Grant Agreement no. 287596

d-LIVER

ICT-enabled, cellular artificial liver system incorporating personalized patient management and support

INSTRUMENT: Collaborative Project (Integrating Project)

OBJECTIVE: ICT-2011.5.1

D1.7: Evaluation and description of the economic burden of chronic liver disease

Due Date of Deliverable: 31st January 2015
Completion Date of Deliverable: 7th April 2015

Start date of project: 1st October 2011 Duration: 48 months

Lead partner for deliverable: Newcastle University

Revision: v1.0

Project co-funded by the European Commission within the 7th Framework Programme (2007-2013)		
Dissemination Level		
PU	Public	✓
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including Commission Services)	
CO	Confidential, only for members of the consortium (including Commission Services)	

Document History

Issue Date	Version	Changes Made / Reason for this Issue
20th March 2015	v0.1	First draft
		For subsequent revisions, enter details of additions/corrections made and by which partner(s).
24th March 2015	v0.2	Revision MS/TW (Charité)
24th March 2015	v0.3	Revised version submitted for sign-off
7th April 2015	v1.0	Final version

Document Main Author(s): Jim Orr (UNEW), Tara Homer (UNEW), Laura Ternent (UNEW), Luke Vale (UNEW), Martin Stockmann (Charité)

Document signed off by: David Wenn (iXscient)

Copyright

Table of Contents

1. Executive Summary

Advanced liver disease can have an unpredictable disease course, largely as a result of episodic decompensation. This can result in frequent unscheduled hospital admissions and out of hours consultations, and it is therefore likely that advanced liver disease is associated with considerable healthcare resource utilisation. The d-LIVER system aims to facilitate much closer patient monitoring than is currently possible and should help to prevent or identify episodes of deterioration earlier. It is possible that this could result in a reduction in the use of healthcare resources such as emergency hospital admission, outpatient clinic attendance or A&E attendance.

There is clear potential for savings in healthcare resource use through d-LIVER. In this deliverable, two analyses are carried out to describe the health economic burden of advanced liver disease, as currently treated. There is a description of the healthcare resource use of patients with advanced liver disease in three European countries (UK, Germany and Italy) and a more detailed health economic analysis of treatment costs by the UK National Health Service.

The data presented shows that there are considerable healthcare resource utilisation and high costs associated with advanced liver disease, particularly with more advanced disease. There is clear potential for savings to be made through the implementation of improved systems of care delivery, such as d-LIVER.

2. Introduction

Advanced liver disease often has an unpredictable disease course, even with optimal care. As a result, patients typically have a high level of healthcare resource utilisation, such as emergency hospital admissions, outpatient attendances and primary care input. The technology developed by d-LIVER aims to facilitate close, home-based monitoring of patients with advanced liver disease with the potential to reduce the need for inpatient admissions and outpatient clinic appointments. This could result in considerable financial savings to healthcare systems which might account for the costs associated with the adoption and running of the d-LIVER system.

Previous studies have provided some detail on the health economic burden of liver disease. Previously unpublished data from Longworth, reported in the recent Lancet Commission on Liver Disease report [1], showed that the secondary care costs of liver disease in the UK were approximately £270 million in 2012/2013. Total National Health Service (NHS) costs of cirrhosis and hepatocellular carcinoma secondary to Alcohol Related Liver Disease (ARLD) were estimated at £566 million in 2007 [2], a figure which is estimated to be rising by 10% every year [3]. Healthcare costs are known to vary between countries, largely as a result of differences in healthcare systems. For example, in a US study of patients with chronic Hepatitis C, the annual cost of compensated cirrhosis was estimated at US$22,752 while End Stage Liver Disease (ESLD) was associated with annual healthcare costs of US$59,995 [4]. By contrast, a UK study estimated the NHS costs of decompensated liver disease at £9,120 [5].

The specific health economic burdens of the proposed clinical indications for d-LIVER guided therapy have also been explored separately. Hepatic Encephalopathy (HE) has been shown to be associated with particularly high costs, both to the individual and to healthcare systems [6, 7] and was estimated to cost more than US$7 billion in the US in 2009 [8]. A study from the UK showed that HE was associated with significantly greater numbers of inpatient admissions compared with matched cirrhotic controls without HE (crude admission ratio of 3.59 (95% CI 3.33-3.87)) [9] and annual inpatient costs were found to be almost five times greater (£10,417 vs £2,301) (unpublished data). With respect to ascites, an Italian study of a new system of structured care delivery for patients with ascites found patients in the control group receiving the current standard of care to have mean secondary care costs of €2,816 (S.D. €3,893.03) per month [10].

Here we carry out two analyses: the first is a descriptive comparison of healthcare resource use in patients with advanced liver disease in the UK, Germany and Italy, while the second is an in-depth analysis of the direct and indirect costs associated with advanced liver disease in the UK. It was impracticable to carry out this analysis for all three countries because the analysis was carried out in collaboration with the Institute of Health and Society at Newcastle University, with access only to standard UK NHS costs.

3. Descriptive analysis of healthcare resource utilisation in the UK, Germany and Italy

3.1. Aim

This first analysis was carried out to describe the level of healthcare resource utilisation in patients with end stage liver disease (ESLD) in three European countries: the UK, Germany and Italy. Data were collected across a range of specific healthcare activities allowing identification of potential targets for healthcare expenditure reductions through the implementation of the d-LIVER system. Comparisons between the three countries were made to identify differences in healthcare resource utilisation, for example as a result of different treatment models.

3.2. Methods

Patients with cirrhosis defined histologically or clinically were identified from the outpatient and inpatient departments of hospitals in the UK (Newcastle upon Tyne Hospitals, City Hospitals Sunderland, South Tyneside Hospital, Cumbria Infirmary, University Hospital of North Durham and University Hospital of North Tees), Germany (Charité - Universitätsmedizin Berlin) and Italy (Humanitas Research Hospital, Milan). Inclusion criteria were biopsy proven cirrhosis or clinically suspected cirrhosis defined as the presence of two or more of the following:

- imaging suggestive of cirrhosis (irregular liver outline and/or splenomegaly measuring >12 cm)
- liver elastography >17.6 kPa
- platelet count $<120x10^3/cm^3$
- previous endoscopic evidence of upper GI varices or portal hypertensive gastropathy
- current or previous diagnosis of ascites or encephalopathy

Patients with a current malignancy (including hepatocellular carcinoma) and those undergoing antiviral therapy for Hepatitis C were excluded. Patients provided informed consent, and ethical approval was granted by the West Country Research Ethics Committee, UK, the Ethics Committee Charité – Universitätsmedizin Berlin, Germany and Humanitas Independent Ethics Committee, Milan, Italy. Demographic, clinical, and laboratory parameters were collected at baseline, patients were examined for evidence of ascites or peripheral oedema and a basic psychometric assessment for hepatic encephalopathy was carried out with the number connection test A (NCT-A).

A Healthcare Utilisation Questionnaire (HUQ) was designed to collect details of direct and indirect healthcare resource use with a recall period of 2 months. Patients were asked to complete the HUQ at 2, 4, 6, 8 10 and 12 months (i.e. the data capture covered a 12 month period). Questionnaires were completed by patients at home and posted back to the investigators. A Health Related Quality of Life (HRQoL) tool, the SF-36 v2, was also completed alongside the HUQ at each scheduled time point. The SF-36 v2 allows the derivation of health state utilities using the SF-6D algorithm [11]. Due to the variation in recruitment and study start dates between centres, the length of follow-up available for analysis at the time of analysis varies. Resource utilisation in the descriptive analysis was therefore expressed per two month period (by dividing the sum of all responses from a single patient by the number of responses) to allow all available data to be included.

While some data were non-parametrically distributed, results were summarised as mean ± standard deviation because the analysis was designed to consider the health economic impacts of ESLD on society, rather than describing the typical patient experience. It was, therefore, important to include outliers in the analysis, for example those patients with high levels of healthcare utilisation. When comparing means across more than two groups, analysis of variance analysis (ANOVA) was used to test statistical significance.

3.3. Results

3.3.1. Patient characteristics

Data were available from 324 patients (166 from the UK, 137 from Germany and 21 from Italy). Summary demographic and clinical data are shown in table 1. The mean age was 59.3 (S.D. 10.9), with more males (61%) than females included. The majority of patients were retired (48%) and 27% were unable to work due to their illness. 19% were in part-time or full-time employment. The mean number of medications taken by patients was 5.9 (S.D. 3.1), consistent with considerable co-morbidities. The majority patients had ARLD (52%) while 13% had Non-Alcoholic Fatty Liver Disease (NAFLD). 35% had liver disease due to another aetiology, including viral hepatitis and autoimmune liver disease. In terms of disease severity, 49% had Child Pugh (CP) A cirrhosis, 37% CPB and 14% CPC. Model for End Stage Liver Disease (MELD) scores were 10 or less in 42%, 10-18 in 41% and more than 18 in 14%. Hepatic Encephalopathy (HE) was recorded in 24% of patients at baseline (7% mild and 17% moderate to severe) but the Number Connection Test (NCT) showed that there were likely a number of patients with undiagnosed covert HE as 38% of patients took longer than 50 seconds to complete the NCT, a rough cut-off used for the diagnosis of Conn grade I-II HE [12]. 35% of patients had ascites at inclusion, of whom 11% had mild and 24% had moderate or severe ascites.

3.3.2. Inpatient hospital admissions

The length of all hospital admissions reported by patients was analysed. Table 2 shows the mean length of emergency, elective and total admissions report per 2 month recall period, analysed by disease severity as measured by CP grade and by country. There were significant differences observed between the three countries, particularly with respect to the length of elective hospital admissions ($p<0.05$ for CP grades A, B and C). These differences were mainly due to higher elective admissions in Germany, compared with the UK and Italy. For example, German CPB patients had a mean elective admission length of 4.03 ± 5.05 days per 2 month period, compared with 0.69 ± 2.67 days in the UK and 0.80 ± 1.79 days in Italy. On the other hand, no statistically significant differences were observed between the three countries for length of emergency admissions. There were clear differences observed between CP grades with increasing disease severity associated with increasing length of hospital stay ($p<0.005$ for emergency, elective and total hospital admissions). Mean length of emergency admission per 2 month period was 0.63 ± 3.11, 2.68 ± 6.05 and 5.16 ± 9.06 days for CPA, B and C patients respectively.

3.3.3. Outpatient resource utilisation

There was a small but significant increase in the number of hospital outpatient clinics attended as liver disease severity increased (table 3). Overall, patients with CPA cirrhosis had 1.4 ± 1.3 clinic attendances per two month period and this increased to 2.0 ± 2.6 for CPB and 2.0 ± 2.3 for CPC ($p=0.022$). There were significant differences in clinic attendance between the three countries with German patients generally attending clinic less frequently than UK or Italian patients. For example, CPC patients in the UK attended clinic a mean of 3.1 ± 2.9 times per two month period while in Germany this was 1.1 ± 1.0 ($p=0.020$). A&E attendance did not vary significantly between countries across all three CP grades but there was a slight increase with increasing disease severity; CPA patients attended A&E a mean of 0.1 ± 0.3 times per two month period while CPC attended 0.2 ± 0.5 times.

