415 results.
27. Medline; exp ASCITES/; 9530 results.
28. Medline; exp ASCITIC FLUID/; 5451 results.
29. Medline; exp PORTASYSTEMIC SHUNT, TRANSJUGULAR INTRAHEPATIC/; 1703 results.
30. Medline; exp HYPERTENSION, PORTAL/; 14977 results.
31. Medline; ascit*.ti,ab; 41507 results.
32. Medline; "refractory ascit*".ti,ab; 1006 results.
33. Medline; "resistant ascit*".ti,ab; 124 results.
34. Medline; (refractory AND ascit*).ti,ab; 1447 results.
35. Medline; (resistant AND ascit*).ti,ab; 1186 results.
36. Medline; exp PARACENTESIS/; 6231 results.
37. Medline; "ascitic drain*".ti,ab; 14 results.
38. Medline; (ascitic AND drain*).ti,ab; 187 results.
39. Medline; "diuretic intolerant ascit*".ti,ab; 0 results.
40. Medline; (diuretic AND intolerant AND ascit*).ti,ab; 0 results.
41. Medline; paracentesis.ti,ab; 2754 results.
42. Medline; 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41; 68607 results.
43. Medline; exp TERMINAL CARE/ OR exp TERMINALLY ILL/; 32287 results.
44. Medline; exp HOSPICE AND PALLIATIVE CARE NURSING/ OR exp PALLIATIVE CARE/ OR exp PALLIATIVE MEDICINE/; 33161 results.
45. Medline; "palliative medicine".ti,ab; 1953 results.
46. Medline; palliat*.ti,ab; 60133 results.
47. Medline; terminal*.ti,ab; 413176 results.
48. Medline; "palliative care".ti,ab; 19607 results.
49. Medline; (palliative AND medicine).ti,ab; 3290 results.
50. Medline; (palliative AND care).ti,ab; 23206 results.
51. Medline; "terminal care".ti,ab; 1433 results.
52. Medline; (terminal AND care).ti,ab; 6107 results.

53. Medline; "end of life care".ti,ab; 6917 results.
54. Medline; (end AND of AND life AND care).ti,ab; 16148 results.
55. Medline; exp HOSPICE CARE/ OR exp HOSPICES/; 6419 results.
56. Medline; (hospice AND care).ti,ab; 6899 results.
57. Medline; hospice*.ti,ab; 10520 results.
58. Medline; 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57; 513482 results.
59. Medline; 42 AND 58; 1450 results.
60. Medline; 59 [Limit to: (Language English)]; 1229 results.

EMBASE search history OVID 7.12.15

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 exp liver disease/ (545006)
2 exp liver cirrhosis/ or exp end stage liver disease/ or exp liver disease/ or exp liver failure/ (545006)
3 exp alcohol liver disease/ (0)
4 exp alcohol liver cirrhosis/ or exp nonalcoholic fatty liver/ (7100)
5 exp chronic liver disease/ (0)
6 exp chronic liver failure/ (1938)
7 exp hepatitis/ (162621)
8 exp biliary cirrhosis/ (8196)
9 exp portal hypertension/ (26918)
10 exp liver cell carcinoma/ (76654)
11 exp liver venoocclusive disease/ (0)
12 "liver disease*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (142278)
13 (liver and disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (328219)
14 "liver fibro*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (12615)
15 (liver and fibro*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (55058)
16 "hepatic disease*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4732)
17 (hepatic and disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (105214)
18 "hepatic fibro*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (8051)
19 (hepatic and fibro*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (24052)

20 "end stage liver disease*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (8293)
21 cirrho*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (124247)
22 "liver cirrho*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (95536)
23 (liver and cirrho*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (116824)
24 exp acute on chronic liver failure/ (219)
25 "chronic liver disease*".mp. (17543)
26 (chronic and liver and disease*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (67045)
27 "chronic liver failure*".mp. (1408)
28 (chronic and liver and failure).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (13208)
29 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (716775)
30 exp ascites/ or exp ascites fluid/ (16895)
31 exp transjugular intrahepatic portosystemic shunt/ (0)
32 exp peritoneum vein shunt/ (0)
33 exp portal hypertension/ (26918)
34 ascit*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (60195)
35 "refractory ascit*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1038)
36 "resistant ascit*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (132)
37 (refractory and ascit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1573)
38 (resistant and ascit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1604)
39 exp paracentesis/ (11284)
40 paracentesis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (4176)
41 "ascitic drain*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (17)
42 (ascitic and drain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (546)
43 "diuretic intolerant ascit*".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)

44 (diuretic and intolerant and ascit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)
45 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (96612)
46 exp terminal care/ (49863)
47 exp palliative therapy/ (50577)
48 exp terminally ill patient/ (0)
49 "palliative medicine".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1754)
50 palliat*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (86230)
51 terminal*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (520830)
52 "palliative care".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (58365)
53 "end of life care".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (8097)
54 (end and of and life and care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2428)
55 (palliative and medicine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (5167)
56 (palliative and care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (61284)
57 "terminal care".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (27037)
58 (terminal and care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (32202)
59 exp hospice care/ or exp hospice/ or exp hospice patient/ (10796)
60 (hospice and care).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (11816)
61 hospice*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (15165)
62 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 (618088)
63 45 and 62 (1852)
64 limit 63 to english language (1522)

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EMBASE search history HDAS 4.12.15

Search Strategy:
1. EMBASE; exp LIVER DISEASE/; 839164 results.
2. EMBASE; exp *END STAGE LIVER DISEASE/ OR exp LIVER FAILURE/ OR exp LIVER DISEASE/ OR exp LIVER CIRRHOSIS/; 839164 results.
3. EMBASE; exp ALCOHOL LIVER DISEASE/; 21258 results.
4. EMBASE; exp NONALCOHOLIC FATTY LIVER/; 25835 results.
5. EMBASE; exp CHRONIC LIVER DISEASE/; 19681 results.
6. EMBASE; exp LIVER FAILURE/; 62817 results.
7. EMBASE; exp CHRONIC LIVER FAILURE/ OR exp HEPATITIS/; 262163 results.
8. EMBASE; exp BILIARY CIRRHOSIS/; 4423 results.
9. EMBASE; exp PORTAL HYPERTENSION/ OR exp LIVER CELL CARCINOMA/; 152653 results.
10. EMBASE; exp LIVER VENOOCCLUSIVE DISEASE/; 1615 results.
11. EMBASE; "liver disease*".ti,ab; 113282 results.
12. EMBASE; (liver AND disease*).ti,ab; 238904 results.
13. EMBASE; "liver fibro*".ti,ab; 18549 results.
14. EMBASE; (liver AND fibro*).ti,ab; 61654 results.
15. EMBASE; "hepatic disease*".ti,ab; 5555 results.
16. EMBASE; (hepatic AND disease*).ti,ab; 85054 results.
17. EMBASE; "hepatic fibro*".ti,ab; 10673 results.
18. EMBASE; (hepatic AND fibro*).ti,ab; 30726 results.
19. EMBASE; "end stage liver disease*".ti,ab; 10697 results.
20. EMBASE; cirrho*.ti,ab; 119649 results.
21. EMBASE; "liver cirrho*".ti,ab; 32466 results.
22. EMBASE; (liver AND cirrho*).ti,ab; 88127 results.
23. EMBASE; exp ACUTE ON CHRONIC LIVER FAILURE/; 1597 results.
24. EMBASE; "chronic liver disease*".ti,ab; 23575 results.
25. EMBASE; (chronic AND liver AND disease*).ti,ab; 63603 results.
26. EMBASE; "chronic liver failure*".ti,ab; 2460 results.
27. EMBASE; (chronic AND liver AND failure).ti,ab; 14161 results.
28. EMBASE; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27; 939418 results.
29. EMBASE; exp ASCITES/ OR exp ASCITES FLUID/; 48656 results.
30. EMBASE; exp TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT/; 2817 results.
31. EMBASE; exp PERITONEUM VEIN SHUNT/; 983 results.
32. EMBASE; exp PORTAL HYPERTENSION/; 29057 results.
33. EMBASE; ascit*.ti,ab; 51791 results.
34. EMBASE; "refractory ascit*".ti,ab; 1645 results.
35. EMBASE; "resistant ascit*".ti,ab; 162 results.
36. EMBASE; (refractory AND ascit*).ti,ab; 2375 results.
37. EMBASE; exp PARACENTESIS/; 5907 results.
38. EMBASE; paracentesis.ti,ab; 4047 results.
39. EMBASE; "ascitic drain*".ti,ab; 43 results.
40. EMBASE; (ascitic AND drain*).ti,ab; 329 results.
41. EMBASE; "diuretic intolerant ascit*".ti,ab; 1 results.
42. EMBASE; (diuretic AND intolerant AND ascit*).ti,ab; 5 results.
43. EMBASE; (resistant AND ascit*).ti,ab; 1618 results.
44. EMBASE; 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43; 97589 results.
45. EMBASE; exp TERMINAL CARE/; 57553 results.
46. EMBASE; exp PALLIATIVE THERAPY/; 92669 results.
47. EMBASE; exp TERMINALLY ILL PATIENT/; 8818 results.
48. EMBASE; "palliative medicine".ti,ab; 2481 results.

49. EMBASE; palliat*.ti,ab; 87184 results.
50. EMBASE; terminal*.ti,ab; 461762 results.
51. EMBASE; "palliative care".ti,ab; 29615 results.
52. EMBASE; "end of life care".ti,ab; 9076 results.
53. EMBASE; (end AND of AND life AND care).ti,ab; 24273 results.
54. EMBASE; (palliative AND medicine).ti,ab; 5038 results.
55. EMBASE; (palliative AND care).ti,ab; 35589 results.
56. EMBASE; "terminal care".ti,ab; 1677 results.
57. EMBASE; (terminal AND care).ti,ab; 9093 results.
58. EMBASE; exp HOSPICE/ OR exp HOSPICE CARE/ OR exp HOSPICE PATIENT/; 18530 results.
59. EMBASE; (hospice AND care).ti,ab; 9977 results.
60. EMBASE; hospice*.ti,ab; 14015 results.
61. EMBASE; 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60; 629212 results.
62. EMBASE; 44 AND 61; 2866 results.
63. EMBASE; 62 [Limit to: (Languages English)]; 2535 results.

