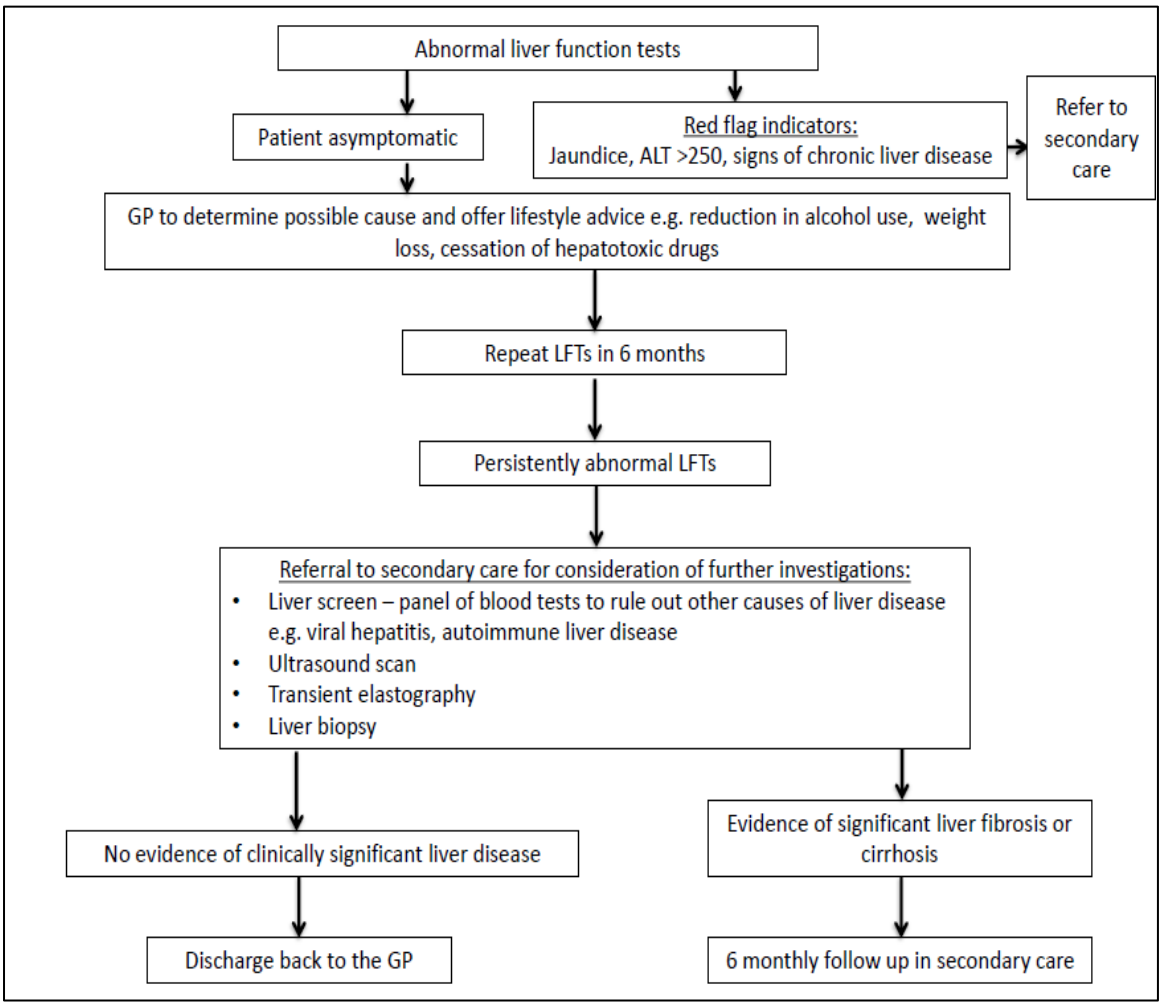
Appendix 1. Innovative risk stratification pathway and standard care

The current status of standard care

In current clinical practice, General Practitioners (GPs) rely upon abnormal liver function tests (LFTs) to identify patients who may be at risk of chronic liver disease. Subsequently, this may prompt a referral to secondary care (Figure 1.1).



Supplementary Figure 1.1: An outline of the standard care pathway

Use of non-invasive tests to identify chronic liver disease

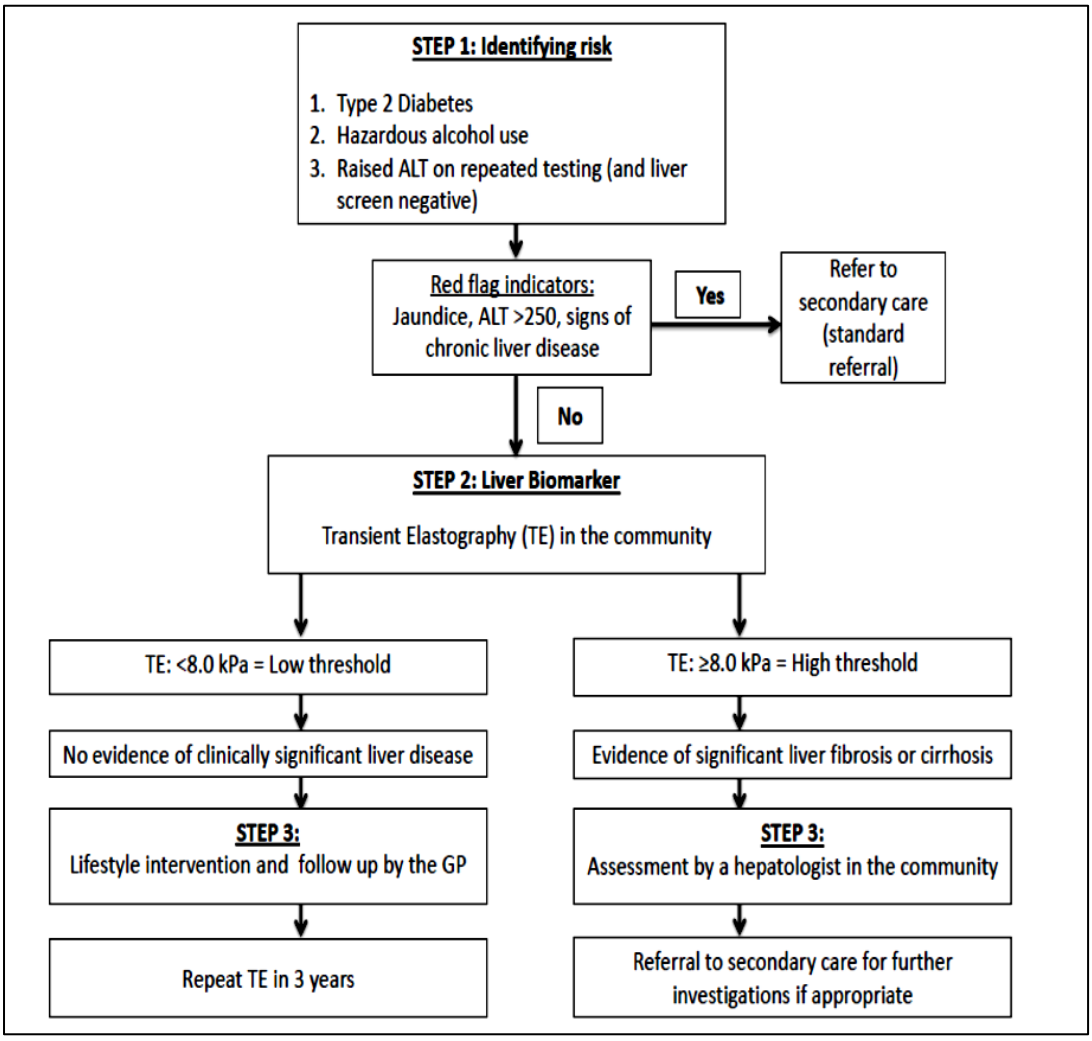
Several non-invasive tests have been developed which use novel imaging techniques or serological markers to measure the amount of fibrosis that is present in the liver. Imaging based modalities such as transient elastography (Fibroscan®, Echosens, Paris) have been demonstrated to be an excellent diagnostic test when used to identify patients who may have significant liver disease or cirrhosis [1]. A Fibroscan® calculates the stiffness of the liver by measuring the propagation of an elastic shear wave [2] for which different thresholds, now established in all major aetiologies, have been demonstrated to correlate with stages of liver fibrosis [3-6].

Using non-invasive tests to provide a timely diagnosis for these patients is clinically important so future management such as hepatocellular carcinoma and variceal surveillance can be organised or a referral for a liver transplant can be planned. Completion of the test may also be the stimulus required for patients with milder forms of fibrotic injury to alter their lifestyle and reduce the probability of their liver disease progressing.

The risk stratification pathway

The risk stratification pathway (RSP) encompasses a new algorithm to target patients in a community setting who have been identified to have a defined risk factor for developing chronic liver disease [7]. This includes patients who have been documented to have hazardous alcohol use, Type 2 diabetes or a raised ALT with no other cause identified. A patient's risk of chronic liver disease is subsequently stratified by completion of a Fibroscan® (Figure 1.2).

A Fibroscan® measurement stratifies a patient to be at either low or high risk of having clinically significant liver disease. Patients at low risk receive brief lifestyle advice from the nursing staff along with a British Liver Trust 'Looking After Your Liver' leaflet [8] but are ultimately discharged back to the care of the GP without the need for any specialist follow up. Patients at high risk with a raised liver stiffness result are reviewed by a consultant hepatologist in the community and where appropriate further investigations are requested or enrolment into cirrhosis surveillance programmes is organised. Following a patient's fibroscan and the results of any further investigations a patient can be stratified to have no/mild liver disease, significant liver disease or compensated cirrhosis.



Supplementary Figure 1.2: The risk stratification pathway

Appendix 2. Transition probabilities

Annual probabilities of progression from undetected fibrosis NMD- and SLD- states

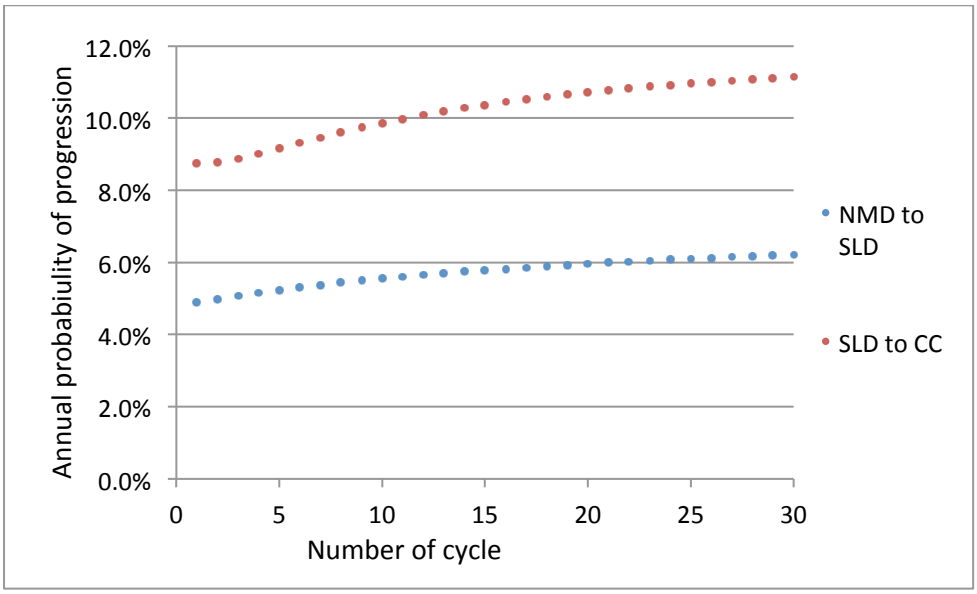
No studies were identified in which progression probabilities between different fibrosis stages (Stage 0 to Stage 1, Stage 1 to Stage 2, etc.), nor from NMD- or SLD- states of disease, were reported for NAFLD. The identified studies focused on long-term mortality in the NAFLD population (see for example the recent study [9]) and could not be used to calculate fibrosis progression probabilities. The only relevant data were obtained from a meta-analysis of studies that assessed paired liver biopsy specimens to estimate the rate of fibrosis progression in patients with NAFLD [10]. In this meta-analysis, annual fibrosis progression rate (FPR) was calculated as the difference in fibrosis stage between the first and last biopsy divided by the time between biopsies in years, and a pooled-weighted annual FPR with 95% confidence intervals was estimated. As the input parameter to the model, we have chosen a subgroup within the meta-analysis which best represents the UK population, and incorporates NAFLD patients with Stage 0 fibrosis at baseline biopsy (see Supplementary Table 7 in [10]). Specifically, the meta-analysis of eight studies from Western countries was used in which the mean FPR was equal to 0.12 (95%CI: 0.06, 0.18), corresponding to one stage of progression over 8.3 years. In the absence of other data, this estimate was used to calculate progression transition probabilities between NMD, SLD, and CC states, based on progression rates between stages of fibrosis, in the following way:

- time taken to progress from Stage 0 to Stage 4 fibrosis was calculated as 33.3 years (33.3 = 4 x 8.33= 4 x (1/0.12)).
- In accordance with expert opinion (NG, SR, MJ, GA, EW, TD, NT), it is assumed that the mean time taken to progress one fibrosis stage is shorter for more significant liver disease and that therefore, the progression rate between Stages 0 to 4 fibrosis is not linear. Hence, employing an exponential function in which the parameter has been used based on expert opinion (NG, SR, MJ, GA, EW, TD, NT, DH, RH) the following mean time intervals for transitions between different stages of fibrosis was derived, keeping total time taken to progress from Stage 0 to Stage 4 equal to 33.3 years:

- **Stage 0 to 1:** 14.8 years
- **Stage 1 to 2:** 9.2 years
- **Stage 2 to 3:** 5.7 years
- **Stage 3 to 4:** 3.6 years

These intervals were then used to obtain the progression rates between different stages of fibrosis assuming an initial distribution of patients between fibrosis stages 0-4 based on the RSP study (Table 2.1.), allowing the annual transition probabilities between the different health states (NMD/SLD/CC) to be calculated. The resultant probabilities (dependent on the cycle number) between NMD, SLD, and CC health states are presented in Figure 2.1.

Supplementary Figure 2.1: Annual probability of progression from NMD- to SLD state, and from SLD- to CC state.



Supplementary Table 2.1: Initial distribution of patients between fibrosis stages 0-4

Fibrosis stages	0	1	2	3	4	Total
% of patients in particular stage	36.2%*	32.8%	17.2%*	9.6%	4.2%	100%
Number of patients (%)**	149 (69.0%)		58 (26.9%)		9 (4.2%)	216 (100%)

*Proportion of patients with Stage 0 fibrosis in NMD and Stage 2 fibrosis in SLD. (From published meta-analysis - at baseline, the distribution of fibrosis for stages 0, 1, 2, 3, and 4 was 35.8%, 32.5%, 16.7%, 9.3%, and 5.7%, respectively [10].
**Based on RSP feasibility study [7].

Annual probabilities of progression from undetected fibrosis NMD- and SLD- states are summarized in Table 2.4a.

Annual probabilities of fibrosis progression when the fibrosis stage has been diagnosed (transitions from NMD+/SLD+ state)

No data were found to support estimation of the effect of detection of liver disease on the transition probabilities between NMD, SLD and CC health states. Despite there being many trials studying the effect of different treatments for NAFLD [11-13], these studies report a change in mean fibrosis score focusing on the impact of intervention on short-term regression or stabilization of fibrosis/cirrhosis rather than on the reduction in rate (or probability) of fibrosis progression. Therefore, from these studies it was not possible to calculate the transition probabilities for the progression of liver fibrosis in those patients who are diagnosed and treated. An individual-patient dataset was obtained from an RCT which studied the histological effect of rosiglitazone in a NAFLD population (Fatty Liver Improvement with Rosiglitazone Therapy, FLIRT trial [14]). Sixty three patients were enrolled (32% patients had type 2 diabetes) all of whom had a liver biopsy at baseline and at 1 year. In this study, the intervention group was offered advice on lifestyle modifications and treated with rosiglitazone while the placebo group was offered advice about lifestyle modifications only. The intervention group was assumed to be equivalent to the identified/ detected arm within our model. As no specific treatment was given to the placebo group it was assumed that the fibrosis progression observed in this group would be equivalent to that seen in the unidentified/undetected arm within our model. Using the individual-patient data from this study, patients were distributed between the three different

health states within our model (NMD/SLD/CC) based upon the documented fibrosis stage at baseline and follow up at 1 year. Subsequently, the transition of patients between the health states could be observed and the effect of rosiglitazone on progression between the different health states could be calculated in relation to the placebo group who did not receive this treatment.

Tables 2.2a and 2.2b summarise the transition of patients in the intervention and control groups.

Supplementary Table 2.2a: Number of patients who transition between NMD (fibrosis stage 0-1), SLD (fibrosis stage 2-3), CC (fibrosis stage 4) health states in the intervention group after 1 year (rosiglitazone, 32/63 patients, [14])

Number of patients	**to NMD**	**to SLD**	**to CC**	**Total**
from NMD	8	4	0	12
from SLD	4	14	1	19
from CC	0	0	1	1
Total	12	18	2	32

Supplementary Table 2.2b: Number of patients who transition between NMD (fibrosis stage 0-1), SLD (fibrosis stage 2-3), CC (fibrosis stage 4) health states in the placebo group after 1 year (31/63 patients, [14])

	to NMD	**to SLD**	**to CC**	**Total**
from NMD	3	3	0	6
from SLD	6	16	2	24
from CC	0	1	0	1
Total	9	20	2	31

From the above transition matrices (ignoring regression to earlier health states) a relative risk (RR) was calculated to reflect the impact of the intervention on the progression of liver disease between NMD, SLD, and CC health states (Table 3b):
NMD->SLD: (4/12) / (3/6) = 0.67 [RR=0.67, 95% CI: 0.21 to 2.07, p=0.7]
SLD->CC: (1/19) / (2/24) = 0.63 [RR=0.63, 95% CI: 0.06 to 6.45, p=0.7]
The RR presented here reflects the effect of early detection and treatment on clinically significant liver disease assuming that:

- Lifestyle intervention is offered to all patients irrespective of the whether they are identified to have clinically significant liver disease.
- Early detection leads to the treatment of clinically significant NAFLD with a glitazone.

Rosiglitazone was withdrawn from clinical use in the UK in 2010 due to an increase in cardiovascular risk [15]. Therefore, we assume that the clinical effectiveness of rosiglitazone on liver disease progression is similar to other glitazones (e.g. pioglitazone), as supported by published evidence [16, 17]. The first assumption makes the effect of our RSP conservative as it may be unrealistic to assume that all patients in both RSP and SC arms will be offered a life-style intervention by the GP. It is also unclear if the effect of lifestyle intervention differs depending on whether a patient is diagnosed with an invasive investigation in a hospital setting compared with a non-invasive test in the community.

In contrast, the second assumption is more optimistic as use of a glitazone is not a standard treatment for all NAFLD in current clinical practice. The RCT also only studied the histological effects of treatment over 1 year and this may be too short to determine whether the subsequent effect on the progression of disease is sustained.

In the extension of this RCT, 22 patients continued on treatment while 18 patients who were initially within the placebo group were started on rosiglitazone at 12 months; all of these patients were observed for a total 40 months [18]. In the first group the mean fibrosis score was 1.75 at 40 months, compared with 1.61 at 12 months (an increase of 0.14) while in the second group the mean fibrosis score was 1.93 at 40 months, compared with 1.89 at 12 months (an increase of 0.03). This suggests that the long-term impact of rosiglitazone may not be as significant, when compared with the short-term effects.

Annual probabilities of fibrosis progression when the fibrosis stage has been diagnosed (transitions from NMD+/SLD+ state) are summarized in Table 2.4b.

Annual transition probabilities from significant liver disease (SLD-/SLD+) and compensated cirrhosis (CC-/CC+) to decompensated cirrhosis, HCC, and death (Table 2.4a-b)

Significant liver disease to HCC

The model assumes that patients can progress from significant liver disease (SLD-/SLD+) to HCC but no data to estimate this probability was available. In their cost-utility analysis [16] the authors calculated the transition probability from the combined health states of fibrosis stages 3 and 4 to HCC, based on a study of 247 NAFLD patients with fibrosis stages 3 and 4 [19] in which 52.2% had cirrhosis (stage 4). Hence, in our model we approximate transition probability from SLD to HCC, assuming that the progression probability from fibrosis stage 2/3 (SLD) is similar to progression from fibrosis stage 3/4 (see Table 2.4a-b).

Significant liver disease to death

It is assumed that mortality from states NMD and SLD (fibrosis stages 0-3) is not increased due to liver disease at this stage of the disease. So, as a base, age-dependent mortality for the general population of England was assumed for transition probability from NMD/SLD to death, and to account for higher mortality due to diabetes, excess mortality (calculated from diabetes-related death rate of 1.4%, from 10-year follow-up in UKPDS study [20] was added to general-population mortality.

Compensated cirrhosis

Progression from compensated cirrhosis (CC) through to decompensation and death were approximated based on published sources and using expert opinion (Table 2.3 for elicitation methods and details of the expert panel members). It is assumed that the available data within the literature reflects diagnosed cases of cirrhosis (CC+) and therefore transition probabilities were adjusted for undiagnosed cases of cirrhosis (CC-) based on expert opinion (Table 2.3a-b).

Results of the study based on data from the UK Clinical Practice Research Datalink (CPRD) for 4537 patients diagnosed with cirrhosis between 1987 and 2002 [21] were used to estimate transition probabilities between stages of cirrhosis according to the Baveno classification (including decompensation). Since there were no results reported

for NAFLD separately, we used data for the non-alcohol related cirrhosis subgroup, which accounted for 49.2% of the cohort (viral hepatitis – 5.2%, autoimmune liver disease – 1.1%, metabolic liver disease – 7.8%, not classified - 38.1%). Annual transition probabilities were taken from the probabilities of progression in the first year after diagnosis (reported in Table 2 in [21]), as annual probabilities for all years were not provided. It was assumed that these patients were known to have cirrhosis (CC+). To approximate transition probabilities from undetected cirrhosis (from CC-) we used transition probabilities for CC+ adjusted by the responses of our panel of experts. (Table 2.3).

