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The Integration of Palliative Care into the Management of End Stage Liver Disease

The Integration of Palliative Care into the Management of End Stage Liver Disease

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ABSTRACT

Introduction: Patients with liver disease seldom receive palliative care (PC), despite an extensive illness burden. Through considering PC in liver disease from a variety of perspectives, I investigate whether clinical models could be improved through the routine integration of PC and, if so, how.

Methods: I used a mixed methods approach to integrate four component studies. An on-line questionnaire study of UK hepatologists examined existing practices and explored the barriers to PC in liver disease. Questionnaire responses were used to purposively select a qualitative sample for semi-structured interviews, which were analysed thematically. The PC needs of patients with liver disease and their carers were explored qualitatively through in-depth interviews of patients with ascites and carers bereaved by liver disease. Interviews were analysed thematically within a single framework. I used generalised linear and logistic regression modelling to examine associations between demographic and healthcare factors (including use of day-case services), and outcomes relating to health-economics (cost, bed days, emergency readmission) and place of death among patients who died from liver disease with ascites in England between 2013-15. I used 'plan-do-study-act' quality improvement methodology to design a supportive care intervention for patients with advanced liver disease, alongside development of a poor-prognosis screening tool.

Results: Questionnaire respondents (305/906 – 33.7% response rate) identified lack of routine consideration and a lack of existing clinical models as the key barriers to PC and were more likely to invoke PC for patients with malignancy. Analysis of 10 qualitative interviews with hepatologists demonstrated recognition of extensive unmet PC needs, however identified a myriad of disease-based, structural and attitudinal barriers which frequently made PC 'inaccessible'. Interviews with 12 patients and five bereaved carers demonstrated that patients' PC needs were often incompatible with the healthcare services available to address them; these being centred in secondary care and focussed on disease-modification. Analysis of data from 13,818 deaths demonstrated that patients attending a day-case service had associated reductions in cost (-£4,240.29; 95% confidence interval (CI) -£4,829.45, -£3,651.12; $p<0.0001$), bed days (-16.68 days; 95%CI -18.13, -15.22; $p<0.0001$), odds of early readmission (odds-ratio (OR) 0.35; 95%CI 0.31-0.40; $p<0.0001$), and odds of dying in hospital (OR 0.31; 95%CI 0.27,0.34; $p<0.0001$). Death from hepatocellular carcinoma was also associated with improved outcomes. Following five plan-do-study-act cycles a supportive care intervention and poor prognosis screening tool were developed. Retrospective application of the screening tool demonstrated a positive predictive value of 81.3% for identifying 1-year mortality.

Conclusion: Clinical models for PC in liver disease which maximise use of ambulatory care, routinely assess for poor prognosis, and proactively address PC needs will improve care and are likely to be cost-effective.

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AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: .....

DATE: .....

ACADEMIC OUTPUT ARISING FROM THIS THESIS

Peer reviewed publications

1. Hudson BE, Hunt V, Waylen A, Verne J, McCune A, Forbes K. '*The incompatibility of healthcare services and end-of-life needs in advanced liver disease: a qualitative interview study of patients and bereaved carers.'* Palliative Medicine. 2018 May;32(5):908-918. doi: 10.1177/0269216318756222.
2. Hudson BE, Round J, Georgeson B, Pring A, Forbes K, McCune A, Verne J. *'Cirrhosis with ascites in the last year of life: a nationwide analysis of factors shaping costs, healthcare utilisation, and place of death; and the impact of day-case paracentesis services.'* The Lancet, Gastroenterology and Hepatology. 2018. Feb;3(2):95-103. doi:10.1016/S2468-1253(17)30362-X.
3. Hudson BE, Ameneshoa K, Gopfert A, Goddard R, Gordon F, Collins P, Portal AJ, Reid C, Verne J, Forbes K, McCune A. *'Integration of palliative and supportive care in the management of advanced liver disease: development and evaluation of a prognostic screening tool and supportive care intervention.'* Frontline Gastroenterology. 2017. Jan8(1):45–52. doi: 10.1136/flgastro-2016-100734

Published abstracts and conference presentations

Oral presentations:

1. Hudson B, Forbes K, McCune A, Verne J. *'The effect of planned care on end of life outcomes and costs in patients with refractory ascites. A retrospective cohort study of deaths in England.*' European Association of Palliative Care. Annual congress. May 2017
2. Hudson B, McCune A, Forbes K, Verne J. *'Inequalities in death from liver disease in England in 2015'* British Association for the Study of the Liver, Annual Congress, Manchester, September 2016. *Winner of best abstract – End of life section.*
3. Hudson B. *'Integrating supportive and palliative care into the active management of decompensated cirrhosis'* European Association of Palliative Care, Annual congress. Dublin. April 2016

Poster presentations:

1. Hudson B, Round J, Georgeson B, Pring A, Forbes K, McCune A, Verne J. *'Cirrhosis with ascites in the last year of life: a nationwide analysis of factors shaping costs, healthcare*

utilisation, and place of death; and the impact of day-case paracentesis services.' British Association for the Study of the Liver national congress. September 2017

2. Hudson B, Forbes K, McCune A, Verne J. *'Challenges in integrating supportive and palliative care in the management of end-stage liver disease. A mixed method study of UK hepatologists'* European Association of Palliative Care. Annual congress. May 2017
3. Hudson B, Forbes K, McCune A, Verne J, Round J. *'The effect of planned care on resource use and end of life outcomes in patients with diuretic resistant ascites. A retrospective cohort study of deaths in England.'* The International Liver Congress 2017 (European Association for Study of the Liver). Amsterdam. April 2017
4. Hudson B, Ameneshoa K, Collins P, Portal J, Gordon F, Verne J, McCune A. *' Development of a palliative and supportive care intervention to identify and manage patients with cirrhosis at high risk of dying'* British Association for the Study of the Liver annual congress. September 2016. *Winner – highly commended award*
5. Hudson B, Verne J, McCune A, Forbes K. *'Delivering supportive and palliative care in advanced liver disease across the UK A mixed methods study of hepatologists' perceptions, current service provision and future challenges'* British Association for the Study of the Liver annual congress. September 2016.
6. Goddard R, Gopfert A, Connely G, Hudson B. *'Incorporating supportive and palliative care into the inpatient management of decompensated cirrhosis – a quality improvement project'* British Society of Gastroenterology, June 2016
7. Hudson B, Forbes K, Verne J, McCune A. *'Poor prognostic screening and integration of supportive and palliative care in the management of end stage liver disease'* European Association of Palliative Care, Annual meeting, April 2016
8. Hudson B, Ameneshoa K, Collins P, Portal AJ, Gordon F, Verne J, McCune A. *'Screening for poor prognosis can improve care for patients with end stage liver disease?'* American Association for Study of Liver Disease, Annual meeting. November 2016

Invited Seminars

1. Title: *'Integrating supportive and palliative care into the management of advanced liver disease'*. University of Birmingham – Annual liver course June 2018 and May 2019
2. Title: *'Advances in the prognostication of end stage liver disease'* British Association for the Study of the Liver. National working group on end of life care. March 2018
3. Title: *'The use of palliative care in liver disease'* Welsh National Liver Meeting – Cardiff. August 2017

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LIST OF ABBREVIATIONS

ArLD	Alcohol related liver disease	NASH	Non-alcoholic steatohepatitis
CTP	Child Turcotte Pugh score	ONS	Office for National Statistics
DGH	District General Hospital	OR	Odds ratio
EOL	End of life	PC	Palliative care
ESLD	End stage liver disease	PDSA	Plan Do Study Act
GP	General practitioner	PPV	Positive predictive value
HCC	Hepatocellular carcinoma	QOL	Quality of life
HE	Hepatic encephalopathy	RCT	Randomised controlled trial
HRG	Healthcare resource group	SPC	Specialist palliative care
ICD-10	International Statistical Classification of Diseases and Related Health Problems version 10	UK	United Kingdom
LVP	Large volume paracentesis	US	United States
LYOL	Last year of life	VOICES	Views of informal carers – evaluation of services
MDT	Multi-disciplinary team	WHO	World Health Organisation
MELD	Mayo end stage liver disease score		

CHAPTER 1 - INTRODUCTION

The introductory chapter of this thesis is subdivided into the following four sections:1a – Background to thesis; 1b – Palliative care in end-stage liver disease – a review of the existing literature; 1c – Thesis aims and objectives; 1d – Outline of thesis and the use of mixed methods.

1A - BACKGROUND TO THESIS

The burden of liver disease in the United Kingdom

There has been a dramatic increase in deaths caused by liver disease in the United Kingdom (UK) over the past 50 years. Between 1970 and 2012 the standardised mortality rate for liver disease rose by approximately 400%.[1] In 2012 there were 11,575 people in England who died with liver disease recorded as their primary cause of death (approximately 2% of all deaths during this period). This increased to 15,234 if those with liver disease recorded as a contributory cause were also included (approximately 3% of all deaths). When compared with the mortality rate in the 1980s this represents an excess of approximately 7 deaths per 100,000 population a year due to liver disease.[2] Overall, liver disease now represents the fifth commonest cause of death in the UK. Liver disease disproportionately affects a younger cohort of patients and is set to overtake ischaemic heart disease as the primary cause of death in working age people over the next decade (18-65).[1, 3] Changes in mortality associated with liver disease are in stark contrast to the considerable improvements seen in other chronic life-limiting conditions such as heart disease, cancer and stroke. Alongside this human cost, liver disease is placing an increasing financial strain on the UK National Health Service (NHS). A recent report from the Foundation for Liver Research estimated the cost to the NHS from alcohol related disease (ArLD) alone over the next 5 years to be approximately 17 billion pounds.[4]

Whilst liver disease has a wide variety of causes, including autoimmune and metabolic conditions, its increasing incidence has been largely attributed to lifestyle factors, specifically alcohol dependency, obesity, and injecting drug use. Approximately 75% of deaths from liver disease in the UK are caused by excess alcohol consumption.[5] Increases in ArLD deaths are mirrored by population trends in alcohol consumption over the same time period.[6] Rising levels of obesity in the UK population have led to an increasing incidence of non-alcoholic steatohepatitis (NASH), or obesity related liver disease.[1] NASH represents the advanced stage of non-alcoholic fatty liver disease, which is now estimated to be present in approximately one quarter of the UK adult population.[7] Injecting drug use remains the commonest method of transmitting hepatitis C. Whilst

newer agents for the treatment of hepatitis C have become available over the past few years, it remains the third most frequent indication for liver transplantation (LT) in the UK.[8]

The lifestyle factors related to liver disease are strongly associated with increasing socio-economic deprivation, and appreciable healthcare inequalities have been observed. Over 36% of deaths from ArLD occur in the most socio-economically deprived quintile of the population.[2] Furthermore, death from liver disease in the most socio-economically deprived population quintile occurs on average 9 years earlier than in the most affluent.[9]

The natural history of liver disease

Illnesses (e.g. viral hepatitis) and substances (e.g. alcohol) can injure liver cells. Whilst the liver has excellent regenerative capacity, over time damage to liver tissue may occur. This initially causes fibrosis, which progresses on to more permanent scarring over time. This scarring is known as cirrhosis, which is defined as the histological development of fibrous, regenerative liver nodules in response to long standing injury to the liver.[10]

Cirrhosis generally remains asymptomatic until complications develop. Diagnosis prior to this stage usually represents an incidental finding, and previously undiagnosed cirrhosis is a common finding at post-mortem examination.[11] Complications of cirrhosis occur secondary to the development of portal hypertension. This refers to increased pressure in the portal vein, the main blood vessel supplying the liver. The most frequently occurring complications of cirrhosis are ascites, jaundice, hepatic encephalopathy and variceal bleeding.

Ascites refers to the build-up of fluid within the abdominal cavity. It is frequently associated with the accumulation of fluid in the pleural (chest) cavity and the limbs. Ascites can initially be managed using diuretics (water tablets). The development of ascites which is resistant to diuretic treatment (refractory ascites) represents a further deterioration in disease severity. Jaundice occurs due to the liver's inability to excrete a pigment called bilirubin. It presents as yellowing of the skin and eyes and itch. Hepatic encephalopathy (HE) represents a neuro-psychiatric syndrome caused by the inability of the liver to metabolise toxic substances, which in turn affect the brain. HE is often fluctuant and can range in severity from mild cognitive impairment to coma. Increasing pressure within the portal vein leads to the formation of collateral blood vessels around the liver known as varices. Varices most commonly arise adjacent to the oesophagus. Rupture of these vessels results in variceal bleeding, which can represent an immediately life-threatening emergency.[10]

The onset of these complications specifically heralds the progression of disease from a 'compensated' to a 'decompensated' state. Notwithstanding these complications, end stage liver disease (ESLD) is associated with a heavy burden of chronic physical and psychological symptoms including muscle cramps, fatigue, pain, sexual dysfunction and depression.[12-14] Whilst international definitions vary somewhat, for the purposes of this thesis the terms decompensated cirrhosis and ESLD are used synonymously and interchangeably.

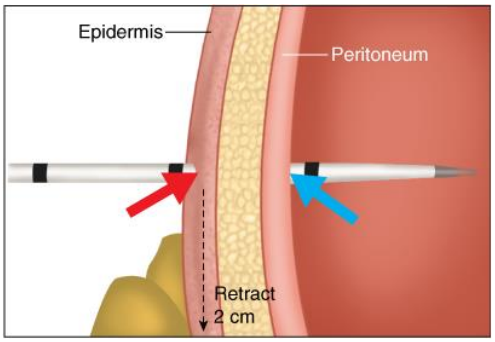
Cirrhosis is the primary risk factor in the development of liver cancer, or hepatocellular carcinoma (HCC). Approximately 90% of HCC occurs among patients with cirrhosis.[15] Every year approximately 2-3% of patients with cirrhosis will develop HCC (higher if caused by viral hepatitis or haemochromatosis – a disease leading to iron deposition in the liver). Six-monthly surveillance using ultrasonography is advised by the major American and European societies to facilitate earlier detection of HCC.[16, 17] The prognosis from HCC is dependent on the size of the lesion and the severity of liver disease at presentation. Whilst resection is possible for a minority of non-cirrhotic patients, LT usually represents the only curative treatment in patients with HCC and cirrhosis.

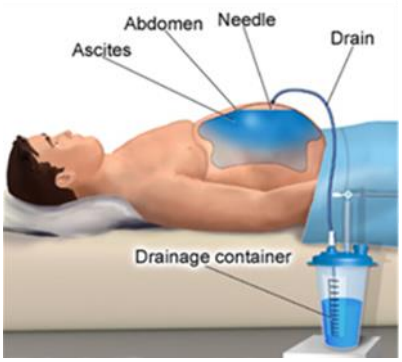
Medical management of decompensated cirrhosis

Treating the complications of cirrhosis frequently requires inpatient admission to an acute hospital. Invasive procedures, for example the use of gastrointestinal endoscopy for the management of variceal bleeding, are commonplace and patients frequently require intensive care unit (ICU) admission.[18]

Ascites is the most frequent complication of cirrhosis, and the commonest reason for hospital admission.[19] Once refractory to medical treatment, patients require intermittent drainage of the fluid (large volume paracentesis - LVP) to achieve symptomatic relief. This procedure is undertaken over a 6-hour period and typically needs to be repeated on a 2 to 4-week basis. Typically volumes of between six and 15 litres are drained during each procedure (figure 1.1).[20] LVP procedures have traditionally been undertaken on an ad-hoc inpatient basis, following a referral from primary care or the emergency department, at the point where a patient's symptoms become intolerable. More recently, day-case LVP programmes have been introduced across the UK. In such instances, patients are admitted to a day-case unit on a planned basis, undergo LVP and are discharged later the same day.

Figure 1.1 – Schematic diagram of large volume paracentesis [21]





LT represents the only cure for ESLD, and has excellent rates of 5-year survival.[22] Strict listing criteria and a shortage of donor organs however mean that this treatment is available to a minority of patients. Listing for transplantation occurs only following an extensive program of medical and psychological assessment, and approximately 50% of patients formally evaluated for transplantation are assessed as ineligible.[23] The vast majority of patients who die from ESLD never undergo formal assessment. Common reasons for this include age, frailty, physical or psychiatric co-morbidity, ongoing issues with addiction and late presentation. 878 liver transplants were performed in the UK in the period April 2015-March 2016.[24] During the same period, in England alone, there were over 15,000 deaths attributed to ESLD.[25] Even among patients listed for transplantation, in the UK approximately 20% die whilst on the waiting list.[8]

Treating the complications of ESLD 'buys time' to allow for re-compensation of the disease (e.g. with abstinence from alcohol or treatment of hepatitis C) or LT. The last year of life (LYOL) in ESLD is however therefore typically punctuated by increasingly frequent hospital admissions,[26-28] and the overwhelming majority of deaths from ESLD occur in hospital (73% overall, 81% in ArLD). This compares with under 40% of cancer related deaths.[2]

Prognosis in ESLD

Numerous scoring systems have evolved to assist physicians in assessing the severity of liver disease and predicting mortality. In 1964, Child and Turcotte selected five criteria (albumin, bilirubin, ascites, encephalopathy, and nutritional status) which they converted into a composite score to predict the mortality of patients undergoing shunt surgery to relieve portal hypertension.[29] In response to criticism of its subjective nature, nutritional status was replaced with prothrombin time in 1973 to create the 'Child Turcotte Pugh' (CTP) score. On the basis of their score, patients are categorised from CTP-A (least severe – 2 year survival = 85%) to CTP-C (most severe - 2 year survival = 30%).[30] Whilst the score was developed to guide a, now antiquated, surgical intervention – prospective studies of prognosis among patients with cirrhosis have subsequently confirmed its utility in predicting 1-year survival.[31] CTP score was previously used as a mechanism to prioritise patients listed for LT, however, it was superseded by the Mayo ESLD Score (MELD) in the late 1990s. The MELD score was developed prospectively among patients undergoing decompressive therapy for portal hypertension. It was based on purely biochemical parameters, removing the subjectivity of clinical assessment.[32] The MELD score was found to be useful for grading risk of death at three time points (1 week, 3 months and 1 year), and has since been used to guide timing and prioritisation of LT.

In a systematic review of 118 studies regarding predictors of mortality in cirrhosis, D'Amico et al summarised the prognosis of patients at varying stages of liver disease and evaluated the accuracy of prognostic scoring systems used to prioritise patients for LT.[33] Transition from compensated to decompensated cirrhosis occurred at an estimated rate of 5-7% per year, and was associated with a fall in median survival from 12 to 2 years respectively. Within the decompensated phase, the onset of specific complications heralded progressive reductions in median survival. These are summarised in table 1.1.

Table 1.1 – Median survival in months at varying stages of ESLD*	
First onset of ascites	2 years
Hepatic encephalopathy	1 year
Refractory ascites	6 months
Refractory ascites with renal failure	1 month
* As reported by D'Amico et al [33]	

Whilst it is possible to estimate survival on a population level, prediction of terminal decline for any individual patient with ESLD is inherently more difficult. Treatment of the causative agent can result in reversal of fibrosis and re-compensation. For patients with ArLD, it has long been recognised that sustained abstinence frequently results in major improvements in liver function, and can avert the need for LT.[34-36] Similarly, hepatitis C now represents an eminently curable condition and newer antiviral therapies have been demonstrated to be safe and effective in patients with decompensated cirrhosis.[37]

The cost of ESLD to healthcare systems

ESLD is associated with substantial financial costs to healthcare systems. In the US, more than 150,000 hospital admissions annually are associated with cirrhosis, with an estimated cost of over $4 billion per year.[38] Patients with cirrhosis place a disproportionate burden on acute hospital services towards the EOL. A recent evaluation of the economic impact of hospitalisation in Italy compared admissions related to cirrhosis to patients with chronic obstructive pulmonary disease (COPD) and heart failure (HF).[19] It reported that costs from admissions associated with cirrhosis were on average 30% greater than for COPD or HF. In this study, ascites was the most common reason for admission among patients with cirrhosis. Increased overall costs were attributed to longer hospital stays among these patients specifically.

Recurrent unplanned hospital admissions are common among patients with cirrhosis. In a large, retrospective population-based cohort study in Hong Kong, cirrhosis was associated with the highest rate of emergency readmission when compared with 10 other common chronic conditions.[39] A single centre US study estimated that 69% of patients admitted with decompensated cirrhosis required at least one emergency readmission, and that 37% of patients were readmitted within a month of discharge - associated with a cost of over $20,000 per admission.[40] Other studies have demonstrated 30-day readmission rates of between 30-40% in patients with decompensated cirrhosis.[27, 28] This is substantially higher than in other life limiting chronic conditions.[39] Readmissions place resource burdens on health care systems, in part due to the duplication of care (e.g. repeated clinical assessments, emergency department visits, and laboratory investigations).[41] As a means of incentive to improve discharge planning, readmissions within 30 days have not been reimbursed within the NHS since 2010.[42]

The principles of palliative care

The concept of palliative care (PC) emerged from a recognition of the suffering associated with dying.[43] It is defined by the World Health Organisation (WHO) as:[44]

"an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"

The WHO further defines a set of principles that constitute appropriate PC, which are outlined in figure 1.2.[44] The 2002 definition was updated from a 1990 version to encompass patients with non-malignant disease and remove any requirements for the underlying disease to be "non-responsive" to curative therapy. [45]

Figure 1.2 – Principles of palliative care as outlined in WHO definition (2002)

Palliative care:

- Provides relief from pain and other distressing symptoms.
- Affirms life and regards dying as a normal process.
- Intends neither to hasten or postpone death.
- Integrates the psychological and spiritual aspects of patient care.
- Offers a support system to help patients live as actively as possible until death.
- Offers a support system to help the family cope during the patient's illness and in their own bereavement.
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated.
- Will enhance quality of life and may also positively influence the course of illness.
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Although general palliative care can be provided by professionals from across a range of healthcare disciplines, specialist palliative care (SPC) was recognised as a medical specialty in 1987. Published guidelines from a range of medical bodies, in particular oncology, urge physicians to work closely with SPC in the management of patients with life-limiting conditions.[46, 47] Such recommendations are supported by a growing literature demonstrating benefit. In a randomised controlled trial (RCT) of patients with lung cancer, Temel et al demonstrated that early use of SPC improved quality of life, mood and even mortality.[48] A recent systematic review and meta-analysis also reported improvements in quality of life (QOL) in patients receiving SPC, particularly when introduced at a relatively early stage.[49]

Defining need in palliative care

For PC to be established, resourced and prioritised within a healthcare system, an understanding of the PC needs of the population served is required. There are varying approaches to the definition and assessment of need. In the 1940s, Maslow, as US psychologist, conceptualised human needs as a hierarchy – which underpinned human motivation.[50] At the fundamental level, he described the basic physiological needs of food, water and shelter. In Maslow's hierarchy, motivation to

achieve higher levels of need (which progress through the need for safety, belonging, self-esteem and ultimately self-fulfilment) only become active once lower level needs are met. The model implies that certain PC needs (e.g. the need for spiritual care) may be irrelevant if lower level needs (e.g. food and water) have not been met. This may represent an important consideration for populations commonly afflicted by liver disease. Nonetheless, Maslow's linear construct has been criticised for being overly simplistic, in that higher level needs may not be mutually exclusive to fundamental ones.[51] An alternative model for describing need was proposed by Bradshaw in 1972.[52] His 'taxonomy of need' was described from the perspective of the person assessing or defining it. He defined four types of need: felt need (based around what an individual felt they needed), expressed need (what an individual demands), normative need (what a professional thinks an individual wants) and comparative need (need as compared with others' situation). Bradshaw's taxonomy is helpful in the context of PC, in that it moves from a reliance on expressed need (which may be impaired due to an individual's illness – e.g. the presence of HE in liver disease) and enables professionals to advocate for interventions which may benefit their patient. Nonetheless, reliance on normative and comparative assessment of need is also imperfect. The insight and knowledge of healthcare professionals will vary greatly, and full assessment of comparative need relies on the needs of the comparator group being fully met.

When need is defined within the context of healthcare, the potential to benefit from intervention also requires consideration. In the absence of an effective intervention, it may be that the 'need' is outside the sphere of healthcare. In their work on healthcare needs assessment, Stevens and Raftery added an additional component to Bradshaw's taxonomy - *"the ability to benefit from healthcare"*.[53] This definition equates healthcare need with the capacity to benefit from healthcare. In the context of PC this may include symptom control or carer support (see fig 1.2). Stevens and Raftery went on to propose a protocol for assessing the healthcare needs of a population, which was adapted for use in PC by Higginson.[54] This assessment of need triangulates the size of the need (based on epidemiological data such as incidence/prevalence/mortality etc), the effectiveness and cost effectiveness of potential services and the services currently available. Within this thesis, I use the term 'need' to describe healthcare need as defined by Stevens and Raftery.[53] The components of healthcare needs assessment in PC, as described by Higginson, are also considered.[54]

Palliative care in non-malignant diseases

Whilst SPC developed initially to support the needs of patients with incurable cancer, comparable needs among patients with non-malignant life limiting diseases have been recognised.[55, 56] A growing body of evidence describes PC needs in patients with 'organ failure' conditions, for

example heart failure, chronic respiratory disease and renal failure.[57-61] The benefits of SPC in these populations has been demonstrated. A RCT of outpatient SPC interventions (including advance care planning (ACP), psychosocial support and caregiver training) for patients with advanced heart failure chronic respiratory disease or cancer, with an expected survival of between 1-5 years, demonstrated improvements in certain symptoms, anxiety and spiritual well-being in the intervention group.[62] A RCT of patients with the same diagnoses but whom were housebound, demonstrated that those receiving in-home SPC benefited from increased satisfaction with care and markedly reduced healthcare costs.[63]

Prospective longitudinal studies of functional decline describe differences in the typical trajectories of patients dying from malignancy as compared to those with 'organ-failures'.[64] Whilst patients with organ failure typically demonstrate a slow deterioration in function, punctuated by acute deteriorations from which they often recover (e.g. infective exacerbations), patients with malignancy usually demonstrate more predictable linear declines in function. Prediction of terminal decline and timing of need for SPC interventions in patients with organ failure may therefore be more challenging. These difficulties in prognostication are reflected in published guidelines from international medical bodies, which advise on when and how to initiate PC in patients with chronic cardiac, respiratory and renal disease.[65-67] All advocate for the early involvement of SPC, shared decision making and explanation of the inherent prognostic uncertainties. There are no equivalent guidelines for ESLD. Elsewhere, prognostic criteria have also been developed to assist clinicians in identifying patients who may be approaching the end of life (EOL). An example, widely used in the UK, is the Gold Standards Framework, which similarly omits any criteria for ESLD.[68]

1B - PALLIATIVE CARE IN END-STAGE LIVER DISEASE – A REVIEW OF THE EXISTING LITERATURE

Despite the burgeoning mortality associated with liver disease and an extensive complex of associated physical and psychological symptoms, until recently, PC in ESLD has received relatively little attention, resulting in a paucity of clinical models guiding its use. A review of the existing literature was undertaken to identify gaps in the existing knowledge base around which the aims and objectives of this thesis could be based.

Methods for literature review

A comprehensive systematic review of academic articles regarding a closely related topic (the patient experience of advanced liver disease) was published by Kimbell et al prior to the commencement of this research in October 2015.[69] This summarised much of the relevant pre-existing academically published work, and I did not wish to replicate this study. It did not however consider grey literature. Use of government data held by Public Health England was planned from an early stage, and the literature review therefore had to therefore extend beyond academic journals alone (such that previous Public Health England/government reports etc could also be considered). During the research and writing up period (October 2015 – October 2018) there was a considerable growth in interest around this topic, reflected by a substantial expansion in published articles and conference papers. The method for literature review had to be responsive to this and retain the ability to iteratively review the evolving field. In comparison with systematic reviews, traditional literature reviews have been criticised for lacking an explicit protocol meaning that the author's subjectivity is implicit, and the completeness of the arguments put forward cannot be assessed.[70] Nonetheless, due to a combination of the factors described above, a decision to not undertake an early formal systematic review was made. A traditional literature review methodology (allowing for iterative and cyclical review of the evidence from a wide variety of sources) was adopted instead.[71]

The initial review of academic literature was conducted using a search of formal databases. Whilst intending to cover all aspects of advanced liver disease, I wanted the thesis to predominantly focus on the needs of patients with non-malignant liver disease outside the field of LT. As such, initial searches excluded articles relating exclusively to LT or HCC. A search of original research articles and review papers (excluding those relating exclusively to LT or HCC) published in English from PubMed, MEDLINE, EMBASE and Google scholar from inception until March 1st 2018, with the

terms: ((“cirrhosis” OR “ESLD” (title/abstract)) AND (“palliative care” OR “end of life care”(title/abstract)) identified 42 papers (table 1.2).

Table 1.2 - Overview of literature on palliative care in ESLD	
Article type	Number of studies
Review articles	9
Qualitative studies	7
Retrospective notes review/audit	6
Case series	4
Retrospective database analyses	4
Survey of healthcare professionals	4
Observational prospective studies	3
Quality improvement projects	3
RCT feasibility studies	2
Total	42

Of the initial studies identified, many utilised methodologies which generate low levels of evidence (e.g. case series).[72] Retrospective reporting of data was commonplace and, outside the context of feasibility studies, there were no data from prospective RCTs. This high-level search was clearly not reflective of all research within the field. The initial search terms were narrow, particularly given the aforementioned exclusions, which were relaxed somewhat as the research period progressed. Search terms and strategies evolved as familiarity with the topic increased, and the literature was reviewed iteratively throughout the research period. Formal database searches were supplemented by scrutiny of reference lists and bibliographies of newly published studies.

Over the past decade all government reports on liver disease have been produced using data held within Public Health England. Public Health England databases were therefore used to search for all reports relating to liver disease over the last 10 years. This review of grey literature was supplemented through review of internet resources (e.g. reports from the British Liver Trust).

Analysis and synthesis of literature review

Hart defined synthesis in literature reviews as *“the act of making connections between the parts. It is not simply a matter of re-assembling them back into the original order but of finding a new order”* .[73] I took a thematic approach to synthesis. Each study or report was summarised and

categorised based on its key themes. Studies addressing similar themes were then read critically and compared. Where a study spanned more than one area, relevant parts were assessed separately within each appropriate thematic area. Literature from outside the field of liver disease was also referenced when it was appropriate to provide context. Gaps within the existing knowledge base were identified and summarised. These were used subsequently to guide the aims and objectives of the thesis.

Literature arising from my review fell within two overarching themes, each with three separate sub-themes. The first theme related to the patient experience of ESLD. This theme encompassed the following subthemes: a) Physical symptoms and QOL in ESLD, b) Psychological symptoms in ESLD, c) The lived experience of ESLD. The second theme related to the use of PC in ESLD. This theme encompassed the following subthemes: a) The utilisation and timing of PC in ESLD, b) Professional attitudes towards PC in ESLD and c) Clinical models for PC in ESLD.

Theme 1 - The patient experience of ESLD

a) Physical symptoms and QOL in ESLD

Much of the literature surrounding this topic utilises validated, self-reported questionnaires which quantitatively assess QOL as compared with normal controls. A 2014 review described consistency in studies demonstrating significant deteriorations in health-related QOL as liver disease severity increased.[74] Reductions in QOL have been attributed to a multitude of causes, including physical symptoms, psychological distress, social isolation and stigma.

The impact of physical symptoms on QOL in ESLD is widely described. SUPPORT, a large prospective study of 9105 seriously ill patients admitted to five United States (US) teaching hospitals between 1989 and 1994, included 575 who died from ESLD.[75] Pain, comparable to that experienced in lung or colonic cancer, emerged as the most commonly distressing physical symptom. Loss of income due to caring responsibilities was frequently described by family members. In a study of 544 patients with cirrhosis, Marchensini et al demonstrated a significant deterioration in QOL following the onset of ascites. Ascites was found to be independently predictive of psychological distress, self-reported physical health and pain.[76] The presence of HE, the main neurocognitive complication of ESLD (described above), is equally highly associated with reductions in patient functioning and QOL. A study of patients undergoing assessment for LT demonstrated patients with HE had significantly lower QOL scores than their non-encephalopathic

counterparts.[77] Impairments in functioning have also been demonstrated in studies of patients with sub-clinical HE.[78]

The symptom complex of ESLD extends beyond the features of hepatic decompensation. In the study of 544 patients described above, Marchensini et al highlighted that most participants felt more afflicted by 'minor' complaints (such as muscle cramps and itch) in their day-to-day lives than by some of the life-threatening complications associated with ESLD. This conclusion was supported by a questionnaire based study of 129 patients with ESLD in Korea which identified fatigue, peripheral oedema, muscle cramps and concentration difficulties as carrying the most substantial symptomatic burden.[79] An analysis of medical records from patients denied or delisted for LT retrospectively assessed patient-reported symptoms against the revised Edmonton Symptom Assessment System for PC.[80] Both physical (65% pain, 58% nausea, 49% lack of appetite, 48% shortness of breath) and psychological (36% - anxiety, 10% - clinical depression) symptoms were commonplace.[81] Health-related QOL studies have demonstrated significantly increased levels of fatigue amongst patients with liver disease across a range of aetiologies, as compared with both normal controls and successfully transplanted patients.[82, 83] A study of 44 cirrhotic patients reported a high frequency of sleep disturbance when compared to normal controls, which was attributed in part to higher levels of depression and anxiety.[84] Sleep disturbance was also reported by 69% of 156 patients in a study investigating depression in ESLD.[14] A 2010 review highlighted the ubiquity of sexual dysfunction (caused by a combination of the disease itself, its treatment and its psychological sequelae) in ESLD, particularly among male patients.[85]

b) Psychological symptoms in ESLD

A high burden of psychological symptoms among patients with ESLD has also been demonstrated. The SUPPORT study, described above in relation to physical symptoms, demonstrated higher levels of psychological distress in patients dying from ESLD compared to those with other types of organ failure. A comparison of health-related QOL between patients with cirrhosis, heart failure and chronic obstructive pulmonary disease arrived at a similar conclusion.[86] Analysis of 250 questionnaire responses from patients with ESLD identified depression as the predominant psychological factor impairing QOL.[87] This conclusion was reiterated by Bianchi et al in their questionnaire study of patients with ESLD, which identified clinical depression in over 50% of their randomly selected sample.[14] A prospective analysis of outcomes in ESLD patients with depression demonstrated increased mortality compared with non-depressed counterparts, independent of liver disease severity.[88]

In addition to these physical and psychological features, patients with ESLD commonly face an array of social and economic afflictions. Issues of ongoing alcohol and drug addiction are commonplace. Many patients do not have existing relationships with primary care making access to treatment circuitous.[89, 90] Societal associations between alcohol dependency and cirrhosis contribute to high levels of stigma. A questionnaire study of 300 patients with cirrhosis demonstrated that most patients perceived stigma on this basis frequently.[91]

Recently (2019), Peng et al considered physical and psychological symptom prevalence and QOL among patients with ESLD through a wide-ranging systematic literature review.[92] Their conclusion, that ESLD was associated with a diverse range of physical and psychological symptoms which impacted considerably upon health related QOL, was consistent with the evidence outlined above (much of which was quoted within the review). They directly compared the prevalence of common symptoms found in ESLD (e.g. pain, breathlessness, fatigue depression) with other life limiting conditions (malignant and non-malignant) and found them to be broadly comparable – although occurring at a significantly younger age in ELSD. Difficulties around managing the symptomatic needs of patients with uncertain prognoses, specifically in relation to liver transplantation, were recognised. Interestingly, the authors argued that to manage the specific complexities associated with ESLD, new collaborative approaches to care were required. Specifically, they recommended models of care which regularly sought input from multiple specialties simultaneously, including primary care, hepatology and SPC. -

c) The lived experience of ESLD

Many of the above studies utilise quantitative questionnaire-based outcome measures to assess health-related QOL. Such methodologies have been criticised for arbitrarily weighting outcome measures, and being restrictive in how they reflect individual experiences.[93, 94] Patient groups have also criticised these probabilistic approaches, arguing that they do not facilitate understanding of their subjective illness experience.[95, 96] Qualitative methodologies can overcome some of these limitations and can be used to better examine the lived experience of a given condition.[69] Although there is a paucity of qualitative data in liver disease, as highlighted by Kimbell et al in her systematic review on the topic,[69] a summary of findings from key studies are described here.

Wainwright performed 10 in-depth interviews of opportunistically recruited patients following LT, and analysed data using grounded theory.[97] He reported two key themes: 'becoming ill' which described the process of deteriorating health and diagnosis (including the social isolation caused

by the stigma of liver disease and its association with alcoholism), and 'not living' which related to the loss of independence and disability associated with advanced disease in the pre-transplant period. Whilst this was the first qualitative study to examine patients' experiences of chronic liver disease it did not achieve theoretical saturation. All patients had undergone successful LT and were discussing previous experiences, risking a degree of recall bias. In addition, the sample reflected a 'cured' population, to whom issues relating to EOLC were not immediately relevant.

Smaller studies have utilised interpretative phenomenological analysis to explore the experience of waiting for transplant, highlighting the paradox of living with a life-limiting disease whilst simultaneously waiting for a curative procedure.[98-100] Phenomenological research aims to describe the life world of participants as it is subjectively experienced, ignoring researchers' prior preconceptions and understanding.[101] In contrast to grounded theory, where it is necessary to develop theory, the objective is to provide rich description of the phenomenon under investigation.[102] As such researchers seek new insights as opposed to developing new theories, or confirming/refuting existing theory.[103] In their study of post LT patients, Forsberg et al argued that this approach was necessary to ascertain the issues that prevent transplant recipients regaining QOL, outside of the factors which are typically focussed on by physicians.[99] For our purposes, these studies were again limited by the fact that only successfully transplanted patients were recruited.

Consistent with the questionnaire study described above,[91] qualitative studies also describe the stigma of cirrhosis in relation to its perceived association with alcohol. [104, 105] A qualitative interview study of 15 patients also suggested that stigma may contribute to delays in accessing healthcare.[106] An interview study of 26 patients with primary biliary cholangitis (PBC - previously termed primary biliary cirrhosis), an autoimmune liver disease not associated with alcohol use, concluded that this same stigma was experienced by patients regardless of the aetiology of their disease.[105]

In the most complete qualitative study of the lived experience of ESLD, Kimbell et al. explored the experiences of patients on an inpatient liver unit – alongside nominated lay and professional carers.[107] A high burden of physical symptoms emerged, particularly relating to fatigue and ascites. Experiences were characterised by multiple uncertainties relating to the disease, the inability to function in everyday life, and in difficulties planning for deteriorating health and death. Poor coordination between healthcare services was described. Whilst descriptive of the lived experience

of ESLD the study did not directly address patients' PC needs, their perceptions of how existing services could be developed, or attitudes towards the increased integration of PC and ACP in their ongoing management. Whilst the study included data from carer interviews, these focussed more on the lived patient experience from the carers' perspective, as opposed to the impact of disease on carers themselves.

Theme 2 – The use of PC in ESLD

a) The utilisation and timing of SPC in ESLD

The 'Views of informal carers of services' (VOICES) study (a questionnaire survey of bereaved carers and relatives in the UK) reported that the quality and co-ordination of care received by patients with liver disease towards the EOL was inferior to in other life-limiting conditions.[108]

Most studies describing rates of utilisation of SPC in ESLD come from the LT literature. Three single centre studies, from transplant units in the UK, US and Canada, each retrospectively assessed the proportion of patients either delisted or assessed unsuitable for transplantation who were referred for SPC over a 12-month period. The UK study reported that 19% of patients were referred, on average 4 days before death.[109] This compared with 7.5% of patients in the US study (a median of 32 days before death),[110] and 11% in the Canadian study.[81] A 2016 US study which retrospectively examined 107 consecutive patients delisted for LT over a 2-year period reported a SPC referral rate of 17%. 89% of referrals occurred during the terminal admission, and 50% within 72 hours of death.

A minority of patients with ESLD are considered for transplantation, and the above studies therefore do not necessarily reflect the wider population. Two retrospective nationwide US hospital database analyses have investigated use of SPC among inpatients with ESLD. In both studies, patients who received a SPC referral were identified through use of hospital coding data. Rush et al included patients between 2006-2012 who had been admitted following two or more previous decompensating events, and reported a SPC referral rate of 0.97% in 2006, which had increased to 7.1% in 2012.[111] Patel et al used the same database to analyse admissions among patients dying from ESLD between 2009-2013. They reported that 30.3% received SPC input prior to death, substantially higher than other estimates in the literature.[112] Their methodology was however heavily criticised, in that its recognition of ESLD patients within the database was unvalidated, and in that over 35% of their final cohort died primarily from causes unrelated to ESLD (typically malignancy).[113]

The studies detailing utilisation of SPC in ESLD are all limited by their methodology. They either represent single centre analyses or use large databases which are imprecise in identifying patients with ESLD. All are retrospective in nature, and therefore risk information bias. The studies are however consistent in their descriptions of remarkably low rates of SPC referral, which occur at a very late stage.

SPC has been shown to less effective when initiated late in the disease trajectory.[114, 115] Consequences of late, as compared with early, referral have been shown to include sub-optimal symptom management, increased suffering and the absence of opportunities to participate in ACP.[116, 117] The latter is of particular pertinence in ESLD, given the potential for HE to render patients incapable of contributing towards decisions regarding their health. Patients with cirrhosis who undergo cardio-pulmonary resuscitation have a mortality approaching 100%,[118] however, data from the aforementioned 'SUPPORT' study showed that only 33% of inpatients with ESLD had do not attempt resuscitation orders recorded.[75] Furthermore, there is some evidence to suggest SPC received only in the last days may be of detriment. An RCT of a brief PC intervention, which included a 'goals of care' discussion with family members, for patients intubated in ICU failed to demonstrate any improvement in anxiety symptoms among family members, and was associated with an increase in symptoms of post-traumatic stress disorder.[119] In contrast, a randomised trial of early SPC for patients with lung and gastrointestinal cancer (vs oncological treatment alone), demonstrated a reduction in anxiety and depression among caregivers in the SPC group.[120]

b) Professional attitudes towards PC in ESLD

Published data describing the attitudes of hepatologists towards PC are limited. In an online survey of health professionals at a single US liver transplant centre, 84% of 88 respondents indicated that the greatest barrier to PC in patients with ESLD was the attitude of the attending physician (although the reasons for such 'attitudes' were not explored). Although 96% of respondents felt that PC input improved overall clinical care, 78% suggested that referral to SPC was only appropriate when death was imminent. The authors postulated that physician confusion surrounding the optimum timing of PC and SPC referral represented a major barrier to best practice.[121] A UK multidisciplinary questionnaire survey of health professionals managing patients with ESLD demonstrated referrals from hepatology teams to SPC were uncommon, and again usually only made when death was imminent. The authors argued that earlier collaboration between hepatology and SPC was fundamental to improving care, however failed to expand on the reasons why this was not currently happening.[122] Both studies had noticeable limitations, which weaken

the strength of their conclusions. The US survey collected data from a single centre, and only considered patients on a LT programme. In contrast, the UK survey (whilst wide ranging) achieved a particularly poor response rate (8% overall and 4% amongst hepatologists). Two review articles put forward potential reasons for the infrequent use of PC in ESLD. These included the uncertain clinical trajectory of liver disease, patient and physician perceptions of PC and a lack of pre-existing clinical frameworks for patients with ESLD.[110, 123] Such assertions were however largely based on clinical experience and expert opinion and the authors recognised the paucity of evidence on this subject.

Low et al explored the views of liver healthcare professionals towards PC as part of a mixed methods QI study.[26] This included retrospective case note reviews, focus groups and interviews. Alongside other healthcare professionals, five doctors were interviewed and three participated in focus groups (all of unspecified seniority). The authors concluded that infrequent utilisation of PC occurred secondary to a lack of skill in initiating discussions, negative perceptions of PC held by patients and families and a poor understanding of PC approaches. Although this study presents the only published qualitative data on this topic to date, it is weakened by its design. Participants were recruited opportunistically and from a single hospital site (a LT centre). The authors noted that their qualitative data did not achieve thematic saturation. The range of professions and seniorities recruited meant that the perspective of hepatologists specifically was indistinguishable from the wider sample.

c) Clinical models for PC in ESLD

Despite the extensive needs of patients with ESLD, there is a paucity of published studies describing clinical models which integrate PC into routine clinical management. In 2015, Baumann et al evaluated the impact of a SPC intervention at the point of initial referral for LT, and longitudinally assessed its impact on mood and physical symptom burden.[124] The intervention consisted of an outpatient consultation with a SPC physician focussing specifically on liver-specific symptomatology, mood, social well-being, and spiritual care. Patients were referred on for further specialty care (e.g. psychiatry, chaplaincy) if appropriate, and were given assistance with care co-ordination. 50% of moderate to severe symptoms improved, and 43% of patients showed an improvement in mood. Patients with a higher initial symptom burden showed the greatest improvement. Whilst these results are undoubtedly positive, the absence of a control group within the study makes it is difficult to distinguish how much of the observed effect was attributable to the SPC intervention. Rossaro et al described a quality improvement (QI) project in 2004 which automatically referred patients to hospice care following assessment for LT if they were denied

transplantation, or if their MELD score increased whilst on the waiting list.[125] A subsequent retrospective evaluation in 2008 reported eight of 157 patients remained on the transplant list following referral to hospice care, of which six were ultimately transplanted.[126] Whilst demonstrating the principle that PC and curative care could co-exist, the study was weakened by not prospectively or objectively assessing the impact of SPC interventions on QOL. Lamda et al prospectively assessed outcomes of unplanned admissions to the Intensive Care Unit (ICU) in patients listed for LT before (control group) and after (intervention group) implementation of a PC intervention at a single tertiary centre.[127] The intervention included family support, a discussion around prognosis and patient preference, and discussion of cardio-pulmonary resuscitation and do not attempt resuscitation orders. As compared with the control group, patients receiving the intervention had earlier documentation of resuscitation status and an increased time between do not attempt resuscitation decisions and death. There was a decreased length of ICU stay, and a shorter time to withdrawal of organ support measures. There was no difference in mortality between the groups. Whilst not a RCT, the presence of a control group in this study does provide more robust evidence of benefit. Nonetheless, this study again reports data from a LT population at a single tertiary centre. Furthermore, the intervention described was designed for patients in whom death was potentially imminent, and therefore would be too late to achieve the potential benefits of early PC described above.

The above studies are all within the field of LT, and therefore unlikely to be reflective of the true ESLD population. Published models of care for patients with ESLD are particularly sparse. The UK Department of Health outlined six key-steps for provision of high quality end-of-life care (EOLC) in 2008.[128] The 2013 NHS document 'Getting it Right – Improving End of Life Care for People Living with Liver Disease' extrapolated these six steps on to a typical trajectory of ESLD.[90] Evidence-based points in the disease trajectory were identified as potential 'triggers' for SPC referral. Whilst the document represented an expert consensus its utility has not subsequently been supported by data pertaining to clinical, QOL or health-economic outcomes.

Gaps in the current literature

The existing literature describes ESLD as a life-limiting condition, associated with extensive physical and psychological morbidities, from which an increasing number of adults are dying, typically at a young age. Despite an increasing body of evidence demonstrating the benefits of SPC in non-malignant disease, it is rarely afforded to patients with ESLD. Better integration of PC in the clinical management of ESLD depends upon answers to questions which are incompletely addressed within the current literature.

Whilst low rates of SPC utilisation in ESLD are widely reported, exploration of the potential reasons for this have been largely neglected. There is a particular paucity of data examining the attitudes and practices of healthcare professionals managing ESLD, and the perceived barriers towards PC within the hepatology community. Identification and understanding of these barriers is vital if they are to be overcome.

Whilst the symptomatic burden of ESLD is described within current literature, the existing evidence is largely based around cross-sectional, quantitative assessments of QOL. A 2015 systematic review of studies describing patient experience in ESLD identified 121 articles, of which only 13 utilised qualitative methodologies.[69] The authors of this review argued that this inequity resulted in a lack of depth within the existing evidence, and that the patient experience of ESLD remained incompletely described. The impact of ESLD on families and carers is also largely unexplored within published studies. Furthermore, examination of the attitudes of patients with ESLD and their carers towards SPC interventions has not been described. A better understanding of the experiences and needs of patients and carers is necessary if future models of PC for ESLD are to be properly informed and fit for purpose.

Whilst there are data which illustrate the costs and healthcare resource implications of cirrhosis more generally, high level studies which specifically examine the LYOL in ESLD are not described within current literature. An understanding of the impact of ESLD on healthcare resources at the EOL is necessary to ensure that future models of care are both appropriately designed and demonstrably cost effective.

Most of the literature surrounding EOLC in patients with ESLD is extrapolated from patients enrolled in LT programmes. As described above, this is not necessarily representative of the wider ESLD population. Consequently, there are a lack of clinical models for PC in ESLD, which identify and address the needs of patients never considered for transplantation. The design of such a model would depend on evidence-based answers to the questions outlined above, specifically: an understanding of the barriers to PC in ESLD, an insight into the PC needs of patients and carers towards the EOL, and an appreciation of how healthcare services are currently utilised by patients with ESLD and the resource implications of this.

1C – THESIS AIMS AND OBJECTIVES

This thesis examines liver disease at the EOL from the perspective of those affected by it and analyses the healthcare systems currently in place to address it. Its overarching purpose is to investigate whether existing clinical models could be improved through the routine integration of palliative care and, if so, how. This requires gaps within the existing literature to be addressed. These include an understanding of the barriers to PC and the PC needs of patients and their carers and an appreciation of the resource implications associated with ESLD at the EOL.

This thesis has four specific aims, set out in detail below. Aim one is to identify and describe in detail the reasons why PC is not currently integrated into routine clinical care for patients with ESLD. The second aim is to explore the PC needs of patients with ESLD and their carers, and to ascertain their perspectives on their healthcare and how this could be improved upon. Aim 3 focusses on the resource implications of ESLD towards the EOL and the factors associated with poorer health-economic and clinical outcomes. The final aim looks to utilise data from across the thesis to inform design of a model of PC for patients with ESLD.

Aim 1 - To identify the existing barriers to integration of PC in the management of ESLD.

This aim is addressed in chapter 2 through a questionnaire based and qualitative interview study of UK hepatologists.

Objectives for Aim 1

a. *Questionnaire study of UK hepatologists*
   - Understand attitudes within the UK hepatology community towards utilisation of PC measures in the management of ESLD.
   - Obtain a representation of current practice in the management of PC needs in patients with ESLD.
   - Identify the perceived barriers to better integration of PC in the management of ESLD.
   - Assess whether clinical practice and attitudes are consistent across clinical settings.
   - Enable purposive recruitment for the qualitative interview study.

b. *Qualitative interview study of UK hepatologists*

   To gain an in-depth understanding of the perspective of hepatologists regarding:
   - The clinical and psychosocial needs of patients who may, or do, die from liver disease.

- The role of the hepatologist in managing this patient population, and how this responsibility is shared with others.
- The role of SPC in managing patients with ESLD.
- The barriers to improving PC for patients with ESLD and how existing services could be improved pragmatically.

Aim 2 - To understand the PC needs of patients with ESLD and their carers, ascertain how existing services meet these needs and explore the attitudes of patients and carers towards PC.

This aim is addressed in chapter 3 through a qualitative interview study of patients with ESLD and carers bereaved by ESLD

Objectives for Aim 2

- Describe the lived experience of ESLD towards the EOL from the perspective of patients and carers.
- Identify and describe the PC needs (including physical, psychological and social needs) associated with ESLD.
- Describe the experience of existing of healthcare services from the perspective of patients and carers.
- Examine the perspectives of patients are carers as to how existing healthcare services may be modified to better meet their needs.
- Examine perceptions of, and attitudes towards, core elements of PC and explore whether further integration of PC could improve upon existing strategies to manage ESLD.

Aim 3 - To assess existing patterns of health-service usage in patients with ESLD in their LYOL and identify the factors associated with improved clinical and economic outcomes towards the EOL.

This aim is addressed in chapter 4 through analysis of national level data pertaining to deaths related to cirrhosis with ascites between 2013-2015.

Objectives for Aim 3

- Describe health-service resource use among patients with ESLD in their LYOL by examining the following outcome measures:

    i. Cost of care within the LYOL.
    ii. Inpatient hospital bed days within the LYOL.
    iii. Early unplanned readmissions to hospital within the LYOL.
- Describe place of death outcomes for this cohort, including the frequency of unplanned hospital death (death occurring during an unplanned/emergency hospital admission).
- Describe crude differences in the above outcomes between patients enrolled in day-case LVP services and patients receiving exclusively unplanned care within their LYOL.
- Assess the associations between the outcome measures described above and independent variables relating to:
    i. Demographic factors (sex, ethnicity, age at death, deprivation, year of death).
    ii. Clinical factors (Cause of death, place of death, time between index presentation and death, number of hospital episodes, LVP requirement).
    iii. Health service factors (enrolment within a programme of day-case LVP).
- Among patients enrolled in a day-case LVP service within their LYOL, to assess the associations between the proportion of care received in a day-case setting and outcomes (as defined above).

Aim 4 - To develop a clinical model of PC for patients with ESLD

This aim is addressed in chapter 4 through use of QI methodology and retrospective examination of clinical records.

Objectives for Aim 4

- Design a prognostic screening tool that identifies patients with ESLD who are at a high risk of dying over the coming year.
- Integrate use of the prognostic screening tool into the routine clinical assessment of patients admitted to hospital with a complication of cirrhosis.
- Design a supportive care intervention which could be offered to patients identified as having a poor prognosis, in parallel to their ongoing disease management.
- Optimise the applicability and acceptability of the clinical model through rapid-cycle testing within a clinical environment.

1D – OUTLINE OF THESIS AND THE USE OF MIXED METHODS

The aims and objectives of this thesis are broad - ranging from gaining an understanding of the PC needs of patients and their carers to assessing patterns of cost and healthcare utilisation within the LYOL. Such breadth is necessary, both to address gaps within existing literature and in meeting the overarching purpose of the thesis - *"to investigate whether existing models of care could be improved through the routine integration of PC into clinical practice and, if so, how"*.

The advantages and disadvantages of traditional methodological approaches were considered when approaching these questions. Whilst qualitative approaches have the potential to provide a detailed understanding of a problem, they may not be generalisable to a wider population. Similarly, whilst quantitative data would allow the impact of certain, measurable variables on numerical outcomes (e.g. cost of care) to be examined – its ability to understand the impact of such factors on any one individual would be limited. As such, a need arose to utilise multiple methodologies, given that a single data source would be insufficient in answering the research questions outlined.

Mixed methods research has evolved to combine or associate data from both quantitative and qualitative sources.[129] Mixed methods approaches may be appropriate where a single data source is insufficient to answer the research question in full (as in this thesis), where there is a need to further explain initial results (for example in explaining the meaning of quantitative findings), or where a need exists to enhance a study with a second method.[130] Several definitions for mixed methods processes have emerged over the years. In 2007, Johnson et al sought a consensus on this, utilising 19 definitions by 21 mixed methods researchers.[131] The following definition was proposed:

"Mixed methods research is the type of research in which a researcher or team of researchers combines elements of qualitative and quantitative research approaches (e.g. use of qualitative and quantitative viewpoints, data collection, analysis, inference techniques) for the purposes of breadth and depth of understanding and corroboration."

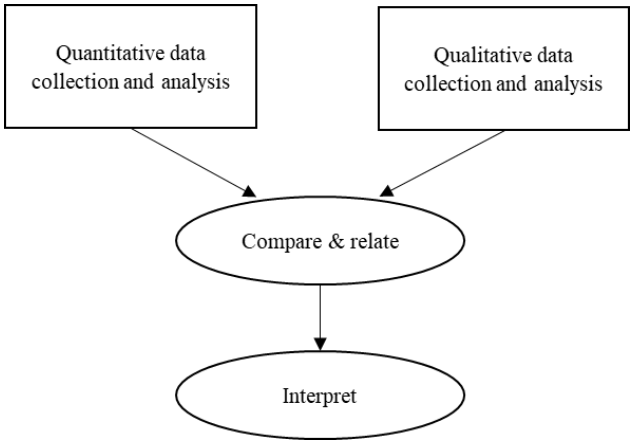
Creswell describes four key factors underpinning the design of any mixed methods study: timing, weighting, mixing and theorising.[129] Timing refers to whether qualitative and quantitative data collection and analysis occur concurrently or sequentially. Whilst there may be an advantage of sequential design in terms of better informing a subsequent study (e.g. qualitative interviews to inform salient points in a subsequent questionnaire study), limitations of time and resource may

make such an approach unfeasible. Weighting refers to whether qualitative or quantitative elements are given primacy in interpretation, particularly should they not concur. Mixing refers to when and how qualitative and quantitative findings are integrated, described by Morse and Neihaus as the "point of interface".[132] This can occur during the collection, analysis or interpretation of the data. Theorising represents a more abstract complex, relating to whether a larger, theoretical perspective guides the overall design. This reflects the fact that researchers often bring pre-existing theories and frameworks to their research, whether they be explicit or implicit. Such theories, often relating to change and advocacy, can shape the questions asked, how data are collected and the implications and recommendations arising from the study.