Appendix 2: Research Ethics Committee approval

NHS
Health Research Authority
NRES Committee South Central - Hampshire A
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1381
Fax:0117 342 0445

17 June 2015

Dr Sumita Verma
Senior Lecturer, Honorary Consultant Hepatologist
University of Sussex
Brighton and Sussex Medical School
North South Road
Falmer, Brighton
BN1 9PX

Dear Dr Verma

Study title:	**Palliative long-term abdominal drains versus repeated drainage in individuals with untreatable ascites due to advanced cirrhosis : a feasibility randomised controlled trial**
REC reference:	**15/SC/0257**
Protocol number:	**173423**
IRAS project ID:	**173423**

Thank you for your letter, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Mrs Maxine Knight, nrescommittee.southcentral-hampshirea@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above

research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [REC cover letter]	1	01 April 2015
GP/consultant information sheets or letters [GP letter]	0.4	01 April 2015
IRAS Checklist XML [Checklist_18042015]		18 April 2015
IRAS Checklist XML [Checklist_13062015]		13 June 2015
Letter from sponsor		
Non-validated questionnaire [hospital service use questionnaire]	0.4	01 April 2015
Other [ED-5D validated questionnaire]	1	01 April 2015
Other [ZBI-12 validated carer burden questionnaire]	1	01 April 2015
Other [AUDIT validated questionnaire]	1	01 April 2015
Other [AHCR validated questionnaire]	0.4	01 April 2015
Other [child pugh score]	1	01 April 2015
Other [capacity o consent checklist]	0.4	01 April 2015
Other [ascites drainage diary]	0.4	01 April 2015
Other [Rocket Medical patient booklet]	1	01 April 2015
Other [Consultee information and declaration]		01 April 2015
Other [Response 1 Ethics Committee]	1	13 June 2015
Other [PIS main]	0.5	13 June 2015
Other [PIS qualitative]	0.5	13 June 2015
Other [PIS carers]	0.5	13 June 2015
Other [SFLDQOL revised]	0.5	13 June 2015
Other [SFLDQOL validation]	1	13 June 2015
Other [SFLDQOL scoring algorithm]	1	13 June 2015
Other [Protocol]	0.5	13 June 2015
Other [Interview schedule]	0.5	13 June 2015
Other [Rocket Medical Discharge letter]	0.5	13 June 2015
REC Application Form [REC_Form_14042015]		14 April 2015

Referee's report or other scientific critique report [letter from funder]	1	01 April 2015
Summary CV for Chief Investigator (CI) [2 page CV]	1	01 April 2015
Validated questionnaire [IPOS questionnaire]	1	01 April 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

15/SC/0257	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

Dr Simon Kolstoe
Chair

Email:nrescommittee.southcentral-hampshirea@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Scott Harfield, Brighton and Sussex Univerisity Hospitals*

Appendix 3: Patient participant information sheet and consent form

REDUCe STUDY
REpeated Drainage in Untreatable Cirrhosis

Palliative Long-term Abdominal Drains
versus
Repeated Drainage for Ascites due to Cirrhosis

PATIENT INFORMATION SHEET

REC ref no: 15/SC/0257

We would like to invite you to take part in a research study. Before you decide whether you would like to take part, it is important you understand what the research is about. Please read this information sheet carefully.
Please feel free to ask us if there is anything that is not clear or if you would like more information.

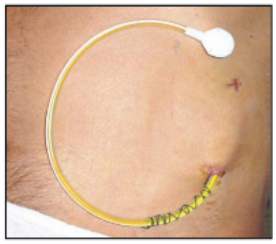
1. Why have I been invited?
You have a liver condition called cirrhosis that has been complicated with untreatable fluid in the stomach (ascites). A liver transplant is not possible.

2. What is the purpose of the research study?
The purpose of this study is to assess a new method to treat untreatable ascites in individuals with advanced cirrhosis.

The usual care of untreatable ascites involves placing a tube called a drain through the skin of the stomach under local anaesthetic. The drain stays in for 4-6 hours and the fluid is collected in a bag connected to the drain. About 10-15 pints can be drained at a time. The fluid quickly builds up again. This means that people with advanced cirrhosis have to come to hospital every one to two weeks to have the ascites drained. Every time this is done there are risks like bleeding, pain and infection.

When ascites is caused by certain other palliative conditions, it is possible to put a drain in the stomach that stays there permanently. This is called a long-term drain (see photograph below). When the fluid builds up, a bag is connected the drain to remove the ascites. 2-4 pints can be removed several times a week as needed. District nurses (and family members if trained) can do this safely, so patients do not have to come to hospital.

Until now, long-term drains have not been used in patients with cirrhosis. This study has been designed to help us understand if long –term drains are better than standard of care in individuals with cirrhosis. This will determine if we need to run a larger study



3. Do I have to take part?

Photograph showing a permanent drain coming out of the stomach.

No, your participation is voluntary. You can also withdraw from the study at any time without giving a reason. Refusal to participate will not affect your future routine medical care.

If you decide to participate in this study, we will ask you to let us know who you would like us to contact in the event of you losing capacity during the study. This person is called your consultee. If you lose capacity during the study, we would approach your consultee and ask them to act in your best interests to decide whether you continue with the study. If they don't think it is in your best interests to continue, then we would keep the data we have collected so far but not collect any further data from you.

If you do not have a consultee we will ask your doctor at the hospital, who is not part of the research team, to act in your best interests and decide whether you should continue in the study.

4. What will happen to me if I take part?

You will be seen by the Research Doctor or Nurse. They will answer any questions or concerns you may have. Within two to three days the Research Doctor will meet you again. If you agree to participate you will be asked to sign a consent form. If you are willing, we will also give your contact phone number to an interview researcher to talk to you later about your experience of ascites draining in more detail. You do not have to agree to this, but it will help us understand more about your views. A separate information sheet and consent form will be provided for this.

Then:

a. The Research Doctor will ask some brief questions about your liver condition, and examine you, after which you will undergo routine clinical tests. This will include taking a small sample of ascitic fluid (around 4 teaspoons, 20ml) to ensure there is no infection present. If infection is found, you will be given antibiotic treatment for five days. We will proceed with the study once this infection has resolved. About four teaspoons (20ml) of blood will also be taken for research purposes (see point 14 below).

b. You will be asked to complete five questionnaires (you will be shown these before you sign the consent form so you know what they look like). These questionnaires will assess your symptoms, quality of life and use of health services and social care professionals (e.g. GP, hospital appointments, district nurses). These will take under an hour to complete. If you wish the Research Doctor or nurse can help you to complete the questionnaires. Additionally they can also be completed with your carer/people you live with.

After this, a computer programme will be used to randomise (like flipping a coin) participants into two groups: routine clinical care and long-term drain. There will be an equal chance of being allocated to either group but neither you nor your doctor will be able to choose which treatment you have.

Depending on which group you are in, slightly different things will occur.

If you are in Group 1 Intervention (long-term drain):

a. At the visit for drain insertion, the Research Doctor will ask some brief questions about your health, and your alcohol and drug use, your liver condition, and examine you, after which you

will undergo routine clinical tests,. This will include taking a small sample of blood (about 4 teaspoons) and ascitic fluid (around 4 teaspoons).

b. The Research Doctor under supervision of a Consultant will insert the long-term drain into you in a side room in the hospital. This will be done using local anaesthetic and ultrasound to ensure that it is put in the best site for you with minimal pain and discomfort. The Research Doctor will explain to you how to look after your drain. As part of routine care, you will receive an antibiotic called ciprofloxacin, one tablet a day, to reduce the risk of infection in the ascites. You can go home later that day and you will be to continue with your usual daily activities.

c. The Research Doctor will arrange for you to have support at home, from a community nurse to drain fluid through the drain when needed. This will be 2-3 times a week and takes around 30 minutes for each visit. Around 2-4 pints may be drained at a time and will be painless. Bags to drain the fluid into will be provided to you. Your carer, if they wish, can take over draining the ascites instead of the community nurse. They will need basic training from the Research Doctor and community nurses first. Whenever your ascites is drained, this needs to be written down in a booklet you will be provided with and the Research Doctor will collect this information from you regularly.

a. The Research Doctor will visit you every two weeks at home for up to 12 weeks. Before each visit s/he will call you to confirm the date and time. Each visit will take up to one hour. She will take about four teaspoons (20 ml) of blood for routine clinical testing and collect the information about amount of ascites drained and if there are any concerns about the drain. She will ask your help in filling in the same three to five questionnaires again at each visit. If you wish the Research Doctor or nurse can help you to complete the questionnaires. Additionally, if you are too unwell, they can also be completed by your carer. If you find it easier, the questionnaires can be answered over the phone within three days of the doctor visit, just let the research doctor know.

If you are in Group 2 Routine Clinical Care (drain in hospital when needed);

a. You will continue to receive current routine clinical care involving hospital visits to drain your ascites and routine bloods every 7-14 days. Your GP can telephone the hospital to arrange this, or you will be able to come yourself. You will receive an antibiotic called ciprofloxacin, one tablet once a day, to reduce risk of infection in the ascitic fluid. The research doctor will collect information about the amount of fluid drained and blood tests from your medical records

b. The Research Doctor will visit you every two weeks at home for up to 12 weeks. Before each visit she will call you to confirm the date and time. Each visit will take up to one hour. She will ask your help in filling in the same three to five questionnaires again at each visit. If you wish the Research Doctor or nurse can help you to complete the questionnaires. Additionally, if you are too unwell, they can also be completed by your carer. If you find it easier, the questionnaires can be answered over the phone within three days of the doctor visit, just let the research doctor know. If the questionnaire assessments coincide with your hospital visits, you can complete them in hospital.

5. What are the side effects, risks and implications of taking part in the study?
Participating in the study requires you to spend time every two weeks with the Research Doctor for up to 12 weeks either face to face and/or over the phone. It is possible that talking about your health may

raise topics that you find upsetting or difficult. Please let us know if this happens so we can provide additional support and advice. The researchers will be well experienced in dealing with such situations. For any out of hours emergency we encourage you to contact your GP who will arrange hospitalisation if needed or to go straight to your nearest A&E department. If you decide to withdraw from the study, and wish for the long-term drain to be removed this can be done under local anaesthetic.

Particular risks for Group 1 Intervention (the permanent long-term drain group):
The long-term drains have been extensively used in ascites due to other palliative conditions. They are considered safe. But, as with any drain that remains in the body, potential complications could occur such as:

- Pain
- Inability to put the drain in
- Leaking of fluid from the drain
- Bleeding
- Drain blockage
- Infection of the skin where the drain is
- Infection of the ascites fluid (peritonitis)

The risks of these complications are low (fewer than 4 in 100 people will experience these complications). Since you will receive antibiotics during the study, the risk of infection, specifically peritonitis is likely to be even lower.

Experienced doctors will put in the drains using local anaesthetic and ultrasound to ensure that the drain is inserted in the best site for you with minimal pain and discomfort. You will also be closely monitored by the community nursing teams and the Research Doctor during home visits, so if any complications do occur, they will be promptly identified and acted upon.

Since this is only preliminary work, it is very unlikely that the research blood results will have any significant implications for you. In the unlikely event that they do, this will be discussed both with you and your GP.

6. What are the possible benefits of taking part?
There is no guarantee that you will benefit directly from taking part in this research study. Information collected about you and others taking part in this study will help us work out if a much larger study should be done.

If additional information about the problems your cirrhosis is giving you is highlighted in the questionnaires, this could also be directly helpful in your treatment and support. We would encourage you to allow us to tell others involved in your treatment to help tailor your care.

7. What happens when the research study stops?
After 12 weeks the study will end and you will continue to receive routine clinical care by your usual hospital consultant and GP. If you have a permanent long-term drain you will have the option to either carry on using it, or have it removed. If you elect to continue using the drains you will be closely monitored by your hospital consultant.

8. What if there is a problem?

Any concern about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Advice on how to raise a concern or complaint is detailed below in section 12.

9. Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. All information that is collected about you during the study will be kept strictly confidential and will be stored in a secure manner compliant with the Data Protection Act. When you join the study, a unique study number will be used to identify your information for the study rather than your name and address being used.

Your medical notes will be seen by authorised members of the research team at your hospital, so that they can collect information needed for the research study, and also to check that it is correct.

However, if you tell us about serious risk of harm to yourself or others we will need to break confidentiality, which means letting your GP know.

10. What if relevant new information becomes available?
Sometimes during the course of a research project, new information becomes available about the equipment being studied. If this happens, your Research Doctor will tell you about it and discuss whether you want to, or should, continue in the study. If you decide not to carry on, your Research Doctor will make arrangements for your standard care to continue. If you decide to continue in the study, you will be given an updated patient information sheet to read and asked to sign an updated consent form.

11. What will happen if I don't want to carry on with the study?
Should you wish, you can withdraw from the study at **any** time, without giving a reason and without this affecting your future routine clinical care. If you have been fitted with a long-term drain you can choose to keep this in; otherwise, if you prefer, you can have it removed under local anaesthetic. In this case you will go back to attending hospital every one-two weeks to have the ascites drained, under local anaesthetic.

12. Complaints
If you have a concern about any aspect of this study, you should ask to speak with the research doctor or nurse at your local hospital. The hospital Patient Advice and Liaison Service (PALS) - 01273 694511 can be contacted if you remain unhappy. If you wish to complain formally, you can do this through the NHS Complaints Procedure. Details of this can be obtained from the PALS team.