Supplementary Table 2.3. Responses obtained from expert panel*

Question related to NAFLD	Responses	Calculation of transition probability
A1. From the literature, we have identified the annual rate of patients progressing from compensated NAFLD through the stages of the Baveno classification, to decompensated NAFLD. (Fleming 2010) Patients with Baveno stage 1 (no ascites, no varices) progressing to Baveno stage 2 (varices, no ascites) over the course of one year = 32 patients out of 1000. How many patients per year, who are not aware of their diagnosis of compensated NAFLD would you expect to progress from Baveno stage 1 to Baveno stage 2? a. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would stay the same. b. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would increase by X=…….. patients, X < 32 c. The number of patients progressing from Baveno stage 1 to Baveno stage 2 would double.	40% increase, 16 patients	Minimal multiplier: 1.4 Maximal multiplier: 1.5(=(16+32)/32) Mean multiplier: 1.45 Annual probability of progression from CC- Baveno stage I to CC- Baveno stage II was obtained by adjusting annual probability of progression from CC+ Baveno stage I to CC+ Baveno stage II using above multiplier.
A2. From the literature we have identified that 6 out of 100 patients known to have compensated NAFLD will decompensate over the course of 1 year. (Mahady, 2012) How many patients out of 100, who are not aware of their diagnosis of compensated NAFLD, would you expect to decompensate per year? a. The number of patients who would decompensate would stay the same b. The number of patients who would decompensate would increase by X=…….. patients, X < 6 c. The number of patients who would	3 patients, 3 patients, 6 patients, 4 patients	Minimal multiplier: 1.5(=(3+6)/6) Maximal multiplier: 2 (=(6+6)/6) Mean multiplier: 1.67 Annual probability of progression from CC- to DC was obtained by adjusting probability of progression from CC+ to DC using above multiplier.

Question related to NAFLD	Responses	Calculation of transition probability
decompensate would double.		
A3. From the literature we have identified that 7 out of 100 patients, known to have compensated NAFLD will die over the course of 1 year. (Fleming 2010) What would you expect the all-cause mortality rate to be for patients who have compensated NAFLD but who are not aware of their diagnosis? a. The number of patients who would die would stay the same. b. The number of patients who would die would increase by X=……, X<7 c. The number of patients who would die would double.	2 patients, 1 patient, 7 patients, 0.1 patients (1 additional to 70/1000)	Minimal multiplier: 1.014=((0.1+7)/7) Maximal multiplier: 2 (=(7+7)/7) Mean multiplier: 1.36 Annual probability of progression from CC- to death was obtained by adjusting probability of progression from CC+ to death using above multiplier.
A4. From the literature we have identified that 30 out of 1000 patients known to have compensated NAFLD will develop a Hepatocellular carcinoma (HCC) over the course of 1 year. (Mahady 2012) How many patients out of 1000, who are not aware of their diagnosis of compensated NAFLD, would you expect to develop an HCC per year? a. The number of patients to develop an HCC would stay the same b. The number of patients to develop an HCC would increase by **X=……** patients, X<30**.** c. The number of patients to develop and HCC would double.	3 patients, 0.5 patients (5 additional to 300/1000), 10 patients, 1 patient, 1 patient,	Minimal multiplier: 1.033=((30+1)/30) Maximal multiplier: 1.33 (=(10+30)/30) Mean multiplier: 1.10 Annual probability of progression from CC- to HCC was obtained by adjusting probability of progression from CC+ to HCC using above multiplier.

*Members: Dr Neil Guha, Dr Toby Delahooke, Dr Martin James, Dr Stephen Ryder, Dr Emilie Wilkes – Nottingham University Hospitals NHS Trust; Dr Nicholas Taylor – Derby Hospitals NHS Foundation Trust.

Compensated cirrhosis to HCC

The transition probability from compensated cirrhosis to hepatoma reported in a cost-utility analysis [16] which was based on 3 observational studies of cirrhosis patients [22] [23] [24], was used as the transition probability from CC+ to HCC. No data for transition probabilities from undetected cirrhosis (CC-) to HCC were available, so the responses of a panel of experts (Table 2.3) were used to approximate the transition probability CC- to HCC.

Compensated cirrhosis to death

Mortality probabilities from the CC state were based on the result of the above mentioned UK population-based study [21], for non-alcohol related cirrhosis, and it was assumed that observed mortality for cirrhosis patients reflected detected cirrhosis (CC+). Consequently, to approximate transition probabilities from undetected cirrhosis

(from CC-) to death we used transition probabilities for CC+ adjusted by the responses of a panel of experts. (Table 2.3).

Transition probabilities for end stage liver disease (Table 2.4c)

It is assumed that progression in end stage liver disease is not affected by the earlier diagnosis of significant liver disease or compensated cirrhosis (SLD and CC); nor by the earlier identification of patients with risk factors for chronic liver disease (NMD). The RSP is not aimed at detecting the complications of cirrhosis hence for both the RSP and SC, the transition probabilities in this part of the model are identical. Published studies on the natural history of end stage liver disease were used and where possible inclusion of data specific for NAFLD or non-alcohol related aetiologies (see Table 2.4c).

Supplementary Table 2.4. Transition probabilities

2.4a. Annual probabilities from undetected fibrosis (NMD- and SLD-) and cirrhosis (CC-) states			
Transition	**Annual probability**	**Data and assumptions**	**Source**
NMD- to SLD	Dependent on cycle number (see Figure 2.1, Appendix 2)	- Average fibrosis progression rate (between fibrosis stages 0-4), for NAFLD patients, baseline fibrosis stage 0, Western countries (meta-analysis of 8 studies): 0.12 (0.06-0.18) [10] - Assumed exponential decrease of time to progression between subsequent fibrosis stages (see Appendix 2) - Initial distribution of patients between fibrosis stages 0-4 from feasibility study and Table 2 in [10]	Supplementary Table 7 in [10] and feasibility study [7]
SLD- to CC	Dependent on cycle number (see Figure 2.1)		
SLD- to HCC	0.4%	Annual probability of developing HCC from fibrosis stages 3 or 4: 0.004 (NAFLD patients), no 95% CI provided and no data on the probability of developing HCC from fibrosis stages 2 or 3	Table 1 in [16], calculated from [19]
CC- to DC*	CCI ->DCIII: 7.3%; CCI->DCIV: 1.3%; CCII->DCIII: 28.5%; CCII->DCIV: 8.5%	Data for detected CC (CC+ to DC, see 3b below), adjusted by expert panel answers (question A1, see Table 2.3)	[21] and expert panel
CC- to HCC	3.3%	Data for detected CC (CC+ to HCC, see 1b below), adjusted by expert panel answers (question A4, see Table 2.3)	[16] based on [22] [23] [24] and expert panel
NMD-/SLD- to death	Probability dependent on age	- Mortality data for general population (life tables assuming percentage of males and initial age as in feasibility study [20]) - Excess mortality due to diabetes (diabetes-related death rate of 1.4%, from 10-year follow-up in UKPDS study)	ONS (life tables), feasibility study [7], UKPDS study [20]
CC-to death*	CCI ->death: 10.2%; CCII->death: 9.0%	Data for detected CC (CC+ to death, see 3b below) adjusted by expert panel answers (question A2, see Table 2.3)	[21] and expert panel
2.4b. Annual probabilities from detected fibrosis (NMD+ and SLD+) and cirrhosis (CC+) states			
Transition	**Annual**	**Data and assumptions**	**Source**

	probability		
NMD+ to SLD	Table 3a adjusted by RR=0.67	Annual probabilities for undetected NMD (NMD- to SLD, see 1a above) adjusted by RR=0.67 (95%CI: 0.21 to 2.07) from FLIRT trial [14], effect of glitazone (see Tables 2.2a and 2.2b)	Supplementary Table 7 in [10] and data from FLIRT trial [14]
SLD+ to CC	Table 3a adjusted by RR=0.63	Annual probabilities for undetected SLD (SLD- to CC, see 1a above) adjusted by RR=0.63 (95%CI: 0.06 to 6.45) from [14], effect of glitazone (see Tables 2.2a and 2.2b)	
SLD+ to HCC	0.4%	As in 1a above, assumed to be the same as annual probability SLD- to HCC (no evidence indicating the effect of SLD detection on HCC development)	Table 1 in [16], calculated from [19]
CC+ to DC	CCI ->DCIII: 6.4%; CCI->DCIV:0.8%; CCII->DCIII: 17.1%; CCII->DCIV: 5.1%	Probabilities of progression between Baveno stages (I and II – compensated cirrhosis, III and IV – decompensated cirrhosis) during the 1st year after diagnosis, Table 2 [21], non-alcohol related.	Table 2 in [21]
CC+ to HCC	3%	Probability of developing hepatoma from compensated cirrhosis: 0.03 (0.007-0.05)	[16], calculated from [22-24]
NMD+/SLD+ to death	Probability dependent on age	- Mortality data for general population (life tables assuming percentage of males and initial age as in feasibility study [7] - Excess mortality due to diabetes (diabetes-related death rate of 1.4%, from 10-year follow-up in UKPDS study) assumed to be as in 4a above (for NMD- to death and for SLD- to death)	ONS (life tables) , feasibility study [7], UKPDS [20]
CC+ to death	CCI ->death: 7.5%; CCII->death: 6.6%	Probability of proceeding to death directly for patients with compensated cirrhosis, during the 1st year after diagnosis, non-alcohol related cirrhosis	Table 2 in [21]

2.4c. Annual probabilities for end stage liver disease

Transition	Annual probability	Data used to calculate probability	Source
DC to HCC	3%	Probability of developing hepatoma from decompensated cirrhosis as in [16] – 0.03 (range: 0.007-0.05)	[16], based on [24] [23] [22, 25]

DC to transplant	Age < 70: 5%, age ≥ 70: 0%	Probability of liver transplant for decompensated cirrhosis as in [16] - 0.05 (range: 0.05-0.25)	[16], based on [26]
DC to death	DCIII ->death: 25.1%; DCIV -> death: 20.4%	Probability of proceeding to death directly for patients with decompensated cirrhosis, detail numbers by Baveno stages: non-alcohol related disease, Table 2 and 3 [21], in the 1st year after diagnosis	[21]
HCC to transplant	Age < 65: 4%, age ≥ 65: 0%	Annual probability of liver transplant for HCC patients in the two age groups [27]	[27]
HCC to death	53.0% - 1st year, 25.5% - 2nd year, 17.2% - 3rd year, 16.7% - 4th year 13.3% - after 4th year	Calculation based on data from the US registries: the 1-, 2-, 3-, 4- and 5-year survival rates for the cohorts diagnosed in 1997-2004 years, as in Table 3 in [28]	[28]
Transplant to death	16.6% - 1st year 3.1% - 2nd and 3rd year 2.9% - after 3rd year	Calculation based on the data published in the meta-analysis of 9 studies, Figure 2 [29], NASH group: 598/717 (1-year patient survival), 468/598 (3-year survival), 461/625 (5-year survival).	[29]

*Where I, II, III, IV refer to the four Baveno stages of cirrhosis

Appendix 3. Utilities

In this appendix, the review concerning primary studies on QoL, useful to obtain utility score, is summarized. The focus here is on the studies employing EQ-5D tool to measure QoL, transferable to utility values in the UK setting.

To ensure consistency, the health utility values for decompensated cirrhosis, HCC and liver transplant have all been used from Chong *et al* which was based on a Canadian population and has clear inputs into a probabilistic sensitivity analysis. It has been assumed that the decrement in QoL associated with chronic liver disease is similar regardless of the underlying aetiology; the same assumption was made in the cost-utility analysis by Mahady *et al* which focused on the NAFLD population [16]. Chong *et al* has also been used in economic evaluations for HCV-related chronic liver disease [30, 31], and for non-HCV cirrhosis [32].

Since the diagnosis of compensated cirrhosis results in further investigations to look for complications, with the possibility of subsequent preventative treatment, a utility decrement was included for compensated cirrhosis once it is diagnosed (CC+). The utility score is assumed to be equal to the difference between the health-related QoL estimates used for the two health states of 'compensated cirrhosis' and 'remaining well with advanced fibrosis (Fibrosis stages 3/4)', in the cost-utility analysis by Mahady *et al*. [16]

The following table provides the summary of utility scores in the primary studies identified, indicating cost-effectiveness analyses using particular studies.