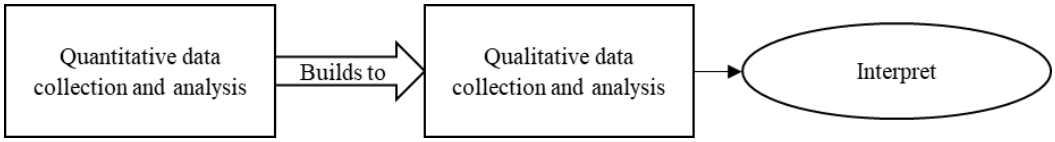
Distinct classifications of mixed methods study designs have evolved, which encompass the principles described above.[133] For example, a convergent parallel design describes a design where qualitative and quantitative components are undertaken simultaneously, with findings from each combined at the interpretative stage. In contrast, and exploratory sequential design (or 'qualitative follow up approach')[134] utilises data from the quantitative component to inform the subsequent qualitative work. Figure 1c shows diagrammatic representations of some of the major mixed methods research design protypes, as classified by Creswell et al.[130]

Figure 1.3 – Key mixed method study design typologies (adapted from Creswell et al) [130]

Convergent parallel



Explanatory sequential



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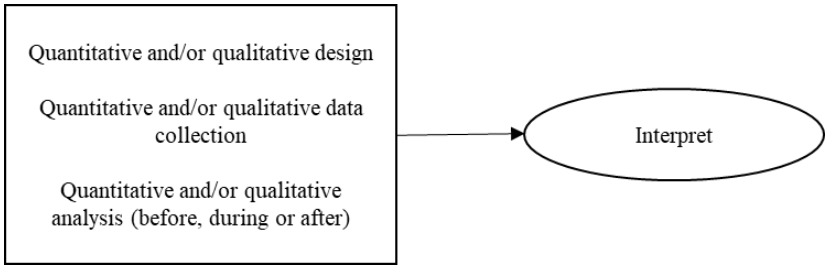
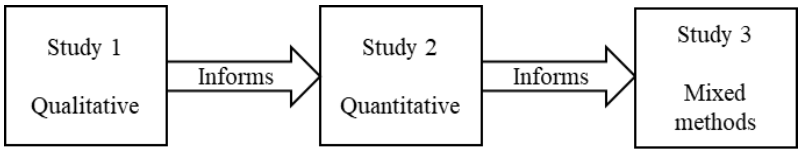


Multiphase



Outline of the thesis

Within this thesis four component studies, with individual methodologies, are used to address the four distinct aims outlined in section 1C. In chapter 2 I explore the barriers to PC in ESLD, utilising both quantitative and qualitative techniques, to examine the practices, attitudes and opinions of hepatologists working in the UK. In chapter 3 I examine the PC needs of patients with ESLD and their carers through in-depth interviews both with patients suffering from refractory ascites and carers who have been bereaved by ESLD. I explore the lived experience of ESLD, experiences of existing healthcare systems, and attitudes towards SPC. In chapter 4 I link high-level data from three national databases to investigate costs, patterns of health-service utilisation and place of death in a nationwide cohort of patients who died from ESLD. I explore the relationships between demographic, clinical and health-service factors (including the use of day-case services) and economic and healthcare outcomes in the LYOL. In chapter 5 I combine data obtained elsewhere in the thesis with QI methodology to design and validate a clinical model which both routinely identifies patients at risk of dying from ESLD within the next year and affords a PC intervention which can run in parallel with ongoing active disease management. In chapter 6 I draw together what can be learned from the thesis as a whole and provide a summary of my overall findings considered against the stated aims. I consider what the thesis adds to the existing literature and discuss its limitations. I finish by suggesting directions for future research and clinical practice which I believe will ultimately improve the care of patients with ESLD.

Mixed methods principles within this thesis and interrelationship between component studies

The thesis as a whole does not represent a single pure mixed methods study. The principles of mixed methods research are nonetheless important. The overarching aim of the thesis was consistent between studies. Topics and objectives equally ‘crossed over’ between studies. Furthermore, there was the potential for questions arising from earlier studies to be addressed in subsequent ones. The approach through which component studies were planned, combined, interrelated and triangulated drew upon the wider principles of mixed methods research, as did the overall structure of the thesis.

The aims and objectives of the thesis emphasise the importance of producing pragmatic and clinically relevant research. As part of this, the aim of formulating a clinical model is stated explicitly (assuming it is supported by the preceding evidence). The research was planned such that data from across the thesis, if appropriate, could be used to inform the design of a clinical model, described in chapter 5. It was less important that the other component studies ran sequentially,

given the objectives they addressed were, whilst strongly related, distinct. Nonetheless, it was important to retain the ability for interim analysis from earlier studies to inform later ones – such that the thesis remained unified and relevant.

Timing of the component studies occurred broadly in the order that the chapters are presented within the thesis. However, due to the constraints of time, data collection between studies overlapped and component studies often ran concurrently. Notwithstanding this, interim analyses were used to inform and triangulate the conclusions made in concurrent studies as described above. Chapter 5 (design of a clinical model) was informed by interim analyses from each of the preceding data chapters. The discussion chapter, which addresses each aim in turn, was written after all data analysis had been completed – meaning that data from across the thesis could be fully triangulated, combined and interpreted at this stage ("mixing" as described by Creswell et al).[129]

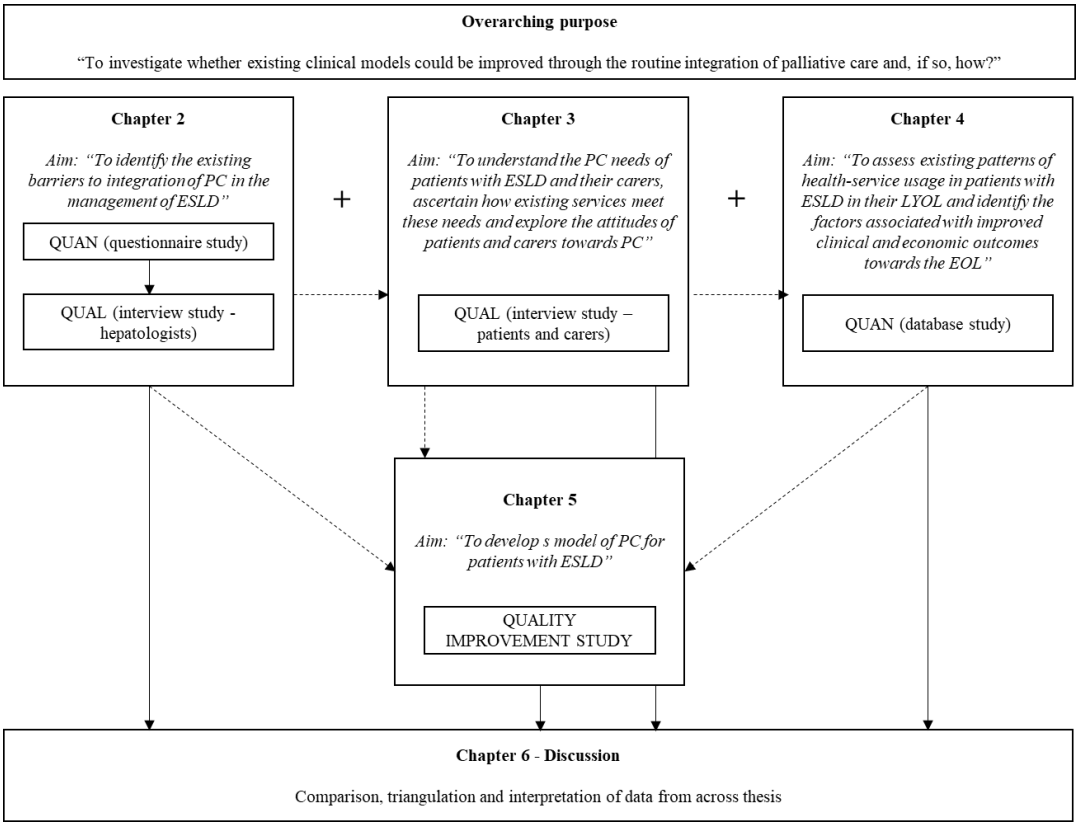
Because qualitative and quantitative components of the thesis addressed broadly distinct objectives, the issue of weighting was somewhat less important than for more pure mixed methods studies with more embedded designs. The exception to this was in chapter 2, which used a purer mixed methods approach (exploratory sequential design - see figure 1b.1). Quantitative and qualitative data were given equal weighting throughout the thesis, with the strengths and weaknesses of each approach considered.

Using Creswell's classification system, the thesis overall most closely resembled a convergent parallel design, although with some modifications allowing for the use of interim analyses.[130] The thesis lends itself to this design in that:

i) There was limited time for data collection, meaning from a purely pragmatic perspective data collection needed to run (in part) concurrently
ii) Equal value was attributed to both qualitative and quantitative aspects
iii) I had an interest in developing skills in both quantitative and qualitative analysis from the outset. This design also allows for data to be analysed separately and independently using the techniques traditionally associated with each data type, which was the case.

Figure 1.4 summarises the planning and execution of each component study, and how each study interrelates. It uses standard notation used for mixed methods research which is described within the figure.[135]

Figure 1.4 –Relationship between component studies and chapters within the thesis



- Solid arrows indicate sequential data collection, with one completed study able to inform the next
- Dashed arrows indicate where interim data analysis was available to partly inform the subsequent study
- + indicates where data collection overlapped or was concurrent
- QUAN reflects quantitative data types whereas QUAL represents qualitative. Capitalisation throughout reflects the equal weighting of data types within the thesis.

CHAPTER 2

OVERCOMING THE BARRIERS TO SUPPORTIVE AND PALLIATIVE CARE IN PATIENTS WITH END STAGE LIVER DISEASE - A MIXED METHODS STUDY OF ATTITUDES IN UK HEPATOLOGY

INTRODUCTION

Chapter 1 describes extensive PC needs in patients with ESLD and juxtaposes this with infrequent and late utilisation of SPC in this group. As the physicians primarily responsible for managing patients with ESLD, hepatologists have a role in the provision of general PC and act as gatekeepers to SPC. As such, there is a clear imperative to better understand the attitudes and practices of hepatologists, such that barriers to PC for patients with ESLD can be identified and overcome. However, there is a paucity of high-quality studies addressing this subject.

Using a mixed methods approach (large-scale questionnaire and in-depth qualitative interviews), this study aims to identify the barriers to better integration of PC in the management of ESLD from the perspective of hepatologists, with a view to informing future models of clinical care.

AIMS AND OBJECTIVES

Aims

This study addresses the first aim of this thesis which is to identify the existing barriers to integration of PC in the management of ESLD.

Objectives

Distinct objectives were established for each section of the study prior to data collection. These are listed below:

Questionnaire study objectives

Through use of a quantitative questionnaire of UK hepatologists and gastroenterologists to:

- Understand attitudes within the UK hepatology community towards utilisation of PC measures in the management of ESLD.
- Obtain a representation of current practice in the management of PC needs in patients with ESLD.
- Identify the perceived barriers to better integration of PC in the management of ESLD.
- Assess whether clinical practice and attitudes are consistent across clinical settings.
- Enable purposive recruitment for the qualitative interview study.

Interview study objectives

Using qualitative interviews with a purposively selected sample of questionnaire respondents, to gain an in-depth understanding of the perspective of hepatologists regarding:

- The clinical and psychosocial needs of patients who may, or do, die from liver disease.
- The role of the hepatologist in managing this patient population, and how this responsibility is shared with others.
- The role of SPC in managing patients with ESLD.
- The barriers to improving PC for patients with ESLD and how existing services could be improved pragmatically.

METHODS

Overall mixed-methods approach

This study utilises both quantitative and qualitative methods to address a single aim. The study adopts an explanatory sequential approach, as described by Creswell, and explained in chapter 1b of this thesis.[130] In this approach, the quantitative component is completed first, informing the subsequent qualitative component. This method was chosen to allow for purposive selection of the qualitative sample, based on questionnaire responses. Aside from informing recruitment to the qualitative component, the questionnaire study was also used to address aims and objectives independently. Data from quantitative and qualitative components were weighted equally in analysis.

Questionnaire study

The questionnaire was designed to both meet study objectives and optimise response rate, which can be adversely affected by questionnaire length.[136] Scrutiny of the literature highlighted some potential barriers to PC in liver disease, however, it did not identify a previously validated tool which could be used in lieu of a novel questionnaire.[110, 121-123]

The questionnaire was constructed for online use. Questions were divided into three key sections each covering different study objectives. The first related to the clinical setting and experience of the respondent (characteristics), the second related to attitudes towards PC and the role of SPC (attitudes) and the third related to the perceived barriers towards PC in ESLD (barriers).

The characteristics section assessed:

- Whether the participant worked as a hepatologist or gastroenterologist (physicians with a more general interest in gastrointestinal disease who typically manage liver disease in smaller hospitals).
- Place of work (e.g. Transplant centre, Tertiary centre, District General Hospital (DGH)).
- Experience (years as a consultant or specialty registrar).

The attitudes section assessed responses to seven clinical vignettes, which were written specifically for the study. The use of vignettes, or hypothetical scenarios, is a recognised technique for eliciting data pertaining to participants' attitude towards a topic, and is a method widely used to examine judgements and decision making among healthcare professionals.[137] Vignettes are designed to simulate real-life situations, through description of very short stories (or 'cases'), containing elements of interest to the researcher. The participants' response to that vignette is then interpreted as reflective of their attitude towards the wider subject of interest.

There are various advantages to the use of vignettes in attitudinal research. Firstly, they provide a flexibility to the researcher, in that they can 'control' for outside variables, meaning the specific subject of interest can be assessed. Secondly, it is often unethical, or impossible, to assess clinical decision making experimentally in real-life settings, and the use of vignettes circumvents the need for this. Thirdly, given that vignettes can be standardised for all participants within a study, results can be compared directly. [138] Vignettes are however not without disadvantages. Critics of vignette research argue that their inherent artificiality means that they are not representative of real-world phenomena, therefore calling into question the validity of any conclusions subsequently drawn.[139] Evans et al considered ways in which this inherent limitation could be mitigated in vignette studies assessing clinician decision making.[137] They recommended that: i) vignettes should reflect real world scenarios as closely as possible, ii) vignettes should attempt to elicit phenomena which have been independently hypothesised to exist in the real world (improving their internal validity) iii) vignettes should reflect situations which were experienced by, and pertinent to, the participants (external validity). Such factors were considered when designing the questionnaire.

I wrote clinical vignettes in consultation with a supervisor who is a consultant hepatologist. They were checked for real-world plausibility, accuracy and clarity by six other clinicians as part of the piloting process (see below). Each vignette briefly described a common clinical scenario, covering a range of disease aetiologies and severities. For each scenario, participants were asked:

- Whether they thought PC was clinically appropriate in the scenario described (i.e. 'should' receive PC).
- Whether they would initiate PC measures in their routine clinical practice (i.e. 'would' initiate PC and/or refer to SPC).

The 'should' responses assessed respondents' attitudes to initiation of PC across a variety of situations. Discrepancies between 'should' and 'would' responses highlighted potential barriers to PC. If, for a given scenario, a respondent recognised clinical need (i.e. 'should' institute PC) but wouldn't initiate PC in their routine practice, then the existence of a 'barrier' to PC was identified. A summary of the vignettes, and the rationale for their inclusion is given in table 2.1.

Table 2.1 – Description of questionnaire case vignettes	
Clinical vignette (abbreviation of case used in text)	**Rationale for inclusion**
56-year-old male. Compensated CTP A NASH cirrhosis. Seen 6 monthly in stable cirrhosis clinic (NASH)	A case of early disease, likely to be asymptomatic. Median time period to decompensation 10-12 years.[33] To assess attitudes/barriers toward instigation of parallel PC measures at an early disease stage.
47-year-old woman. PBC. UKELD = 52. Listed for transplantation. (PBC)	A case of advanced disease (patients with a UKELD >49 are potentially eligible for LT). Autoimmune aetiology (i.e. nothing to suggest ongoing addiction). To assess attitudes/barriers towards PC in cases where treatment intent is curative, but prognosis uncertain (approximately 20% of patients listed for LT do not survive until transplantation).
78-year-old man. NASH cirrhosis. Refractory ascites and renal impairment. Requiring 2 weekly LVP (RA)	A case of end-stage liver disease (ESLD - median survival under 1 month).[140] Not of transplantable age and no curative treatment modalities available. To assess attitudes/barriers to PC in end-stage, non-malignant disease.
67-year-old man. Decompensated CTP B cirrhosis starting DAAs for chronic (HCV) (HCV)	ESLD (1-year survival approximately 60%) [33], but with potentially disease modifying medications available. Assesses attitudes/barriers to palliative care where prognosis is uncertain.
37-year-old woman. Alcohol dependency. Being discharged following 3-week admission for severe alcoholic hepatitis (first presentation) (ALC)	Severe alcoholic hepatitis, associated with a mortality of 20-30% at 1 month, and 30-40% mortality at 6 months.[141] Survival heavily dependent upon the ability to maintain abstinence from alcohol. Prognosis with abstinence would be good, however rates of relapse are high. [142]

	Assesses attitudes/barriers to PC where prognosis is associated with addiction and in cases of uncertain prognosis.
52-year-old man of no fixed abode with ArLD. Ongoing addiction issues with alcohol and drug use. Recurrent ED attendances. CTP C cirrhosis with jaundice, ascites and grade 1 encephalopathy (CTP-C)	ESLD (median survival under 1 year), [140] complicated by a potentially reversible aetiology (alcohol), and difficult social circumstances which may restrict access to healthcare. Assesses attitudes/barriers to PC in patients from marginalised social groups with ongoing addiction.
64-year-old man. HCC. CTP A cirrhosis. Delisted for transplantation as tumour now outside criteria. (HCC)	Although HCC is in this case incurable, median survival 2 years (early stage of cirrhosis).[109] Assesses attitudes/barriers to PC in liver disease associated with malignancy.
ArLD: Alcohol-related liver disease; CTP: Child Turcotte Pugh classification of cirrhosis (A least severe, C most severe)[30]; DAA: Direct acting anti-viral agent; ED: Emergency department; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cirrhosis; LVP: Large-volume paracentesis; RA: Refractory ascites; UKELD: United Kingdom model of end-stage liver disease score	

The barriers sections asked respondents to rate their level of agreement with eight statements (table 2.2). Each statement referred to a potential barrier to PC in liver disease either cited in previous literature and/or based on the clinical experience of the author and supervisor.[121-123] A Likert scale was used. This provides categorical response options for each statement (e.g. strongly disagree to strongly agree).[143] An earlier questionnaire version, which asked respondents to 'rank' reasons (most important to least important), was changed following piloting (see below) due to the time taken to complete the section. Prior completion of the qualitative phase of this study may have better informed the questionnaire. However, it was felt that the potential for the questionnaire to inform purposive sampling for the qualitative study afforded a greater overall benefit.

Table 2.2 – Potential barriers to palliative care cited in questionnaire

Abbreviation	Exact questionnaire wording
Not considered	PC is of value in this patient group, but referral is not routinely considered by physicians managing ESLD.
Framework	There is no clearly established clinical framework or pathway for patients with ESLD requiring PC.
Improve	ESLD often has potential for clinical improvement (e.g. LT / abstinence / antiviral treatment). Physicians are reluctant to refer to PC when the disease is potentially reversible.
Trajectory	The illness trajectory in ESLD is often uncertain. Prognostication and identification of a clear "terminal phase" is difficult.
Resources	There are currently insufficient resources to offer SPC to most patients.
ICU	Early involvement of SPC can risk patients not being managed appropriately by other specialties (eg. ICU/A&E) should they decompensate.
Hospice	SPC services and the hospice movement are not appropriately set up for the needs of patients with ESLD.
Not required	For the majority of patients with ESLD there is no need for PC.

Piloting and distribution of questionnaire

The questionnaire underwent three drafts (each subsequently modified by a consultant hepatologist supervisor) prior to piloting. Piloting was undertaken by six clinicians at University Hospitals Bristol (University Hospitals Bristol - three hepatologists, one gastroenterologist, two specialty registrars (SpRs). Each participant was asked to comment specifically on: the time taken to complete the questionnaire, whether the questions were clear and unambiguous, whether the vignettes were plausible and related to clinical practice, whether the on-line format was user-friendly.

Verbal and written feedback was received from each participant. Following piloting, a ranking question was changed to a graded 'Likert-scale' response, clinical vignettes were shortened (and one removed due to undue complexity/lack of clarity), and layout of the on-line form was changed such that questions were spread across three (vs one) pages. The revised version was independently piloted by two separate assessors (one hepatologist, one specialty registrar) as well as being re-checked by the initial participants, prior to distribution.

A recent Cochrane review highlighted a number of evidence-based factors which had the potential to improve questionnaire response rate. These included pre-notification, follow-up contact (including a note that others had responded) and avoidance of the word 'survey' in email subject title.[136] Whilst such strategies were adopted where possible, not all those highlighted in the review were feasible. For example, we did not have sufficient resources to offer material or financial incentives to participants.

Distribution of questionnaires was co-ordinated through liaison with the British Society of Gastroenterology and British Association for the Study of the Liver. Both organisations emailed their members with an on-line link to the questionnaire and sent two follow-up reminder emails at two-weekly intervals. Statistical analysis was conducted using Stata V14.2.[144]

Qualitative interview study

Rationale for qualitative methodology

Overcoming barriers to PC in ESLD depends on understanding the attitudes and values of the clinicians acting as gatekeepers to care. Whilst a broad understanding may be obtained from quantitative data, qualitative approaches are better able to provide in-depth explanations of these phenomena.[145-147] Open-ended questions can stimulate the considered, in-depth responses required to provide detailed insights into the study question. Furthermore, qualitative research is of particular benefit where there is little pre-existing research on the topic being studied.[148]

Rationale for use of semi-structured, one-to-one interviews

One-to-one interviews enable the interviewer to seek opinions, pursue in-depth information around the topic, and to follow-up on responses.[149] In contrast to the classical biographical interview, expert interviews typically focus more on participants' capacity in a certain field. In this instance however, the attitudes and motivations of the participants themselves are of equal importance.

There are no published qualitative studies on the perceptions of hepatologists towards PC, however similar literature in other medical fields exists. Wright & Forbes used one-to-one interviews to explore haematologists' perceptions of PC in haematological malignancy. They considered a flexible, in-depth approach to interviews to be the best method of gathering information about participants' individual experiences.[150] In contrast, in their study of physician attitudes to PC in patients with heart failure, Hanratty et al used a focus group methodology.[151] They argued that, as well as being an efficient means of data collection, focus groups allowed participants to utilise others' frames-of-reference to help identify the most salient topics.

Given our focus was on the experiences and knowledge of individuals (as opposed to an exploration of professional cultures or norms) one-to-one interviews were used for our study. The nature of the research area is inherently sensitive. A face-to-face format, as opposed to a telephone interview or focus group, allowed questioning to proceed at a pace acceptable to the participant and for the interview to be modified to explore issues raised. It also created a confidential environment where participants could discuss their practice and opinions without fear of disapproval from colleagues. Furthermore, we wanted to attain both geographical and experiential spread amongst our sample, and organisation of focus groups in this context would have been logistically difficult.

In contrast to Wright and Forbes, [150] we adopted a semi-structured interview format. As well as allowing for themes to emerge organically from the data, semi-structured interviews permit the use of 'theory-

driven' or 'hypothesis-directed' questioning. As such, this enabled themes from the questionnaire study and existing literature to be explored specifically. It also allowed the use of 'confrontational questioning', where theories of the participant could be re-examined in light of competing alternatives.[152]

Sampling

Sampling was undertaken with the objective of including participants who were reflective of the UK hepatology community. This meant actively recruiting participants from a range of clinical settings, experiences, and opinions, and avoiding simply inviting enthusiastic volunteers.

Purposive sampling selection is criterion-based, such that participants have particular characteristics which enable a detailed exploration of the central themes.[153] The use of purposive sampling has two principal aims; firstly to ensure that all key constituents of relevance to the subject matter are covered, and secondly to ensure there is sufficient diversity in the sample for themes to be explored adequately.[154]

As part of the questionnaire, participants were invited to provide their email address if they were prepared to undertake a one-to-one interview. Questionnaire responses from willing respondents were scrutinised, with the objective of achieving a sample which encompassed the following characteristics:

- Range in experience (assessed by the number of years practising at consultant level).
- Range in clinical environments (DGH, tertiary centre, transplant centre, academic), with approximately 50% working in a LT centre.
- Range of geographical region.
- Range of attitudes towards PC in ELSD. This was based on the number of 'should' responses in the clinical vignette section of the questionnaire (see table 2.1).
- Appropriate gender split (In 2015, 82% of UK consultant gastroenterologists and hepatologists were male).[155]

Data saturation

Sample size in qualitative studies is difficult to determine, however it is usually small for a variety of reasons. Phenomena only need to appear once to form part of the analytical map, and as such there will reach a point where little new evidence is obtained from further interviews. The type of data is also rich in detail and, to do justice to the analysis, sample sizes need to be kept reasonably small. Finally, there are the pragmatic limitations of resource and time.[152]

We continued interviews until the point of data saturation. In their description of grounded theory, Strauss and Corbin describe this as the point where additional interviews fail to expand upon findings.[156] Whilst

it is not possible to determine the point of saturation prior to collection of data, Guest et al suggest that thematic saturation typically occurs within the first 12 interviews, with basic themes emerging after six.[157] Morse argues that the sample size required to reach saturation is dependant on a number of features (including data quality, scope of study and topic). She suggested that more experienced and articulate participants are often more willing to share experiences. In such cases, richer data are obtained from each interview such that, typically, fewer interviews achieve saturation.[158] Given these considerations, an estimated sample size of 8-12 participants was determined prior to recruitment. A sampling matrix was designed to convert sampling criteria into an organised form and participants were invited on the basis of this (table 2.3).

Table 2.3 – Sampling matrix

Clinical Setting	**Non-transplant**		**Transplant**	
	DGH	**Tertiary**	**Clinical**	**Academic**
	2-3	2-3	3-4	1-2
Gender	**Female**		**Male**	
	2-3		6-9	
Years' experience	**0-9**	**10-19**		**20+**
	3-4	3-4		3-4
Pre-interview attitude to palliative care (Assessed by number of clinical vignettes in questionnaire where PC referral thought to be clinically appropriate (max 7)	**0-1**	**2-3**		**4+**
	3-4	3-4		3-4

Recruitment and consent

Participants were invited to participate by email which explained the purpose, content and structure of the proposed interview. For respondents who accepted this invitation, a mutually convenient date was arranged for interview. One reminder email was sent after two weeks in cases of non-response. Immediately prior to interview the structure of the interview was re-visited, and verbal consent taken from each participant (written consent was not deemed necessary by the ethics committee).

Production and design of topic guide

A topic guide was constructed prior to the commencement of interviews. As well as acting as an 'aide memoire' in the interview itself, this had the additional benefit of ensuring a degree of consistency between interviews, whilst still allowing flexibility to explore issues salient to each individual.

The topic guide design was primarily based around study objectives, specifically regarding participants' experience in managing patients with ESLD, the perceived needs of this patient group, the respective role of the hepatologist and SPC services, and the barriers to improving PC. Hypotheses arising from the questionnaire study were considered secondarily. Following mapping of the range of topics to be covered an order in which they would be addressed, with potential opening lines, was devised. Whilst this allowed for variation, it provided an organised structure which avoided 'jerky' or unnatural progressions.

Two pilot interviews were undertaken with consultant hepatologists at University Hospitals Bristol. Although the invitation email stated that interviews would last at least 30 minutes, two participants requested that their interviews did not exceed this, owing to their busy clinical schedule. As such pilot interviews were scheduled to not exceed 30 minutes. The initial topic guide was rationalised following the pilot as some key topics had not received sufficient time to achieve appropriate analytical depth. Approximate timings were established to ensure that key topics were covered in adequate depth in all interviews. Data from pilot interviews was not included in analysis. The finalised topic guide is shown in table 2.4.

Table 2.4 – Topic guide		
Stage *(mins)*	**Topic** *Example questions*	**Rationale & Notes**
Context *(1-2)*	**Context setting** Introduction (time/date/interviewee/role) Job/role in managing patients with ESLD *Can you briefly describe your current post and your typical day to day work?*	A logical introduction to the interview as well as providing important contextual information.
Opening *(3-4)*	**Career and motivations** *What were the reasons you became a hepatologist? Which parts of your job do you most enjoy?*	Easier opening questions to ease participant into topic and to establish rapport. Discussion of the motivations of hepatologists may provide insight into some of the 'physician centred' barriers to PC.
Core *(key questions here. Min 20 minutes)*	**Role of the hepatologist** *Can you tell me a bit about your experience of managing patients with liver disease towards the EOL?*	Addressing the objectives relating to the clinical and psychosocial needs of patients with liver disease, the role of the hepatologists and how this role should be shared.
	Clinical needs *What do you think are the main needs of patients with liver disease towards the EOL?*	
	The use of PC in ESLD *Do you think PC is of benefit in patients with ESLD? (if so – how? when should it be introduced?) What is your experience of accessing SPC services for your patients?*	Address the use of PC in liver disease and the perceptions and anxieties surrounding PC (Questioning will depend on participant's attitude towards PC) services.
	Anxieties around PC *Do you have any anxieties about involving PC specialists in the management of ESLD? AND/OR*	

	Some hepatologists are reluctant to involve SPC in the management of their patients– why do you think this is?	
	Barriers to care *In your experience, what are the factors which can make it difficult for patients with ESLD to access SPC services? (Potential prompts – NHS/funding/logistics, families, patients, attitudes)* **Skills** *Do you think hepatologists are adequately trained and equipped to deliver this aspect of patients' care?*	Addressing objective identifying barriers to improving PC.
Winding down *(2-3 mins)*	**Service design** *"If you were designing a perfect palliative care service for patients with liver disease – how would it be designed? What would it look like? What barriers would we need to overcome?"*	Addressing key question of how services can be pragmatically improved. Also, helpful 'summary' question which encompasses participant's main views. Good "winding down" topic as finishes the interview on a positive and constructive note.
Summary & closure *(2-3 mins)*	**Summarise key points** Ask for any necessarily clarifications and questions. Ask any important topics or views not covered? Thanks, and conclude.	Ensures researcher has understood participant's key opinions accurately and allows for correction and clarification. If time, also allows for exploration of topics particularly important to participant.

Conduct of field work

During two pilot interviews digital recording equipment was tested. Interview technique and appropriateness, timing and clarity of questioning was reviewed after each pilot interview. Interviews were arranged at participants' places of work at a mutually convenient time. All interviews were digitally recorded. Once the digital recorder was turned off, the participant was given the opportunity to discuss any issues raised. Consent to transcribe and analyse the interview was confirmed. A reflexivity diary (recording immediate thoughts, body language or emotions displayed, potential bias etc) was completed immediately following each interview. Interviews were transcribed verbatim using a professional transcription service approved by the University of Bristol. Audio files, transcripts, and diary entries were analysed iteratively, such that emerging themes could be determined and data saturation defined. Within four weeks of interview, each participant was sent a copy of their transcript and a summary of the 'key points' which they had made. Participants were invited to correct or amend any misinterpretations or retract any transcribed section of the interview. No participant elected to make any changes to their transcript, and no corrections to 'key points' were made. Data were collected in accordance with the Data Protection Act 1998.[159] Audio files were copied onto a laptop computer and encrypted. All data were anonymised, with each participant given a pseudonym in the written report.

Data analysis

Rationale for analytic approach

A range of analytic approaches were considered. Given the paucity of pre-existing literature a purely inductive, 'grounded theory' approach was considered. This technique allows themes to emerge organically from the data, and has the advantage of avoiding pre-conceptions or pre-existing hypotheses.[160] Elements of our data however made it less suitable for a pure grounded theory analysis. The preceding questionnaire study, pre-existing literature in other medical specialties, and the clinical experience of the researcher (a senior registrar training in hepatology), all created a pre-existing context. The clinical expertise contributed further to this. Our interview structure was designed to cover pre-existing hypotheses and topics, occasionally in time limited settings. Whilst this structure did not preclude a grounded theory analysis, this method of data collection was considered less conducive to a purely inductive analytic approach. Interpretative phenomenological analysis aims to describe the subjective 'life world' of participants, however it depends on the researcher ignoring prior pre-conceptions and understandings.[101] Given the structured nature of the interviews, the specific pre-existing hypotheses and the prior experience of researcher this analytic approach was also unsuitable.

Thematic analysis often includes themes that are anticipated, however it also allows them to emerge organically from the data.[161] Through systematically working through the data the researcher discovers,

interprets and reports patterns and clusters of meaning. This allows topics to be identified, that are progressively integrated into higher order themes - the importance of which lies in their ability to address pre-existing research questions.[162] This approach considers 'a priori' concepts, and risks data being 'superimposed' to support their adoption. To guard against this the analytical method allows emergent concepts to be captured and revisited and ensures that any conclusions surrounding 'a priori' concepts are firmly grounded within data.

Analytic method

A thematic approach was considered the most appropriate technique for analysis. I modified a method outlined by Spencer et al,[163] which follows distinct analytic stages. Interview transcripts were analysed iteratively alongside field notes, the reflexivity diary, and audio recordings. Nvivo 10 software was used to code, store and organise data.[164] The analytic process is outlined in table 2.5.

Table 2.5 – Approach to thematic data analysis – adapted from Spencer et al [163]

DATA MANAGEMENT					ABSTRACTION AND INTERPRETATION		
ORGANISING			DESCRIBING		EXPLAINING		
METHODS			RESULTS			CONCLUSIONS	
Familiarisation	Constructing an initial thematic framework	Indexing and sorting	Reviewing data extracts	Data summary and display	Constructing categories	Identifying linkage	Accounting for patterns
Transcripts read and re-read, in conjunction with listening to audio files. Interview memos re-visited. Topics, areas of interest, and data relevant to research question identified, and initial 'codes' assigned. Coding inventory checked against topic guide and research objectives.	Underlying links between codes identified and sorted into groups. Groups sorted hierarchically (per level of generality) – into descriptive themes and subthemes. Notes describing each theme and subtheme made and logged on Nvivo.	INDEXING Transcripts imported to Nvivo and re-read 'line by line'. Data indexed (Nvivo) as per themes and sub-themes in thematic framework. Multiple labels assigned to some data. SORTING Using Nvivo, data reassembled as per their index.	Amalgamated data from each index read and re-read. Non-indexed data re-read to ensure important themes not missing from framework. Themes merged or subdivided to reflect material. Thematic framework edited as above, and finalised.	Construction of a framework matrix, where each theme/subtheme becomes a column heading. Each participant assigned a row within the matrix. Matrix filled in for each participant with a data summary – incorporating quotations and researcher field notes where appropriate.	Range of views within each theme is studied, and the elements which characterise and differentiate responses are determined. Once elements have been identified they are sorted by their key dimensions. These are sorted into higher order classifications – or typologies of response.	BETWEEN PHENOMENA Search for connections between separate strands of thematic analysis. BETWEEN SUBGROUPS Search for links based on subgroup of participant (e.g. experience of participant / clinical setting).	Construction of conjectures and explanations for patterns of data. EXPLICIT Explanations put forward directly by the participant. IMPLICIT Inferred underlying logic developed by the researcher.

Techniques to ensure rigour and trustworthiness of findings

Techniques to ensure rigour and trustworthiness of findings fell into categories relating to credibility and confirmability.[165] Credibility refers to the extent to which participants' views are faithfully reproduced. Iterative questioning was employed throughout interviews. This involved explicitly checking participants' meaning throughout interviews, to ensure that responses were being interpreted accurately. Throughout the study period frequent debriefing sessions, involving discussions with supervisors, were utilised to discuss findings and concerns, and to modify future interviews where necessary. 'Member-checks' of key-points following interview (described above), confirmed that participants' views had been accurately represented. [166]

Confirmability refers to the degree of objectivity within analysis. In qualitative interviews the researcher inevitably brings their own preconceptions and values and cannot act as a fully neutral observer.[167] By being open about the researcher's own experiences, and how these have affected the nature of the research, readers can make their own judgement regarding the authenticity and persuasiveness of the work. The process through which the researcher reveals the values, interests and influences associated with their own subjective experiences is termed reflexivity.[168] The technique of 'reflexive bracketing' (recognition and reflection of investigators' preconceptions and assumptions regarding the phenomena of interest) was exercised in relation to this, through use of a reflexivity diary.[169] As a senior registrar training in hepatology I had considerable personal experience in treating patients with ESLD within the NHS and brought to each interview preconceived ideas of how patients should be managed optimally. Awareness of this potential lack of neutrality was considered throughout to mitigate against possible bias.

Every third interview transcript was coded independently by a supervisor (an experienced qualitative researcher outside the field of hepatology). Coding and themes were discussed at regular meetings throughout the study, and differences were resolved through discussion. This 'triangulation' helped to ensure dependability of the findings.

Ethical considerations

Ethical approval for both sections of this study was granted by the Hampshire B ethics committee (reference number: 16/SC/0041). The phone number of the researcher was provided after each interview in case any participant wished to discuss any issues further, or retrospectively withdraw their consent. The study was sponsored by the University of Bristol.

RESULTS

Questionnaire study

305/906 responses were returned (33.7%). 61.4% of respondents were of consultant grade, of which 62.3% worked in a DGH. Years of experience amongst consultants was positively skewed. Participant characteristics are summarised in table 2.6.

Table 2.6 – Characteristics of questionnaire respondents

		Years of consultant experience n (%)								
		Overall	N/A	0-5	5-9	10-14	15-19	20-24	25-29	30+
Clinical setting n (%)	SpR	110 (38.6)	110 (100)	-	-	-	-	-	-	-
	DGH Gastro	80 (28.1)	-	22 (27.5)	10 (12.5)	16 (20.0)	15 (18.8)	11 (13.8)	4 (5.0)	2 (2.5)
	DGH Hep	29 (10.2)	-	11 (37.9)	6 (20.7)	5 (17.2)	5 (17.2)	2 (6.9)	0 (0)	0 (0)
	Tertiary Hep	41 (14.4)	-	13 (31.7)	10 (24.4)	8 (19.5)	5 (12.2)	2 (4.9)	2 (4.9)	1 (2.4)
	LT	25 (8.8)	-	11 (44.0)	5 (20.0)	3 (12.0)	2 (8.0)	3 (12.0)	1 (4.0)	0 (0)
	Overall	285 (100)	110 (38.6)	57 (20.0)	31 (10.9)	32 (11.2)	27 (9.5)	18 (6.3)	7 (2.5)	3 (1.1)

DGH: District General Hospital; Gastro: Gastroenterologist; Hep: Hepatologist; SpR: Specialty registrar; Tertiary: Tertiary non-transplant centre; LT: Liver transplantation centre

Attitudes to PC

Across the sample, instigation of PC was thought to be clinically appropriate in a mean of 3.29 of the 7 cases described. On average, gastroenterologists considered PC appropriate in fewer cases. Overlapping of 95% confidence intervals (CI), as compared with the wider sample, however indicated that this difference was not significant at the 5% level ($p>0.05$). Similarly, whilst there was a slight trend towards lower rates of SPC referral among more experienced clinicians, the number of respondents with over 25 years of experience was low, and there were no statistically significant differences between groups. The mean number of cases where there was a discrepancy between what the participant considered optimum practice ('should' responses) and self-reported clinical practice ('would' responses) was 1.71 (52.0% of cases where PC was thought appropriate). Although transplant hepatologists had a lower mean number of discrepancies per respondent (potentially suggestive of

fewer barriers to PC in this clinical setting) this was not significantly different to other groups. Table 2.7 summarises responses by group.

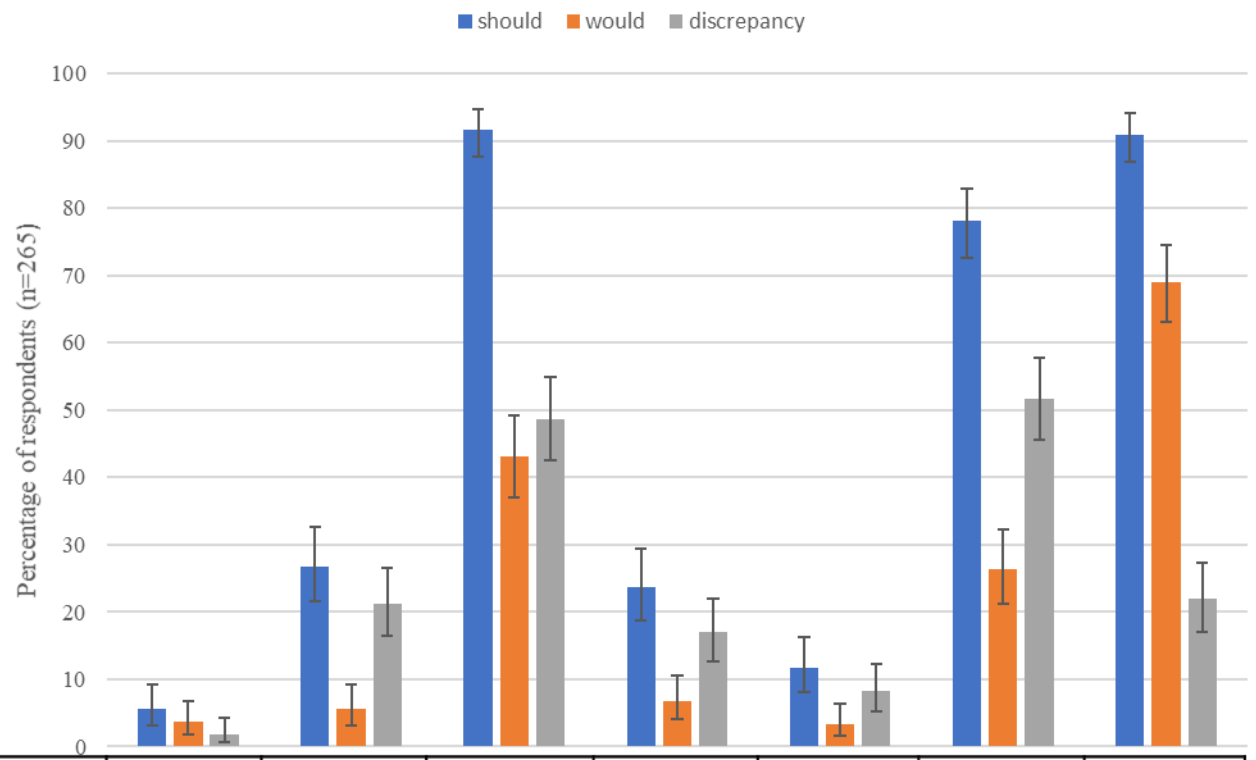
Table 2.7 – Attitudes and barriers to PC by clinical setting and experience					
		Cases where PC appropriate (max =7)		No. of cases with discrepancy	
		Mean (95% CI)	SD	Mean (95% CI)	SD
Clinical setting	SpR	3.36 (3.06-3.65)	1.48	1.84 (1.59-2.08)	1.21
	DGH Gastro	2.83 (2.5-3.16)	1.39	1.55 (1.19-1.91)	1.51
	DGH Hep	3.71 (3.11-4.31)	1.54	1.87 (1.32-2.39)	1.38
	Tertiary Hep	3.26 (2.83-3.69)	1.31	1.63 (1.29-1.97)	1.02
	Transplant Hep	3.63 (3.12-4.12)	1.17	1.29 (0.82-1.77)	1.12
Years of consultant experience	0-5	3.39 (3.07-3.71)	1.17	1.52 (1.19-1.84)	1.18
	5-9	3.28 (2.78-3.76)	1.28	1.79 (1.35-2.23)	1.15
	10-14	3.26 (2.60-3.91)	1.65	1.59 (1.11-2.07)	1.22
	15-19	2.96 (2.16-3.75)	1.88	1.50 (0.85-2.14)	1.53
	20-24	3.28 (2.57-3.98)	1.41	2.00 (1.05-2.94)	1.91
	25-29	2.83 (2.40-3.26)	0.41	1.00 (-0.14-2.14)	1.10
	30+	2.33 (-0.53-5.20)	1.15	0.33 (-1.10-1.77)	0.58
Overall		3.29 (3.11-3.46)	1.44	1.71 (1.54-1.86)	1.30

Attitudes to PC by clinical vignette

Opinions as to the appropriateness of PC and discrepancies between optimum care and self-reported practice (should vs 'would' responses) were analysed for each vignette. The two cases in which there was no remote possibility of cure (RA and HCC – see table 2.1 for description of cases), received the highest proportion of 'should' responses (91.7% and 90.9% respectively). The discrepancy between optimum and actual practice was however significantly higher in the example of non-malignant liver disease (RA), despite there being a worse overall prognosis in this case (48.7% (95% CI 42.5%-54.9%) vs. 21.9% (17.1%-27.4%)). The highest discrepancy between 'should' and 'would' responses (51.7%) was in the CTP-C case which described a patient of no fixed abode with ESLD and alcohol dependency. A minority of respondents felt PC appropriate in cases where prognosis was uncertain, but there was a reasonable probability of cure (PBC, HCV, ALC), whereas a very small minority (5.7%

(3.2%-9.2%)), felt PC appropriate in the patient with fully compensated liver disease. A summary of responses to clinical vignettes is shown in figure 2.1.

Figure 2.1 - Perceived appropriateness of SPC intervention by case (attitudes), and discrepancies between self-reported practice (barriers) - 95% CI



Case	NASH	PBC	RA	HCV	ALC	CPC	HCC
% should instigate SPC (95% CI)	5.7 (3.2-9.2)	26.8 (21.6-32.6)	91.7 (87.7-94.7)	23.8 (18.8-29.4)	11.7 (8.1-16.2)	78.1 (72.7-82.9)	90.9 (86.8-94.1)
% would instigate SPC (95% CI)	3.8 (1.8-6.8)	5.7 (3.2-9.2)	43.0 (37.0-49.2)	6.8 (4.1-10.5)	3.4 (1.6-6.4)	26.4 (21.2-32.2)	69.1 (63.1-74.6)
% discrepancy (95% CI)	1.9 (0.6-4.4)	21.1 (16.4-26.6)	48.7 (42.5-54.9)	17.0 (12.7-22.1)	8.3 (5.3-12.3)	51.7 (45.5-57.9)	21.9 (17.1-27.4)

Barriers to PC

Respondents rated their level of agreement with eight statements citing potential barriers to integration of PC in liver disease (table 2.2). Each response category was assigned a numerical score (strongly disagree = 1, strongly agree = 5). Mean scores were calculated. On this basis, statements were subsequently ranked in order of importance, both overall and across clinical settings.

Lack of routine consideration of PC was ranked most highly overall (mean agreement 3.96 (CI: 3.85-4.07)/5). That PC interventions were 'not required' in ESLD was ranked lowest across all clinical settings and was the only statement that, on average, the sample as a whole 'disagreed' with (i.e. mean score <3 – 2.31 (CI:2.19-2.42). Among consultant respondents, 'lack of resources' was of higher importance to respondents working outside a transplant centre although differences between groups did not reach statistical significance. Similarly, the lack of established clinical frameworks was of greater concern to non-transplant physicians. Responses are summarised in table 2.8.

Table 2.8 – Ranking of potential barriers to palliative care intervention in ESLD by clinical setting of respondent

		Clinical setting																	
		Overall sample			SpR			Gastro			Hep DGH			Hep 2			Hep Tx		
		Mean (95% CI)	SD	**Rank**	Mean (95% CI)	SD	**Rank**	Mean (95% CI)	SD	**Rank**	Mean (95% CI)	SD	**Rank**	Mean (95% CI)	SD	**Rank**	Mean (95% CI)	SD	**Rank**
Potential barrier (see table 3.2)	Not considered	3.96 (3.85-4.07)	0.87	**1**	4.1 (3.91-4.29)	0.89	**1=**	3.83 (3.64-4.01)	0.78	**2=**	3.96 (3.67-4.25)	0.72	**3=**	3.78 (3.47-4.10)	0.96	**4**	4.13 (3.71-4.55)	0.96	**1**
	Framework	3.94 (3.81-4.06)	0.99	**2**	4.1 (3.90-4.28)	0.91	**1=**	3.9 (3.67-4.15)	1.0	**1**	4.00 (3.6-4.4)	0.98	**1=**	4.03 (3.71-4.33)	0.94	**1**	3.31 (2.78-3.85)	1.21	**4=**
	Improve	3.8 (3.69-3.90)	0.85	**3**	3.84 (3.84-4.02)	0.85	**3**	3.74 (3.53-3.96)	0.91	**4**	3.8 (3.48-4.11)	0.76	**5**	3.94 (3.71-4.18)	0.73	**3**	3.43 (3.01-3.86)	0.99	**3**
	Trajectory	3.71 (3.59-3.82)	0.94	**4**	3.78 (3.60-3.98)	0.91	**4**	3.55 (3.31-3.79)	1.0	**5**	3.96 (3.57-4.35)	95	**3=**	3.65 (3.37-3.93)	0.84	**5**	3.6 (3.16-4.06)	1.03	**2**
	Resources	3.67 (3.53-3.82)	1.17	**5**	3.41 (3.16-3.65)	1.17	**6**	3.83 (3.57-4.09)	1.11	**2=**	4.00 (3.60-4.40)	0.98	**1=**	4.00 (2.62-4.37)	1.14	**2**	3.31 (2.68-3.95)	1.42	**4=**
	ICU	3.44 (3.30-3.58)	1.11	**6**	3.67 (3.44-3.90)	1.1	**5**	3.27 (2.98-3.56)	1.2	**7**	3.48 (3.06-3.89)	1	**6**	3.37 (3.06-3.68)	0.94	**6**	3.17 (2.67-3.67)	1.15	**7**
	Hospice	3.15 (3.01-3.30)	1.12	**7**	3.02 (2.78-3.26)	1.14	**7**	3.31 (3.03-3.56)	1.14	**6**	2.96 (2.51-3.41)	1.11	**7**	3.29 (2.95-3.63)	1.04	**7**	3.26 (2.75-3.78)	1.18	**6**
	Not required	2.31 (2.19-2.42)	0.95	**8**	2.16 (1.97-2.34)	0.87	**8**	2.59 (2.35-2.82)	0.97	**8**	2.15 (1.82-2.49)	0.83	**8**	2.37 (2.04-2.70)	1	**8**	2.00 (1.57-2.43)	1	**8**

Barriers (table 3.2) ranked on a 1(strongly disagree) to 5(strongly agree) scale. Scores >3 = agreement with statement. Scores <3 = disagreement

CI: Confidence interval; DGH: District General Hospital; Gastro: Gastroenterologist; Hep: Hepatologist; SD: Standard deviation; SpR: Specialty registrar; Tertiary: Tertiary non-transplant centre

Qualitative interview study

Recruitment took place between February and November 2016. Sixty-two questionnaire respondents indicated willingness to participate, of whom 15 were invited for interview. Three failed to respond, and 12 agreed to take part. Two interviews were cancelled by participants at short notice. The duration of interviews ranged from 24 to 50 minutes. Participant characteristics are summarised in table 2.9. Table 2.10 compares characteristics of those recruited to the initial target sampling matrix.

Table 2.9 – Participant characteristics

Participant	Gender	Experience (years)	Pre-interview attitude to palliative care (Assessed by number of 'should' responses to clinical vignettes – max = 7)
Dr A	F	0-9	3
Dr B	M	10-19	5
Dr C	M	20+	1
Dr D	M	20+	3
Dr E	M	10-19	3
Dr F	M	20+	4
Dr G	M	0-9	1
Dr H	M	10-19	2
Dr I	M	20+	2
Dr J	F	0-9	3

Table 2.10 - Recruitment compared with sampling matrix

Actual numbers participating in bold *(Target numbers in italics)*

Clinical Setting	Non-transplant		Transplant	
	DGH	Tertiary	Clinical	Academic
	2 *(2-3)*	**2** *(2-3)*	**5** *(3-4)*	**1** *(1-2)*
Gender	Female		Male	
	2 *(2-3)*		**8** *(6-9)*	
Years' experience	0-9	10-19		20+
	3 *(3-4)*	**3** *(3-4)*		**4** *(3-4)*
Pre-interview attitude to palliative care (see above)	0-1	2-3		4+
	2 *(3-4)*	**6** *(3-4)*		**2** *(3-4)*

Construction of thematic framework

Six themes emerged from the data, each constituting two subthemes (Table 2.11). The underlying concept of 'inaccessibility to palliative care' (described below) unified these themes.

Table 2.11 – Final themes and subthemes

1 – CLINICAL NEED a – **Need** for PC in liver disease b – Training and **skills** gap within hepatology	2 – DISEASE BARRIERS a – Unpredictable **trajectory** b – **Timing** the "palliative" phase
3 – HEPATOLOGIST BARRIERS a – Career **motivations** b – **Responsibility** towards patients	4 – PERCEPTION BARRIERS a – Healthcare **professionals** b – **Patients** and families
5 – STRUCTURAL BARRIERS a – Primacy of **malignancy** b – Service and **resource**	6 – IMPROVING CARE a – **Recognising** patient decline and scoring b – **Integration** of services

Theme 1 - Clinical need

Participants' experience of managing patients with ESLD was discussed. This elicited their perception of the disease burdens, gained insight into the current services available, and established whether participants felt there was any need to improve upon current models of clinical care. Two subthemes emerged, regarding a need to improve current services and a training and expertise gap within the consultant hepatologist workforce. The emergence of this theme and subthemes is summarised in table 2.12.

Table 2.12 – Emergence of coding framework for 'clinical need' sub-themes

Questions used to explore theme	Examples of initial codes	Broad themes	Final sub-theme
"Can you tell me a bit about your experience of managing patients with liver disease towards the end of life?" "What do you think are the main needs of patients with liver disease towards the end of life?"	High symptom burden, encephalopathy frightening and unpredictable, extremely distressing symptoms, psychological exhaustion, social isolation, could be done so much better, blind spot in current care	Very high physical and psychological symptom burden. Encephalopathy particularly difficult. Unpleasant mode of death. Currently care is poor. Room for substantial improvement.	**Need** for PC in liver disease
"Do you think hepatologists are adequately trained and equipped to deliver this aspect of patients' care?" "Do you think PC interventions are of benefit in patients with ESLD?"	No formal training, don't know where to start, don't have the time, not routinely considered, PC can add value, hepatologists should retain overall control	Once curative options exhausted don't know where to turn. Hepatologists feel ill equipped and not trained to deal with this aspect of care. Lack of time. PC input welcome, notwithstanding certain caveats.	Training and **skills** gap within hepatology

Subtheme 1a - Need for PC in liver disease

All participants described extensive experience of managing patients with liver disease towards the EOL. This was frequently illustrated with real life clinical examples. Participants universally acknowledged death from liver disease to be immensely difficult and unpleasant for patients, both from a physical and psychological perspective. In terms of physical symptoms, some participants described the typical death from liver disease as being uniquely unpleasant. The cognitive and behavioural impairment associated with encephalopathy was commonly highlighted as the most difficult physical feature, however ascites, itch, pain, breathlessness, gastrointestinal haemorrhage, and cramps were all cited as examples of the high symptomatic burden. Most participants recognised the potential benefits of PC input in improving physical symptom management.

Box 2.1 – Physical symptoms in ESLD

Dr A: "I mean I'm biased – but the modes of death are often quite horrific ... they go bright yellow, they go cachectic, they're ascitic, they vomit blood - I can imagine that's much more distressing than perhaps an expected death from cancer where they've been prepared for that."

Dr J: "But they also have other vague symptoms. Like if you actually properly speak to patients, they've often got pruritus, they get cramps, nausea - they're actually really common symptoms in that patient group that we never really ask them about. Breathlessness, a lot of them are breathless even if they don't have ascites."

Dr F: "Encephalopathy is definitely the most problematic feature – and it's really scary. Suddenly the person becomes confused, the family often won't know what to do in the home environment."

Dr I: "I would argue that patients on the (LT) waiting list, with all their multiple symptoms, would benefit from the sort of expertise you can get from community palliative nurses."

In addition to physical symptoms, participants described a high psychological burden. Participants felt this was exacerbated by the fact that patients with ESLD commonly came from marginalised groups within society and had limited social support. Those who commented on this aspect also described how it made provision of good quality care logistically difficult.

Box 2.2 – Psychological burden and social isolation in ESLD

Dr A: "What would you call them? – A marginalised population. So, they're often maybe active alcoholics who don't engage with the community services as such, or marginalised in that they've often got Hep B or Hep C and have come over from, say for example, Somalia and don't speak any English. In that way, they don't know how to access care the same way as a white, British, middle class person."

Dr J: "A lot of our patients are completely detached, they've got no family or social support, and that creates difficulties both in the patient's psychology, but also for us in trying to manage patients and help them in the final days of their life."

Participants recognised that the high burden of physical and psychological symptoms were managed poorly within existing structures of care. Participants frequently described care as being 'disease focused'

as opposed to 'symptom-focused' towards the EOL. It was generally recognised that this approach adversely affected patients' QOL. Participants universally agreed that these elements of care (i.e. increased focus on physical and psychological symptoms) should be improved.

Most participants recognised the need to improve the availability of PC in order to bridge this gap. The 'core benefits' of PC were described in terms of improving control of physical symptoms, affording psychological and social support, and in opportunities for ACP. One participant (Dr C) disagreed with the prevailing viewpoint, arguing that care needed to remain firmly based around disease modification and cure, and that increasing access to SPC would compromise patients' hope.

Box 2.3 – The clinical necessity of improving PC in ESLD

Dr I: "(We need to) pay greater attention to the symptoms that the patient is complaining of and addressing those, rather than what people often try to do which is to prevent a complication or address their overall disease. We don't often look at it from the pain perspective of the patient. What is their main complaint, that they would like alleviating in the next few months?"

Dr E: "Not many of our (treatments) are directed at symptomatic care … in terms of distress, anxiety, discomfort, fluid management, depression, all those things … there's probably a blind spot for most of us."

Dr B: "So amongst our core group of patients, we've got a 25% three-month mortality rate. How people can say that palliative care doesn't have a role in that is staggering to me really."

Dr C: "Even when there is no hope, there is a potential for reversibility – and so therefore I worry about the term 'end-of-life' treatment for patients with cirrhosis, particularly if they're young. Because even in the worse cases, if you come to my clinic you'll see patients that were dead, nearly dead, or had no hope who in 5, 10, 15 years are leading very fruitful lives … and so therefore these (palliative care) connotations, I think we should get rid of. And I would fight tooth and nail if I can to argue that that is what should happen."

Subtheme 1b – Training and skills gap within hepatology

Participants recognised that, with the exception of HCC, PC was seldom used in patients with ESLD. One participant referred to a departmental audit which had demonstrated how rarely SPC were involved in patients' care.

Box 2.4 – Infrequent use of PC in ESLD

Dr A: "We've audited here and looking at, on average, how many admissions people have before they access palliative care and how long before their death before they are referred to palliative care and, certainly in this hospital, they've had on average four or five admissions – often within close proximity – and they're refused palliative care until they're within days of dying which is not the model we should be aiming for."

Some participants explained that aspects of PC were typically managed (if at all), by hepatologists or general practitioners (GPs). The skills of participants in delivering these aspects of care were explored. Several participants recognised that they found conversations relating to poor prognosis particularly difficult and that this represented a personal skills gap. This created the temptation for such conversations to be avoided. Some participants expressed a fear that approaching issues surrounding PC and prognosis would create a "fall out" in terms of the reactions of patients and relatives, which they feared they would not be able to deal with.