13. Will my GP be informed?
With your agreement, we will inform your GP if you decide to take part in this study.

14. What will happen to any samples I give?
All routine blood samples you give will be used at the time and the reason for the test explained. Research blood samples will be labelled with your study number and no other identifiers will be used. They will be stored and tested later in future ethically approved research, for proteins and chemical associated with advanced cirrhosis and in addition may also include genetic testing. At the end of the study all research blood samples will be destroyed in accordance with the hospital procedures.

15. What will happen to the results of the research study?

The results of the research study will be written up and published in a scientific journal and discussed at medical conferences. Your personal information will not be identifiable in any way. If you/your carer would like to be sent or emailed a copy, please give us your contact details.

16. Who is organising the research?
The research is being organised by a leading liver disease specialist at Brighton and Sussex University Hospital NHS Trust and Brighton & Sussex Medical School as well as collaboration with other hospitals, community trusts and palliative care services in Sussex. Your doctor will not receive any personal financial payment if you take part.

The study is being funded by a Research for Patient Benefit grant from the Department of Health.

17. Who has reviewed the study?
To protect your interests, all research in the NHS is looked at by an independent group of people, called a Research Ethics Committee. This study has been reviewed and approved by the Hampshire A NRES Committee South Central

18. Contact for further information
If you or your relatives have any questions or concerns about the study, now or in the future, please call:
Please insert principal investigator and research fellow details here:
Principal Investigator
Name:
Address:
Telephone:
Email:

Research Fellow
Name: Dr Lucia Macken
Address: Clinical Investigation and Research Unit (CIRU)
Level 10, The Royal Alexander Hospital, (part of The Royal Sussex County Hospital)
Eastern Road
Brighton
BN2 5BE
Telephone: via CIRU reception, direct dial 01273 664437 or via hospital switchboard on 01273 696955 ext. 3522

Thank you for taking the time to read this information sheet and for considering taking part in this research study

Consent Form

REDUCe Study

Consent Form Main Study
REC Ref no: 15/SC/0257

	Please initial box
I confirm that I have read and understand the information sheet version ____ for the above study-dated __/___/____. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected	☐
I understand that relevant sections of my notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission to these individuals to have access to my records	☐
I consent to giving four teaspoons of blood (20 ml) for future ethically approved research. I understand that the blood will be stored in an anonymised manner. I understand that analysis of my blood samples may include genetic analysis.	☐
I agree to my GP being informed of my involvement in this study	☐
I agree to take part in this study	☐

_____ _____ _____
Name of Patient Date Signature

_____	_____	_____
Name of Person Receiving Consent	Date	Signature

Nominating a Consultee

I understand that during the course of this study it may become necessary for the research team to contact someone to represent my best interests (known as a consultee). In my opinion I would nominate the following as the person best able to do this:

Name:……

Relationship to participant: ……

(This individual would normally be a 'personal consultee' i.e. next of kin, closest relative or friend. If the nominated individual is NOT a 'personal consultee' but a 'nominated consultee' i.e. a paid carer, please provide information where possible to explain this choice.)

……..

……..

Address of Consultee:……

……..

Contact number of Consultee: ……

Appendix 4: Capacity to give consent checklist

REDUCe Study

Title of study: Palliative long-term abdominal drains versus repeated drainage in individuals with untreatable ascites due to advanced cirrhosis: a feasibility randomised controlled trial

ASSESSING CAPACITY TO CONSENT- CHECKLIST FOR RESEARCHERS RECEIVING CONSENT FOR THE REDUCe Study

At ***this specific time*** of gaining consent for this person is there any evidence that:

- The person does **not** have a general understanding of what decision they need to make and why they need to make it?
- The person does **not** have a general understanding of the likely consequences of making this decision?
- The person is **unable** to understand, retain, use or weigh up the information relevant to this decision?

Appendix 5: Study standard operating procedures (SOPs)

Standard Operating Procedure (SOP) Manual for conduct of the study: Palliative long-term abdominal drains versus repeated drainage in individuals with untreatable ascites due to advanced cirrhosis: a feasibility randomised controlled trial

Study Acronym: REDUCe (Repeated Drainage Untreatable Cirrhosis)

REDUCe study_SOP_manual Version 4.0 LM 23.01.2018

Localise with hospital name site document

Owners: Dr Lucia Macken Clinical Research Fellow, Dr Max Cooper co-PI, Justine Boles Senior Trial Manager Jean Timeyin Trial Manager

Add name of local PI and Co PI

- **Dr Sumita Verma, Chief Investigator (CI)**

Senior Lecturer in Medicine, Brighton and Sussex Medical School (BSMS), Honorary Consultant Hepatology, Brighton and Sussex University Hospital (BSUH) and Kings College London (KCL)
Phone: 01273 877890
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Email: s.verma@bsms.ac.uk

- **Dr Louise Mason, Co-Investigator**

Consultant in Palliative Medicine, BSUH
Phone: 01273 523021
Email: louise.mason@bsuh.nhs.uk

- **Dr Catherine Evans, Co-Investigator**

NIHR Clinical Lecturer in Palliative Care, Cicely Saunders Institute, KCL
Phone: 0207 848 5579
Email: Catherine.evans@kcl.ac.uk

- **Professor Heather Gage, Co-Investigator**

Coordinator of Health Research Group, School of Economics, University of Surrey
Phone: 01483 68 6948
Email: h.gage@surrey.ac.uk

- **Dr Mark Austin, Co-Investigator**

Consultant Gastroenterologist and Hepatologist, BSUH
Phone: 01273 696955
Email: mark.austin@bsuh.nhs.uk

- **Dr Nick Parnell, Co-Investigator**

Consultant Gastroenterologist and Hepatologist, BSUH
Phone: 01273 696955
Email: nick.parnell@bsuh.nhs.uk

- **Dr Max Cooper, Co-Investigator**

Senior Lecturer in General Practice, BSMS
Phone: 01273 643768
Email: m.cooper@bsms.ac.uk

- **Dr Lucia Macken, Research Fellow, BSUH**

Gastroenterology Registrar
Email: lucia.macken@bsuh.nhs.uk

- **Jean Timeyin**

Trial Manager
Brighton & Sussex Clinical Trial Unit (BSCTU)
Phone: 01273 696955 ext. 7447
Email: REDUCE.BSUH@bsuh.nhs.uk
cc. jean.timeyin@bsuh.nhs.uk

- **Dr Stephen Bremner, Trial Statistician**

Senior Lecturer in Medical Statistics, BSMS
Will oversee the statistical analysis
Phone 01273 644126

- **Names and contact information of Sponsor**

Mr Scott Harfield
R & D Manager
Research & Development
Brighton and Sussex University Hospital
Brighton, BN2 1HQ
Phone 01273 696955 ext. 7497

Index

SOP Code	Title	Version	Date
REDUCE-SOP 01	Identifying, pre-screening, gaining consent, screening and randomising potential participants	4.0	23-Jan-18
REDUCE SOP 02	Qualitative component and interviews	3.0	23-Jan-18
REDUCE SOP 03	Recruitment of informal carers	3.0	23-Jan-18
REDUCE SOP 04	Timeline/overview post randomisation	1.0	23-Oct-15
REDUCE SOP 05	Randomisation / Baseline visit	4.0	23 Jan 18
REDUCE SOP 06	Documentation in healthcare records	1.0	23-Oct-15
REDUCE SOP 07	Drain insertion	4.0	23 Jan 18
REDUCE SOP 08	Study visits	2.0	23-Jan-18
REDUCE SOP 09	Distress Protocol	2.0	23-Jan 18
REDUCE SOP 10	Study Overview Community Nurses (Integrated Primary Care Team Nurses)	3.0	23 Jan 18
REDUCE SOP 11	Advice for Out of hours GP teams	2.0	23-Jan 18
REDUCE SOP 12	On call medical registrars / medical on call team	2.0	23-Jan 18
REDUCE SOP 13	Study withdrawal / end of study period for participant	2.0	23Jan -18
REDUCE SOP 14	SAE and SUSAR reporting procedure	3.0	23 Jan 18

Purpose

The purpose of this document is to outline standard operating procedures (SOPs) for the conduct of the REDUCe trial.

This document is to complement BUT NOT REPLACE the trial protocol **v6.1 – 19 Jan 2018** which is the definitive guide to trial procedures. It will serve as a practical guide for researchers collaborating in the study as well as to other healthcare professionals who may come into contact with study participants.

Trial aims

Our ultimate aim is to improve end of life care of individuals with advanced cirrhosis and untreatable (refractory) ascites by conducting a randomised controlled trial (RCT) comparing palliative long-term abdominal drains (LTAD) with the current standard of care - repeated large volume paracentesis (LVP). However, prior to conducting this trial, we need to assess if LTAD in the community is acceptable and feasible and remove uncertainties in the research design of the definitive trial. Hence this current research proposal is for a feasibility RCT to inform the development of a phase III RCT.
(LTAD) (provided by Rocket Medical), is currently commonly used in malignant ascites.

Trial setting

The REDUCe trial will be conducted at the Brighton and Sussex University Hospital (BSUH) Trust, which includes the Royal Sussex County Hospital (RSCH), Princess Royal Hospital (PRH); Worthing Hospital (part of Western Sussex Hospitals NHS Foundation Trust, WSHT) and Plymouth Hospitals NHS Trust. The trial will be expanded to include Blackpool Victoria Hospital and Southampton Hospital after obtaining regulatory approvals. The trial will run over three years from October 2015-October 2018. Study recruitment is planned to open in October 2015 and the last planned patient recruitment will be by 1st June 2018.

Patients will be identified by the medical teams across all in-patient and out-patient settings at the sites conducting the research. Once identified, the research team will follow standard ethical principles in terms of pre-screening, approaching potentially eligible patients and gaining consent from patients willing to participate. There are two arms in the study; participants will be randomised to one arm. The two arms are comparing the current standard of care, i.e. repeated LVP, with the intervention i.e. LTAD. Participants in the LTAD arm will have their ascites managed in the community via community nurse visits localise to facilitate regular drainage of small volumes of ascites, their care is otherwise as standard.

Participants will be followed up to a maximum of three months, after which time those in the LTAD arm will have the option to have the drain removed by the research team in hospital or to leave it in situ. If they choose to continue with the LTAD, this will then continue under the supervision of a consultant Gastroenterologist/Hepatologist at their recruiting hospital.

REDUCE SOP 01 - Identifying, pre-screening, gaining consent and screening potential participants
V4.0 – 23 Jan 18

Identification and pre-screening

Potentially eligible patients will be identified by the medical teams across all in-patient and out-patient settings at the sites conducting the research. Medical teams identifying potentially eligible patients will largely be the Gastroenterology/Hepatology teams as it will be they who will make the decision on eligibility for liver transplantation. The medical teams will be made aware of the study through multidisciplinary teams meetings (MDTs) and the trial flyer.

The medical teams from all sites will alert the Principle Investigator, clinical research fellow or research nurse of potentially eligible patients using the following contact details:

Principle Investigator: **Mobile (localise)**

Research Nurse: Localise

Research Fellow: study mobile number: Localise

The research team will pre-screen healthcare records and recent blood results of identified patients, if potentially eligible in accordance with inclusion and exclusion criteria (see below) the patient will then be approached by the Principle Investigator, clinical research fellow or the research nurse to discuss participation in the study. Potential participants expressing an interest will be given the following Patient Information Sheets when initially approached by the Principle Investigator, research fellow or research nurse, or a member of the research study team after being identified as eligible to participate in the trial.

1. **REDUCe PIS Patient Main version 4.0 – 13 Oct 2017**
2. **REDUCe PIS Qualitative Interviews version 1.0 - 08 Sept 2015**
3. **REDUCe PIS Quality of Life - Carers Questionnaire version 3.0 – 22 Sept 2016**

At this point the mode of contact for the next discussion will be decided upon.