Supplementary Table 3.1: Summary of utility values for liver disease*

Study	**Country**	**Tool**	**Population**	***Value***	***CC+/CC-***	***DC (DC)***	***HCC***	***LT***	***PLT (3m)***	***PLT (6m)***	***PLT (1y)***	***PLT (2y)***	***CEAs***
[33]	UK	EQ-5D	Liver Transplantation: Total respondents (455), LT(408), PLT(48),Died before LT(23),Died after LT(58)	Mean					0.64	0.69	0.71	0.73	[32]
[34]	Belgium	EQ-5D	CHB patients Total 421 , CHB 127, CC 69, DC 2, HCC 10, PLT 60, ICAR 153	Mean (95% CI)	0.78 (0.73 - 0.84)	0.70 (0.17-1)	0.67 (0.44-0.90)					0.82 (0.75-0.88)	[35]
[36]	Italy	EQ-5D	Population (%): HCV(31.8), HBV(20.3), Other hep (7.8) ,Cirrhosis(20.4),LT(11.9), HCC(7.8)	Mean (SE)	0.73 (0.278)		0.757 (0.327)	0.767 (0.256)					
[37]	UK	EQ-5D	HCV population(N): Mild HCV(185),Moderate HCV(71),Cirrhotic(40)	Mean	0.55	0.45	0.45						[38]
[39]	Canada	EQ-5D	HCV population(%): No biopsy (18), MMHCV(23),CC(12),DC(5),HCC(8),LT(16), SVR monotherapy(19)	Mean (95% CI)	0.74 (0.66 – 0.83)	0.66 (0.46– 0.86)	0.65 (0.44– 0.86)	0.69 (0.62– 0.77)					[30-32]
[40]	Several (reporting UK only)	SG	CHB, UK population	Mean	0.66	0.37	0.43	0.57				0.64	[35]

Study	Country	Tool	Population	*Value*	*CC+/CC-*	*DC (DC)*	*HCC*	*LT*	*PLT (3m)*	*PLT (6m)*	*PLT (1y)*	*PLT (2y)*	*CEAs*
[41]	UK	EQ-5D	Population(N) : PBC(122), ALD(155), PSC(70)	Mean (95% CI)		0.49 (SE=0.056)*	0.49 (SE=0.056)*	0.51 (0.053)*	0.52 (0.061)*^	^	^	^	[38]

*No values were reported for NMD – no/mild liver disease or SLD – significant liver disease.

CC – compensated cirrhosis; DC – decompensated cirrhosis; LT – liver transplant; PLT – post liver transplant; CHB - chronic hepatits B

MMHCV – mild/moderate HCV; PBC - primary biliary cirrhosis; ALD - alcoholic liver disease; PSC – primary sclerosing cholangitis; SVR - sustained virological response; ICAR - 'inactive carrier' [of virus]. *Values reported in [38] obtained from [41] study. ^ Presented in Graph (Figure 2)

Appendix 4. Resource use and costs

Differences in resource consumption from implementation of RSP compared with SC may occur due to:

- The RSP intervention;
- Patients being diagnosed with significant liver disease or compensated cirrhosis (SLD+/CC+) at an earlier stage when interventions (lifestyle modifications +/- treatment) may reduce the progression of liver disease to more costly health states;
- Positively identifying those patients who are at risk of liver disease (NMD+) and increasing awareness of how lifestyle modifications can reduce the probability of developing significant liver disease and thus reducing the progression of liver disease to more costly health states;
- The reduction in referrals to secondary care and subsequent diagnostic tests for those patients stratified to be at low risk for chronic liver disease (NMD+) in the RSP

Resource use data

For the patients who are identified/ detected the costs for the NMD+/SLD+/CC+ health states differ between the RSP and SC arms due to the specific diagnostic investigations and therapeutic interventions which occur within each health state. E.g. Patients stratified to have no/mild liver disease (NMD+) in the RSP would not require a referral to secondary care for further investigations compared with the same patients in the SC arm who may still require a referral and further investigations before the same diagnosis could be obtained. It is also assumed that patients who are unidentified/undetected (NMD/SLD-/CC-) accrue no extra costs in either of the RSP or SC arms.

Resource use for each health state was derived from evidence based practice. This includes evidence from the scientific literature along with local and national guidelines in the UK and clinical practice guidelines from EASL (European Association for the Study of the Liver) and AASLD (American Association for the Study of Liver Disease). Where limited evidence was identified within specific health states, expert opinion was sought from a panel of regional liver specialists which has been previously described.

In two cases there was disagreement between cost or resource use estimates derived from the literature and that reported by the members of the expert panel and local finance departments. In such cases, a range was used for the cost or resource use with the lower and upper bounds represented by the two estimates:

1) OGD: The cost was estimated to be £277 based on NHS reference costs (HRG-4 code HRG FZ60Z). A local cost derived from an audit [7] estimated the cost to be £416. Due to the large difference in estimates, a range of £277-416 was used for this cost item.

2) There was uncertainty regarding the level of resource used associated with certain conditions, in particular, the number of inpatient admissions in DC and the number of outpatient visits in DC and HCC. A range was constructed for each resource use item based on the evidence from a previous costing study of liver cirrhosis and information obtained from the expert panel (a detailed breakdown of resource use in DC is found in Tables 4.2-4.5).

The resource use across the model states are described in the following subsections.

Resource use data for NMD

In the RSP arm, patients within this health state have been stratified to have no/mild liver fibrosis following the result of their fibroscan in primary care. Subsequently, patients diagnosed with NAFLD were assumed to be referred to a dietician and commenced on pioglitazone while ALD patients were referred for brief alcohol intervention. A referral to secondary care is not required and ongoing management of these patients can be completed by the GP. If patients remained in NMD in subsequent years, they had a fibroscan repeated every 3 years and an annual appointment with their GP. NAFLD patients were assumed to have a yearly appointment with a dietician and continued treatment with pioglitazone. Two thirds of ALD patients were assumed to require repeated psychological intervention [42] following failure of the intervention in the first year.

In the SC arm patients were identified by their GP following persistently abnormal LFTs and subsequently referred to secondary care for further investigations which constitutes a full liver screen (LFT, Hepatitis B/C and autoimmune serology) an ultrasound scan, a fibroscan and a liver biopsy. Following a histological diagnosis of no/ mild liver fibrosis patients were assumed to receive the same interventions as those patients in the RSP arm depending on the underlying aetiology of their liver disease. If patients remained in NMD in subsequent years they were seen yearly by the GP and the NAFLD patients continued with pioglitazone.

Resource use data for SLD

Patients stratified to have significant liver disease in the RSP arm by the result of their fibroscan in primary care were referred for further investigations in secondary care. This included a full liver screen, an ultrasound scan and a liver biopsy. Patients diagnosed with NAFLD were assumed to be referred to a dietician and commenced on pioglitazone while ALD patients were referred for brief alcohol intervention and commenced on acamprosate. If patients in the RSP arm remained in SLD in subsequent years it was assumed they would continue to have the same resource use apart from the initial diagnostic investigations. Again two thirds of ALD patients would require repeated psychological intervention.

In the SC arm the resource use in the first year and the subsequent years was assumed to be the same as the RSP arm although the patients would have initially been identified by their GP following persistently abnormal LFTs and only received their diagnosis following a referral to secondary care. Thus the only difference in resource use is an additional LFT.

Resource use data for CC

Patients stratified to have compensated cirrhosis in the RSP arm following their fibroscan in primary care, were referred to secondary care for further diagnostic investigations and enrolled into surveillance pathways. Thus, along with having a full liver screen, an ultrasound scan and a liver biopsy to confirm the diagnosis these patients would also have had an OGD for variceal surveillance and a repeat abdominal ultrasound and alpha fetoprotein every 6 months for HCC surveillance. Patients identified to have varices were prescribed carvedilol as primary prophylaxis for variceal bleeding. Again, patients diagnosed with NAFLD were also assumed to be referred to a dietician while patients with ALD were referred for a brief alcohol intervention.

If patients in the RSP arm remained in CC in subsequent years they would continue to have a six monthly follow-up in secondary care along with an abdominal ultrasound scan and an alpha fetoprotein for HCC surveillance. For their variceal surveillance they would only require an OGD every 2 years. As in the previous health states patients

diagnosed with NAFLD are assumed to have a yearly appointment with a dietician while two thirds of patients with ALD are referred for repeated psychological intervention.

In the SC arm, resource use in CC was assumed to be the same as the RSP arm in the first and subsequent years although patients would have initially been identified differently and only received their diagnosis following further diagnostic investigations in secondary care.

Resource use data for DC

In the DC health state, the resource use in RSP and SC arms was assumed not to differ. However, there were large differences in the services used according to the decompensating event which occurred; patients were assumed to present with ascites, a variceal bleed or encephalopathy. The cost for this health state was weighted based on the proportion of patients presenting with each decompensating event as identified in d'Amico et al [43]. In this study 51.6% of patients decompensated with ascites as their initial presentation, while 22.8% presented with a variceal bleed and 25.5% presented with encephalopathy. For patients presenting with a subsequent event the proportions were slightly different; 52.4% presented with ascites, 18.8% with a variceal bleed, and 28.8% with encephalopathy. The former was used in the cost for the first year and the latter for the subsequent years spent in this health state. Due to uncertainty in certain cost categories, ranges were constructed using expert opinion and estimates from Bennett et al.[44].

Irrespective of which decompensating event the patient presented with all patients within this health state continued to have variceal and HCC surveillance and thus required an OGD every two years along with a six monthly alpha fetoprotein and abdominal ultrasound. NAFLD patients were assumed to have an annual appointment with a dietician while ALD patients were referred for brief alcohol intervention, as in NMD-CC.

As previously discussed, there was uncertainty regarding the number of inpatient admissions for each decompensating event along with the number of outpatient visits that would be required. Therefore, in agreement with the expert panel, a range was constructed for patients presenting with ascites or a variceal bleed as an emergency or planned admission. For those patients who presented with a variceal bleed a further resource was included to account for the additional OGDs that would be required to complete endoscopic variceal band ligation. Each decompensating event was treated with medications as detailed in Table 4.8.

For patients who remained within DC the resource use in subsequent years remained the same apart from those patients with ascites who instead of having a planned admission would be reviewed in the medical day case unit for paracentesis of their ascites.

Resource use data for HCC

As in the DC health state, the resource use for the treatment of HCC was assumed to be the same for both the RSP and SC arms. The resource use varied according to the different treatment strategies and subsequently the cost was weighted according to the proportion of patients undergoing each treatment identified from the study by Schutte et al[45]. In this study 17.7% of patients underwent surgical resection, 6.9% had radiofrequency ablation (RFA), 32.7% had transarterial chemoembolisation (TACE) and 42.7% were prescribed sorafenib; a systemic therapy for patients who are not suitable for surgery or locoregional therapies. The yearly cost of sorafenib was calculated based on the daily dosage used by the panel of experts along with the preparation and cost information from the British National Formulary [46]. For patients undergoing a liver resection an initial hospital admission and a planned follow up

admission were assumed to be required along with a repeat resection in 17.1% of patients who would be identified to have tumour recurrence [47]. Patients undergoing TACE or RFA had a hospital day case admission for the procedure and a planned day case admission at follow-up. In agreement with the expert panel it was agreed that all patients would have three follow-up telephone consultations with a specialist nurse along with 4-7 hospital outpatient visits.

For subsequent years in both arms of the model the resource use remained the same excluding the initial resource use and costs of the different treatment options which would only have been undertaken during the first year following diagnosis.