Box 2.5 – Hepatologists' skill gap – poor prognosis discussions

Dr H: "What you really ideally want to do is … say look, this is probably about the amount of time you're going to have left, I'm telling you this because it will help you plan things that you might want to do, etc … but those are all really tricky conversations. I don't feel I'm necessarily any good at it – because I often don't quite know what I'm aiming for. At what point would you know whether you'd actually be doing it well? I'm never quite sure."

Dr C: "So therefore there is a follow up, the patient is weeping, the family is gone, they need to sort out the will, somebody needs to do something, you know? It creates a whole cascade of events. And so as soon as you start the discussion it opens a floodgate. And you say – 'well how the hell am I going to manage this?'"

Potential reasons for this skills gap were explored. Participants admitted to having received little or no formal training in PC, or advanced communication skills. Two participants explained that they thought that the 'type' of individual who became a hepatologist was generally not skilled in these aspects of care (see 'motivations' theme).

Box 2.6 – Reasons for the hepatologist skills gap – training and personality type

Dr C: "Zero, completely zero. I don't even think about it. I don't even know how to do it. I have no phone that I can pick to call a nurse to say hey listen, can you come and have a look at so and so, to coordinate home care, you know? So it's completely outside my domain, so zero … its inherently not what we're trained to do and that's why I say it needs to be built into the training modules, how to approach it, what is the opening line, how to deal with it, that sort of stuff. We just don't have it. I wouldn't know where to start."

Dr J: "I think the type of person that goes into hepatology is not always the best kind of person to have these kinds of chats with patients, based on their personality and their communication skills and all that kind of stuff. It may not necessarily be sensible if they're forced to have these conversations with patients. It may cause more harm than good."

Dr I: "Then the skill set to be able to have that conversation. Maybe some hepatologists are good at this, but by any means not all of them are."

Given the recognition that hepatologists were not fully equipped to manage these aspects of care, the data were scrutinised to explore attitudes towards SPC services. Most participants recalled positive previous experiences of SPC and recognised their skills as important. Nonetheless, attitudes were not universally positive. One participant (Dr C) expressed anger that SPC professionals were sometimes involved in the management of his patients due to his perception that they lacked experience in managing liver disease.

Box 2.7 – Hepatologist attitudes to SPC

Dr E: "If you put the patient at the centre of it and say 'what would be best for them?' well, I think having some input from people who manage dying patients all the time and understand their fears and worries, can access other support services, even things like financial things that patients can access if they've got a terminal diagnosis. You know, making life easier at home, counselling support. I don't think those sort of things we touch on very often as hepatologists."

Dr D: "I think they're good at talking to people about dying and the end of life and they can bring those skills from other disease areas."

Dr A: "I've only ever had really positive experiences from them, I have to say. When I've referred patients and I've struggled to – whatever it is – control vomiting, I've found they've been really useful and really helpful. I've never found them prohibitive" Dr C: "We can't just have just somebody else who sees it as their job to provide (palliative) care for a disease they don't understand."

Theme 2 - Disease barriers

Four key themes emerged describing the barriers to PC for patients with ESLD: barriers relating to the disease itself, barriers relating to the attitudes and practises of hepatologists, barriers relating to the fear of misperception (from both patients and fellow healthcare professionals), and barriers relating to NHS structures and resources. This 'disease barriers' theme relates to features in the natural history of liver disease which are not conducive to traditional models of PC. Within this theme two subthemes emerged: the unpredictable clinical course of liver disease (unpredictable trajectory), and difficulty in knowing when to institute PC (timing of the palliative phase). Table 2.13 summarises the emergence of these themes.

Table 2.13 – Emergence of coding framework for 'disease barriers' sub-themes

Questions used to explore theme	Examples of initial codes	Broad themes	Final theme
Can you tell me a bit about your experience of managing patients with liver disease towards the end of life? *In your experience, what are the factors which can make it difficult for patients with ESLD to access SPC services?*	Intrinsic unpredictability of disease, uncertain recovery, aggressive interventions in end stage disease, uncertainties around alcohol behaviour, uncertainty of transplant waiting list, easy in hindsight, not as difficult as we make it, err on the side of caution, don't want to give up too early, fear of failure	The progression of ESLD is unpredictable up until a very late stage. Difficult to identify which patients will need palliative care and which will recover – particularly in ArLD. Fear of "giving up" too soon.	Unpredictable **trajectory**
	Recognising the EOL, not wanting to stop active care, palliative care when recovery is uncertain, when should I think about this?, don't want to give up too soon, fear of failure, need a crystal ball, parallel planning	Difficult identifying a terminal phase outside last days of life. Potential points are decompensation or transplant assessment. Concept of 'parallel planning.	**Timing** of the palliative phase

Subtheme 2a - Unpredictable trajectory

Most, but not all, participants described the trajectory of liver disease as inherently unpredictable. The often-aggressive nature of life prolonging measures meant participants commonly faced a clinical

dilemma in determining the best approach. ArLD was frequently cited as an example, due the potential for improvement if the patient successfully changed their behaviour. Patients listed for LT were also cited as a group in whom prognosis was fundamentally uncertain.

Box 2.8 – Unpredictable clinical trajectories

Dr F: "So for someone who presents, let's say, with first presentation of ascites and they're actively drinking and alcohol's the cause, then clearly a lot of them, if they abstain, will make a pretty good recovery and they won't need palliative care, but not all of them will … so there's a fear of writing people off, that clinical anxiety that someone who is rescuable you're not going to rescue."

Dr I: (discussing patients listed for LT) "You know that at least 20% are going to die before getting a transplant, so in a certain sense you need palliative care for the people who are going to die. But of course, you don't want them to die and so you're trying to keep them alive all the time."

Whilst some participants reflected on past cases where they had regretted not instigating PC at an earlier stage, it was common for participants to persist with aggressive management even when the possibility of recovery was remote. Fears of "giving up too soon" were expressed recurrently. Some participants spoke of palliative and curative care as being mutually exclusive approaches. These participants felt particularly conflicted about how best to manage prognostic uncertainty.

Box 2.9 – The perceived conflict between palliative and curative care

Dr E: "It's very easy with hindsight to say 'well, they were always going to die', but when you're in it and there's that glimmer of hope, particularly when you've got options like transplant and things that are held there like a carrot not only to the patients but to the physicians, I don't think people are comfortable denying what they feel may be a potential treatment, however remote that actually is in reality."

Dr G: "The main issue is this concept of giving up I think. And once you flick onto a palliative care pathway, you know, that's it – game over."

Whilst almost all the sample recognised the benefits of PC, participants feared squandering opportunities for cure. Most participants demonstrated insight into this, and discussions surrounding the optimum timing of PC naturally followed.

Subtheme 2b - Timing of the palliative phase

Participants recognised that timely identification of patients who were dying from liver disease was poor, and that this created a fundamental barrier to PC. Participants described getting "caught up" in active management, without always considering the wider prognosis. Participants in transplant centres identified the point of being assessed unfit for transplantation as a potential trigger for PC. Participants outside transplant centres argued that, in isolation, this approach would 'miss' large numbers of patients, as only a minority of the ESLD population are suitable for LT. The onset of decompensation (i.e. ascites, encephalopathy, jaundice or variceal haemorrhage) was also identified as a potential trigger for PC, however, some participants felt that this was too early in the disease trajectory. Most participants felt that robust, evidence-based systems which systematically identified patients who stood to benefit from PC would be a valuable addition to their armamentarium.

Box 2.10 – Recognition of decline and timing of palliative intervention

Dr D: "I think one thing we're not good at is recognising where people are near the end of their life and we can get a little bit, you know, tied up in all the things that we can do, so managing a variceal bleed or draining ascites, without standing back and saying, well actually, the development of the, of ascites or the development of the significant portal hypertension that gives you a variceal bleed is actually prognostically a very bad sign."

Dr A: "I think once they've got to that stage (assessment for transplantation), if you're not offered a transplant, you're pretty much confining them to palliative care and death, if you've got to that decision; although it won't be imminent, it's going to happen at some point you would predict in the next 1 to 2 years."

Dr F: "I think for every patient that ends up in hospital with a decompensating event we need to be at least thinking about it (PC). And we certainly don't do that well at the moment."

Dr I: "If I wanted to give one reason why management of the end stage of life in patients with liver disease is so poor, it is because most people have great difficulty in defining when the patient has got to that end stage … however a good hepatologist they are, they still have people who die and I would still be sure that a better and more objective use of the data would have been to demonstrate to them that it was quite clear that their patient was not going to survive, earlier than the final moment."

Distinguishing between curative and palliative phases of disease appeared to create a delay in the initiation of PC. Participants were challenged as to whether they felt curative and palliative approaches were mutually exclusive. The concept of a co-existent approach was termed "parallel planning". Opinion was divided as to the plausibility of this approach. Some participants felt this offered an elegant solution to the curative/palliative dichotomy arguing that, if explained sensitively, such an approach could be adopted at the point of transplant assessment or decompensation, with the PC elements retracted if the disease improved. The opposing view was that, whilst this presented a neat theoretical solution, the reality risked creating confusion amongst patients, families and fellow professionals and that no evidence-based framework for this approach existed.

Box 2.11 – Parallel planning – arguments for and against

Dr I: "I think parallel, when you think about it, it makes total sense. Not to just say 'right, we switch now and you're totally symptomatic'. For a significant bunch of patients in the middle – mortality, although maybe uncertain, will still be high … what we're saying – that you should be concentrating on supportive care – they are not mutually exclusive. They are absolutely not mutually exclusive things."

Dr B: "[I support] the concept of patients, going on the (transplant) waiting list even, being at least introduced to palliative care services or the concept of palliative care services – because obviously, at that stage, I think the death on the transplant waiting list is 22%; so one in five patients will never make it to transplant."

Dr E: "But it's a very difficult balance because you give mixed messages and how that's delivered and framed without creating confusion is probably quite a big challenge that we've not really addressed properly."

Dr J: *[I: Do you think we can integrate a parallel approach to patients with uncertain prognosis?]* "Not at the moment, no. I don't think that current mentality of patients or staff allows it."

Theme 3 - Hepatologist barriers

Data relating to the attitudes and motivations of the sample population, and how this impacted upon clinical decision making (and ultimately patient care), led to emergence of this third theme – which describes physician centred barriers to PC. Data surrounding this theme fell broadly into two subthemes

relating to the motivations of participants to specialise in hepatology and perceptions around their responsibility towards patients (table 2.14).

Table 2.14 – Emergence of coding framework for 'hepatologist barriers' sub-themes			
Questions used to explore theme	Examples of initial codes	Broad themes	Final theme
What were the reasons you became a hepatologist? *Which parts of your job do you most enjoy?* *Some hepatologists are reluctant to involve SPC in the management of their patients– why do you think this is?*	Saving lives, back from the brink, working with disadvantaged groups, hepatologist as a hero, giving life back, inspiring individuals, inequity of liver disease, working with reversible disease	Enjoyment of working with critically ill patients. Satisfaction in salvaging patients in life threatening situations. Pride in advocating for an otherwise disadvantaged cohort.	Career **motivations**
	Others not trained or able, need to retain control, fear patients won't be afforded appropriate care, control over disease outcome, decision maker, threatened by others on their turf	Fear that others won't do the job right. Desire to retain overall control of the patient journey.	**Responsibility** towards patients

Subtheme 3a - Career motivations

Participants were asked about their motivations for choosing a career in hepatology. Two broad motivations recurred frequently. The first related to an enjoyment of working with critically unwell patients, and the satisfaction experienced when patients were salvaged from otherwise life-threatening situations. This was commonly expressed in the context of LT, however other examples included management of variceal haemorrhage, and septic shock on the ICU. Some participants reflected upon the fact that this 'trait' occasionally resulted in dogmatic persistence with aggressive therapies, even in situations of ever-increasing futility. Even amongst the participants who didn't cite examples of life or death emergencies, the potential to reverse underlying disease mechanisms was described (e.g. antiviral treatment in hepatitis C). Some participants described memories of an inspiring mentor during their junior doctor years, sometimes recounting the witnessing of a 'heroic act'.

The second recurring motivation was the desire to work with a cohort of patients who had been otherwise disadvantaged throughout life, often specifically referring to patients with alcohol or drug dependency.

Participants expressed a desire to advocate for a group that who were perceived as having the odds stacked against them, and who were often stigmatised by society and others within the medical profession. Whilst on one hand this contrasted with the more 'interventionalist' motivations, in other ways it was similar, in that both viewed the specialty as in some way 'heroic' and 'fighting against the odds'.

Box 2.12 – Career motivations

Dr A: "So it's seeing sick, decompensated liver disease patients, giving them that hope of transplantation … giving them that option of longevity and survival again with transplantation, that's what I like most about it."

Dr D: "One of the satisfying things about hepatology, is that you can see people who are very, very ill, you know, particularly say someone with decompensated cirrhosis from alcohol who's on your ward, jaundice and ascites, maybe having had a variceal bleed, and then 3, 6 months down the line, they could be sitting in front of you in clinic, their jaundice has gone, their ascites has gone away and they're re-compensated because they've stopped drinking. And that's, you know, that's very satisfying to see."

Dr I: "For many hepatologists it's in their DNA to continue to the very, very nth degree, struggling through with the patients with multiple organ failure, in ICU. We've just been having a jolly conversation will all of my hepatology colleagues about one of our transplant patients and a range of responses, you know, exactly describes that. Keep going, keep going, keep going."

Dr B: "So the number of times you'd hear, 'Oh, the alcoholics are a waste of time. It's all related to alcohol. What's the point? They all die anyway' and I just thought, 'We are approaching this completely the wrong way' … If you look at liver disease, it's got the greatest proportion of life years lost than any other disease and I think that should be considered a national scandal."

Although all participants recognised that death was extremely common in ESLD, no participants described a desire to alleviate suffering towards the EOL as a motivating factor in their career choice. The strong sense of advocacy, and an awareness of the potentially life prolonging benefits of good treatment, contributed to a perceived participants feelings of responsibility towards patients with liver disease.

Subtheme 3b – Responsibility for patients

Participants described a sense of responsibility towards their patients. This sometimes manifested in a fear that colleagues in other medical specialities were not always sufficiently qualified to medically manage

the complications arising from liver disease. Concerns regarding care not being appropriately escalated by ICU physicians due to their perceptions of futility were commonplace. Participants feared involving SPC risked may risk reinforcing this perception. Some participants also feared that referral to SPC risked their patients being 'lost' to physicians who did not have appropriate experience. Management of pain was cited as an example of this, with participants expressing a fear that SPC physicians may prescribe high doses of opioids, which could exacerbate HE. Whilst views of SPC were generally positive, participants expressed concerns that increasing their involvement may come at the cost of ceding overall control of the decisions around their patient's medical management.

Box 2.13 – Responsibility for patients

Dr J: "It's still a struggle to get patients into intensive care with liver disease … that again is multifactorial but in part really it's two barriers. There's this traditional idea that patients with liver disease don't do well in ICU. And there's this fear amongst hepatologists that if a patient gets labelled with palliative care or DNAR that nothing active will be done."

Dr D: "If we say, 'Oh this patient is terminally ill', and they go to the hospice and maybe get prescribed an opioid or something and develop confusion … well they may then have something (encephalopathy) that's reversible – that we could actually improve, so it's the sort of anxiety of letting go of those patients."

Dr E: "I guess it's like anything; there's always some sort of perception of threat, subliminal or otherwise. These are my patients, this is my expertise, I'm in a position where I look after liver patients, I know best."

Theme 4 - Perception barriers

This theme relates to perceptions around the terminology surrounding PC, and the feared consequences of clinical intentions being misunderstood. Data from this theme fell broadly into two categories relating to fears of misperceptions among healthcare professionals, and patients and families (Table 2.15).

Table 2.15 – Emergence of coding framework for 'perception barriers' sub-themes

Questions used to explore theme	Examples of initial codes	Broad themes	Final theme
Can you tell me a bit about your experience of managing patients with liver disease towards the end of life? *Do you have any anxieties about involving SPC in the management of ESLD?*	Others might not give them a chance, others won't understand what I mean, supportive care a preferred term, I still want my patient to receive care, if you don't use the term you miss the point	Misperception of terminology by colleagues risks appropriate interventions being withheld. Counter view – not using the word palliative misses the point and perpetuates the stigma.	Healthcare **professionals**
	Associated with cancer and death, takes away hope, don't want patients to feel I'm giving up on them, patients won't understand the nuance	Terminology of palliative care means imminent death to the layman. Don't want to remove all hope. Don't want my patients to feel like I'm giving up on them. Supportive care as a preferable terminology.	**Patients** and families

Subtheme 4a - Healthcare professionals

Participants recognised the benefits of PC in terms of improved symptom control, psychological and social support, and opportunities for ACP (see theme 1). Nonetheless, there were widespread anxieties around use of the label 'palliative' to describe such interventions. These related to how others might interpret the term. Participants feared that misunderstanding of the terminology could lead to clinical interventions being inappropriately withheld. This fear of misperception related specifically to three professional groups – ICU physicians (see also Box 2.13 – quote 1), GPs, and nursing staff. This fear often contributed to a reluctance to initiate PC until a very late stage.

Box 2.14 – Fear of the misperception of other healthcare professionals

Dr H: "I have this problem with the word palliative and that does produce some reluctance to, say, get a community palliative team to review … Whenever I sort of say to the GP in a letter, you know, I think this patient would benefit from some community palliative support, I'm always thinking I don't like that word because I'm not saying they're necessarily going to die imminently - which palliative can often imply."

Dr D: "Another anxiety I think is that, so you involve palliative teams and you have that chat, but then a patient comes into hospital with something that is potentially reversible, but because of the involvement of palliative care they might not get the right care. So, you know, someone comes into ED (emergency department) or AMU (acute medical unit) with encephalopathy and they don't get an ascitic tap to diagnose their SBP (spontaneous bacterial peritonitis)."

Dr G: "And I've come across it with colleagues who, for example, won't place patients on a DNAR order because they feel that means that the [nursing] team looking after them will just give up."

Subtheme 4b – Patients and families

Concerns that use of the term "palliative" would cause unnecessary distress to patients and families were equally widely expressed (see also Box 2.5, quote 2). Participants typically thought the term "palliative care" had strong societal connotations of definitively irreversible, and typically malignant, disease. It was thought that the more nuanced concepts around symptom control in the context of uncertain prognosis would be lost amongst many patients, and that the term "palliative" would equate to a loss of hope for many. Some participants feared this misunderstanding risked adversely affecting the doctor-patient relationship, with patients and families reacting with anger and a feeling that the doctor was 'giving up' on them.

Participants were challenged as to whether they felt the term "supportive care" would be preferable in this regard. Amongst participants who saw the term "palliative" as problematic this suggestion was met with universal approval, with participants often commenting that this would remove a major barrier to PC. A diary entry, taken at the time of interview with Dr C (one of the more senior clinicians interviewed) read that he *"visibly relaxed when the discussion moved to talk of 'supportive' as opposed to 'palliative' care"*.

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Box 2.15 – Perceptions of PC terminology amongst patients and families

Dr G: "Palliative care as a whole tends to mean death and dying and going through that process to most people. So I think, I think there is a huge problem with the language."

Dr J: "If you say 'palliative care nurse' to a patient who's not quite right at the end but is in that phase, they're often put off by the word 'palliation' … they think of, again, someone who's got cancer that's about to die tomorrow."

Dr I: "They (patient and wife) balked at the name palliative care … because they've seen him resuscitated from so many different catastrophes, they didn't like the idea that palliative care was some sort of, well, me washing my hands of him - like I was just going to allow him to die from now on."

Dr C: Palliative in the common or garden language means that you're dying and I need to do something to keep you comfortable. That is what the literal translation is to an ordinary individual … it is a word lost in translation. Palliative care is a terminology that evolved for cancer patients who had no hope, were sort of no hopers. And so therefore I think we should get rid of these two words and find a new word which is something enhancing, something else, to give hope as opposed to taking hope away … supportive care is a million times a better word than end of life care or palliative care. So yeah, it talks about enhancement, it talks about focusing on the quality of your life."

The opinion that the term "palliative" was problematic was not universal. An interesting counter argument emerged from two participants who thought existing terminology to be appropriate. When asked about the term "palliative", both felt that avoidance of its use equated to avoidance of the most central issue – that the possibility of death was real and imminent. That "fallout" from such discussions may occur, and that current training and resources were suboptimal, represented separate challenges. These participants argued that fear of the term related not to a fear of its misperception, but to a fear of its associated reality. A different perspective again came from a participant who felt the terminology was often more of a problem to doctors than it was to patients who, in her opinion, often held more realistic prognostic expectations than their physicians. The juxtaposition of these feared perceptions of "palliative" care,

against the perceived role of the hepatologist as a heroic curer of life-threatening disease and fighter of inequality, is striking.

Box 2.16 – Opposing views, supportive of use of the term "palliative"

Dr B: "I think we need to start having that clear conversation about what the disease is, what the disease means for them, what palliative care actually means and how it can help them for their disease at that point in time ... as long as it's done sensitively and properly and you make it very clear that you don't think the patient is imminently about to succumb to their disease but they may have an uncertain trajectory. I think that's a conversation we don't have anywhere near often enough as I've already said, because we find it very hard to say to somebody, 'You've got a disease which may well kill you. We don't know when, and it could be at any time'."

Dr A: "Often, relatives say to me, 'Well yeah, that's what we thought' but no one had ever acknowledged it to them, and they often thought that whole referral process for transplant was crazy – because they'd recognised that someone who's bedbound was no way going to be fit enough for a 12-hour operation – but often, it's the doctor – that's the one who's not able to let go."

Theme 5 - Structural barriers

This theme relates to barriers to SPC caused by healthcare resource limitations and service structure. Data from this theme fell into two broad themes: the primacy of malignant disease in SPC, and the wider structural and resource constraints of the NHS (table 2.16).

Table 2.16 – Emergence of coding framework for 'structural barriers' sub-themes

Questions used to explore theme	Examples of initial codes	Broad themes	Final theme
In your experience, what are the factors which can make it difficult for patients with ESLD to access SPC services? *If you were designing a perfect PC service for patients with liver disease – how would it be designed? What would it look like? What barriers would we need to overcome?*	Can't access services unless cancer, services not set up for benign diseases, hospices can't cope with liver disease, focus on cancer, out of sight out of mind	PC services are predominantly designed and funded for patients with malignant disease. Due to current organisation of PC services referral not always thought about in benign disease.	Primacy of **malignancy**
	Services are fragmented, lack of community services, palliative care not on tap, would struggle to cope with the volume of caseload	Existing resources are limited, and expansion difficult in current financial context. Community and secondary care services are not adequately integrated.	Service and **resource**

Subtheme 5a - Primacy of malignancy

The discrepancy in access to SPC between malignant and non-malignant disease, highlighted both in the questionnaire study and the non-hepatological literature, was explored further in interviews. One participant described working in an institution where referrals to SPC were not possible outside the context of malignancy, whereas others described patients with liver disease as having substantially reduced levels of access to SPC services. That services were already overstretched within the context of malignant disease alone was cited as one potential reason for this. One participant felt the physical placement of SPC departments (typically within oncology units) perpetuated already low referral levels, and that a proactive approach to benign disease from SPC formed an important part of future solutions.

Box 2.17 – The primacy of malignant disease in PC

Dr A: "What we don't have, at the moment, is the funding or the services to do that (refer patients with benign liver disease to SPC). We can only access palliative care for people with cancer. Conversely the people we see with cancer and are on the transplant list are much less likely to die than the people with decompensated liver disease; although they can access palliative care."

Dr E: "We don't even have a regular palliative care attendance at our cancer MDT (multi-disciplinary meeting) because of stretched services. So, the thought that they've got capacity to take on the patients with non-malignant disease be it liver or heart failure – they just haven't opened it up as an option … Liver disease often has got a much worse prognosis than many cancers, but it's just not given the same access to specialist services."

Dr F: "I think there's a psychological barrier, which is that palliative care still has a cancer label to it, and getting the providers of care to recognise that they've got to step outside the cancer arena and look at benign disease at the end of life still isn't happening."

Dr G: "Not having palliative care on tap is a problem. You have to make an active referral to palliative care. If palliative care was part of everyday working and readily accessible and available on the ward – like in oncology – reviewing, actively reviewing patients on the ward and sort of 'looking for work' as it were, then I think they would become sort of plugged in to everyday working and that would make it much, much easier."

Subtheme 5b - Structure and Resource

Four key resource barriers emerged. Participants recognised that successful implementation of PC measures was labour intensive, and that clinical time was already extremely stretched. Secondly, participants recognised that improving services required increased funds and felt the only way this could be realised pragmatically was through the development of clinical models which were demonstrably cost-effective. Thirdly, the fragmented organisation of NHS structures was considered prohibitive – in that one secondary care institution commonly received patients from multiple areas, with multiple commissioning bodies and multiple methods of funding. As such services were "not joined up", making co-ordinated management between hospital and community difficult. Finally, a "workforce gap" was identified in primary care. Participants recognised that good PC was reliant on strong community support, however, they felt that existing community services had neither sufficient capacity or expertise to adequately manage ESLD. Participants' frustrations around service and resource limitations invoked the greatest unanimity in opinion of any theme.

Box 2.18 – Structural and resource barriers

Dr J: "It's the time. At the moment, hepatology is hammered, shall we say. We've got too big a volume load, busy clinics. It's very difficult to see how we could add that volume of work into what we're doing at the moment."

Dr G: "Being brutal about it, the way that this would work is if there was, if there was some kind of financial incentive, for example if there was a CQUIN[+] payment or something of that sort for providing this sort of care for patients with liver disease – then I think it would happen … realistically if there's not money that comes with, it'll be difficult to build in."

Dr F: "Fragmentation of health service provision in the community is a huge issue, so one CCG (clinical commissioning group) deciding they want to do it one way and another CCG deciding well, we'll do it a different way, is an absolute pain. It's impossible, and it automatically disrupts any response, given that the identification hub is invariably secondary care ... It's never commissioned as a holistic service that links primary and secondary care, so I think NHS structures are a huge barrier."

Dr F: "We're always very keen for the community services to do more, but how are we actually going to achieve it? Where's your workforce? Where are the staff going to come from to actually enable this to happen? Where are both GPs and the nursing and other healthcare staff who will have the skill sets to do it?"

Dr I: "An awful lot of the day to day management would need to involve primary care ... my personal experience is that GPs have very poor knowledge about liver disease in general and particularly about the issue we're discussing now – I mean about supportive care for people dying from liver disease. They always refer to the hospital and whilst I understand why that is, that's not necessarily the best thing for the patient."

[+] CQUIN = Commissioning for Quality and Innovation National Goals – a tariff received conditional on demonstrating improvements in quality in specific areas of patient care

Theme 6 - Improving care

Interviews concluded with a discussion around how provision of PC could be improved. Data from this theme fell broadly into two subthemes: improving timely recognition of terminal decline, and the design of services which were integrated across the spheres of hepatology, SPC, and primary care.

Table 2.17 – Emergence of coding framework for 'improving care' sub-themes			
Questions used to explore theme	Examples of initial codes	Broad themes	Final theme
"If you were designing a PC service for patients with liver disease – how would it be designed? What would it look like? What barriers would we need to overcome?" *(Participant specific depending on key barriers identified)* *"How to you think we can get over the barrier of … to improve PC services in the future?"*	Too tied up in active interventions to notice, signposting of poor prognostic features, use of routine scoring to predict terminal phase, legitimising the discussion with evidence, making it routine and not exceptional care	Systems which routinely identify patients at risk of terminal decline are required to ensure timely referral. Evidence-based scoring systems based on physiological parameters may help legitimise the discussion.	**Recognising** patient decline and scoring
	Need to enable and support community services, specialist nurses at the centre of patient care, maintain hepatology input and don't discharge completely, joined up point of access for patients	PC interventions are best organised as integrated care, with input from hepatology, community and SPC. Specialist nurses have a role in co-ordinating care and as a point of access towards the EOL.	**Integration** of services

Subtheme 6a - Recognising patient decline and scoring

Strategies to improve PC commonly centred around discussion of systems which could improve recognition of the terminal phase. This typically led on from issues raised in sub-theme 2b ('timing of the palliative phase'), which highlighted the phenomenon of getting caught up in active disease management at the expense of considering the wider prognosis. Participants described potential solutions to this in terms of flags based on physiological parameters, which would signpost physicians towards PC interventions. Development of scoring systems was identified as a possible means of achieving this. Some participants felt that routine scoring may help "legitimise" entry into poor prognosis discussions, in that if such aspects of care were standardised they could not be misinterpreted as the doctor "giving up".

Box 2.19 – Scoring systems to identify poor prognosis

Dr E: "It gives you a way into that conversation and it then takes away the sort of finger in the air, don't like the look of this kid, but it also takes away, I would say, some discrimination. So, an objective measure that you're flagging on this, there's reasonable evidence says that, you know, this might well not be something you'll survive."

Dr F: "I reckon we've got 17 different scoring systems that predict whether people are going to live or not – and we use them in particular contexts which is normally about assessment for transplantation; but never to appropriately plan end of life care. So I think there's a big gap there."

Dr I: "There is a whole range of ways of prognosticating people with ESLD ... my personal view is we should use scoring systems much more than we do. And we should be transmitting that information to our patients much more than we do."

Subtheme 6b - Integration of services

The capacity to orient patients' care within the community, whilst still maintaining access to the expertise within secondary care, was identified as an important facet of future service design. The difficulties implicit in navigating fragmented services were recognised, and the concept of a single point of patient contact and access was cited as a potential solution for this. Most participants felt this role would be best suited to hepatology specialist nurses, but recognised the need for expansion of personnel in this area and evidence to support their cost effectiveness. A model through which hepatology, SPC, and community care could be integrated cohesively emerged as being important to participants.

Box 2.20 – Integrated service design

Dr B: "If you've got a good, robust pathway that cuts across secondary care into primary care, with palliative care, and with hepatology specialist nurses acting as a fulcrum for it, you might expect to see a reduction in unplanned admissions. You might expect to see shorter lengths of stay."

Dr C: "So the nurse is the primary port of call for these individuals ... let's say a hepatology specialist nurse who is community based. So, everything comes to him or her and she or he has contact with the GP and the hospital services. There are lined up services, there's the patient, there is a district nurse type person, there's a GP and there's a hospital. And it is an integrated care that you're giving to this individual patient."

Dr F: "It has to be a service based in the community that has links into secondary care. So with my particular definition of it, these are people who've had a hospital admission and you need to have something that you can trigger before the point of discharge to pick them up from there … I accept what you say about 'if cost was no object' but, in reality, it always will be."

Typology of the 'reluctant referrer'

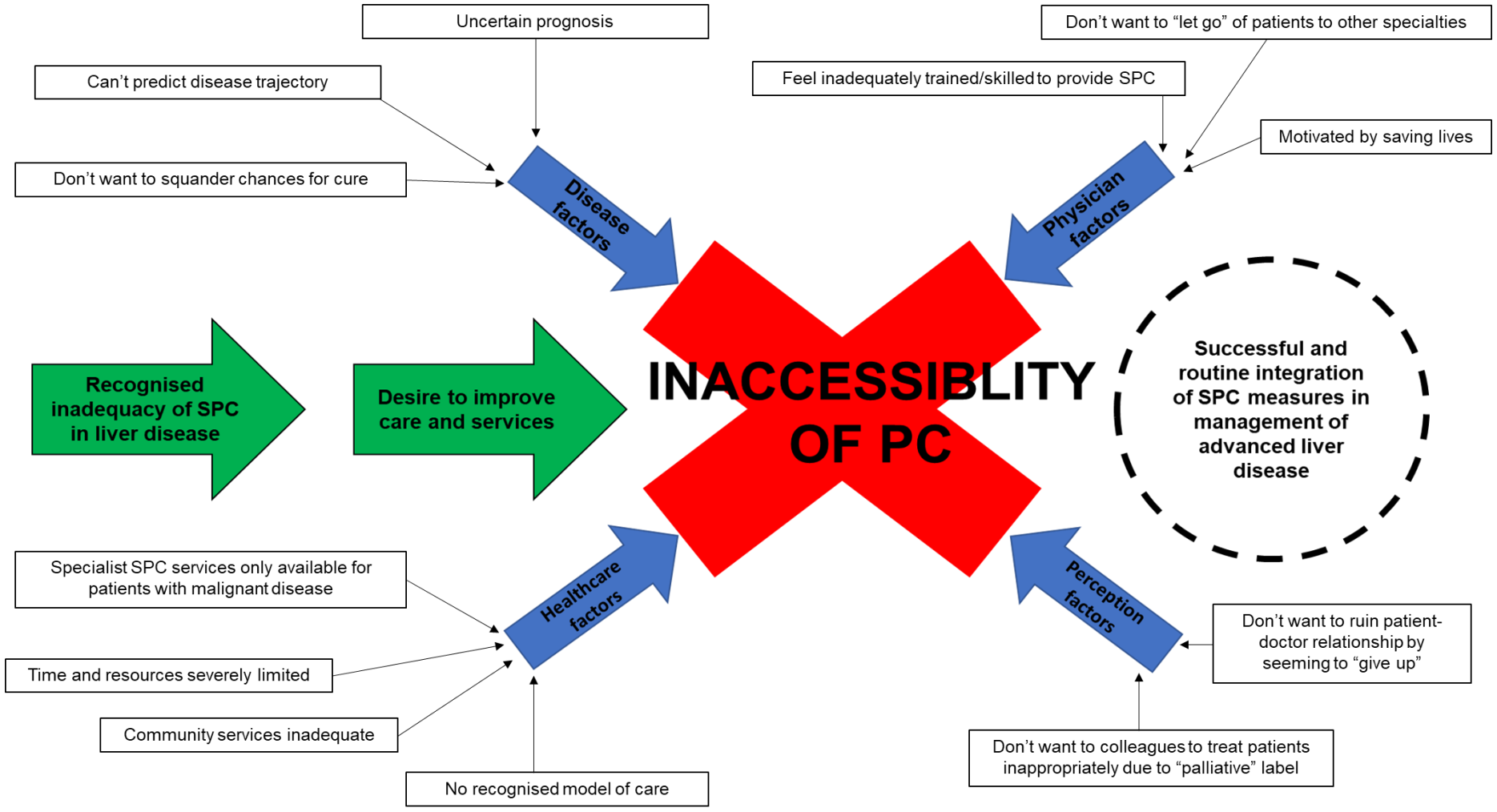
Analysis of individual responses from within the final thematic framework revealed a typology of participant. Drs C, G, H and J all considered curative and PC to be mutually exclusive entities. Further analysis of responses from these participants highlighted other commonalities across different themes. All four worked in liver transplant units and described transplantation as a key facet in their motivation and career choice. All specifically expressed anxieties about the term "palliative care", and how their use of it could be incorrectly perceived by others. All held similar reservations about the service and resource barriers faced in improving current services (although such reservations were also consistent amongst the remainder of the sample). Questionnaire responses from these participants were reviewed, with specific attention to their 'attitudes' to PC (assessed by number of 'should' responses to the clinical vignettes i.e. number of cases where PC was considered clinically appropriate, max = 7). Whilst the mean score amongst all respondents was 3.29, and amongst the remainder of the qualitative sample 3.33 (range 2-5), amongst these four participants it was 1.75 (range 1-3). For the purposes of the ongoing discussion, this typology is termed 'reluctant referrer'.

Unifying theme – Inaccessibility of PC

Participants recognised that the quality of PC for patients with ESLD was deeply unsatisfactory. Although participants sincerely wanted to improve care for their patients, they felt unable to do so for a wide range of reasons. Hepatologists felt insufficiently resourced or skilled to provide PC themselves, however, could

not access SPC, and perceived community services to be inadequate. The inherent uncertainties in disease trajectory inhibited participants from actively identifying appropriate patients, fearing that getting it 'wrong' could thwart the possibility of cure (a key professional motivation). Even when PC needs were recognised explicitly, participants feared others' perceptions of a 'palliative' label may result in a breakdown in the doctor-patient relationship, or inappropriate care from colleagues. The combined effect of these multiple factors led to the perception that PC frequently felt inaccessible to physicians. Revisiting the data subsequent to my initial analysis, revealed that participants repeatedly referred to issues around "accessing" PC for their patients (see box 2.17 for examples). This perceived "inaccessibility" of PC emerged as a unifying theme. This is summarised diagrammatically in figure 2.2.

Figure 2.2 – Inaccessibility of palliative care – a unifying theme



DISCUSSION

Summary of main findings

This mixed methods study of UK hepatologists identifies widespread recognition of extensive and unmet PC needs among patients with ESLD. Multiple barriers to PC however contributed to a sense that PC was frequently inaccessible to physicians managing ESLD, meaning pragmatic improvements to current models of care were difficult to acheive.

An on-line questionnaire survey demonstrated significant discrepancies in self-reported practice towards patients with malignant versus non-malignant disease. Patients with HCC were significantly more likely to receive PC than those with non-malignant disease, even in cases where the prognosis was worse. A minority of respondents felt it appropriate to instigate PC in cases of advanced disease where prognosis was uncertain if there remained a possibility of cure. A lack of routine consideration, and the absence of recognised clinical frameworks were identified as key barriers to PC in ESLD, however respondents also agreed with a wide spectrum of other cited potential reasons. On average, participants disagreed that there was ‘no role’ for SPC in managing patients with ESLD, however other responses highlighted that referral seldom occurred outside the context of concomitant malignancy.

Qualitative thematic analysis of data from 10 in-depth, semi-structured interviews of purposively selected questionnaire respondents demonstrated a recognition of unmet clinical need and the inadequacy of existing services. However, a myriad of structural, disease-based, and attitudinal barriers to PC were identified. This resulted in a perception that PC was ‘inaccessible’ within existing care models, which were widely recognised as sub-optimal. An unpredictable disease trajectory contributed to uncertainties around the appropriate timing of PC. This was compounded by fears of “giving up” too early, among a sample who were typically motivated by a desire to save life and redress inequality. Participants feared labelling their patients as ‘palliative’, due to concerns that their intentions would be misunderstood by patients and families and that access to life-prolonging interventions from other medical specialities may be curtailed. Despite overwhelmingly positive experiences of SPC services, participants rarely referred patients. SPC services were perceived as being overly stretched and primarily designed for patients with malignancy. Equally however, participants felt inadequately skilled to provide these aspects of care themselves and considered community services unsatisfactory. Participants identified the need to develop robust systems which: identified appropriate patients routinely and in a timely fashion, integrated hospital care with community services, expanded the hepatology specialist nurse workforce to facilitate co-ordination of care, and which were demonstrably cost effective.

A ‘reluctant referrer’ typology was identified, which reflected the particular anxieties around the use of PC in ESLD expressed by four participants. Reluctant referrers considered PC appropriate in fewer of the questionnaire clinical vignettes than the remainder of the sample. The opinions of reluctant referrers did not dominate the qualitative data, and it is not possible to generalise their data to a wider population. Nonetheless, it is interesting to consider their responses within the context of the questionnaire survey. 127/265 (48%) of all questionnaire respondents felt PC to be appropriate in 3 or fewer clinical vignettes provided (max = 7, overall mean = 3.29). The multiple barriers to PC in ESLD created a sense of that PC was often inaccessible to participants within the qualitative sample. This emerged from the data as a unifying theme.

Strengths and Limitations

This represents the largest study of hepatologists’ attitudes towards PC and is the first to use qualitative methods to explore the perspectives of this specific professional group. Our response rate of 33.7% may have limited generalisability, however it did achieve the 33% considered standard for online surveys, [170] and was considerably higher than in comparable studies.[122] Ease of completion was prioritised in questionnaire design so as to maximise response rate. This may have adversely affected the quality and depth of the quantitative data. Items ranked on ordinal scales were analysed using descriptive statistics which assume continuity, meaning subsequent descriptions of statistical significance were somewhat flawed. Furthermore, the multiple-choice format prevented nuanced responses, and assumed categorical opinions.

Adopting a mixed methods approach allowed an assessment of pre-existing attitudes to be included in purposive sampling, improving the validity of our qualitative findings. Within interviews however, the extent to which participants felt able to fully and honestly share their views was difficult to quantify. The possibility that views expressed may have been modified to ‘please’ the researcher, particularly given his pre-declared research interest, must be considered.

Although ‘reflexive bracketing’ was used throughout, it is difficult to fully eliminate researcher bias within qualitative studies.[148] Interviewers may subconsciously bias interviewees to answer questions in certain ways, for example by inadvertently responding judgementally, or through asking leading questions. Given the clinical experience of the interviewer, the risk of bias and assumption of meaning was perhaps somewhat higher in this study. As Sheldon and Sargeant reflect: [171]

“It can be difficult to remain immersed yet retain the ability to stand back and question ‘the taken for granted’ in an environment in which language and behaviours appear familiar.”

Relationship to existing theory and research

The literature pertaining to hepatologists' attitudes towards PC is limited to a single centre, mixed methods study which included hepatologists among participants.[26] This study did not achieve thematic saturation, and the views of hepatologists specifically were indistinguishable from those of other healthcare professionals within the published data. Nonetheless, this study identified a lack of skill among healthcare professionals in initiating prognostic discussions, a reluctance to refer patients to SPC when prognosis was uncertain, and a perception that patients and families perceived PC negatively. These findings are broadly corroborated and extended by our study.

Many of the themes identified in this study relate to prior research surrounding the barriers to PC in other medical specialties. Difficulties among physicians in recognising the terminal stages of illness, described in theme 2b of this study, are widely described. Christakis and Lamont prospectively evaluated physicians' predictions of survival in 468 terminally ill patients, and demonstrated systematically optimistic estimates.[172] In a questionnaire-based survey of hospice referral amongst US physicians, Brickner et al described physician-reported difficulties in predicting terminal decline. Fears around the perceptions of patients and families in relation to PC, similar to those identified in the 'perception barriers' theme of this study, were also described.[173] A semi-structured interview study of 18 healthcare professionals managing heart failure demonstrated that PC referral was commonly delayed by physicians', both due to difficulties in identifying the terminal phase and because of perceptions that PC was reserved for patients in whom death was imminent and inevitable.[174] A large interview study of American oncologists highlighted commonplace beliefs that curative and PC were mutually exclusive. The authors interpreted this as being fundamental in preventing high quality EOLC.[175] The perception of a palliative-curative 'dichotomy' was also described by participants within our study, in particular those within the 'reluctant referrer' typology. A systematic review looking at transitions between curative and PC suggested that physician difficulties identifying the 'transition phase' may be overcome through incorporation of PC earlier in the disease trajectory.[176]

In a 2002 focus group study of clinicians managing heart failure, Hanratty et al identified fears of losing professional para of patients as prohibitive to SPC referral. Difficulties surrounding the unpredictable clinical course of heart failure, and poor co-ordination between healthcare sectors were also described. Although this study is somewhat dated and sampled a different professional group, their findings are clearly comparable to this study.[151]

Difficulties associated with the terminology of PC, identified in theme 4 (perception barriers) are also described elsewhere. Whilst in the field of paediatrics and performed outside of the UK, a survey-based

comparison of the terms 'palliative' and 'supportive' care among the parents of children with cancer demonstrated that the term 'palliative' evoked greater negative emotions, and that 'supportive' was favoured.[177] A survey-based study of US medical oncologists demonstrated a significantly increased likelihood of SPC referral for patients undergoing active treatment when the term supportive, as opposed to palliative, was used.[178] A qualitative interview study of 17 oncologists investigated the impact of changing the name of a service from 'palliative' to 'supportive' care.[179] The majority of oncologists favoured the term supportive, largely because they perceived that their patients preferred it. This rationale also relates to the fears of patients' misperceptions identified in sub-theme 4b (perception barriers – patients and families) of this study. A recent Australian interview study of 25 patients with advanced cancer and their caregivers has also highlighted that 'palliative care' and EOLC are often initially perceived as synonymous, and that negative connotations, associated with diminished levels of care, are commonplace.[180]

The concept of parallel planning was highlighted in the 'disease barriers' theme of this study as a potential strategy to approach patients with advanced disease but uncertain prognosis. Strategies to approach such scenarios have been identified elsewhere. The AMBER care bundle was designed to improve care for inpatients who may be in the last two months of life but whose recovery was uncertain.[181] Such approaches are however not without complexity, and the explicitly expressed concerns of participants in our study regarding "mixed messages" and "confusion", are in part, supported in the literature. An observational study, comparing the AMBER care bundle to standard care, demonstrated that, whilst awareness of prognosis appeared better in the AMBER care group, the information received was judged less easy to understand.[182] Although small and retrospectively designed, this study highlights the complexities of a 'parallel planning' approach.

A perceived inequity in the provision of PC for patients with decompensated liver disease, as compared to those with HCC, was highlighted in both the questionnaire and interview sections of this study. Extensive and unresolved PC needs have also been widely reported among patients dying from other non-malignant organ failures.[57, 59, 61] Despite shifts in national policy and legislature,[183] inequities in the availability of SPC services for patients with non-malignant disease are widely recognised.[184-187]

Implications for practice

Implications for practice are described in terms of key recommendations. The accounts of 'reluctant referrers' have merited particular focus, as it is likely that the greatest changes to individual practice will be required by this group.

Recommendation 1 – Evidence based guidelines to trigger PC

The barrier of unpredictable disease trajectories in achieving timely PC has been noted outside the context of liver disease in both cancer and non-cancer settings, [174-176] and our findings are consistent with this. Whilst appreciating its theoretical benefit, anxieties regarding 'premature' referral, combined with implicit difficulties predicting the 'terminal phase' were frequently prohibitive to SPC involvement. Evidence-based prognostic scoring – centred around objective clinical parameters – has the potential to legitimise the introduction of such interventions, particularly amongst 'reluctant referrers'. Furthermore, by normalising prognostic scoring as part of routine care, the issue of PC 'not being routinely considered' (the highest ranked barrier in the questionnaire study) may be overcome.

Recommendation 2 – A focus on non-malignant disease

Discrepancies in the provision of PC to patients with malignant vs. non-malignant liver disease were demonstrated clearly in both sections of this study. This is consistent with wider literature detailing inequalities in access to PC for patients with non-malignant disease.[184] Whilst definitions of curability and utilisation of 'best supportive care' approaches are clearly embedded into international guidelines for the management of HCC,[16] such approaches are not advocated for in equivalent guidelines for non-malignant liver disease.[188] A specific focus on redressing this balance is required in future guidelines and models of care.

Recommendation 3 - use of the term 'supportive care'

Removal of the term 'palliative' from the lexicon is a controversial step, and one that may indeed be considered retrograde by those who feel that such barriers should be approached through physician and patient education, as opposed to perpetual terminological drift.[189] Nonetheless, the term appeared prohibitive, particularly among 'reluctant referrers'. Such perceptions were not exclusive to hepatologists, and similar fears among patients and physicians are described in the wider literature.[177-180] Change of terminology to 'supportive' is not in itself a solution, and does risk reinforcing pre-existing misperceptions. Nevertheless, it does appear to increase acceptability in an otherwise potentially resistant group.

Recommendation 4 – Parallel planning

Use of the term 'supportive' may also encourage adoption of a 'parallel planning' approach, which represents a further recommendation from this study. Perceptions of conflict between curative and palliative approaches were commonplace, particularly amongst the 'reluctant referrer' group. The consequence of this was that PC interventions were commonly disregarded, due to anxieties about making the 'wrong call' with respect to a patient's disease trajectory. This was also reflected in questionnaire data,

where respondents rarely instigated PC in cases of advanced disease whilst curative options remained available. The natural history of liver disease is such that approaches which preclude patients undergoing active treatment are unlikely to be fit for purpose. How such dual models of care are best communicated to patients and families however represents an important and complex question for future studies.

Recommendation 5 – Integrated service design

Participants expressed nervousness about losing patients with ESLD to a separate service, arguing that their specific expertise was required to manage disease complications optimally. This phenomenon of 'ownership' has also been identified in similar studies of other physicians.[151] Juxtaposed to this was participants' recognition of considerable gaps in their own abilities and training in providing these aspects of care. Achieving optimum care will require an integrated approach, encompassing active in-reach from SPC, such that their input forms a routine part of multi-disciplinary decision making and physician training. The stretched nature of existing SPC and liver services is however evident, and how future models of care are resourced to address this requires thought.

Recommendation 6 – Expansion of community hepatology services

Whilst the potential benefits of increasing the proportion of care delivered in the community were recognised, perceived deficiencies in manpower and expertise within primary care emerged. Expansion of community hepatology is likely to require outreach from hospital services. Coordination from a single hub would have the added benefit of reducing fragmentation of care between services. This model would however require considerable expansion of the hepatology specialist nurse workforce and, again, demonstration of cost effectiveness will be central to realising improvements.

Implications for future research

The Gold Standards Framework include prognostic criteria for cardiac, pulmonary, renal and neurological disorders, however omit criteria for liver disease.[68] Evidence based models which incorporate prognostic screening into ongoing active disease management require development. The optimum content of PC interventions for patients with ESLD is not established within current literature. Research involving patients with ESLD and their families is vital in addressing this question. Finally, within the context of ever-increasing resource limitations, demonstration of cost effectiveness will be essential if changes to existing service models are to be adopted pragmatically. Analysis of the cost implications of PC interventions and increased community support is vital to their future implementation.

CONCLUSION

This study of hepatologists' attitudes towards PC demonstrates the challenges faced if PC for patients with ESLD is to improve. Appreciable discrepancies in care between patients with benign and malignant life-limiting disease are identified. A reluctance to instigate PC prior to the exhaustion of all curative options is highlighted. An unpredictable clinical trajectory, misperceptions of the term ‘palliative’, and resource limitations are identified as key barriers to PC. Such factors contributed to a sense that PC was ‘inaccessible’ to hepatologists.

We recommend: the introduction of evidence-based guidelines which trigger PC interventions routinely for appropriate patients, the development of clinical models which are designed to run in parallel with active disease management (particularly for patients with non-malignant disease), replacement of the term ‘palliative’ with ‘supportive’ within the common lexicon and improved integration between hepatology, SPC and community services. For such aspirations to be realised, further research must address the absence of existing clinical models for delivering PC in ESLD, the specific PC needs of patients with ESLD and how novel models of care can be realised within the context of pre-existing resource limitations.

CHAPTER 3

THE PATIENT AND CARER EXPERIENCE OF END-STAGE LIVER DISEASE. A QUALITATIVE EXAMINATION OF PALLIATIVE CARE NEEDS, PERCEPTIONS OF EXISTING SERVICES AND PREFERENCES FOR FUTURE CARE.

INTRODUCTION

The existing literature, described in chapter 1 of this thesis, highlights the profound physical and psychological impact of ESLD and the social stigma associated with this condition. Whilst reductions in QOL are reported as being higher than in other life limiting conditions, [74, 75] patients with ESLD seldom receive PC. [81, 109, 110] Chapter 2 of this thesis describes barriers to PC for patients with ESLD, which include a lack of established clinical models for delivering PC in this group.

Literature surrounding the patient experience of ESLD has typically focussed on patients who have undergone successful LT, and therefore does not reflect of the experience of most patients. Whilst qualitative studies have investigated the lived experience of ESLD outside the context of LT, no study has addressed directly the expressed PC needs of patients and carers, the optimum design of services for patients with ESLD, or issues surrounding death and bereavement in ESLD. Answers to these questions are essential if future clinical models for PC are to fully consider patient and carer need.

AIMS AND OBJECTIVES

Aims

This study addresses the second aim from this thesis, outlined in the introduction. This is to understand the PC needs of patients with ESLD and their carers, ascertain how existing services meet these needs and explore the attitudes of patients and carers towards PC.

Objectives

Using qualitative interviews with patients with cirrhosis and refractory ascites and carers bereaved by ESLD, the specific objectives of this study were to:

- Describe the lived experience of ESLD towards the EOL from the perspective of patients and carers.
- Identify and describe the PC needs (including physical, psychological and social needs) associated with ESLD.
- Describe the experience of existing of healthcare services from the perspective of patients and carers.
- Examine the perspectives of patients are carers as to how existing healthcare services may be modified to better meet their needs.
- Examine perceptions of, and attitudes towards, core elements of PC and explore whether further integration of PC could improve upon existing strategies to manage ESLD.

METHODS

Study design

Rationale for qualitative methodology

Most studies investigating symptoms and quality of life in ESLD have used quantitative methods, focussing particularly on health-related QOL indices. Whilst a small number of qualitative studies have focussed on the lived patient experience of ESLD, these are not extrapolated into an understanding of patients' PC needs, nor how health services could be better designed to meet these needs. Furthermore, these studies do not explore patients' understanding of their prognosis. Designing PC interventions which are 'fit for purpose' requires in-depth understanding of the needs of the patients for whom they are intended. A qualitative methodology allows in-depth exploration of individual attitudes and experiences of disease and healthcare, affording a detailed insight into the PC needs of this population and how they should be addressed.

Rationale for semi-structured interview design

Qualitative studies relating to the patient experience in ESLD are scarce, however have adopted a range of methodological approaches. In their study of the lived experience of ESLD, Kimbell et al used serial in-depth interviews in a multi-perspective study of patients, carers and healthcare professionals. They argued that this methodology was most appropriate given that the illness experience was 'inherently subjective' and represented by 'individual, context-bound accounts'.[107] Semi-structured interviews have also been used in studies of QOL following LT and in auto-immune liver disease.[104, 190] The topic guides in these studies were based on previous evidence around quantitatively validated QOL scores, with modification by the authors. In contrast, other studies have employed a less structured approach. In his study of patients post liver-transplantation, Wainwright argued that in-depth interviews with 'as few prompts as possible' were optimal, as this reduced inherent researcher bias, and allowed a pure 'grounded theory' analytic approach, which allowed themes to arise organically from the data. This was felt most appropriate in an area where little was known.[97, 160] In contrast one study, investigating experiences of LT survivors, utilised a focus group methodology. The authors argued that this represented the most effective and efficient means of obtaining rich data among a group who shared a common experience.[100]

A semi-structured interview approach was chosen for this study. Although limited, the literature in this area provides descriptions of the lived experience of ESLD. As such, there is a degree of pre-existing theory. This study aims to build on this through specific exploration of PC needs and potential interventions. A semi-structured interview design allows for a higher degree of interviewer direction,

whilst still allowing for new theories to arise. Use of focus groups with carers was considered initially, however early feedback from potential recruits highlighted that individuals felt uncomfortable at the prospect of a group discussion, which is perhaps unsurprising given the inherently sensitive nature of the topic. Interviews can proceed at a pace that is acceptable to participants and allow for certain areas/topics to be curtailed (or indeed the interview terminated) should they cause undue distress. Furthermore, there may be substantial heterogeneity in participants' experience, meaning the topics covered within a focus group would not necessarily be universally relevant or appropriate (e.g. whilst alcohol dependency may be an important factor for some participants it will be irrelevant to others).

Sampling

As described in chapter 2, qualitative sampling techniques differ substantially from those in quantitative research. The purposive sampling technique utilised in chapter 2 enabled selection of a sample reflective of a wider population, based on earlier response to a questionnaire. The pragmatic considerations of sampling in this study were different given the smaller pool of available participants from a single hospital site. The sample needed to encompass both patients with ESLD who had an appreciable risk of dying over the next 6-12 months and carers who had been bereaved by liver disease within a relatively recent period, such that recall bias was minimised. In addition, participants had to have the cognitive ability, availability and willingness to participate in an in-depth interview. To meet these requirements a criterion-based opportunistic sampling technique was adopted, such that participants were selected on the basis of pre-determined measures (see 'recruitment' below).[191] Whilst the purposive technique described in chapter 2 had the advantage of ensuring diversity within the sample, such an approach would not have been able to achieve sufficient recruitment within the time available. As such there was no pre-determined 'sampling frame' for this study. Data were collected until the point of thematic saturation (see chapter 2).

Recruitment and consent

Patients

Ascites is the most common complication of cirrhosis. Once ascites becomes refractory to medical treatment (refractory ascites), patients have a median survival of 6 months.[33] At this stage patients commonly require intermittent drainage of fluid to achieve symptomatic relief. This procedure is termed large-volume paracentesis (LVP) and is explained further in chapter 4. Within University Hospitals Bristol there is the opportunity for patients to undergo LVP on a day-case unit. This cohort of patients, who have ESLD and attend hospital regularly, were targeted for recruitment. Patients with moderate or severe HE were excluded due potential impairment in capacity (see ethics - below). Inclusion and exclusion criteria are shown in table 3.1.

All patients attending University Hospitals Bristol day-case unit for paracentesis between March 2016 – January 2017 were considered for inclusion in the study by the hepatology specialist nurse running the LVP service. Individuals who met inclusion criteria were offered a patient information sheet (see appendix) and invited to participate by the hepatology specialist nurse. Assuming agreement, at their subsequent attendance for LVP (typically 2 to 4 weeks following initial approach) the hepatology specialist nurse asked if the patient was still willing to participate, allowing a period in which to consider the information and discuss with relatives and loved ones. Patients were only approached by myself if still willing to participate. Written consent was obtained prior to proceeding with the interview (see conduct of field work below).

Relatives and carers

The methodology for recruiting bereaved carers was based on the established VOICES study.[108] A database of all patients who die from liver disease at University Hospitals Bristol is kept within the hepatology department. The registered next of kin was contacted by post a minimum of four months and maximum of two years following the death. A one-month period either side of the anniversary of the death was avoided. The letter explained the purpose of the research, invited recipients to participate in an interview, and contained a patient information sheet and a stamped addressed envelope for return. A single reminder was sent after 2 weeks if no response was received. Those who replied were subsequently contacted by telephone to arrange a convenient time for interview, either at the hospital or in their own home.

Table 3.1 – Inclusion/Exclusion criteria		
	Patient recruitment	Relative/carer recruitment
Inclusion criteria	1. Diagnosis of cirrhosis (of any aetiology). 2. Attending day-case unit for LVP at University Hospitals Bristol. 3. Under the care of a consultant hepatologist at University Hospitals Bristol. 4. Able to provide fully informed written consent to participate in research.	1. Carer or relative of a patient who was under the care of University Hospitals Bristol, and died from a complication of cirrhosis between January 1st 2014-January 1st 2017. 2. Able to provide fully informed written consent to participate in research. 3. Self-directed reply to postal invitation.
Exclusion criteria	1. Inability or refusal to provide informed written consent to participate in research. 2. HE of grade 2 or above (West-Haven criteria). 3. Inability to complete an interview in fluent spoken English.	1. Inability or refusal to provide informed written consent to participate in research. 2. Inability to complete an interview in fluent spoken English.