		UK (n=166)	Germany (n=137)	Italy (n=21)	All centres (n=324)
Age		60.3 ± 11.0	57.3 ± 10.7	64.0 ± 9.3	59.3 ± 10.9
Male sex		99 (60%)	76 (61%)	16 (76%)	191 (61%)
Employment	Full-time	15 (9%)	24 (18%)	3 (14%)	42 (13%)
	Part-time	12 (7%)	7 (5%)	0 (0%)	19 (6%)
	Retired	79 (48%)	59 (44%)	17 (81%)	155 (48%)
	Unemployed	3 (2%)	16 (12%)	0 (0%)	19 (6%)
	Unable to work due to illness	56 (34%)	31 (23%)	0 (0%)	87 (27%)
Marital stat.	Married	81 (49%)	85 (62%)	16 (76%)	182 (56%)
	Single	40 (24%)	13 (9%)	1 (5%)	54 (17%)
	Living with partner	14 (8%)	24 (18%)	0 (0%)	38 (12%)
	Widowed	11 (7%)	5 (3.6%)	3 (14%)	18 (6%)
	Separated/divorced	19 (11%)	10 (7.3%)	1 (5%)	30 (9%)
BMI		29.7 ± 8.5	27.6 ± 5.6	28.0 ± 5.6	28.7 ± 7.2
Number of regular medications		6.5 ± 3.1	5.4 ± 2.8	3.9 ± 2.8	5.9 ± 3.1
Aetiology	ARLD	95 (57%)	64 (47%)	8 (38%)	167 (52%)
	NAFLD	29 (17%)	12 (9%)	2 (10%)	43 (13%)
	Other	42 (25%)	61 (45%)	11 (52%)	114 (35%)
Child Pugh	Grade A	90 (54%)	52 (38%)	16 (76%)	158 (49%)
	Grade B	60 (36%)	57 (42%)	4 (19%)	121 (37%)
	Grade C	16 (10%)	28 (20%)	1 (5%)	45 (14%)
MELD	≤ 10	82 (49%)	44 (32%)	10 (48%)	136 (42%)
	10-18	65 (39%)	58 (42%)	9 (43%)	132 (41%)
	> 18	13 (8%)	30 (22%)	1 (5%)	44 (14%)
Enceph.	None	125 (75%)	99 (72%)	20 (95%)	244 (75%)
	Mild	7 (4%)	16 (12%)	0 (0%)	23 (7%)
	Moderate – severe	32 (19%)	22 (16%)	1 (5%)	55 (17%)
NCT	≤50 seconds	93 (56%)	93 (68%)	6 (29%)	192 (59%)
	>50seconds	68 (41%)	40 (29%)	14 (67%)	122 (38%)
Ascites	None	108 (65%)	77 (56%)	18 (86%)	203 (63%)
	Mild	35 (21%)	1 (1%)	1 (5%)	37 (11%)
	Moderate – severe	18 (11%)	59 (43%)	2 (10%)	79 (24%)

Table 1: Baseline demographic and clinical parameters. Continuous variables are summarised as mean ± S.D. and categorical variables as number and percentage. (BMI- Body Mass Index, MELD- Model for End Stage Liver Disease, NCT- Number Connection Test).

	Child Pugh A				
	UK	Germany	Italy	All countries	**p**
Emergency admission length/2months	0.45 ± 2.32	0.87 ± 4.29	0.93 ± 2.58	0.63 ± 3.11	0.697
Elective admission length/2months	0.08 ± 0.53	1.06 ± 1.86	2.40 ± 9.02	0.63 ± 3.03	**0.010****
Total admission length/2months	0.53 ± 2.37	1.93 ± 5.67	3.33 ± 9.12	1.26 ± 4.69	**0.046***

	Child Pugh B				
	UK	Germany	Italy	All countries	**P**
Emergency admission length/2months	2.53 ± 6.26	2.92 ± 6.02	2.00 ± 4.47	2.68 ± 6.05	0.912
Elective admission length/2months	0.69 ± 2.67	4.03 ± 5.05	0.80 ± 1.79	2.13 ± 4.17	**<0.0005****
Total admission length/2months	3.22 ± 6.82	6.83 ± 8.29	2.80 ± 4.38	4.75 ± 7.58	**0.038***

	Child Pugh C				
	UK	Germany	Italy	All countries	**P**
Emergency admission length/2months	3.95 ± 8.59	6.33 ± 9.62	0.00 ± 0.00	5.16 ± 9.06	0.630
Elective admission length/2months	0.25 ± 0.87	7.76 ± 10.18	0.00 ± 0.00	4.21 ± 8.25	**0.019***
Total admission length/2months	4.20 ± 8.78	14.76 ± 14.90	0.00 ± 0.00	9.66 ± 13.33	**0.045***

	Child Pugh A	**Child Pugh B**	**Child Pugh C**	**All patients**	**P**
Emergency admission length/2months	0.63 ± 3.11	2.68 ± 6.05	5.16 ± 9.06	1.96 ± 5.54	**<0.0005****
Elective admission length/2months	0.63 ± 3.03	2.13 ± 4.17	4.21 ± 8.25	1.61 ± 4.51	**<0.0005****
Total admission length/2months	1.26 ± 4.69	4.75 ± 7.58	9.66 ± 13.33	3.55 ± 7.78	**<0.0005****

*** significant at 1% level; * significant at 5% level*

Table 2: Length of inpatient hospital admissions. The mean reported length of emergency, elective and total hospital admission per 2 month period is shown ± S.D. p values are from ANOVA and show statistical significance of differences observed between countries (top three table sections) and between Child Pugh grades (bottom table section).

	Child Pugh A				
	UK	Germany	Italy	All countries	**p**
Clinic attendances/2months	1.6 ± 1.5	0.9 ± 0.9	1.5 ± 1.3	1.4 ± 1.3	**0.006****
A&E attendances/2months	0.1 ± 0.2	0.1 ± 0.4	0.0 ± 0.0	0.1 ± 0.3	0.346

	Child Pugh B				
	UK	Germany	Italy	All countries	**p**
Clinic attendances/2months	2.2 ± 1.6	1.8 ± 3.5	1.7 ± 2.5	2.0 ± 2.6	0.617
A&E attendances/2months	0.2 ± 0.5	0.1 ± 0.4	0.2 ± 0.4	0.1 ± 0.4	0.377

	Child Pugh C				
	UK	Germany	Italy	All countries	**p**
Clinic attendances/2months	3.1 ± 2.9	1.1 ± 1.0	2.0 ± 0.0	2.0 ± 2.3	**0.020***
A&E attendances/2months	0.2 ± 0.6	0.2 ± 0.5	0.0 ± 0.0	0.2 ± 0.5	0.951

	Child Pugh A	**Child Pugh B**	**Child Pugh C**	**All patients**	**p**
Clinic attendances/2months	1.4 ± 1.3	2.0 ± 2.6	2.0 ± 2.3	1.7 ± 2.0	**0.022***
A&E attendances/2months	0.1 ± 0.3	0.1 ± 0.4	0.2 ± 0.5	0.1 ± 0.4	**0.005****

*** significant at 1% level; * significant at 5% level*

Table 3: Outpatient resource utilisation: clinic and A&E attendances. The mean reported number of clinic and A&E attendances per 2 month period is shown ± S.D. p values are from ANOVA and show statistical significance of differences observed between countries (top three table sections) and between CP grades (bottom table section).

3.3.4. Primary care resource use

Table 4 shows primary care resource use. There were no statistically significant differences between the three countries with respect to General Practitioner (GP) and nurse consultations or home visits, except for nurse home visits in the CPC patients. However, this was skewed because the only Italian CPC patient included in this analysis reported 60 nurse home visits in a two month period (equivalent to one visit every day). The number of GP consults increased with disease severity (e.g. 1.3 ± 1.4 per 2 months for CPA and 2.2 ± 1.4 for CPC, p=0.001). Similarly the number of nurse home visits increased significantly (CPA: 0.1 ± 0.5 per 2 months, CPC: 1.9 ± 9.7, p=0.029). There were no significant differences in the number of GP home visits or practice nurse consults with disease severity.

3.3.5. Telephone consultations and out of hours consultations

Data on telephone consultations with all health professionals (GP, hospital doctor, nurses, other) were collected as part of the health utilisation questionnaire, and were analysed in combination here (see table 5). There were no differences seen in the number of telephone consultations by either country or disease severity. Out of hours consultations, including consultations with GPs out with normal working hours or unscheduled reviews by hospital doctors, were also analysed as one group. There was no statistically significant difference between the countries but an increase was observed with increasing CP score (CPA: 0.0 ± 0.3 OOH consultations per 2 months, CPB: 1.0 ± 5.3 per 2 months, p = 0.019).

	Child Pugh A				
	UK	Germany	Italy	All countries	**p**
GP consults/ 2months	1.0 ± 1.6	1.5 ± 1.0	1.6 ± 1.0	1.3 ± 1.4	0.051
GP home visits/ 2month	0.1 ± 0.5	0.1 ± 0.3	0.0 ± 0.0	0.1 ± 0.5	0.446
Practice nurse consults/ 2months	0.4 ± 0.6	0.3 ± 2.1	0.0 ± 0.0	0.3 ± 1.3	0.518
Nurse home visits/ 2months	0.2 ± 0.6	0.1 ± 0.3	0.0 ± 0.0	0.1 ± 0.5	0.397

	Child Pugh B				
	UK	Germany	Italy	All countries	**p**
GP consults/ 2months	1.6 ± 2.3	2.1 ± 1.5	2.6 ± 1.9	1.9 ± 2.0	0.225
GP home visits/ 2month	0.3 ± 0.7	0.2 ± 0.7	0.0 ± 0.0	0.2 ± 0.7	0.601
Practice nurse consults/ 2months	1.0 ± 1.1	1.2 ± 8.5	0.0 ± 0.0	1.1 ± 5.6	0.901
Nurse home visits/ 2months	0.8 ± 2.4	1.2 ± 4.7	0.8 ± 1.8	1.0 ± 3.5	0.855

	Child Pugh C				
	UK	Germany	Italy	All countries	**p**
GP consults/ 2months	2.1 ± 1.3	2.2 ± 1.5	3.0 ± 0.0	2.2 ± 1.4	0.84
GP home visits/ 2month	0.2 ± 0.6	0.0 ± 0.1	0.0 ± 0.0	0.1 ± 0.4	0.347
Practice nurse consults/ 2months	2.2 ±3.4	0.0 ± 0.0	0.0 ± 0.0	0.9 ± 2.4	0.019
Nurse home visits/ 2months	0.3 ± 0.6	0.4 ± 1.0	60.0 ± 0.0	1.9 ± 9.7	**<0.0005****

	Child Pugh A	**Child Pugh B**	**Child Pugh C**	**All patients**	**p**
GP consults/ 2months	1.3 ± 1.4	1.9 ± 2.0	2.2 ± 1.4	1.6 ± 1.7	**0.001****
GP home visits/ 2month	0.1 ± 0.5	0.2 ± 0.7	0.1 ± 0.4	0.1 ± 0.6	0.234
Practice nurse consults/ 2months	0.3 ± 1.3	1.1 ± 5.6	0.9 ± 2.4	0.7 ± 3.7	0.255
Nurse home visits/ 2months	0.1 ± 0.5	1.0 ± 3.5	1.9 ± 9.7	0.7 ± 4.1	**0.029***

*** significant at 1% level; * significant at 5% level*

Table 4: Primary care resource utilisation. The mean reported number of GP consults, GP home visits, practice nurse consults and nurse home visits per 2 month period is shown ± S.D. p values are from ANOVA and show statistical significance of differences observed between countries (top three table sections) and between CP grades (bottom table section).