Resource use data for transplant

The cost of the first year in the liver transplant health state was based on the only published study reporting the cost of transplant and follow-up care in a UK health setting [48] and is assumed to be the same for both arms of the model. The cost estimate from this study included the pre-transplant work up, the inpatient admission for the procedure and subsequent follow up care inclusive of immunosuppressive regimes to prevent organ rejection. Thus the final cost included all care received in the 27 months from when the patient was listed for a liver transplant.

Ouwens et al [49] was the only study identified by the investigators which explicitly reported the annual cost following a liver transplant in year 2 onwards and thus was used as the estimate for the subsequent years spent in the liver transplant state. The cost for the first year was estimated by subtracting the cost of Ouwens et al from the total cost of Longworth et al which as previously discussed was based on a time period of 27 months. The other studies selected by the investigators were assessed with the cost estimates converted to 2014 GBP and subsequently used to construct a range for this health state. The characteristics of the studies and cost estimates in 2014 GBP are listed in Tables 4.6-4.7.

Source of unit costs

Most of the unit costs used to populate the pathway model are derived from NHS reference costs, PSSRU and NHS pay scales [50, 51]. Where a cost could not be identified through UK-based published unit cost scales, a search of the literature was conducted or local finance departments were queried to obtain the unit cost. All costs are inflated to the 2013/14 financial year using the Department of Health hospital & community health services (HCHS) index [51]. For certain categories, multiple possible unit costs are available. In such cases, the minimum and maximum costs are listed. Unit costs are summarized in Table 4.8.

Primary care

The unit cost of GP and nurse consultation are sourced from PSSRU 2014 and time assumptions from the GP workload survey 2007 [51, 52].

Secondary care

The unit costs of hospital services are derived from NHS reference costs 2013/14 [50]. Cost of admitted care is derived from the mean cost of admission (assumed min. length of stay 1 night) and varies across emergency and planned care. Outpatient visits are assumed to involve a consultant.

Laboratory costs

The costs of laboratory tests and diagnostic scans are derived from published studies of liver disease, published sources of unit costs for the UK NHS and local costs quoted by the finance department. The cost of a fibroscan is derived from the York Health Economics evaluation of ultrasound elastography in the diagnosis of liver fibrosis [53]. The cost of a fibroscan includes the cost of an appointment with a Band 7 nurse in addition to maintenance cost of equipment. The cost of an ultrasound, a liver biopsy and an OGD are derived from NHS reference costs [50]. The local cost of an OGD was found to be substantially higher than the national average (£416 vs. £276.93); both are included to form a confidence interval. Unit costs of LFTs, alpha fetoprotein and autoimmune liver screen are derived from UK-based published studies. [32, 54]

Medications

Cost of medications is derived from the BNF[46]. The cost of medications used in a 12 month period was derived using information on daily dose, pack size and cost per pack. Details in Table 4.9.

Other services

Patients identified to be at risk or diagnosed with significant liver disease (both in RSP and SC) are assumed to be referred to additional services in the form of a dietician appointment (NAFLD).

Supplementary Table 4.1: Summary of unit costs across healthcare sector

Type	Resource use	Diagnosis	Unit cost	Notes	Unit cost source
Primary care	GP clinic visit		46	Based on patient contact of 11.7 minutes	[51]
Secondary care	Nurse telephone consultation		8.40	Based on consultation length of 6 mins, band 5 NHS staff earnings estimate for qualified nurse	[51]
	emergency admission	Liver cirrhosis	1685.99	Based on elective admission, HRG GC17K	NHS reference costs 2013/14 [50]
	emergency admission	Ascites	1484.31	Based on elective admission, HRG FZ91M	[50]
	emergency admission	Oesophageal varices with bleeding	1317.1	Based on elective admission, HRG FZ38P	[50]
	emergency admission	HCC	1842.42	Based on elective admission, HRG GC12K	[50]
	emergency admission	Encephalopathy	2379.99	Based on non-elective admission, HRG AA22G	[50]
	outpatient visit	Liver fibrosis, cirrhosis, ascites,	217.30	Based on consultant-led	[50]

Type	Resource use	Diagnosis	Unit cost	Notes	Unit cost source
		varices or HCC – first visit		outpatient visit, TFC 306	
	outpatient visit	Liver fibrosis, cirrhosis, ascites, varices or HCC – follow-up visit	175.72	Based on consultant-led outpatient visit, TFC 306	[50]
	Planned admission	Ascites	1070.26	Based on elective admission, HRG FZ91M	[50]
	Planned admission	Oesophageal varices with bleeding	901.32	Based on elective admission, HRG FZ38P	[50]
	Planned admission	Liver cirrhosis	1061.54	Based on elective admission, HRG GC17K	[50]
	Planned admission	HCC resection	5362.01	Based on elective admission, HRG GA06D	[50]
	Planned admission	HCC follow-up	1535.32	Based on elective admission, HRG GC12K	[50]
	Transplant	First year cost	89282	Based on Longworth et al - cost of first 12 months, inflated to 2014 prices	[48]
	Transplant	Subsequent years cost	17077	Based on Ouwens et al - cost in subsequent years, convered to GBP and inflated to 2014 prices	[49]
	Day case	Day case chemoembolisation (TACE)	639.53	Based on day case cost, HRG GC12F	[50]
	Day case	HCC follow-up	359.98	Based on day case, HRG GC12K	[50]
	Day case	Ascites	400.15	Based on ascites, HRG FZ91M	[50]
	TIPS stent	Variceal bleed	3930	Based on local cost	Harman et al - Economic modelling of early TIPS insertion for acute variceal haemorrhage [55]
Tests	OGD (lower estimate)		276.93	Based on outpatient visit, HRG FZ60Z	[50]
	OGD (upper estimate)		416	Local cost estimate	Harman et al - Economic modelling of early TIPS insertion for acute variceal haemorrhage [55]
	Fibroscan		37.30	York HE Consortium: An Economic Evaluation of Ultrasound Elastography in the Diagnosis of Liver	

Type	Resource use	Diagnosis	Unit cost	Notes	Unit cost source
				Fibrosis [53]	
	Hep B/C scan		30	Local cost estimate	Cost of HCV and HBV combined serology quoted by QMC virology department
	liver biopsy		546.02	Based on day cost procedure, HRG CZ36Y, inflated to 2014	[50]
	Liver function test		4.52	[54] ,average across 3 sites	
	ultrasound		49.35	Based on outpatient visit, HRG RA23Z	[50]
	alpha fetoprotein		4.52	[32]	
	Autoimmune liver screen		13	Wright et al (2006), average across 3 sites	
	Dietician appointment		80	Dietician outpatient visit	[50]
	Hospital transport		231	Based on NHS ref cost: ambulance service code ASS02	[50]

Supplementary Table 4.2: Breakdown of resource use and cost across model states in RSP, first year

State	Type	Service	Units	Min cost (£)	Max cost (£)	Source
NMD	Tests	Fibroscan	1	37.31	37.31	[7, 56]
	Primary care	GP appointment	1	46.00	46.00	[7]
		Dietician appointment	1	80.00	80.00	[57]
	Medication	Glitazone		19.44	19.44	[57]
Annual cost per patient for NMD state		*NAFLD*		*182.75*	*182.75*	
SLD	Tests	Liver function test	1	4.52	4.52	[58]
		Fibroscan	1	37.31	37.31	[7, 56]
		Hep B/C serology	1	30.00	30.00	[58]
		Ultrasound	1	49.35	49.35	[58]
		Liver biopsy	1	546.02	546.02	[59]
		Autoimmune liver screen	1	13.00	13.00	[58]
	Primary care	GP appointment	1	46.00	46.00	[58]
	Secondary care	Consultant outpatient visit	2	393.02	393.02	[58]
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medication‡	Glitazone		19.44	19.44	[57]
Annual cost per patient for SLD state				*1218.65*	*1218.65*	
CC	Tests	OGD††	1	276.93	416	[60]
		Fibroscan	1	37.31	37.31	[7, 56]
		LFT	1	4.52	4.52	[58]
		Hep B/C serology	1	30.00	30.00	[58]

State	Type	Service	Units	Min cost (£)	Max cost (£)	Source
		Liver biopsy	1	546.02	546.02	[59]
		Ultrasound for HCC	2	98.70	98.70	[61]
		Alpha fetoprotein	2	9.04	9.04	[61]
		Autoimmune liver screen	1	13.00	13.00	[58]
	Primary care	GP appointment	1	46.00	46.00	[58]
	Secondary care	Outpatient visits	2	393.02	393.02	[58]
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡			116.92	116.92	[57, 60, 62, 63]
Annual cost per patient for CC state				***1651.46***	***1790.53***	
DC	Tests	OGD††	1	276.93	416	[60]
		Additional OGD for variceal bleed††	4	1107.72	1664	[60]
		Ultrasound	2	98.70	98.70	[61]
		Alpha fetoprotein	2	9.04	9.04	[61]
	Primary care	GP appointments	4	184.00	184.00	a
	Secondary care	Emergency admission if ascites	1-3	1484.31	4452.93	[64],a
		Emergency admission of variceal bleed	1-3	1317.10	3951.30	[60],a
		Emergency admission - encephalopathy	1-3	2379.99	7139.97	[65],a
		Planned admission, ascites	0-1	0	1070.26	[44, 64]
		Planned admission, variceal bleed	0-1	0	901.32	[44],a
		Outpatient visits, ascites variceal bleeds or encephalopathy	3-6	568.74	1095.90	[44],a
		TIPS stent – in 13% of patients with variceal bleed	1	3930	3930	[55, 60]
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡	NAFLD ascites		115.05	115.05	[64]
		NAFLD variceal bleeding		20.09	20.09	[60]
		NAFLD encephalopathy		3508.67	3508.67	[66]
Annual cost per patient for DC state*				***4221.30***	***9122.52***	
HCC	Secondary care	Nurse telephone consultations	3	25.20	25.20	a
		Hospital admission HCC resection	1	5362.01	5362.01	[44, 61, 67]
		Hospital admission – follow-up	1	1535.32	1535.32	[44], a
		Day case chemoembolisation (TACE) or radiofrequency ablation (RFA)	1	639.53	639.53	[44, 61, 67]
		Day case follow-up	1	359.98	359.98	[44],a
		Outpatient visits	4-7	744.46	1271.62	[44]a
		Hospital admission - tumour recurrence (probability 17.1%)	1	916.90	916.90	[47]
	Medications	Sorafenib		38879.17	38879.17	[61]
Annual cost per patient for HCC state*				***19150.55***	***19677.76***	
Transplant	Secondary care	first year cost based on Longworth et	1		89282.20 (Range	[48, 49]

State	Type	Service	Units	Min cost (£)	Max cost (£)	Source
		al, subtracting cost for 2nd year based on Ouwens et al		56300.60,184574.29)†		
Annual cost per patient for Transplant state					*89282.20 (Range 56300.60, 184574.29)*	

a: expert opinion - panel of hepatologists (Dr Neil Guha, Prof Guru Aithal, Dr Martin James, Dr Stephen Ryder, Dr Toby Delahooke, Dr Emilie Wilkes, Dr Nick Taylor)

* Based on d'Amico et al[68]: ascites 51.6%, bleeding 22.8%, encephalopathy 25.5%.

** Based on proportion of patients in each treatment based on local audit data - surgical resection 17.7%; RFA 6.9%; TACE 32.7%; sorafenib 42.7% [45]

† Range of estimates derived from studies of the cost of the transplant and follow-up care in first year. Please refer to Table 8 for estimates and references.

‡ For breakdown of medications used and cost, please refer to Table 9

†† Interval based on cost of OGD: lower estimate £277 based on NHS reference costs, HRG-4 code FZ60Z; upper estimate based on local cost found in Harman et al [55] of £416.