Production and design of topic guide

The topic guide was designed around the study aims. Specifically, this included the participants experience of ESLD, their experiences of healthcare and PC, and the ways in which they felt current services could be improved. Interviews were structured to ensure that key objectives were given sufficient time within the interview and that there was scope for new themes to arise organically. Once key topics and questions were identified, a general interview order was determined – allowing for flexibility within any given interview. The interviews were designed to progress from general introductory topics, to less sensitive and more general topics (e.g. the experience of healthcare services), on to more sensitive issues at the end of the interview (e.g. understanding of prognosis and ACP discussions). Prior to moving on to the next 'section' of the interview, permission was asked to discuss the next topic – meaning participants could avoid topics they might find distressing and withdraw consent at any stage. Interviews were not time limited, however participants were given an estimated expected length of 45-60 minutes at the commencement of the interviews. The topic guide is shown in table 3.2.

Table 3.2 – Topic Guide		
Broad theme	**Specific topics covered**	**Examples of questions used** [+]
Experience of liver disease	Lived experience of ESLD Supportive and palliative care needs: a) Physical b) Psychological c) Social and spiritual d) Caregiver	"Could you talk a little bit about the physical symptoms you've experienced with your liver disease, and how these have affected how you live your day-to-day life?" "Aside from the physical symptoms you've described, in what other ways has liver disease affected you." "What sort of impact has all of this had on your relationships with friends and family?"
Experience of healthcare	Diagnosis Changes in healthcare as disease progressed Logistics of care	"Can you tell me about how you first found out that you had liver disease." "As your disease has progressed, how have you been supported by the health service?" "In terms of how your healthcare has been organised, have there been any frustrations or difficulties along the way?"
Perceptions and attitudes towards supportive and palliative care	Understanding of disease and prognosis Advance care planning Symptom management Care priorities at the end of life Bereavement [++]	"How do you think things are going to progress with your liver disease?" "When diseases get to an advanced stage, doctors sometimes use palliative care – which focuses more on a patient's symptoms, and planning for what would happen if things got worse, as opposed to focussing on trying to cure the disease. How would you feel about using palliative care to help with your condition?" "Around the time (your relative) was dying, what were the things which were most important to you and your family? Looking back, how do you think the health service could have better helped with those things?" [++]
Recommendations for future care	How could existing services better meet need	"Looking back, if we were designing the perfect healthcare system for people with ESLD, what things do you think we should be doing better?"
[+] Examples of actual questions cited, however there was variation in wording between interviews [++] Carer interviews only		

Conduct of field work

Prior to both patient and carer interviews practice interviews were undertaken with colleagues to check flow of the questions, approximate timings, and to test recording equipment. The order of questioning was modified slightly following these interviews. Patient interviews were undertaken during attendance for LVP at the University Hospitals Bristol medical day-case unit. Carer interviews either took place in a clinic room at University Hospitals Bristol, or at the participant's home – depending on individual preference. The topic guide was used as a reference in each interview, however was adhered to flexibly dependant on participants' responses. All interviews were recorded digitally. A reflexivity diary was completed immediately following each interview, detailing immediate thoughts, body language and emotions displayed during each interview. Interviews were transcribed verbatim, alternately by myself and a professional transcription service approved by the University of Bristol.

Following each interview a letter was given to each participant, thanking them and providing contact details for ongoing help and support should it be required. I telephoned each participant two weeks after the interview. This afforded an opportunity to check well-being, answer any ongoing questions, and to check that the central points from their interview had been interpreted correctly. The discussion concluded with participants being offered a written transcript and/or digital recording of their interview (one from seventeen accepted), and an opportunity to modify their responses or withdraw their interview from subsequent analysis (no modifications or withdrawals were made). I was unsuccessful in contacting two of the patient participants, both of whom attended subsequent hospital appointments. Data saturation (see chapter 2) was obtained after 15 interviews. Two further interviews were completed to ensure saturation.

Data analysis

Initial analysis of each interview involved listening to the audio recording, reading and re-reading the transcript, and revisiting field notes. After this, line-by-line coding of the transcript was undertaken. Codes were organised into themes which were iteratively reviewed and refined, ultimately forming a thematic map (figure 3.1). Emerging themes were discussed regularly at research team meetings. The team included individuals with expertise in hepatology, nursing, palliative medicine, and qualitative research. Four of 17 (24%) transcripts were coded independently by two researchers, before coming together to compare analyses. Differences were resolved through discussion. Data were collected and stored in accordance with the Data Protection Act 1998, as described in chapter 2.[159] Data were anonymised with all participants and named individuals given pseudonyms in the written report.

Data were organised using a thematic approach, similar to that described in chapter 2 (see figure 2.3). Analysis was directed towards both organic development of theory, and development of existing knowledge. As such, whilst analysis utilised elements of grounded theory (including line-by-line coding, constant comparison, and memo-writing)[192], it also incorporated pre-existing and 'a priori' concepts. Nvivo10 software was used in data storage and coding.[164] The consolidated criteria for reporting qualitative research (COREQ) were developed as a framework to ensure high quality reporting of qualitative interview and focus group studies.[193] They encompass a checklist of 32 items and are widely used by journals appraising and publishing qualitative studies. These criteria were used to guide the reporting of this study.

Rationale for analytic approach

Modifications of the method described in chapter 2 were necessary in this study. In contrast to chapter 2, this study describes data from two groups (patients and carers) with two chronologically distinct perspectives (current and retrospective). It could be argued that these differences would be better explored in separate studies, however we felt it was more appropriate to analyse them as part of the same thematic framework. The two perspectives are intrinsically linked and complementary to each other. The study objectives were consistent, and applicable equally to each group. Pragmatically there was a limited pool of potential participants– so achieving data saturation in the context of two studies with two distinct objectives would have been considerably more difficult within the time frame. As such (with the exception of one subtheme) data were organised into a single thematic framework.

Non-thematic analytic approaches were also considered. Given our study aimed both to build upon existing theory and seek new insights around specific pre-defined objectives, interpretative phenomenological analysis was not considered appropriate. Whilst elements of grounded theory [156, 194] (line-by-line coding, constant comparison, and memo-writing) underpinned elements of our analysis, a purely inductive approach was also not considered suitable. Whilst limited, there is an existing theory surrounding this topic which informed the study objectives, semi-structured interview design, and topic guide. A thematic approach allowed for themes to arise organically from the data, whilst also enabling exploration of anticipated topics and 'a-priori' concepts.[161]

Rigour and trustworthiness of findings

The underlying concepts of credibility, confirmability, reflexivity and transferability are discussed in chapter 2. Techniques to guarantee rigour were employed during interviews, in the post-interview period, and during analysis. Within interviews, iterative questioning and 'member-checking' was used, such that

the interviewer's interpretation of participants' meaning were checked explicitly throughout. As described above, participants were telephoned approximately 2 weeks subsequent to their interview to ensure that the main points from their interview had been interpreted correctly. This active 'collaboration' with participants adds further credibility to their accounts.[166] Every fourth interview was 'double-coded' independently by my supervisor. Meetings were scheduled throughout the research period to analyse data iteratively and modify the thematic framework, ensuring dependability of the findings.

As a senior registrar in hepatology, I brought my own preconceived ideas and values, and thus was not entirely 'neutral' to the topic. In recognition of this, reflexive bracketing was exercised throughout interviews and analysis, to mitigate against possible bias. Conversely, Fetterman argues that "working with people day in and day out for long periods of time is what gives ethnographic research its validity and vitality", and this 'prolonged engagement' with the cohort in some ways enhances credibility of the findings.[195]

Ethical considerations

Patients with ESLD are at risk of developing HE which may impair participants' capacity to provide fully informed consent. Nonetheless, HE is a potentially distressing feature of ESLD and it was important that this was represented in our sample. We decided to include patients with grade 1 encephalopathy or below, as defined by the West-Haven criteria. [196] Potential features of grade 1 encephalopathy include trivial lack of awareness, shortened attention span and impaired performance of addition or subtraction. Whilst we considered excluding all patients with any documented history of HE, we felt this would reduce the transferability of our findings. All patients were assessed by two independent clinicians under the auspices of the Mental Capacity Act regarding their ability to consent prior to inclusion within the study. Previous qualitative research on patients with ESLD has utilised similar exclusion criteria.[107]

Contacting bereaved relatives regarding the death of a loved one risks causing emotional distress. We adopted the established methodology of the VOICES questionnaire as described previously.[108] We used the departmental database to identify the next of kin of patients who had died from liver disease between 4 months and 2 years from the commencement of the study.

Both patient and carer interviews addressed potentially distressing topics. This was outlined in the patient information sheet. In addition, participants were provided with a contact number and email address, and a 24-hour 'crisis-line' if they became distressed subsequent to the interview. It was emphasised at the start

of each interview that participants were able to terminate the interview or withdraw consent at any point. Part of the 2-week follow-up telephone call was dedicated to checking participant well-being.

Ethical approval was granted by the Hampshire B NHS Research Ethics Committee prior to commencing the study. Approval was also granted by the research and development department at University Hospitals Bristol. The study was sponsored by the University of Bristol.

RESULTS

In this and subsequent sections, the following collective terms are used to describe the sample:

- 'participants' – referring to the whole sample (patients and carers)
- 'patients' – referring only to patient participants
- 'carers' – referring only to carer participants
- 'decedents' – referring only to the deceased relatives of carer participants

Recruitment and interviews

Recruitment took place between 02/05/2016 and February 24/02/2017. Patient and carer interviews ran contemporaneously. Of 17 patients approached initially, 13 agreed to be interviewed. Four patients declined at initial approach and one died between initial approach and interview, so that 12 patients were interviewed in total. Patients declining interview were similar for age, sex and disease aetiology. Seven replies were received from 19 postal invitations to carers. Two carers withdrew before interview, so that five carers were interviewed in total. Twelve patient and five carer interviews were completed.

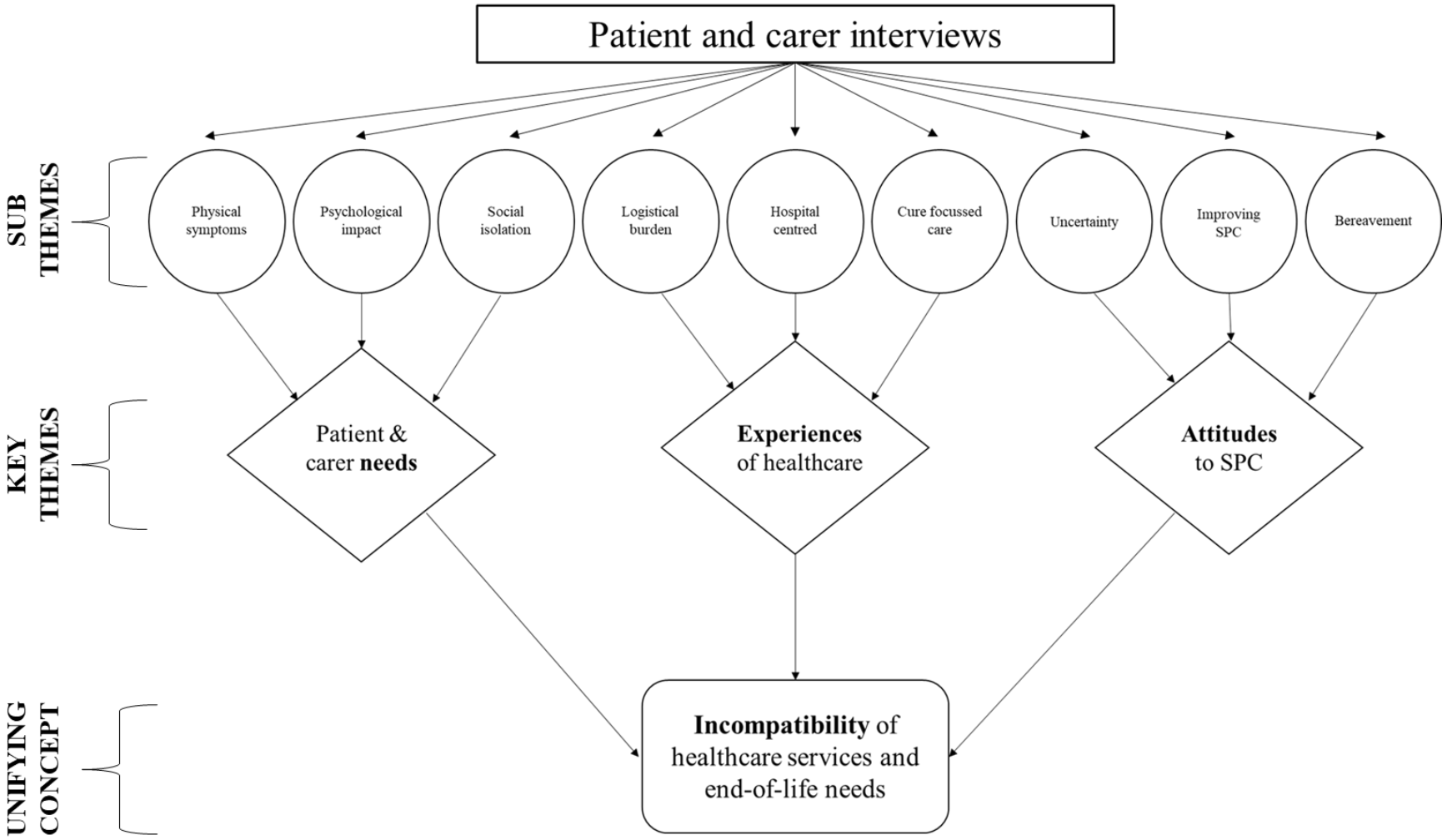
All patient interviews were undertaken in a private cubicle in University Hospitals Bristol during attendance for day-case LVP. Patient interviews lasted between 27-58 minutes. Other than one patient, who asked for their interview to be done during a subsequent LVP appointment, there were no logistical issues. Carer interviews lasted between 29-96 minutes. These occurred by appointment in a private clinic room at University Hospitals Bristol (3 interviews – Miss M, Mrs N, Mrs O), or at the carer's home (Mr P, Mr Q). There were no logistical difficulties. 3 months following the completion of the final patient interview (02/06/2017) 6 of 12 patient participants had died. Of the remainder, five were alive (one was listed for liver transplantation and one was undergoing assessment for liver transplantation) and one had been lost to follow up. Table 3.3 summarises characteristics and interviews of the 17 participants.

Construction of thematic framework

Three themes, encompassing nine sub-themes, emerged from the data. These were connected by a unifying concept, relating to the perceived incompatibility between healthcare services and EOL needs. The final thematic map is summarised in figure 3.1.

Table 3.3 – Characteristics of study participants				
Participant	Patient/relative	Age	Cause of death/bereavement	Interview duration (mins)
Patients				
Mr A	Patient	60-69	ArLD	54
Mrs B	Patient	60-69	HCC	32
Mr C	Patient	60-69	NASH & HCC	46
Mr D	Patient	70-79	ArLD	58
Mrs E	Patient	50-59	ArLD	40
Mr F	Patient	50-59	ArLD	33
Mr G	Patient	70-79	ArLD	36
Mr H	Patient	50-59	ArLD	47
Mr I	Patient	40-49	ArLD	29
Mr J	Patient	50-59	ArLD & NASH	35
Mrs K	Patient	60-69	NASH	43
Mr L	Patient	40-49	ArLD	27
Relatives and carers				
Miss M	Partner	50-59	ArLD	70
Mrs N	Wife	50-59	ArLD	96
Mrs O	Wife	60-69	ArLD & HCC	61
Mr P	Husband	50-59	ArLD	38
Mr Q	Father	70-79	ArLD	29
ArLD = Alcohol related liver disease, NASH = Non-alcoholic steatohepatitis, HCC = Hepatocellular carcinoma				

Figure 3.1 – Thematic map



Theme 1 – Patient and carer needs

Participants described a high burden of physical and psychological symptoms, and experienced increasing social isolation as the disease progressed. Three sub-themes emerged, regarding the effect of liver disease on physical health and functioning, psychological well-being, and its social and financial impact. The emergence of this theme and subthemes is shown it table 3.4.

Table 3.4 – Emergence of coding framework for 'patient and carer needs' sub-themes

Examples of exploratory questions	Examples of initial codes	Broad themes	Final sub-theme
"Can you describe the symptoms you get with the liver disease? How do these affect how you go about your day-to-day life?"	Ascites, hernia, breathlessness, 2-week cycle, pain, fatigue, weakness, disability/loss of mobility, encephalopathy.	Ascites and the cycle of paracentesis, weakness and fatigue, encephalopathy and caregiver burden & health	Physical impact
"How do you think the liver disease has affected how you are in yourself?" "What's been the most difficult thing to cope with?" "What were the most difficult things for you about looking after someone with liver disease?"	Addiction, self-blame, "undeserving" of treatment, depression, anger, suicidal ideation, rejection for transplantation and lack of support, day-to-day uncertainty, unclear trajectory	Addiction, guilt and self-blame, depression and anger, uncertainty	Psychological impact
"Do you think the liver disease has affected any other aspect of your life?" "How did you cope financial aspects of looking after someone, and having to stop work?"	Loss of income, stopping work to become a carer, loss of work and loss of self-esteem, cost of attending hospital, no sick-pay, having to rely on others, changing relationship dynamics, isolation from social events, being "grounded", stigma of cirrhosis and association with alcohol	Financial impact, changing relationship dynamics and dependence, social isolation, stigma of cirrhosis	Social isolation

Subtheme 1a – Physical impact

Patients reported a high burden of physical symptoms which impacted considerably on their day-to-day life. Ascites was particularly detrimental to QOL. Restrictions in physical mobility and breathlessness were described as disabling. High volumes of intra-abdominal fluid led to secondary umbilical hernias and lower back pain. The resultant pain was often difficult to treat given restrictions in available analgesics for patients with liver disease. Frequently patients described their lives as being structured around a "cycle", whereby they could perform tasks, sleep, and enjoy social interactions in the days following LVP, but became increasingly incapacitated and dependant whilst awaiting their next drainage.

Box 3.1 – Ascites and the "cycle" of paracentesis

Mr A (patient): "In the garden, there are things that I would love to do and about a week before I'm due to be drained, I just can't do them … A couple of days before drainage day I find it difficult to get my socks and shoes on and stuff like that. It impacts on your life and, again, your plans."

Mrs B (patient): "Cause the first week I'm fine; I can bend about and do a little bit more. By the time it's two weeks, then it starts getting really uncomfortable."

Mr D (patient): "The next two or three days is, 'Hurry, hurry, hurry. Got to do this, this,' and I've got loads of energy pushing out because I know I've got to get it done before the week is finished, because at that point when the week is up this [points to abdomen] starts bloating out again I'm done for, I'm finished."

Mrs E (patient): "My back's always playing me up now so I have to sit down more – I can't stand up for long. And that gives me lots of pain – but they can't give me nothing for it – because the drugs all mess with the liver."

Physical weakness and extreme fatigue also emerged as disabling features of disease. This had knock on effects, in terms of social interaction, employment and managing basic household tasks. Patients described being rendered "house bound" due to exhaustion. Mr H, a 58-year-old man with three teenage children, described not being able to get upstairs to the toilet – meaning he had spent the last 3 months confined to a downstairs room with a commode.

Box 3.2 – Weakness and fatigue

Mr I (patient): "Just tired all of the time. And these days I just cannot hold a conversation with nobody. I can't concentrate."

Mr J (patient): "Before all this, I was active, I ran a garage – worked as a mechanic … used to work all the time – very active … I tried once. Couldn't do anything. Exhausted. So I had to stop. Haven't touched a spanner since I came out of hospital that first time."

Mr F (patient): "Well I'm just so tired, and weak in my legs, and with the swelling as well I can't walk very far … so I'm pretty much housebound these days."

Mr H (patient): "I've just learnt to go backwards up the stairs – because I couldn't walk up normally. I can't use the bathroom – can't get in and out of a bath – so I need to get that sorted out. I've been using a commode."

Four of five carers highlighted HE as the most upsetting physical symptom associated with ESLD. In addition to the increased care required during exacerbations, the associated loss of dignity, awareness and comprehension emerged as being exceptionally stressful. Some carers reported associated periods of insomnia due to fears about their loved one being unsupervised or worrying about how things may deteriorate further. Exacerbations commonly coincided with hospital admission, however the strain of managing HE in the home environment was also described. One participant cited the difficulties of administering lactulose (a strong laxative medication used in the management of HE) given her husband's unwillingness to take it, and the secondary faecal incontinence. Memories of these episodes emerged as a uniquely difficult feature of bereavement, with participants finding it difficult to reconcile these behaviours with the person they knew.

Box 3.3 – The impact of encephalopathy upon carers

Mrs N (carer): "That was a horrible time because he didn't even recognise me … I was always in fear and dread that would come back because I was told it does recur … I just felt very sad that this very proud, dignified man was in such a state that he would do something that he would be appalled about if he knew; this behaviour was just not John ... I didn't really grieve properly. I don't still think I have but I believe that in my heart, I lost John when he had the encephalopathy. That was when I lost the man I'd known."

Mrs O (carer): “I don't think he realised that he really needed to keep taking the lactulose to help ... We had lots of episodes where he would be okay one day and the next day be, like, really out of it … his personality sort of changed almost. First of all, I think it was just a bit of mild confusion and then other days he was just totally unaware of things … It's very difficult to make somebody take the lactulose when they’re like that.”

Mr P (carer): “I said ‘there ain’t no-one there my princess, no-one’ ‘yes there is they’re on the settee and the settee’s like this now’. She was confused and falling over everywhere and for two months she didn’t sleep at all, and I didn’t sleep because I was so worried.”

An associated physical burden of disease on carers emerged, with participants describing deteriorations in their own health brought on by their “all-consuming” role as a carer. In one carer this manifested in substantial weight gain, and multiple missed GP and hospital appointments for her diabetes and hypertension, which were not prioritised due to the volume of hospital appointments and care required for her partner. Other carers described severe insomnia, or sometimes disabling back pain – due to the need to lift their loved ones around the house. Due to the relatively young age of those being cared for, some participants felt that this physical burden was not fully appreciated by those around them.

Box 3.4 – The impact on the physical health of carers

Mr Q (carer): “It got so that she couldn’t get out of the bath in the end … she got in the bath one day and she said, ‘Dad. I can’t get out the bath.’ So I went, ‘Alright. Cover yourself up, let the water out of the bath and I’ll come up and lift you.’ I went up and I literally had to lift her out of the bath and I couldn’t move properly for days because of the arthritis in my back – it was agony. She was only 40, so I don’t think anyone really believed me. That I had to do all that stuff.”

Mrs O (carer): “I'd tried to get his bottoms off and that and I did my back, and after that, I just couldn't lift him. He was absolutely covered in, you know (faeces), well it was everywhere … from then on I found it difficult. I didn't sleep very well because James was wakeful … probably for about a year, I couldn't leave him on his own.”

Subtheme 1b – Psychological impact

Participants described major psychological burdens associated with liver disease. Among patients suffering from ArLD, past and present battles with addiction were described commonly, with some highlighting their repeated failed attempts to stop drinking as the single most difficult aspect of their disease. For some, this had resulted in social isolation, whilst others linked it inextricably with their depression. Patients who had successfully abstained from alcohol expressed guilt, sometimes implying they were undeserving of treatment due to the "self-inflicted" nature of their disease. One carer described how his late wife had explained that she was undeserving of a liver transplant, even after she had successfully achieved abstinence at a transplantable age. Past addictions were a common source of ongoing distress among carers, with previous conflicts surrounding alcohol often forefront in their mind. Two participants described finding hidden stores of alcohol after the death of their loved ones – which led to ongoing anger and confusion.

Box 3.5 – Addiction, guilt and self-blame

Mr H (patient): "It's my bloody fault. It was me that put it down my neck. No-one else did it, no-one else forced me to do it. So yeah, I do blame myself, yeah."

Mr I (patient): "I'm causing the damage. And what am I doing about it. Nothing. All I'm doing is drinking. And I think it takes away the pain – but you just get more pain. Then you get depressed."

Mr F (patient): "When I was abstinent it was all different. I could get on with my family 'cos they were happy that I wasn't drinking … well now I'm drinking again they don't want to see me."

Mr P (carer): "I said well surely they'd give you a liver transplant, she went I don't deserve one of those, I said why not, she said no she said … I've done it to myself , let the young ones have it."

Mr Q (carer): "After she passed away … my niece came up, she went over to help clean out her flat, and she brought over with her about a dozen big bottles of vodka, empty ... I still just can't understand it."

Mrs N (carer): "I was thinking, 'If you could do it (not drink) now, why wouldn't you do it before?' It's like, until it became a problem, he wasn't going to do anything. And he'd have still been here now."

Depression and anger were frequently described. Some patients with ArLD expressed anger that they had not been sufficiently informed about the potential impact of alcohol. Two participants described previous suicidal thoughts, which they both attributed to the impact of the liver disease. Being assessed as unsuitable for LT was highlighted as a particularly difficult point in the disease journey for both patients and carers.

Box 3.6 – Depression and anger

Mr J (patient): "I go from like – being miserable about [not being suitable for transplant] to anger. I get angry about it. Deep down anger."

Mr I (patient): "If I was going to take my own life I'd think of better ways than that to do it. I'd take a box of tablets. See you later … I've tried it twice in the past … cirrhosis, depression. It's a long way to return from with all of this."

Mr Q (carer): "Before she went to sleep one night, she said, 'I don't want to wake up in the morning'… all she said for the next few months was, 'I don't want to live any more,' something like that, all the time – once or twice a week maybe."

Mrs N (carer): "He just shut down [after being told he was not suitable for transplant]. He didn't talk. John wouldn't talk. We did have a psychologist appointment but he wouldn't talk to her very much either. It was brutal."

The unpredictable nature of liver disease, in terms of the ability to function on a day-to-day basis, the overall prognosis, and the possibility of cure/transplantation was described as distressing by patients and carers alike. Whilst some participants reported that they were able to "get used to it", others commented that it had made planning for the future and achieving their goals towards the EOL impossible. Carers described difficulties more in terms of the day-to-day fluctuations in health, as opposed to the difficulties predicting life expectancy which were more commonly raised by patients.

Box 3.7 – Living with uncertainty

Mr H (patient): "I told them that, I want you to tell me the truth (yeah), no holds barred like (yeah), but they couldn't answer it. Because they didn't know. It was hard."

Mr A (patient): "I have no aim. I can't plan because in December, I was given three to five months and it's May now, so that guidebook on Greece. I'd love to go to Greece but I can't make plans."

Mrs O (carer): "Day-to-day I just didn't know what to expect. James could wake up feeling quite well and reasonably happy and then another day he'd be really unwell and down. It's difficult to see somebody like this … you just feel helpless and don't know what to do for the best really."

Subtheme 1c – Social isolation

Most participants, carers, and decedents were of working age when liver disease developed and loss of income was commonplace. Participants were often self-employed in physical jobs (e.g. roofer/mechanic). The considerable costs associated with attending hospital appointments, such as travel and car parking, exacerbated financial strains. Among the participants who experienced major financial hardship, all felt that information regarding potential sources of assistance/benefits were not available within the NHS. Loss of self-esteem associated with unemployment was also described. Carers often stopped work to assume full time caring responsibilities, compounding the loss of income experienced by their partner. One carer, who continued to work as a builder throughout the duration of his wife's illness, described exhaustion at having to fulfil both roles, however he could not afford to stop work.

Box 3.8 – Financial impact

Mr J (patient): "We didn't have insurance or sick pay or nothing so we got nothing from the garage. My wife had to start working, but then she had to work to look after me, so that all got too much and she had to stop as well."

Mr K (patient): "I was a roofer since I was 17. I had to stop 'cause of the drink and the swelling on my legs and that … at the minute things are alright. But I worry about what's going to happen."

Miss M (carer): "I did used to have an income. I'm self-employed at my home, but I couldn't really do much that would have made much of an income myself because I was looking after him all the time."

Mr P (carer): "I always had to be up with her, overnight like … I still had to go work in the day, so I was like really tired all the time."

Patients expressed frustration at having to rely on others for basic care and commented on how this changed the dynamic of their relationships. Patients who had children or grandchildren described difficulties in fulfilling caregiving duties. One patient described not being able to disclose the severity of his condition fully to his three teenage children because of this. Some participants attributed their lack of self-esteem to an increasing dependence on those around them. Carers described an increasing burden of responsibility as the disease progressed. Shifts in the dynamic of relationships were described, with one participant comparing it to a parent-child relationship. Carers described the strains put on their relationship, recalling frequent arguments and, in one case, episodes of emotional and physical abuse.

Box 3.9 – The changing dynamic of relationships

Mrs K (patient): "Depending on somebody else to drive you everywhere and do everything, including putting your socks on for you becomes hard, because I've been a very independent, active person. I get frustrated and, I suppose, it's been tough for us to deal with."

Mr H (patient): "Well I've said I've got a bad liver – cirrhosis – and I explained things like that to [the teenage children]. And, well I think they took it alright, but they worry. It's like I can't be a proper dad to them no more. They've got school and that – and I don't want them to worry about their dad. So I just keep telling them I'll be alright".

Miss M (carer): "It became like doing it (caring) to your own child … I thought he'd got over the old behavioural patterns, back from when he was an alcoholic, but some of them came back, I think because he felt so powerless being ill. Some of the physical aggression came back. It brought up issues between us as a couple that brought out our worst."

Increasing social isolation was described as the disease developed. Patients were commonly confined to their own home due to physical limitations, with some patients commenting that their only social interactions occurred during their fortnightly visits to the hospital for LVP. Patients who were attempting to maintain abstinence described being ostracised from long-standing social circles which centred around alcohol, for example the pub. Participants frequently linked their low mood to increasing social isolation. Carers also described high levels of isolation and substantial limitations in their leisure activities. This

was typically attributed to the high volume of time required in providing care. One carer likened the experience to being "grounded" whilst another described ringing 111 when lonely, because she didn't feel there was anybody else she could call.

Social isolation was exacerbated by a stigma associated with a diagnosis of cirrhosis. This was universally attributed to a perceived association with irresponsible alcohol use, even among patients with non-alcohol-related aetiologies. Patients and carers both reported that this inhibited them discussing the disease and its management within families, among wider social circles, and with medical professionals. Carers sometimes reported feeling ashamed or defensive, feelings that in some cases continued in bereavement. Patients with ArLD often reported feeling judged by medical professionals, resulting in feelings of embarrassment about their condition.

Box 3.10 – Social isolation and stigma

Mr J (patient): "Well I haven't got a social life any more. Obviously can't go to the pub now – which is where all my mates are at … but I haven't seen my mates for years."

Mr L: "I used to do football on the weekends; I don't do that anymore. I used to ride a push bike; I don't do that anymore … I go down there [a friend's house] sometimes, but I have to get a lift home and a lift back up – and that usually means a taxi which I can't afford now I'm not working – so I don't often do that anymore. Most of time I'm just stuck inside by myself which gets depressing … I can't have a drink now either; I'm not allowed to drink … I can't go to the pub any more – which is where they all hang out."

Mr F: "It actually got to the stage where I quite enjoyed going up there (for LVP) ... Otherwise I didn't really see anyone else. I got to know the nurses up there really well – they were like family."

Miss M (carer): "I used to be able to do my own things and get on with my own life in the mornings but, as time went on, there wasn't really enough time for me to do even that … one day I went home and I called 111 because I just didn't want to be on my own. I didn't know who else to call."

Mrs N (carer): "I was basically grounded … it felt like all we'd do was go backwards and forwards to hospital."

Mr C (patient): “One of the worst parts, was with the name cirrhosis. Because everyone assumes cirrhosis is do with alcoholics and drinking and what have you. And you mention that word to people and they, well they give that look back at you.”

Mrs E (patient): “(the doctors on a ward round) made me feel like I was ignorant like. And like it was all my fault and quite, well, I didn’t feel like arguing with them … I was just so embarrassed about it all I just wanted them all to go away.”

Mrs N: “It was difficult to tell people about it - the cirrhosis. I mean it’s a horrible thing - but I always want to say to people, ‘He was always a drinker but never a drunk.’”

Theme 2 – Experience of healthcare.

Interviews explored participants' first-hand experiences of healthcare. Specific questions were asked about the extent to which services were 'patient-centred', how well participants understood their disease and its treatment at each stage, and how care was coordinated. Emergence of the theme and subthemes is summarised in table 3.5.

Table 3.5 – Emergence of coding framework for 'experiences of healthcare' subthemes

Examples of exploratory questions used	Examples of initial codes	Broad themes	Final theme
"Can you tell me a bit about your experience of coming up to the hospital for drains and appointments?"	Burden of repeated appointments, parking, transport costs, car parking, all-consuming, loss of earning, childcare costs	Transportation difficulties, costs of attending care, reliance on carer	Logistical burden
"How much has your GP been involved in looking after you?" "How did you find it when you had to come into hospital"	GP not involved in day to day care, lack of primary/secondary co-ordination, reliance on hospital, inpatient admission, hepatology ward unsuitable, pivotal role of hepatology specialist nurse	Primacy of secondary care, cure-focussed care, negative experience of inpatient admission, central role of hepatology specialist nurse	Hospital centred care
"Do you think you always understood what was going on with your liver disease?" "Do you think that your priorities were similar to your doctors?"	Physician focus on cure, "dropped like a hot-potato", medical jargon, time limited consultations, obsessed with alcohol, differing agendas, ignoring symptoms at expense of cure	Information gap at diagnosis, understanding investigations and treatments, perceptions of cirrhosis, differing priorities, care centred around cure	Cure focussed care

Subtheme 2a – Logistical burden

An overwhelming logistical burden associated with repeated hospital appointments and procedures was described consistently. One carer recalled having over 100 hospital appointments within one calendar year. In those undergoing assessment for LT this burden was accentuated, with one patient fearing that any missed appointment could result in his being precluded from consideration. All patients (and four of five decedents) attended regular appointments for day-case LVP, on top of outpatient clinics. Centralisation of services within secondary care meant this typically involved regular, long and expensive journeys to the hospital. Among patients travelling long distances, there was frustration that appointments could not be better coordinated, for example, such that a scan and a clinic visit fell on the same day. Use of public transport was not feasible for some patients, which had further financial implications. Patients were typically dependent upon family members to attend appointments. As well as affecting factors such as carer income and childcare, this also created a sense of guilt among some patients. Carers described the burden of multiple hospital appointments as all-consuming and exhausting. Difficulties in accessing appointments with a disabled relative, and inadequate car parking were repeatedly raised as areas of anxiety and stress.

Box 3.11 – Logistical burden of liver disease

Mr H (patient): "It's expensive for starters, and the wife has to come – so she has to get someone to pick up the kids for school and look after them at the end and, well it's like a lot to organise."

Mr G (patient): "Well. I can't be doing with the public transport, because I'm diabetic and have the fluid … it costs me about 20 pounds a time and I'm up here every 2 weeks"

Mr J (patient): "[it takes me an] hour and a half on the bus. Then I have to walk up the hill, then I've got to go hour and a half back. It's all the clinics as well, clinics up here all the time. Well those days the wife can't go to work because I need her with me – and so we lose money from that. And then the scans. We don't seem to get them on the same day or anything. Like last week we had to come up three times … but I'll take that if they can get me a new liver. There's been lots of times when I haven't really been well enough to come but I always come. If you miss one that's your chance out the window."

Miss M (carer): "It was all making medical appointments for him, staying in hospital with him, going to hospital with him in the taxi because he was very uncomfortable, didn't want to be on his own because he wasn't really well enough to go on his own … I had to give up work in the end."

Mrs N (carer): "I can't remember when he started having the more regular drains but all I do know was that in 2015, we had over 100 medical appointments."

Subtheme 2b – Hospital centred care

Participants consistently described care as being centred within the hospital environment. Beyond the point of diagnosis contact with primary care was limited, and typically bypassed if any changes or deteriorations occurred. Although some participants felt that their GPs were not abreast of developments within their care, others were highly complimentary. One carer described a situation where she tried to manage a deterioration towards the EOL within the home environment with support from primary care but was triaged as an emergency directly to hospital by her GP against the wishes of her husband (the patient).

Box 3.12 – Hospital centred care

Mr I (patient): "He said it looks like you've got liver disease. And I was like – what does that mean? Oh, its best that the hospital tell you. They'll tell you better than what I would."

Mr L (patient): "The GP is nice, but if I needs anything I comes up here. The GP – they don't seem to be on it. Don't know what's going on like."

Miss M (carer): "He didn't want, necessarily, to be rushed in … but even so I was worried. I paced it out a bit and phoned his GP, but she said, 'No, you do really need to call 999'."

Mrs N (carer): "I got the GP and we came in here to the GP Support Unit where she got it spot on. Our GP is first class and excellent. She got it spot on straightaway".

All patients and decedents within our sample had experienced inpatient hospital admission at least twice within the last year or LYOL respectively. Of five decedents, two died during hospital admission. Inpatient admissions became increasingly frequent as the disease progressed. Despite widespread praise for nursing staff, hospital admission was described negatively by all participants. The environment of a hepatology ward was thought to be fundamentally unfavourable to recovery. Participants described being surrounded by other patients who were confused, noisy, and suffering from drug and alcohol withdrawal. Carers described the loss of dignity associated with periods of encephalopathy as being exacerbated by a lack of privacy on the ward. Avoidance of hospital admission emerged as a key priority towards the EOL.

Box 3.13 – Inpatient admission

Mrs E (patient): "I hate being in hospital. Everyone uses all these long words and its scary and I just want to get out."

Mr P (carer): "The only thing she really didn't like was when she got admitted. Absolutely hated it - if there was any way we could have kept her away from that, especially near the end, things would have been better … she needed some privacy - and everyone else on the ward was playing up, screaming in pain - it was just so noisy and so scary. She always kept saying to me, I don't want to stay here, I want to come home."

Mrs N (carer): "It was the most dreadful time … when he was confused, he tried to get into the wrong bed and defending his dignity, I suppose, that upset me … it was very shocking and they're horrible memories of that time. One of the things he wanted at the end was to stay in his own bed. He didn't want a hospital bed. I worked out afterwards that I think, in his head, he thought a hospital bed meant a bed in hospital."

Mrs O (carer): "There were a lot of people with probably drug problems I imagine and drink. Some of the younger men there were dreadful. Smoking out the window, coming back with drinks. It was chaotic, to be honest. Not a place, if you're not well, to be."

Mrs M (carer): "Even when they proved to him on the spot in his home that he was in danger of losing his oxygen level, by doing an oxygen test, he still wouldn't go into hospital, even though they said to him he'd be more likely to die."

Participants described the pivotal role played by hepatology specialist nurse in coordinating care. As well as coordinating appointments and performing LVP, hepatology specialist nurses answered day-to-day queries and provided advice and emotional support for both patients and carers. Participants described reliance on hepatology specialist nurses for queries surrounding their overall healthcare, regardless of whether it was related to their liver disease, often bypassing primary care. Some participants described frustrations regarding the responsiveness of the hepatology specialist nurse service and expressed concerns that there was no alternative avenue of care if they were unavailable.

Box 3.14 – The role of the hepatology specialist nurse

Mr C: "The hardest part is getting hold of anyone on the phone. Especially the specialist nurse … sometimes you get a bit of a scare with things and you just need someone to talk to."

Mr H (patient): "There's a couple of people up at the hospital I can trust and I asks them. Like Rachel – the nurse that does my drains ... we've got Rachel's number – but it's really hard to get through to her. When I did get through she was great."

Mrs N (carer): "These wonderful people had become friends almost; certainly Jane, Emily and Rachel, because we'd had so much interaction with them over the year with drains, with the varices … check-ups, tests, follow-ups and all of that."

Subtheme 2c – Cure focussed care

Participants' accounts of physician-led hospital care, whilst generally positive, were described as centred around disease modification and cure. This sometimes came at the expense of symptomatic management or addressing the participants' agenda. In particular, this manifested in patients and decedents who had been assessed for LT and found to be unsuitable, and in patients with ArLD who had been unsuccessful in achieving abstinence.

Participants who underwent assessment for LT described alarm at how dramatically input from secondary care physicians fell following the decision not to list them for transplantation. One patient compared it to being "dropped like a hot potato". Patients with ongoing alcohol use described an unrelenting focus from physicians on abstinence. This resulted in perceptions that they were being "blamed" for their condition and meant issues of symptomatic management were commonly left unaddressed in consultations. One patient attributed his reluctance to seek medical help to the fear of being repeatedly castigated about his alcohol use, whilst another described being "told off" every time he went to clinic. Symptom relief was often the primary agenda of participants during outpatient consultations. However, such issues were perceived as being "side-lined" in a time-limited setting, where the physician's focus was on pursuing diagnostic investigations. There were two exceptions to these trends. Mrs B (patient) and Mrs O (carer) both described their clinical encounters as being strongly focussed around exploration of symptoms and understanding of disease.

Box 3.15 – Cure focussed care

Mr A (patient): “Once they’d worked out I wasn’t going to have a transplant well, this is my perception again, well they dropped me like a hot potato [laughter].”

Mrs K (patient): Their main focus now, last time I saw Dr Smith, was maintaining me at the level I’m at now for the long haul, towards waiting for transplant. I’m not sure what might happen if that’s not an option.”

Mrs N (carer): “It was just an observation at that time (after being declined for transplantation), that you’ve been on an almost twice weekly basis interaction with this team of people in hepatology and all of a sudden, they’re not there anymore really.”

Mr I (patient): “All the doctors want to talk about is drink. And I don’t want to talk about drink anymore. I already know what drink does to you. I want to talk about how to feel better.”

Mr F (patient): “They talk about the alcohol a lot – all the time in fact – I’m always getting told off in clinic! Not that I always want to listen!”

Mr J (patient): “In clinic – well they just look at me … but they don’t actually ask me how I’m feeling. They look at the numbers on the computer. And every time I go to clinic she goes, “well you look well”, but I don’t feel well. I wouldn’t be here if I was well … They’re doctors aren’t they. Curing is their job. So that’s what they’re going to be focused on isn’t it?”

Mr C (patient): “I remember asking the London doctor if there was anything he could do (about my abdominal pain and swelling) – he just said yes there is, but he just needed to get the tests done first. He’s never said more than that.”

Theme 3 – Attitudes to supportive and palliative care

Experiences of, and attitudes toward, central tenets of PC (understanding of disease and prognosis, ACP, symptom management, care at the EOL and bereavement) were explored during interviews. Perspectives on how healthcare systems and interactions could be improved to meet patient and carer need were also sought. Emergence of this theme and subthemes is shown in table 3.6.

Table 3.6 – Emergence of coding framework for 'attitudes to SCP' subthemes

Examples of exploratory questions used	Examples of initial codes	Broad themes	Final theme
"What do you understand about how things are going to progress with your liver disease?"	Lack of understanding at diagnosis, hiding info from carers, mixed messages, changing perceptions, "in the dark", perceptions of cirrhosis, uncertainty, understanding of prognosis, planning for the future, not seen as terminal, transplant the 'light at the end of the tunnel'	Lack of understanding, information gap at diagnosis, uncertainty around prognosis, LT seen as last hope, understanding of terminal decline	Uncertainty
"How would you feel about having more detailed discussions about the future, and being involved in decisions about your care?" "How could we change healthcare services to better meet your needs?"	Experience of PC, understanding disease trajectory, don't want to give up hope, not knowing what to expect, time to address patient concerns, symptom control, unable to communicate place of death preference, practical support at EOL	Appreciation of opportunities for ACP, time in consultations, not losing hope, addressing the patient's agenda, end-of-life care	Improving PC
"Can you talk to me a bit about what happened around the time of the death, and how you coped with things afterwards?"	Anger at ongoing addiction, remembering encephalopathy, lack of bereavement support, isolation	Bereavement, difficulties processing previous addictions, distress from encephalopathy	Bereavement

Subtheme 3a – Uncertainty

Participants' understanding of their condition and its prognosis at various stages was explored. Only three participants (2 patients, 1 carer) recalled having any clear perception of what cirrhosis meant prior to their diagnosis. In each case this was because of a friend or relative who had died from liver disease. These participants had all perceived cirrhosis to be a terminal and uncurable condition prior to their diagnosis.

At the point of diagnosis an 'information gap' was commonly described. Most patients were diagnosed at the point of index decompensation (e.g. first development of ascites or variceal haemorrhage), however some patients did not appreciate that this event was caused by liver disease. One patient equated successful banding of oesophageal varices following a gastrointestinal haemorrhage to cure, and stated he only discovered he had liver disease some months later whilst being used as a teaching case for medical students. Two others thought that their index LVP would cure their ascites definitively. Other patients described being prescribed tablets, but not understanding why they were taking them. Participants who recalled being informed of their liver disease at the point of diagnosis often described medical information as being difficult to understand, and that there was an absence of information surrounding prognosis. One patient reported finding out that her variceal haemorrhage was caused by liver disease only by overhearing doctors talking about her on a ward. There were notable exceptions to this trend within the sample. Mrs B (patient) and Mrs O (carer), both described receiving clear, unambiguous information about their disease and its prognosis at first presentation. In both cases cirrhosis was complicated by a concomitant HCC. Three of five carers interviewed did not attend hospital appointments with their relative around the time of diagnosis. In each of these cases, carers described that the decedent hid information surrounding the diagnosis from them, with symptoms being downplayed, often for months.

Box 3.16 – Information at diagnosis and perceptions of cirrhosis

Mr I (patient): "Liver disease runs right through my entire family … my Dad died from it and my mother had it. My brother died of it too, so I knew what was going on … people always think your liver will heal. But when you've got cirrhosis it never heals."

Mr C (patient): "I had no idea [that the varices were related to the liver]. It was later on – a lady came along with some students, and it was explained to the students and I was sitting there thinking to myself – well I never knew that. I thought I had the all clear! … the first time I came in [for drainage of ascites] the man said – so you're going to be one of our fortnightly regular visitors – and we just laughed at him – thought he was joking – but it turns out we are."

Mr L (patient): I went back to my GP and he gave me stronger tablets, but it (the ascites) wasn't getting any better … I only found out [that it was related to liver disease] a couple of months after when I was speaking with Emily (hepatology specialist nurse)."

Mrs O (carer): "(at his first appointment) he was told that he had tumours on his liver and we were told that the outlook wasn't very promising and that he probably would only live for about 18 months."

Mr P (carer): "When she went to the doctors and all I said 'what did they say?', 'Oh just the same usual thing … I've got a bit of trouble with', and she did say then, 'liver' and I said 'Oh is it bad?', she went, 'no, no'. She'd never told me anything because she knew I'd get upset."

As the disease progressed participants described being frequently unaware of the objective of ongoing medical investigations or their results. This left some patients confused about their treatment and disease trajectory, and nervous about asking questions or raising concerns relating to their symptoms.

Patients were asked about how well they understood their prognosis now, and their expectations for the future, whilst carers were asked if they recalled being adequately informed about prognosis throughout the LYOL. A mixed pattern of responses emerged. Whilst most patients described considerable uncertainty about the future and their prospect of recovery, two patients were clearly aware of the life-limiting nature of their condition and had started to plan for the EOL. Some patients recalled asking direct questions regarding prognosis, however reported receiving mixed messages which led to confusion and anger. With one exception (Mrs O), carers described being unaware of the underlying prognosis until very late on. For example, three carers explained that they did not understand the prognostic implication of developing RA. One carer (Mr Q) only realised the life-limiting nature of his daughter's liver disease after she had died. Of note, from two patients and one decedent who had cirrhosis complicated by HCC, two described being fully informed of their prognosis. This was the case with only one of the remaining 14 participants, all of whom had cirrhosis without malignancy.

Box 3.17 –Understanding of disease and appreciation of prognosis

Mr F (patient): “I’ve never seen a scan result. No blood test results. Nothing. Lots of tests. But nothing. I’m blind about any information or detail about what’s going on, and the tests which are done to me.”

Mr C (patient): “I don’t know [how things are going to progress]. I really don’t know. At the back of your head you know what the end result will be – but – now it’s just very, very difficult to define anything. What to expect or anything. It really is difficult.”

Mr D (patient): “I just said, 'Doc, what's my life expectancy then?' and he said, 'Well, between two and three years.' … then, and this is a big bone of contention, another doctor said, a few months later after that 'In your advanced state I would say you've only got months to live.”

Mrs N (carer): “It was obviously serious, but it wasn’t viewed as a terminal diagnosis at that time; certainly not by us … [the doctor] was very upbeat and very reassuring – perhaps a bit too reassuring. She said, ‘If it does come back, we’ll just find him a new liver’.”

Mrs M (carer): “We knew he had to come into hospital every so often to have the water drained, but as far as how they couldn’t ultimately do anything about it, that information was delayed a lot lot longer.”

Mr Q (carer): “I didn’t even consider the liver would kill you; I just didn’t know. [When she was in hospital during her terminal admission] they just told me it was a liver problem. They didn’t give me any expectations of her passing away with it ... nobody said she was on her last legs or anything.”

Mrs B (patient): “I spoke to my son and we’ve gone through everything. I’ve sorted most things out; the will’s all sorted out. We even spoke about the funeral … I don’t know how long I’ve got, but I’m positive about it. I’m going to get on and make the best of what I’ve got left, ‘cause life is precious.”

Mr G (patient): “Don’t get me wrong – I’d like to stay for ever – but no one comes here to stay for ever – you come here to live for a time and when the time comes you have to go – and around now, well this is my time.”

Subtheme 3b – Improving PC

Only one patient (Mrs B - who had incurable HCC) recalled being afforded a referral to SPC. Whilst she declined this referral, she explained how it helped facilitate discussions with her family and that is was comforting to know that services were readily available should her condition deteriorate. The remaining patients were asked about their attitudes to ACP and discussing prognosis. Responses varied considerably, however fell broadly into two groups: those who welcomed the opportunity to discuss such issues, and those who felt anxious and uncertain about the prospect of being confronted with discussions around their own mortality. One patient expressed frustrations that he had had inadequate opportunities to address these issues and felt doctors "shied away" from matters of death and dying. In the latter group, two patients feared that such conversations equated to "giving up" or "losing hope". Among carers, three had direct experience of SPC. However, in each case this related to care in the last days of life, and was such more reflective of EOLC as opposed to PC per se. These carers were grateful that their loved one had had the opportunity to die outside of the hospital and were complimentary about the care they had received. Carers felt that earlier opportunities for ACP would have improved their understanding of the disease which was typically described as poor.

Box 3.18 – Attitudes towards and experiences of ACP

Mr D (patient): "I'd just like to know, so that I can be prepared … (those discussions are) absolutely crucial because that's what this damned disease does. It kills you. And they've got all the knowledge and experience in this unit of liver problems and yet they seem to shy away from - well, death is over there but it's not here. But you damn well know that you're going to die."

Mrs E (patient): "I suppose it is [important to talk about] really. A lot of people plans their funeral ahead don't they … but you don't want to give up completely do you. I don't want to give up, and it feels like that is what I'd be doing if I was to go down that path."

Mr C (patient): I'd be a bit scared about it though. Scary but advantageous I suppose. Even if you glean the information – it's probably better than living in the dark. But then again sometimes ignorance is bliss – I don't want to lose hope."

Miss M (carer): "I never quite knew when he would, or if he would, deteriorate … I wonder if it would have given me more emotional resilience and made me understand how somebody might behave if they were dying. And if he'd agreed to it, I don't know if he would have done, but if he'd have agreed to it, it might have given him some ideas about what to expect and that might have made him less scared."

Participants described how they felt existing models of care could be improved upon to better meet their needs. Without prompting, this typically included elements of PC. Participants raised certain issues recurrently. Two of these issues, an increased physician focus on symptom control within consultations (see box 3.15) and improved access to information about the condition and its prognosis (see box 3.17), are described above. Time limitations within clinical consultations were described frequently. Participants commonly felt that there was too much information to take on board during medical consultations and suggested that a more iterative approach would be beneficial. This time pressure also contributed to issues around symptom control being recurrently unaddressed. Participants also repeatedly described difficulties in communicating care preferences. One patient, who was aware of the terminal nature of his condition, repeatedly expressed a preference to die in his own home. He expressed frustration that this information was not readily made available to other medical practitioners such as his GP. Carers, similarly, universally identified structures which allowed them to express care preferences which kept their loved ones out of hospital as paramount to improving future services. Carers also commented frequently that simple practical supports, such as the issuing of a disabled car parking badge, would have been enormously beneficial.

Box 3.19 – Improving care towards the end of life

Mr A (patient): "I'm not really a people person, but if you tell someone the really bad news, they need to go back and think about it and talk about it with their family and digest it; then they could actually cope better with the rest of the information that comes afterwards. But it all gets crammed into one clinic, and it's too much to take in."

Mr I (patient): "Listen. Listen to how I'm feeling and stop going on about the drink. And it's so easy to sit there and listen. And the person will tell you exactly what's wrong with them. What's making them feel crap."

Mr D (patient): "And there's another point that I feel quite strongly. I want to die at home. I don't want to die in hospital. I don't want to die in an operating theatre. I don't want to die in a hospice where that's where you go to die … I've told them, and they try. But it seems like there's nowhere for it to go in your notes – and the GP – well they just send you straight back in soon as you get bad, and then they come out with their doctor spiel. It's not good enough, really."

Mrs E (patient): "I'd prefer to be at home. I don't want to die in hospital ... But no-one's ever actually asked me that before."

Miss M (carer): “Even though he didn't want to be rushed into hospital in an ambulance, that still happened … and that was quite traumatic. It would have been nice if there was a way that everyone would have known that was what he wanted.”

Mrs N (carer): “I have to say that Blue Badge was the biggest gift, in terms of continuing to function but making life easier … It would have been very helpful throughout that process beforehand.”

Subtheme 3c –Bereavement

Issues surrounding death and bereavement were approached with carers. Difficulties processing the death of their loved ones, and a lack of bereavement support emerged. Aside from one participant, who was given a leaflet about sources of charitable support, no formal bereavement care was offered. Carers described feeling isolated following death and were often still struggling to come to terms with some of the features that had plagued the final months of life – specifically ongoing alcohol dependency and encephalopathy.

Box 3.20 – Bereavement

Mr P (carer): “Those last days was quite hard for me. When it came to near the end she was just like babbling, and not making sense - that was quite upsetting … so yeah - well, I still find it upsetting now.”

Mr Q (carer): “After she died I went to pot. I just couldn’t do anything, couldn’t walk about, couldn’t go shopping – nothing. And even now I’m not really over it, what with it being down to the drink as well. Well I’m by myself aren’t I. You never think your kids will go first.”

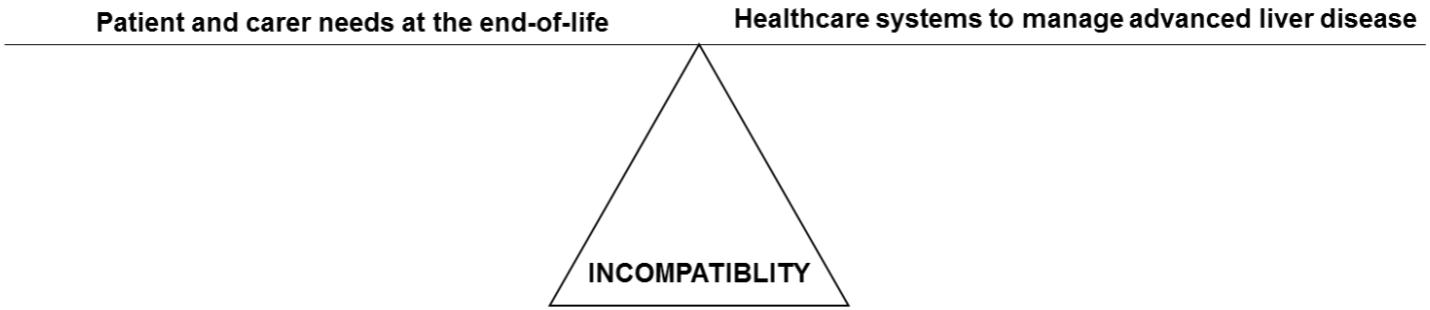
Divergent cases - Typology of the "informed" participant

Analysis of individual responses within the final thematic framework revealed a typology of participant who did not describe/recall the uncertainties around prognosis typically expressed by other participants. These 'informed' participants (Mr A, Mrs B and Mr G (patients) and Mrs O (carer)) were able to describe discussions with medical professionals around death and dying and had expressed preferences regarding their future care. In contrast to the rest of the sample, Mrs B and Mrs O did not describe an 'information gap' at diagnosis and Mr A, Mrs B and Mr G expressed a clear understanding of the terminal nature of their disease. Whilst there was no obvious demographic characteristic linking this typology, all related to cases where transplantation had been explicitly ruled out (Mr A was declined following assessment & Mr G was not of transplantable age) or where there was concomitant HCC. Mr C also had HCC, however he was being considered for (curative) LT at the time of the interview.

Unifying theme – Incompatibility of healthcare services and end of life needs

As liver disease progressed, so the needs of patients and carers became increasingly distinct from the services available to address them. Meeting EOL needs within existing structures seemed analogous to the idiom of fitting a 'square peg in a round hole'. Loss of mobility and financial security coincided with the need to attend increasingly frequent appointments, sited further away from the patient's home. Maximum disease impact occurred at a point where physicians' input had often been concluded (e.g. once assessed unsuitable for transplantation), and after impairment of hepatic function had contraindicated standard pharmacological approaches to symptom control. Requests made by healthcare professionals to avoid long-standing social circles revolving around alcohol occurred around times of escalating social isolation. Needs to make plans for the future were typically met by diagnostic and prognostic uncertainty. Incompatibility of healthcare systems with EOL needs emerged as a unifying theme (figure 3.2).