	Child Pugh A				
	UK	Germany	Italy	All countries	**p**
Phone consults/ 2months	0.5 ± 1.5	0.3 ± 0.7	0.3 ± 1.0	0.4 ± 1.3	0.641
OOH consults/ 2 months	0.1 ± 0.4	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.3	0.649

	Child Pugh B				
	UK	Germany	Italy	All countries	**p**
Phone consults/ 2months	0.5 ± 0.8	1.4 ± 4.8	0.7 ± 1.3	0.9 ± 3.2	0.371
OOH consults/ 2 months	0.1 ± 0.3	0.3 ± 0.8	0.7 ± 1.3	0.2 ± 0.6	0.071

	Child Pugh C				
	UK	Germany	Italy	All countries	**p**
Phone consults/ 2months	0.2 ± 0.5	0.5 ± 1.4	0.0 ± 0.0	0.4 ± 1.1	0.717
OOH consults/ 2 months	0.2 ± 0.7	1.7 ± 7.1	0.0 ± 0.0	1.0 ± 5.3	0.717

	Child Pugh A	**Child Pugh B**	**Child Pugh C**	**All patients**	**p**
Phone consults/ 2months	0.4 ± 1.3	0.9 ± 3.2	0.4 ± 1.1	0.6 ± 2.2	0.156
OOH consults/ 2 months	0.0 ± 0.3	0.2 ± 0.6	1.0 ± 5.3	0.2 ± 1.9	**0.019***

*** significant at 1% level; * significant at 5% level*

Table 5: Telephone consultations and out of hours (OOH) consultations. The mean reported number of telephone consultations and out of hours consultations per 2 month period is shown ± S.D. p values are from ANOVA and show statistical significance of differences observed between countries (top three table sections) and between CP grades (bottom table section).

3.4. Discussion

This analysis of a large number of patients with cirrhosis from three different European countries demonstrates the level of healthcare resource utilisation associated with ESLD. In general resource utilisation increased as disease severity increased. For example, mean total length of hospital admission was 1.26 ± 4.69 days per 2 months for CPA, increasing to 4.75 ± 7.58 days for CPB and 9.66 ± 13.33 days for CP. This represents considerable inpatient bed days in advancing disease, equivalent to annual admissions of 29 and 58 days per year for CPB and C patients respectively. In addition, utilisation of other resources, including outpatient attendance, A&E attendance, GP consultations, nurse home visits and out of hours consultations, all increased with worsening severity of liver disease. These results indicate that there is considerable potential for reduced healthcare utilisation through improved structured care delivery with the d-LIVER system. Closer monitoring should facilitate prevention or earlier detection of decompensation which could help to reduce the need for emergency admission hospital and reduce the number of out of hours consultations. In addition, fewer outpatient reviews and GP consultations might be required because of the close remote monitoring made possible by the system. The savings made through reduced healthcare resource utilisation should be factored into future cost effectiveness analyses of d-LIVER.

4. Detailed health economic analysis of UK patients

4.1. Aim

The second analysis, a detailed health economic analysis of UK patients, was carried out to estimate costs and quality-adjusted life years of patients with ESLD. These results will inform policy-makers of the current costs and effectiveness of monitoring and managing ESLD. The following outcomes are reported:

1. Costs to the National Health Service (NHS)
2. Direct and indirect costs to the patient and the patient's main caregiver
3. Quality-adjusted life years (QALYs) estimated by the Short-Form 6 Dimensions (SF-6D) derived from responses to the Short-Form 36 (SF-36).

The perspective of the data presented here is the health service (NHS), patient and the patient's main caregiver. The main costs collected are those from the utilisation of health services, i.e. the average total cost over a period of time to the NHS for treating a patient with ESLD. As noted above, further analysis will take a broader perspective, in which individual patient costs and costs borne by the patient's main caregiver are included. These patient and caregiver costs include direct (e.g. travel costs and out-of-pocket payments) and indirect (e.g. time spent travelling to and at healthcare appointments) costs.

4.2. Methods

4.2.1. Estimation of Costs

Costs were collected from routine sources (e.g. NHS reference costs [13]) and were based on the healthcare resource use of each individual patient over a one-year follow-up period. Costs were summarised into the following categories:

1. Secondary care costs
2. Primary care costs
3. Treatment costs
4. Home care costs
5. Individual costs to patients

Estimation of the use of resources involved three main components: identification, measurement and valuation. To identify and measure resource, the HUQ captured data relating to primary care, secondary care, medical procedures, daily medications and home help. Patient-related costs including out-of-pocket expenses were also collected via the HUQ. A time and travel questionnaire was used to capture the costs of accessing and using health services e.g. patient and caregiver time and travel costs for each healthcare visit. The frequency of use of each NHS resource was expressed in mean and median values along with appropriate measures of distribution. Further details for each area of service use are given below.

Secondary Care Costs

Secondary care refers to healthcare provided in a hospital setting; this can refer to inpatient admissions, Accident and Emergency and outpatient visits. The HUQ collected information on the number of nights an individual spent in hospital in the preceding two months and whether this was an elective or emergency admission. In order to provide a more accurate estimation of average inpatient costs associated with ESLD, a distinction was made as to whether patients were admitted as an emergency or planned admission because there are different unit costs associated with each type of admission.

Primary Care Costs

Primary care costs were categorised as consultations with GPs or practice nurses. Primary care costs were further distinguished by how the consultation was given (i.e. practice consultation, home visit, telephone consultation or out-of-hours consultation) and appropriate unit costs were applied.

Treatment costs

A list of medical procedures frequently undergone by patients with ESLD was included in the HUQ, along with a list of daily medications which are commonly taken by patients with ESLD. This list was informed by expert clinical opinion.

The list of medical procedures included a range of diagnostic procedures and treatments. These included, but were not limited to, blood tests, draining of ascites and endoscopy. Patients indicated which, if any, medical procedures they have undergone during the previous two months and the frequency of those procedures. From this, the average number of each procedure that patients underwent was estimated. In addition, an "Other tests or procedures" category recorded additional procedures carried out. This information is presented as the average total costs for all patients and average total costs by CP score over the one-year follow-up for all procedures reported.

From the list of medications provided, patients were asked to indicate which, if any, of the medications they were taking and how many times a day they took the medication.

Home Care Costs

Due to the severity of ESLD, a number of patients may need assistance at home. This care could be provided by a family member or friend or by a home-help worker provided by the NHS. The health service questionnaire asks patients what type of care they needed assistance with (e.g. cleaning, meal preparation etc.), who provided this care and how many hours of care was provided weekly. If home care was provided by an NHS carer, this was included in total NHS costs. The time costs of relatives and friends who provided home help is presented with social costs of ESLD.

Individual costs to patients

Information on patient out-of-pocket payments for private medical and/or personal care was captured by the HUQ. This included items such as dentist appointments, spectacles, nursing home costs, surgical consultations and home cleaning. One limitation of including additional patient costs for other healthcare is that patients included healthcare that was not directly related to liver disease.

4.2.2. NHS unit costs

Details of all unit costs for health care resources are listed in Appendix A and B. The unit costs for NHS services that were used were collected from routine sources (NHS reference costs 2013/2014 [13]). For unit costs collected from other sources (e.g. Private Patient Tariffs 2011/12 [14]) we chose the NHS reference costs as our base year and inflated costs to 2014 values. Further details of the estimation of unit costs are provided in Appendix A and B.

4.2.3. Patient and caregiver time and travel unit costs

Despite the majority of healthcare costs being absorbed by the NHS, patients and their main caregivers still incur costs. The main costs are travel expenses and the cost of time that patients and/or their main caregiver spend travelling to and attending healthcare appointments. The unit costs of travelling and accessing healthcare by patients and carers was estimated from responses to the time and travel questionnaire. A unit cost for each form of contact with health services was calculated. The average monetary cost of travelling to a specific type of care was either taken directly from the monetary costs reported by the patient for fares or for travel by car the monetary cost was estimated by combining the mileage with information on the cost per mile taken from routine sources [15]. For time costs, the average time spent travelling to and actually receiving each specific type of care was estimated from the responses to the time and travel questionnaire. These data were combined with information on the type of activity that was displaced by accessing care, obtained from the respondent (e.g. lost wages) or from routine sources (for the cost of housework, leisure time, etc.). Patients indicated what their usual activities would have been if they were not receiving care. This time cost was also estimated for the patient's main caregiver if they attended appointments with the patient. The cost of time was valued at the national median wage rate per hour [16] if the patient or caregiver missed paid work. If the patient/caregiver reported that they had lost leisure time this was valued at the Department of Transport cost per hour of leisure time [17].

The number of days absent from paid employment due to ESLD was captured and the national median wage rate per hour was used to estimate the loss in earnings from absence at work due to ESLD. The average number of days absent from paid employment due to ESLD was compared to the average number of days absent due to any illness. This comparison highlights the effect (if any) ESLD has on a person's ability to work.

If a patient's relative and/or friend provided home care, this cost was estimated based on the type of home care provided, how long each type of care is provided for and whether or not this relative/friend had to travel to provide this home care.

Details used to estimate these costs are summarised in Table 6.

Resource	**Cost (£)**	**Source**
Paid work/hour	13.81 (6.50)	ONS Annual survey of hours and earnings 2014 – provisional results *Median (Minimum) UK wage 2014*
Leisure time - commuting	6.84	Department of Transport TAG UNIT 1.3 User and Provider Impacts Jan 2014 *Market price values*
Leisure time – other activity	6.10	Department of Transport TAG UNIT 1.3 User and Provider Impacts Jan 2014 *Market price values*
Cost per mile	0.3768	AA Motoring costs 2014 *Purchase price of car when new up to £13,000 at 10,000 miles/year*

Table 6: Patient/caregiver costs.

Table 7 presents a summary of the unit costs generated from patient responses to the time travel questionnaire. We estimated the average total time and travel cost for each healthcare visit based on responses to the time travel questionnaire. For patient costs for inpatient stay, we multiplied the average total cost per minute of a patient's time for an inpatient admission by 60 to estimate the average hourly cost. This hourly rate was multiplied by 24 to estimate the total cost of an inpatient stay.

Resource	Cost £ (SD)	Source
Average patient time cost per inpatient stay (per minute)	0.23 (0.1)	Time travel questionnaire *(average cost per patient minute based on other activity – 0.23/minute (0.0864)*
Average patient time cost per inpatient stay (per night)	331.20	Time travel questionnaire *(average cost per patient minute based on other activity – 0.23/minute*60minutes*24hours)*
Total average caregiver travel cost per inpatient stay	0.00 (-)	Time travel questionnaire *(average travel cost per carer based on type of travel)*
Total average patient time cost per outpatient visit	29.63 (21.7)	Time travel questionnaire *(average cost per patient's time based on other activity and time spent at hospital clinic)*
Total average carer's time cost per outpatient visit	34.16 (23.5)	Time travel questionnaire *(average cost per carer's time based on other activity and time spent at hospital clinic)*
Total average patient travel cost per outpatient visit	53.74 (91.3)	Time travel questionnaire *(average travel cost per patient based on type of travel)*
Total average caregiver travel cost per outpatient visit	0.00 (-)	Time travel questionnaire *(average travel cost per carer based on type of travel)*
Total average patient's time cost per GP visit	10.30 (6.6)	Time travel questionnaire *(average cost per patient's time based on other activity and time spent at GP practice)*
Total average carer's time cost per GP visit	12.05 (9.8)	Time travel questionnaire *(average cost per carer's time based on other activity and time spent at GP practice)*
Total average patient travel cost per GP visit	1.25 (0.5)	Time travel questionnaire *(average travel cost per patient based on type of travel)*
Total average caregiver travel cost per GP visit	0.00 (-)	Time travel questionnaire *(average travel cost per carer based on type of travel)*

Table 7: Estimated patient and caregiver time and travel costs.