Supplementary Table 4.3: Breakdown of resource use and cost (£) across model states in model, RSP, subsequent years

State	Type	Service	Units	Min cost	Max cost	Source
NMD	Tests	Fibroscan (every3 years)	0.333	12.43	12.43	[69]
	Primary care	GP appointment	1	46.00	46.00	a
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medication	Glitazone		19.44	19.44	[57, 62]
Annual cost for NMD state				*157.87*	*157.87*	
SLD	Tests	Liver function test	1	4.52	4.52	a
		Fibroscan	1	37.31	37.31	a, [69]
	Primary care	GP appointment	1	46.00	46.00	a
	Secondary care	Consultant outpatient visits	1	175.72	175.72	a
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡	Glitazone		19.44	19.44	[57, 62]
Annual cost for SLD state				*362.99*	*362.99*	
CC	Tests	OGD††	0.5	138.47	208.00	[60]
		Fibroscan	1	37.31	37.31	[69], a
		LFT	2	9.04	9.04	a
		Ultrasound for HCC	2	98.70	98.70	[61], a
		Alpha fetoprotein	2	9.04	9.04	[61]
	Primary care	GP appointment	1	46.00	46.00	a
	Secondary care	Outpatient visits	2	351.44	351.44	a
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medication‡			116.92	116.92	[60, 70]
Annual cost for CC				*886.92*	*956.45*	

State	Type	Service	Units	Min cost	Max cost	Source
state						
DC	Tests	OGD††	1	276.93	416	[60]
		Additional OGD for variceal bleed††	4	1107.72	1664	[60]
		Ultrasound	2	98.70	98.70	[61]
		Alpha fetoprotein	2	9.04	9.04	[61]
	Primary care	GP appointments	4	184.00	184.00	a
	Secondary care	Emergency admission for ascites	1-3	1484.31	4452.93	[64], a
		Emergency admission of variceal bleed	1-3	1317.10	3951.30	a, [60]
		Emergency admission, encephalopathy	1-3	2380.00	7139.97	[65], a
		Day case, ascites	6	2400.90	2400.90	[44, 64]
		planned admission, variceal bleeds	0-1	0	901.32	[44], a
		Oupatient visits, ascites or variceal bleeds	3-6	527.16	1054.32	[44], a
		TIPS stent – 13% of patients with variceal bleed	1	3930	3930	[55, 60]
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡	NAFLD ascites		115.05	115.05	[64]
		NAFLD variceal bleeding		20.09	20.09	[60]
		NAFLD encephalopathy		3508.67	3508.67	[66]
*Annual cost for DC state**				5524.99	9887.17	
HCC	Secondary care	Nurse telephone consultations	3	25.20	25.20	a
		Hospital admission – follow-up	1	1535.32	1535.32	[44], a
		Day case follow-up	1	359.98	359.98	[44], a
		outpatient visits	4-7	702.88	1230.04	[44], a
		Hospital admission - tumour recurrence (probability 17.1%)	1	916.90	916.90	[47], a
	Medications	Sorafenib		38879.17	38879.17	[61]
*Annual cost for HCC state***				*17908.99*	*18436.21*	
Transplant	Re-transplantation OR subsequent care	Based on Longworth et al, probability 5%	0.05	4464.11 (range 2815.03,9228.71)†		[48]
		Based on Ouwens at al – prob 95%	0.95	16223.33 (range 12733.94,16223.33)†		[49]
*Annual cost for transplant state****				*20687.44 (range 15548.97-25452.04)*		

a: expert opinion - panel of hepatologists (Dr Neil Guha, Prof Guru Aithal, Dr Martin James, Dr Stephen Ryder, Dr Toby Delahooke, Dr Emilie Wilkes, Dr Nick Taylor)

* Based on d'Amico et al [68]: ascites 52.4%, bleeding 18.8%, encephalopathy 28.8%.

** Based on proportion of patients in each treatment based on local audit data - surgical resection 17.7%; RFA 6.9%; TACE 32.7%; sorafenib 42.7% [45]

*** The mean cost for the transplant state in subsequent years was calculated based on probability of 5% of retransplantation in subsequent years after the first procedure[44], in which case the cost for first year of transplant from Longworth et al [48] would be applied; in other cases (probability 95%) the follow-up year cost from Ouwens et al [49] would be applied.

† Range of estimates derived from studies of the cost of follow-up care in subsequent years. Please refer to Table 8 for estimates and references.

‡ For breakdown of medications used and cost, please refer to Table 9

†† Interval based on cost of OGD: lower estimate £277 based on NHS reference costs, HRG-4 code FZ60Z; upper estimate based on local cost found in Harman et al [55] of £416.

Supplementary Table 4.4: Breakdown of resource use and cost (£) across model states, standard care, first year

State	Type	Service	Units	Min cost	Max cost	Source
NMD	Tests	Fibroscan	1	37.31	37.31	[57, 69]
		LFT	2	9.04	9.04	[58]
		Hep B/C serology	1	30.00	30.00	[58]
		Autoimmune liver screen	1	13.00	13.00	[58]
		Ultrasound	1	49.35	49.35	[58]
		Liver biopsy	1	546.02	546.02	[59]
	Primary care	GP appointment	1	46.00	46.00	[58]
	Secondary care	Consultant outpatient visit	2	393.02	393.02	[58]
	Other services	Dietician services	1	80.00	80.00	[57]
	Medications	Glitazone		19.44	19.44	a, [57]
Annual cost for NMD state				*1223.18*	*1223.18*	
SLD	Tests	Liver function test	2	9.04	9.04	[58]
		Fibroscan	1	37.31	37.31	[69]
		Hep B/C serology	1	30.00	30.00	[58]
		Ultrasound	1	49.35	49.35	[58]
		Liver biopsy	1	546.02	546.02	[59]
		Autoimmune liver screen	1	13.00	13.00	[58]
	Primary care	GP appointment	1	46.00	46.00	[58]
	Secondary care	Consultant outpatient visit	2	393.02	393.02	[58]
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡	Glitazone		19.44	19.44	[57]
Annual cost for SLD state				*1223.18*	*1223.18*	
CC	Tests	OGD	1	276.93	416	[60]
		Fibroscan	1	37.31	37.31	[69]
		LFT	2	9.04	9.04	[58]
		Hep B/C serology	1	30.00	30.00	[58]
		Liver biopsy	1	546.02	546.02	[59]
		Ultrasound for HCC	2	98.70	98.70	[61]
		Alpha fetoprotein	2	9.04	9.04	[61]
		Autoimmune liver screen	1	13.00	13.00	[58]

State	Type	Service	Units	Min cost	Max cost	Source
	Primary care	GP appointment	1	46.00	46.00	[58]
	Secondary care	Outpatient visits	2	393.02	393.02	a, [58]
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡			116.92	116.92	[60, 63]
Annual cost for CC state				***1655.98***	***1795.05***	
				2354.64	***2493.71***	
DC	Tests	OGD††	1	276.93	416	[60]
		Additional OGDs for variceal bleed††	4	1107.72	1664	[60]
		Ultrasound	2	98.70	98.70	[61]
		Alpha fetoprotein	2	9.04	9.04	[61]
	Primary care	GP appointments	4	184.00	184.00	a
	Secondary care	Emergency admission if ascites	1-3	1484.31	4452.93	a, [64]
		Emergency admission of variceal bleed	1-3	1317.10	3951.30	[60], a
		Emergency admission for encephalopathy	1-3	2379.99	7139.97	[65], a
		Planned admission, ascites	0-1	0	1070.26	[44, 64]
		Planned admission, variceal bleed	0-1	0	901.32	[44], a
		Outpatient visits, ascites or variceal bleeds	3-6	568.74	1095.90	[44], a
		TIPS stent - in 13% of patients with variceal bleed	1	3930	3930	[55, 60]
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications	NAFLD ascites		115.05	115.05	[64]
		NAFLD variceal bleeding		20.09	20.09	[60]
		NAFLD encephalopathy		3508.67	3508.67	[66]
Annual cost for DC state*				***4221.30***	***9122.52***	
HCC	Secondary care	Nurse telephone consultations	3	25.20	25.20	a
		Hospital admission HCC resection	1	5362.01	5362.01	[44, 61, 67]
		Hospital admission – follow-up	1	1535.32	1535.32	[44], a
		Day case chemoembolisation (TACE) or radiofrequency ablation (RFA)	1	639.53	639.53	[44, 61, 67]
		Day case follow-up	1	359.98	359.98	[44], a
		Outpatient visits	4-7	744.46	1271.62	[44], a
		Hospital admission - tumour recurrence (probability 17.1%)	1	916.90	916.90	[47], a
	Medications	Sorafenib		38879.17	38879.17	[61]
Annual cost for HCC				***19150.5***	***19677.76***	

state				***5***	
Transplant	All services	First year cost: based on Longworth et al and subtracting cost for 2nd year from Ouwens et al	1	89282.20 (Range 56300.60,184574.29)†	[48, 49]
Annual cost for transplant state				***89282.20(Range 56301.60,184574.29)***	

a: expert opinion - panel of hepatologists (Dr Neil Guha, Prof Guru Aithal, Dr Martin James, Dr Stephen Ryder, Dr Toby Delahooke, Dr Emilie Wilkes, Dr Nick Taylor)

* Based on d'Amico et al [68]: ascites 51.6%, bleeding 22.8%, encephalopathy 25.5%.

** Based on proportion of patients in each treatment based on local audit data - surgical resection 17.7%; RFA 6.9%; TACE 32.7%; sorafenib 42.7% [45]

† Range of estimates derived from studies of the cost of the transplant and follow-up care in first year. Please refer to Table 8 for estimates and references.

‡ For breakdown of medications used and cost, please refer to Table 9

†† Interval based on cost of OGD: lower estimate £277 based on NHS reference costs, HRG-4 code FZ60Z; upper estimate based on local cost found in Harman et al [55] of £416.