Figure 3.2 - The incompatibility of healthcare services and end of life needs in ESLD



Increasing physical disability	Care centred within hospitals, away from the community (increased cost/increased travelling/reduced access)
Financial hardship	
Need for carer earnings	Increased dependency on carer to attend appointments
Focus on symptoms	Focus on disease modification and cure
Reducing guilt/blame/depression caused by ongoing alcohol addiction	Need to focus on abstinence to achieve clinical improvement
Need for certainty to plan for future	Inherently uncertain disease trajectory
Reducing the impact of social isolation	Avoidance of situations involving alcohol
Maximum distress/need when not listed for transplant	Decrease in appointments following decision not to list for transplant
Increasing requirement for medications to control symptoms (e.g. opioids for pain/sedatives for cognitive impairment)	Reduction in available medications which do not impair liver function
Desire to avoid inpatient admission	Increased frequency of exacerbations requiring inpatient admission
Loss of privacy and dignity in the ward environment	Need for maximum nursing 'visualisation' due to cognitive impairment
Understanding potentially terminal nature of condition	Not wanting to impede potentially life sustaining approaches

DISCUSSION

Summary of main findings

Analysis of in-depth interviews from 12 patients and five bereaved relatives has demonstrated the extensive physical, psychological and social burdens faced by patients with ESLD and their families towards the EOL, and highlights that their PC needs are frequently incompatible with the healthcare services available to address them.

A wide-ranging complex of physical symptoms contributed to considerable levels of disability, and participants frequently had to re-structure their lives around a "cycle" of LVP appointments. Physical disability was compounded by psychological issues, which often related to past or current alcohol dependence. Depression and guilt surrounding the "self-inflicted" nature of the condition were described frequently. The disabling physical and psychological features of the disease were associated with escalating levels of social isolation, stigma, and financial insecurity. Carer participants described neglect of their own health, isolation from family and friends and exhaustion. Psychological distress, which extended into bereavement, particularly related to cognitive impairments related to HE and behaviours associated with addiction.

Participants relied on hospital services for the majority of their care, with GPs often bypassed and perceived as not abreast of ongoing developments. hepatology specialist nurses assumed a crucial role in communication and co-ordination of care. The need for frequent hospital attendances created a heavy logistical burden, particularly in relation to transport and carer time. Participants described encounters with physicians as being time limited and focussed on cure and disease modification. This meant issues surrounding symptom control and discussion of prognosis were not always adequately addressed. Patients with ongoing alcohol addiction described an unrelenting physician focus on abstinence. Participants who were declined for LT (a uniquely difficult period both symptomatically and psychologically) recalled that this coincided with a sharp reduction in physician support. Periods of inpatient admission, which were ubiquitous among the sample, were described as deeply unpleasant and undignified.

Uncertainties around the nature of cirrhosis and its prognosis were commonly described at all stages of disease. This contributed to difficulties in ACP and led to PC needs being frequently unaddressed. It is noteworthy that this observation did not hold true for participants who had concomitant untreatable HCC or who had been explicitly declined for LT. These 'informed participants' understood their underlying prognosis and were afforded opportunities for ACP and referral to SPC. Attitudes toward the central tenets of PC were generally positive, particularly in relation to an increased focus on symptomatic management and opportunities to express preferences for future care. Nonetheless, some participants

feared that discussions around prognosis and ACP would lead to a loss of hope for recovery and be unduly distressing. Participants valued avoidance of inpatient hospital admission highly, and carers regretted that they had not had opportunities for ACP discussions earlier in the disease process. Increased consultation times (allowing for discussion of the disease and its prognosis), an increased focus on physical symptom control, assistance with logistical and financial issues and improved bereavement support were also identified as ways through which models of care could be improved practically. PC needs frequently appeared mismatched to the healthcare services available to address them, leading to the emergence of incompatibility as a unifying theme (fig 3.2).

Strengths and Limitations

This is the first study of patients and bereaved carers in ESLD to focus on how existing services meet patient needs towards the EOL, ascertain perspectives on how such services could be improved pragmatically, and explore attitudes toward PC interventions directly. The methodology of in-depth semi-structured interviews allowed for both specific areas of interest to be addressed and for original themes to arise from the data organically. Recruitment of bereaved relatives provided a unique perspective on liver disease at the EOL which has not been explored previously.

Although the qualitative design did not seek generalisability, it is important to reflect on limitations in our sampling method. We recruited patients with refractory ascites attending a day-case LVP service. This may not be reflective of the overall ESLD population, particularly given the exclusion of patients with severe HE and those accessing healthcare in an entirely ad-hoc fashion. Whilst a range of aetiologies were included, patients with autoimmune liver disease and viral hepatitis were missing from the sample. Ethical considerations meant recruitment of bereaved relatives was somewhat limited, and those responding to postal invitation may again not have been reflective of the wider population. Carer interviews were also retrospective and therefore susceptible to recall bias. Although data saturation was reached within the sample as a whole, a distinct analysis of carer perspectives would be likely to require further data. All participants were recruited from a single UK hospital, and experiences of care may therefore differ from those of patients undergoing treatment elsewhere.

As discussed in chapter 2, it is difficult to eliminate researcher bias within qualitative interviews.[148] 'Reflexive bracketing' was however used throughout to minimise this effect. Every attempt was made to create a non-threatening interview environment in which participants felt assured of confidentiality and could freely express their views. Nonetheless, it is possible that participants did not feel able to fully discuss all aspects of their disease. This is perhaps exemplified by the absence of data around male sexual dysfunction which has been identified elsewhere as a feature affecting HRQOL in ESLD. [76, 85]

Comparison with existing literature and theory

The considerable physical and psychological features of ESLD described in our study are consistent with quantitative health related QOL questionnaire studies, specifically in relation to weakness and fatigue, depression, the stigma of cirrhosis, and the association between ascites and physical disability.[14, 74, 76, 82, 91] The findings relating specifically to HE, identified by carer participants as a uniquely difficult and distressing feature of ESLD, are corroborated by the multi-perspective interview study by Gronkjaer et al.[197] In common with our data, carer participants also reported anxieties around the unpredictable nature of HE and described the stress associated with 'loss of control' during overtly encephalopathic episodes. Our findings are also consistent with Kimbell et al's qualitative serial interview study of patients with ESLD, and nominated lay and professional carers.[107] Kimbell's unifying theme was 'uncertainty'. This encompassed difficulties in managing an uncertain disease trajectory, inadequate time and inaccessible language in medical consultations, a lack of understanding of disease at diagnosis, and discontinuity of care between healthcare sectors. Although our study looked more specifically at PC needs in ESLD, many of these themes were also highlighted in our data. Male sexual dysfunction has been reported as a major factor impeding QOL in some questionnaire studies of ESLD, however this did not emerge from our data or Kimbell's interview study. [76, 85] It may be that, despite the in-depth and confidential nature of qualitative interviews, there remain issues which participants are unwilling to discuss.

A recent qualitative study of English GPs highlighted a lack of experience in managing patients with ESLD and identified deficiencies in service organisation which constrained their ability to contribute to EOLC. This lack of experience is consistent with our finding that GPs were frequently bypassed after the point of diagnosis, and that care was centred in the hospital environment. These barriers would need to be overcome if future models involving community services were to be embraced.[198]

The 'information gap' around prognosis and disease trajectory in patients with non-malignant disease, described in our study, is consistent with two smaller qualitative studies which looked at service provision for patients with cirrhosis outside the context of PC. In an interview study of patients with non-malignant ascites, Day et al reported that, whilst patients typically understood the indication for LVP, they often did not recognise the associated deterioration in the severity of their disease.[199] In a single centred Danish interview study of patients with cirrhosis attending an outpatient clinic, Fagerstrom et al reported that patients frequently did not understand that cirrhosis was a life limiting condition.[200] The identified typology of the 'informed participant' is consistent with Fan and Eiser's qualitative description of 33 patients with hepatocellular carcinoma in Taiwan. This highlighted that better understanding of the disease and its prognosis was associated with an improved sense of control and QOL.[201] The incompatibility of managing PC needs within current healthcare systems has not been directly identified within existing

literature, however elements of this theme have been touched upon elsewhere. The difficulty in balancing the need to use drugs to control pain in ESLD, whilst simultaneously preserving hepatic function was identified in a recent review on pain in cirrhosis.[202] In a qualitative study of eight 'survivors' of LT, Lumby highlighted the paradox of having a terminal illness whilst simultaneously waiting for a potentially life-saving procedure.[100] This 'death-life paradox' compares with the incompatibility between patients' PC needs and the 'cure focussed' approach to care described in our study.

Studies of relatives bereaved by liver disease and studies which directly addressed the attitudes of patients with cirrhosis towards PC interventions were not identified.

Implications for future research

This study highlights specific PC needs which are not met by existing services. Studies to develop and prospectively evaluate specific PC interventions for patients with ESLD are required. A paucity of community services for patients with ESLD is identified, which adversely affects patient and carer experiences towards the EOL. Models of community hepatology and improved coordination between primary and secondary sectors merit attention. Our findings highlight the challenges faced by patients and carers coping with addiction towards the EOL. An evaluation of how services can adapt to meet the specific needs of this group better is long overdue. Whilst carer perspectives were considered in this study, its primary focus was identification of patient need and modification of existing services. Further studies which specifically investigate caregiver burden and models of support are required.

Implications for practice

A specific aim of this study was to inform future models of PC in ESLD. The key findings of the study have therefore been put in the context of specific recommendations. These are summarised in figure 3.3.

Changing structures of care

Key finding: Care for patients with ESLD was heavily centred in secondary care. GPs were commonly perceived as not being abreast of developments in care and were sometimes reluctant to manage ESLD in the community, despite the wishes of patients. Lack of involvement of primary care after the point of diagnosis meant patients and carers became increasingly reliant on secondary care services as the disease progressed. The physical, logistical, and financial difficulties associated with repeated hospital attendances meant this structure of care delivery was often incompatible with patients' PC needs.

Recommendation: Whilst it may be appropriate for liver services to be centred in secondary care, communication and liaison with primary care needs to be improved. Integrated, but community-based, services have been central to the delivery of established models of PC in cardiac and renal disease.[203, 204] Whilst models of community hepatology are currently lacking, they have the potential to improve patient experience, and potentially reduce pressure on hospital services. hepatology specialist nurses, who currently hold a key role in coordinating patient care, would be well placed to improve these links – which may involve outreach of traditionally hospital-based services (e.g. LVP) into community settings.

Reducing the information gap

Key finding: Participants described misunderstandings relating to their disease from the point of diagnosis onwards and were often unaware of the rationale of ongoing investigations. This resulted in a poor understanding of prognosis, contributed to a reluctance to ask questions, and caused ongoing confusion which precluded ACP and extended into bereavement. The time allocated to clinical consultations was often inadequate.

Recommendation: Patients diagnosed with cirrhosis should receive a full explanation of their condition, including proposed treatments and investigation at the point of diagnosis. The increased time required to undertake such discussion thoroughly should be recognised. The potentially life-limiting nature of the disease should be explained, including in cases where management is focussed towards cure. Patients should be afforded repeated opportunities to discuss their prognosis and the potential uncertainties surrounding this, accepting that some patients may not wish to engage in such discussions.

Managing inpatients with decompensated cirrhosis

Key finding: Participants (particularly carers) found experiences of inpatient admission towards the EOL distressing. Admissions were commonly associated with cognitive impairment (e.g. HE or alcohol withdrawal). The hepatology ward was not perceived as being conducive to dignity or recovery due to the behaviour of other ward patients who were similarly affected. In some cases, this resulted in avoidance of health-care professionals due to fear of hospital admission.

Recommendation: Community management of patients managed without curative intent should be facilitated wherever possible, accepting the need to improve current provision of community hepatology (see above). Care for inpatients with dementia has received considerable attention over the last decade, with nationally recognised audit standards mandating specific care plans to ensure respect and dignity,

dementia friendly ward environments, and access to specialist mental health services. [205, 206] Production of similar guidelines for patients admitted with cognitive impairment associated with liver disease would be likely to improve patient and carer experience of hospital admission.

Increased carer support, and focus on the logistical aspects of care

Key finding: There is a high logistical and financial burden associated with ESLD, which predominantly falls upon carers. Logistical elements of care, and carer well-being, are neglected in current models of care.

Recommendation: Practical, written information regarding financial benefits, options for hospital transport, and caregiver support should be readily available within hepatology clinics, and clinicians should actively signpost carers towards sources of support. Utilisation of specific carer need assessment tools should be considered, particularly when approaching the EOL.[207]

Facilitating a change in focus

Key finding: Managing patients' PC needs often appeared incompatible with their ongoing medical care. In the context of ongoing life-sustaining treatments this may be difficult to avoid (for example one would not wish to avoid hospital admission for a deteriorating patient who is listed for LT). Nonetheless, there are a proportion of patients for whom curative strategies have failed, for example patients who are assessed as unsuitable for LT, or those who are repeatedly unsuccessful in achieving abstinence from alcohol. Such patients often describe wide-ranging PC needs which are not addressed through current models of care.

Recommendation: Physicians should routinely assess prognosis and, in appropriate patients, facilitate a 'switch' in focus towards a supportive approach. Such a switch should be communicated to the patient explicitly, and between health professionals in primary and secondary care. Patients managed supportively should be encouraged to express preferences for future care, which may contrast with physician preferences. For patients with alcohol dependency this may include physician acceptance of continued drinking (such that the issue is 'off the table' during consultations), allowing focus on symptomatic management. Equally it may mean that strategies for symptom control are prioritised over disease modification (e.g. use of opioids for pain control in patients with encephalopathy). It should be recognised that patients rejected for LT have particularly high PC needs, and that medical consultations may be needed around this time – even when curative options have been exhausted. Some of these approaches are controversial, would be counterintuitive to many hepatologists, and would undoubtedly require major

cultural change. Nonetheless, an acceptance that traditional models of care are frequently incompatible with PC needs is necessary if EOLC in ESLD is to improve.

CONCLUSION

ESLD is associated with a debilitating complex of physical symptoms, substantial psychological distress, and a considerable financial and logistical burden. Healthcare services are heavily centred in secondary care and focussed upon disease modification and cure. Addressing the PC needs of patients and carers is often incompatible with existing models of care. Novel approaches, which explicitly recognise the life-limiting nature of liver disease and improve coordination with community services, are required to meet the needs of patients with ESLD and their carers towards the EOL.

FIGURE 3.3 – LINKS BETWEEN KEY FINDINGS AND KEY RECOMMENDATIONS

KEY FINDINGS		KEY RECOMMENDATIONS
Hospital centred care	Changing structures of care	Increased liaison with General Practice Expansion of community hepatology services
Poor understanding of the implications of advanced liver disease	Reducing the information gap	Open, sufficiently timed discussion of disease, prognosis and treatment plan from point of diagnosis
In-patient admission a deeply unpleasant feature of end-stage disease	Managing inpatients better	Standards of care for patients with cognitive impairment, and facilitation of community management where appropriate
Lack of carer support and no focus on logistical and financial aspects of disease	Increasing carer support	Signposting to sources of financial and logistical support, and care-giver needs assessment
SuPC needs often incompatible with ongoing disease modifying approach	Facilitating a change in focus	Explicit shift to a supportive, symptom focussed, patient-centred approach where there is no curative intent

CHAPTER 4

CIRRHOSIS WITH ASCITES IN THE LAST YEAR OF LIFE: A NATIONWIDE ANALYSIS OF FACTORS SHAPING COST, HEALTH-CARE USE, AND PLACE OF DEATH IN ENGLAND

INTRODUCTION

Death from ESLD is typically associated with complications arising from cirrhosis, namely ascites, jaundice, HE and variceal haemorrhage. Qualitative data from chapter 3 of this thesis demonstrated the considerable impact of these complications and their treatments on patients and carers, and highlighted the negative impact of hospital admissions towards the EOL. Ascites represents the most frequent complication of cirrhosis and is associated with high rates of hospitalisation and readmission. [208, 209] Once refractory to medical treatment, patients require intermittent LVP, as described in chapter 1 (see figure 1.1). Median survival drops to 6-months at this stage in the disease trajectory.[33]

Whilst treatment of refractory ascites with LVP has traditionally required inpatient admission, certain UK centres now offer day-case services. Chivenge et al describe the development of such a service within the NHS.[210] Within their model, patients have direct access to day-case LVP (performed by specialist nursing staff) when their ascites becomes symptomatic. Issues surrounding ACP and PC are introduced at enrolment into the programme, reflecting the prognostic significance of developing refractory ascites. The authors postulate that increasing the availability of planned, day-case LVP has the potential to reduce pressure on acute services, prevent re-admissions, reduce healthcare costs and improve EOLC. Data assessing the economic impact of day-case LVP services is however currently limited to single centre analyses and the uniformity of day-case LVP services across the NHS is unreported.

The medical management of decompensated cirrhosis is costly and has a considerable wider economic impact on healthcare systems (described in chapter 1). Chapter 2 of this thesis (quantitative and qualitative examination of attitudes of hepatologists towards PC) highlighted resource limitation as a key barrier to improving PC in ESLD. Much of the healthcare costs associated with ESLD arise secondary to high rates of re-admission to hospital. [27, 39, 40] Readmission to hospital within 30 days is also associated with a lower quality of preceding clinical care. Following examination of 22 studies, each investigating the association between quality of inpatient care and subsequent re-admission, a US meta-analysis estimated that the risk of early readmission increased by 55% when quality of care during the previous admission had been assessed as low.[211] For this reason, since 2010, costs arising from hospital readmissions within 30 days have not been reimbursed to providers within the NHS.[42]

Over 70% of deaths secondary to ESLD (over 80% for ArLD) occur in hospital, compared with under 40% for cancer.[2] Death outside of the hospital environment was valued highly by qualitative participants in chapter 3. Place of death has been used as a surrogate for quality of EOLC elsewhere. Whilst often of low quality, surveys of the public typically estimate approximately two-thirds of people favour a death at home,[212] and the hospital environment has been described as a sub-optimal environment for quality EOLC.[213, 214]

Resource limitation has been identified as a key barrier to PC in ESLD, however population based studies which detail the determinants of cost, hospitalisation and readmission within the LYOL are lacking. As such, there is a paucity of evidence on which to base decisions pertaining to resource allocation and service design. Furthermore, data from chapter 3 of this thesis and beyond suggest that avoidance of hospitalisation towards the EOL and death outside of hospital are highly valued by patients and carers. Equally however, studies exploring the factors associated with these outcomes (hospitalisation and death outside hospital) are lacking. Whilst new models of day-case LVP create the potential for cost saving, their impact has not been assessed beyond single centre studies. Expansion of such services requires evidence of their cost effectiveness and benefit to patients.

This study uses national level data to assess patterns of health service use in patients with ESLD and to assess the factors which are associated with improved outcomes, both economically and clinically, in the LYOL. As part of this analysis, I explore whether enrolment within a day-case LVP service is associated with improved outcomes.

AIMS AND OBJECTIVES

Aims

This study addresses the third aim from this thesis, outlined in the introduction. This is to assess existing patterns of health-service usage in patients with ESLD in their LYOL and identify the factors associated with improved clinical and economic outcomes towards the EOL.

Objectives

Through retrospective analysis of data pertaining to deaths occurring in England secondary to cirrhosis with ascites between 2013-2015, the specific objectives of this study were to:

- Describe health-service resource use among patients with ESLD in their LYOL by examining the following outcome measures:
    i. Cost of care within the LYOL
    ii. Inpatient hospital bed days within the LYOL
    iii. Early unplanned readmissions to hospital within the LYOL
- Describe place of death outcomes for this cohort, including the frequency of unplanned hospital death (death occurring during an unplanned/emergency hospital admission).
- Describe crude differences in the above outcomes between patients enrolled in day-case LVP services and patients receiving exclusively unplanned care within their LYOL.
- Assess the associations between the outcome measures described above and independent variables relating to:
    i. Demographic factors (sex, ethnicity, age at death, deprivation, year of death).
    ii. Clinical factors (Cause of death, place of death, time between index presentation and death, number of hospital episodes, LVP requirement).
    iii. Health service factors (enrolment within a programme of day-case LVP).
- Among patients enrolled in a day-case LVP service within their LYOL, to assess the associations between the proportion of care received in a day-case setting and outcomes (as defined above).

METHODS

Database building

Case identification via Office for National Statistics (ONS) mortality databases

The ONS mortality database consists of all deaths registered in England. Death certificate data was searched for all causes of death occurring secondary to liver disease as defined by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).[215] There is a standard set of ICD codes used by Public Health England, and within UK government reports, to define liver disease. [2, 5] These same codes were selected here. Table 4.1 shows the ICD-10 codes which were included within the initial search. Patients who had a listed ICD-10 code as their primary or contributory cause of death were extracted.

Table 4.1 – ICD-10 codes extracted from ONS mortality database		
Cause of death category	ICD-10 codes within category	ICD-10 code description
1. Alcohol related liver disease (ArLD)	K70*	Alcoholic liver disease
2. Viral liver disease	B00.8	Herpes virus hepatitis
	B25.1	Cytomegaloviral hepatitis
	B15*	Acute hepatitis A
	B16*	Acute hepatitis B
	B17*	Other acute viral hepatitis
	B18*	Chronic viral hepatitis
	B19*	Unspecified viral hepatitis
3. Non-alcoholic steatohepatitis (NASH)	K76*	Fatty liver disease
4. Hepatocellular carcinoma (HCC)	C22*	Primary liver cell cancer
5. Other chronic liver diseases	B58.1	Toxoplasma hepatitis
	D86.8	Hepatic sarcoidosis
	I82.0	Budd-Chiari syndrome
	K71*	Toxic liver disease
	T39.1	Poisoning/overdose
	Y83.0	Complication of LT (immediate/operative)
	Z94.4	Complication of LT (delayed)
	I81*	Portal vein thrombosis
	I85*	Oesophageal varices
	K72*	Hepatic failure, not elsewhere classified
	K73*	Chronic hepatitis, not elsewhere classified
	K74*	Fibrosis and cirrhosis of the liver (primary biliary cirrhosis included)
	K75*	Other inflammatory and infective disease of the liver (autoimmune hepatitis included)
* - Indicates inclusion of all 4-digit ICD-10 codes within this category		

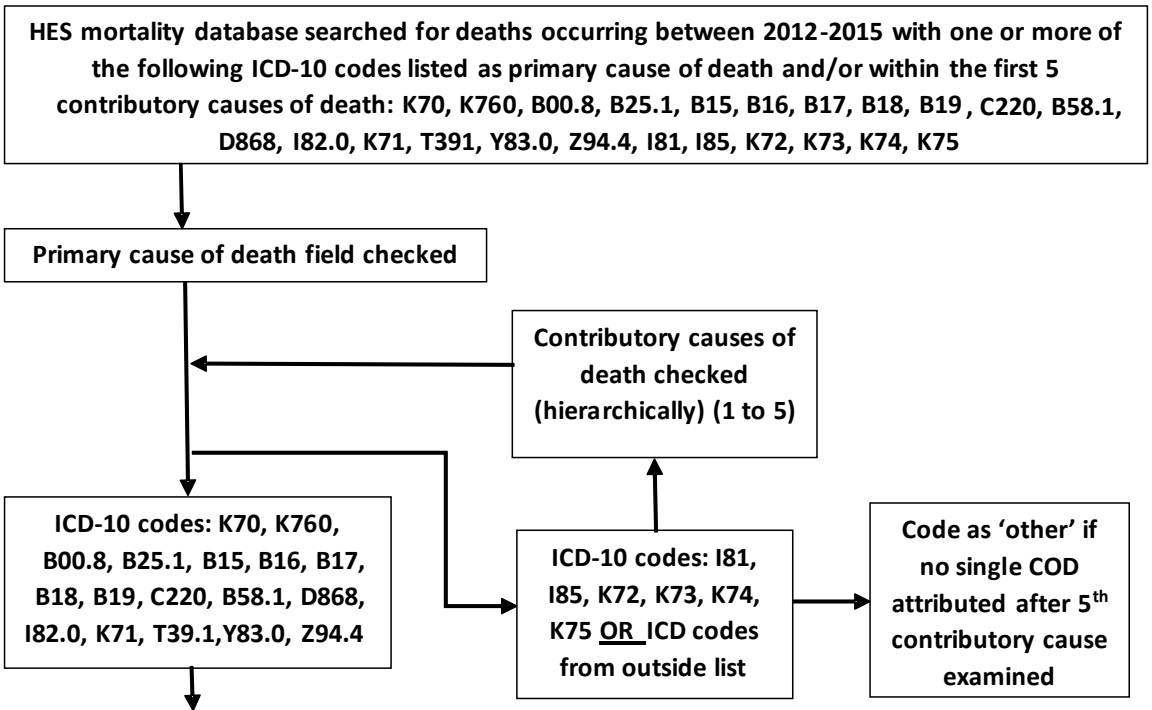
Other demographic data fields were simultaneously extracted from the same database (table 4.2).

Table 4.2 Supplementary fields extracted from ONS database

- Unique patient identifier (for linkage to other databases)
- Year of death
- Sex
- Index of Multiple Deprivation rank
- Quintile and decile of Index of Multiple Deprivation
- Place of death
- Date of death
- Primary cause of death by ICD-10 code (as listed on death certificate)
- First five contributory causes of death listed hierarchically in order listed on death certificate.

A singular cause of death classification was attributed to each case. This was necessary: i) to enable comparison between aetiological groups in subsequent analysis, ii) to attribute a single predominant aetiology for each individual (multiple liver ICD-10 codes may be attributed to one individual e.g. hepatocellular carcinoma on a background of hepatitis C), iii) to minimise classification of cause of death as "other" (e.g. a patient dying of oesophageal varices (primary) caused by ArLD (secondary) should be classified as "ArLD" as opposed to "other", although the varices may be listed hierarchically higher within the death certificate). An algorithm was designed to attribute a single cause of death for each patient (figure 4.1).

Figure 4.1 - Algorithm for attributing a singular cause of death per patient from ONS mortality database



ICD-10 code	Single COD code attributed
K70	Alcohol related liver disease ('arld')
B00.8, B25.1, B15, B16, B17, B18, B19	Viral hepatitis ('viral')
K760	Non-alcoholic steatohepatitis ('nash')
C220	Hepatocellular carcinoma ('hcc')
B58.1, D868, I82.0, K71,K83,T39.1, Y830, Z94.4	Other liver diseases ('other')

Linkage of identified patients to Hospital Episode Statistics (HES) database

Patient identifiers from the above search were linked to the HES database. Episodes from the last 12 months of life were obtained for each patient. The fields extracted from each hospital episode are shown in table 4.3.

Table 4.3 – Data fields extracted from Hospital Episode Statistics database (per episode)

- Admission and discharge date
- Admission type (i.e. elective, emergency etc)
- Admission source (i.e. GP, Accident and Emergency etc)
- Discharge destination
- Episode duration (bed days – defined by number of overnight stays)
- Admission duration (bed days)
- Codes for any procedures undertaken during the course of the episode
- Healthcare Resource Group (HRG) codes relating to the episode (used subsequently to assign tariff information)
- Total number of episodes and admissions in last year of life
- Total number of LVP procedures in LYOL (taken from count of procedure codes)
- Total number of admissions including LVP
- Time between initial presentation within LYOL and death

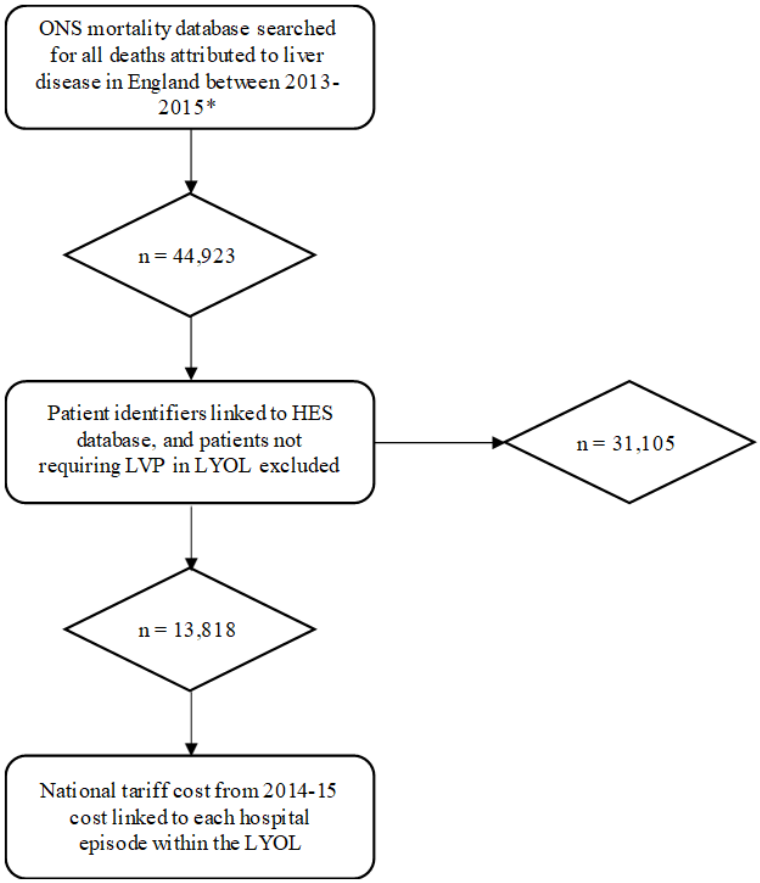
Patients who underwent LVP were identified through the procedure code field of the HES database. All patients who underwent one or more LVP procedure within the LYOL were included. The final database therefore included all patients who died from liver disease in England between 1st January 2013- 31st December 2015, and who underwent one or more LVP within their LYOL.

Linking cost data

Each episode listed within the HES database is attributed a healthcare resource group (HRG) code, based on the diagnosis and type of admission.[216] The national tariff payment system attaches a tariff cost to each code.[217] As described in the Health and Social Care Act 2012, a tariff represents the cost to the payer (e.g. clinical commissioning group or local authority) for the healthcare service specified, provided for the purposes of the NHS.[218] Where length of hospital stay exceeds a pre-defined "trim point", a long stay payment on a daily rate is added to the tariff. Through combining the tariff cost and, where applicable, the cost of stay beyond the trim point, an episode cost was created. The sum of costs within the LYOL was calculated for each individual. The study period spans four financial years (2011-2012 to 2015-2016). Tariffs for each of these years varied slightly. To enable comparison between individuals, tariffs from the 2014-15 year were universally linked to their respective HRG codes, regardless of year. Cost was calculated for all episodes, regardless of whether LVP was undertaken. As such, a total healthcare cost from the LYOL was calculated for each patient. Case selection and database construction is summarised

in figure 4.2. The most common HRG codes from the final dataset, alongside their frequency and associated tariffs are shown in appendix 3.

Figure 4.2 – Database construction and case identification



* Deaths extracted from the ONS mortality database using the following ICD-10 codes: K70 (alcohol related liver disease); B008, B251, B15, B16, B17, B18, B19 (viral liver disease); K760 (non-alcoholic steatohepatitis); C220 (hepatocellular carcinoma); B581, D868, I820, K71, K83, T391, Y830, Z944 (other liver diseases)

Figure legend; HES: Hospital episode statistics; ICD-10: International Statistical Classification of Diseases and Related Health Problems (10th revision); LVP: Large volume paracentesis; LYOL: Last year of life; ONS: Office for National Statistics

Determination and definition of variables

Both outcome measures (dependent variables) and predictors (independent variables) were determined prior to analysis. Definition of variables is given in table 4.4.

Dependent variables were: cost (cumulative cost from all hospital-based episodes within the LYOL), inpatient bed days (number of nights in the LYOL spent as a hospital inpatient), early unplanned readmission within LYOL (binary outcome, positive if patient underwent one or more unplanned admission within 30 days of discharge from a previous inpatient episode), and unplanned hospital death (binary outcome, positive if death had occurred in hospital during an unplanned admission).

The rationale for use of each of these outcome measures is described in the introductory section of this chapter. To summarise, cost reflects existing resource utilisation and provides a downstream estimate of the resources required to deliver future clinical care. Readmission was used given both its association with suboptimal preceding clinical care and its economic impact on NHS hospitals (readmissions within 30 days are not reimbursed within the NHS). Inpatient bed days was used to reflect hospitalisation, given both the economic impact of hospital admission on healthcare services and the fact that avoidance of hospital admission was valued highly by qualitative participants in chapter 3. Furthermore, these same outcome measures are used frequently and as standard within comparable literature, and so their use here also allows us to compare our findings with those from similar studies.[40, 219-224]

I used a newly created variable (unplanned hospital death) as an outcome measure as opposed to crude place of death. Crude place of death has been criticised as a surrogate for quality EOLC. Management of complex and changing symptoms (such as those associated with ESLD) may be more successfully managed in a hospital environment, [225, 226] and an increasing body of evidence suggests that place of death does not represent an over-riding priority for patients or families.[227] Nonetheless, it is also unlikely that place of death is entirely obsolete as an indicator of PC and ACP. The newly created variable excludes terminal admissions which were planned/elective to address this criticism. Whilst the opportunity to express a preference regarding place of death may represent a yet superior metric, it is one which is considerably more difficult to measure.

The associations between independent variables and outcomes (dependent variables) were determined through regression analysis (see below). This allowed for statistical correction when comparing groups such that confounding (e.g. on the basis of deprivation) was reduced. We determined our independent variables based on the demographic and clinical information available in the combined database, and on pre-existing hypotheses (specifically that enrolment within a day-case service would have a positive association with wider outcomes in the LYOL). To investigate the impact of enrolment in a day-case

service, we categorised patients into two care groups: day-case care and unplanned care. Patients who attended a day-case service within their LYOL were classified as day-case care, whereas patients who had all LVP procedures undertaken during an unplanned, inpatient admission were classified as unplanned care.

Secondary analysis investigated the impact of the proportion of LVP procedures performed in a day-case setting on the same outcomes among patients enrolled in a day-case service. This was to determine whether a 'dose-response' relationship existed (i.e. did outcomes improve as the proportion of overall care in a day-case setting increased). For patients in the day-case group we calculated a 'paracentesis ratio'. This was defined as the number of LVP procedures undertaken in day-case care as a proportion of the total number of LVP procedures (day-case and unplanned) performed in the LYOL.

Table 4.4 – Definition of variables used in analysis		
Dependent/outcome variables		
Variable	**Definition**	**Variable type**
Cost	Total cumulative costs as calculated as sum of HRG tariff costs for each episode within LYOL	Continuous
Inpatient bed days	Total number of days spent as a hospital inpatient within the LYOL. 1 day is counted when a hospital bed is occupied at 2am	Continuous integer
Early unplanned readmission	Any readmission within 30 days from discharge from a previous inpatient admission within the LYOL.	Binary
Unplanned hospital death	Death occurring in hospital following unplanned admission.	Binary
Independent/predictor variables		
Variable	**Definition**	**Variable type**
Sex	Gender at death	Binary
Ethnicity	Due to a large number of categories this was transformed to a binary category – white British vs non-white British	Binary
Age at death	Age at death	Continuous integer
Deprivation quintile	The Index of Multiple Deprivation 2015 combines information from the seven domains to produce an overall relative measure of deprivation based on postcode. The Index of Multiple Deprivation quintile refers to the quintile of deprivation, where 1 is reflective of the most deprived 20% of the English population and 5 the least [228]	Ordinal categorical
Year of death	Year of death	Ordinal categorical
Care group	Day-case (access to a day-case LVP service in the LYOL) vs unplanned care (no access to DC LVP in the LYOL). Planned care if one or more LVP carried out in a day-case unit in the LYOL	Binary
Cause of death	Defined by ICD-10 coding of death certificate data. One of 5 categories applied as per algorithm (see figure 4.2)	Non-ordinal categorical
Place of death	As per Office for National Statistics mortality database categorisation (1. Care home 2. Hospice 3. Home 4. Hospital 5. Other places)	Non-ordinal categorical
Time to death (TTD)	The number of full days between index presentation to secondary care within the last year of life and death	Continuous integer
Paracentesis episodes	Number of LVP procedures undertaken within the LYOL	Continuous integer
Non-paracentesis episodes	Total hospital episodes within the last year of life which did not involve LVP	Continuous integer
Paracentesis ratio (secondary analysis in day-case group only)	Number of day-case LVP admissions/Total number of LVP admissions	Continuous ratio

Univariate analysis

Stata (version 14.2) was used to perform all statistical analysis.[144] An unadjusted comparison of care groups was undertaken. Distribution of demographic data was visualised graphically and followed an approximately normal distribution. Whilst demographic data were approximately normally distributed, cost and inpatient bed-days demonstrated significant right skew. Parametric methods of data analysis (e.g. t-tests/chi-squared) typically assume that data are normally distributed. Nonetheless, non-parametric tests risk providing misleading results when the sample size is large. In studies where sample size is large, summarising results with parametric tests is therefore preferred, even when data are heavily skewed.[229] As such, parametric tests were used to determine whether unadjusted differences between care groups were statistically significant (unpaired t-tests for continuous variables and chi-squared tests for categorical outcomes).

Multivariate analysis - Regression modelling

Regression modelling expresses the dependency of one variable (the outcome or dependent variable) on one or more independent (or predictor) variables. It is able to estimate the magnitude of effect of the independent variable of interest (e.g. enrolment within a day-case service) on the dependent variable (e.g. cost), following correction for the impact of other independent variables which may confound the outcome (e.g. cause of liver disease, deprivation).[230]

The type of regression model used is dependent upon the expression of the dependent variable (i.e. continuous vs binary vs categorical), the distribution of the data, and the relationship between the dependent and independent variables. In cases where the dependent variable is binary (e.g. unplanned hospital death) logistic regression is used to estimate odds ratios (OR) for each independent variable within the model. Where the dependent variable is linear and continuous, linear regression models are used to estimate the magnitude of effect for each independent variable.

Multivariable linear models

Multivariable linear regression estimates the magnitude and direction of impact of each independent variable, expressed as coefficients of the linear equation. This approach, which comes from the statistical theory of multiple regression, is summarised by the multiple regression equation (figure 4.3).[230]

Figure 4.3 – The Multiple Regression Equation – Ordinary Least Squares Method

$$\mathbf{Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + ... \beta_k X_k + \varepsilon}$$

Where:

Y = Dependent variable (e.g. cost)

β_0 = A constant (equivalent to Y axis intercept graphically)

β_1...= Coefficient for that variable

X_1…= The independent variable

k = Number of independent variables

ε = Error

Assuming:

Y is continuous with normally distributed residuals

ε is constant for all values of Y

Observations are independent

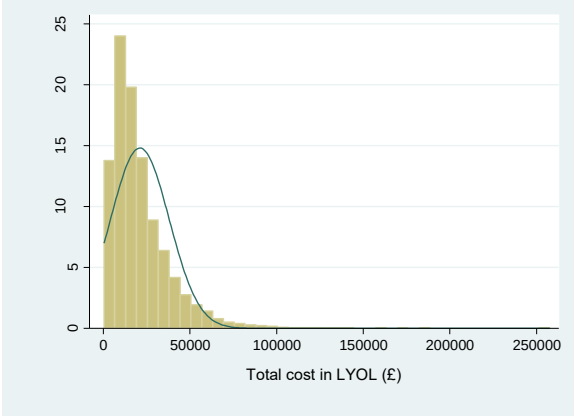
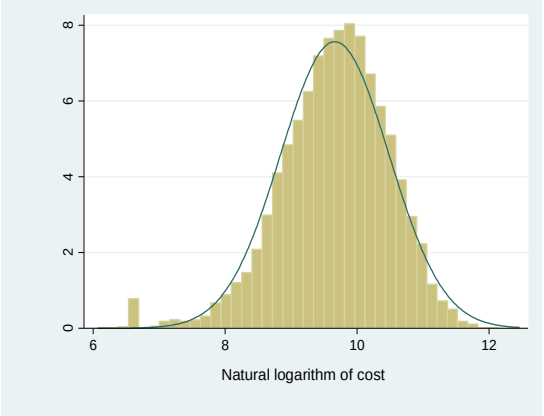
Fitting regression models

The continuous dependent variables of cost and inpatient bed days required linear regression models to be fitted, whilst for the binary variables (early unplanned readmission and unplanned hospital death) logistic models were required.

In standard multivariate linear regression (ordinary least squares regression), the proportion of variance in dependent variables which is explained by the model (i.e. the 'fit' of the model) is significantly improved if the dependent variable is normally distributed.[231] Distribution of continuous dependent variables (cost and inpatient bed days) across the sample was visualised graphically. Positive skew was demonstrated in both cases.

Positive skew is acknowledged to be a typical feature of cost and healthcare-utilisation data.[232] In such cases, the dependent variables require transformation such that model fit is optimised. Natural logarithms can be used to normalise distribution of the variable and improve the linear fit of the subsequent model. The effect of using natural logarithm transformation on the variable of cost is demonstrated in figure 4.4.

Figure 4.4 – Effect of natural logarithmic transformation on the distribution of cost (theoretical perfect normal distributions superimposed)

Distribution of raw data	Distribution following log transformation
	

Logarithmic transformation of skewed data has three key disadvantages.[232] Firstly, zero values cannot be log transformed, meaning patients who have zero data are excluded from analysis (for example, patients who have no inpatient bed days in their LYOL). Secondly, the ultimate presentation of results from the regression analysis is difficult for the reader to interpret. It relies on the calculation of a regression co-efficient, which is calculated following conversion of the log-transformed value to its exponential form. For example, the change in cost accounted for by the presence of a given independent variable (e.g. enrolment in a day-case service) would be expressed as a decimal value, as opposed to an actual cost per patient. This makes data less compatible for future use in service planning and healthcare commissioning. Thirdly, if data are logarithmically transformed to achieve normality the arithmetic means (generally considered to be the most relevant measure for healthcare policy decisions) are not able to be directly compared.

For health-economic data which are non-normally distributed with a large number of zero values, transformation using generalised linear modelling is a preferred method.[233] Generalised linear modelling allows extension of ordinary least squares regression to dependent variables which are not normally distributed. Whilst the model transformation does include ‘log-linking’ of data, it is able to directly estimate the variable of interest (e.g. cost) without having to re-transform the data, and is substantially more precise than ordinary least squares based methods.[232] I used generalised linear modelling to analyse continuous dependent variables.

Logistic regression was used to examine binary outcome measures (early unplanned readmission and unplanned hospital death). Logistic regression allows examination of the impact of independent variables on the probability of a binary response occurring.[234] In logistic regression the probability that the outcome of interest occurs must be between 0 and 1, and the assumption of normally distributed data therefore becomes obsolete (outcomes are binary). Logistic regression replaces probability of the outcome with the log of the odds of the event of interest occurring (logit). This value will always be between 0 and 1. The log likelihood is maximised numerically using an iterative algorithm.[235] The assumptions of linear regression (see below) do not apply in logistic regression, however predictor variables must still be independent. The logistic regression output provides a co-efficient for the independent variables which relates to a difference in log odds. This is then exponentiated to give an OR.[234]

Post-estimation calculations and assumptions of linear regression

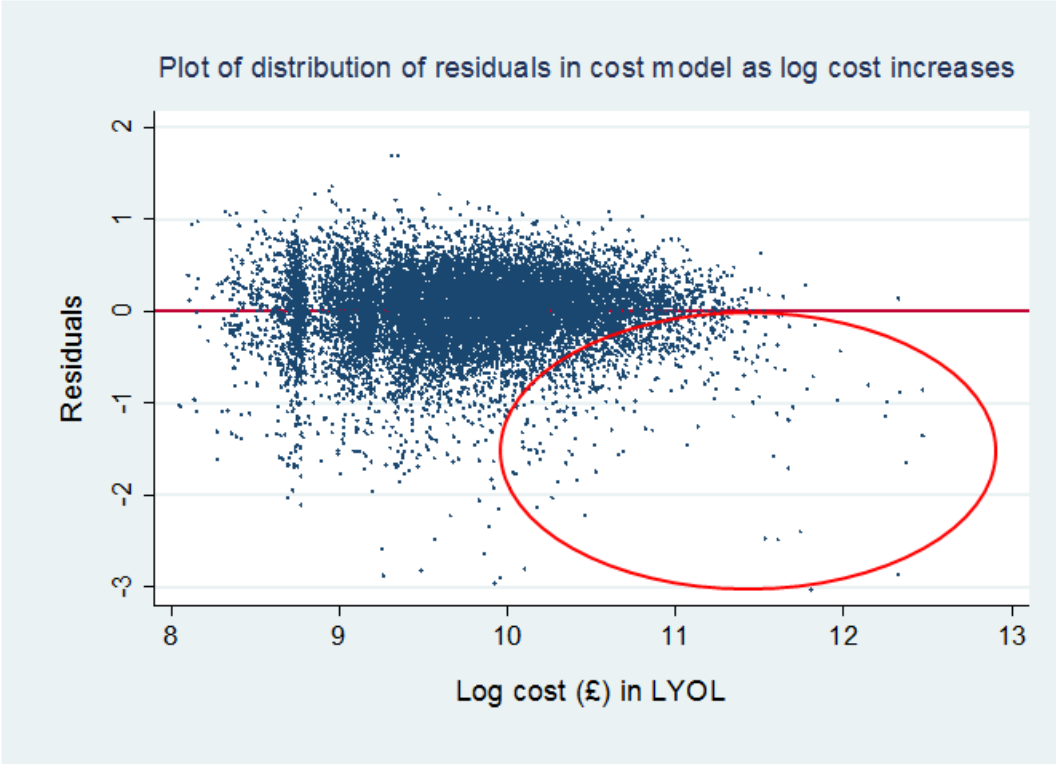
For hypothesis testing to be valid within a multivariate linear regression model, the following statistical assumptions regarding the data must be met:[230]

1. The distribution of residuals of the dependent variable is normal (normality)
2. The variance of distribution of the dependent variable is constant for all values of the continuous independent variables (homoscedasiticity)
3. The relationship between dependent and independent variables should be linear (linearity)
4. Observations should be independent (independence)

Post-estimation analysis of data relating to continuous dependent variables was undertaken to assess each of these assumptions. Generalised linear modelling allows for non-normally distributed dependent variables through 'log-linking' of data, as explained above.

Homoscedasticity refers to the assumption that the magnitude of variance (i.e. the residual) is unaffected by the size of the dependent variable. In other terms, it assumes that the error term in the multiple regression equation (ε – figure 4.4) is independent of the dependent variable (Y). Heteroscedasticity within the model (for example - the variance in cost increasing as actual values of cost increase), risks biasing hypothesis testing, and reduces predictive value. To visualise the data for homoscedasticity, residuals were plotted against the predicted values. An example of this plot (using the cost model) is shown in figure 4.5.

Figure 4.5 – Residuals plotted against cost from cost model.



The untransformed plot shows an approximately even distribution of residuals around the residual line, however towards the higher values of cost, there is a disproportionate cluster of negative residuals. This is indicative of heteroscedasticity at the higher end of the cost values. Heterodasticity was demonstrated statistically for both dependent continuous variables (cost and inpatient bed days) using the Breusch-Pagan test, which regresses the dependent variable against the square of the residuals in the model.[236] Whilst the model used will therefore be somewhat less precise for the higher values of cost and inpatient bed days, this represents a common limitation of health-economic data and does not invalidate the methodology.[237] Furthermore, generalised linear modelling provides a more robust estimate when the dataset demonstrates a degree of heteroscedasticity when compared with ordinary least squares or log-transformed alternatives.[232, 238]

Linear regression assumes an approximately linear relationship between dependent and independent variables. As categorical variables within the model are not ordered, this only applies for continuous independent variables. In smaller datasets, linearity can be checked visually through use of direct scatterplots, and through plotting residuals against fitted values. With large datasets, such as this one, however it becomes impossible to discern the nature of the relationship, as the scatterplot becomes saturated, and analytical methods are required. This was done by analysing the impact of adding a power

term (e.g. quadratic or cubic) to the independent continuous variables – (for example paracentesis episodes) and performing a simple univariate ordinary least squares regression model (i.e. one dependent variable -e.g. cost, and one independent variable – e.g. paracentesis episodes). Overall model fit was compared using adjusted R^2 values from each model (a measure of how well observed outcomes are replicated by the model). R^2 values range from 0 to 1, where 1 indicates that the regression line perfectly fits the data.[239] A non-linear relationship would see an improvement in R^2 following addition of the power term, whilst linear relationships would be unaffected, or indeed worsened. This analytical check demonstrated linearity with each continuous variable (table 4.5).

Table 4.5 – Analysis of non-linearity in multiple regression models in the cost model

	Adjusted R^2 values		
Independent variable	Simple linear model	Addition of a quadratic power term	Addition of a cubic power term
Paracentesis episodes	0.22	0.18	0.22
Non-paracentesis episodes	0.55	0.47	0.55
Time to death	0.22	0.18	0.23

The fourth assumption relates to the independence of observations, such that dependent and independent variables for each observation are independent of one another. This is complex to assess when individual episode data are analysed (as one person would have multiple, time dependent episodes). However, given each observation relates to summative values from an individual, independence is implicit.

Missing data

Any missing data for a given individual meant that their data was unable to be included in regression analyses. For episodes to be extracted from the HES dataset, an HRG code was required. Similarly, the ONS mortality dataset required requisite demographic data. As such, missing data within the dataset were extremely rare. The distribution of missing data was nonetheless analysed to ensure the absence of any pattern. This is detailed in appendix 3.2.

RESULTS

Unadjusted results and demographics

44,923 deaths secondary to liver disease occurring between January 1st 2013 and December 31st 2015 were identified. Of these, 13,818 (30.8%) underwent LVP within their LYOL and were included in analysis (figure 4.2). 73,858 admissions, encompassing 127,495 unique episodes, were analysed. Mean age at death was 61.9 years (standard deviation (SD) 13.0). 9,125/13,818 (66.1%) of the population were male, and 11,512/13,818 (83.3%) of white British ethnicity. ArLD was the most common cause of death (6,376/13,818, 46.1%). Deprivation was positively skewed, with 4,059/13,818 (29.4%) of deaths occurring within the most deprived economic quintile compared with 1,869/13,818 (13.5%) within the least deprived.[228] The mean total cost of hospital care per person in the LYOL was £21,113 (SD 16,881), equating to an average cost of £7,718 per month of care received (i.e. mean cost per month between index presentation in the LYOL and death). A mean of 35.2 days (SD 33.4) were spent as a hospital inpatient in the LYOL, equating to a mean of 33.2% of days between index presentation in the LYOL and death. Excluding index admissions, 17,888/34,068 (52.5%) of emergency admissions within the LYOL occurred within 30 days of a previous discharge. 10,045/13,818 (72.7%) of deaths occurred during an unplanned hospital admission. Of the 2,464/13,818 (17.8%) of patients who only had one admission in the LYOL, 2,063/2,464 (83.7%) died during that admission. Unadjusted comparison between care groups demonstrated a lower proportion of ArLD, a higher proportion of HCC, a higher LVP burden, and a longer average time between index presentation and death in the day-case group. Table 4.6 summarises unadjusted results and population demographics and displays a baseline comparison of care groups.

Table 4.6 – Baseline Demographics and unadjusted comparison between care groups					
Care group		**Day-case care**	**Unplanned care**	**Overall**	**p-value[+]**
n (%)		2,625 (19.0)	11,193 (81.0)	13,818 (100)	
Sex n (%)	Male	1788 (68.1)	7337 (65.6)	9125 (66.1)	0.013
Ethnicity n (%)	White British	2,225 (84.8)	9,287 (83.0)	11,512 (83.3)	0.026
Mean age at death (SD)		63.9 (11.9)	61.4 (13.2)	61.9 (13.0)	<0.0001
Deprivation quintile n (%)	Most deprived	650 (24.8)	3,409 (30.5)	4, 059 (29.4)	<0.0001
	Least deprived	384 (14.6)	1,485 (13.3)	1,869 (13.5)	0.066
Year of death n (%)	2013	812 (31.0)	3,652 (32.6)	4,464 (32.3)	0.004
	2014	831 (31.7)	3,759 (33.6)	4,590 (33.2)	
	2015	982 (37.4)	3, 782 (33.8)	4,764 (34.5)	
Cause of death n (%)	ArLD	848 (32.3)	5,528 (49.4)	6,376 (46.1)	<0.0001
	Viral	89 (3.4)	321 (2.9)	410 (2.97)	
	NASH	318 (12.1)	1,063 (9.5)	1,381 (10.0)	
	HCC	721 (27.5)	1,622 (14.5)	2,343 (17.0)	
	Other	649 (24.7)	2,659 (23.8)	3,308 (23.9)	
Place of death n (%)	Care home	148 (5.6)	493 (4.4)	641 (4.6)	. <0.0001
	Hospice	269 (10.3)	508 (4.5)	777 (5.6)	
	Hospital	1,494 (56.9)	8,847 (79.0)	10,341 (74.8)	
	Home	670 (25.5)	1,249 (11.2)	1,919 (13.9)	
	Other	44 (1.7)	96 (0.9)	140 (1.0)	
Mean time to death (days between index presentation and death in LYOL) (SD)		250 (103)	171 (124)	186 (124)	<0.0001
Mean total emergency admissions in LYOL (SD)		4.1 (3.4)	3.1 (2.6)	3.3 (2.8)	<0.0001
Mean total non-emergency admissions in LYOL (elective, day-case or other) (SD)		6.2 (10.7)	1.1 (4.8)	2.1 (6.7)	<0.0001
Patients with only one hospital admission in LYOL n (%)		52 (2.0)	2,404 (21.5)	2,456 (17.8)	<0.0001
Mean total LVP in LYOL (SD)		6.3 (6.2)	1.9 (1.6)	2.7 (3.5)	<0.0001

Mean non-LVP episodes in LYOL (SD)	8.4 (12.0)	6.1 (7.4)	6.5 (8.5)	<0.0001
Number of unplanned hospital deaths n (%)	1,249 (47.6)	8,796 (78.6)	10,045 (72.7)	<0.0001
Early unplanned readmissions/total readmissions [++] (%)	4,618/8,928 (51.7)	13,270/25,140 (52.8)	17,888/34,068 (52.5)	0.085
Mean total inpatient bed days in LYOL (SD)	32.8 (34.7)	35.8 (33.1)	35.2 (33.4)	<0.0001
Mean bed occupancy [+++] (SD)	13.8 (13.6)	37.8 (34.5)	33.2 (33.0)	<0.0001
Mean total cost (£) in LYOL (SD)	26,584 (20,908)	19,835 (15,515)	21,113 (16,881)	<0.0001
Mean cost (£) per month of care received in LYOL (SD) [++++]	3,654 (3,424)	8,669 (15,338)	7,718 (14,024)	<0.0001

+ p value for difference between day-case and unplanned care groups

++number of emergency admissions in LYOL which occurred within 30 days of discharge (index admission and planned admissions excluded)

+++ % of days between index presentation in LYOL and death as hospital inpatient

++++ (Total cost in last year of life/days between index presentation in LYOL and death) x 30 – i.e. cost per month of care received in LYOL

ArLD: Alcohol related liver disease, HCC: Hepatocellular carcinoma, LYOL: Last year of life, NASH: Non-alcoholic steatohepatitis

Multivariate regression analysis

Continuous dependent variables – Cost and inpatient bed days

The independent variables associated with the highest reductions in overall cost were the presence of HCC (-£4,505; 95%CI -£5,137, -£3,872; p<0.0001), enrolment in a day-case service (-£4,240; 95%CI -£4,829, -£3,651; p<0.0001), and death occurring outside a hospital or care home (death at home; -£2,275; 95%CI -£2,871, -£1,679; p<0.0001, death in a hospice; -£1,250; 95%CI -£2,143, -£357; p=0.006). Cost correlated positively with rising socio-economic deprivation, increasing LVP requirement, and number of hospital episodes.

The independent variables associated with the fewest inpatient bed days in the LYOL were enrolment in a day-case service (-16.98 days; 95%CI -18.45, -15.51; p<0.0001), HCC (-10.30 days; 95%CI -11.88, -8.72; p<0.0001), and death at home (-3.87 days; 95%CI -5.35,-2.38; p<0.0001). Death occurring in a care home was associated with significantly more inpatient bed days in the LYOL when compared with death in hospital (18.37 days; 95%CI 16.01, 20.73; p<0.0001).

Table 4.7 shows the generalised linear modelling outputs for the cost and inpatient bed days models.