Estimation of NHS Costs

The unit cost for each healthcare resource for each patient was multiplied by the frequency of resource use for that patient. The resultant costs for each patient were then used to estimate the average cost of each area of resource use. The costs for each patient (for each area of resource use) were summed to produce a total cost for each patient by level of care (e.g. primary care, secondary care etc.) and overall. These data were then used to estimate the average total costs by level of care and overall. This process allowed us to identify high cost areas in the provision of healthcare for ESLD patients.

Equation 1: Estimation of average total NHS costs

NHS average total costs = (total secondary care costs + total primary care costs + total medical procedure costs + total medication costs + total NHS carer costs) / N

N = Number of patients in the analysis

Estimation of patient and caregiver costs

Costs borne by patients and their main caregivers were estimated using the same process as described above for estimating costs for time and travel. These unit costs were combined with the number of each type of specific NHS appointment (e.g. GP visits) to estimate a cost of using that type of service by that patient. These data were used to estimate average total costs analogous to those estimated for NHS costs described above.

Out of pocket expenses for self-purchased healthcare were measured and valued to produce average total costs of self-purchased healthcare. All patient and caregiver costs were then combined to produce an estimated average of total patient and caregiver costs.

The average total cost per patient and the average total cost per caregiver were generated using unit costs collected from routine sources [16, 17] (refer to Table 6) and the time and travel questionnaire. These unit costs were combined with the average length of each healthcare appointment, average travel costs and average days off work to generate total average costs. By breaking down the costs into time and travel, it gives a greater insight into the costs patients and their main caregivers are subject to when dealing with ESLD.

Equation 2: Estimation of average total patient and caregiver costs

Patient and caregiver average total costs = (travel costs for attending secondary care appointments + time costs for attending secondary care appointments + travel costs for attending primary care appointments + time costs for attending primary care appointments + out of pocket payments + time costs for providing home help + travel costs for providing home help) / N

N = Number of patients in the analysis

Average overall NHS and patient costs

The costs for each patient were combined to produce a total overall cost for that patient. These data were then used to estimate an average total overall cost to the NHS for treating a patient with ESLD.

Equation 3: Estimation of average total cost (ATC)

ATC = NHS average total costs + patient and caregiver average total costs.

Estimation of QALYS

The SF-36v2 is a multi-purpose short-form health questionnaire and was administered to patients with the HUQ at every 2 months during the one-year study. This questionnaire is regularly used in economic evaluations to assess patients' quality of life [18, 19]. The SF-36v2 comprises 36 questions that incorporate both physical health and mental health. The dimensions of physical health are physical functioning, role-physical, bodily pain and general health. The dimensions of mental health are vitality, social functioning, role-emotional and mental health. These eight health concepts combined give us an indication of the health profile of a patient with end stage liver disease. The responses to this questionnaire can be converted into a utility value using an algorithm devised by Brazier et al [11]. Multiple imputation techniques were used for patients with complete missing utility data at any given time point. If a patient partially responded to the questionnaire we examined their pattern of responses, and based on the pattern of missing

responses made assumptions accordingly. Sensitivity analysis was performed to test the robustness of all assumptions. The utility values were calculated at scheduled time points (i.e. every 2-months) during the follow-up period. The area under the curve method [20] was used to estimate QALYs for every patient. The area under the curve approach puts a time weight onto each utility score which allows the estimation of QALYs. Since the SF-36v2 was administered after 2, 4, 6, 8, 10 and 12 months we are missing a baseline utility value. We have assumed that the questionnaire administered at 2-months is our baseline questionnaire and have amended our area under the curve equation accordingly to estimate QALYs. Equation 4 is the algorithm we used to estimate QALYs using 10-months of utility data.

Equation 4: Estimation of QALYs

*QALYs = ((sf-6d 2months * (2/10)) + (sf-6d 4months * (2/10)) + (sf-6d 6months * (2/10)) + (sf-6d 8months * (2/10)) + (sf-6d 10months * (2/10)) + (sf-6d 12months * (2/10))) * (10/12)*

Assumptions made in estimation of costs (valuation of resource use) and QALYs

All unit costs for secondary care resources were sourced from NHS reference costs [13]. Inpatient stays, both elective and non-elective, were costed as excess bed days. This estimates the actual cost of an inpatient visit and removes any costs incurred from procedures etc. We had no indication whether a patient was admitted to an Intensive Care Unit or High Dependency Unit and hence assumed all admissions were to a General Ward. If a patient reported "Yes" to being admitted to hospital and "0" number of nights as their length of stay we have assumed that they were in hospital as a day case. Information on the number of A&E and outpatient visits in the last 2 months was also collected. A disease-specific cost was used for outpatient visits, Hepatology outpatient visit and the national average A&E cost was used to estimate the cost of an A&E visit.

With respect to primary care costs, there was difficulty in estimating a unit cost for an out-of-hours consultation with a GP because of the introduction of NHS 111 telephone service. We have assumed that the unit cost of an out-of-hours consultation is equivalent to a 17.2 minute GP clinic consultation, costing £3.20 per minute with the addition of a time cost for travel. This generates a cost in excess of a GP home consultation and is more representative of the actual cost of out-of-hours consultations with a GP compared to the current estimated cost of £7.50 per person for using out-of-hours GP services [21]. The HUQ provides information on the number of consultations for each type of consultation at a primary care level. In addition, information on out-of-hours and telephone consultations with a hospital doctor was also collected. It was assumed in the first instance that a telephone consultation was with a consultant, in sensitivity analysis we assumed this was with a registrar and adjusted unit costs accordingly.

With respect to other procedures, no unit costs were estimated for a small number of procedures listed because assumptions could not be sensibly made given the vast range of procedures provided. Also, for some procedures we were not able to seek the unit cost as the patient recorded a number instead of a name of procedure. As a consequence of this the costs of procedures were not incorporated into total NHS costs or the other estimates of cost.

A number of daily medications taken by patients with ESLD were recorded in the HUQ. Patients indicated whether they had taken a daily medication in the last 2-months and if so which from the list did they take and how many times a day they took this medication. The unit costs of medications were sought from the BNF [22] and we estimated the cost per drug. An assumption

was made about the dosage of each medication based on data contained in the BNF [22]. This unit cost was multiplied by the number of times daily the patient took the medication and then by 60 as we assumed they had the drug every day for the last 2-months. In some instances a patient recorded taking a daily medication but did not indicate that they were taking any of the medications listed in the HUQ. We did not enter an "Other medication" section here as it could result in patients reporting non-liver related medications.

If a patient was provided with home help by a relative or friend, we estimated the hourly cost of this help based on responses to the time-travel questionnaire. In this questionnaire patients were asked to report what their relative or friend would have been doing if they had not provided home help. We used the average hourly rate of paid work and multiplied it by the weekly hours reported by the patients for home help. This answer was then multiplied by 8 to estimate the total cost of home help for the last two-months for each patient.

With regards to travel costs, we assumed a visit to a GP practice would incur the same cost as a visit to a practice nurse and the travel costs to an A&E visit would be the same as the travel costs for a hospital/clinic visit. We made these assumptions to prevent overburdening the patient with additional questions in the time-travel questionnaire when sensible assumptions could be made about travelling to various healthcare appointments. If a patient was accompanied by a caregiver on a visit and travelled by car, we only costed this information for the patient to prevent double counting travel costs. All travel costs were doubled to account for a return trip.

Handling missing data

Both the HUQ and SF-36v2 had missing responses from patients over the one-year follow-up period. In order to generate a more accurate estimation of costs borne by the NHS for managing and monitoring ESLD, we used imputation techniques to estimate missing responses. The last value carried forward technique [23] was used for patients missing responses to one HUQ. Since the time horizon between follow-up periods was short we could sensibly assume the healthcare resources used in the previous two-months were a good estimation of resource use in the following two-months. If a patient was missing responses to more than one HUQ we used the average of their reported HUQ responses to estimate missing responses (excluding responses generated from the last value carried forward technique). These costs were estimated from the responses from the first five HUQ only as they will be compared to the average QALY score estimated from SF-36v2 responses. If there was only partial responses to the HUQ (e.g. a patient responded "Yes" to using a healthcare service and the number of visits was missing) we looked at the pattern of responses for that patient over the one-year period and made imputations based on their resource use.

For missing SF-36v2 responses, we used multiple imputation techniques to estimate the value of the missing utility score. We controlled for baseline utility and other patient characteristics to estimate missing utility scores that were used in our QALY calculation. If a patient had partially completed the SF-26v2, similarly to the HUQ, we looked at their pattern of responses to that question over the one-year follow-up and made assumptions accordingly. Responses to the SF-36v2 are presented as the average total utility score every 2-months and QALYs are estimated based on actual responses to the SF-36v2 and with imputed responses to missing SF-36v2.

Data analysis of cost data

Cost and QALY comparison

The HUQ and SF-36v2 were administered at the same time points throughout the study. As previously mentioned, the SF-36v2 had no baseline questionnaire and hence we used month 2 as our baseline and estimated QALYs over a 10-month period. The HUQ captures one-year of resource use as it is retrospective and states "In the last two months…". In order to compare costs and QALYs over the same time horizon, we originally planned to use costs at month 2 as a baseline and use this as an effect modifier in our regression analysis of costs. However, given the

current response rates for 2-months (n=83) and 12-months (n=48) questionnaires, this data analysis strategy was not appropriate. For the results presented here, we used responses at 2-months in our analysis and when additional data becomes available, further analysis will be undertaken. Therefore for comparisons between costs and QALYs, we have compared costs incurred in months 0-10 with QALYs for the period from month 2 to month 12.

Sensitivity Analysis

Sensitivity analysis was conducted to explore any uncertainty surrounding the estimates and assumptions used in our cost and QALY analyses. Both deterministic and stochastic sensitivity analyses were performed to test for the effect of assumptions made around estimating resource use and unit costs as well as statistical imprecision. An example of deterministic sensitivity analysis would be the exploration of alternative unit costs applied to the different resources used. Deterministic sensitivity analyses included a high/low analyses and stochastic sensitivity analysis were undertaken to present the level of statistical variance around the primary outcome measures (costs and QALYs) using a bootstrapping technique. Bootstrapping was used because parametric methods used to estimate single sample confidence intervals may not be appropriate given the likely heavily skewed and non-normally distributed nature of the data. The bootstrapping approach is an alternative approach to estimating confidence intervals around estimates of costs and QALYs.

Regression Analysis

Regression analysis (OLS) was specified where costs and QALYs were the dependent variable. Independent variables included in the regression analyses were: age, gender, severity of liver disease and type of liver disease, and were used to predict any key drivers of cost or QALYs.