Supplementary Table 4.5: Breakdown of resource use and cost (£) across model states, standard care, subsequent years

State	Type	Service	Units	Min cost	Max cost	Source
NMD	Primary care	GP visit (NAFLD)		46.00	46.00	a
	Medications	Glitazone (NAFLD)		19.44	19.44	a
Annual cost for NMD state				***65.44***	***65.44***	
SLD	Tests	Liver function test	2	9.04	9.04	a
		Fibroscan	1	37.31	37.31	[69]
	Primary care	GP appointment	1	46.00	46.00	a
	Secondary care	Consultant outpatient visits	1	175.72	175.72	a
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡	Glitazone		19.44	19.44	[57]
Annual cost for SLD state				***367.51***	***367.51***	
CC	Tests	OGD††	0.5	138.47	208	[60]
		LFT	2	9.04	9.04	a
		Ultrasound for HCC	2	98.70	98.70	[61]
		Alpha fetoprotein	2	9.04	9.04	[61]
	Primary care	GP appointment	1	46.00	46.00	a
	Secondary care	Outpatient visits	2	351.44	351.44	a
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡			116.92	116.92	[60, 63]
Annual cost for CC state				***849.61***	***919.14***	
DC	Tests	OGD††	1	276.93	416	[60]
		Additional OGDs for variceal	4	1107.72	1664	[60]

State	Type	Service	Units	Min cost	Max cost	Source
		bleed††				
		Ultrasound	2	98.70	98.70	[61]
		Alpha fetoprotein	2	9.04	9.04	[61]
	Primary care	GP appointments	4	184	184	a
	Secondary care	Emergency admission - ascites	1-3	1484.31	4452.93	[64]
		Emergency admission – variceal bleeding	1-3	1317.10	3951.30	[60]
		Emergency admission - encephalopathy	1-3	2379.99	7139.97	[65], a
		Day case, ascites	6	2400.9	2400.9	[64], [44]
		planned admission, variceal bleeds	0-1	0	901.32	a, [44]
		Outpatient visits, ascites or variceal bleeds	3-6	527.16	1054.32	a, [44]
		TIPS stent - in 13% of patients with variceal bleed	1	3930	3930	[60], [55]
	Other services	Dietician appointment	1	80.00	80.00	[57]
	Medications‡	NAFLD ascites		115.05	115.05	[64]
		NAFLD variceal bleeding		20.09	20.09	[60]
		NAFLD encephalopathy		3508.67	3508.67	[66]
Annual cost for DC state*				***5524.99***	***9887.17***	
HCC	Secondary care	Nurse telephone consultations	3	25.20	25.20	a
		Hospital admission, follow-up	1	1535.32	1535.32	a, [44]
		Day case follow-up	1	359.98	359.98	
		Outpatient visits	4-7	702.88	1230.04	a, [44]
		Hospital admission - tumour recurrence (probability 17.1%)	1	916.90	916.90	[47], a

State	Type	Service	Units	Min cost	Max cost	Source
	Medications	Sorafenib		38879.17	38879.17	[61]
Annual cost for HCC state				*17908.99*	*18436.21*	
Transplant	Re-transplant OR subsequent care	Based on Longworth et al and Ouwens et al, refer to Table 8 for details, probability 5%	0.05	4464.11 (range 2815.03,9228.71)†		[48], [49]
		Based on Ouwens at al – prob 95%	0.95	16223.33 (range 12733.94, 16223.33) †		[49]
*Annual cost for Transplant state****					*20687.44 (range 15548.97-25452.04)*	

a: expert opinion - panel of hepatologists (Dr Neil Guha, Prof Guru Aithal, Dr Martin James, Dr Stephen Ryder, Dr Toby Delahooke, Dr Emilie Wilkes, Dr Nick Taylor)

* Based on d'Amico et al [68]: ascites 52.4%, bleeding 18.8%, encephalopathy 28.8%.

** Based on proportion of patients in each treatment based on local audit data - surgical resection 17.7%; RFA 6.9%; TACE 32.7%; sorafenib 42.7%[45]

*** The mean cost for the transplant state in subsequent years was calculated based on probability of 5% of retransplantation in subsequent years after the first procedure[44], in which case the cost for first year of transplant from Longworth et al[48] would be applied; in other cases (probability 95%) the follow-up year cost from Ouwens et al[49] would be applied.

† Range of estimates derived from studies of the cost of the transplant and follow-up care in first year. Please refer to Table 8 for estimates and references.

‡ For breakdown of medications used and cost, please refer to Table 9

†† Interval based on cost of OGD: lower estimate £277 based on NHS reference costs, HRG-4 code FZ60Z; upper estimate based on local cost found in Harman et al [55] of £416.

Supplementary Table 4.6. Breakdown of cost studies of liver transplant used to derive the cost for transplant state in first and subsequent years

Study	design	services	time period	Converted to 2014 GBP	original cost	currency (year)
Longworth et al (2003)[48]	Prospective cohort	inpatient, outpatient, medications, other services, tests	Cost in first 27 months	106359 first 2 years	66,049	GBP (1999)

Study	design	services	time period	Converted to 2014 GBP	original cost	currency (year)
Ouwens et al (2003)[49]	Retrospective cohort	hospital, primary care costs	first and subsequent years	84574 first year, 17077 subsequent years	76600 first year; 15467 average for follow-up years	USD (1992)
Taylor et al (2002)[71]	Retrospective cohort	hospital: inpatient, medications, tests	first and subsequent years	56301 first year, 4615 subsequent years	69892 transplant + 9800 first 12 months follow-up; 2nd year follow-up 6533	CAD (1998)
Filipponi et al (2003)[72]	Retrospective cohort	secondary care	cost of transplant and initial admission only	Total cost transplant + follow-up, non-viral 80001-89958	non-viral 83577-93979	EUR (2000)
Best et al (2001)[73]	Retrospective cohort	primary, secondary care	first year cost	136382	143363 (first year cost in 1998, used most recent year due to changes in clinical practice over study period noted by authors)	USD (2000)
Lang et al (2009)[74]	Based on literature	secondary care	cost of transplant and initial admission only	184574	247679	USD (2009)
Agthoven et al (2001)[75]	Retrospective cohort	secondary care	cost of transplant and initial admission only	123241	81642	EUR (1996)
van der Hilst et al (2008)[76]	Meta-analysis	secondary care	cost of transplant and initial admission only	105899 for US, 67094 (other OECD countries)	$163438 for US, $103548 (other OECD countries)	USD (2005)
Bennett et al[44]	Meta-analysis	Secondary care	Cost of transplant, inpatient, outpatient care and medications in first year; cost of hospital care in subsequent years	95766 in first year; 13404 in subsequent years	$95608 in first year; $13382 in subsequent years	USD (1997)

Study	design	services	time period	Converted to 2014 GBP	original cost	currency (year)
Lin et al[77]	Modelling study (using prospective and retrospective previously collected data)	Secondary care	Cost of hospital resource use in first and subsequent years following transplant	75171 in first year; 2492 in outpatient care in subsequent years	$86078 in first year; $2952 in outpatient care in subsequent years	USD (2003)

Supplementary Table 4.7. Summary of cost estimates of first 12 months following liver transplant (including initial transplant admission) and subsequent years

Source	Estimate	Notes†
First year cost		
Taylor	56301	Cost in first year
Filipponi, lower estimate	62924	Cost in first 2 years minus Ouwens estimate for 2nd year cost
van der Hilst	67094	Cost in first year
Filipponi, upper estimate	72881	Cost in first 2 years minus Ouwens estimate for 2nd year cost
Lin	75171	Cost in first year
Ouwens	84574	Cost in first year
Longworth	89282	Cost in first 2 years minus Ouwens estimate for 2nd year cost
Bennett	95766	Cost in first year
Agthoven	123241	Cost in first year
Best	136382	Cost in first year
Lang	184574	Cost in first year
Cost in subsequent years		
Bennett	13404	Cost in second year, excluding cost of possible re-transplant, already incorporated

Source	Estimate	Notes[†]
		in the state cost
Ouwens	17077	Cost in second year

[†]In certain cases, cost was calculated based on multiple sources due to differences in length of follow-up or cost estimation methods across individual studies. Some studies included cost in the first 2 years following transplant (e.g. Logworth et al). In order to estimate the cost of first year, the most reliable estimate of second year cost (Ouwens et al) was subtracted from 2-year estimates

Supplementary Table 4.8. Summary of unit costs across healthcare sector

Type	Resource use	Diagnosis	Unit cost	Notes	Unit cost source
Primary care	GP clinic visit		46	Based on patient contact of 11.7 minutes	[51]
Secondary care	Nurse telephone consultation		8.40	Based on consultation length of 6 mins, band 5 NHS staff earnings estimate for qualified nurse	[51]
	emergency admission	Liver cirrhosis	1685.99	Based on elective admission, HRG GC17K	NHS reference costs 2013/14 [50]
	emergency admission	Ascites	1484.31	Based on elective admission, HRG FZ91M	[50]
	emergency admission	Oesophageal varices with bleeding	1317.1	Based on elective admission, HRG FZ38P	[50]
	emergency admission	HCC	1842.42	Based on elective admission, HRG GC12K	[50]
	emergency admission	Encephalopathy	2379.99	Based on non-elective admission, HRG AA22G	[50]
	outpatient visit	Liver fibrosis, cirrhosis, ascites, varices or HCC – first visit	217.30	Based on consultant-led outpatient visit, TFC 306	[50]
	outpatient visit	Liver fibrosis, cirrhosis, ascites, varices or HCC – follow-up visit	175.72	Based on consultant-led outpatient visit, TFC 306	[50]
	Planned admission	Ascites	1070.26	Based on elective admission, HRG FZ91M	[50]
	Planned admission	Oesophageal varices with bleeding	901.32	Based on elective admission, HRG FZ38P	[50]
	Planned admission	Liver cirrhosis	1061.54	Based on elective admission, HRG GC17K	[50]

Type	Resource use	Diagnosis	Unit cost	Notes	Unit cost source
	Planned admission	HCC resection	5362.01	Based on elective admission, HRG GA06D	[50]
	Planned admission	HCC follow-up	1535.32	Based on elective admission, HRG GC12K	[50]
	Transplant	First year cost	89282	Based on Longworth et al - cost of first 12 months, inflated to 2014 prices	[48]
	Transplant	Subsequent years cost	17077	Based on Ouwens et al - cost in subsequent years, convered to GBP and inflated to 2014 prices	[49]
	Day case	Day case chemoembolisation (TACE)	639.53	Based on day case cost, HRG GC12F	[50]
	Day case	HCC follow-up	359.98	Based on day case, HRG GC12K	[50]
	Day case	Ascites	400.15	Based on ascites, HRG FZ91M	[50]
	TIPS stent	Variceal bleed	3930	Based on local cost	Harman et al - Economic modelling of early TIPS insertion for acute variceal haemorrhage [55]
Tests	OGD (lower estimate)		276.93	Based on outpatient visit, HRG FZ60Z	[50]
	OGD (upper estimate)		416	Local cost estimate	Harman et al - Economic modelling of early TIPS insertion for acute variceal haemorrhage [55]
	Fibroscan		37.30	York HE Consortium: An Economic Evaluation of Ultrasound Elastography in the Diagnosis of Liver Fibrosis [53]	
	Hep B/C scan		30	Local cost estimate	Cost of HCV and HBV combined serology quoted by QMC virology department
	liver biopsy		546.02	Based on day cost procedure, HRG CZ36Y, inflated to 2014	[50]
	Liver function test		4.52	[54] ,average across 3 sites	

Type	Resource use	Diagnosis	Unit cost	Notes	Unit cost source
	ultrasound		49.35	Based on outpatient visit, HRG RA23Z	[50]
	alpha fetoprotein		4.52	[32]	
	Autoimmune liver screen		13	Wright et al (2006), average across 3 sites	
Other services	Alcohol referral services IF ALD		778.66	Psychological community-based programme: £741.67 (NICE (2011) - Alcohol-use disorders, inflated to 2014)	[70]
	dietician appointment IF FLD		80	Dietician outpatient visit	[50]
	Hospital transport		231	Based on NHS ref cost: ambulance service code ASS02	[50]

Supplementary Table 4.9. Breakdown of the cost of medications

State	Medication	Dose	Daily frequency	Unit cost	Pack supply	Days supply	Yearly cost
NMD	Pioglitazone	30	1	1.49	840	28	19.44
Subtotal							19.44
SLD	Pioglitazone	30	1	1.49	840	28	19.44
	Acamprosate	666	3	28.92	111888	56	188.63
Subtotal							208.06
CC	Carvidilol	12.5	1	1.54	350	28	20.09
	Multivitamins	2	1	11.93	90	45	96.83
Subtotal							116.92
DC	Carvidilol – secondary prophylaxis for variceal bleeding	12.5	1	1.54	350	28	20.089
	Thiamine – Prevention of Wernicke-Korsakoff syndrome	100	1	1.5	2000	20	27.39
	Spironolactone - ascites	100	2	3.55	2800	14	92.62
	Furosemide - ascites	40	2	0.86	1120	14	22.44
	Rifaximin - encephalopathy	550	2	259.23	56	28	3381.56
	Lactulose - encephalopathy	20	3	2.9	500	8.333333	127.11
	NAFLD ascites						115.05
	NAFLD variceal bleeding						20.09
	NAFLD encephalopathy						3508.67
HCC	Sorafenib	400	2	2980.47	22400	28	38879.17
Subtotal							38879.17
Transplant	Tacrolimus	2	2	111.36	100	25	1626.97
	Azathioprine	100	1	3.54	2800	28	46.18
	Prednisolone	29.23	1	1.33	140	4.7896	25.27
Subtotal first year							1698.42
Subtotal subsequent years							1626.97