Table 4.7 –Effect of independent variables on cost and inpatient bed days as estimated by generalised linear modelling					
		Cost in LYOL+		**Inpatient bed days in LYOL +**	
		£ (95% CI)	**p-value**	**Days (95% CI)**	**p-value**
Gender	Female	Reference group			
	Male	435 [24, 845]	0.038	-1.04 [-2.07, -0.02]	0.046
Ethnicity	White British	Reference group			
	Non-white British	441 [-82, 964]	0.098	1.97 [0.77, 3.18]	0.003
Age at death (per increase of one decade)		-166 [-334, 3]	0.054	0.64 [0.22, 1.06]	0.003
Deprivation quintile (1=most deprived)	1	Reference group			
	2	-363 [-910, 185]	0.194	-0.06 [-1.43, 1.31]	0.931
	3	-704 [-1278, -130]	0.016	-0.01 [-1.44, 1.43]	0.992
	4	-704 [-1313, -97]	0.023	-1.58 [-3.10, -0.06]	0.041
	5	-924 [-1568, -279]	0.005	0.22 [-1.39, 1.83]	0.789
Year of death	2013	Reference group			
	2014	1762 [1284, 2239]	<0.0001	-0.07 [-1.27, 1.12]	0.905
	2015	3163 [2689, 3636]	<0.0001	-0.78 [-1.96, 0.40]	0.195
Enrolled in day-case service?	No (unplanned)	Reference group			
	Yes (day-case)	-4240 [-4829, -3651]	<0.0001	-16.98 [-18.45,-15.51]	<0.0001
Cause of death	ArLD	Reference group			
	Viral	455 [-710, 1620]	0.444	2.26 [-0.65, 5.16]	0.128
	NASH	194 [-509, 897]	0.589	1.43 [-0.32, 3.19]	0.109
	HCC	-4505 [-5137, -3872]	<0.0001	-10.30 [-11.88, -8.72]	<0.0001
	Other	-1237 [-1762, -712]	<0.0001	-2.43 [-3.74, -1.12]	<0.0001
Place of death	Hospital	Reference group			
	Care home	1990 [1044, 2935]	<0.0001	18.37 [16.01, 20.73]	<0.0001
	Home	-2275 [-2871, -1678]	<0.0001	-3.87 [-5.35, -2.38]	<0.0001

	Hospice	-1250 [-2143, -357]	0.006	0.16 [-2.07, 2.39]	0.886
	Other Places	-1395 [-3334, 544]	0.158	-0.98 [-5.82, 3.95]	0.691
Time to death (per increase of one month)		685 [632, 739]	<0.0001	1.80 [1.67, 1.93]	<0.0001
LVP procedures in LYOL (per increase of one episode)		1796 [1730, 1862]	<0.0001	1.92 [1.76, 2.09]	<0.0001
Non-LVP episodes (per increase of one episode)		925 [901, 950]	<0.0001	1.01 [0.94, 1.07]	<0.0001
Observations++		13, 815	13, 790		

+ As predicted by generalised linear model

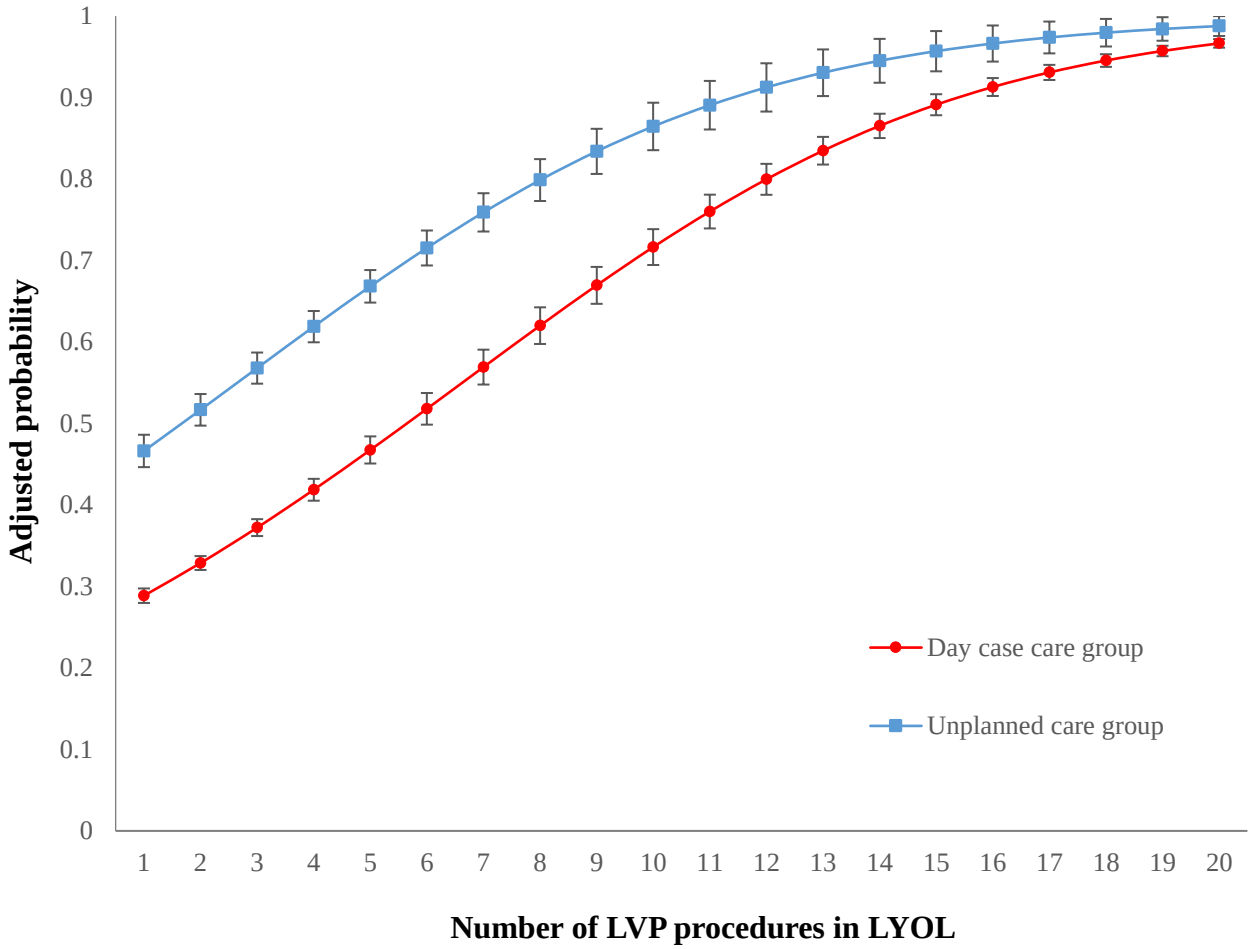
++ Only observations with a complete set of dependent and independent variables included in analysis (appendix 4.2 details missing data)

ArLD: Alcohol related liver disease, HCC: Hepatocellular carcinoma, LVP: Large volume paracentesis, LYOL: Last year of life, NASH: Non-alcoholic steatohepatitis

Binary dependent variables – early unplanned readmission and unplanned hospital death

The primary factor associated with reduced odds of early unplanned readmission within the LYOL was enrolment within a day-case service (OR 0.35; 95%CI 0.31,0.40; p<0.0001). Non-white ethnicity (OR 1.22; 95%CI 1.08, 1.36; p=0.001) and viral liver disease (OR 1.42; 95%CI 1.10, 1.83; p=0.006) were also associated with an increased probability of early unplanned readmission, although at a smaller magnitude. The odds of early unplanned readmission increased as the LVP requirement (a surrogate for severity of liver disease) increased. The difference in the odds of early unplanned readmission between care groups became less as LVP requirement (i.e. severity of disease) increased (figure 4.6).

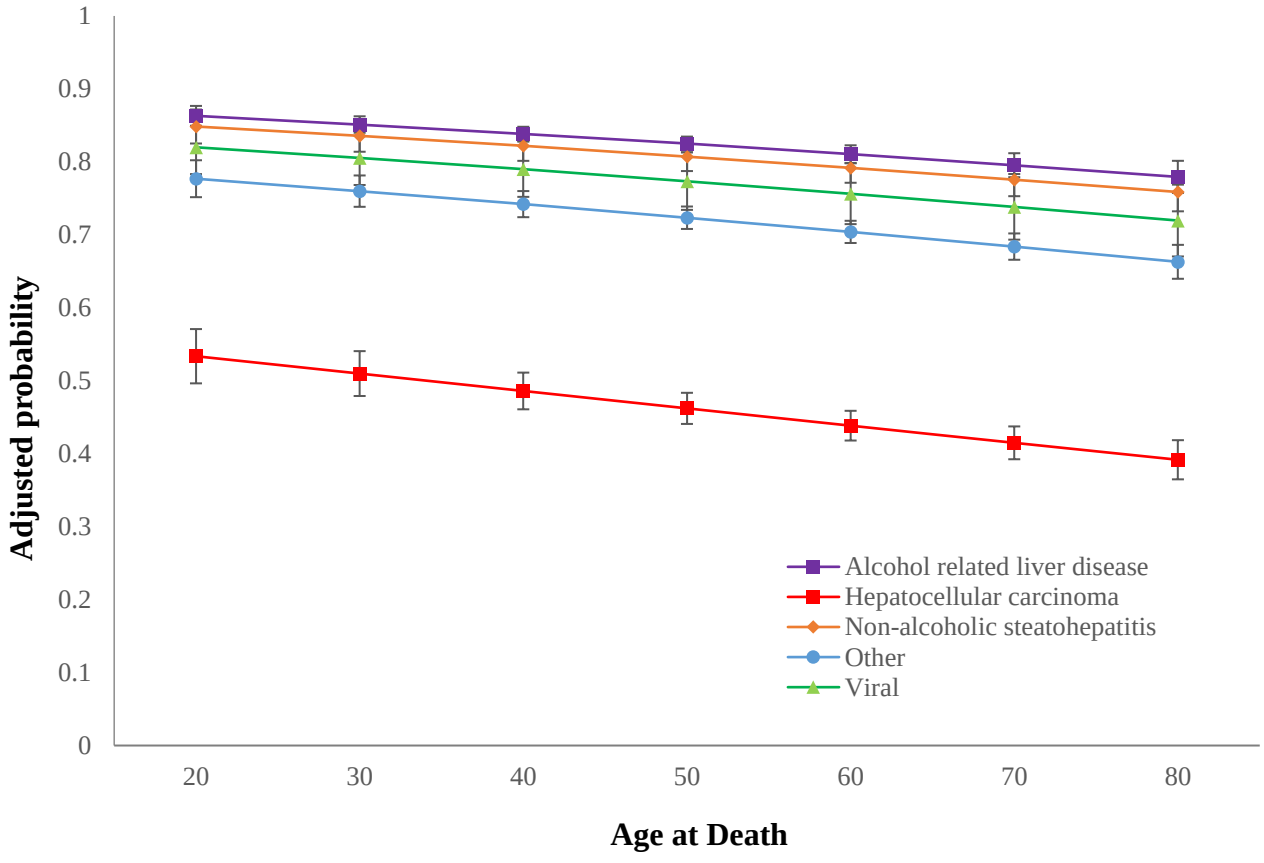
Figure 4.6 – Adjusted probability of having any early unplanned readmission within the last year of life by care group and large volume paracentesis requirement (95 % confidence intervals)



The independent variables which were most strongly associated with a reduced probability of unplanned hospital death were the presence of HCC (OR 0.16; 95%CI 0.14,0.18; p<0.0001) and enrolment within a day-case service (OR 0.31; 95%CI 0.27,0.34; p<0.0001). Worsening socio-economic deprivation, non-white ethnicity, increasing LVP requirement, and a younger age at death were associated with an increased probability of unplanned hospital death.

When compared with other aetiologies, HCC was distinctly associated with a reduced probability of unplanned hospital death. Figure 4.7 demonstrates the relationship between cause of death and age on the adjusted probability of unplanned hospital death following correction for all other independent variables.

Figure 4.7 – Adjusted probability of unplanned hospital death by cause of death and age (95% confidence intervals)



Logistic regression outputs for the binary dependent variables (early unplanned readmission and unplanned hospital death) are shown in table 4.8.

Table 4.8 – Effect of independent variables on odds of early unplanned readmission and unplanned hospital death as estimated by logistic regression modelling[+]					
		Early unplanned readmission		**Unplanned hospital death**	
		OR [95% CI]	**p-value**	**OR [95% CI]**	**p-value**
Gender	Female	Reference group			
	Male	1.06[0.97,1.16]	0.173	0.91 [0.83,0.99]	0.034
Ethnicity	White British				
	Not white British	1.22[1.08,1.36]	0.001	1.17 [1.04,1.31]	0.007
Age at death (per increase of one decade)		1.22[1.08,1.36]	0.001	1.17 [1.04,1.31]	0.007
Deprivation quintile (1=most deprived)	1	Reference group			
	2	1.04[0.92,1.17]	0.513	0.92[0.82,1.04]	0.177
	3	0.97[0.86,1.10]	0.668	0.90[0.80,1.02]	0.111
	4	0.95[0.83,1.08]	0.412	0.83 [0.73,0.95]	0.006
	5	1.02[0.89,1.17]	0.77	0.82 [0.72,0.94]	0.005
Year of death	2013	Reference group			
	2014	1.04[0.94,1.15]	0.449	0.90 [0.81,1.00]	0.043
	2015	1.02[0.92,1.13]	0.672	0.92[0.83,1.02]	0.126
Enrolled in day-case service?	No (unplanned)	Reference group			
	Yes (day-case)	0.35[0.31,0.40]	<0.0001	0.31[0.27,0.34]	<0.0001
Cause of death	ArLD	Reference group			
	Viral	1.42[1.10,1.83]	0.006	0.71 [0.55,0.92]	0.009
	NASH	1.13[0.97,1.32]	0.116	0.88[0.75,1.03]	0.108
	HCC	1.04[0.91,1.19]	0.542	0.16[0.14,0.18]	<0.0001
	Other	1.14[1.02,1.28]	0.026	0.53[0.48,0.60]	<0.0001
Place of death	Hospital	Reference group			
	Care home	1.10[0.91,1.33]	0.325	Place of death omitted as an independent variable due to co-linearity	
	Home	0.80[0.71,0.90]	<0.0001		
	Hospice	0.86[0.71,1.03]	0.098		
	Other Places	1.10[0.91,1.33]	0.325		
Time to death (per increase of 1 month)		0.90[0.89,0.91]	<0.0001	0.92[0.91,0.93]	<0.0001

LVP procedures in LYOL (per increase of one episode)	1.28[1.25,1.31]	<0.0001	1.01 [1.00,1.03]	0.027
Non LVP episodes in LYOL (per increase of one episode)	1.27[1.26,1.29]	<0.0001	1.02[1.01,1.02]	<0.0001
Observations ++	11,731		13,790	

+ ORs exponentiated from multivariable logistic regression models

++ Only observations with a complete set of dependent and independent variables included in analysis (appendix 4.2 details missing data). Patients who died on index admission not included in early unplanned readmission model.

ArLD: Alcohol related liver disease, HCC: Hepatocellular carcinoma, LR: Likelihood ratio, LVP: Large volume paracentesis, LYOL: Last year of life, NASH: Non-alcoholic steatohepatitis

Secondary analysis - The impact of the proportion of overall care received in a day-case setting

The 2,625 patients who were enrolled in a day-case service within their LYOL were investigated separately in a secondary analysis. Regression modelling was undertaken in this sub-group as described above (generalised linear modelling for continuous dependent variables, logistic regression for binary dependent variables). When compared with the regression outputs from the primary analysis, similar associations between independent and dependent variables were observed. Notably, death caused by HCC remained the independent variable most strongly associated with highly significant reductions in cost and inpatient bed days and a reduced probability of unplanned hospital death. Regression outputs from generalised linear modelling (continuous dependent variables) and logistic regression (binary dependent variables) are given in tables 4.9 and 4.10 respectively.

Table 4.9 - Effect of independent variables on cost and inpatient bed days as estimated by generalised linear modelling among patients enrolled in a day-case service					
		Cost [+]		**Inpatient bed days** [+]	
		£ (95% CI)	**p-value**	**Days (95% CI)**	**p-value**
Gender	Female	Reference group			
	Male	963 [-194,2120]	0.103	-2.00 [-4.29,0.30]	0.088
Ethnicity	White British	Reference group			
	Non-white British	-176 [-1681,1328]	0.818	4.61 [1.63,7.59]	0.002
Age at death (per increase of one decade)		-548 [-1046, -50]	0.031	-0.22 [-1.21,0.77]	0.665
Deprivation quintile	1	Reference group			
	2	-1239 [-2827,349]	0.126	-1.18 [-4.33,1.97]	0.461
	3	-1164 [-2762,433]	0.153	-0.79 [-3.96,2.38]	0.624
	4	-495 [-2141,1151]	0.556	-1.54 [-4.80,1.72]	0.355
	5	-2166 [-3950,-382]	0.017	-1.12 [-4.66,2.41]	0.533
Year of death	2013	Reference group			
	2014	2909 [1557,4261]	<0.0001	1.06 [-1.63,3.74]	0.44
	2015	4170 [2872,5469]	<0.0001	-0.14 [-2.71,2.44]	0.916
Paracentesis ratio (per increase of 0.1)[++]		-1,939 [-2,131,-1,748]	<0.0001	-4.71 [-5.09,-4.33]	<0.0001
Cause of death	ArLD	Reference group			
	Viral	-770 [-3829,2288]	0.622	-0.65 [-6.71,5.41]	0.834
	NASH	-1792 [-3657,73]	0.06	-2.98 [-6.68,0.72]	0.114
	HCC	-4505 [-6103,-2907]	<0.0001	-8.95 [-12.11,-5.78]	<0.0001
	Other	-1566 [-3090,-43]	0.044	-3.57 [-6.59,-0.55]	0.021
Place of death	Hospital	Reference group			
	Care home	-44 [-2451,2364]	0.972	10.94 [6.17,15.71]	<0.0001
	Home	-3000 [-4333,-1666]	<0.0001	-5.01 [-7.65,-2.36]	<0.0001
	Hospice	-1277 [-3169,616]	0.186	-1.98 [-5.73,1.77]	0.301
	Other Places	83 [-4112,4279]	0.969	-1.03 [-9.35,7.29]	0.808
Time to death (per increase of one month)		515 [338,692]	<0.0001	1.34 [0.99,1.69]	<0.0001

LVP procedures in LYOL (per increase of one episode)	1384 [1286,1482]	<0.0001	0.90 [0.71,1.09]	<0.0001
Non-LVP episodes (per increase of one episode)	586 [540,633]	<0.0001	0.50 [0.40,0.59]	<0.0001
Observations	2,625		2,624	

+ As predicted by generalised linear model

++ Change in outcome associated with a step change in the paracentesis ratio of + 0.1 (i.e. increasing the proportion LVPs performed in a day-case setting by 10% in the LYOL, e.g. 3 day-case 7 inpatient vs 2 day-case 8 inpatient)

HCC: Hepatocellular carcinoma, LVP: Large volume paracentesis, LYOL: Last year of life, NASH: Non-alcoholic steatohepatitis

Table 4.10 - Effect of independent variables on odds of early unplanned readmission and unplanned hospital death as estimated by logistic regression modelling among patients enrolled in a day-case service[+]							
		Early unplanned readmission			**Unplanned hospital death**		
		OR [95% CI]		**p-value**	**OR [95% CI]**		**p-value**
Gender	Female	*Reference group*					
	Male	0.86	[0.69,1.07]	0.180	0.93	[0.77,1.11]	0.414
Ethnicity	White British	*Reference group*					
	Non-white British	1.53	[1.15,2.04]	0.004	0.91	[0.72,1.15]	0.441
Age at death (per increase of one decade)		1.05	[0.96,1.16]	0.278	0.94	[0.87,1.02]	0.164
Deprivation quintile (1=most deprived)	1	*Reference group*					
	2	1.19	[0.88,1.61]	0.254	1.23	[0.96,1.58]	0.101
	3	0.93	[0.69,1.25]	0.612	1.07	[0.83,1.37]	0.598
	4	0.87	[0.64,1.18]	0.363	0.99	[0.76,1.27]	0.912
	5	1.14	[0.81,1.59]	0.453	0.93	[0.70,1.23]	0.603
Year of death	2013	*Reference group*					
	2014	1.12	[0.87,1.45]	0.388	1.07	[0.87,1.32]	0.535
	2015	1.03	[0.80,1.32]	0.819	0.98	[0.80,1.20]	0.856
Paracentesis ratio (per increase of 0.1)[++]		0.67	[0.63,0.69]	<0.0001	0.89	[0.86,0.91]	<0.0001
Cause of death	ArLD	*Reference group*					
	Viral	1.58	[0.87,2.85]	0.133	0.8	[0.50,1.26]	0.327
	NASH	0.92	[0.65,1.31]	0.652	0.79	[0.59,1.04]	0.094
	HCC	0.95	[0.71,1.29]	0.763	0.22	[0.17,0.27]	<0.0001
	Other	0.88	[0.66,1.17]	0.381	0.50	[0.40,0.63]	<0.0001
Place of death	Hospital	*Reference group*					
	Care home	0.85	[0.55,1.32]	0.459	Omitted from regression due to co-linearity		
	Home	0.82	[0.63,1.05]	0.112			
	Hospice	1.06	[0.74,1.52]	0.740			
	Other Places	1.8	[0.81,4.00]	0.152			
Time to death (per increase of one month)		0.98	[0.95,1.02]	0.471	0.97	[0.94,0.99]	0.036

Number of LVP in LYOL (per increase of one episode)	1.13	[1.10,1.15]	<0.0001	1.02	[1.00,1.03]	0.026
Number of non-LVP hospital episodes in LYOL (per increase of one episode)	1.20	[1.17,1.23]	<0.0001	1.02	[1.01,1.04]	0.001
Observations	2,613			2,613		

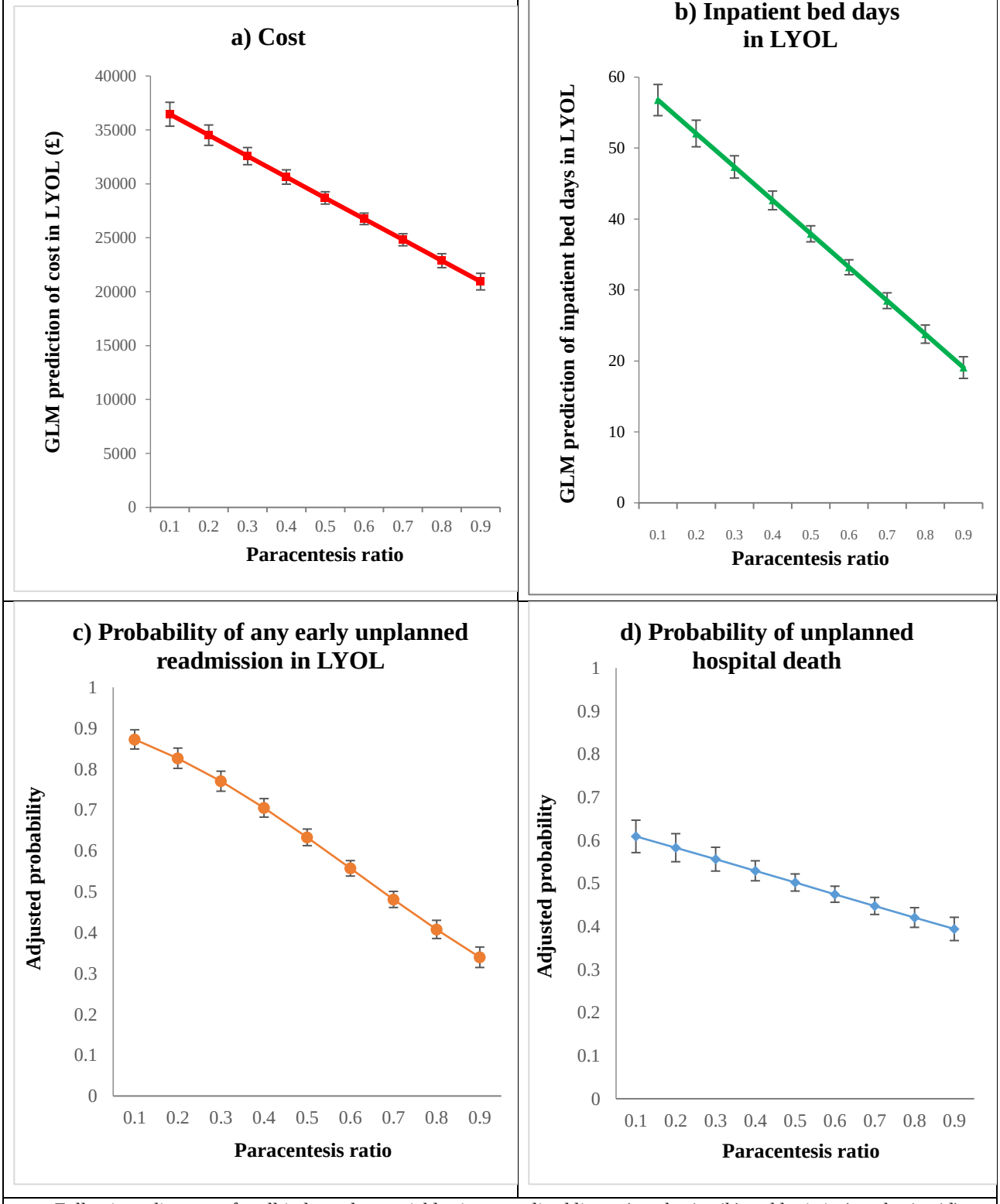
+ Odds ratios exponentiated from multivariable logistic regression models

++ Change in outcome associated with a step change in the paracentesis ratio of + 0.1 (i.e. increasing the proportion LVPs performed in a day-case setting by 10% in the LYOL, e.g. 3 day-case 7 inpatient vs 2 day-case 8 inpatient)

ArLD: Alcohol related liver disease, HCC: Hepatocellular carcinoma, LR: Likelihood ratio, LVP: Large volume paracentesis, LYOL: Last year of life, NASH: Non-alcoholic steatohepatitis

The objective of the secondary analysis was to assess the impact of the proportion of care received in a day-case setting (paracentesis ratio) on previously defined outcomes. In the regression tables this is presented numerically as the effect of increasing the paracentesis ratio by 0.1 following statistical correction for all other independent variables. The same linear and logistic models are presented graphically in figure 4.8, which demonstrate the effect of the paracentesis ratio on outcomes, following correction for all other independent variables.

Figure 4.8 – Relationship between the proportion of total LVP procedures in the LYOL performed in a day-case setting (paracentesis ratio) and outcomes among patients enrolled in a day-case LVP service (95% CIs) +



+ Following adjustment for all independent variables in generalised linear (graphs 4a, 4b) and logistic (graphs 4c, 4d) regression models
GLM = Generalised linear modelling

DISCUSSION

Summary of main findings

This is the first study to use national level data to examine patterns of resource use and EOL outcomes among patients who die from cirrhosis. High levels of resource use, early readmission and unplanned hospital death were demonstrated across the cohort. The cost to hospitals is however likely to be higher than the mean LYOL cost calculated in our analysis (£21,113). We use the sum of all potentially chargeable HRG tariffs in the LYOL, however, 52.5% of repeat admissions occurred within 30 days of discharge. Costs from these admissions would not have been reimbursed within the NHS.[42] Furthermore, the wider opportunity costs (e.g. staff time, bed capacity etc) from these admissions and the subsequent lost revenue from reimbursable admissions, will also not have been identified. The early re-admission rate of 52.5% is higher than other estimates in the literature.[40, 220, 224] Possible reasons for this are discussed below. The unplanned hospital death rate was high (72.7%), when compared with rates of hospital death from other causes (e.g. cancer, 38%).[240]

Regression models were used to determine the associations between the outcome variables of cost and inpatient bed days in the LYOL (generalised linear modelling), and the odds of early unplanned readmission and unplanned hospital death (logistic regression). This analysis does not claim to establish causality; indeed, many of the reported associations may be endogenous. Nonetheless, two independent variables had particularly striking associations, in terms of both magnitude of effect and level of statistical significance; enrolment in a day-case service, and cause of death (specifically, death caused by HCC).

Compared with patients receiving exclusively unplanned care, enrolment in a day-case service was associated with substantial and highly significant reductions in cost (-£4,240.29; 95%CI -£4,829.45 to -£3,651.12; $p<0.0001$), number of inpatient bed days (-16.68 days; -18.13 to -15.22; $p<0.0001$), odds of early readmission (OR 0.35; 0.31 to 0.40; $p<0.0001$), and odds of dying in hospital following unplanned admission (OR 0.31; 0.27 to 0.34; $p<0.0001$). Among patients enrolled in a day-case service, a strong 'dose-response' relationship was observed between increasing proportions of care received in a day-case setting (paracentesis ratio) and outcomes (figure 4.8). When compared with death occurring secondary to non-malignant liver disease, death occurring secondary to HCC was associated with lower costs (-£4,505; -£5,137 to -£3,872; $p<0.0001$), fewer inpatient bed days (-10.30 days; -11.88 days to -8.72 days; $p<0.0001$) in the LYOL, and a markedly reduced probability of unplanned hospital death (OR=0.16; CI 0.14 to 0.18; $p<0.0001$). There was no significant associated change in the probability of early unplanned readmission occurring in the LYOL.

Many other statistically significant associations between other independent variables and outcomes were also seen within the regression outputs. When considering these statistical associations, it is important to be cognisant of the distinction between statistical and clinical significance. Given the large sample size many statistically significant associations are expected. However, when the magnitude of the co-efficient is minimal this does not necessarily reflect a clinically significant difference. For example, increasing age at death was associated with a statistically significant increase in inpatient bed days (p=0.003). However, the magnitude of this difference only equated to 0.64 days in the LYOL for every decade increase in age at death. It would be misleading to comment on every statistically significant association. Nonetheless, beyond the two factors which had the most clear and substantial association with outcomes (enrolment in a day-case service and HCC), there were other variables which are likely to hold clinically, as well as statistically, significant associations – albeit of a smaller magnitude.

Deaths which occurred in a care home were associated with increased costs (£1990; £1004 to £2935; p<0.0001) and a substantially increased number of inpatient bed days (18.37 days; 16.01 to 20.73; p<0.0001). This contrasted with deaths occurring at home which were associated with reduced costs (-£2275; -£2871 to -£1678; p<0.0001) and reduced bed days (-3.87 days; -5.35 to -2.38; p<0.0001). Increasing cost was associated with both increasing socio-economic deprivation (least deprived quintile: -£924; -£1568 to -£279; p = 0.005), and later year of death (2015 (vs 2013) £3163; £2689 to £3636; p<0.0001). As would be expected, an increasing time exposed to healthcare services (time to death), LVP requirement, and number of non-LVP hospital episodes all correlated with increasing cost and inpatient bed days within the LYOL.

Comparison with existing literature

Our study demonstrates that attendance at a day-case service is associated with substantial and highly significant improvements in outcomes in the LYOL. This is consistent with the findings of small, single centre, retrospective, observational studies from UK centres which have introduced nurse-led day-case LVP services. Menon et al estimated that the cost saving accrued 10 months after introduction of a nurse led day-case gastroenterology service at a UK district general hospital amounted to £281,522. Although this included provision of an infusion service, the majority of savings reported were attributed to reduced inpatient stays for LVP.[241] Further to the health economic advantages of day-case LVP, Chivenge et al also described benefits in terms of proactive introduction of PC and ACP in this group.[210] It is plausible that these additional aspects of care may have contributed to the significantly reduced rates of unplanned hospital death associated with day-case care in our study.

There have been three prospective studies assessing the clinical and economic impact of pro-active outpatient management strategies in decompensated cirrhosis. Morano et al compared outcomes in

ambulatory cirrhotic patients designated to a "care management check-up" group (involving proactive multidisciplinary input in a day-case setting with access to rapid, same day procedures and investigations), as compared to standard care (followed up "on demand" in line with existing guidelines). As well as significant improvements in mortality and readmission rates in the day-case group, overall costs per patient month of life were approximately 50% lower.[242] This is similar to our (unadjusted) figure of 57.9% reduction in mean cost per month of care received in the day-case group. An Australian study trialled a nurse-led chronic disease management programme against standard of care among 60 patients with decompensated cirrhosis.[243] Although an improved standard of clinical care was reported in the intervention group, significant differences in bed occupancy and readmission rates were not seen. Finally, a study which intensified outpatient follow up for patients with HE reported a reduction in 30-day readmissions of 40%[219]. None of these studies considered quality of EOLC as an outcome measure.

When compared with deaths caused by non-malignant liver disease, the presence of HCC was associated with substantial reductions in cost and inpatient bed days and was associated with a highly significant reduction in the odds of unplanned hospital death. This finding appears to correlate with data from elsewhere in this thesis. In chapter 2, data from both a quantitative questionnaire and a qualitative interview study of consultant hepatologists highlighted that physicians were significantly more likely to instigate PC measures in patients with malignancy as compared to those with decompensated cirrhosis alone, irrespective of the overall prognosis. In chapter 3, qualitative data from patients and carers highlighted that patients with HCC tended to be better informed and more aware of their prognosis than patients with non-malignant ESLD. A recent retrospective cohort study from the US used a national database to identify the factors associated with PC referral during the terminal admission of patients dying from ESLD.[112] The authors identified that the presence of HCC was associated with a significantly higher probability of receiving PC input. Furthermore, PC consultation was associated with lower costs and fewer invasive procedures during the admission. This study was however heavily criticised for statistical inconsistencies following its publication.[113] Unresolved PC needs in patients dying from other non-malignant organ failures are also extensively reported in the wider literature.[57-61, 244] This may in part be reflected by the relatively low percentage of deaths from non-malignant disease which occur in a hospice environment.[240]

The unadjusted early unplanned readmission rate of 52.5% in our study is notably higher than other estimates in the literature. A US study from a tertiary centre reported a 30-day readmission rate of 20% in a cohort of patients with ESLD,[245] a figure broadly corroborated by a similar single centre prospective US study on hospital use in decompensated cirrhosis.[246] A US study of 402 patients admitted with a complication of cirrhosis reported a readmission rate of 69% - however readmissions outside the 30-day window were included (37% readmission rate within 30 days).[40] However, our data cannot be compared on a like-for-like basis to these studies. In the first two studies, index admissions were not excluded from

the denominator and patients referred to a hospice or care home were excluded. Perhaps more importantly our data relates exclusively to the LYOL. It is likely that the burden of readmission increases in this period. Indeed, Berman et al note that readmission is, in and of itself, strongly and independently predictive of mortality.[245]

Implications for practice and research

The methodology of this study means that we cannot attribute a causal relationship between independent variables and outcomes. Nonetheless, the substantial and significant improvements in outcomes associated with enrolment within a day-case service strongly support their wider adoption. Existing examples of successful programmes within in the UK have been implemented by hepatology specialist nurses under the overall care of a specialist physician within a secondary care institution.[210, 241] For such programmes to become commonplace a wider investment in growth, training, and development of the hepatology specialist nurse workforce, would likely be required. The correlation between the increased proportion of care received in a day-case setting and reduced costs, highlighted in our secondary analysis, mean that potential cost savings may be accentuated for patients referred at an earlier point in their disease trajectory. The benefits of ambulatory approaches to care have been realised in other chronic life limiting conditions, most notably in heart failure – a condition with comparatively high rates of morbidity, mortality and healthcare utilisation. Numerous clinical trials have demonstrated significant benefits from proactive, nurse-led models of outpatient and day-case care. A pooled meta-analysis of 18 studies in 2004 reported a 25% reduction in risk of readmission among patients enrolled in nurse-led support.[247] This approach is recognised and recommended within international guidelines.[248]

The benefits associated with day-case care could plausibly be enhanced through the redirection of services towards the community, particularly among patients in whom curative options are not being pursued. Qualitative data from chapter 3 of this thesis demonstrate the financial, physical and logistical burdens of reliance on centralised hospital care towards the EOL. Furthermore, PC may be better delivered in community settings, where patients are able to access care closer to home in a more responsive fashion.[249] LVP seldom occurs outside of hospital in patients with ascites, however a programme of day-hospice care for patients with ESLD at St Luke's hospice in Basildon has reported reduced hospital stays, improved access to multidisciplinary community care, and improved QOL.[250] International guidelines recommend administration of human albumin solution and monitoring of renal function for patients undergoing LVP.[188] Nonetheless, towards the EOL, patients may be willing to accept the risks of foregoing these interventions in exchange for a convenient and responsive service away from the hospital environment. Whether these potential benefits would be offset by the 'economies of scale' afforded by secondary care is however debateable, and prospective, pilot studies investigating models of community hepatology are warranted.

Whilst reasons for the improvements in outcomes associated with an HCC diagnosis cannot be extrapolated from these data, the potential implications of this are worthy of discussion. Despite recent policy and legislative shifts in the UK which mandate access to PC regardless of diagnosis,[183] persistent inequities in provision and availability of SPC for patients with non-malignant disease persist.[184] Retrospective observational studies from the USA, Canada and the UK consistently report that patients with non-malignant ESLD are seldom referred to SPC.[81, 109, 110] A potential reason for this, highlighted in chapter 2 of this thesis, may be the reluctance of physicians to instigate PC in cases where prognosis is uncertain. Hepatologists commonly perceived prediction of terminal decline in non-malignant liver disease as being more difficult. Indeed, there are no nationally or internationally recognised guidelines which support SPC referral in this group. This contrasts with international guidelines for the management of HCC, where definitions of curability and criteria for instigation of 'best supportive care' are clearly embedded.[16] Development of evidence-based models of care for patients with decompensated cirrhosis, which afford parallel access to both disease modifying interventions and PC, are required.

In this study 14.9% of patients died during their only hospital contact. This number appears alarmingly high and is suggestive of late diagnosis and sub-optimal access to care among an appreciable minority of patients. The figure adds weight to the argument that national screening programmes for cirrhosis in high risk populations are required.[251]

Strengths and Limitations

Issues with the accuracy and completeness of death certificate data are widely recognised.[252-254] HES data are based on coding which is typically performed by non-clinical staff, which has been shown to adversely affect data quality.[255] Studies have demonstrated difficulties with precise reproducibility of HES codes based on clinical records,[256] and it is inevitable that there will have been some inaccuracies.

Ascites develops in approximately 60% of patients with compensated cirrhosis over 10 years,[257] and we expected the proportion of patients undergoing LVP in their LYOL (30.8%) to be higher. A nationwide, US study of admissions secondary to cirrhotic ascites reported that diagnostic paracentesis (not LVP) was undertaken in 51% of cases.[258] There are no comparable studies with which to compare incidence of LVP. LVP is only required in cases of severe ascites and is not necessary in all patients. Nonetheless, omissions in HES coding may have resulted in some patients not being captured within our dataset. We used tariffs from a single financial year (2014) to enable accurate comparison between patients and to avoid the need to adjust with inflation indices. The disadvantage of this approach is that reported costs will not be reflective of the true costs for patients who died in 2013 or 2015.

Whilst we correct for a wide range of independent variables in our analysis, there are important factors which we do not consider that may have affected outcomes. Specifically, liver disease severity at presentation and the presence of co-morbidities have been reported to independently impact upon readmission and resource use.[27, 245] We analysed data from a cohort who died from cirrhosis, indicating a universally advanced disease stage; however, our dataset does not include these specific factors, nor the wider facilities available at individual healthcare institutions. This weakens the level of adjustment and creates potential for confounding. Corroboration through a prospective study would be required to fully adjust for these factors.

Nonetheless, this study represents the largest analysis of resource use and readmission in cirrhosis to date and is unique in its consideration of EOL outcomes. It provides insights into clinical, demographic, and organisational factors impacting quality of EOLC, and affords powerful data to support the cost-effective transformation of current care models.

CONCLUSION

The typical model of secondary care focusses upon reactive responses to urgent issues, as opposed to proactive management of chronic disease.[259] Cirrhosis is associated with high costs, readmission rates, morbidity and mortality. [39, 40, 208, 224, 260] As such, it represents a condition where changing traditional models of care delivery may confer considerable benefit, particularly towards the EOL. In this study, day-case services were associated with lower costs, reduced pressure on acute hospital services, and better outcomes in the LYOL. This is likely to reflect a superior clinical model, and expansion of day-case services is likely to be both cost effective and clinically beneficial. The presence of HCC was also associated with significant improvements in outcomes in the LYOL, providing further evidence that inequities in EOLC between patients with malignant and non-malignant liver disease exist. Evidence based clinical models which facilitate identification of patients with non-malignant end-stage disease and support subsequent improvements in their EOLC are required urgently.

CHAPTER 5

DEVELOPMENT OF A CLINICAL MODEL FOR INTEGRATING PALLIATIVE CARE INTO THE MANAGEMENT OF END-STAGE LIVER DISEASE

INTRODUCTION

Our qualitative study of patients with ESLD and bereaved carers (Chapter 3) demonstrated that existing hepatology services are often incompatible with the needs of patients towards the EOL. Management was centred in secondary care, with patients and carers often unaware of their prognosis and not afforded opportunities to express preferences about their future care. Our mixed methods study of hepatologists' attitudes (Chapter 2) highlighted commonplace difficulties in identifying patients who stood to benefit from PC, and identified concerns surrounding 'premature' SPC referral. A lack of formalised prognostication criteria was frequently cited as a barrier to initiating PC.

Whilst hepatologists recognised the potential benefits of PC for their patients, the unpredictable clinical trajectory of liver disease meant it was typically introduced late, or not at all. Hepatologists commented that there was a paucity of clinical frameworks through which PC could be delivered pragmatically. They described anxiety that PC interventions were mutually exclusive to ongoing active disease management. In our questionnaire study of hepatologists, the absence of established clinical frameworks was cited by as the second most important barrier to PC, behind 'lack of routine consideration'. Evidence-based models of care, which identify patients proactively at an appropriate stage of disease and offer PC interventions (in parallel to ongoing active management if necessary) are required.

The Gold Standards Framework is a widely used screening tool to identify patients who are likely to have a short life expectancy, and who may benefit from PC.[68] The Gold Standards Framework initially used the 'surprise question' ("would you be surprised if this patient died within the next year"), to screen for patients in whom PC may be required. It has since developed into a more sophisticated tool, which includes markers of functional decline and disease specific indicators. Whilst it includes guidelines for cardiac, pulmonary, renal and neurological disorders, criteria for liver disease are omitted.

Although Chapter 2 of this thesis reported that physicians' difficulties in confidently predicting terminal decline was a key barrier to timely PC, there are numerous scoring systems which predict prognosis in liver disease, including Child-Pugh-Turcotte and MELD, which are described in chapter 1. Common to all prognostic scores in liver disease, CTP and MELD were both designed and used to guide curative interventions (shunt surgery or LT respectively). To our knowledge, there is no prognostic score which has been validated to support physicians in making timely referral to SPC. The 2013 NHS document

'Getting it Right – Improving end of life care for people living with liver disease' listed evidence-based triggers which could be used by physicians to prompt EOL discussions (figure 5.1).[90] Nonetheless, these factors have never been formally validated in the context of triggering a PC intervention.

Figure 5.1 – 'Triggers' for SPC referral in ESLD – as described in 'Getting it Right – Improving End of Life Care for People Living with Liver Disease'.[69]

1. ≥1 unplanned hospital admission with decompensated in last 12 months
2. Liver disease severe enough to require LT (as assessed by prognostic scoring, e.g. MELD)
3. Decreasing performance status or function
4. Presence of ascites, hydrothorax or HE which is unresponsive to treatment
5. Deteriorating renal function
6. Episodes of spontaneous bacterial peritonitis, or severe infection
7. Recurrent variceal haemorrhage
8. HCC which is metastatic or progressive despite locoregional therapy
9. Ongoing alcohol consumption in survivors of acute alcohol related hepatitis

AIMS AND OBJECTIVES

Aim

This study addresses the fourth aim of this thesis which is to develop a clinical model of PC for patients with ESLD.

Objectives

Through using QI methodology and by retrospectively examining clinical records, the specific objectives of this study were to:

- Design a prognostic screening tool that identifies patients with ESLD who are at a high risk of dying over the coming year.
- Integrate use of the prognostic screening tool into the routine clinical assessment of patients admitted to hospital with a complication of cirrhosis.
- Design a supportive care intervention which could be offered to patients identified as having a poor prognosis, in parallel to their ongoing disease management.
- Optimise the applicability and acceptability of the clinical model through rapid-cycle testing within a clinical environment.

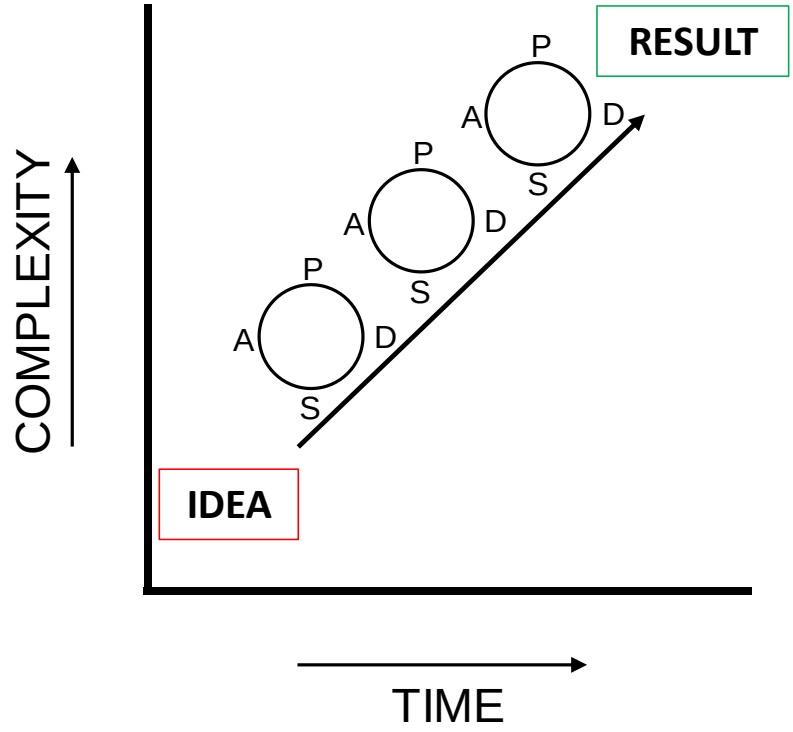
METHODS

Plan-Do-Study-Act methodology

Clinical research has traditionally involved trials of a pre-determined intervention, whilst attempting to control for variation or confounding factors (e.g. RCT). Whilst traditional approaches provide robust evidence, they are time consuming and resource intensive. The effects of any given intervention are unknown and there is therefore an implicit theoretical risk to participants, although it has been demonstrated patients cared for within studies typically have better outcomes than those outside them.[261] Furthermore, RCTs are not pragmatic in addressing the nuances of local issues. These limitations have, in part, contributed to the utilisation of QI methodology in healthcare over the last decade.[262]

QI methodologies originate from industry. Shewhart and Deming describe a four-stage iterative process – Plan-Do-Study-Act (PDSA).[263] An intervention is identified (plan), enacted (do), its impact examined (study), and modifications identified (act), prior to repetition of the cycle up until the point it is "fit for purpose" (figure 5.2).[264] In common with other scientific methodologies, PDSA cycles predict outcome, test and measure change, and assess impact on the outcome of interest. In contrast however they have key advantages, including rapid assessment of interventions (with flexibility to quickly modify following feedback), engagement of key stakeholders throughout the process (increasing the likelihood of eventual adoption of the intervention), and reduced costs. The small scale, iterative nature of each cycle means that local factors can be considered, risk to patients is reduced and tangible improvements in patient care can be made relatively quickly.[265]

Figure 5.2 Rapid-cycle Plan(P)-Do(D)-Study(S)-Act(A) methodology (adapted from McQuillan et al) [264]



Despite the theoretical and pragmatic advantages, systematic reviews of studies which have utilised QI methodology have consistently criticised a lack of rigour in the identification and reporting of hard clinical outcomes subsequent to implementation of interventions.[262, 266] What evidence there is suggests that interventions are more likely to be effective if they are multi-faceted, and able to adapt iteratively to local factors and unforeseen obstacles.[267, 268] Whilst no formal criteria for the publication of PDSA cycles currently exist, the SQUIRE guidelines (Standards for Quality Improvement Reporting Excellence) have been proposed as a potential framework for reporting in peer reviewed journals.[269] These guidelines explicitly include rapid-cycle PDSA methodology and are adhered to in the reporting of this study.

PDSA methodology was used in the design, implementation and validation of a poor prognosis screening tool in this study. Many of the factors associated with successful QI were present (engaged local clinical team and stakeholders, clear clinical objectives, pre-existing evidence base). Given the limitations of time and resource, a clinical trial would not have been pragmatic in this context.

Design, modification, and implementation of prognostic screening tool

The prognostic screening tool was designed for use amongst patients admitted to hospital with a pre-existing diagnosis of cirrhosis. We aimed to design a screening tool which would identify patients in

whom death was likely to occur within 12 months, in line with Gold Standards Framework criteria.[68] Key 'stakeholders' were involved at the commencement of the process and were consulted for feedback after each PDSA cycle. Each were involved in implementation and use of the clinical tool on a day-to-day basis. Collectively these individuals made up the 'steering group', which consisted of two consultant hepatologists, two consultant SPC physicians, six junior ward doctors, four ward nursing staff and four specialist nurses (three from hepatology, one SPC).

We did not aim to re-validate existing evidence-based prognostic scores for ESLD. Instead, we aimed to utilise existing criteria which were simple, objective and reproducible. We adapted prognostic criteria which had been identified in the 2013 NHS document 'Getting it right – improving end of life care for patients with liver disease' (see figure 5.1).[90] Following discussion amongst stakeholders, five of these criteria were selected and adapted. Criteria were selected on the basis of their ease of use, objectivity, and their importance as part of the wider clinical assessment of the patient. The criteria selected were: CTP Score C, two or more hospital admissions within the last 6 months, ongoing alcohol use in the context of known alcohol related liver disease (ArLD), unsuitability for LT, WHO Performance status 3 or 4. For patients who had not undergone formal transplant assessment, the presence of ongoing alcohol misuse in the context of previously diagnosed ArLD, age >75, and the presence of untreated extra-hepatic malignancy were used as surrogates for being unsuitable for transplantation.

Rapid-cycle PDSA methodology was utilised to integrate prognostic screening into the routine assessment of inpatients. In parallel with this, a PC intervention was developed. This intervention was informed by data from chapter 3 of this thesis, where a mismatch between the needs of patients with ESLD and the services available to address them was recognised. Identified areas of unmet need included having sufficient time within consultations to discuss prognosis, a focus upon symptom management (which was often side-lined at the expense of disease modification), an opportunity to express preferences regarding future care, and poor communication between primary and secondary care (meaning care was often centred within the hospital environment). Six PDSA cycles were undertaken over a 6-month period between March – August 2016. Modifications were suggested by stakeholders after each cycle and studied and observed over at least a 2-week period prior to further modifications being suggested. Stakeholder feedback was obtained using a proforma based on the worksheet recommended by the Institute for Healthcare Improvement (figure 5.3), and through regular meetings of the steering group.[270] Rates of correct completion of prognostic screening were audited after each cycle. The two streams were developed in parallel such that the PC intervention was made available to patients who had a positive poor prognosis screen on admission.

Figure 5.3

Stakeholder feedback sheet (modified from Institute for Healthcare Improvement).[252]

CYCLE NO ___	Poor prognostic screening tool	Supportive and palliative care intervention
Aim: What is our objective, and what should be the first (next) test of change.		
Plan: What is required to achieve this change? What is the predicted effect of the change?		
Do: What happened when you implemented the intervention/screening tool?		
Study: How did this compare to the predictions?		
Act: Are further modifications required for the next cycle? If so what?		

Validation of prognostic screening tool

Our study of hepatologists' attitudes to PC (chapter 2) indicated that clinical tools which ultimately triggered PC would be unlikely to be adopted in the absence of hard evidence that they were strongly predictive of death. Furthermore, whilst not wanting to miss potentially suitable patients, the resource implications and clinical appropriateness of including every patient admitted with liver disease also required consideration. The screening tool was therefore designed with the aim of identifying patients who were at risk of death within the next year. We did not attempt to supersede existing, well validated, prognostic scores for liver disease. We aimed to utilise this pre-existing evidence to help create a pragmatic clinical tool.

We calculated three simple tests of diagnostic accuracy for criteria within the tool: sensitivity, specificity, and positive predictive value (PPV). Sensitivity relates to the proportion of true positives (i.e. deaths within 1-year of admission), who are correctly identified by the test (i.e. positive screen from prognostic tool). Specificity relates to the proportion of true negatives who are correctly identified by the test.[271] The sensitivity and specificity however do not tell us the probability that the 'test' (prognostic screen) will give a correct 'diagnosis' (death within 1 year). For this, a PPV is required. This relates to the proportion of patients who have a positive poor prognostic screen, who go on to die within the next year.[272] All these values are proportions, and as such confidence intervals were calculated using standard methods for proportions and their differences.[273]

We used a local database which captures all admissions at University Hospitals Bristol in patients with a pre-existing diagnosis of cirrhosis. Consecutive patients admitted over two distinct 90-day periods were identified retrospectively (periods commencing 1st July 2013 and 1st November 2014). Two distinct periods were used to reduce potential variability (e.g. with season/clinician) and to improve validity. Clinical and electronic records for each patient were retrieved and scrutinised. The presence or absence of the five selected criteria were assessed by two independent physicians at the point of the index admission to hospital within the study period. Junior doctors (within four years of qualification) were chosen as the physician assessors, to reflect the seniority of doctor who would be filling out the proforma following its implementation. A random selection of 10 clinical records were reviewed by a consultant hepatologist (blind to previous clinicians' scoring) to ensure that scores were being attributed accurately – no discrepancies in score were identified. If scores were not consistent between clinicians, or there was insufficient information in clinical records to provide a score, patients were excluded from analysis. Mortality one-year from the date of index admission was determined using the hospital's electronic database. For patients admitted more than once within the 3-month period the chronologically first admission was assessed (i.e. each patient counted once only). The predictive value of individual criterion, cumulative scores (e.g. total score of 3 criteria or above), and combinations of commonly positive criteria,

were calculated through determination of sensitivity, specificity and PPV for death one year following admission.

Ethical Issues

Approval for this study was granted by the local clinical audit department at University Hospitals Bristol, with whom the project was registered. As the study utilised QI methodology, formal ethical review was not deemed necessary.

RESULTS

Determination of trigger for intervention and validation of prognostic score

In total 83 patients, 51 from period A (31st July – October 29th, 2013) and 32 from period B (1st November 2014 – January 30th, 2015), were admitted to University Hospitals Bristol with a pre-existing diagnosis of cirrhosis. Ten were excluded from analysis. All exclusions were due to there being insufficient clinical information recorded within the notes to accurately calculate a prognostic score. There were no discrepancies in allocation of score between the two independent physician assessors for any patient. Patient demographics are summarised in table 5.1.

Table 5.1 – Demographics of patients used to validate prognostic score

		Period A (31.07.13–29.10.13)	Period B (1.11.14–30.1.15)	Overall
Patients admitted		51 (61.4)	32 (38.6)	83 (100.0)
Patients excluded from subsequent analysis*		7 (13.7)	3 (9.4)	10 (12.0)
Patients included in analysis		44 (86.3)	29 (90.6)	73 (88.0)
Male		42 (82.4)	24 (75.0)	66 (79.5)
White British ethnicity		44 (86.3)	27 (84.3)	71 (85.5)
Primary cause of liver disease	Alcohol	35 (68.6)	19 (59.4)	54 (65.1)
	NASH	11 (21.6)	9 (28.1)	20 (24.1)
	Viral	3 (5.9)	3 (8.6)	6 (7.2)
	Autoimmune	2 (3.9)	0 (0.0)	2 (2.4)
	Other	0 (0.0)	1 (3.1)	1 (1.4)
Median age at admission (IQR)		53 (42-69)	57 (46-70.5)	54.5 (47-66)
Death within 1 year of admission date		27 (52.9)	14 (43.8)	41 (49.4)

* Excluded patients: All excluded from subsequent analysis due to insufficient clinical information recorded to retrospectively apply prognostic score. Demographics: Male 8/10 (80%), White British 7/10 (70%), Median age 69 (IQR 49-82), ArLD 8/10 (80%), NASH 2/10 (20%), Death within 1-year 5/10 (50%).

The predictive capacity of each prognostic criteria, cumulative scores, and combinations of commonly positive scores were calculated (table 5.2)

Table 5.2 – Predictive value of prognostic criteria for 1-year mortality following index admission						
Prognostic criteria	**n (%)**	**Died n (%)**	**Alive n (%)**	**Sens (95% CI)**	**Spec (95% CI)**	**PPV (95% CI)**
CTP C	36 (49.3)	28 (77.8)	8 (22.2)	77.8 (60.8 - 89.9)	78.4 (61.8-90.2)	77.8 (60.8 - 90.0)
Unsuitable for transplant	62 (84.9)	34 (54.8)	28 (45.1)	94.4 (81.3-99.3)	24.3 (11.8-41.2)	54.8 (41.7-67.5)
WHO Performance status 3 or 4	14 (19.2)	11 (78.6)	3 (21.4)	30.6 (16.3-48.1)	91.8 (78.1-98.3)	78.6 (0.49 - 0.95)
Continuing alcohol usage (in ArLD)	44 (60.3)	25 (56.8)	19 (43.2)	69.4 (51.8-83.6)	48.6 (31.9-65.6)	56.8 (41.0 - 71.7)
>2 admissions within last 6 months	7 (9.6)	4 (57.1)	3 (42.8)	11.1 (3.1-26.1)	91.8 (78.1-98.3)	57.1 (18.4 - 90.1)
Cumulative prognostic score ≥ 2	57 (78.1)	33 (57.9)	24 (42.1)	91.7 (77.5-98.2)	35.1 (20.2-52.5)	57.9 (44.1 - 70.1)
Cumulative prognostic score ≥ 3	32 (43.8)	26 (81.3)	6 (18.8)	72.2 (54.8-85.8)	83.7 (68.0-93.8)	81.3 (63.6-92.8)
Cumulative prognostic score ≥ 4	7 (9.6)	6 (85.7)	1 (14.3)	16.7 (6.3 - 32.8)	97.3 (84.8 - 100.0)	85.7 (42.1 - 99.6)
CTP C + continuing alcohol	24 (32.9)	21 (87.5)	3 (12.5)	58.3 (40.8-74.4)	91.8 (78.1-98.2)	87.5 (67.6-97.3)
CTP C + any other prognostic criteria	34 (46.6)	28 (82.4)	6 (16.7)	77.8 (60.8 - 89.9)	83.8 (68.0-93.8)	82.4 (65.4 - 93.2)
Total	73 (100.0)	36 (49.3)	37 (50.7)	-	-	-

Design and implementation of tool (PDSA cycles)

The steering group considered the following criteria as acceptable 'triggers' for implementation of the PC intervention: CTP-C disease, a cumulative prognostic score of 3 or above, the presence of CTP-C disease in the presence of at least one other poor prognostic criteria. This was agreed based on each having approximately equivalent predictive value for 1-year mortality (table 5.2). Following feedback from junior ward doctors and nursing staff (who would be completing the screening), a cumulative prognostic score of 3 was chosen as the trigger. This was largely because it was felt that documentation of each criteria formed an important part of the wider clinical assessment of each patient, and the tool acted as a useful prompt for this.

Six PDSA cycles were completed subsequent to this decision (figure 5.3). The screening tool was initially displayed as a wall chart, however it was seldom filled in and so was added to the agenda of the weekly multi-disciplinary team (MDT) meeting. Confusion expressed by junior doctors regarding accurate completion of scoring led to production of objective guidelines, which were made available via the hospital intranet, and ultimately printed on the back of the finalised MDT proforma. Inconsistencies in documentation of MDT discussions in medical notes resulted in production of a printed MDT proforma for each patient, which also improved consistency in written records. Ward nursing staff fed back that it would be useful to add a section on escalation of care decisions within this proforma. They also described the sheets as being difficult to locate within the medical notes, meaning important clinical information was difficult to find out of hours. As a result, the sheets were coloured blue, and sited at the front of each patient's notes. The final MDT discussion sheet continues to form part of the standard documentation for patients admitted with a diagnosis of cirrhosis to University Hospitals Bristol (figure 5.4). Three months after its finalisation, an audit (performed over 4 weeks) demonstrated accurate and full completion in 24/27 (88.9%) of cases. This compared with 2/9 (22.2%), two weeks following completion of the first PDSA cycle.