The key independent variables in the cost regression model were identified as age, gender, CP score, baseline utility score (i.e. from the 2 month questionnaire), employment status and type of liver disease. These independent variables were identified using expert opinion. Given our small sample size, many variables were collapsed into dummy variables. We generated a dummy variable for patients who were employed (part-time or full-time) all other patients were regarded as not in current employment whether that was due to their liver disease, age (retired) or some other factor. Our sample had a relatively large range of types of liver disease; we combined these to look at the impact of alcoholic liver disease and NAFLD vs. all other types of liver disease to determine the impact this had on costs. However, we expect the severity of the disease to have more of an impact on costs than the disease aetiology. Table 8 and Equation 5 provide information on the regression model where cost is specified as the dependent variable. Table 9 is a list of predictions we made on the relationship between costs and each independent variable.

Dependent Variable	**Independent Variable**
NHS Costs	Age (A) Sex (S) Employment Status (E) Child Pugh Score (CPB) Child Pugh Score (CPC) Baseline utility (U) Type of liver disease (ALD) Type of Liver disease (NAFLD)

Table 8: Independent Variables used in the cost regression.

Equation 5: Regression model with costs as the dependent variable

$$NHS\ costs = ß_0 + ß_1A + ß_2S + ß_3E + ß_4CPB + ß_5CPC + ß_6U + ß_7ALD + ß_8NAFLD + \hat{e}$$

Independent Variable	**Prediction of relationship with costs**
Age	We would expect there to be a positive relationship with age - as we get older our health deteriorates and older patients tend to have a higher healthcare resource use.
Gender	We would expect men to incur a higher cost than women as they tend to have poorer health.
Child Pugh Score	We would expect both CPB and CPC to incur higher costs than CPA we would also expect to see a greater difference in the costs incurred by CPC patients compared to CPA patients than the increase between CPB and CPA patients.
Baseline utility	We would expect to see a negative relationship between costs and baseline utility; if baseline utility is close to 1 the patient has reported good health and we would expect lower healthcare costs.
Employment Status	Patients who are employed will be in overall better general health and we would hence assume that employment has a negative relationship with costs.
Type of Liver disease	We expected that aetiology might impact costs of treatment.

Table 9: Predicted relationship of independent variables on total costs.

The key independent variables in the QALY regression were age, gender, employment status, type of liver disease, severity of liver disease and total costs. The regression model, with QALYs as the dependent variable, is explained in further detail in Table 10 and Equation 6. The predictions of the relationship between QALYs and independent variables are presented in Table 11.

Dependent Variable	**Independent Variable**
QALYs	Age (A) Sex (S) Employment Status (E) Child Pugh Score (CPB) Child Pugh Score (CPC) Total costs at 10-months (TC) Type of liver disease (ALD) Type of Liver disease (NAFLD)

Table 10: Independent Variables used in the QALY regression.

Equation 6: Regression model with QALYs as the dependent variable

$$QALYs = ß_0 + ß_1A + ß_2S + ß_3E + ß_4CPB + ß_5CPC + ß_6TC + ß_7ALD + ß_8NAFLD + \hat{e}$$

Independent Variable	**Prediction of relationship with QALYs**
Age	We would expect there to be a negative relationship between QALYs and age. As patients get older we would expect their health-related quality of life (HRQoL) to reduce.
Gender	We would expect men to incur a lower QALY score than women as women tend to have a better health status
Child Pugh Score	We would expect both CPB and CPC to incur lower QALY values than CPA we would also expect to see a greater difference in the QALY reduction in CPC patients compared to CPA patients than the decrease in QALYs between CPB and CPA patients.
Total cost	We would expect to see a negative relationship between total costs and QALY values if patients have a better HRQoL they would be using less healthcare resources and hence incur less costs.
Employment Status	Patients who are employed will be in overall better general health and we would hence assume that employment has a positive relationship with QALYs.
Type of Liver disease	We expected aetiology to affect quality of life – previous studies have varied but NAFLD has been shown to be associated with greater impairment

Table 11: Predicted relationship of independent variables on QALYs.

Costs and health-related quality of life (SF-36v2 score at 2-months) are independent variables in each other's regression model to determine if there is a relationship between the amount of money the NHS spends on managing and monitoring ESLD and the HRQoL experience by a patient. We would expect an inverse relationship between these two variables; as costs increase (due to ill-health) we would expect QALYs to decrease.

Net Benefit

The net benefit statistic is used to compare treatments in an economic evaluation as it overcomes some of the limitations of a cost-effectiveness ratio (as it is difficult to statistically analyse a ratio of two correlated measures). For a given intervention, the net benefit statistic is estimated by multiplying effectiveness by society's willingness to pay for additional effectiveness. From the product of this, costs are subtracted. In comparisons of two or more treatments, the treatment with the greatest net benefits is considered to be the most efficient.[23] When considering a cost and outcome description for a single treatment the net benefit for a single treatment can still be calculated and it can be used to illustrate the trade-off between costs and effects for that treatment. In this study, net benefit is calculated on an individual basis for all patients with ESLD.

Equation 7: Net Benefit Analysis

$$Net\ Benefit_i = QALY_i . \lambda - Cost_i$$

λ = Willingness to pay threshold for a QALY (e.g. £20,000[24]).

We varied the willingness to pay threshold from £30,000 to £10,000 to determine the impact on the cost-effectiveness of treating patients with ESLD as society's willingness to pay decreases. The results were presented as the total average net benefit for all patients with ESLD and then by CP score. The £30,000 limit is the upper end for society's willingness to pay for a QALY based on NICE guidance [24], whilst the £10,000 is more consistent with recent empirical research on society's willingness to pay for a QALY. By calculating the net benefit of treating patients with ESLD, we can identify clinical conditions, based on patients with the lowest net benefit, which drive costs and hence reduce benefits the most.

4.3. Results

Eighty-five patients with ESLD completed 12 months follow-up by December 2014.

Initially, we estimated costs based on the information provided only; no imputations were made for missing data. This analysis effectively assumes that any data that was missing had a zero value. Table 12 provides descriptive statistics on the resource use of patients over the complete one-year follow-up period. These results highlight the main areas of healthcare resource use of patients with ESLD. In secondary care, the median outpatient visits an ESLD patient had over a 12-month period was 7. Admissions to hospital, on average, tend to be emergency admissions over elective admissions. From the mean results and the interquartile range, we can identify that a small number of patients have had a high number of admissions in 12-months with one patient reporting a maximum of 55 nights as an inpatient and another patient 37 outpatient visits in 12-months.

With regards to primary care, consultations with a GP or practice nurse are the most frequently used healthcare resources. Again we can identify a small number of patients having a very high number of consultations with one patient has reported 48 consultations with a GP over 12-months and another patient 28 consultations with a practice nurse.

The most routinely performed medical test is a blood test with patients reporting a median of 6 blood tests per year. Ultrasounds were the next most frequent test with patients reporting having on average 1 ultrasound per year.

With regards home help, on average, patients with ESLD received most help with personal care and the least with medical care. We assumed that medical care provided by a carer or relative related to care such as collecting prescriptions, changing bandages etc. as all other medical care would be provided by a healthcare professional. For other care, patients reported receiving help with their shopping, gardening and outdoor care.

We would expect to see a small number of patients having a very high level of resource use in the data as patients' resource use increases as their disease progresses. We have categorised the severity of liver disease based on patients' CP scores: 43 patients were classified as CPA, 36 as CPB and 6 as CPC.

Resource use	N	Mean usage (SD)	Median (IQR)	Source
Secondary care				
Emergency inpatient stay	85	2.96 (8.53)	0.00 (0.00 - 1.5)	HUQ q1
Elective inpatient stay	85	1.52 (4.68)	0.00 (0.00 – 0.00)	HUQ q2
Outpatient appointment	85	8.2 (6.82)	7.00 (3.00 – 11.00)	HUQ q3
A&E attendance	85	0.34 (0.87)	0.00 (0.00 – 0.00)	HUQ q4
Primary care				
GP practice visits	85	5.2 (6.92)	3.00 (1.00 – 6.00)	HUQ q6
GP home visits	85	0.39 (1.12)	0.00 (0.00 – 0.00)	HUQ q7
Practice nurse visits	85	3.4 (4.20)	2.00 (1.00 – 4.00)	HUQ q8
Nurse home visits	85	1.6 (4.82)	0.00 (0.00 – 0.00)	HUQ q9
Telephone consultations with GP	85	0.75 (1.57)	0.00 (0.00 – 1.00)	HUQ q10
Telephone consultations with nurse	85	0.51 (1.28)	0.00 (0.00 – 0.00)	HUQ q10
Telephone consultations with hospital doctor	85	0.26 (0.95)	0.00 (0.00 – 0.00)	HUQ q10
Out-of-hours consultations with GP	85	0.09 (0.57)	0.00 (0.00 – 0.00)	HUQ q11
Out-of-hours consultations with nurse	85	0.09 (0.57)	0.00 (0.00 – 0.00)	HUQ q11
Out-of-hours consultations with hospital doctor	85	0.18 (0.74)	0.00 (0.00 – 0.00)	HUQ q11
Medical procedures				
Number of tests/procedures	85	4.05 (1.46)	4.00 (3.00 – 5.00)	HUQ q5
Blood Test	85	8.42 (7.31)	6.00 (3.50 -12.00)	HUQ q5
X-ray	85	1.11 (1.76)	0.00 (0.00 -1.00)	HUQ q5
Ultrasound	85	1.89 (1.60)	1.00 (1.00 – 3.00)	HUQ q5
CT Scan	85	0.72 (1.11)	0.00 (0.00 – 1.00)	HUQ q5
MRI Scan	85	0.49 (1.19)	0.00 (0.00 – 1.00)	HUQ q5
Endoscopy	85	0.71 (1.12)	0.00 (0.00 -1.00)	HUQ q5
Drainage of ascites	85	0.45 (1.52)	0.00 (0.00 -1.00)	HUQ q5
Medication				
Reported taking medication daily	85	-	5.00 (4.00 – 6.00)*	HUQ q12
Home Help				
Personal care (hours)	85	129.17 (286.88)	0.00 (0.00 – 48.00)	HUQ q13
Medical care (hours)	85	38.2824 (127.04)	0.00 (0.00 – 5.00)	HUQ q13
Meal Preparation (hours)	85	97.69 (211.55)	0.00 (0.00 – 60.00)	HUQ q13
Housework (hours)	85	115.48 (217.25)	0.00 (0.00 – 188.00)	HUQ q13
Other care (hours)	85	64.28 (169.28)	0.00 (0.00 – 40.00)	HUQ q13
NHS carer hours	85	2.73 (19.31)	0.00 (0.00 – 0.00)	HUQ q 13

*Table 12: Total average healthcare resource use (SD=standard deviation, IQR=interquartile range, HUQ=health utilisation questionnaire) *The median value of 5 suggests that patients reported taking medications for 10 months out of the year.*

4.3.1. Costs

The total annual cost for managing and monitoring ESLD was estimated from actual responses to the HUQ; no imputations were made for missing responses. Table 13 presents the average total costs for 12 months by CP score and highlights the total average costs over 12-months for each classification of CP score. As a patient's disease progresses from CPA to CPB there is an increase in the average NHS costs for monitoring ESLD by £4756 per patient, an average increase in costs of 168%. When a patient progresses from CPB to CPC we observed a slight decrease in the total average cost of £418 per patient, a 5.5% reduction in costs. There are a number of possible reasons for this counter-intuitive result. Our sample size for this analysis (n=85) is relatively small and there is missing data at every 2-month follow-up phase, hence the results are more sensitive to outliers in our dataset (i.e. high cost patients). Our analysis will be re-run at a later stage with more patients when all patients complete their one-year follow-up. The number of patients with CPC in our study is exactly one sixth of patients with CPB hence too few data are available to make reliable estimates of costs for this group. Also, one patient with CPC died before month 4 during the study and hence their costs burden was reduced to £0. If a patient is classified with CPC their disease has progressed to the final stages of ESLD they may be too ill to complete the questionnaires. Table 14 highlights the response rates at every 2-month follow-up period and shows that the percentage of patients with CPC responding to the HUQ halves at month-6 of the study. Thus, it is likely that the data we have over the follow-up period relates to the healthier individuals with CPC and that those who are not as well (and who might be expected to incur higher costs) have either died or are unable to return the questionnaires. The decrease in responses to the questionnaire over the one-year follow-up and appears to be sensible as CPA consistently has a higher percentage of respondents and patients with CPC have the higher percentage of non-respondents.