Inclusion criteria

- Age ≥18 years

- Untreatable (refractory) ascites defined as:
    - Ascites that is unresponsive to fluid and sodium restriction and high dose

diuretic treatment (spironolactone 400 mg and or furosemide 160 mg) and/or intolerance of diuretics.
    - Recurs rapidly after LVP (need for one or more LVP per month)

- Child Pugh Score >9 unless specifically decided by the medical team that they are to receive only palliative treatment. If <9, participant is considered palliative by medical team

- Registered with a GP Localise to your catchment area

- Ability to speak, read and understand English

- Capacity to give informed consent as defined using the Capacity to Consent Checklist

- Provide signed, informed consent prior to any study specific procedures

Exclusion criteria

- Either loculated or chylous ascites

- Presence of > grade 1 hepatic encephalopathy (specified by West Haven Criteria)

- Evidence of active infection that in the investigator's opinion would preclude insertion of LTAD (for example, bacterial peritonitis) – such patients would need to receive appropriate treatment and could then be reconsidered

- A candidate for liver transplantation

- Psychosocial issues which, in the opinion of the medical team, will preclude study participation

Potential participants will not be excluded if they are already participating in another ongoing study as long as their researchers are confident that participation in the current study will be logistically feasible and not too onerous for participants. If this case arose the sponsor will be informed of the other study prior to approaching/gaining consent from potential participants.

The Principle Investigator/ research fellow/nurse will contact the potential participant at least 48 hours from initial discussion and receipt of the PIS, depending on previously arranged contact plans which, since this is a complex study involving a vulnerable end of life cohort, could either be in an in-patient or out-patient setting or in a Clinical Investigation Research Unit /department.. This will be to discuss any further questions and confirm if the patient is willing to participate. If the patient would prefer this to be a telephone conversation this will be at the patient's request

and will have been arranged at the initial meeting. If this is the case, arrangements will be made to gain face to face consent at a later date if the patient is willing to participate in the study.

If the patient confirms they would like to take part in the study their written consent will be gained by Principle Investigator or clinical research fellow. The consent process will be recorded in the healthcare records as source documentation. The version/date of the consent form should be noted. The outcome of screening of potential participants will also be recorded in the Screening and Enrolment log by the research team. Any research team member who approaches a potential participant (whether or not they agree to participate) regarding the study must document this event in the healthcare records and in the REDUCe Screening and Enrolment log. This will allow investigation of the acceptability of the intervention in the study. The healthcare records of patients recruited into the study will be labelled by the research nurse as per the usual hospital procedures pertaining to research participants.

Consent process participants / carers / healthcare professionals

The consent process will include a capacity assessment which will also be performed at each subsequent trial related visit, using the REDUCe Capacity to consent checklist **v1.0 - 08 Sept 2015**.Consent will be informed and written consent sought/gained by the clinical research fellow
/Principle investigator (PI) to be part of the trial, including the embedded qualitative study.
This will include gaining consent for a sample of research blood to be taken at baseline,stored in the research laboratory Localise **(REDUCE Study laboratory Manual v.1.2)**for the duration of the trial, as well as for contact details to be conveyed to the qualitative researcher (See Qualitative component SOP 02).

Participants will also be asked to provide details of a Consultee to act in their best interests with regards to the trial should they lose capacity regarding continuing in the study during the duration of the planned follow up period. These details should be completed in the Consultee information sheet **version 0.4, April 2015** and the Consultee declaration form should be completed by the consultee and signed by the researcher. 3 copies should be taken – 1 for the medical notes, 1 for the consultee and 1 for the patient file.

If they are unable to nominate a Consultee, their usual medical consultant, independent from the research team, will be consulted to decide whether it is in their best interests to continue in the study. If this is the case, this should be documented in the source documents/healthcare records.

For all participants, after consent has been gained to be included in the trial, potential informal carers will be identified who will also be approached **(see SOP 03)** by the Principle Investigator, clinical research fellow or the research nurse, an information sheet will be provided for questionnaire assessment. Consent will be gained from the carer after at least 48 hours of them being given the PIS, by the

clinical research fellow/Principle Investigator to confirm participation in the carer burden as well as service use assessments. While it will be ideal for carers to participate, if they decline, it will not preclude the participant from taking part in the study.

As part of the qualitative study the Principle Investigator/research fellow/nurse will approach clinical staff to discuss involvement in qualitative interviews to be performed by the qualitative researcher. If they agree to be involved, their consent will be gained by the research fellow/Principle Investigator for their details to be conveyed securely to the qualitative researcher. **(see Qualitative component SOP 02)**

Screening

After gaining consent to participate in the trial, participants will be screened according to inclusion/exclusion criteria (see above) and the medical healthcare records reviewed, to ensure that all required assessments for screening are completed. These will be according to the trial protocol using the checklist which is in the protocol

- Capacity check and Informed Consent (this may be done prior to screening visit date, but it should be recorded in a source document that participant is still happy to proceed at the screening visit)
- Demographics
- Eligibility checks: Inclusion/exclusion criteria
- Alcohol usage questioning
- Risk factors/substance misuse questioning
- Liver disease score (Child Pugh, MELD, UKELD)
- Haematology and Biochemistry (Hb, WCC, Platelets, APPT, INR, Bilirubin, AST, ALT, Alkaline phosphatase, GGT, Total protein, Albumin, Sodium, Potassium, Urea, Creatinine, eGFR, CRP, Blood glucose)
- Liver imaging(ultrasound/CT/MRI) (if not done in **previous 6 months**)
- Diagnostic ascitic tap (if not done in previous **48 hours**) (Protein, Albumin, WCC, Neutrophils, Culture Positive/negative, Culture organism, Chylous)
- Blood culture (if not done in previous **48 hours**)
- Urine dipstick (if not done in previous **48 hours**)
- Urine culture (if not done in previous **48 hours**)
- Medical History
- Liver disease history and assessment
- Examination and vital signs
- Assessment of transport methods available to participant (in case the participant is to travel localise with hospital details for LTAD insertion)

Once the participant has been registered in the MACRO electronic CRF (case report form) hosted for the study by KCTU (Kings Clinical Trials Unit)], a Trial Number will

be generated, which is a unique ID in the format P-XX(site number)-XXX(sequential number), with 01 representing the BSUH study site, 02 representing Worthing , 03 representing Plymouth, 05 representing the Blackpool site and 06 representing Southampton.

After screening, the research team member must ensure the following actions are performed:

- Update the REDUCe Screening and Enrolment log **v3.0 – 20 Oct 2016**

- The screening log is kept in the Investigator Site File which should be stored in a secure location in CIRU/department. It will be the responsibility of the Research Fellow/Research Nurse to ensure it is available for completion when required and filed securely when not in use.

- Document in the healthcare records if patient was approached to participate in the study and their decision.

REDUCE SOP 02 - Qualitative component and interviews
V3.0 – 23 Jan 18

Potential participants interested in the main REDUCe trial will be approached by the Principle Investigator, research fellow or research nurse to discuss the trial, including the qualitative component as detailed in **SOP 01**. Participants expressing an interest will be given a patient information sheet **(PIS)** for the qualitative interviews at the same time as the one for the main study. If a participant who gives consent to take part in the main REDUCe study also expresses a willingness to participate in the qualitative interviews their consent will be sought for their contact details to be conveyed to Dr Max Cooper via NHS.net to NHS.net secure email. This will be documented in their hospital healthcare records at the time of gaining consent for trial participation, at or after the baseline visit, along with their preferred method of contact and on the Screening and Enrolment log.

Clinical staff for inclusion in the qualitative interview section of the study will be identified via the research fellow, Chief Investigator or Principle Investigator . Such participants will include the research nurse, community nurses and other clinicians caring for participants in hospital or the community. They will initially be approached by the Principle Investigator/research fellow/nurse and if interested will be given the REDUCe PIS Qualitative Interviews version **1.0 - 08 Sept 2015**. If happy to proceed, the Principle Investigator /research fellow will seek their consent to convey contact details to Dr Max Cooper/qualitative researcher. Interviews will be arranged at their place of work or by telephone.

Main Study Trial Numbers will be used for the participants, and for Clinical Staff, the following codes will be used:
CS- XX(site number)-XXX(sequential number)

After transcription, interview content will be anonymised and only be identifiable to Dr Max Cooper/qualitative researcher.

If recruitment for participant interviews proves problematic, participants will be asked whether they would be willing to undertake a follow up interview one to two months' later. In that event, Dr Max Cooper or the qualitative researcher will approach the Principle Investigator/research fellow/nurse prior to telephoning the participant in order to confirm that it is still appropriate to do so, particularly as the main study is being conducted in patients who are nearing the end of their lives and it is expected that some participants will die as a consequence of their disease during the course of their involvement in the study.

Specific considerations:

- The qualitative component consists of one or two 20-40 minute interviews

- If the participant wishes to proceed, the research fellow/ Principle Investigator will gain consent to share their name, study identification number and

telephone number with Dr Max Cooper/qualitative researcher. This will be documented in their hospital healthcare records after screening, having been deemed eligible to participate in the trial and baseline visit.

- These details will be transferred confidentially via NHS email to maxcooper@nhs.net

- A log of participants will be kept on the Qualitative Screening and Enrolment log **v1.0 – 22 Oct 2015**.

- Dr Max Cooper/qualitative researcher will telephone participant to address any further questions, seek consent and proceed to interview

- Interviews may be either face-to-face or by telephone according to participants' preference and the interviewer's availability to travel

- For interviews by telephone, verbal consent will be sought but signed for by Dr Max Cooper/qualitative researcher

- Participants will be informed when audio recording is about to commence and stop. The recordings will be stored on a password protected medical school computer. This is as per other telephone interview studies in this Division. They will be transferred to transcriber(s)' computer digitally using password protected email or encrypted memory stick.
- Transcribers used will be approved suppliers (Essential Secretary).

- Participants will be asked if they are willing to be approached for a second interview in 1-2 months' time

- Interviews will be transcribed and anonymised within one calendar month.

- Consent audio files will be saved separately to the interview audio files, and will not be transcribed. Instead, consent files will be stored on password protected backed up university computers.

- Audio versions, other than the consent process, will then be deleted and the transcribed version only identifiable via the study Trial Number. Transcribed versions will be stored on medical school/university hospital password protected computers and password protected emails.

- The interviews will be analysed using Thematic Analysis and qualitative software such as Nvivo

- Consent forms will be kept in a locked cabinet within the Division of Primary Care and Public Health at BSMS and returned to the Investigator Site File in the care of the research fellow/nurse or Dr Max Cooper prior to archiving.