A PC intervention was developed in parallel with the screening tool. Whilst views and expertise from all members of the steering group were considered, this was led by SPC professionals who were able to utilise experiences of successful interventions in other disease areas. Due to concerns surrounding the terminology 'palliative', elicited in chapter 2 of this thesis, 'supportive care' was adopted to describe the intervention. Initially a consultant hepatologist-led discussion with the patient and their family surrounding prognosis and ACP was suggested for all patients who screened positive. Initial feedback from consultant hepatologists highlighted a skills gap in the advanced communication skills required to lead such discussions (consistent with the qualitative and quantitative research presented in chapter 2 of this thesis). This led to organisation of training sessions with SPC consultants and nurses. A poor prognosis letter, sent to the patient's GP on discharge, was introduced to improve continuity of care and

communication between primary and secondary care. Consultant hepatologists commented that they sometimes struggled with managing complex symptom control issues. As a result, a consultation with SPC was made available when requested. Doctors of all grades commented that patients were commonly requesting an ongoing point of contact following discharge from hospital (after the poor prognosis discussion). As a result, each patient who received the supportive care intervention was allocated a named hepatology specialist nurse, who knew their case, and who they could contact following discharge. The parallel development of the prognostic screening tool and supportive care intervention is summarised in figure 5.4.

Description of the finalised supportive care intervention

In 2014, through a process of expert consensus, the 'Template for Intervention Description and Replication' (TIDieR) guideline was published as a means to improve the completeness of reporting and replicability of new clinical interventions.[274] This guideline includes a 12 item 'checklist', against which the final version of the supportive care intervention is described here.

The intervention (referred to as the 'supportive care intervention') was designed to provide a package of clinical care which could be offered to patients with cirrhosis who had been identified (through use of the aforementioned poor prognostic screening tool) as having a high chance of dying within the coming 12 months. The need to develop this intervention arose from a paucity of pre-existing frameworks through which PC could be delivered to this population. This was highlighted in chapter 2 of this thesis.

The intervention consists of five parts. The first is a poor prognosis discussion between the patient (alongside their next of kin/carer if possible) and their primary consultant, who would usually be a hepatologist or gastroenterologist. This is undertaken in a private side room or outpatient consultation room and without interruption. The objective of this discussion is to explain the prognosis and discuss any uncertainties around this, explain the plan for ongoing treatment and to answer any questions. In our experience, these discussions typically lasted for approximately 30 minutes. The second part consists of a letter sent to the patient's GP (with the patient copied in), summarising the content of the poor prognosis discussion and explaining the key outcomes and decisions arising from it. Whilst not mandated, an example structure for such a letter which could be adopted can be accessed using the following url: http://www.swscn.org.uk/wp/wp-content/uploads/2018/02/Poor-Prognosis-Letter-Project.pdf. The third part of the intervention affords the patient an opportunity to express preferences for future care via a formal process of advance care planning. This offer will not be taken up by all patients. When applicable, this is undertaken during a face to face or telephone consultation, typically lasting 30-60 minutes. An objective of this process is to produce a mutually agreed formal document, copies of which are kept within the patient's medical notes and GP records. The patient is also offered a copy of the document. Examples

of features sometimes included within advance care planning documents included: whether there was a preference to avoid hospital admission in the event of clinical deterioration, agreed ceilings of care for future hospital admissions, any interventions (e.g. emergency endoscopy) for which the patient had explicitly denied consent. Advance care planning can be undertaken with any appropriately qualified healthcare professional involved in the patient's care. In University Hospitals Bristol however, this was typically done with either the allocated hepatology specialist nurse, consultant hepatologist, SPC nurse or SPC consultant (or any combination of the above). The fourth part was the offer of a separate face to face consultation with a specialist (nurse or doctor) in palliative medicine to address issues of symptom control. This was necessary only for patients with complex symptom control needs. When required, a 1-hour outpatient or inpatient consultation was provided, with further follow up offered if necessary. The final part of the intervention (applicable to all patients) involves a named hepatology specialist nurse being allocated explicitly to the patient. The allocated hepatology specialist nurse facilitates co-ordination and continuity of care and enables the social and psychological needs of patients and families to be addressed iteratively. A single point of access for patients and their families is provided via a telephone helpline with an answerphone (and call back) facility. To provide this element of the intervention an overall hepatology specialist nurse workforce sufficient to provide a call back service during working hours (Monday to Friday) is required. The modifications made to the intervention as it was developed are described above. This is a novel intervention, and as such the extent to which the intervention was delivered 'as planned' is not yet reported, however it is being assessed in a current study.

Figure 5.4 – Summary of PDSA cycles leading to introduction of prognostic screening tool and supportive care intervention

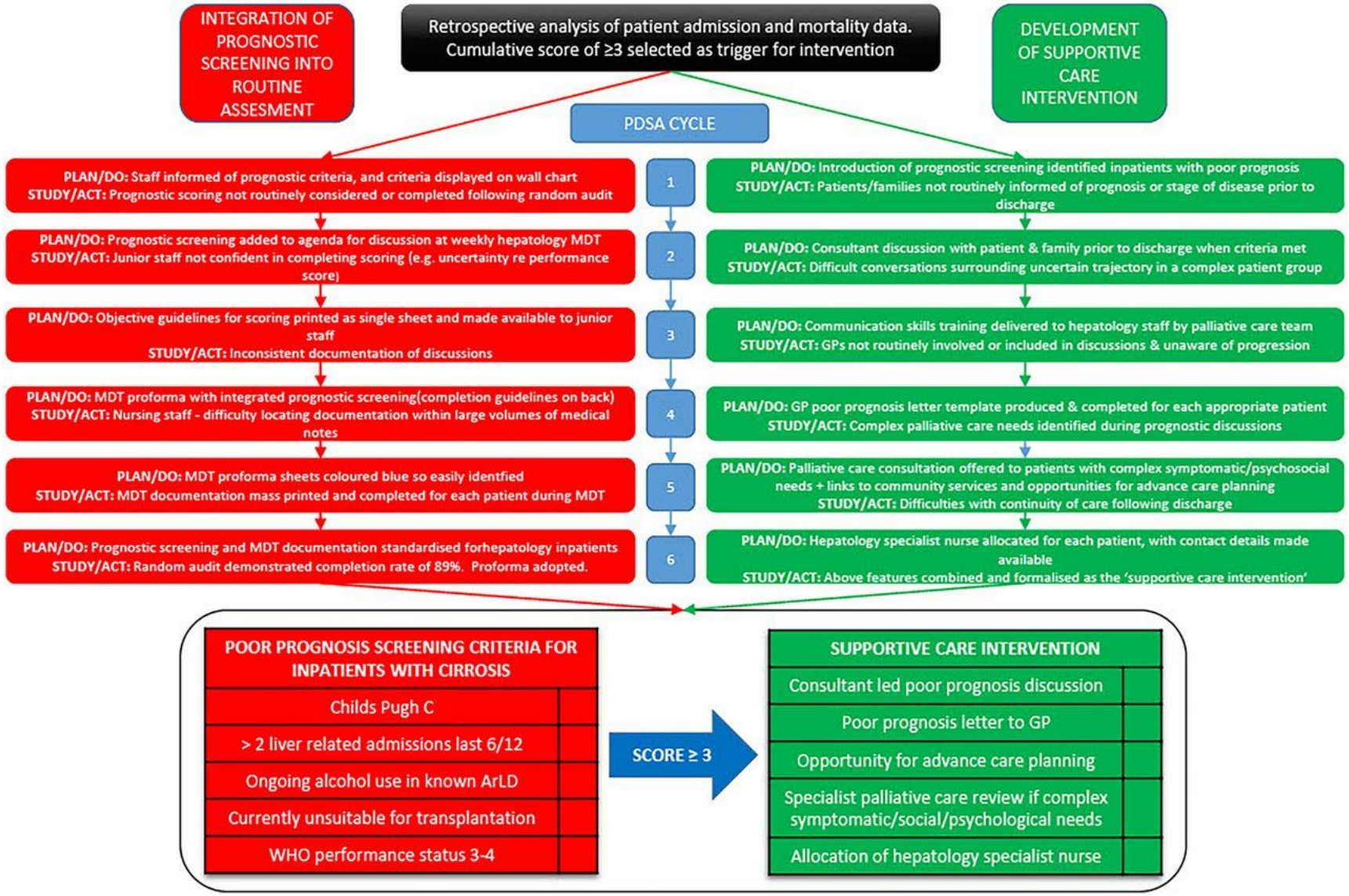


Figure 5.5 – Final MDT proforma, including guidelines for completing poor prognostic score (back of sheet)

LIVER MDT Date: _____

Patient name: _____
Patient number: _____
Date of admission: _____
Consultant in charge: _____

Primary Diagnosis:

- ☐ Cirrhosis (UKELD score =__)
- ☐ Varices
- ☐ Encephalopathy
- ☐ Ascites
- ☐ Addiction issues

Current Issues:

Discussion and plan:

Ceiling of care:

- ☐ Full
- ☐ Ward-based
- ☐ Symptomatic

Poor prognosis screening: **cirrhotic patients only**	
Criteria	Tick
Child Pugh Grade C	
> 2 liver-related admissions last 6 months	
Ongoing alcohol use (ARLD patients)	
Unsuitable for transplant work-up	
WHO performance status 3-4	

Total score:	
If total score > 2, consider:	
Poor prognosis discussion with patient/family	
Poor prognosis letter to GP	
Advance care planning discussions	
Specialist palliative care referral	
Allocation of hepatology specialist nurse	

COMPLETED BY: .....
SIGNED: .....
GMC NUMBER: .....

Calculating the Child Pugh Score for Cirrhosis Mortality	Parameter	Points assigned		
		1	2	3
	Ascites	Absent	Mild	Moderate-Severe
	Encephalopathy	None	Grade 1-2	Grade 3-4
	Bilirubin (micromol/L)	<34.2	34.2 – 51.3	>51.3
	Albumin (g/L)	>35	28-35	<28
	INR	<1.7	1.7-2.3	>2.3

Child Pugh A	5 – 6 points	100% 1 year survival
Child Pugh B	6 – 9 points	81% 1 year survival
Child Pugh C	> 10 points	45% 1 year survival

West Haven Grading of Encephalopathy	
Grade	**Criteria**
1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
2	Lethargy or apathy
	Minimal disorientation of time or place
	Subtle personality changes
	Inappropriate behavior
	Impaired performance of subtraction
3	Somnolence to semi-stupor but responsive to verbal stimuli
	Confusion
	Gross disorientation
4	Coma

WHO performance status	
0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of the time
3	Capable of only limited self-care Confined to bed or chair >50% of the time
4	Completely disabled. Cannot carry out self-care. Totally confined to bed or chair

Suitability for liver transplant assessment

A patient's current suitability for liver transplant assessment and work up is multifactorial and complex. Decisions regarding this are made at consultant level with support from the MDT.

There are however some clear factors which, when present, render patients unsuitable at the current time, and for whom "unsuitable for transplant work up" can be ticked on the poor prognosis scoring criteria:

- Ongoing alcohol use in the context of previously diagnosed alcohol related liver disease
- Ongoing disruptive substance abuse
- Untreated malignancy (not including HCC)
- Life expectancy < 1 year due to non-hepatic co-morbidity
- Age >75 (unless exceptional circumstances)

DISCUSSION

Summary of main findings

This study presents a clinical model which utilises a prognostic score to trigger a supportive care intervention for patients admitted to hospital with cirrhosis who are at a high risk of dying within the next year. Retrospective analysis demonstrates that the presence of three or more poor prognostic criteria (as defined within the tool) on admission has a PPV for death within one year of 81.3% (95% CI: 63.6%-92.8%). Whereas many established models for predicting mortality in liver disease exist, these are all designed with the purpose of identifying patients for curative or therapeutic interventions.[30-32] To our knowledge, this is the first clinical tool which utilises prognostic criteria to trigger a supportive care intervention among patients with cirrhosis.

Retrospective data from two cohorts of patients with cirrhosis admitted over two distinct periods demonstrate a heavy burden of disease. Overall 1-year mortality was high (41/83 – 49.4%), and there was a high prevalence of advanced liver disease (36/73 – 49.3% CTP-C), and ArLD (54/83 – 65.1%). Although data were collected from a single site, demographics were broadly consistent with wider estimates of the UK liver disease population, being that the cohort was young (median age = 54.5, IQR 47-66), predominately white (71/83, 85.5%) and predominantly male (66/83, 79.5%).[5, 275] Data describing socio-economic status were not collected.

Our prognostic score adapted five, previously described, binary criteria, outlined in the 2013 NHS document 'Getting it Right – Improving end of life care for people living with liver disease'.[90] Calculation of sensitivity, specificity and PPV showed CTP-C disease to be the best performing individual criterion (sensitivity 77.8% (60.8 – 89.9), specificity 78.4% (61.8-90.2), PPV 77.8% (60.8-90.0)). The predictive value for CTP-C disease was enhanced either through combination with another prognostic criteria, or as part of a cumulative prognostic score. CTP-C disease, a cumulative score of 3 or above, and the presence of CTP-C disease in the presence of at least one other poor prognostic criteria each had excellent (and approximately equivalent) ability to identify patients at high risk of death over the coming year. Whilst our model utilised a cumulative prognostic score of 3 or above as its trigger for intervention, this decision was made on the basis of local factors, and other units adopting the principle of prognostic screening may wish to adapt this. Notwithstanding the need for flexibility relating to local factors, inclusion of a CTP score within screening criteria did appear to improve predictive ability substantially.

Through close liaison with key stakeholders locally using rapid-cycle PDSA methodology, we were able to integrate the clinical model into routine practice locally. 24/27 (88.9%) patients received full and accurate implementation of the screening tool (+/- supportive care intervention) in an audit undertaken

over 4 weeks, 3 months after its final implementation. Parallel development of a supportive care intervention, informed in part from data reported elsewhere in this thesis, resulted in the following 'care bundle' being initiated for patients who screened positive for poor prognosis: a consultant hepatologist-led poor prognosis discussion with the patient and their family, a poor prognosis letter sent to the GP informing them of current management and expectations for treatment, involvement of the SPC team to review current symptom control, an opportunity for ACP, introduction and involvement of a hepatology specialist nurse (whose contact details were made available following discharge). A rolling programme of training in advanced communication skills, delivered by the SPC department for hepatology staff of all grades, is ongoing.

Comparison with existing literature

Whilst there is no comparable prognostic tool in hepatology with which to compare our model, prognostic screening tools for hospital inpatients exist outside the field of liver disease. O'Callahan et al prospectively assessed 501 hospital inpatients at New Zealand teaching hospital using the Gold Standards Framework prognostic indicator guidance, as assessed by two SPC physicians.[276] They reported sensitivity, specificity and PPV of 62.6%, 91.9%, and 67.7% respectively. Whereas our prognostic criteria are objective there is a degree of subjectivity in application of Gold Standards Framework criteria. A study using the 'surprise question' as a means of prognostic screening in patients with end-stage renal disease undergoing peritoneal dialysis, found one-year mortality to be 24.8% in the "no" group, vs 6.6% in the "yes" (PPV = 24.8%).[277] A community based study of patients with heart failure found that neither the Gold Standards Framework nor an alternative model (Seattle Heart Failure Model), accurately predicted which patients were in the LYOL.[278] The predictive value of our tool compares favourably to each of these examples, although it was assessed retrospectively meaning there was a risk of information bias.

The high one-year mortality (41/83, 49.4%) among all patients admitted to hospital acutely with cirrhosis in our study is consistent with estimates in the wider literature.[279, 280] In this context it could be argued that prognostic screening is moot, and that all patients admitted with a complication of their cirrhosis should be afforded supportive care interventions, particularly if such interventions have the capacity to run in parallel with curative care. A recent Scottish study demonstrated that almost 30% of all hospital inpatients died within a year of admission, suggesting that such an approach could even be considered in a wider context.[281] Current evidence however suggests that, in the absence of a pre-defined trigger, PC interventions are rarely initiated, both in patients with liver disease and more widely. The frequent inability of individual physicians to recognise and discuss poor prognosis has been cited as an argument for a more systematic and rigourous approach to prognostic screening for hospital inpatients.[282]

Phoolchund et al retrospectively reviewed 106 consecutive patients who had been declined for LT following assessment, or delisted due to clinical deterioration.[109] Only 17/106 (19%) had any form of PC input, a median of 4 days before death. Other international studies reached similar conclusions. Poonja et al, retrospectively analysed 102 patients removed from the Canadian liver transplant list and reported that, despite a median survival of only 59 days, only 10% were referred to SPC.[81] Both studies were limited methodologically by being retrospective, single centred, and including only patients under the auspices of a LT programme (and therefore representative of a minority of the overall liver disease population). Patients delisted from a transplantation programme are likely to represent a group in whom the high likelihood of death is more easily recognised, and it is possible that PC interventions are less common still among unselected patients with ESLD.

These findings are also consistent with chapter 2 of this thesis. In the questionnaire study of UK hepatologists, lack of routine consideration, and the absence of pre-existing clinical models were the two most highly ranked barriers to PC – suggesting both the need for a routine PC referral trigger, and a 'care bundle' which could be subsequently offered to patients. Qualitative data also highlighted uncertainties around accurately predicting terminal decline as a key barrier to SPC referral – with anxieties around "wrongly" referring patients with reversible disease commonly expressed. Whilst our supportive care intervention was designed explicitly to run in parallel with ongoing active management if necessary, these data suggest that our scoring system being strongly predictive of 1-year mortality may increase uptake amongst the wider hepatology community.

Most previous models of PC delivery for patients with ESLD have been designed around patients delisted or declined for LT, and are therefore not directly comparable to this study.[124-127] A feasibility study into the use of a dedicated 'supportive care liver nurse' to co-ordinate care for patients with ESLD was published recently (subsequent to publication of the peer-reviewed paper arising from this chapter).[283] Patients were also recruited following an inpatient admission with ESLD, and the role of the supportive care liver nurse was largely similar to that of the allocated hepatology specialist nurse in our model. The intervention was examined prospectively using questionnaires, interviews and case note analysis, and proved to be welcomed by patients, carers and healthcare professionals alike, as well as improving communication between primary and secondary care. Whilst it is likely that our model will have resulted in similar benefits, we did not obtain prospective data to robustly support this assertion. A RCT of the supportive care liver nurse by the same group is being planned following this feasibility study.

Strengths, Limitations, and implications for practice and research

To my knowledge, this study presents the first clinical model for patients admitted to hospital with cirrhosis, that routinely screens for factors pertaining to poor prognosis, and implements a supportive care

intervention for those with an objectively high risk of death within one year. It reconciles some of the hepatologists' barriers to PC highlighted in chapter 2 of this thesis, specifically in objective identification of patients with poor prognosis, and in providing a framework for their ongoing care. Equally, it allows ongoing disease-modifying therapies to continue in parallel, taking account of commonly expressed fears of "premature" SPC referral. Indeed, during the evolution of the model, some patients were identified simultaneously as being candidates for LT.

Nonetheless, limitations in the methodology and design impact on how generalisable the model is to other clinical settings. Although there were no discrepancies in scoring between the physicians who independently reviewed clinical records, the data were examined retrospectively. Clinicians assessing the patient prospectively, and in a busy clinical environment, may have attributed scores differently. Both retrospective data collection, and the QI project, were undertaken at a single UK site. Whilst our patient demographics were broadly comparable to wider UK estimates for liver disease, there will inevitably be unidentified factors which are specific to the Bristol catchment area.[5, 275] Furthermore, the QI work revolved around pre-existing local clinical structures (for example, a weekly liver MDT meeting), meaning the model would need a period of local adaptation wherever it was introduced – limiting its transferability. Our model only looked at patients admitted to hospital and has not been trialled or validated in an outpatient setting, again limiting its breadth.

A recent systematic review of QI methodology criticised many published works for failing to collect data between PDSA cycles, and statistically analyse the impact of each change iteratively.[265] Although simple audit data on rates of completion of the prognostic tool was recorded after each cycle, no equivalent outcome measures were determined for the supportive care intervention. Whilst the clinical team universally felt patients were receiving better care as a result of the tool, there were no patient data to support this assertion (e.g. qualitative interview, readmission rates, QOL scores etc). As such, this study fails to provide hard evidence that introduction of prognostic screening and a supportive care intervention actually improves quality of care or patient experience.

Further work is required, both to validate the prognostic screening tool prospectively, and also to demonstrate that it is transferable to different sites and clinical contexts. The supportive care intervention also requires prospective evaluation to demonstrate whether it improves clinical outcomes at the EOL for patients dying from liver disease, and their families.

CONCLUSION

PC interventions are seldom afforded to patients with ESLD. This is in part due to physician difficulties in identifying patients who stand to benefit, and a paucity of clinical models available for providing supportive care in this group. The clinical model presented in this study provides a template through which patients at risk of dying within the next year can be routinely identified. It describes a supportive care intervention, developed using QI methodology. Although the supportive care intervention was informed by previous qualitative work presented elsewhere in this thesis, we cannot conclude that introduction of this clinical model improves clinical outcomes or quality of life, and further prospective evaluation is required.

This clinical model remains in use at University Hospitals Bristol. Since the publication of the manuscript which arose from this chapter a version of this model has been adopted by at least seven NHS trusts throughout the UK.[284]

CHAPTER 6

DISCUSSION AND CONCLUSIONS

Context of thesis

This thesis considers the provision of PC for patients with ESLD through examination of the perspectives of patients, carers and healthcare professionals, scrutiny of high-level national databases, and utilisation of quality improvement (QI) methodology to propose a model of integrated care. When I began this research in 2015, few hepatologists took an active interest in this field, and there was a paucity of data to support clinical practice. Deficiencies in EOLC were being increasingly recognised nationally, and SPC was beginning to assume a more prominent role in the wider political agenda. In May 2015, a report entitled 'Dying without Dignity', published by the Parliamentary and Health Service Ombudsman, outlined failures and inequities in the provision of SPC across England.[285] This was shortly proceeded by the first reading of the 'Access to Palliative Care Bill' in the House of Lords, which aimed to legislate for universal access to PC for all who required it towards the EOL.[286] Around this time, a Lancet commission on liver disease was established, primarily to address the dramatic increase in deaths from liver disease in the UK over the past 40 years.[1] In its first implementation report, also published in 2015, the commission highlighted the *"parallel role [of hepatologists/gastroenterologists] in prolonging life through optimum disease focused treatment and in providing high-quality palliative care for those whose lives cannot be saved".*[287] This thesis, and the peer-reviewed publications and presentations arising from it, therefore contribute to the field at an important juncture in the evolution of PC for patients with ESLD and address important clinical questions which have been hitherto overlooked.

Summary of findings against stated aims

At the start of this thesis I outlined four aims, based around unanswered questions arising from the existing literature. Each aim was addressed sequentially in subsequent chapters. Here, I summarise the main findings from each chapter, against these stated aims.

Aim 1 - To identify the existing barriers to integration of PC in the management of ESLD

The first aim arose from multiple studies which reported that referrals to SPC for patients with ESLD occurred infrequently and late. [81, 109-112] Whilst consistent in their conclusions, these studies failed to explore potential reasons for this observation. Identifying the barriers to PC for patients with ESLD was considered important for the design of future clinical models which sought to overcome them.

Chapter 2 investigated the attitudes and practices of UK hepatologists towards the use of PC in ESLD and explored barriers to PC. Responses to an on-line questionnaire demonstrated significant inequities in the use of SPC, with patients with malignant liver disease much more likely to be referred regardless of overall prognosis. A minority of questionnaire respondents felt PC was appropriate when there remained a possibility of cure, and inherent uncertainties in the trajectory of ESLD were therefore widely considered prohibitive to timely PC. Whilst the majority of respondents felt there was a role for SPC in the management of ESLD, most agreed that it was never routinely considered. The absence of evidence-based clinical models, which identified patients who stood to benefit and provided a framework for their ongoing management, was frequently cited as a barrier to PC. Ten respondents from the questionnaire study were purposively selected for in-depth qualitative interview. Analysis of data from these interviews demonstrated widespread recognition of extensive PC needs in patients with ESLD but highlighted several barriers. Participants described difficulties in predicting clinical trajectory and were anxious about "prematurely" referring patients to SPC, which was often considered to be mutually exclusive to ongoing active disease management. Concerns were expressed about the term "palliative", with its perceived connotations around death and dying. Participants feared their patients may lose hope and that input from other medical specialties would be curtailed inappropriately. Participants felt inadequately trained to provide PC themselves, however described existing SPC services as stretched. This combination of structural, disease-based and attitudinal barriers led to a perception that PC was inaccessible to hepatologists within the sample – who often felt unable to provide PC for their patients, despite explicit recognition of its potential benefit. The need to develop novel clinical models to address this was universally recognised.

In summary, the key barriers to SPC for patients with ESLD identified through this chapter were as follows: i) perceptions that SPC was generally reserved for patients with malignancy, ii) physician difficulties in predicting trajectory and identifying patients who may stand to benefit from PC, iii) negative connotations of the term 'palliative', iv) skills and training gap among hepatologists, v) structural and resource limitations, vi) lack of recognised clinical models which integrate PC into the ongoing management of ESLD.

Aim 2 – To understand the PC needs of patients with ESLD and their carers, ascertain how existing services meet these needs, and explore the attitudes of patients and carers towards PC (chapter 3)

There is a paucity of published literature describing the lived experience of ESLD outside the field of LT. Furthermore, no study had addressed specifically how existing health services met the needs of patients with ESLD and their carers towards the EOL or explored their attitudes towards PC. Attention to these issues was considered necessary for the design of a patient-centred model of PC in ESLD.

This aim was addressed principally in chapter 3 of this thesis, through an in-depth qualitative interview study of 12 patients with refractory ascites and five carers who had been recently bereaved by ESLD. Thematic analysis of the data revealed that an accumulating complex of physical and psychological symptoms were frequently compounded by worsening social isolation, financial insecurity and an ever-increasing logistical burden of hospital appointments. Participants were heavily reliant on secondary care, and GPs were frequently bypassed. Physician encounters were perceived as being time pressured, with strategies for active disease management typically prioritised over discussions of prognosis and symptom control. Attitudes towards the central tenets of PC were generally positive, particularly in relation to the increased focus on symptom control and opportunities for ACP (especially in relation to the avoidance of hospital admission at the EOL). Nevertheless, some participants feared that the explicit instigation of PC would result in a loss of hope. Improved symptomatic management, longer consultation times, assistance with financial and logistical issues, and improved bereavement support were identified as ways through which existing care models could be improved. A mismatch between the healthcare services available to patients with ESLD and their PC needs was identified, leading to the emergence of incompatibility as a unifying theme.

Aim 3 – To assess existing patterns of health-service usage in patients with ESLD in the LYOL and identify the factors associated with improved clinical and economic outcomes towards the EOL (chapter 4)

Understanding the patterns of cost and health-service utilisation among patients with ESLD towards the EOL is necessary to inform optimum design of future services and support appropriate resource allocation. The absence of such data within the existing literature led to the creation of the third aim, which was addressed in chapter 4. Three national datasets were linked to enable analysis of data from the LYOL of patients who died from ESLD with ascites between 2013-2015. The relationships between demographic, clinical, and service factors (including enrolment in day-case large-volume paracentesis (LVP) services) and economic and health-care outcomes in the LYOL were investigated using multivariable regression models.

As well as demonstrating the high economic and health-service burdens associated with ESLD in the LYOL, regression analyses were able to identify the factors most associated with improved economic and clinical outcomes. Two strongly significant associations were observed. The first related to a global improvement in outcomes seen among patients enrolled in a day-case LVP service. This effect appeared to be ‘dose-dependent’ in that, among patients enrolled in day-case services, outcomes improved further as the proportion of care delivered within a day-case setting increased. Future models of care which utilise this approach (potentially in community settings) are likely to be cost saving and reduce pressures on acute hospital services. The second related to a substantial and significant inequity between patients dying

from HCC as compared to those dying from non-malignant ESLD. Deaths caused by HCC were associated with lower costs, fewer inpatient bed days, and a significant reduction in the probability of unplanned hospital death. This finding raised questions around the differences in care provided for these two groups of patients towards the EOL.

Aim 4 – To develop a model of PC for patients with ESLD (chapter 5)

The final, and unifying, aim of this thesis looked to propose a pragmatic and transferable clinical model of PC for patients with ESLD. The absence of established models was recognised in chapter 2 as a key barrier to PC in ESLD. This related in part to physician difficulties in identifying patients who stood to benefit from PC interventions, and in the lack of routine consideration of PC in the management of ESLD. Furthermore, descriptions of what constituted a PC intervention for patients with ESLD (outside the field of LT) were lacking in existing literature.

Clinical records from two distinct cohorts of patients admitted to hospital with cirrhosis were analysed retrospectively against five poor prognostic criteria.[90] The presence of three or more poor prognostic criteria on admission (CTP-C liver disease, 2 or more admissions in the prior 6 months, ongoing alcohol use in the context of known alcohol-related liver disease (ArLD), unsuitability for LT, and World Health Organisation (WHO) Performance status 3 or 4) had a PPV for death at 1-year of 81.3%.

Chapter 3 of this thesis highlighted a mismatch between the PC needs of patients with ESLD and the services available to address them. It also identified facets of care which could be improved upon. This was used as a starting point for the design of a PC intervention, which was developed using QI methodology. This process resulted in the production of a 'supportive care bundle', consisting of a consultant led prognostic discussion, a poor prognosis letter to the patient's GP, an opportunity for ACP, a SPC referral if required and the allocation of a named hepatology specialist nurse as a future point of contact and to co-ordinate ongoing clinical care. This intervention was afforded to all patients who had positive poor prognostic screen on admission (i.e. the presence of 3 poor prognostic criteria as outlined above). In addition to ongoing use at University Hospitals Bristol, the poor prognostic screen and supportive care intervention have since been adopted by several other hospital trusts within the UK.

Unifying themes from the thesis

The cost of ESLD to the individual and society and the questionable value of current healthcare

Data from across the thesis reinforce the considerable costs associated with ESLD, both from the perspective of the individual and society. The economic burden of liver disease in the LYOL, and its impact on the capacity wider of acute healthcare services, was demonstrated in Chapter 4. Heavy use of

acute hospital services was demonstrated, with a mean of 33.2% of days between index presentation in the LYOL and death being spent as a hospital inpatient. Of patients discharged from hospital within the LYOL, 52.5% were readmitted within 30 days and 74.8% of patients died in hospital. This heavy reliance on secondary care, demonstrated in chapter 4, was corroborated by qualitative data in chapter 3, where patients and bereaved carers described the burden of frequent hospital appointments and admissions. These resulted in a considerable financial strain for the individuals affected.

Qualitative data from chapters 2 and 3 demonstrated the impact of ESLD on patients and families. Hepatologists described the multiple physical and psychological symptoms as uniquely distressing and recognised universally that the social isolation commonly associated with ESLD frequently compounded these difficulties. This depiction of ESLD was replicated in chapter 3, where patients described wide-ranging and disabling physical symptoms, alongside substantial psychological morbidity – typically relating to depression and/or ongoing addiction. The detrimental impact on the wellbeing of carers was also described, with carer participants describing neglect of their own physical and psychological health as a knock-on effect of caring for a loved one with ESLD.

In chapter 2, hepatologists identified resource limitations as a key barrier to improving existing services. However, chapter 4 demonstrated that the NHS is already spending a huge amount on caring for patients with ESLD, largely through its funding of unplanned hospital care. Qualitative data from chapters 2 and 3 indicated that QOL for patients with ESLD and their carers is exceptionally poor. Furthermore, chapter 3 also demonstrated that existing healthcare services are often incompatible with the needs of patients and carers at the EOL on a variety of levels. The juxtaposition of high expenditure with poor outcomes and incompatible services raises the question of whether we are receiving 'value for money' as a society. It compels us to look at ways in which we could do better and provides impetus to change the existing structure of healthcare services for patients with ESLD.

Changing existing models of care – the development of community hepatology

Data from chapters 2, 3 and 4 are consistent in their description of the heavy use of secondary care services among patients with ESLD towards the EOL. In chapter 2, hepatologists recognised that the provision of good quality PC required strong community support, however they described existing primary care services as having both inadequate capacity and expertise to manage ESLD. In chapter 3, patients and carers described a reliance on hospital services, with GPs frequently circumvented from decisions around ongoing care. This reliance on hospital services contributed considerably to the poor QOL described by participants. Frequent hospital visits were associated with substantial financial costs and logistical burdens. Patients and carers detested hospital admission, and frequently described the value they attached to avoiding such admissions towards the EOL. Nonetheless, participants frequently bypassed their GP

when seeking healthcare due to widely held perceptions that GPs were not equipped to deal with their needs. Some participants described bringing care closer to home as a way in which services could be improved.

In chapter 4 I demonstrated that enrolment in a day-case service for large-volume paracentesis (LVP) in the LYOL was associated with substantial and highly significant reductions in cost, number of inpatient bed days, probability of unplanned hospital readmission and probability of unplanned hospital death. As described above, time spent outside the hospital environment and death outside of hospital were valued highly by both patients and carers (chapter 3) – adding to the economic argument for expansion of day-case services. Chapter 3 recruited patients from a day-case LVP service. Even in this context (i.e. quantitatively associated with improved outcomes in the LYOL), patients and carers still described substantial logistical burdens associated with attending appointments, in part due to the distances involved in travelling to and from hospital. It is plausible that movement of day-care services into community settings, potentially including LVP, would be associated with an accentuation of the economic benefits described in chapter 4, as well as being preferable to patients and carers.

In chapter 2, several barriers to a community-based clinical model were identified. These included fragmentation in the way primary care was funded and delivered between areas served by a single hospital, an insufficiency in workforce numbers within primary care and a lack of expertise and experience surrounding the management of ESLD. Whilst hepatology is traditionally considered a hospital-based specialty, these barriers could potentially be overcome through the redirection of services into the community. The importance of the hepatology specialist nurse in managing patients towards the EOL emerged strongly from the qualitative data in chapter 3 and formed part of the supportive care intervention described in chapter 5. Expansion of this element of the workforce to provide community-based care towards the EOL may be both beneficial and cost-saving both to the patient (reduction in hospital appointments and high quality of care) and to hospitals (reduction of bed days, readmissions and acute healthcare costs).

What represents high quality PC in ESLD and the pervasive problem of uncertainty

Descriptions of current care, by physicians in chapter 2 and patients and carers in chapter 3, are remarkably similar. Both recognised that quality of care suffered from being focussed around disease modification at the expense of symptom control, that community services were underdeveloped, that discussions surrounding overall prognosis were rare and that opportunities for ACP were limited. Both described aspects of PC which were ‘desirable’ similarly. These included the opportunity to express preferences about future care, the improved control of physical symptoms, sufficient time to engage in proper discussions around prognosis and the ability to provide assistance with the financial and logistical burdens

associated with ESLD. Equally, some patient and physician participants expressed anxiety that the explicit instigation of PC would be associated with a loss of hope.

These areas of consensus provided a useful starting point in the design of a PC intervention for ESLD and were utilised in design of the supportive care bundle in chapter 5. Nonetheless, they also demonstrate a consensus on the pervading difficulty of uncertainty in ESLD, which in my opinion remains the fundamental barrier to high-quality PC in this population. Patients and carers often described occasions where explicit questions around prognosis and future care planning were avoided, or where they were provided with mixed messages from within the healthcare team. Uncertainty associated with their condition was particularly difficult to come to terms with. Despite the existence of validated prognostic tools to predict survival, physicians described widespread difficulties in identifying which patients stood to benefit from PC and feared "giving up" too early. Physician difficulties in predicting clinical trajectory in ESLD were also substantiated by the questionnaire study in chapter 2.

The supportive care bundle proposed in chapter 5 attempted to get around this issue by offering a "parallel planning" approach to patients with poor but uncertain prognoses. Nonetheless, as demonstrated in chapter 3, when a prospect of cure remains, however remote, the default will be to initiate long-standing but flawed models of acute care. As such, for some patients, parallel planning risks limiting the potential effectiveness of a purely palliative approach. The potential benefits of such an approach were demonstrated in chapter 3, through the description of "informed participants", each of whom had an unequivocally terminal diagnosis. Both physicians and patients evidently find uncertainty difficult to live with. Addressing how best to approach this remains a major challenge in the management of ESLD.

The primacy of malignancy in SPC

Results from the questionnaire survey of hepatologists presented in chapter 2 demonstrated that physicians were significantly more likely to involve SPC in the management of patients with HCC than in patients with non-malignant liver disease who had a worse prognosis. In the following qualitative interview study, hepatologists reported that SPC within their hospitals was frequently organised around cancer services and described ongoing perceptions that SPC was essentially reserved for patients with malignancy. Participants who had experienced HCC (either from the perspective of a patient or carer) constituted much of the "informed participant" typological group, who were able to recall discussions with medical professionals around death and dying and who had been afforded opportunities to discuss their future care. The differences in economic outcomes at the EOL between patients with malignant and non-malignant disease were described in chapter 4. Patients with HCC accrued significantly lower costs and fewer inpatient bed days in their LYOL and had a markedly reduced probability of dying in hospital. Chapters 2 and 3 of this thesis demonstrate substantial differences in the care provided to patients with ESLD who

have concomitant HCC (remembering that approximately 90% of patients with HCC also have cirrhosis). Chapter 4 used multivariable regression analyses of retrospective data and does not claim to demonstrate causality. Nonetheless, particularly considering the data provided elsewhere in this thesis, it seems highly plausible that these differences in outcomes, at least in part, relate to differences in the approach to care.

How this thesis extends existing literature

This thesis considers PC in ESLD from a variety of perspectives, and through use of a range of methodologies. Each topic has a specific literature, and the relationships to individual studies within this thesis are discussed in detail within individual chapters. Here I summarise the key ways in which the thesis as a whole has extended the literature.

Clearer definition of the barriers to PC in ESLD

That patients with liver disease seldom receive PC has been demonstrated widely, and indeed formed a premise for this thesis.[81, 109-112] This phenomenon had also been observed in patients dying from other diseases.[56, 185-187] Work in these fields had identified physician-related barriers to PC, which included difficulties in predicting terminal decline, misperceptions of PC as being synonymous with EOLC, fears of loss of professional 'ownership' of patients and difficulties in managing uncertain disease trajectories.[151, 172, 174-176] Prior to this thesis, literature relating specifically to the barriers to PC in ESLD was limited to two questionnaire studies (one of which was single centred, and one of which was limited by an extremely poor response rate), [121, 122] and a mixed methods QI project from a single UK site.[26] The scope of these studies was extended substantially by chapter 2, which reported the largest questionnaire study, and first in-depth qualitative interview study, of UK hepatologists into the barriers to PC in ESLD. Our study provided further evidence to support some key conclusions from these studies, namely that difficulties in timing PC, a lack of skill and confidence among hepatologists and a poor understanding of PC, were key barriers to PC in patients with ESLD. It extended these findings to demonstrate widespread differences in self-reported practice when managing patients with malignant vs. non-malignant disease, numerous pragmatic structural and resource limitations faced within the NHS, and a lack of functioning and established clinical models for managing patients' PC needs.

Views of patients and carers towards existing healthcare services and SPC

The lived experience of ESLD has been described previously in both qualitative and quantitative studies. Chapter 3 of this thesis concurs with the conclusions of many of these studies, specifically in its findings of a heavy symptomatic burden,[74, 75] an 'information gap' faced by patients in understanding their disease and its prognosis, [199, 200] the pervasiveness of uncertainty as a feature of ESLD [107] and the particular strain of HE on patients and families. [197, 288] Our study however extended this literature in its exploration of how

existing healthcare services met patients' EOL needs. It is the first to demonstrate the incompatibility of existing structures in managing the needs of patients and carers at the EOL. Furthermore, its conclusion that for some patients 'parallel planning', or concurrent curative and palliative care, may not be the optimum approach in meeting EOL needs, is in fact at odds with previous models of PC in ESLD. [90] The study was also the first to directly examine the views of patients with ESLD and their carers towards SPC, eliciting aspects which were perceived both positively and negatively. In combination, these findings supported the argument for the design of novel models of PC for patients with ESLD.

Qualitative study of carers bereaved by ESLD

Examination of the impact of ESLD on carers has received particularly little attention in the existing literature. Whilst the views of carers bereaved by ESLD were examined quantitatively as part of the VOICES study, [108] and carer participants have formed part of a multi-perspective interview studies on ESLD, [107, 197, 288] this was the first qualitative study to recruit bereaved carers specifically. The data from these carer interviews highlighted deficiencies in the current provision of PC in this group and highlighted the lack of financial and logistical support currently available. Whilst the number of carers recruited was relatively low, their insights provided unique data which was able to be incorporated into subsequent clinical models. Their interviews also raised important questions for future studies, particularly in relation to potential mechanisms for carer support.

Analysis of national level data from the LYOL

Chapter 4 of this thesis presented the first analysis of national level data from the LYOL to investigate patterns of hospital usage, cost and place of death outcomes in patients dying from ESLD. It also represents the first study to link HES, ONS and national NHS tariff databases to provide wider estimates of the cost of ESLD to the NHS. Whilst other US studies have used national databases to estimate rates of SPC provision for patients with ESLD, [111, 112] these have utilised hospital admission data (i.e. unplanned admission to hospital with decompensated cirrhosis) as their inclusion criteria. Through linkage of ONS mortality data, ours is the first study in liver disease to study a cohort in which all patients were deceased. As such it was able to make novel observations about cost, service delivery and outcomes at the EOL in patients with cirrhosis. The study demonstrated high levels of cost and resource utilisation. The rate of early unplanned readmission in the LYOL was significantly higher than other estimates in the literature, highlighting that use of acute services escalated towards the EOL.[40, 219, 224] The study was also unique in considering place of death, as an (imperfect) surrogate for quality of EOLC. Through demonstration of the resource implications of liver disease at the EOL, the data both made the case for adequate funding of existing liver services and supported the development of cost-effective future models of care.

Day-case care and community hepatology

The use of day-case services to provide LVP for patients with ESLD had been adopted by some centres in the UK prior to this thesis. The potential of such services to improve patient care and reduce costs had previously been demonstrated only through small retrospective audits at single centres.[210, 241] Through retrospective analysis of all UK deaths from cirrhosis with ascites, chapter 4 was able to demonstrate a strong association between the use of day-case services and a reduction in overall cost and use of unplanned hospital care. Whilst falling short of the level of evidence provided by a randomised controlled trial, the magnitude of the association demonstrated lends strong support to the argument that access to day-case services should be afforded to all patients with ESLD as a standard of care. Indeed, quoting the peer-reviewed publication arising from this chapter, this recommendation has since been adopted by the British Association for the Study of the Liver (the national association for the management of liver disease in the UK).[289] Analysis of qualitative data from chapter 3 pertaining to day-case LVP services suggests that the benefits of such care could be augmented further if day-case services were to be provided in the community, highlighting an important area for future study.

The differences in care between HCC and non-malignant ESLD

The differences in the PC provided to patients with HCC as compared to those with non-malignant ESLD emerged as a key unifying theme from this thesis and is described above. Whilst comparable differences have been reported previously in other organ-failure conditions, [56, 184-187] this difference has not previously been demonstrated explicitly in liver disease. The otherwise similar clinical course of HCC and non-malignant ESLD makes the contrast particularly stark.

Validated prognostic criteria for instigation of PC in ESLD

The difficulties in identifying patients with non-malignant ESLD who stand to benefit from SPC is described above. Prior to this thesis, prognostic scores in liver disease were designed to guide therapeutic interventions or prioritise patients for LT. [290] The Gold Standards Framework, a commonly used guideline in identifying patients for PC, omits criteria for liver disease.[68] Whilst criteria for SPC referral in ESLD had been proposed, they were based on expert opinion and had not been validated for this purpose.[90, 291] Validation of the prognostic score described in chapter 5 (described subsequently in citing literature as the 'Bristol Prognostic Score') [289, 292-295] represents the first validated clinical tool to routinely identify patients with ESLD for PC, based on their risk of death within a one-year period.

Proposal of a model of PC for patients with ESLD

Previous clinical models for the provision of PC in ESLD have been based in the field of LT, recruiting patients either at the point of assessment, following refusal of transplantation as a therapeutic option or following removal from the LT waiting list due to clinical deterioration. [124-127] Given only a minority of patients with ESLD are referred for LT these models may not reflect the needs of the wider ESLD population. Existing models of PC in this group have been based around expert opinion only.[90] The QI project, described in chapter 5, describes the development of a clinical model which was based around the specific PC needs of patients with ESLD identified in chapter 3 of this thesis. It benefited from iterative modifications made by the clinicians directly involved in its implementation. Its subsequent adoption in other hospital trusts across the UK demonstrates it can work in a variety of settings.

Limitations

I have discussed the limitations of each study in the individual chapters in which they are presented. Here, I consider the limitations of a thesis as a whole in the context of the wider literature.

Generalisability of participants

The thesis incorporates data from a wide variety of participants in a range of settings, from in-depth qualitative interviews of bereaved carers to HES data from thousands of patients who died from ESLD. The conclusions drawn, and the recommendations made subsequently, tend to generalise the findings to the wider population studied (e.g. hepatologists, patients with ascites).

Whilst the response rate of 33.7% to the questionnaire study in chapter 2 represented the largest study of hepatologists' opinions to date in this area, the barriers to PC perceived by the 66.3% of non-respondents are arguably more pertinent. Chapter 3 recruited patients exclusively from a single centre enrolled in a day-case LVP programme to understand the perspective of patients with ESLD. However, data from chapter 4 subsequently showed that under 20% of patients dying with cirrhosis and ascites were enrolled in such programmes within their LYOL. Chapter 4 also highlighted the significantly heavier use of acute hospital services (i.e. inpatient care) in patients not enrolled within day-case programmes. The findings described in chapter 3, particularly in relation to experiences of healthcare and therefore PC needs, may therefore differ in patients for whom day-case services are either unavailable or not accessed. Whilst the qualitative methodology in chapter 3 did not seek generalisability per-se, the findings were incorporated subsequently into the design of the supportive care bundle, which was targeted at inpatients with ESLD (chapter 5). This mismatch, between the evidence supporting the content of the supportive care

intervention and the setting in which it was subsequently targeted (inpatients with ESLD), is a possible limitation of the model.

The pre-existing models of PC in ESLD are largely based on studies of patients enrolled in LT programmes.[124-127] A strength of this thesis lies in the recognition that patients with ESLD in whom LT is never considered (a substantial majority) represent a distinct population with different needs. The contraposition of this is that participants in each study within this thesis are not necessarily enitrely typical of the populations they are purported to represent.

Assumptions surrounding death

Whilst the interviews with bereaved carers in chapter 3 and the retrospective analysis of national data in chapter 4 utilised vastly different methodologies, they were consistent in using death as the fundamental criterion for recruitment. In doing so, there was both an implicit selection bias and an assumption that PC did/would have represented an appropriate clinical intervention. The uncertainty associated with ESLD emerged as a key theme from the thesis overall (described above), corroborating previous studies on this topic.[107] It was a key barrier to the earlier utilisation of PC by hepatologists (chapter 2). If PC were to be routinely integrated into the earlier management of ESLD, we might therefore assume that some patients who received PC would go on to survive their illness. Some patients interviewed in chapter 3 feared the instigation of SPC would lead to them losing hope for survival, a concern shared by some hepatologist interview participants in chapter 3. For the fears of both hepatologists and patients to be allayed there is perhaps a need to demonstrate that the utilisation of PC in ESLD both improves QOL and does not unduly reduce survival. Whilst such effects have been demonstrated prospectively in other diseases,[48] the distinct characteristics of the ESLD population mean that these findings are not necessarily transferable. In common with other models of PC in ESLD, [124-127, 283] the supportive care bundle proposed in chapter 5 is not evaluated prospectively against a control group. Whilst I believe this thesis provides strong evidence for the wider adoption of PC in ESLD, it fails to demonstrate that it would not impact upon overall prognosis.

Quality of quantitative data

Quantitative data from various sources were used in chapters 2, 4 and 5. In each case, there were limitations in data quality. Conclusions derived from chapter 2 were made on the basis of self-reported practice within a questionnaire, which was not verified subsequently. Other studies exploring this topic are similarly limited.[121, 122] In chapters 4 and 5, data were both observational and retrospectively analysed. The retrospective methodology meant records were used which were not designed for the purposes of either study. There was therefore a relative absence of data on potential confounding factors (e.g. severity

of liver disease – chapter 4, prior enrolment in a day-case service – chapter 5) and the observational nature of the analysis meant that causal relationships could not be drawn. Despite this, causality was implied in subsequent arguments – particularly with respect to the use of day-case services and the differences in care between patients with malignant and non-malignant liver disease. Two comparable US studies also utilised large datasets to investigate patterns of care at the EOL.[111, 112] They differ from our study in their identification of patients in that they look forward from the point of admission as opposed to backwards from the point of death. These studies were also able to identify patients who received SPC input as an inpatient, information which was unavailable in our analysis. However, the retrospective and observational nature of the subsequent analysis was common to all studies – which were therefore exposed to similar potential biases and inaccuracies in coding.

Lack of formal cost-effectiveness analysis

Implementing new models of service delivery, particularly within resource limited settings, requires consideration not only of their cost, but also of their cost-effectiveness. Cost-effectiveness considers the economic cost of an intervention against a defined clinical outcome, as compared with an alternative (or existing) clinical model.[296] Such analyses can be used to maximise the health benefit for a population where there is a fixed healthcare budget, and are essential when new clinical interventions are introduced across the NHS. Within the NHS, the National Institute of Clinical Excellence (a national UK body which produces guidelines around clinical practice and the use of new health technologies) use Quality Adjusted Life Years to assess the cost-effectiveness of any new intervention. Quality Adjusted Life Years assess the cost of an intervention against both gains in the patient's life expectancy and their QOL, with the National Institute for Clinical Excellence considering £20,000-£30,000 per Quality Adjusted Life Year as an acceptable 'threshold'.[297]

The evidence base around the cost-effectiveness of PC interventions remains relatively small. A 2014 systematic review of 46 studies found that PC interventions were consistently more cost effective than comparator groups.[298] However, the authors commented on the low number of high quality studies identified (5 RCTs vs 34 cohort studies) and the paucity of evidence in this area. There are challenges in applying standard methods of cost-effectiveness analysis to new PC interventions which may account for this. For example, it may be difficult to capture the full costs involved (e.g. informal care costs) or measure the impact of an intervention at the EOL using standard QOL metrics. Quality Adjusted Life Years have been criticised specifically in the context of PC, in that the limited life expectancy of the patient may wrongly negate the measured value of an otherwise high-quality intervention.[299, 300] Nonetheless, novel interventions will need to demonstrate cost-effectiveness if they are to be adopted widely, and newer, more bespoke methodologies for assessing cost-effectiveness research in PC are continually being developed.[301]

A limitation of this thesis is that it omits any formal analysis of cost-effectiveness. In chapter 4 the raw costs of two alternative clinical models for patients with ascites (planned and unplanned care) are compared, however the nature of the analysis (large-scale database and retrospective) means that it is not possible to compare duration and quality of life between the two groups. In chapter 5 a novel intervention is proposed, however the costs of this (as compared with standard care) are described but not quantified. For novel PC interventions to be adopted within future national guidelines for managing ESLD, formal cost-effectiveness analysis will be required. This thesis provides evidence which suggests that ambulatory models of LVP are likely to be cost effective, however formal and prospective cost-effectiveness analysis of this is required. Similarly, the cost of implementing the supportive care intervention described in chapter 5, alongside a prospective evaluation of its impact on QOL, would likely be required for it to implemented widely. Formal assessment of the cost-effectiveness of PC in ESLD forms an important question for future research.

Implications for future research

The limitations of this thesis are common to much of the wider literature on PC in ESLD. Patients with liver disease often arise from within marginalised groups in society, and research populations are not necessarily fully reflective of this. For example, the 15% of the patients identified in chapter 4 who died without any prior contact with healthcare services are not represented in any of the qualitative data. Studying the needs of marginalised patient groups, who potentially stand to benefit the most from strong models of PC, remains a key challenge for future studies.

For PC to be adopted within international guidelines for managing ESLD higher level evidence of benefit and cost-effectiveness is likely to be required. Many of the limitations described above would be overcome through a well-designed, multicentre prospective study of outcomes of patients with ESLD receiving a defined PC intervention against a control group. This thesis provides a potential starting point, both in terms of inclusion criteria (prognostic score) and intervention (supportive care bundle). Despite the logistical and pragmatic challenges that setting up and funding such a study would involve, I believe it is key to ensuring the adoption of PC as a 'standard of care' for patients with ESLD.

The expansion of community hepatology services for patients with ESLD formed a key recommendation from multiple chapters within this thesis. However, the details of how this should be delivered, staffed and funded, and how it would be received by patients, remain undefined. This thesis only provides evidence of the potential for benefit. Design of clinical and business models which incorporate models of community care, and the subsequent study of clinical and economic outcomes of patients enrolled in such services, should form a key part of future research and service development.

Finally, study of the impact of ESLD on carers appears to have been particularly neglected in the literature. Whilst this thesis offers some insight into the impact of ESLD on their lives, studies into carer needs are largely absent and models of carer support specific to liver disease are yet to be developed. This is likely to represent a key area of unmet need and should be considered as a priority for future research.

Implications for clinical practice

Specific recommendations for clinical practice are described in the discussion of each chapter. The key recommendations of the thesis as a whole are summarised here.

Changing the structures of care delivery towards the EOL

Current models of healthcare for patients with ESLD are based in secondary care, and frequently rely on the unplanned use of acute services. Qualitative data from chapter 3 demonstrated that this structure of care was detrimental to the QOL of patients and carers with ESLD. Furthermore, the economic analysis presented in chapter 4 demonstrated that models of care which moved away from a reliance on acute services were associated with significant reductions in cost and bed occupancy. Qualitative data from interviews with hepatologists in chapter 2 however highlighted anxieties that the removal of hospital-based services, even for patients with non-curable disease, would be detrimental, due to the complexity of managing ESLD. Doubts around the capacity of existing community to services to manage this patient population were also commonplace.

Given the evidence described above it is plausible that a more community based service model would improve patient care towards the EOL and be cost-effective. However, existing primary care services do not have the capacity or expertise to provide such care at present.[198] I believe the onus is therefore on the hepatology community to change their traditional model of working such that they are able to deliver direct, integrated clinical care in community settings for patients in whom it is appropriate, utilising hepatology specialist nurses and community SPC when required.

Communicating uncertainty to enable parallel planning

As described above, uncertainty has emerged as a pervasive theme throughout this thesis. In this context it is interesting to juxtapose the ‘information gap’ surrounding the prognosis and trajectory of ESLD described by patients and carers in chapter 3, against the fear of being ‘misperceived’ described by hepatologists in chapter 2. Perceptions that the explicit instigation of PC would be associated with a loss of hope for the future were described in chapter 2 and 3, and it seems likely that this fear explains in part why such care is introduced late, if at all. Whilst there may be issues around the terminology of PC, and

the language we use is certainly important, I do not believe changing the lexicon represents a complete solution.

The concept of parallel planning affords a neat theoretical approach to PC for patients in whom prognosis is uncertain. Whilst the limitations of parallel planning are described in chapter 3, I support the wider concept. However, to be able to initiate parallel planning fully we need to first be able to better explain uncertainty to our patients. Allocating sufficient time and expertise (and therefore by extension hard resource) does, I believe, represent part of the solution. How we explain the inherent uncertainties of ESLD to our particular patient cohort, in a way which is both nuanced and fully comprehended, remains a considerable challenge which, as yet, is incompletely understood. Nonetheless, overcoming this key barrier to the timely initiation of PC in ESLD is something for which we should continue to strive.

Recognising physiological decline robustly

The identification of patients who stand to benefit from LT is widely recognised as key responsibility of hepatologists, and multiple validated scoring systems are available to guide this process. Indicators directing physicians towards PC are however scant. Both quantitative and qualitative data in chapter 2 highlighted the difficulties faced by physicians in identifying patients who stood to benefit from PC. This perhaps in part explains the escalation in use of acute services in patients with ESLD towards the EOL, evidenced in chapter 4. Chapter 5 proposes a model for identifying inpatients, however its design was based on local factors, and identified only patients admitted to hospital acutely. Whilst it has been adopted in various forms at other institutions, there is a need to more comprehensively integrate objective prognostication, which directs physicians both towards transplantation and PC, into the routine management of ESLD. Robust systems, ideally cited within national and international guidelines and measurable as an indicator of performance, are required if access to PC is to become less physician dependant in the future.

Focussing on non-malignant ESLD

This thesis has identified inequity in the care provided to patients with malignant and non-malignant liver disease towards the EOL. It could be argued that the trajectory in HCC is somewhat easier to predict (perhaps accounting for the presence of 'best supportive care' approaches within international guidelines),[16] and that the barrier of "uncertainty" is, to an extent, removed in this group. Nonetheless, responses to the questionnaire in chapter 2 showed how rarely SPC was utilised in non-malignant liver disease, even where participants recognised explicitly that it was clinically indicated.

These inequities must be addressed. The solutions are likely to be multifaced. A training and skills gap among hepatologists in the provision of PC was identified in chapter 2. The programme of training delivered by SPC physicians and nurses to hepatology staff, described as part of the QI project in chapter 5, represents one approach to tackling this. Undoubtedly a cultural change within hepatology is required for PC in ESLD to be fully embraced, and there will always be room to further improve upon prognostic scoring to identify the patients who stand to benefit most. However, in my opinion, there is also a need for the SPC community to expand its reach and fully embed itself into the management of non-malignant disease. Whilst SPC for patients with non-malignant disease has developed enormously over the last decade, services all too often remain centred (geographically, economically and culturally) within oncology. The focus on non-malignant disease needs to remain a key priority for the SPC community over the coming years, such that these long-standing perceptions are gradually changed. Certainly, for patients with liver disease, the impetus has never been stronger.