	N	**Mean costs (£) (SD)**	**Minimum costs**	**Maximum costs**
All patients	85	5146 (5388.8)	37	26255
CP classification				
A	43	2825 (2752.9)	297	12606
B	36	7581 (6928.6)	37	26255
C	6	7163 (7251.5)	2145	21363

Table 13: Annual Average Total costs for all patients with ESLD and by Child Pugh Score.

CP classification	**Month 2**	**Month 4**	**Month 6**	**Month 8**	**Month 10**	**Month 12**
A (n=43)	42 (98%)	42 (98%)	41 (95%)	38 (88%)	35 (81%)	27 (63%)
B (n=36)	35 (98%)	35 (97%)	33 (92%)	27 (75%)	21 (58%)	19 (53%)
C (n=6)	6 (100%)	5 (83%)	3 (50%)	3 (50%)	2 (33%)	2 (33%)

Table 14: Response rates to the HUQ at every 2-months based on Child Pugh score.

Other procedures reported by patients were collected via the HUQ. On average, patients reported having over £450 worth of additional procedures in one-year. This is a conservative estimation of the costs associated with other procedures as a unit cost could not be sourced for all other procedures as previously mentioned.

	N	Mean costs (£) (SD)	Minimum costs	Maximum costs
All patients	85	462(1433.4)	0.00	11853.00*
CP classification				
A	43	453 (1818.6)	0.00	11853.00
B	36	523 (961.3)	0.00	4010.00
C	6	160 (358.3)	0.00	899.00

*Table 15: Total average costs for other procedure (N= number of patients; SD = Standard Deviation) *One patient reported having 3 hip replacements.*

There is a trend towards an increase in costs for other procedures in patients classified as CPB compared to CPA. This is to be expected as ESLD progresses the number of additional treatments and tests will increase as the managing and monitoring of the ESLD intensifies. Again, CPC has produced counter intuitive results but this could be due to the very low number of CPC in our sample and the reduction in their response rates over time (note statistical comparisons have not been performed as the sample size is too small and we would not expect to detect any statistically significant results).

We used imputation methods to estimate the total average cost of treating patients over a 10-month period with ESLD to determine what impact this would have on overall costs. Table 16 presents the results from this analysis.

	N	Mean costs (£) (95% CI)	Minimum costs	Maximum costs
All patients	85	5773 (4612.38 – 7154.8)	111	26671
CP classification	**N**	**Mean costs (£) (SD)**	**Minimum costs**	**Maximum costs**
A	43	2872 (2859.4)	310	12350
B	36	8349 (7093.9)	111	26671
C	6	11111 (6873.9)	2146	20274

Table 16: Total average costs for 10 months with imputed values for missing HUQ responses N= number of patients; SD = Standard Deviation; 95% CI = 95% Confidence Interval.

Total NHS and patient/caregiver costs

Table 17 provides a detailed description of the total costs of managing and monitoring ESLD. These costs include NHS costs and societal costs. The societal costs included are time and travel costs for patients and their main caregiver for attending healthcare services. Time costs of relatives and friends for caring with patients with ESLD. All costs were estimated over a 10-month period. We initially planned to include the cost of absence from paid employment in this estimation of societal costs but because the small numbers of patients responding to this question (n=11), this was not included.

	N	Mean costs (£) (SD)	Minimum costs	Maximum costs
All patients	85	15887 (20941.0)	164	109104
CP classification				
A	43	7981 (11250.4)	396	44918
B	36	25028 (26622.6)	164	109104
C	6	17710 (14128.4)	2349	41103

Table 17: Total costs (NHS and Societal costs) for 10-months.

4.3.2. Quality Adjusted Life Years

Table 18 shows the total average utility values at each two-month follow-up period with a steady decrease in response rates as the study progresses. QALY values were estimated based on actual responses to the SF-36v2 at every scheduled 2-month follow-up. Only 31 patients had completed all six questionnaires. Data is presented as total average QALY value for all patients with ESLD and total average QALY value based on CP scores. The table shows that patients with ESLD have an average QALY value of 0.620. There is a trend towards a decrease in QALY values from CPA to CPB and CPC (although again this has not been tested due to the small sample size). We used multiple imputation techniques to estimate missing SF-36v2 responses and the results are in Table 19.

	N	Mean (SD)	Median (IQR)
2 months after study entry	79	0.612 (0.151)	0.595 (0.5080 – 0.700)
4 months after study entry	76	0.614 (0.165)	0.598 (0.470 – 0.736)
6months after study entry	73	0.600 (0.144)	0.593 (0.512 – 0.670)
8 months after study entry	65	0.616 (0.140)	0.595 (0.524 – 0.689)
10 months after study entry	56	0.616 (0.133)	0.583 (0.522 – 0.679)
12 months after study entry	41	0.631 (0.132)	0.603 (0.529 – 0.728)
QALYs (overall)	31	0.620 (0.144)	0.603 (0.527 - 0.697)
CPA	18	0.667 (0.124)	0.642 (0.565 – 0.795)
CPB	12	0.583 (0.111)	0.580 (0.4970 - 0.618)
CPC	1	0.218 (-)	-

Table 18: Total average QALYs for 10 months with no imputations for missing SF-36 responses.

	N	Mean QALYs (95% CI)	Minimum QALYs	Maximum QALYs
All patients	85	0.616 (0.586 – 0.645)	0.22	0.99
CP classification	**N**	**Mean QALYs (SD)**	**Minimum QALYs**	**Maximum QALYs**
A	43	0.639 (0.138)	0.34	0.99
B	36	0.585 (0.119)	0.41	0.89
C	6	0.634 (0.235)	0.22	0.86

Table 19: Total average QALYs for 10 months with imputed values for missing SF-36 responses (N= number of patients; SD = Standard Deviation; 95% CI = 95% Confidence Interval).

The inclusion of multiple imputation techniques has reduced the average of all patients with ESLD from 0.620 to 0.616. The total average QALY values associated with CPA have been slightly reduced by 0.028 QALYs. The total average QALY values for CPB remain relatively consistent but the average total QALY values for CPC have increased. Again caution needs to be taken when interpreting these results due to the high proportion of CPC patients with missing utility values. Sensitivity analysis will be performed around these results and further imputations will be used to estimate QALY values.

4.3.3. Sensitivity Analysis

A deterministic sensitivity analysis was performed in the first instance to explore the variation in costs from the assumptions in our base case analysis. The high-low analysis resulted in a variation of costs of less than 1% (0.5% - 0.7%) in the average total NHS costs per patient and in the average total NHS and societal cost per patient. We also performed an extreme analysis looking at the impact of a procedure costs as these had been excluded from our base case analysis because we were unable to cost some of the procedures used. We assumed the cost of other procedures cost £10,000 for one patient. This resulted in an increase of £118 (2%) in average total cost per patient.

A stochastic sensitivity analysis, which explores the impact of the statistical imprecision surrounding estimates of costs and QALYs was undertaken to allow presentation of the level of variance around outcome measures used in our analysis. Uncertainty surrounding the outcome measures used in our analysis was estimated using the bootstrapping technique. The results of the bootstrapping simulation are presented on the 'cost-effectiveness plane', which highlights the relationship between costs and QALYs for patients with ESLD. Bootstrapping was also used to estimate confidence intervals for both costs and QALYs. Figure 1 is an illustrative example of the relationship between costs and QALYs in patients with ESLD. The majority of the patients are close to the average estimate of costs and QALYs for patients with ESLD over a 10-month time frame.

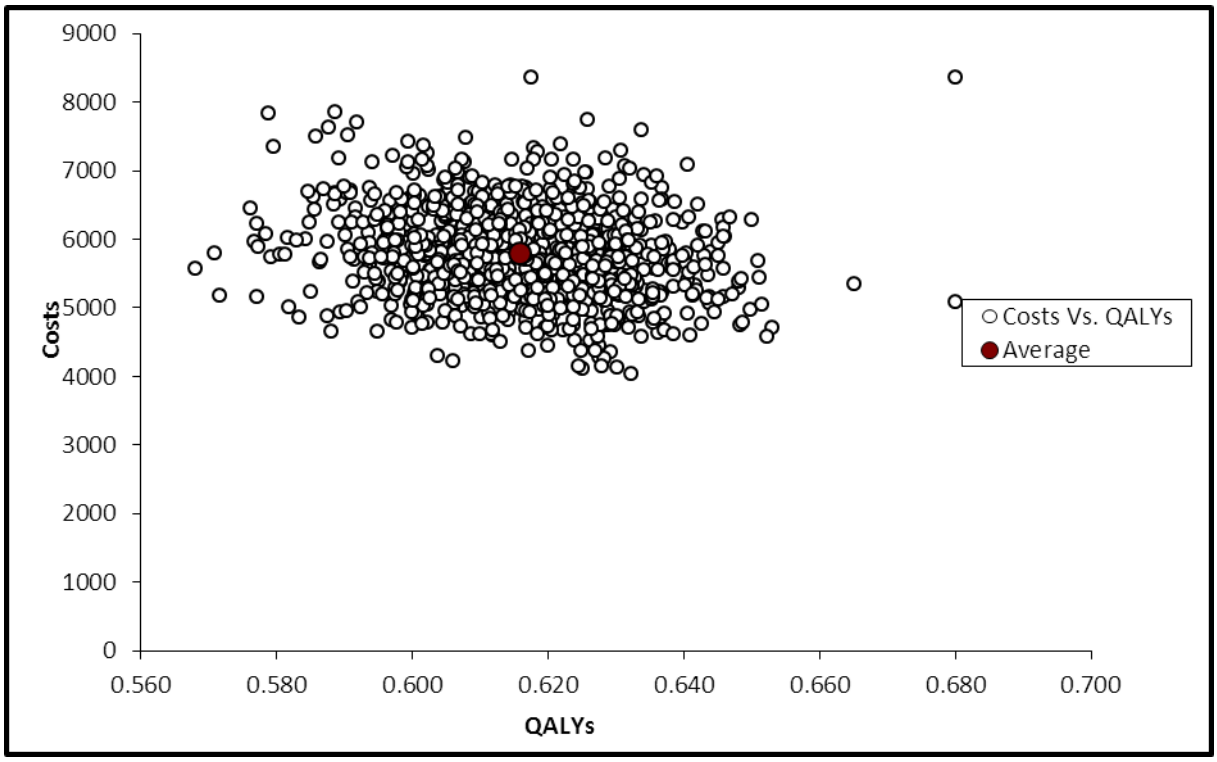

Figure 1: Scatterplot of bootstrapped costs and QALYs for patients with ESLD.