REDUCE SOP 03 - Recruitment of informal carers
V3.0 – 23 Jan 18

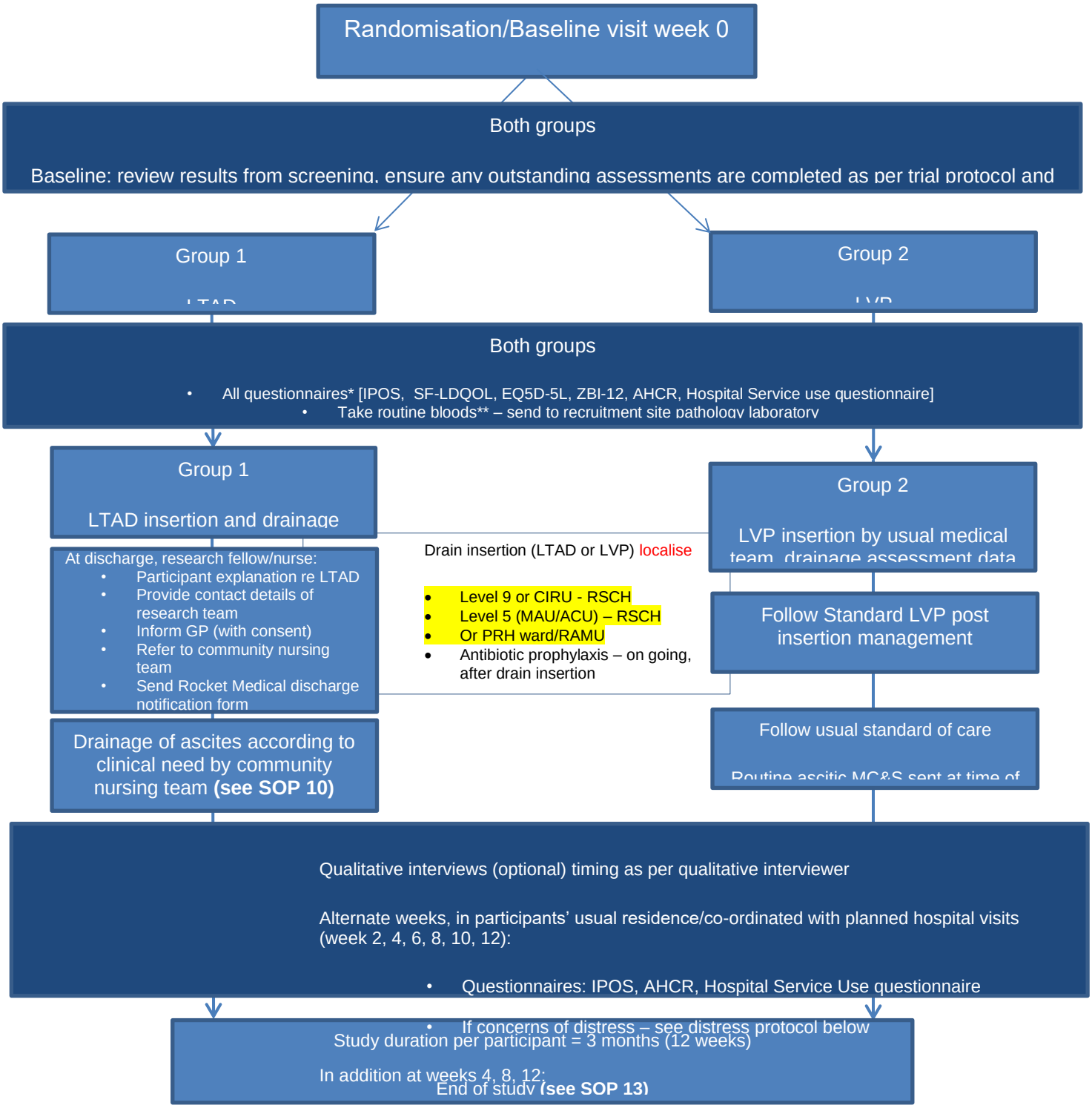
For all trial participants, potential informal carers will be identified (defined below) who will be approached by the research team. If the informal carer expresses an interest in study participation in parallel with the patient participant, a participant information sheet **(REDUCe PIS Quality of Life - Carers Questionnaire version 3.0 – 22 Sept 2016)** will be provided for the carer questionnaire focused aspect of the study. This aspect aims to assess the impact of care-giving, with respect to the patient participant, on the informal carer from their perspective (Zarit Burden Interview). This questionnaire is expected to take 10 minutes to complete and will be collected at baseline followed by every four weeks for the duration of the participant's involvement in the study.

The informal carer will also assist with completion of the in house modified ambulatory and home care record (AHCR) which is a tool to measure costs both to informal carers as well as to the participant and healthcare system. The AHCR questionnaire will be completed at baseline followed by alternate weeks and is expected to take about 20 minutes to complete. If the carer is willing to participate, consent will be gained after at least 48 hours after initial approach by the clinical research fellow/CI/PI.

Once consent has been gained the research fellow/nurse will arrange completion of the questionnaires at a convenient time. If the carer prefers, the questionnaires could be conducted over the telephone. The research fellow/nurse will, if possible, co-ordinate the questionnaires to be completed during the scheduled visit to the participant, if this is acceptable to the carer.

An informal or unpaid carer is defined as any person, such a family member, friend or neighbour who is giving regular, ongoing assistance to another person without payment for the care given.

REDUCE SOP 04 - Timeline/overview post randomisation
V1.0 – 23 Oct 15



*IPOS (Integrated Palliative Care Outcome Scale), SF-LDQOL (Short Form Liver Disease Quality of Life), EQ5D-5L (measure of quality adjusted life years), ZBI-12 (Zarit Burden Interview), AHCR (modified ambulatory and home care record)
**Full blood count, clotting screen, liver function including GGT, renal function and electrolyes, C-reactive protein, blood glucose

REDUCE SOP 05 - Randomisation / Baseline visit
V4.0 – 23 Jan 18

After the consent process is complete, the research team will complete the screening process using the protocol assessment schedule, described in **SOP 01**.
In view of the nature of the cohort, there are no pre-determined time limits between screening and randomisation but randomisation should be done between 48 hours of the screening visit and up to 14 days preceding the baseline visit.
If the participant is confirmed as eligible, Randomisation should be undertaken and a Baseline visit should be scheduled. This visit could be performed as an inpatient or on CIRU/department, as appropriate localise.

Randomisation will be carried out up to 14 days preceding the baseline visit, before any baseline study procedures are carried out.

Randomisation will be carried out by the Principle Investigator/ Research Fellow/nurse by logging onto the web based system at:
https://cturandomisation.iop.kcl.ac.uk/REDUCe/Login.aspx?ReturnUrl=%2fREDUCe

Log on details have been provided for the research fellow by KCTU. In the event of a forgotten password the contact at KCTU is Caroline Murphy
caroline.murphy@kcl.ac.uk

The following information is required to be entered to randomise:

- Participant ID number created by MACRO after initial registration details are entered
- Recruiting site
- Gender
- Child Pugh Score
- Participant initials and date of birth

Once the randomisation is complete the system will automatically generate a confirmation email sent to the Principle Investigator/ research fellow/nurse and REDUCE.BSUH@BSUH.NHS.UK informing the research team of the outcome of allocation, i.e. participant randomised to Group 1 LTAD or group 2 LVP as standard of care. The next allocation will only be generated upon actioning a request from the Principle Investigator research fellow/nurse. There is no blinding in the study.

This information should be immediately documented in the source documents (print out from the randomisation system may be used).

In the event of planned or unplanned leave on the part of the clinical research fellow the Chief Investigator/ Principle Investigator will follow the screening, seeking of consent and randomisation process during that period.

The research fellow/Principle Investigator will review the investigations (and sign off as reviewed in clinical notes or by signing and dating the lab print outs) and arrange

any outstanding procedures which had not already been undertaken as per routine care prior to the consent process. This will be following the protocol **v6.1 19 Jan 2018** and specifics are listed below. Any new results requiring action will be fed back, with participants' agreement, to the consultant usually managing their care for appropriate clinical action.

- Capacity check
- Medical history
- Liver screen – HBsAg, HCV antibody, HIV antibody, ANA (antinuclear antibody), AMA (Anti-mitochondrial anti-bodies), SMA (smooth muscle antibody), LKM (kidney microsomal antibody), serum ferritin, serum copper, serum caeruloplasmin, serum alpha-1 antitrypsin, fasting cholesterol, fasting triglyceride, fasting HDL cholesterol, fasting chol:HDL ratio, Fasting LDL cholesterol (**if not done in last three months**).
- Adverse event review
- Concomitant medications review
- Alcohol usage questioning
- Risk factors/substance misuse questioning
- Liver disease score (Child Pugh, MELD, UKELD)
- Examination, height and weight, and vital signs (temperature, pulse, blood pressure). Height, weight and vital signs will be recorded on CIRU/department using calibrated equipment
- Haematology and Biochemistry (Hb, WCC, Platelets, APPT, INR, Bilirubin, AST, ALT, Alkaline phosphatase, GGT, Total protein, Albumin, Sodium, Potassium, Urea, Creatinine, eGFR, CRP, Blood glucose)
- Diagnostic ascitic tap (if not done in previous **14 days**): Protein, Albumin, WCC, Neutrophils, Culture Positive/negative, Culture organism, Chylous
- Blood culture (if not done in previous **14 days)**
- Urine dipstick (if not done in previous **14 days**)
- Urine culture (if not done in previous **14 days**)
- Liver disease history and assessment
- LVP/LTAD insertion depending on randomisation outcome (**Clotting (INR and platelet count) will be performed within the preceding 7 days of LTAD drain insertion**)

- LTAD (Group 1) drainage assessment using appropriate drainage diary

- LVP (group 2) drainage assessment using appropriate drainage diary (as per usual procedures for recording in clinical area where patient has LVP performed)

- 20 ml of blood collected for future research (10 ml saved as serum, and 10ml as whole blood) will be collected using packs made up by CIRU laboratory (lab) staff and according to the instructions on the Sample Request Form kept within the packs (These should be processed according to the**(REDUCE Study laboratory Manual v.1.2)**The research blood sample and the standard of care bloods should be delivered to their respective labs within four hours of collection

- Completion of questionnaires (participant):
    - IPOS
    - SF-LDQOL
    - EQ5D-5L
    - ZBI-12 (informal carer participant)
    - AHCR (With help of informal carer participant if appropriate)

- Hospital Service Use questionnaire (will be completed by research fellow/nurse at intervals)

Data collected will be recorded either on CRF worksheets, as source documents, by the Principle Investigator /research fellow/nurse, (questionnaires, vital signs, alcohol/drug history, liver disease assessment), or in hospital healthcare records. Laboratory and imaging results will be printed from hospital Localise computerised systems and reviewed (signed and dated) by the research fellow/PI before being stored in the participant files on CIRU/department. Data will be transferred from source documents directly into the eCRF by the data officer/delegated member of the research team.
Drainage diary data will be collected by the research fellow/nurse at visits every two weeks. For participants in the LTAD arm the carbon copy from each drainage diary will be removed from participants' usual place of care at each visit; the original top sheet will be retained by the community nurses for their community records. The carbon copy will have the participant study number but no personally identifiable data. The original top sheet will have a patient sticker attached by the community nursing team as per their usual practice. The research fellow/nurse will provide a new LTAD drainage diary at each visit.

Data that will be recorded in source documents includes:

• Informed consent process including consent form/PIS version and a copy of the signed consent form
• Participants eligibility
• Description of adverse events and actions taken (causality assessed by PI or delegated individual)
• A copy of the PIS
• A research sticker should be placed on the front of the notes
• Medical history and concomitant medications
• Missed / late visits with reasons
• Deviations from the protocol with reasons
• If the participant /carer withdraws, this should be entered along with reason for withdrawal
• Any other issues pertinent to the study
• Each visit should be documented - this can be on CRF worksheets as source document – includes capacity assessment, if Consultee was approached, if so identifying them, noting whether the participant is still happy to participate, and whether there are any new AEs or concomitant medications

Those randomised to the LVP arm (group 2) will have paracentesis performed by the usual medical team as per standard of care, arranged as per local protocol on the basis of clinical need (e.g. GP referral to Ambulatory Care Unit), Rapid Access Medical Unit (RAMU) or other appropriate clinical area (or if clinically appropriate during admission under a medical team) localise as necessary. A drainage assessment will be performed by assessing medical records and the drainage diary completed by the research fellow/nurse. Post procedure care will be followed as standard.

Those randomised to the LTAD arm (group 1) will have the LTAD inserted, under ultrasound guidance, either in the medical assessment unit/ ward or CIRU/Department Localise by the delegated medical personnel Localise. Any ascites drained at this time will be recorded in the usual manner for that clinical area, and data collected by the Principle Investigator/research fellow/nurse on to the REDUCe drainage diary (see below), After discharge, data will be recorded in the manner detailed below.