Impact of thesis

A summary of the academic output arising from this thesis is provided towards the beginning of the document. Chapters 2, 3, 4 and 5 have all been presented individually in both oral and poster formats at national and international conferences. Chapters 3, 4 and 5 have been published as original research articles in high-quality peer-reviewed journals.[284, 302, 303] These publications have in turn resulted in several invited seminars. All three articles attracted editorials from their respective journals,[221, 295, 304] and received subsequent published positive correspondence.[305] From the perspective of clinical care, the data provided in chapter 4 of the thesis has been used to underpin national recommendations on the provision of day-case LVP, [289] and has been used to justify best-practice recommendations for the management of cirrhosis and ascites internationally.[221, 306-308] The clinical model described in chapter 5 has been adopted, in some form, by at least seven NHS trusts and has been cited in a number of recent review articles on PC in ESLD. [292-294] Since the inception of this thesis, a national specialist interest group on EOLC in liver disease has been formed through the British Association for the Study of the Liver in which I remain actively involved. Some of the questions for further research raised through this thesis are being investigated currently by Dr Hazel Woodland, a current MD student, also under the supervision of Professor Forbes.

Subsequent to the viva examination of this thesis the Royal College of Physicians published updated national standards for hospitals providing liver services. These now the mandate that day-case LVP be made available to patients with refractory ascites and require hospitals to record the proportion of LVP procedures undertaken in a day-case setting. They also require services to routinely use a prognostic tool to identify patients who may benefit from PC. Papers arising from this thesis were cited directly to support these new quality metrics.

Concluding argument

This thesis has considered, from a variety of perspectives, how patients with ESLD are cared for towards the end of their lives and how this care might be improved. It has highlighted the barriers faced by hepatologists in providing PC, the devastating emotional and physical impact of ESLD on patients and carers, and the mismatch between the needs of patients and the services currently available to address them. It has examined ESLD from a health economic standpoint, providing evidence to support models of care which have the potential to both improve patient experience and reduce cost. It proposes a novel clinical model which both identifies patients who stand to benefit from PC and provides a structure for their ongoing clinical care.

Realising the recommendations from this thesis will however rely on a much simpler fundamental concept – that of honest, open and timely communication between physician and patient about the life-limiting nature of their disease. The unmet needs of patients and carers, described so eloquently within the qualitative data, will never be addressed until they are able to be elicited and validated by clinicians. Clinical models to avoid emergency admission and reduce cost, however comprehensive, will always rely on patients' understanding of their purpose and the reasons why they are appropriate for them. Without this understanding, unplanned care, with all of its inadequacies both for patients and healthcare systems, will remain the default for patients with ESLD. Communicating the intrinsic uncertainties of liver disease and its treatments to our patients and their families is at the heart of integrating PC into the management of ESLD, something no clinical model in and of itself will ever overcome. As I begin my career as a consultant hepatologist, it is my biggest and most exciting challenge.

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APPENDICES

Appendix 1 – Research Ethics Committee documents

1.1 - Consent form – patient interviews
1.2 - Consent form – carer interviews
1.3 - Patient information sheet – patient interviews
1.4 - Patient information sheet – carer interviews
1.5 - Letter to patient following interview
1.6 - Letter to carer following interview
1.7 - Supporting statement from British Liver Trust
1.8 - Correspondence with Hampshire B research ethics committee

Appendix 2 – Supplementary information relating to chapter 2 of this thesis

2.1 – On-line questionnaire survey
2.2 – Invitation to participate in interview letter

Appendix 3 – Supplementary information relating to chapter 4 of this thesis

3.1 – Most common HRG codes in dataset with linked episode tariffs
3.2 – Distribution of missing data

Appendix 1 - Research Ethics Committee approved documents

1.1 – Consent form – patient interviews

Study Number: School of Clinical Sciences: Study 2553

Study Arm: Interview of patients with advanced liver disease

Site: University Hospitals Bristol NHS Trust

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Integration of palliative and supportive care into the active management of patients with advanced liver disease.

Name of Researcher: Dr Benjamin Hudson **Please initial each box and sign below**

1. I confirm that I have read the information sheet (dated 04.03.16 version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand relevant sections of my medical notes (including blood results) and data collected during the study, may be looked at by individuals from University Hospitals Bristol NHS Trust and the University of Bristol, where it is relevant to my taking part in this research. This may include individuals from bodies regulating the conduct of the research. I give permission for these individuals to have access to my records ☐
4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. I provide consent for this anonymised data to be used in the future. I consent for this information to be used should my clinical condition deteriorate, or after my death. ☐
5. I give my permission for my interview with the research team to be audio recorded for use by the research team. I give my permission for anonymised and unidentifiable quotes from the interview to be used in the study write up and in any subsequent publications. ☐
6. I understand that the information I provide will be held in strict confidence. Under the Data Protection Act 1998, should the researchers become concerned that information has been disclosed which might result in potential harm to myself or others, I accept their obligation to notify the relevant authority (this would be discussed with you first wherever possible) ☐
7. I agree to take part in the above study, and for my GP to be informed of my participation. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 1.2 – Consent form carer interviews

Study Number: School of Clinical Sciences: Study 2553
Centre: University Hospitals Bristol
Participant Identification Number for this trial:
Study Arm: Carer and relative interviews

CONSENT FORM

Title of Project: Integration of palliative and supportive care into the active management of patients with advanced liver disease.

Name of Researcher: Dr Benjamin Hudson

Please initial each box and sign below

1. I confirm that I have read the information sheet (dated 05.12.16 version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. I understand that data collected during the study, may be looked at by individuals from University Hospitals Bristol NHS Trust and the University of Bristol, where it is relevant to my taking part in this research. This may include individuals from bodies regulating the conduct of the research ☐
4. I give my permission for the interview in which I partake to be audio recorded for use by the research team. I give my permission for anonymised and unidentifiable quotes from the interview to be used in the study write up and in any subsequent publications. ☐
5. I understand that the information I provide during the interview will be held in strict confidence. Under the Data Protection Act 1998, should the researchers become concerned that information has been disclosed which might result in potential harm to yourself or others, I accept their obligation to notify the relevant authority. Wherever possible, this would be discussed with you first. ☐
6. I agree to take part in the above study, and for my GP to be informed of my participation. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix 1.3 – Patient information sheet – patient interviews

Study title

Integration of palliative and supportive care into the active management of patients with advanced liver disease.

Invitation and brief summary

Patients with liver disease commonly experience a range of difficulties in terms of physical symptoms, psychological well-being and social support as their disease becomes advanced. In the NHS patients with liver disease are primarily managed by hepatologists (liver specialists), who focus primarily on the medical aspects of liver disease. This research project aims to investigate whether involving specialists in palliative and supportive care can improve patients' symptoms, mood and quality of life. We also want to find out if this could enable patients to better understand their disease, and be more involved in the decisions that are made about their care.

As part of this research we are performing a series of interviews on patients with advanced liver disease to get a better understanding of their experiences in the NHS. We are interested to see what is done well, and what could be improved.

What's involved?

Explanation and background

Liver disease has become increasingly common in the United Kingdom over the past 30 years, and is the 5th commonest cause of death in the United Kingdom (UK). Most of the research and developments in liver disease have surrounded ways in which liver disease can be cured, for example with liver transplantation or new drugs. There is limited research on what patients with advanced liver disease experience in terms of their symptoms and quality of life once their disease has reached an advanced stage. Research in this area may help us design services that improve quality of life for patients with liver disease. Part of this care may include talking about the future, and discussing the issues that can affect patients towards the end of their life.

To further our understanding of how advanced liver disease affects patients, and to help us improve services for these patients, we are completing a series of interviews on patients with advanced liver disease.

Why have I been invited to take part?

We have invited you to participate in this study because you have ascites (fluid on the abdomen) which indicates your liver disease is relatively advanced. By better understanding your experience we hope to be able to improve care for future patients in a similar position.

What would taking part involve?

We want to ask you about how your disease affects your life, what you understand about your disease, and how you think the services that are currently offered to you could be improved. If you agree to be interviewed a researcher will come to talk to you during your paracentesis

(fluid drainage) at the Bristol Royal Infirmary. The interview will last approximately 45 minutes and will be audio recorded. Your details will be anonymised and information you provide to us will be kept confidential – in a similar way to when you visit your doctor. This will involve a one off interview. After you are finished you will not be contacted again by the research team, unless you ask to be informed about the results of the research.

What benefits of taking part?

The main benefit of taking part is that you have the opportunity to offer views that may improve care for future patients and their families. You are unlikely to get any specific benefits yourself, although some patients do find that talking about their disease can be helpful for them.

What are the possible disadvantages and risks of taking part?

The interview will take approximately 45 minutes. You will be attending routinely for your paracentesis and the interview will take place during the time when the fluid is draining off. Some people can find talking about their disease distressing, and there is a potential that some of the discussion might upset you. Should this happen to you there are some phone numbers, through which you can access help, at the end of this information sheet (see - *'What should I do if the interview causes me to become distressed?')*.

There are rare circumstances in which the researcher would be obliged to breach confidentiality. This is just the same as with any consultation with a doctor or nurse. Examples of this include somebody who described continuing to drive after a doctor had told him/her it was unsafe, or someone highlighting that a child or vulnerable adult was at risk. If you tell us important information about your medical condition during the course of the interview the researcher would ask your consent to inform your consultant and/or GP about this so that they could act on the information.

Further Questions and Answers

Q: What if I want to stop the interview or I change my mind?

A: You can withdraw your participation in the study at any point. This won't affect the care you receive in any way.

Q: What information will you keep following my interview and will it be kept confidential?

A: We will audio record our interview with you and then write down what has been said. We will also collect some basic information about your condition, so we can tell how advanced your liver disease is. All of your data will be anonymised and kept confidential. Once we have completed the analysis of our data we will destroy the recording of your interview and any other data. Once we have finished the interview the research team will identify your case using only a research number.

We may use direct quotations from your interview when we are writing up the results of the study, and in scientific journals. If we do this we will make sure that the quote is anonymous, and does not include any information that could identify you.

The information you provide during the interview will be held in strict confidence. Under the Data Protection Act 1998, should the researchers become concerned that information has been disclosed which might result in potential harm to yourself or others, they will need to notify the relevant authority. Wherever possible this will be discussed with you first.

Q: What will happen to the results of this study?

A: We hope the results of this study will be used to help us improve care for patients with advanced liver disease in the NHS. This may include us writing up the results in scientific papers, or presenting them at medical conferences. The results will also be used to make up part of a doctoral thesis.

Q: Who is organising and funding this study?

A: This study is being funded by the David Telling Charitable trust and is being organised jointly between University Hospitals Bristol NHS Trust and the University of Bristol

Q: Who will be interviewing me?

A: You will be interviewed by Dr Ben Hudson, a senior registrar in hepatology who is currently completing a doctorate on this topic.

Q: Who has reviewed this study?

A: This study has been reviewed by the University of Bristol school of clinical sciences, as well as by the departments of hepatology and palliative medicine at University Hospitals Bristol NHS Trust. The study has obtained a favourable opinion from the South Central – Hampshire B Research Ethics Committee.

Q: How do I consent to the study?

A: If you are willing to take part in the study please inform the hepatology specialist nurse when you attend for your next drain. They will pass on your details to the research team who will then come to discuss the study with you and will ask for your written consent prior to proceeding with the interview. You can change your mind about participating in the study at any time.

Q: Will my GP know about my involvement in the study

ou are feeling extremely distressed or worried, and don't think you can wait to contact the hepatology team there is a 24-hour crisis number that is available. This number is 0330 5550334. The crisis team managing this phone line will not know the background to your case, however will be able to provide help for you in an emergency.

Q: Who do I contact if I have further questions

A: If you have general questions about research at University Hospitals Bristol, your rights, and what to expect as a participant in research, answers to most questions can be found on University Hospitals Bristol website, or by following the link: **http://www.uhbristol.nhs.uk/research-innovation/information-for-patients-and-the-public**.

If the website does not answer your question, you can contact Catherine Down at University Hospitals Bristol research and innovation department. She is independent of this particular research project and will be able to address any questions or concerns. Catherine can be contacted at **Catherine.Down@UHBristol.nhs.uk** or Tel: 0117 34 20233.

Questions which are specific to this research project can be addressed to the primary researcher, Dr Ben Hudson. He can be contacted via email (**ben.hudson@uhbristol.nhs.uk**) or via the Department of Hepatology secretaries at University Hospitals Bristol NHS Trust. Should you have any concerns or complaints following participation in this research please contact the University Hospitals Bristol patient advice and liaison service on 0117 342 1050.

Appendix 1.4 – Patient Information Sheet – Carer interviews

Study title

Integration of palliative and supportive care into the active management of patients with advanced liver disease.

Invitation and brief summary

Patients with advanced liver disease commonly experience a range of difficulties in terms of physical symptoms, psychological well-being and social support as they approach the end of their life. This can present particular difficulties for their families and carers. This research project is investigating whether the care that is currently provided for patients with advanced liver disease and their families is meeting their needs successfully. From this we hope to be able to suggest ways in which the NHS can improve care for patients and families in the future.

As part of this project we want to interview families and carers of patients who have died from liver disease so we can better understand their experience of care in the NHS. We would like to discuss ways in which this care could be improved for patients and their families in the future.

What's involved?

Explanation and background

Liver disease has become increasingly common in the United Kingdom over the past 30 years, and is now the 5th commonest cause of death in the United Kingdom (UK). Most of the research and developments in liver disease have surrounded ways in which liver disease can be cured, for example with liver transplantation or new drugs. There is limited research on what patients experience in terms of their symptoms and quality of life, and how this impacts upon their families. Research in this area may help us to design services that improve patients' quality of life, and the quality of life of their families and carers.

Why have I been invited to take part?

We have invited you to take place in this study because you are the documented next of kin of a patient who has died from liver disease at the Bristol Royal Infirmary within the last 3 years. If you cannot take part in person we would encourage you to pass on this invitation to another family member or carer of the deceased who may be willing to help with this research.

What would taking part involve?

If you are willing to take part in this study we would ask you to reply to the letter, either via the stamped addressed envelope enclosed or via the email address given on the letter (**ben.hudson@uhbristol.nhs.uk**). You would then receive a phone call or email inviting you to participate in an interview – which would take no longer than 1 hour. During the interview, we would ask you about your experience of looking after your loved one towards the end of their life, and what support you received from the NHS. We are interested to know how you think this care could be improved in the future. We would seek your permission to audio record the session so that we can analyse what has been said. You would be asked whether you would prefer to be interviewed at the Bristol Royal Infirmary or in your own home. If you chose to be interviewed at the Bristol Royal infirmary we would reimburse your travel expenses, however we would unfortunately not be able to offer you a fee.

What benefits of taking part?

The main benefit of taking part is having the opportunity to offer views that may improve care for future patients and their families. You are unlikely to get any specific benefits yourself, although some people may find that discussing their experiences is therapeutic.

What are the possible disadvantages and risks of taking part?

The interview will take no longer than 1 hour. We are unfortunately unable to pay you for this time. Some people can find talking about the death of a loved one distressing, and there is a potential that you will find some of the topics that we discuss upsetting. If you become particularly upset, or find the session extremely difficult we will ask your permission to contact your GP, and will be able to provide contact details for further bereavement counselling. Whilst the interview is confidential and you will be anonymous to those analysing or reading the research there are rare circumstances in which the researcher would be obliged to break confidentiality. This is just the same as with any consultation with a doctor or nurse. Examples of this include a participant describing continuing to drive after a doctor had told him/her it was unsafe, or a participant highlighting a situation where a child or vulnerable adult is at risk.

Further Questions and Answers

Q: What if I want to pull out of the discussion or I change my mind?

A: You are at liberty to withdraw your participation in the study at any point without any consequence.

Q: What if I feel that I can't take place in the study?

A: Participation is entirely voluntary. If you feel as though you can't take place yourself, we would ask that you pass on the invitation to another member of your family who might consider attending instead.

Q: What information will you keep following my information and will it be kept confidential?

A: We will undertake an audio recording of the interview and will write down what has been said so it can be analysed further. All of your data will be anonymised and kept confidential. Once we have completed the analysis of our data we will destroy the recording. We will not be using or keeping any of your personal data.

We may use direct quotations from the interview when we are writing up the results of the study, and in scientific journals. If we do this we will make sure that the quote is anonymous, and does not include any information that could identify you.

The information you provide during the interview will be held in strict confidence. Under the Data Protection Act 1998, should the researchers become concerned that information has been disclosed which might result in potential harm to yourself or others, they will need to notify the relevant authority. Wherever possible this will be discussed with you first.

Q: What will happen to the results of this study?

A: We hope the results of this study will be used to help us improve the care of patients with advanced liver disease being cared for in the NHS. This may include us writing up the results in scientific papers, or presenting them at medical conferences. The results will also be used as part of a doctoral thesis.

Q: Who is organising and funding this study?

A: This study is being funded by the David Telling Charitable trust and is being organised jointly between University Hospitals Bristol NHS Trust and the University of Bristol.

Q: Who will be interviewing me?

A: The interview will be led by Dr Ben Hudson, a senior registrar in hepatology who is currently completing a doctorate on this topic.

Q: Who has reviewed this study?

A: This study has been reviewed by the University of Bristol school of clinical sciences, as well as by the departments of hepatology and palliative medicine at University Hospitals Bristol NHS Trust. The study has obtained a favourable opinion from the South Central – Hampshire B Research Ethics Committee.

Q: How do I consent to the study?

A: If you are willing to take part in the study please complete the enclosed reply slip and return it in the stamped addressed envelope provided.

Q: Will my GP know about my involvement in the study

A: We will write to your GP informing them of your participation in the study.

Q: Who do I contact if I have further questions or concerns

A: If you have general questions about research at University Hospitals Bristol, your rights, and what to expect as a participant in research, answers to most questions can be found on University Hospitals Bristol website, or by following the link:

http://www.uhbristol.nhs.uk/research-innovation/information-for-patients-and-the-public.

If the website does not answer your question, you can contact Catherine Down at University Hospitals Bristol research and innovation department. She is independent of this particular research project and will be able to address any questions or concerns. Catherine can be contacted at **Catherine.Down@UHBristol.nhs.uk** or Tel: 0117 34 20233.

Questions which are specific to this research project can be addressed to the primary researcher, Dr Ben Hudson. He can be contacted via email (**ben.hudson@uhbristol.nhs.uk**) or via the Department of Hepatology secretaries at University Hospitals Bristol NHS Trust.

Should you have any concerns or complaints following participation in this research please contact the patient advice and liaison service on 0117 342 1050.

Appendix 1.5 – Letter to patient following interview

Re: Participation in study 'Integration of palliative care into the management of advanced liver disease'

Dear participant

Firstly, please allow me to extend our sincere thanks for participating in our study. We hope that the results of this study may improve the quality of care for patients with liver disease in the future, and we are extremely grateful for your help.

Your participation in the study is now complete. We hope that any questions or concerns you may have had will have been answered by the research team. The research team do not plan to contact you again unless you have indicated that you would like to be kept informed of the results of the study.

It is possible that some of the issues raised during your interview may have caused you to become upset and that you feel you require further support. If this is the case, we would recommend you contact the hepatology specialist nurse team in the first instance. If required they can arrange for you to be followed up by an appropriate healthcare professional. They can be contacted on 0117 3423316 between 9am to 5pm Monday to Friday. If you call outside these hours, or there is no-one available to take your call, there is an answerphone service and someone will get back to you at the earliest opportunity. This is the best way to make contact with us if you need further help or support.

If you are feeling extremely distressed or worried, and don't think you can wait to contact the hepatology team there is a 24-hour crisis number that is available. This number is 0330 5550334. The crisis team managing this phone line will not know the background to your case, however will be able to provide help for you in an emergency.

Thank you again for your time and help in assisting us in this important area of research.

Yours faithfully

[redacted]

Dr Ben Hudson
MB BCh, BSc (hons), MRCP (gastro)
Clinical research fellow – University Hospitals Bristol

Appendix 1.6 – Letter to carer following interview

Re: Participation in study 'Integration of palliative care into the management of advanced liver disease'

Dear participant

Firstly, please allow me to extend our sincere thanks for participating in our study. We hope that the results of this study may improve the quality of care for patients with liver disease in the future, and we are extremely grateful for your help.

Your participation in the study is now complete. We hope that any questions or concerns you may have had will have been answered by the research team. The research team do not plan to contact you again unless you have indicated that you would like to be kept informed of the results of the study.

It is possible that some of the issues raised during your interview may have caused you to become upset and that you feel you require further support. If this is the case, we would recommend you contact the hepatology specialist nurse team in the first instance. If required they can arrange for you to be followed up by an appropriate healthcare professional. They can be contacted on 0117 3423316 between 9am to 5pm Monday to Friday. If you call outside these hours, or there is no-one available to take your call, there is an answerphone service and someone will get back to you at the earliest opportunity. This is the best way to make contact with us if you need further help or support.

If you are feeling extremely distressed or worried, and don't think you can wait to contact the hepatology team there is a 24-hour crisis number that is available. This number is 0330 5550334. The crisis team managing this phone line will not know the background to your case, however will be able to provide help for you in an emergency.

Thank you again for your time and help in assisting us in this important area of research.

Yours faithfully

[redacted]

Dr Ben Hudson
MB BCh, BSc (hons), MRCP (gastro)
Clinical research fellow – University Hospitals Bristol

Appendix 1.7 – Supporting statement from British Liver Trust

2 Southampton Road, Ringwood BH24 1HY
Telephone: 01425 481320
Helpline: 0800 652 7330
Email: info@britishlivertrust.org.uk
www.britishlivertrust.org.uk

BRITISH LIVER TRUST

Pioneering liver health

For the attention of the Research Ethics Committee

16th December 2015

SUPPORTING STATEMENT

The British Liver Trust is the largest charity in the UK concentrating on liver health through providing ● increased awareness and prevention, ● promoting earlier detection, ● supporting and advocating for those with and affected by liver disease and ● encouraging relevant research.

RE: **RESEARCH PROPOSAL – INTEGRATING PALLLIATIVE AND SUPPORTIVE CARE INTO THE MANAGEMENT OF ADVANCED LIVER DISEASE**

The British Liver Trust enthusiastically supports Dr Ben Hudson in this very important research. As highlighted within the project proposal, deaths from liver disease in the UK are continuing to increase and for many people with liver disease they are diagnosed very late and consequently have a very poor survival rate and would benefit from effective supportive and palliative care. It is, therefore, essential we know more about the holistic needs of both those with and affected by end stage liver disease and wherever possible finding the best ways of meeting those needs.

This study will help to provide further evidence as to why the inclusion of palliative care can improve quality of life for patients with liver disease and their families and where the involvement of specialist palliative care services would further enhance this.

The British Liver Trust will be happy to continue to support this work and will help disseminate questionnaires to people with and affected by liver disease, provide patient and carer representation on the steering group and ensure wide distribution ~~of the~~ findings once published.

Please do not hesitate to contact me if you require any further information.

Yours faithfully

[redacted]

Andrew Langford

Appendix 1.8 – Correspondence with Hampshire B Research Ethics Committee

NHS
Health Research Authority

South Central - Hampshire B Research Ethics Committee
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1384

09 February 2016

Dr Benjamin Hudson
[redacted]

Dear Dr Hudson

Study Title:	**Integration of palliative care into the management of patients with advanced liver disease**
REC reference:	**16/SC/0041**
Protocol number:	**2553**
IRAS project ID:	**193380**

The Research Ethics Committee reviewed the above application at the meeting held on 27 January 2016. Thank you for attending to discuss the application.

Provisional opinion

The Committee was unable to give a favourable opinion based on the information and documentation received so far.

The Committee requested the following information before confirming its final opinion:

1) Clarify potential participants will only receive one reminder letter, should they fail to respond to the initial invitation to the study.

2) Provide a 24 hour crisis number to all patient participants.

3) Submit separate consent forms for each study groups.

4) Permission to audio record the discussion of the focus group should be written into the PIS and consent forms for the relatives of patients, along with mention of the potential use of anonymised and unidentifiable quotes.

5) Under 'Explanation and background' in each PIS, 'Research in this area will help us' should be replaced by 'Research in this area may help us' and 'might' inserted to give 'which might not only extend'.

6) Under 'What are the benefits of taking part?' in the focus group PIS, the first sentence should be replaced by 'The main benefit of taking part is that you have the opportunity to offer views that may improve care for future patients and their families'

7) Under 'What are the benefits of taking part?' in the additional clinic PIS, 'patients' should be replaced by 'participants', and 'you are also helping' should be replaced by 'you may also be helping'.

8) The focus group Consent Form should include an item whereby participants agree to respect the confidentiality of other members of the group and those mentioned in discussion.

9) The following standard confidentiality clause is added to the PISs:

'I understand that the information I provide during the focus group will be held in strict confidence. Under the Data Protection Act 1998, should the researchers become concerned that information has been disclosed which might result in potential harm to yourself or others, they will need to notify the relevant authority. Wherever possible, this will be discussed with you first.'

10) The REC Reference listed within the PIS should be updated to read: South Central – Hampshire B Research Ethics Committee.

The Committee delegated authority to confirm its final opinion on the application to the Chair, together with other named members, Mrs Janet Brember and Mrs Angela Iveson.

The Committee nominated Mrs Siobhan Bawn, the REC Manager, to be the point of contact should further clarification be sought from the applicant upon receipt of the decision letter.

The Committee nominated Professor Ron King, The Chair, to be the point of contact for the REC Manager if further information was required.

When submitting a response to the Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link:
http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 10 March 2016.

Summary of the discussion at the meeting

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

You were welcomed into the meeting and the discussion continued.

Ethical issues raised by the Committee in private discussion, together with responses given by the researcher when invited into the meeting

- **Social or scientific value; scientific design and conduct of the study**

The Committee informed you that they felt the IRAS section of the application had been very well written.

- **Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity**

The Committee acknowledged the sensitive manner in which you intend to handle the contacting of potential participants. However, the Committee noted you intend to send two reminder letters to potential participants and requested this was reduced to one reminder.

You agreed to reduce the reminder letter frequency to one set reminder letter.

The Committee were satisfied with this.

The Committee noted the patient interviews will take place whilst the patient is undergoing their routine drainage procedure and queried whether this would take place on a ward and if so, how would you ensure confidentiality is upheld.

You advised the drainage procedure in Bristol takes place in a private side room, which would aid the researchers in protecting the patients confidentiality throughout the 45 minute interview.

The Committee were satisfied with this response.

The Committee discussed the potentially distressing nature of the topics covered within this study and queried how quickly participants would be able to access the assistance of a relevant healthcare professional, in the event of distress.

You advised a mental healthcare professional would be holding emergency clinics on a daily basis, enabling any patient in crisis to very quickly be granted access to appropriate support.

The Committee were satisfied with this response and suggested a 24 hour crisis number is also provided to all patient participants.

You agreed to arrange this.

- **Informed consent process and the adequacy and completeness of participant information**

The Committee requested separate consent forms are submitted for each of the study groups. During the discussion it became apparent you had attempted to submit these consent forms. The REC Manager confirmed these had not been received and advised you to revisit the IRAS checklist once you received the Committee's decision letter.

You agreed to do this.

The Committee advised permission to audio record the discussion of the focus group should be written into the PIS and consent forms for the relatives of patients.

The Committee requested the following standard confidentiality clause is added to the PISs:

'I understand that the information I provide during the focus group will be held in strict confidence. Under the Data Protection Act 1998, should the researchers become concerned that information has been disclosed which might result in potential harm to yourself or others, they will need to notify the relevant authority. Wherever possible, this will be discussed with you first.'

The Committee requested the REC Reference is updated to read: South Central – Hampshire B Research Ethics Committee.

The PIS for relatives should mention the potential use of anonymised and unidentifiable quotes from the focus groups being used in the study write up and any subsequent publications.

The focus group Consent Form should include an item whereby participants agree to respect the confidentiality of other members of the group and those mentioned in discussion.

The Committee pointed out that other changes to the PIS noted by members would be required.

You accepted this.

Suitability of the summary of the research

The Committee approved the summary of the research for publication.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper	1	18 December 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Palliative care in liver disease. Insurance letter. 18.12.2015]	1	11 December 2015
GP/consultant information sheets or letters [Palliative care in liver disease. GP letter 1. Patient interviews. V1. 18.12.2015]	1	18 December 2015
Letter from funder [Palliative care in liver disease - Letter from funder. 06.03.2015]	1	18 December 2015
Letters of invitation to participant [Palliative care in liver disease. Focus group invitation letter. V1. 18.12.15]	1	18 December 2015
Other [Palliative care in liver disease. Participant information sheet 2	1	18 December 2015
- focus groups. V1. 18.12.15]		
Other [Palliative care in liver disease. Participant information sheet 3a. Clinical intervention-BRISTOL. V1. 18.12.15]	1	18 December 2015
Other [Palliative care in liver disease. Participant information sheet 3b. ROYAL FREE. Clinical intervention. V1. 18.12.15]	1	18 December 2015
Other [Palliative care in liver disease. GP letter 2. Focus groups. V1. 18.12.2015]	1	
Other [Palliative care in liver disease. Supporting statement - British Liver Trust. V1. 18.12.15]	1	18 December 2015
Other [Confirmation re missing Consent Form]		28 January 2016
Participant consent form [Palliative care in liver disease. Consent form 1. Patient interviews. V1. 18.12.15]	1	18 December 2015

Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 1 - patient interviews. V1. 18.12.15.]	1	18 December 2015
REC Application Form [REC_Form_07012016]		07 January 2016
Referee's report or other scientific critique report [Palliative care in liver disease. Scientific review. V1. 18.12.15]	1	18 December 2015
Research protocol or project proposal	1	18 December 2015
Summary CV for Chief Investigator (CI)	1	18 December 2015
Summary CV for supervisor (student research) [Palliative care in liver disease. CV. Prof Karen Forbes. V1. 18.12.15]	1	18 December 2015
Validated questionnaire [Palliative care in liver disease - Short Form of Liver Disease Quality of Life Instrument]	1	18 December 2015

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet
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.

16/SC/0041	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Professor Ron King Chair

[redacted]

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments.

Copy to: Dr Birgit Whitman
Dr Elinor Griffiths

South Central - Hampshire B Research Ethics Committee

Attendance at Committee meeting on 27 January 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Diane Ackerley	Retired Doctor	Yes	

Mrs Lisa Armstrong	Senior Lecturer Social Work	No	
Mrs Ravina Barrett	Pharmacist	Yes	
Mr Brian Birch (Acting AVC)	Consultant Urological Surgeon	Yes	
Mrs Janet Brember	Pharmacist	Yes	
Ms Julie Brinton	Speech and Language Therapist	Yes	
Mr Mark Cassidy	Senior Lecturer in Radiography	Yes	
Dr Alessandro di Nicola	Lecturer in Philosophy	Yes	
Ms Susan Edwards	Lead Contract Manager, NHS South West and Central Contract Support Unit	Yes	
Mrs Angela Iveson	Acute Oncology Clinical Nurse Specialist	Yes	
Professor Ron King (Chair)	Mathematician (Retired)	Yes	
Mr Geoff Lowndes	Chartered Engineer (Retired)	Yes	
Dr Andrew Scott (Vice Chair)	Course Leader, M.Sc. Clinical Exercise Science	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Siobhan Bawn	REC Manager
Miss Libby Watson	Deputy Regional Manager

Department of Hepatology
Bristol Royal Infirmary
Marlborough Street
BS2 8HW
17.02.2016

Re: Integration of palliative care into the management of patients with advanced liver disease
REC reference: 16/SC/0041, Protocol no. 2553, IRAS project ID: 193380
South Central – Hampshire B Research Ethics Committee

Dear Professor King,

Please accept my thanks on behalf of our team on your committee's detailed and thorough review of the above project, and for providing specific points of feedback for us to address. We have uploaded any documents which have been amended, and added other documents which were not submitted at the time of the committee meeting on the 27th of January 2016. All the changes made to previously submitted documents have been tracked, so that the areas which we have changed and updated are now highlighted in red. A summary of our responses to the specific information required by the committee is given below. It is numbered as per the points raised in the provisional opinion letter dated 09 February 2016.

1. *Clarify potential participants will only receive one reminder letter should they fail to respond to the initial invitation to the study*

I can confirm that only one postal reminder will be sent to participants, as opposed to the two reminders stated in our initial application. The updated study protocol is attached to this application (see document - Palliative care in liver disease. Research protocol. V2. 17.02.16. Page 10)

2. *Provide a 24 hour crisis number to all patient participants*

We have provided a 24 hour crisis number which will be available to all patient participants. In addition to this we have provided contact details for the hepatology specialist nursing team, who will act as the first point of contact during working hours. The hepatology specialist nursing team co-ordinate each patient's overall routine clinical care, and will be aware of each individual's participation in the study.

They will be able to quickly arrange prompt and appropriate specialist review (e.g. to liaison psychiatry, or to a hepatology or palliative care clinic) if required.

We have provided contact details for both services in the patient information leaflets for the 'patient interview', and 'clinical intervention' arms of the study (see documents – i) Palliative care in liver disease. Participant information sheet 3b. ROYAL FREE. Clinical intervention. V2. 17.02.16. ii) Palliative care in liver disease. Participant information sheet 3a. Clinical intervention-BRISTOL. V2. 17.02.16, iii) Palliative care in liver disease. Participant information sheet 1 - patient interviews. V2. 17.02.16.)

In addition to this we have composed a letter which will be distributed to each patient participant directly following their interview or clinic appointment (depending on which arm of the study they are enrolled). This letter re-iterates these contact details, should the participant have mislaid their initial patient information sheet (see documents – i) Palliative care in liver disease. Letter to participants following interview 1. V1. 17.02.2016 ii) Palliative care in liver disease. Letter to participants following clinic intervention - ROYAL FREE V1. 17.02.2016, iii) Palliative care in liver disease. Letter to participants following clinic intervention - BRISTOL. V1. 17.02.2016).

3. *Submit separate consent forms for each study groups*

4. *Permission to audio record the discussion of the focus group should be written into the PIS and consent forms for the relatives of patients, along with mention of the potential use of anonymised and unidentifiable quotes.*

8. *The focus group Consent Form should include an item whereby participants agree to respect the confidentiality of other members of the group and those mentioned in discussion*

Please accept my apologies for incorrectly attaching consent forms for arms 2 and 3 of the study to the IRAS form on the initial application. The consent forms have been updated in accordance with the advice provided by the committee, with additional sections on the use of anonymised and unidentifiable quotes in subsequent publications, an item by which participants in the focus group arm agree to respect the confidentiality of other members of the group and those mentioned in the discussion, and a standard confidentiality clause (which has also been added to the patient information sheets). (See documents – i) Palliative care in liver disease. Consent form 1. Patient interviews. V2. 17.02.16, ii) Palliative care in liver disease. Consent form 2. Focus groups. V2. 17.02.2016, iii) Palliative care in liver disease. Consent form 3. Clinical intervention. V2.17.02.16).

5. *Under 'Explanation and background' in each PIS, 'Research in this area will help us' should be replaced by 'Research in this area may help us' and 'might' inserted to give 'which might not only extend'.*

6. *Under 'What are the benefits of taking part?' in the focus group PIS, the first sentence should be replaced by 'The main benefit of taking part is that you have the opportunity to offer views that may improve care for future patients and their families'*

7. *Under 'What are the benefits of taking part?' in the additional clinic PIS, 'patients' should be replaced by 'participants', and 'you are also helping' should be replaced by 'you may also be helping'.*

9. *The following standard confidentiality clause is added to the PISs:*

   'I understand that the information I provide during the focus group will be held in strict confidence. Under the Data Protection Act 1998, should the researchers become concerned that information has been disclosed which might result in potential harm to yourself or others, they will need to notify the relevant authority. Wherever possible, this will be discussed with you first.'

10. *The REC Reference listed within the PIS should be updated to read: South Central – Hampshire B*

    Research Ethics Committee.

All of the above changes in wording have been made to the patient information sheets. In addition to its inclusion, the statement included in point 9 regarding the data protection act and confidentiality has also been added to the consent forms.

The updated patient information sheets are attached to our response (see documents – i) Palliative care in liver disease. Participant information sheet 1 - patient interviews. V2. 17.02.16, ii) Palliative care in liver disease. Participant information sheet 2 - focus groups. V2. 17.02.16, Palliative care in liver disease., iii) Participant information sheet 3a. Clinical intervention-BRISTOL. V2. 17.02.16., Palliative care in liver disease., iv) Participant information sheet 3b. ROYAL FREE. Clinical intervention. V2. 17.02.16.)

As you will be aware, prior to submitting our response we asked for clarification from the committee chair regarding one statement from the minutes of the committee meeting.

"You advised a mental healthcare professional would be holding emergency clinics on a daily basis, enabling any patient in crisis to very quickly be granted access to appropriate support"

The liaison psychiatry team at University Hospitals Bristol (UHB) work very closely with the hepatology team, and share the care of a large number of our patients. A mental health care professional from this team will be holding daily emergency clinics Monday-Friday, and participants will have prompt access to these clinics if required. These clinics however do not run at the weekend. There will be an emergency, 24-hour crisis number available to all patient participants which will provide emergency mental health assistance out of hours and at weekends. Within working hours, the initial contact will be the patient's

own hepatology specialist nurse, who will then arrange for emergency review from a mental health professional from within the UHB liaison psychiatry team if required. Within working hours we believe this is preferable to use of the "crisis number" as the hepatology specialist nursing team will know each participant entering into the study and what the study has involved. This also allows a structure for subsequent follow up of the patient. The hepatology specialist nursing team will also be familiar to all of the study participants.

We received an email response to the above clarification from Libby Watson (Deputy Regional Manager, South Central – Hampshire B Research Ethics Committee), who informed us that this arrangement had been run past the Chair who considered these arrangements to be sound and acceptable.

We hope that these responses and the updated documents are satisfactory to the committee. If there are any further queries or concerns, please do not hesitate to contact me.

Yours sincerely

Dr Benjamin Hudson (MB BCh, BSc (hons), MRCP (gastro))
Clinical Research Fellow and Principal Investigator
University Hospitals Bristol, University of Bristol

NHS
Health Research Authority

South Central - Hampshire B Research Ethics Committee
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Telephone: 0117 342 1384

25 February 2016

Dr Benjamin Hudson
[redacted]

Dear Dr Hudson

Study title:	**Integration of palliative care into the management of patients with advanced liver disease**
REC reference:	**16/SC/0041**
Protocol number:	**2553**
IRAS project ID:	**193380**

Thank you for your letter of 17 February 2016, 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, Mrs Janet Brember and Mrs Angela Iveson.

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 opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Siobhan Bawn, at:
[redacted]

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.

Conditions of the favourable opinion

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

1. The participant documents require proof-reading for typographical errors prior to finalisation.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

has been reviewed. In the meantime no study procedures should be initiated at 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	1	18 December 2015
Covering letter on headed paper	2	17 February 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Palliative care in liver disease. Insurance letter. 18.12.2015]	1	11 December 2015
GP/consultant information sheets or letters [Palliative care in liver disease. GP letter 1. Patient interviews. V1. 18.12.2015]	1	18 December 2015
GP/consultant information sheets or letters [Palliative care in liver disease. GP letter 2. Focus groups. V1. 18.12.2015.docx]	1	18 December 2015
IRAS Checklist XML [Checklist_17022016]		17 February 2016
Letter from funder [Palliative care in liver disease - Letter from funder. 06.03.2015]	1	18 December 2015
Letters of invitation to participant [Palliative care in liver disease. Focus group invitation letter. V1. 18.12.15]	1	18 December 2015
Other [Palliative care in liver disease. Supporting statement - British Liver Trust. V1. 18.12.15]	1	18 December 2015
Other [Palliative care in liver disease. Letter to participants following interview. V1. 17.02.2016.doc]	1	17 February 2016
Other [Palliative care in liver disease. Letter to participants following clinic intervention - BRISTOL. V1. 17.02.2016.doc]	1	17 February 2016
Other [Palliative care in liver disease. Letter to participants following clinic intervention - ROYAL FREE V1. 17.02.2016]	1	17 February 2016
Participant consent form [Palliative care in liver disease. Consent form 1. Patient interviews. V2. 17.02.16]	2	17 February 2016
Participant consent form [Palliative care in liver disease. Consent form 2. Focus groups. V2. 17.02.2016.doc]	1	17 February 2016
Participant consent form [Palliative care in liver disease. Consent form 3. Clinical intervention. V2.17.02.16]	1	17 February 2016
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 1 - patient interviews. V2. 17.02.16]	2	17 February 2016
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 2 - focus groups. V2. 17.02.16.docx]	2	17 February 2016
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 3a. Clinical intervention-BRISTOL. V2. 17.02.16..docx]	2	17 February 2016
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 3b. ROYAL FREE. Clinical intervention. V2. 17.02.16..docx]	2	17 February 2016
REC Application Form [REC_Form_07012016]		07 January 2016
Referee's report or other scientific critique report [Palliative care in liver disease. Scientific review. V1. 18.12.15]	1	18 December 2015
Research protocol or project proposal	2	17 February 2016
Summary CV for Chief Investigator (CI)	1	18 December 2015
Summary CV for supervisor (student research) [Palliative care in liver disease. CV. Prof Karen Forbes. V1. 18.12.15]	1	18 December 2015
Validated questionnaire [Palliative care in liver disease - Short Form of Liver Disease Quality of Life Instrument]	1	18 December 2015

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

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk 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 management permissions 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 within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

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 contest the need for registration they should contact Catherine Blewett [redacted] the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

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

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s)

NHS
Health Research Authority

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/

16/SC/0041	**Please quote this number on all correspondence**

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

Yours sincerely

[redacted]

Professor Ron King (Chair)
Chair

Email: [redacted]

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Dr Birgit Whitman*
Dr Elinor Griffiths, University Hospitals Bristol

NHS
Health Research Authority

South Central - Hampshire B Research Ethics Committee
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1384

14 March 2016

Dr Benjamin Hudson
[redacted]

Dear Dr Hudson

Study title:	**Integration of palliative care into the management of patients with advanced liver disease**
REC reference:	**16/SC/0041**
Protocol number:	**2553**
IRAS project ID:	**193380**

Thank you for your letter of 10th March 2016. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 25 February 2016

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Response to favourable opinion with conditions letter. 04.03.16.doc]	3	04 March 2016
Participant consent form [Palliative care in liver disease. Consent form 2. Focus groups. V3. 04.03.2016.doc]	3	04 March 2016
Participant consent form [Palliative care in liver disease. Consent form 3. Clinical intervention. V3.04.03.16.doc]	3	04 March 2016
Participant consent form [Palliative care in liver disease. Consent form 1. Patient interviews. V3. 04.03.16.doc]	3	04 March 2016
Participant consent form [Palliative care in liver disease. Consent form 2. Focus groups. V3. 04.03.2016.doc]	2	04 March 2016
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 2 - focus groups. V3. 04.03.16.docx]	3	04 March 2016
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 3a. Clinical intervention-BRISTOL. V3.	3	04 March 2016

04.03.16^.docx]		
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 3b. ROYAL FREE. Clinical intervention. V3. 04.03.16^.docx]	3	04 March 2016
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 2 - focus groups. V3. 04.03.16.docx]	3	04 March 2016
Participant information sheet (PIS) [Palliative care in liver disease. Participant information sheet 1 - patient interviews. V3. 04.03.16.docx]	3	04 March 2016

Approved documents

The final list of approved documentation for the study is therefore as follows:

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Covering letter on headed paper	1	18 December 2015
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Participant consent form [Palliative care in liver disease. Consent form 3. Clinical intervention. V3.04.03.16.doc]	3	04 March 2016
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Validated questionnaire [Palliative care in liver disease - Short Form of Liver Disease Quality of Life Instrument]	1	18 December 2015

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

16/SC/0041 **Please quote this number on all correspondence**

Yours sincerely

[redacted]

Mrs Siobhan Bawn
REC Manager

E-mail: [redacted]

Copy to: Dr Birgit Whitman
Dr Elinor Griffiths, University Hospitals Bristol

A Research Ethics Committee established by the Health Research Authority

Appendix 2 – Supplementary information relating to chapter 2 of this thesis

Appendix 2.1 – On-line questionnaire survey

Palliative care in advanced chronic liver disease

Page 1/3 - Clinician demographics

1. To which of the below societies do you belong

- ○ BSG
- ○ BASL
- ○ BSG and BASL
- ○ Neither BSG or BASL

2. What is your current post?

- ○ Consultant hepatologist - transplant centre
- ○ Consultant hepatologist - tertiary non transplant/level 2 centre
- ○ Consultant hepatologist - District General Hospital
- ○ Consultant gastroenterologist
- ○ Specialty registrar/trainee in gastroenterology/hepatology

3. If applicable, how many years have you been a consultant

- ○ Specialty registrar
- ○ Under 5
- ○ 5-9
- ○ 10-14
- ○ 15-19
- ○ 20-24
- ○ 25-29
- ○ Over 30

Next

4. The stage of liver disease at which the involvement of palliative care specialists is seen as appropriate (if at all) can vary between clinicians. Even when thought to be appropriate, referral is not always possible for a variety of reasons (e.g. resource limitations/lack of a clear referral pathway/time etc.)

Please read the below clinical vignettes

In your *day to day routine practice* which of the below cases *would you* refer to a specialist in palliative medicine?

***In your opinion* which of the below cases *should* be referred to a specialist in palliative medicine? (assuming no resource limitation or barrier to referral)**

Please tick all boxes that apply (leave blank if you feel referral would be inappropriate)

	I would refer in my routine practice	Ideally should be referred in my opinion
56 year old male. Compensated childs A NASH cirrhosis. Seen 6 monthly in stable cirrhosis clinic.	☐	☐
47 year old woman. Primary biliary cirrhosis - UKELD 52. Listed for transplantation.	☐	☐
78 year old man. NASH cirrhosis with diuretic resistant ascites and renal impairment. 2 weekly outpatient paracentesis.	☐	☐
67 year old man with decompensated childs B cirrhosis starting direct acting antiviral therapy for chronic hepatitis C virus infection.	☐	☐
37 year old woman. Alcohol dependency. Being discharged following 3 week admission for severe alcoholic hepatitis (first presentation).	☐	☐
52 year old man of no fixed abode. Ongoing addiction issues with alcohol and drug use. Recurrent A & E attendances. Childs C cirrhosis with jaundice, ascites and grade 1 encephalopathy.	☐	☐
64 year old man. Hepatocellular carcinoma. Childs A cirrhosis. Delisted for transplantation as tumour now outside criteria.	☐	☐
None of the above cases	☐	☐

Comments

5. Palliative care specialists are seldom involved in the management of advanced chronic liver disease.

Potential reasons for this have been cited.

Please rate to what extent you agree with each of the reaons cited below.

	Stongly disagree	Disagree	Neutral	Agree	Strongly agree
Advanced liver disease often has potential for clinical improvement (e.g. transplantation / abstinence / antiviral treatment). Physicians are reluctant to refer to palliative care when the disease is potentially reversible.	○	○	○	○	○
For the majority of patients there is no need for specialist palliative care input. Hepatologists are appropriately qualified to provide these aspects of care, and referral is unnecessary for most patients.	○	○	○	○	○
There are currently insufficient resources to afford specialist palliative care services to the majority of patients.	○	○	○	○	○
There is no clearly established palliative care referral framework or pathway for patients with advanced chronic liver disease.	○	○	○	○	○
Early involvement of palliative care can risk patients not being managed aggressively/appropriately by other specialties (eg. ITU/A&E) should they decompensate.	○	○	○	○	○
The illness trajectory in advanced liver disease is often uncertain and individual prognostication and identification of a clear "terminal phase" is difficult.	○	○	○	○	○
Palliative care and the hospice movement are not appropriately set up for the needs of patients with advanced liver disease.	○	○	○	○	○
Palliative care is of value in this patient group, but referral is not routinely considered by physicians managing advanced liver disease.	○	○	○	○	○

Other (please specify)

7. Please indicate to what extent you agree with the following statement.

"There is no role for specialist palliative care in the management of advanced chronic liver disease"

	Stongly disagree	Disagree	Neutral	Agree	Strongly agree
There is no role for specialist palliative care in the management of advanced chronic liver disease	○	○	○	○	○

Comments

8. This survey is part of a wider research initiative looking at the use of palliative care in advanced liver disease. If you would be willing to be contacted to undertake a more extensive interview (30-45 minutes) as part of this work please leave your email address in the box below. Thank you for your time.

Prev Done

Appendix 2.2 – Invitation to participate in interview letter

University of BRISTOL

University Hospitals Bristol NHS
NHS Foundation Trust

University Hospitals Bristol
Marlborough Street
BS2 8HW
[redacted]
26.02.2016

Re: Physician attitudes towards palliative care in advanced liver disease

Dear Dr

Thank you for responding to the recent questionnaire, distributed by BASL and the BSG liver section, investigating physician attitudes to specialist palliative care in advanced liver disease. The response rate of 33.6%, better than expected for surveys of this type, affords us a reasonably broad sample of opinion across the UK hepatology community.

The survey forms part of a more extensive research initiative looking at the optimal use of palliative care in advanced liver disease. As well as analysis of Public Health England and UK blood and transplant data into the service usage amongst patients with liver disease towards the end of life, we are also completing a series of qualitative studies amongst patients with advanced liver disease, families and carers who have been bereaved by liver disease, and physicians caring for patients with liver disease.

As part of the questionnaire you kindly indicated that you would consider taking part in a more detailed interview. We are aiming to complete these interviews between March-July 2016, and have aimed to invite a cross section of the UK hepatology community to take part. The interview would last approximately 30-45 minutes and would be audio recorded. We would visit participants at their place of work at a time convenient to them. Data would be anonymised however we may ask to use direct quotations from the interviews in subsequent publications. The interviews would cover:

- A small amount of your background (career, special interests etc)
- Your opinions towards current provision of palliative care to patients with advanced liver disease
- The stage at which palliative care should be introduced in the management of patients with advanced liver disease (if at all)
- The potential difficulties/risks of palliative care specific to patients with liver disease
- Whether specialist palliative care should be routinely integrated into management of patients with advanced liver disease in the UK, and possible strategies for achieving this.

In combination with the data from the questionnaire, we ultimately aim to publish a paper describing current attitudes towards palliative and supportive care in advanced liver disease amongst UK hepatologists.

If you would still be willing to participate, please email [redacted] so that a convenient time and place can be arranged over the next few months.

Many thanks again for your interest in this study

Yours sincerely

[redacted]

Dr Benjamin Hudson – Clinical research fellow – University of Bristol

[redacted]

Professor Julia Verne – Lead for Liver Disease and Clinical Lead of National End of Life Care Intelligence Network, Public Health England

[redacted]

Professor Karen Forbes – Professor of palliative medicine – University of Bristol

[redacted]

Dr Anne McCune – Consultant Hepatologist – University Hospitals Bristol NHS Trust

Appendix 3 – Supplementary information relating to chapter 4 of this thesis

Appendix 3.1– Most common HRG codes in dataset with linked episode tariffs

(refer to https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015 for full explanation of tariffs and costs applied)

HRG code	Number of appearances in dataset	HRG name	Outpatient procedure tariff (£)	Combined day case / ordinary elective spell tariff (£)	Day case spell tariff (£)	Ordinary elective spell tariff (£)	Ordinary elective long stay trimpoint (days)	Non-elective spell tariff (£)	Non-elective long stay trimpoint (days)	Per day long stay payment (for days exceeding trimpoint) (£)	Reduced short stay emergency tariff applicable?	% applied in calculation of reduced short stay emergency tariff	Reduced short stay emergency tariff (£)
GC15C	14358	Non-Malignant Liver Disorders with Major CCs	-	2,654	-	-	20	3,250	33	214	Yes	25%	813
FZ13Z	12529	General Abdominal Procedures	-	787	-	-	5	787	5	215	No	-	-
GC15A	5812	Non-Malignant Liver Disorders with Catastrophic CCs	-	6,634	-	-	73	6,127	69	214	Yes	25%	1,532
FZ60Z	4348	Diagnostic Endoscopic Procedures on the Upper GI Tract 19	344	344	-	-	5	724	5	215	No	-	-

		years and over											
GC15B	**4337**	**Non-Malignant Liver Disorders with Severe CCs**	**-**	**4,259**	**-**	**-**	**32**	**4,435**	**46**	**214**	**Yes**	**25%**	**1,109**
FZ47A	**3786**	**Non-Malignant General Abdominal Disorders with length of stay 2 days or more with Major CC**	**-**	**2,795**	**-**	**-**	**21**	**2,795**	**21**	**215**	**No**	**-**	**-**
GC01B	**3593**	**Liver Failure Disorders without Interventions**	**-**	**1,816**	**-**	**-**	**15**	**2,566**	**22**	**214**	**Yes**	**25%**	**642**
FZ47C	**3370**	**Non-Malignant General Abdominal Disorders with length of stay 1 day or less**	**-**	**401**	**-**	**-**	**5**	**684**	**5**	**215**	**No**	**-**	**-**
LA08E	**3052**	**Chronic Kidney**	**-**	**265**	**-**	**-**	**5**	**489**	**5**	**202**	**No**	**-**	**-**

		Disease with length of stay 1 day or less associated with Renal Dialysis											
GC12A	**2663**	**Malignant Liver and Pancreatic Disorders with length of stay 2 days or more**	**-**	**2,205**	**-**	**-**	**15**	**2,988**	**32**	**214**	**No**	**-**	**-**
FZ47B	**2646**	**Non-Malignant General Abdominal Disorders with length of stay 2 days or more without Major CC**	**-**	**1,895**	**-**	**-**	**10**	**684**	**10**	**215**	**No**	**-**	**-**
GC01A	**2463**	**Liver Failure Disorders with Interventions**	**-**	**3,356**	**-**	**-**	**30**	**4,788**	**46**	**214**	**Yes**	**25%**	**1,197**
GB02A	**2089**	**Endoscopic/ Radiology**	**-**	**3,456**	**-**	**-**	**13**	**5,294**	**44**	**214**	**No**	**-**	**-**

		category 3 with Major CC											
FZ38F	**1841**	**Gastrointestinal Bleed with length of stay 1 day or less**	**-**	**413**	**-**	**-**	**5**	**413**	**5**	**215**	**No**	**-**	**-**
GC12B	**1434**	**Malignant Liver and Pancreatic Disorders with length of stay 1 day or less**	**-**	**410**	**-**	**-**	**5**	**528**	**5**	**214**	**No**	**-**	**-**
DZ11A	**1397**	**Lobar, Atypical or Viral Pneumonia with Major CC**	**-**	**4,107**	**-**	**-**	**46**	**3,166**	**32**	**192**	**Yes**	**25%**	**792**
FZ38D	**948**	**Gastrointestinal Bleed with length of stay 2 days or more with Major CC**	**-**	**2,634**	**-**	**-**	**24**	**2,634**	**24**	**215**	**No**	**-**	**-**
WA03V	**800**	**Septicaemia with Major CC**	**-**	**5,217**	**-**	**-**	**47**	**3,729**	**41**	**204**	**Yes**	**25%**	**932**
WA18X	**790**	**Admission for Unexplained**	**-**	**731**	**-**	**-**	**5**	**1,921**	**16**	**204**	**Yes**	**25%**	**480**

		Symptoms with Intermediate CC											
GB02B	**774**	**Endoscopic/ Radiology category 3 with Intermediate CC**	**-**	**1,264**	**-**	**-**	**5**	**3,528**	**29**	**214**	**No**	**-**	**-**
EB01Z	**713**	**Non-Interventional Acquired Cardiac Conditions**	**-**	**989**	**-**	**-**	**5**	**577**	**5**	**208**	**No**	**-**	**-**
SA09D	**635**	**Other Red Blood Cell Disorders with CC**	**-**	**441**	**-**	**-**	**5**	**2,287**	**21**	**236**	**Yes**	**25%**	**572**
GB03A	**623**	**Endoscopic/ Radiology category 2 with CC**	**-**	**912**	**-**	**-**	**5**	**5,568**	**48**	**214**	**No**	**-**	**-**
FZ29Z	**589**	**Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed**	**-**	**611**	**-**	**-**	**5**	**2,327**	**20**	**215**	**No**	**-**	**-**
JD03A	**530**	**Intermediate Skin Disorders category 2**	**-**	**2,589**	**-**	**-**	**23**	**3,056**	**33**	**224**	**Yes**	**25%**	**764**

		with Major CC											
AA22A	**519**	**Non-Transient Stroke or Cerebrovascular Accident, Nervous System Infections or Encephalopathy with CC**	**-**	**3,708**	**-**	**-**	**73**	**3,875**	**46**	**204**	**Yes**	**25%**	**969**
LA07E	**518**	**Acute Kidney Injury with Major CC without Interventions**	**-**	**3,654**	**-**	**-**	**58**	**3,357**	**37**	**202**	**Yes**	**25%**	**839**
WA03X	**518**	**Septicaemia with Intermediate CC**	**-**	**2,935**	**-**	**-**	**17**	**2,511**	**21**	**204**	**Yes**	**25%**	**628**
AA26A	**516**	**Muscular, Balance, Cranial or Peripheral Nerve Disorders; Epilepsy; Head Injury with CC**	**-**	**891**	**-**	**-**	**5**	**1,191**	**13**	**204**	**No**	**-**	**-**

FZ31D	**513**	**Disorders of the Oesophagus with length of stay 2 days or more with Major CC**	**-**	**3,879**	**-**	**-**	**36**	**3,816**	**43**	**215**	**No**	**-**	**-**
FZ43C	**502**	**Non-Malignant Stomach or Duodenum Disorders with length of stay 1 day or less**	**-**	**366**	**-**	**-**	**5**	**377**	**5**	**215**	**No**	**-**	**-**

Appendix 3.2 - Distribution of missing data

There were 28 missing observations from the dataset which were distributed amongst the sample as listed below

		Missing data variable (n)	
		Inpatient bed days (n=25)	Age (n=3)
Gender	Female	10	1
	Male	15	2
Ethnicity	White British	22	1
	Non-white British	3	2
Deprivation quintile (1=most deprived)	1	5	1
	2	4	0
	3	8	0
	4	2	2
	5	6	0
Year of death	2013	9	0
	2014	12	0
	2015	4	3
Enrolled in day-case service?	No (unplanned care)	24	3
	Yes (planned care)	1	0
Cause of death	ArLD	12	0
	Viral	0	0
	NASH	2	1
	HCC	4	0
	Other	7	2
Place of death	Hospital	20	3
	Care home	1	0
	Home	3	0
	Hospice	1	0
	Other Places	0	0