4.3.4. Net Benefit

We estimated the potential net benefit of managing and monitoring patients with ESLD. Table 20 shows that for all patients with ESLD and for all CP scores, net benefit is positive at a threshold of £10,000, £20,000 and £30,000. A negative net benefit suggests for a single treatment does not have a simple practical interpretation. In this context and assuming this pattern would not change in the future, a negative net benefit suggests that it would be more efficient for these people to die immediately and incur no further costs. Such a conclusion would most likely be judged unacceptable.

There is a trend towards a reduced net benefit as ESLD progresses from CPA to CPC. Of note that at a threshold of £30,000, 19% of CPB patients had a negative net benefit and 17% of CPC patients had a negative net benefit. As would be expected, as the willingness to pay threshold decreased, the proportion of people with a negative net benefit increases. At a threshold of £10,000 for the willingness to pay for a QALY, the net benefit of treating patients with CPB and CPC is negative. This highlights the variation in the cost-effectiveness of treating patients with different severity of ESLD. A more meaningful interpretation of a negative net benefit suggests that as society's willingness to pay decreases, alternative methods for managing and monitoring ESLD should be explored for patients with more advanced ESLD. This analysis will be re-run on a larger sample size and we will use other clinical indications such as the presence of ascites or hepatic encephalopathy in our net benefit analysis to determine the impact they have on NHS costs and HRQoL.

Patient Group	Costs	QALYs	λ = £10,000 Net Benefit (SD)	λ = £20,000 Net Benefit (SD)	λ = £30,000 Net Benefit (SD)
All patients	5773 (6087.2)	0.616 (0.139)	386 (6557.7)	6545 (7269.3)	12704 (8159.0)
CPA	2647 (2476.3)	0.640 (0.140)	3520 (3508.9)	9913 (4503.0)	3520 (3509.0)
CPB	8349 (7093.9)	0.585 (0.119)	-2498 (7613.6)	3352 (8272.1)	9203 (9039.0)
CPC	11111(6874.0)	0.634 (0.235)	-4773 (6078.7)	1564 (614.8)	7902 (7042.7)

Table 20: Total costs and QALYs for 10-months and Net Benefit Results.

4.3.5. Regression Analysis

Costs

Only CPB and CPC were statistically significant predictors of costs in the regression analyses, where patients classified as CPB or CPC incur a higher cost than CPA patients. The regression was re-run with ascites and hepatic encephalopathy as independent variables instead on CP scores. While both complications of ESLD increased, costs were not statistically significant for either. The results of the regression analysis on costs are presented in Table 21.

Just over 30% of the variability in costs is explained by our regression model. As a patient's liver disease progresses, the average NHS cost for treating ESLD increases by nearly £5000 when patients move from CPA to CPB and by £8000 when patients move from CPA to CPC. No other covariates were statistically significant in explaining our model. Care should be taken in interpreting these data given the small sample size. This makes the results imprecise (so that confidence intervals are sufficiently wide to include important difference in either direction) and unreliable (in that the addition of more patients into the analysis might change both mean estimates as well as potentially narrowing the confidence intervals).

Independent Variable	Categories	Coefficient	SE	p-value	95% CI	
Child Pugh Score	CPA ^					
	CPB	4986.75	1240.01	0.000***	2517.05	7456.44
	CPC	7999.69	2432.63	0.002***	3154.68	12844.7
Employment	Unemployed^					
	Employed	-2129.78	2012.21	0.293	-6137.44	1877.88
Type of Liver disease	Other ^					
	NAFLD	-1595.40	1717.24	0.356	-5015.58	1824.77
	ALD	-433.91	1605.18	0.788	-3630.91	2763.09
Baseline utility value		-7166.64	4147.21	0.088	-15426.51	1093.24
Age		34.57	69.38	0.620	-3018.68	2322.62
Gender	Female^					
	Male	-348.03	1340.91	0.796	-3018.68	2322.62
_cons		6432.60	5259.44	0.225	-4042.488	16907.69

Number of obs.	85
F(8, 75)	4.30
Prob > F	0.0003
R-squared	0.3115
Adj R-squared	0.2391
Root MSE	5310

Table 21: Regression Results for costs.

QALYs

Employment and age were significant predictors of differences in QALYs. CP scores were not significant in this regression model. The results of the regression model are presented in Table 22.

Independent Variable	Categories	Coefficient	SE	p-value	95% CI	
Total costs 10-months		-4.63e-06	2.75e-06	0.096	-0.00001	8.39e-07
Child Pugh Score	CPA ^					
	CPB	-0.0291	0.03312	0.382	-0.09511	0.03680
	CPC	0.0585	0.06290	0.355	-0.06675	0.18380
Employment	Unemployed^					
	Employed	0.1122	0.04777	0.021**	0.01702	0.20730
Type of Liver disease	Other ^					
	NAFLD	-0.0485	0.04179	0.249	-0.13175	0.03469
	ALD	-0.0252	0.03899	0.520	-0.10286	0.05244
Age		0.0052	0.00168	0.003***	0.00183	0.00851
Gender	Female^					
	Male	0.0336	0.03263	0.306	-0.03135	0.09862
_cons		0.3135	0.11889	0.010	0.07672	0.55033

***Significant at 1%; **Significant at 5%; ^Reference category; SE=Standard Error; CI=Confidence Interval

Number of obs.	85
F(8, 75)	2.66
Prob > F	0.0125
R-squared	0.2188
Adj R-squared	0.1366
Root MSE	0.12957

Table 22: Regression Results for QALYs.

Nearly 22% of the variability in QALY scores is explained by our model. Patients with ESLD in current employment have a higher QALY value. We could easily assume that these patients are in better health and hence that's why they are in current employment. QALY values tend to increase with age which is a counter intuitive result; we would expect older patients tend to have lower QALY values however the increase in QALYs in minimal. The regression model was re-run with ascites and hepatic encephalopathy as independent variables instead on CP scores. The presence of ascites resulted in a negligible increase in QALY values, which is counter intuitive, and the presence of hepatic encephalopathy caused a reduction in QALY values. Neither of these independent variables was statistically significant in our regression model. As with costs, care should be taken in interpreting these data as they are based on a small sample size.

4.4. Discussion

An economic analysis was designed to capture both costs and QALYs over a 12-month period. We presented the total average resource use and total average NHS costs as annual summaries. We then compared costs and QALYs estimated over a 10-month period.

The economic results from this study indicate that the NHS costs for treating patients with ESLD for 10-months are over £5500. The burden on the NHS increases significantly as patients' ESLD progresses. We used Child Pugh classifications to highlight disease progression. In our regression analysis, CP scores were the only statistically significant variables that explained variations in costs. We repeated the analysis with ascites and hepatic encephalopathy as independent variables but these variables were not statistically significant in our analysis which could be due to our relatively small sample size. Our initial analysis of QALYs with incomplete SF-36v2 responses indicated the decline in health-related quality of life over a 10-month period. Despite our missing responses our results indicated a decline in QALY values as ESLD progresses. We used multiple imputation techniques to estimate our missing utility values which may have led to an over-estimation of CPC QALY values compared to CPB QALY values. This can largely be explained by our small sample size of which only 7% of patients were classified as CPC. None of the indications of liver disease were statistically significant in our regression analysis on QALYs.

When we looked at the various types of home help provided to patients with ESLD the average number of home help hours over one-year was approximately 445 hours; this is inclusive of all types of care i.e. personal care and meal preparation. The average hours provided by NHS carers for all types of care was relatively low (<1%) compared to the total average hours of care provided for all the types of care. This highlights that the burden of home help and caring for patients with ESLD on a daily basis falls on relatives and friends. Caution needs to be taken interpreting these results because this is based on actual responses to the HUQ and could lead to an underestimation of actual hours of care as all non-responses were interpreted as zero.

We performed a net benefit analysis at three willingness-to-pay thresholds. Our results indicated that while net benefit is on average positive for all stages of ESLD there is a decline in the value of the net benefit as ESLD progresses. Again our results showed, as expected, that CPA had the highest net benefit and CPC had the lowest net benefit at both willingness-to-pay thresholds.

Our study is the only study to capture both costs and impacts on quality of life over a 10-month period in this population. We used specially designed data collection tools to perform a comprehensive analysis of secondary, primary and other care sectors, including costs borne by patients and their families. All of our results are presented as total average costs/QALYs for all patients with ESLD and in addition they are presented by CP classification.

Some limitations of our study include the small sample size. Additional data analysis will be performed once all patients have completed their one-year follow-up. The lack of CPC patients has also impacted our results as we had a very small representative of this patient group (n=6) and within that representative group a large amount of missing data. Since this analysis was performed on a cohort of patients, we do not have a comparator, and hence it is not possible to establish the cost-effectiveness of monitoring and managing ESLD with other methods of managing and monitoring ESLD. The net benefit results suggest that as society's willingness-to-pay threshold decreases, the current methods of monitoring and managing patients with advanced ESLD (CPB and CPC) may not be cost-effective.

In any study using primary data collection tools, there is a need to balance recall bias, respondent burden and response efficiency. Patients in this study were asked to complete HUQ every two months. In retrospect this could have led to respondent burden and respondent fatigue, which in turn can affect the quality of data collected. Future studies of this type should consider a longer recall period (e.g. 3-6 months). In addition, QoL data was also collected every two months. Short

recall periods for QoL data can help capture decreases in HRQoL but are subject to the same issues as the cost data collection; namely respondent burden and recall bias.

We are planning additional analyses once all the patients have their one-year follow-up completed. We will re-run all our original analyses to determine what impact a larger dataset has on our overall results. We will re-run the regression models on costs and QALYs to determine if the presence of ascites and/or hepatic encephalopathy has any statistically significant input on costs. Since we will have a larger sample size we will perform a four-arm comparison on the presence and absence of ascites and hepatic encephalopathy and identify any differences in costs and QALYs between the four groups.

5. Conclusions

The d-LIVER system will allow very close monitoring of the ESLD patient which could lead to improved care through a reduction in or early recognition of episodes of decompensation, for example with ascites or encephalopathy. Clearly there will be costs associated with the adoption and running of this technology and, while these costs are not currently known because it is difficult to speculate on specific manufacturing and other costs, it is possible to consider the potential for cost savings to healthcare delivery through adoption of d-LIVER. The two analyses presented here have provided important detail on the health economic burden of ESLD. Resource use and costs increase with increasing disease severity which is relevant because patients likely to benefit from d-LIVER will tend to have Child Pugh B or C cirrhosis. We have estimated the current costs of treating a patient with CPB cirrhosis at £8,000/year and CPC at £11,000/year, demonstrating the considerable healthcare costs. We have also demonstrated that these disease stages are associated with considerable healthcare resource utilisation, including inpatient hospital admissions, outpatient consultations and GP consultations. These could all potentially be reduced through the implementation of d-LIVER and would therefore be important factors to consider in future cost effectiveness analysis. Ultimately, the effects of the d-LIVER system need to be shown in future prospective interventional studies.