Post drain insertion
Both study groups will have details of drain insertion documented in their healthcare records as is the standard procedure post insertion. Both groups will be prescribed the antibiotic ciprofloxacin 500mg (or an equivalent antibiotic if there is any contraindication to Ciprofloxacin or according to local antibiotic policy) by the research fellow/Principle Investigator at the baseline visit, which is to be taken once a day, as prophylaxis for potential infection, such as spontaneous bacterial peritonitis (SBP). All participants will be provided with a three month supply of antibiotics upon discharge and be given counselling on administration. This will be obtained from the hospital pharmacy if outpatients, and inpatient pharmacy for in patients. Localise as necessary

The research fellow/nurse will be responsible for ordering replacement LTAD drainage packs once one is used for REDUCe trial LTAD insertion. The research fellow/nurse will ensure that at any one time there are two drainage packs on site localise according to local agreement with Rocket Medical, utilising the Rocket Medical REDUCe trial stock ordering procedure form. The supplies which should be requested for one complete drainage pack are:

- 1 Insertion kit (Code R54400-16-MT)
- 35 (7 Boxes of 5) Drainage Bags (Code R54401)

Rocket Medical will supply the LTAD drainage packs which will be stored in CIRU/department .Localise as necessary Each pack will include the LTAD as well as seven boxes, each box containing five drainage bags. The drain packs usually take up to three days to be delivered from Rocket Medical to CIRU Localise. The unique serial number for LTAD inserted and consumables provided to participants will be logged in each participants file to enable tracking of equipment as well as the REDUCe Rocket Medical Drains and Bags log **v1.0 11 Oct 2015**.

After the LTAD is inserted and prior to discharge from hospital, the research fellow/nurse/Principle Investigator will explain to the participant how the drain will be used and provide them with the drainage pack, which contains all drainage bags expected to be required over the course of the study. At the participant's request they can be provided with supplies for the initial three weeks with arrangements made thereafter such as further provision of consumables to their usual place of residence by the research fellow/nurse during scheduled visits. In the event that consumables are used faster than anticipated, the community nurses will need to inform the research fellow in order to expedite delivery. Localise

The research fellow/nurse will provide participants with a "Rocket Medical IPC Peritoneal Catheter Information Sheet", which provides information about the LTAD device, and (with patient consent) will send* the Rocket IPC Abdominal Discharge Letter **v 2 0 - 03 Feb 2016**, to the participant's community nursing team and GP (with consent for GP to be informed). ***This will be via secure nhs.net mail or fax, following local procedures and receipt of this information will be confirmed**. The letter explains that the participant has been discharged with a Rocket Medical LTAD as per participation in the REDUCe Trial. General overview guidance regarding the drainage system as well as contact details for Rocket Medical are included.

With participant's consent their GP will be sent a letter (REDUCe GP letter **v2 0 - 03 Feb 2016**) by the research nurse or research fellow, to inform them of their participation in the study, the letter will include the contact telephone number of the Principle Investigator/ research fellow/nurse (see below). The GP will also be telephoned by the Principle Investigator/ research fellow/nurse to ensure they have contact numbers for the research team and provided with relevant information about the trial.

The participant will be provided with the contact number of CIRU/department reception (see below) as well as their drainage diary sheets which are to be kept at their usual place of residence with their community healthcare records. Prior to discharge from hospital the research fellow/nurse will contact the appropriate lead community nurse Localise to update them. This will ensure that visits can be organised by the community team to perform recu rrent drainage and arrange necessary disposal of clinical waste. The community nursing team will be provided with the contact telephone number of the research fellow/nurse (see below) Localise as necessary. Calls received by the research fellow/nurse will be documented in a telephone log which is to be kept in participants' files stored in CIRU/department.

Prior to discharge from hospital, after the LTAD has been inserted, the research fellow/nurse will provide participants with the REDUCe Participant Study Card **v1.0 19 Oct 2016**. The participant name and study number as well as the date of LTAD insertion will be written on the Participant Study Card using an indelible ink marker. The Card includes contact details of the study team as well as advice on initial management for non-specialist clinicians in the event a participant is admitted to hospital out of hours.

Rocket Medical will be informed by the research fellow/nurse of the participant's discharge, using the "Rocket Medical Discharge Notification" form for participants

specifically in the study, in order that Rocket Medical can organise any further support for participants/carers, or training for community nurses as required.
Research Nurse: Localise as required

Research Fellow: Localise as required

Principle Investigator: Localise as required (The above can also be undertaken by the Principle Investgator if required) please localise

Each planned follow up visit with participants will begin with a capacity assessment of the participant as per the protocol. If the participant is felt to have lost capacity to continue with the study their nominated Consultee will be approached. If there is no nominated Consultee, their usual medical consultant, independent from the research team, will be consulted to decide whether it is in their best interests to continue in the study **(see SOP: 1)**.

The community nurses Localise as necessary will perform risk assessments during their home visits as per their usual practice and inform the research team of any concerns that have been identified in terms of safety of the research team. The research fellow/nurse will co-ordinate their scheduled visits for follow up questionnaires and routine bloods with the community nurses' planned visits Localise. **However if this is not possible, arrangements will be made for the research fellow to be accompanied by another member of the research team or other appropriate professional at BSUH. As far as possible, lone visits would be avoided (Sussex Community Trust - Lone Worker Policy v6.0 - 09 Sept 2015).** Localise as necessary

The Principle Investigator/research fellow accompanied by at least one more person – either a community nurse or another staff member an) will meet with the participant every two weeks (+/- 3 days), collect blood samples for routine tests, record vital signs, liver disease score, review concomitant medications, alcohol/risk factors and substance misuse information, liver disease assessment, complete questionnaires and perform an adverse event review. Localise as necessary

Drainage diary data recorded by the community nurse/ localise as necessary and/or carer will be collected by the research fellow/nurse from participants in the LTAD arm by removing the carbon copy from each drainage diary from participants' usual place of care at each visit. The original top sheet will be retained by the community nurses/ Localise as necessary for their records. The carbon copy will have the participant study number but no personally identifiable data. The original top sheet will have a patient sticker attached by the community nursing team /Localise as necessary as per their usual practice. The research fellow will provide a new LTAD drainage diary at each visit.

At the scheduled visits every two weeks (+/- 3 days) the research fellow/localise will complete questionnaires relating to the study according to the protocol (see timeline overview above). This will include the carer burden questionnaires which, as far as possible, will be co-ordinated to occur during the same visit but, at carers' request, could be conducted over the telephone.

Data from the visits will be recorded on CRF worksheets and research continuation sheets except for drainage diary data which will be collected from a copy of the original drainage diary. The original drainage diaries will remain at the participants' usual place of residence. In the event a participant is admitted to hospital or dies during the study period, the community nursing team / localise will extract the

drainage diaries to enable the research fellow/nurse access to the drainage data. This also applies if a participant reaches end of the study at 12 weeks.

Routine blood samples will be collected using standard techniques. Routine standard of care bloods will be transported to the normal laboratory by the research fellow/nurse, according to standard specimen delivery procedures, to be processed in the usual manner.

Palliative care needs and concerns will also be assessed using the Integrated Palliative Outcome Scale (IPOS). If the participant is unable to complete the IPOS the research fellow/nurse will ask the community nurses/localise for information to enable a staff version of the IPOS questionnaire to be completed by the research fellow/nurse**. If a palliative care need is identified during questionnaire completion, with the participants agreement, this will be discussed at a mini multi-disciplinary team (MDT) meeting (comprising the research fellow, Principle Investigator and a Specialist Palliative Care, Macmillan Clinical Nurse Specialist independent of the trial conduct) in order that management of their unmet need can be discussed, and a management plan suggested (e.g. contacting GP to suggest symptom review and treatment).** Localise as necessary

The mini MDT may recommend referral to a specialist palliative care service if complex need is identified, in line with usual clinical practice. The Principle Investigator/research fellow/nurse would then discuss with the GP and or community nursing team/Localise regarding making this referral, after seeking agreement from the participant. The mini MDT will take place weekly, but can be called ad hoc if there is concern and the distress protocol is activated. The outcome and decisions made should be documented in the source documents. Localise

The distress protocol, **SOP 09,** sets out urgent action to be taken if uncontrolled physical symptoms or psychological distress is identified.

In the event the Princlple Investigator/research fellow/nurse is unable to contact a participant or there are concerns over a participant's health meaning the Princlple Investigator/ research fellow/nurse was unable to contact them despite a planned visit, the Princlple Investigator/ research fellow/nurse will follow the usual community nurse protocol in terms of escalation as is appropriate for a researcher **(Sussex Community Trust Responding to no reply, missed or deferred visits protocol - Adult Services v1.0 25 Nov 2014)**, for example if there was concern the participant was in a property but unable to answer the door due to being unwell. Localise as necessary

Data from CRF worksheet and source data will be entered into the eCRF MACRO by the data officer/delegated member of the research team once the research fellow/nurse has delivered these data to CIRU/department. CRF worksheets and a copy of other source data will be stored in participants' files. The Hospital Service use questionnaire will be completed retrospectively by both the health economics researcher and the research fellow/nurse by reviewing medical records once a participant finishes the study.

REDUCE SOP 09 - Distress Protocol
V2.0 – 23 Jan 18

The Clinical Research Fellow/nurse and other members of the research team will meet with the participant every two weeks to take routine bloods, vital signs, collect drainage diary information and complete questionnaires relating to the study. Palliative care needs and concerns will also be assessed using the Integrated Palliative Outcome Scale (IPOS) **questionnaire. If a specific palliative care need is identified either as a result of completing the questionnaires or clinically during the study period, this will be discussed at a weekly mini multi-disciplinary meeting (MDM) where referral to a specialist palliative care service can be offered if clinically appropriate**. Localise as necessary

If a participant becomes distressed or raises concerning issues during completion of questionnaires which may warrant a change in their medical management, a member of the research team will seek consent, which will be transcribed into **a file note and amalgamated into the healthcare records, from the participant to discuss these either at the mini MDM, with the patient's GP or as otherwise clinically appropriate. Once consent is gained the researcher must hand over any clinically relevant details to the appropriate team**. Localise as necessary

If the participant reports ideas of self-harm or risk to themselves or others this will be discussed urgently with the CI and a senior member of the participant's own medical team or GP. Depending on the circumstances confidentiality may need to be broken.

In the following table are symptom scores that should trigger an urgent response by a researcher. The Principle Investigator/research fellow/nurse will use clinical judgement to respond to the situation which would begin with exploration of the symptom initially and may or may not require activation of the distress protocol. Any new severe symptom should be explored. The Chief Investigator must be informed if the distress protocol is activated; the action taken should be recorded as a file note which will then be amalgamated into the health records by the researcher.

Tool	**Symptom/question**	**Severity**	**Combined with**	**Severity**
IPOS*	Pain/nausea/vomiting/dyspnoea	4 (Overwhelming)	n/a	n/a
IPOS*	Depressed (Q5)	4 (Always)	Able to share feelings with family (Q7)	4 (not at all/with anyone)
SF-LDQOL	Questions 5, 6, 7, 9, 24	Consistently worst response in any one question should prompt exploration		
EQ-5D-5L	Any question	Worst response in any of the questions should prompt exploration		
*Same action would apply if IPOS completed by proxy staff responses				

If researcher is present during the disclosure:

- Verify symptom and any intervention currently in place for it
- Screen for risk of self-harm/risk to self or others
- Seek participant's consent to discuss disclosure with MDT/participant's GP/medical team as appropriate

Depending on severity of concern if disclosure relates to ideas of self-harm/risk to self or others, participant's consent may not be necessary - if severe concern discuss with CI immediate

REDUCE SOP 10 - Study Overview Community Nurses (Integrated Primary Care Team Nurses)
V3.0 – 23 Jan 18

Study participants in the standard of care arm will receive care as usual. Participants in the long term abdominal drain LTAD arm will have the tunnelled drain inserted in hospital under ultrasound guidance by the clinical research fellow/Localise as necessary The type of LTAD to be used in the study is manufactured by Rocket Medical (this is currently the device of familiarity to community teams due to its use for malignant ascites management).

Both study groups will be prescribed the antibiotic ciprofloxacin 500mg once a day (or an equivalent antibiotic if there is any contraindication to Ciprofloxacin), as prophylaxis for potential infection, such as spontaneous bacterial peritonitis (SBP). All participants will be provided with a three month supply of antibiotics upon discharge, to cover the duration of study follow-up.

After the LTAD is inserted and prior to discharge from hospital, the research fellow will explain to the participant how the drain will be used and provide them with the drainage kit, which includes all drainage bags expected to be required over the course of the study. At the participant's request they can be provided with supplies for the initial three weeks with arrangements made thereafter; the preferred option however would be to supply all the boxes on initial discharge.

The research fellow/nurse will provide participants with a "Rocket Medical IPC Peritoneal Catheter Rocket Medical Information Sheet". With patient consent the Rocket IPC Abdominal Discharge Letter **v2 0 - 03 Feb 2016** will be sent to the participant's community nursing team and GP **(see SOP 07)** Localise as necessary. The Rocket Medical discharge letter informs the community nursing team and GP that participants have been discharged with a Rocket Medical LTAD as per participation in the REDUCe Trial. General overview guidance regarding the drainage system as well as contact details for Rocket Medical are included.

With participants' consent their GP will be sent a letter (REDUCe GP letter **v2 0 - 03 Feb 2016**) to inform them of their participation in the study, the letter will include the contact telephone number of the Principle Investigator/ research fellow/nurse. Localise as necessary The GP will also be telephoned by the research fellow to ensure they have their contact number.

The participant will be provided with the contact number for CIRU/department reception, the LTAD information booklet (known as Rocket IPC Peritoneal Catheter Information for patient and nurses), as well as their REDUCe specific drainage diary sheet which is to be kept at their usual place of residence with their community healthcare records. Localise as necessary. Prior to discharge from hospital the research fellow/nurse will contact the appropriate lead community nurse to update them. This will ensure that visits can be organised by the community team Localise as necessary to perform recurrent drainage and arrange necessary disposal of clinical waste. The community nursing team /Localise will be provided with the contact telephone number of the research fellow/nurse.

Rocket Medical will be informed of the participant's discharge, using the Rocket Medical discharge notification form for participants specifically in the study, by the clinical research fellow/nurse in order that Rocket Medical can organise any further support for participants/carers, or training for community nurses as required. The unique serial number for LTAD inserted as well as for consumables will be recorded in the participants' file to enable tracking REDUCe Medical Drains and Bags Log **v1.0-11 Oct 2015**.

In the LTAD arm of the study the community nurses/ Localise will visit participants at their usual residence to carry out ascites drainage as clinically indicated but drainage episodes should be limited to two or three times a week at most. The amount to be drained will be dependent on clinical need, but would usually be 1-2L at a time. Each time drainage is performed it will be recorded by the community nurses Localise in the REDUCe specific drainage diary which will be kept in the participant's usual place of residence. The drainage diary for the LTAD arm will be an original top sheet with a carbon copy. The drainage diary will carry the participant study ID but no other identifiable information. Community nurses Localise can attach a patient sticker to the original top sheet as per their usual practice but not to the carbon copy.

At each visit performed by the research fellow/nurse, the carbon copy from each drainage diary will be removed from participants' usual place of care in order to collect the drainage data; the original top sheet will be retained by the community nurses for their community records Localise. The research fellow/nurse will provide a new LTAD drainage diary at each visit. The drainage bags and ascites drained will be disposed of by the council as per the usual manner for that region.

The community nurses Localise will perform risk assessments during their home visits as per their usual practice and inform the research team of any concerns that have been identified in terms of safety of the research team. The research fellow/nurse will co-ordinate their scheduled visits for follow up questionnaires and routine bloods with the community nurses' planned visits/ Localise. However if this is not possible, arrangements will be made for the research fellow/nurse to be accompanied by another member of the research team or other appropriate professional from the recruiting centre.. As far as possible, lone visits would be avoided.

The contact telephone number for the Research Fellow Localise (as well as the research nurse on Clinical Investigation Research Unit (CIRU)/Department to be used **"in hours"** only (9am-5pm) during week days will be provided to participants' respective GPs (with consent) and community nursing teams. localise

The telephone number of the research nurse and the research fellow are as follows:

Research Nurse: Localise

Research Fellow: Localise

Calls received will be documented in a telephone log which is to be kept in participants' files. Out of hours, participants or community healthcare professionals

should contact the out-of-hours GP service or the participant should attend Accident and Emergency (A&E) for emergency trial related problems. For non-trial related problems standard procedures should be followed.

The research fellow and other members of the research team will meet with the participant every two weeks, collect blood samples for routine tests, record, vital signs, collect drainage diary information recorded by the community nurse/localise and or carer and complete questionnaires relating to the study.

Specialist palliative care needs will also be assessed using the integrated palliative outcome scale (IPOS) at the scheduled visits every two weeks. If the participant is unable to complete the IPOS the research fellow/nurse will ask the community nurses /localise for information to enable a staff version of the IPOS questionnaire to be completed by the research fellow/nurse.

If a palliative care need is identified during questionnaire completion, with the participants agreement, this will be discussed at a mini multi-disciplinary team (MDT) meeting (comprising the research fellow/nurse, one of the Co-investigators and a Specialist Palliative Care, Macmillan Clinical Nurse Specialist independent of the trial conduct) in order that management of their unmet need can be discussed, and a management plan suggested (e.g. contacting GP to suggest symptoms review and treatment). The mini MDT may recommend referral to a specialist palliative care service if complex need identified, in line with usual clinical practice. The research fellow/nurse would then discuss with the GP and or community nursing team regarding making this referral, after seeking agreement from the participant. The mini MDT will take place weekly, but can be called ad hoc if there is concern and the distress protocol is activated. Localise as necessary

As the study is to be carried out within the palliative phase of illness, the cohort of participants will be in the last months of their lives. The research team acknowledge this can be difficult for healthcare professionals involved in the care of any patient near the end of life, or actively dying and especially in a cohort with advanced liver disease, when death usually occurs in hospital. In the event that a usual provider of health care in the community, or the clinical research fellow/research nurse witness or are involved in a distressing event or situation**, they need access to support and the opportunity for debrief. Should such a situation arise, debriefing will be provided localise, with onward referral if required.** Localise as necessary (IDENTIIFY APPROPRIATE PERSON

If a participant in the LTAD arm dies during the study period the drain will be left in situ as per the usual practice by the community nursing team/localise who will also follow standard procedures with regards to informing the undertakers of the presence of the drain.

Specific considerations:

- Participants will be referred to community nursing team Localise on discharge from hospital after LTAD insertion and specific information regarding the study will be conveyed to the community nursing teams at this point as required

- After gaining participant consent to do so, their GP will be informed of entry into study on discharge by research nurse or fellow

- Participant will be discharged with drainage packs including expected requirement of drainage bags unless requested otherwise by the participant

- The contact details of the research fellow will be given to the participants' GP, with consent and community nursing team/localise on discharge from hospital in the event of study related queries

- The community nursing team/localise should contact the research team/research fellow using the contact details provided above if they identify a concern regarding the ascites drained, drain site or of the need to expedite delivery of further consumables if the participant is not initially discharged home with the complete pack

- The community nursing team/localise should inform the research fellow/nurse immediately of any events including admission to hospital or death of the participant

- In the event a participant is admitted to hospital or dies during the study period, the community nursing team/localise will extract the drainage diaries to enable the research fellow access to the drainage data. This also applies to if a participant reaches end of the study at three months

- Community team/localise will arrange visits with participant in order to drain ascites as per clinical need however this should not exceed three drainage episodes per week.

- Community nurses /localise will train carer if they wish to perform drainage in the interim, in line with current practice in other patients with indwelling drains. If assistance with this is required, the community nursing teams/localise should contact Rocket Medical to request specific training using the Rocket Medical discharge letter. This is the usual procedure for non-trial patients with LTAD

- Community nurses/localise will record drainage episodes in the drainage diary provided, these are to remain in the participants' usual place of residence until a new drainage diary is provided at the scheduled visit from the research fellow every two weeks for the twelve week follow up period

- REDUCe LTAD drainage diaries will consist of an original top sheet with a carbonated copy. The study ID number, but no other identifiable information will be present on the drainage diary

- The community nurses /localise can affix a patient label to the top sheet of the drainage diary as is their usual practice, this should not be placed on to the carbon copies

- The research fellow will collect the carbon copy from the participants' usual place of residence at scheduled visits every two weeks. At this point a new drainage diary will be provided by the research fellow, the community nurses/localise can then file the original top sheet in the community healthcare records /localise

- If interim drainage is performed by another person in the interim, the community nurse/localise will teach that person to record information on drainage in the drainage diary

- The drainage bags will be disposed of in the usual way by the council as per standard arrangements in that region

- The research fellow/nurse will collect drainage information from the drainage diaries, routine bloods, vital signs and complete questionnaires with the participant at the scheduled visits every two weeks for the duration of study follow up

- If the participant is unable to complete the questionnaires, the research fellow/nurse may ask the community nurses/localise for information in order to complete a staff version of the questionnaires

- If any of the healthcare team/localise involved in the care of the study participant experiences a distressing event relating to the care of the participant, **debriefing will be provided as necessary by** -localise

- At the end of the study, those who remain with the LTAD in situ should continue to receive care as standard from the community nursing team/localise. The research fellow/nurse will inform Rocket Medical that the participant is no longer in the study using the standard Rocket Medical discharge notification form, in order that the community nursing team /localise can order further supplies as required as per their usual prescription arrangements

- Since the study is being conducted in patients who are nearing the end of their lives as a result of advanced liver disease, Adverse Events (AE) directly related to liver disease are expected and **will not automatically** require the community nurse/localise to contact the research fellow/nurse, these include:

    - hepatic encephalopathy
    - jaundice
    - gastrointestinal bleeding

- An event will be considered a Serious Adverse Event (SAE) if it results in hospitalisation and is directly related to the LTAD - this will include:

    - drain leakage or blockage
    - Cellulitis at the drain site

- Abdominal pain not settling with usual analgesia i.e. suspicion of peritonitis
- Anything else which in the opinion of the community nurse/localise is directly related to the LTAD and requires hospitalisation

- If the community nurse/localise is unsure, the fall back position would be to contact the research fellow/PI for advice.

REDUCE SOP 11 - Advice for Out of hours GP teams
V2.0 – 23 Jan 18

Study participants in the standard of care arm will receive care as usual. Participants in the long-term abdominal drain arm (LTAD) will have the LTAD inserted in hospital under ultrasound guidance by the clinical research fellow/localise. Both study groups will be prescribed antibiotic prophylaxis, ciprofloxacin 500mg once a day (or an equivalent antibiotic if there is any contraindication to Ciprofloxacin), to cover the participants for spontaneous bacterial peritonitis (SBP).

Participants will be provided with a "Rocket Medical IPC Peritoneal Catheter Rocket Medical Information Sheet" which provides information about the LTAD device, as well as the REDUCe Participant Study Card **v1.0 19 Oct 2016** (which includes the participant name, study number and the date of LTAD insertion. The Card includes contact details of the study team as well as advice on initial management for non-specialist clinicians in the event a participant is admitted to hospital out of hours on discharge.

With participants consent a Rocket IPC Abdominal Discharge Letter **v 2 0 - 03 Feb 2016** will be sent to the participant's community nursing team and GP (with consent for GP to be informed). The letter explains that the participant has been discharged with a Rocket Medical LTAD as per participation in the REDUCe Trial. General overview guidance regarding the drainage system as well as contact details for Rocket Medical are included.