6. References

1. Williams, R., et al., *Tackling liver disease in the UK: a Lancet Commission.* Lancet, 2014. **384**(9958): p. 1902.
2. Scarborough, P., et al., *The economic burden of ill health due to diet, physical inactivity, smoking, alcohol and obesity in the UK: an update to 2006–07 NHS costs.* Journal of Public Health, 2011. **33**(4): p. 527-535.
3. Anon, *Department of Health consultation on a strategy for improving liver disease outcomes in England.* 2011.
4. Gordon, S.C., et al., *Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection.* Hepatology, 2012. **56**(5): p. 1651-1660.
5. Wright, M., et al., *Health benefits of antiviral therapy for mild chronic hepatitis C: randomised control trial and economic evaluation.* Health Technology Assessment, 2006. **10**(21): p. 130.
6. Bajaj, J.S., et al., *The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers.* The American journal of gastroenterology, 2011. **106**(9): p. 1646-53.
7. Poordad, F.F., *Review article: the burden of hepatic encephalopathy.* Alimentary pharmacology & therapeutics, 2007. **25 Suppl 1**: p. 3-9.
8. Stepanova, M., et al., *In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009.* Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association, 2012. **10**(9): p. 1034-41.e1.
9. Orr, J.G., et al., *P478 Resource use associated with hepatic encephalopathy in patients with liver disease.* Journal of Hepatology. **60**(1): p. S228-S229.
10. Morando, F., et al., *How to improve care in outpatients with cirrhosis and ascites: A new model of care coordination by consultant hepatologists.* Journal of Hepatology, 2013. **59**(2): p. 257-264.
11. Brazier, J., J. Roberts, and M. Deverill, *The estimation of a preference-based measure of health from the SF-36.* Journal of Health Economics, 2002. **21**(2): p. 271-292.
12. Weissenborn, K., et al., *The number connection tests A and B: interindividual variability and use for the assessment of early hepatic encephalopathy.* Journal of Hepatology, 1998. **28**(4): p. 646-653.
13. *NHS reference costs*. 2013-14: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014.
14. Bajaj, J.S., et al., *The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers.* Am J Gastroenterol, 2011. **106**(9): p. 1646-53.
15. *Car Running Costs 2014/2015*. 2014, Automobile Association: http://www.theaa.com/motoring_advice/running_costs/.
16. *Annual Survey of Hours and Earnings, 2014 Provisional Results*. 2014, Office of National Statistics http://www.ons.gov.uk/ons/rel/ashe/annual-survey-of-hours-and-earnings/2014-provisional-results/stb-ashe-statistical-bulletin-2014.html.
17. Leevy, C.B. and J.A. Phillips, *Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy.* Digestive diseases and sciences, 2007. **52**(3): p. 737-41.
18. Parry, S., et al., *The STRIDE (Strategies to Increase confidence, InDependence and Energy) study: cognitive behavioural therapy-based intervention to reduce fear of falling in older fallers living in the community - study protocol for a randomised controlled trial.* Trials, 2014. **15**(1): p. 210.

19. Grant, A., et al., *Clinical and economic evaluation of laparoscopic surgery compared with medical management for gastro-oesophageal reflux disease: 5-year follow-up of multicentre randomised trial (the REFLUX trial).* Health Technology Assessment, 2013. **17**(22): p. 167.
20. Morris, S., N. Devlin, and D. Parkin, *Economic Analysis in Health Care*. 2010, Chichester: John Wiley & sons, Ltd.
21. General", C.a.A., *Out-of-hours GP services in England*. 2014, Department of Health and NHS England: http://www.nao.org.uk/wp-content/uploads/2014/09/Out-of-hours-GP-services-in-England1.pdf.
22. Bass, N.M., *Review article: the current pharmacological therapies for hepatic encephalopathy.* Alimentary pharmacology & therapeutics, 2007. **25 Suppl 1**: p. 23-31.
23. Drummond, M.F., et al., *Methods for the Economic Evaluation of Health Care Programmes*. Third ed. 2005, New York: Oxford University Press.
24. National Institute for Health and Care Excellence (NICE), *Guide to the methods of technology appraisal 2013*. 2013, National Institute for Health and Care Excellence London, UK.
25. Galant, L.H., et al., *Functional status, respiratory muscle strength, and quality of life in patients with cirrhosis.* Rev Bras Fisioter, 2012. **16**(1): p. 30-4.
26. Hargreaves, J., *Assessing the most clinically and cost effective method of closing skin after surgical procedures.* 4th September 2010.

Appendix A – Unit costs for healthcare resources

Health Care Resource	Cost (£)	Source
1. Emergency Admission	275	NHS ref costs 13/14
2. Elective Admission	327	NHS ref costs 13/14
3. Outpatient visit	188	NHS ref costs 13/14
4. A&E visit	124	NHS ref costs 13/14
5. Blood test	21.50	Private Patient Tariffs 2011/12 *(FBC)*
6. X-ray	42	Private Patient Tariffs 2011/12
7. Ultrasound	47	NHS ref costs 2013/14
8. CT scan	80	NHS ref costs 2013/14
9. MRI scan	138	NHS ref costs 2013/14
10. Endoscopy	625	Private Patient Tariffs 2011/12 *Gastroscopy*
11. Draining ascites	773	Private Patient Tariffs *Clinical radiology Drainage*
12. GP visit	37	PSSRU 2013
13. GP home visit	95	PSSRU 2013
14. Practice nurse visit	11.37	PSSRU 2013 *£44/60mins * 15.5mins*
15. District nurse visit	37	NYHS ref costs 2013/14
16. GP phone call	27	PSSRU 2013
17. Hospital Doctor phone call	11.72 (4.73)	PSSRU 2013 *Consultant £99/60mins * 7.1mins (Registrar)*
18. Nurse phone call	4	PSSRU 2013 *£34/60mins * 7.1mins*
19. GP out-of-hours visit	103*	PSSRU 2013
20. Hospital doctor out-of-hours visit	87	NHS ref costs 2013/14 *Emergency Medicine, No Investigation with No Significant Treatment*
21. Nurse out-of-hours visit	24.08	PSSRU 2013 *Nurse 24 hour ward 84/60minutes * 17.2minutes*
22. NHS carer	19	PSSRU 2013
23. Ambulance transfer	231	NHS ref costs 13/14
24. Ambulance car service	10.06	ISD 13/14 *R190*
Medications (cost per one tablet/sachet)		
25. Spironolactone	0.08	BNF.org
26. Furosemide	0.03	BNF.org
27. Propranolol	0.11	BNF.org
28. Lactulose	0.25	BNF.org
29. Rifaximin	4.63	BNF.org
30. Eplerenone	1.53	BNF.org
31. Bumetanide	0.25	BNF.org

Appendix B – Unit costs for Other Procedures

Procedure	Cost (£)	Source
Colonoscopy	731.38	Private Patient Tariffs 2011/12
Pacemaker check	62.42	Private Patient Tariffs 2011/12
Leg Doppler ultrasound	83	NHS ref costs 2013/14
Hernia repair	915.53	Private Patient Tariffs 2011/12 Day case operation cost – Intermediate (inc. local anaesthetic)
Iron infusion (intravenous)	7.97	BNF.org 50mg/ml – 2-ml amp
Testosterone injection (subcutaneous)	19.62	BNF.org 250mg/ml - 1ml amp
Coronary angiogram	1168	Private Patient Tariffs 2011/12 Fundus Fluorescein angiography
Treatment for mouth disorder	3.36	BNF.org Corticosteroid 4 daily *4 days
Podiatry	31	NHS ref costs 2013/14 AHP Podiatrist, tier 1, General Podiatry
Eye tests	67.62	Private Patient Tariffs 2011/12
Dietician	41.62	Private Patient Tariffs 2011/12
Vaccination	31.18	BNF.org 1-ml prefilled syringe (Hep A and Hep B)
Physiotherapy	41.62	Private Patient Tariffs 2011/12
ECG	64.50	Private Patient Tariffs 2011/12
Chest drain	568.04	Private Patient Tariffs 2011/12
Blood transfusion	122/unit	NHSBT Platelet Strategy 2011-2014
Variceal banding (endoscopy procedure)	889	NHS ref costs 2013/14 GI bleed with single intervention
Vitamin K infusion (intravenous)	2.39	BNF.org 1-ml amp + 50ml vial glucose
Transarterial Chemo-Embolisation (TACE)	1007.08	Private Patient Tariffs 2011/12
Transjugular liver biopsy	1681.25	Private Patient Tariffs 2011/12
Percutaneous liver biopsy	490	Private Patient Tariffs 2011/12
Transjugular intrahepatic portosystemic shunt insertion (TIPSS)	1205.79	Private Patient Tariffs 2011/12
Flexible sigmoidoscopy	731.38	Private Patient Tariffs 2011/12
Bone densitometry scan	70	NHS ref costs 2013/14 Dexa Scan
Vitamin B12 injection (intramuscular)	2.90	BNF.org
Bone scan	70	NHS ref costs 2013/14 Dexa Scan
Alpha pump placement (new procedure-not likely to be listed)	804.21	Private Patient Tariffs 2011/12 Clinical Radiology – Drainage

Procedure	Cost (£)	Source
Encephalopathy psychometric testing	312	NHS ref costs 2013/14 Outpatient Neuropsychology tests
Haemodialysis	138/session	NHS ref costs 2013/14 Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over
Kidney stone removal	1113.20	Private Patient Tariffs 2011/12 Stone removal (Lithotripsy)
Platelet infusion	232	NHSBT Platelet Strategy 2011-2014
Preoperative assessment	69.18	Private Patient Tariffs 2011/12
Diabetic eye screening (retinal photography)	69.18	Private Patient Tariffs 2011/12 Fundus Photography (inc. retina- google)
Stitches	20.62	Hargreaves (2010) [26]
ENT	92	NHS ref costs 2013/14
Flu vaccination	4.15	BNF.org
Removal of Keratosis	293.36	Private Patient Tariffs Skin surgery minor procedure inc. local anaesthetic
Antibiotic drip	19.32	BNF.org Penicillin with 0.9% saline with NaCl
Diabetes clinic	69	NHS ref costs 2013/14
Ferritin	4.20	BNF.org
Dermatologist	98	NHS ref costs 2013/14
Urine test	10.21	Royal Victoria Infirmary's NuTH costing tool
Hysteroscopy	651.27	Private Patient Tariffs 2011/12
Endometrial biopsy	313.15	Private Patient Tariffs Minor procedures cervix/uterus
Hip replacement	3923	NHS ref costs 2013/14 Major hip procedures for trauma category 1
Liver profile (LFTs)	21.85	Private Patient Tariffs 2011/12
Bronchoscopy	107.16	Private Patient Tariffs 2011/12
Renal Profile	21.85	Private Patient Tariffs 2011/12
Heart operation	4010	NHS ref costs 2013/14 Other non-complex cardiac procedures
Dental Specialist	119	NHS ref costs 2013/14
Optometry Specialist	97	NHS ref costs 2013/14
Echocardiogram	104.24	Royal Victoria Infirmary's NuTH costing tool
Hearing aid fitting	73	NHS ref costs 2013/14
Hearing test	49	NHS ref costs 2013/14

Procedure	Cost (£)	Source
Sputum test	30.89	Royal Victoria Infirmary's NuTH costing tool
Spirometry	52.02	Private Patient Tariffs 2011/12
Cystoscopy	159.18	Private Patient Tariffs 2011/12
Cataract surgery	892.64	Private Patient Tariffs 2011/12 Phacoemulsification of lens with implant – unilateral