With participant's consent their GP will be sent a letter (REDUCe GP letter **v2 0 - 03 Feb 2016**) by the research nurse or research fellow, to inform them of their participation in the study, the letter will include the contact telephone number of the Principle Investigator research fellow/nurse (see below). Once the participant is discharged from hospital they will be referred to the community nursing service to organise visits in order to perform recurrent drainage. Rocket Medical will be informed of the participants' discharge and can organise any further support for participants/carers, or training for community nurses as required. With the participants' consent, their usual GP will also be informed of their involvement in the trial.

The contact telephone number for the Principle Investigator Research fellow/nurse, to be used **"in hours"** only (9am-5pm) during week days will be provided to the participants' respective GP (with consent) and community nursing teams.

The telephone number of the Principle Investigator/ research nurse / research fellow are as follows:

Principle Investigator: Localise

Research Nurse: Localise

Research Fellow: Localise

Out of hours, participants may contact either the out-of-hours GP service or attend Accident and Emergency (A&E) for trial related problems. For non-trial related problems standard procedures should be followed.

The research team have met Dr Robin Warshafsky, Deputy Medical Director IC24, Lead for the out-of-hours GP service who is aware of the trial, has attended the training session on the study and to whom a copy of the SOP will be made available. Localise

The clinical research fellow and other members of the research team will meet with the participant every two weeks over the study follow up (12 weeks) to take routine bloods, vital signs, collect drainage diary information and complete questionnaires relating to the study. **Specialist palliative care needs will also be assessed using the integrated palliative outcome scale (IPOS) questionnaire. If a specific palliative care need is identified this will be discussed at a mini multi-disciplinary meeting where referral to a specialist palliative care service can be offered depending on the particular need**.
Localise

Participants will be followed up to a maximum of 12 weeks, after which time those in the LTAD arm will have the option to have the drain removed or to leave it in situ. If they choose to continue with the LTAD, this will then continue under the supervision of a consultant Gastroenterologist/Hepatologist.

Specific considerations and advice in the event the out of hours GP team is contacted by a study participant or carer:

- For trial related queries **"in hours"** (9am-5pm) during week days, the Principle Investigator/clinical research fellow or research nurse can be contacted using the provided contact details (see above)

- For non-trial related concerns or queries care should proceed as usual

- The study is being conducted in patients approaching the end of their lives as a result of advanced liver disease. As such, Adverse Events (AE) directly related to liver disease are expected and **will not automatically** require the research fellow/nurse to be contacted, these include:
    - hepatic encephalopathy
    - jaundice
    - gastrointestinal bleeding

- Participants in the standard of care arm (large volume paracentesis) will receive care as usual

- It is expected that some participants will die as a consequence of their disease during the course of their involvement in the study. General palliative care principles should proceed as required, according to participant preference. Only drain/intervention related complications would usually warrant research team/acute setting assessment and care

- An event will be considered a Serious Adverse Event (SAE) if it results in hospitalisation and is directly related to the LTAD - this will include:

    - drain leakage or blockage
    - Cellulitis at the drain site
    - Abdominal pain not settling with usual analgesia i.e. suspicion of peritonitis
    - Anything else which in the opinion of the out of hours GP is directly related to the LTAD and requires hospitalisation

    - If a hospitalisation occurs, the research fellow/nurse should be notified, so that an assessment of whether this was related to the LTAD can be made.

- In the LTAD arm, specific consideration should be given to long term drain related problems:

    - Higher risk of ascitic fluid infection
    - Drain site cellulitis
    - Drain site leakage
    - Drain blockage

If there is a specific drain or study related query, the out of hours GP team should inform the research team by telephone using the number above, however this is not an “out of hours or on call service”. Regarding specific advice the assessor ought to use clinical judgement in terms of management.

REDUCE SOP 12 - On call medical registrars / medical on call team
V2.0 – 23 Jan 18

The REDUCe trial has two arms, standard of care, in which repeated large volume paracentesis is performed by the usual medical team as per the current established local pathways. In this arm routine bloods and questionnaires will be collected from participants every two weeks.

Participants in the long-term abdominal drain (LTAD) arm will have the long term tunnelled drain inserted in hospital under ultrasound guidance by the clinical research fellow. On discharge from hospital their GP, with their consent, is informed of their participation in the study. They are referred to the community nurse team/localise who arranges visits in their usual place of residence to drain small volumes of ascites. Routine bloods and questionnaires will be collected from participants every two weeks. In every other respect, care for participants in the LTAD arm is otherwise as per standard of care and is to follow usual pathways.

Both study groups will be prescribed antibiotic prophylaxis as standard of care, ciprofloxacin 500mg once a day (or an equivalent antibiotic if there is any contraindication to Ciprofloxacin), to cover the participants for spontaneous bacterial peritonitis (SBP).

The contact telephone number for the Principle Investigator, clinical research fellow/nurse, to be used **"in hours"** only (9am-5pm) during week days, will be provided to the participants' respective GP, with consent, and community nursing teams. Out of hours, participants will be advised to contact either the out-of-hours GP service or attend Accident and Emergency (A&E) for trial related problems. For non-trial related problems standard procedures should be followed.

Participants will be followed up to a maximum of 12 weeks, after which time those in the LTAD arm will have the option to have the drain removed or to leave it in situ.

Specific considerations and advice in the event the on call medical team is contacted by a healthcare professional regarding a participant in the study:

For trial related queries **"in hours"** (9am-5pm) during week days the Principle Investigator, clinical research fellow or research nurse can be contacted regarding trial related queries using the following contact details:

Principle Investigator: Localise

<u>Research Nurse:</u> Localise

<u>Research Fellow:</u> Localise

- For non-trial related concerns or queries care should proceed as usual
- The trial is being conducted in patients approaching the end of their lives. As such it is expected that some participants will die as a consequence of their

disease during the course of their involvement in the study. General palliative care principles should proceed as required according to participant preference. Only drain/intervention related complications would usually warrant research team/acute setting assessment and care

- The research team should be informed if a trial participant attends A&E, the acute medical service or is admitted to hospital in order to record this information in the trial file. The research team should be contacted by telephone using the number above

- At morning handover on the Acute Medical Units the gastroenterology team should also be informed or any trial participants' attendance, in order that they can inform the research team

- Participants in the standard of care arm ought to receive care as usual

- In the LTAD arm, specific consideration should be given to long term drain related problems:

    - Higher risk of ascitic fluid infection
    - Drain site cellulitis
    - Drain site leakage
    - Drain blockage

REDUCE SOP 13 - Study withdrawal / end of study period for participant
V1.0 – 23 Oct 15

Participants (including informal carers, or staff, involved in the qualitative research) can choose to withdraw from the study at any time. They do not need to give a reason, but should be encouraged to do so if they are comfortable with this. If they choose to, this should be recorded as a case file note with the participant Trial number and stored in the participants' and site files.

If a participant loses capacity to make a decision to continue in the study during the study period this is not an automatic reason for withdrawal, however the nominated Consultee will be approached to determine whether it is in the participant's best interests to continue in the study.

The Principal Investigator and Clinical Trial Manager must be informed when a participant is withdrawn or chooses to withdraw from the study and documentation of this event / procedure must be made in the participants healthcare records as well as a copy placed in the participants' and site file by the researcher.

Participants will be followed up to a maximum of 12 weeks, if the participant has not succumbed to their illness during that period of time, those in the LTAD arm will have the option to have the drain removed or to leave it in situ. In the event a participant dies during the study period the community nursing team/localise will extract the drainage diaries to enable the research fellow/nurse access to the drainage data. This also applies to if a participant reaches end of the study at 12 weeks

If participants choose for the LTAD to remain in situ, this will then continue under the supervision of a consultant Gastroenterologist/Hepatologist to whom they will be referred by the clinical research fellow/Principle or Chief Investigator. This will be in writing to the lead consultant and GP (with consent). Prophylactic ciprofloxacin (or an equivalent antibiotic if there is any contraindication to Ciprofloxacin) will be continued in both groups as standard of care. These individuals will continue to be managed in the community and in case of any clinical concerns or queries the usual procedure will be followed i.e. contact community nurses, GP or if needed their Gastroenterologist.

In those who wish to have the LTAD removed, this will be performed by the research fellow under the supervision of Dr Austin as required Localise. They will then continue to receive standard care by their usual medical team. Those in the LVP arm (standard of care) will continue as per usual standard of care, their usual Gastroenterologist/Hepatologist will be informed of the end of their involvement in the study by the research fellow or Principle Investigator.

For participants in the LTAD arm who have not succumbed to their illness by the end of the study and who wish for the LTAD to remain in situ, Principle Investigator/ the clinical research fellow/nurse will Localise send a notification to Rocket Medical using the standard Rocket Medical discharge notification form. This is the same standard form as is used to notify Rocket Medical of when a non-trial patient is discharged with LTAD in situ to allow contact with the community nursing team for support and ordering of further supplies as required.

When a participant completes study follow up their GP (with consent) will be sent (as per documented in **SOP 07**) the REDUCe end of study GP notification letter **v1.0 20 July 2016**, informing them they are no longer a study participant and that their care has reverted to their usual Gastroenterologist/Hepatologist. This letter will be amended as appropriate depending on which study arm the participant is in. For those in the LTAD group who opt to continue with LTAD, the letter contains details regarding ongoing ordering of drainage bags. The letter also requests the GP continue prescription of the prophylactic antibiotic (Ciprofloxacin at BSUH) in both groups as standard of care.

Standard end of study procedures will be followed in terms of documentation and study monitoring

- Only those SAEs that are related (i.e. Serious Adverse Reaction, or SAR) to the study intervention (LTAD group 1) should be reported in an expedited manner to BSCTU (immediately).
- If a community nurse or other staff member suspects that a SAR has occurred, they should notify the research fellow/nurse immediately via the REDUCe study mobile number: 07825 928139, CIRU reception, direct dial 01273 664437 or via hospital switchboard on 01273 696955 ext. 3522.

- A REDUCE SAE form should be completed; Version 1.0 – 07/09/2015

- If only minimal information is available, submit the form anyway and provide follow up information by updating the form as soon as this becomes available.

- The form must be reviewed and signed off by the Chief Investigator / Principle Investigator or Co-Investigator at the site.

- Note: The SAEs should be assessed on whether the nature, seriousness, severity or outcome of the event would be expected according to side effects ever previously seen with the LTAD.

(i.e. unexpected does not mean 'unforeseen at this time').

- The form should be sent by email to Trial.Monitors@bsuh.nhs.uk and
- the REDUCE Trial Management team by emailing REDUCE.BSUH@BSUH.nhs.uk

- The team will respond with confirmation of receipt. If this has not been received within 4 hrs, please telephone 01273 696955 ext 7447 to ensure the report has been received.

- The REDUCE Trial Management team will send to the CI to review for expectedness.

- Any Suspect, Unexpected, Serious Adverse Reactions (SUSARs) will be reported to the REC by the CI (or delegate).

- Follow up reports will be requested from the REDUCE Trial Management team until the event has been resolved and a final report is received.

Appendix 6: Hospital service use proforma

V1.0 – 11 Sept 2015

REDUCe study : Hospital Service Use proforma

Patient ID_____-

Date entered study:_____

Date left study: _____

Date of hospital service	Hospital transport Specify: In / Out / Both / None			A&E attendance NOT admitted	Clinic appointment (specify which)	Tests or treatments (specify which)	Type of attendance	Specialist team e.g. alcohol, psychiatric, palliative, during stay or OP visit	Day case (specify, e.g. ascites)	A&E attendance results in admission	In hospital stay			Initials and date data extracted
	999	Hospital car	Ambulance				In patient, outpatient or day case?				Number of nights	Medical treatment (drugs)	Other procedures	

Please tick the relevant columns and provide details where asked

Peer reviewed publications

Chapter 3

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. https://doi.org/10.1111/liv.14162

Chapter 4

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Chapters 5 and 6

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