Appendix 5. One-way sensitivity analyses

Many of the model parameters were subject to one-way sensitivity analysis, using hypothetical increases or decreases, to determine the key drivers of the model results. These assumed extreme values of input parameters. The following parameters were included in one-way sensitivity analyses:

- Costs
- transplant (1st and subsequent years), range as in Table 3
- HCC (1st and subsequent years), range as in Table 3
- DC (1st and subsequent years), range as in Table 3
- NMD in the RSP (subsequent years), fibroscan once per 5 years as an alternative to base-case (once per 3 years)
- CC in the RSP (1st and subsequent years), range as in Table 3
- CC in SC (1st and subsequent years), range as in Table 3
- Utilities
- Transplant, limits of 95%CI, Table 2
- HCC, limits of 95%CI, Table 2
- DC, limits of 95%CI, Table 2
- utility decrement for cirrhosis detection, arbitrary 0-0.2 (see Table 2)
- Transition probabilities
- Effect of detection/intervention on fibrosis progression, lower limit of 95%CI for progression rate reduction (Table 2.4b in Appendix 2) – maximal effect, and no effect (RR=1) – minimal effect.
- Effect of detection/intervention on cirrhosis progression/mortality, minimal and maximal multipliers based on expert panel responses (see Table 2.3 in Appendix 2)
- Fibrosis progression, limits of 95%CI, Table 1a, and range for acceleration of progression as indicated by experts (see Appendix 2)
- Cirrhosis progression/mortality, limits of 95% CI in [21], see Table 2.4b in Appendix 2
- Probabilities of detection NMD/SLD/CC in RSP and SC, arbitrary increase and decrease by 20 percentage points (0% assumed if negative percentage).
- Mortality after transplant, alternative value as in [16]
- Probability of developing HCC from cirrhosis, range as in [16], see Table 2.4b in Appendix 2
- Cut-off age for transplant from both DC and HCC, arbitrary from 65yrs to 80 yrs

The detailed assumptions and the results of one-way sensitivity analyses are presented in Table 5.1.

Supplementary Table 5. 1. Assumptions and results of one-way sensitivity analyses (NAFLD model)

Parameter (base-case value)	Minimal/ maximal / alternative value	Comment / source	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
		Base case	512	0.24	2138
Costs (£)					
Cost of transplant	56301	The lowest estimate identified [78], see Table 4.7 (Appendix 4)	512		2138

Parameter (base-case value)	Minimal/ maximal / alternative value	Comment / source	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
(1st year), 89282	184574	The highest estimate identified [27], see Table 4.7	512		2138
Cost of transplant (subsequent years), 20687	15549	The lowest estimated cost, see Tables 4.3, 4.5, and 4.6-4.7	512		2138
	25452	The highest estimated cost, see Tables 4.3, 4.5, and 4.6-4.7	512		2138
Cost of HCC (1st year), 19414	19151	Assumed 4 outpatient visits per year, see Table 4.2	513		2143
	19678	Assumed 7 outpatient visits per year, Table 4.2	511	0.24	2134
Cost of HCC (subsequent years), 18172	17909	Assumed 4 outpatient visits per year, see Table 4.3	514		2148
	18436	Assumed 7 outpatient visits per year, Table 4.3	509		2129
Cost of DC (1st year), 6672	4221	The lowest estimate (see Table 3)	600		2507
	9123	The highest estimate (see Table 3)	423		1770
Cost of DC (subsequent years), 7706	5525	The lowest estimate (see Table 3)	716		2992
	9887	The highest estimate (see Table 3)	307		1285
Cost of NMD, RSP (subsequent years), 158	153	Fibroscan test once per 5 years	490		2050
Cost of CC, RSP, 1721	1651	The lowest and the highest estimate (see Table 3 for details)	499		2086
	1791		524		2191
Cost of CC, RSP (subsequent years), 921	887		497		2079
	956		526		2200
Cost of CC, SC, 1725	1656		514		2150
	1795		509		2127
Cost of CC, SC (subsequent years), 884	850		515		2151
	919		508		2125
Utilities					
Transplant utility, 0.69	0.62	Lower 95%CI limit [39] see Table 2		0.24	2138
	0.77	Upper 95% CI limit [39], see		0.24	2138

Parameter (base-case value)	Minimal/ maximal / alternative value	Comment / source	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
		Table 2			
HCC utility, 0.65	0.44	Lower 95%CI limit, Table 2	512	0.24	2115
	0.86	Upper 95%CI limit, Table 2		0.24	2163
DC utility, 0.66	0.46	Lower 95%CI limit, Table 2		0.27	1929
	0.86	Upper 95%CI limit, Table 2		0.21	2398
Utility decrement for detection of CC, 0.1	0	Arbitrary assumption		0.29	1789
	0.2	Arbitrary assumption		0.19	2658
Probabilities					
Reduction of progression from SLD to CC (relative risk, RR), 0.63	0.06	Lower limit of 95%CI, see Appendix 2	-766	0.40	-1895
	1	Assumed no effect	971	0.16	5948
Reduction of progression from NMD to SLD (relative risk, RR), 0.67	0.21	Lower limit of 95%CI, see section Appendix 2	-594	0.32	-1852
	1	Assumed no effect	1126	0.19	5969
Probability of decompensation multiplier (CC- to DC)*, 1.7	1.5	Minimal and maximal multipliers based on expert panel responses (see Table 2.3)	600	0.22	2686
	2.0		364	0.26	1373
Mortality from CC-multiplier, 1.4**	1.0		488	0.24	2069
	2.0		549	0.25	2246
Probability of HCC multiplier (CC- to HCC)*, 1.1**	1.0		543	0.24	2282
	1.3		413	0.24	1695
Probability CCI to CCII multiplier (undetected), 1.45	1.4		513	0.24	2144
	1.5		510	0.24	2133
Fibrosis progression rate	0.06	Lower 95%CI limit in [79]	857	0.12	7032
	0.18	Upper 95%CI limit in [79]	321	0.35	928
Acceleration of progression**, 14.8 / 9.2 / 5.7 / 3.6**	13.1 / 9.2 / 6.5 / 4.1	The lowest acceleration rate as indicated by experts	549	0.21	2561
	16.5 / 9.1 / 5.0 / 2.7	The highest acceleration rate as indicated by experts	478	0.27	1800
Probability CCI ->DCIII, 16.4%	14.4%		557	0.24	2346
	18.5%		470	0.24	1953
CCI->DCIV, 0.8%	0.4%		525	0.24	2195
	1.5%		489	0.24	2044
CCII->DCIII, 17.1%	13.8%		518	0.24	2163
	20.8%		506	0.24	2117

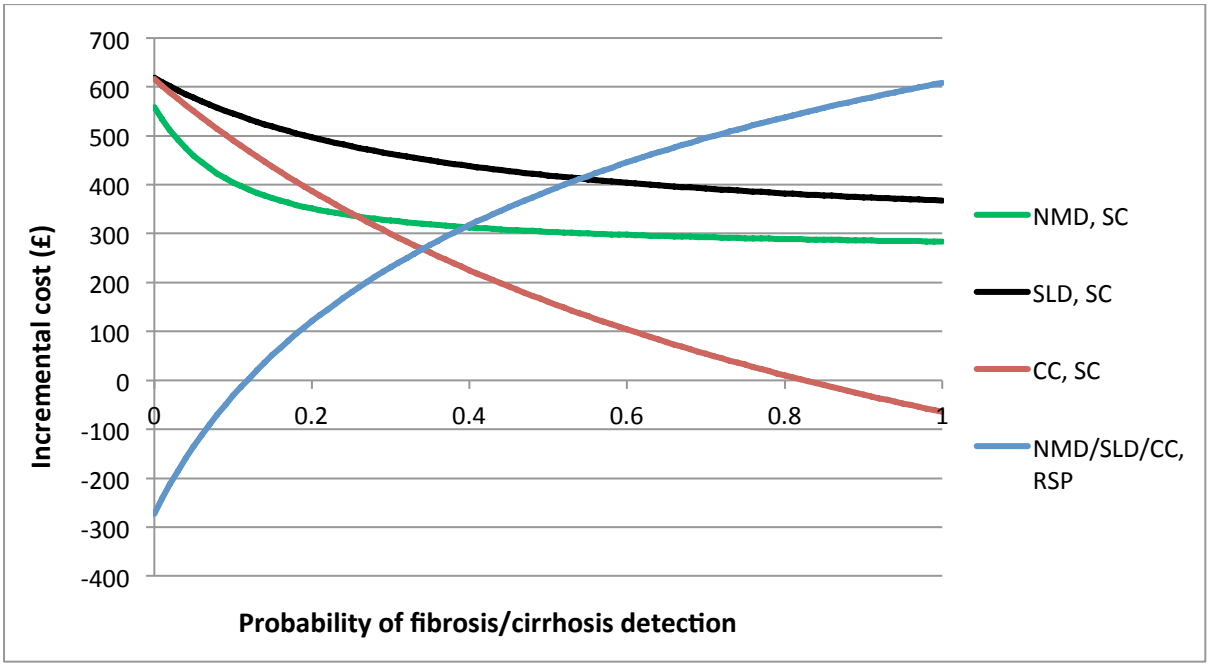
Parameter (base-case value)	Minimal/ maximal / alternative value	Comment / source	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
CCII->DCIV, 5.1%	3.3%	Lower and upper limits of 95% CIs in [21]	517	0.24	2160
	7.5%		506	0.24	2115
CCI ->death, 7.5%	6.1%		491	0.24	2072
	9.1%		533	0.24	2207
CCII->death, 6.6%	3.9%		509	0.24	2128
	10.3%		515	0.24	2152
DCIII to death, 25.1%	22.3%		413	0.23	1783
	28.1%		601	0.25	2442
DCIV to death, 20.4%	16.2%		474	0.24	2005
	25.2%		543	0.24	2247
CC1 to CCIII, 3.2%	2.3%		515	0.24	2154
	4.4%		507	0.24	2118
DCIII to DCIV, 3.2%	2.1%		517	0.24	2158
	4.6%		505	0.24	2115
Probability of detection NMD/SLD/CC RSP, 73.7%	53.7%	Arbitrary increase and decrease by 20 percentage points (0% assumed if negative percentage).	408	0.20	2032
	93.7%		586	0.27	2204
Probability of detection NMD, SC, 2.0%	0%		557	0.25	2265
	22.0%		344	0.20	1719
Probability of detection SLD, SC, 16.5%	0%		619	0.35	1773
	36.5%		443	0.18	2497
Probability of detection CC, SC, 8.2%	0%		613	0.26	2382
	28.2%		313	0.20	1530
Mortality 1st year after transplant, 16.6%	12%	Alternative input parameter [16]	512	0.24	2138
Probability CC+ to HCC, 3%	0.7%	The minimal value in [16]	561	0.24	2313
	5%	The maximal value in [16]	467	0.24	1969
Cut-off age for transition probability to transplant from both DC and HCC	65 yrs	Assumed cut-off for DC to transplant the same as for HCC	512	0.24	2138
	70 yrs	Assumed cut-off for HCC to transplant the same as for DC	512	0.24	2138
	80 yrs	Arbitrary	-495	0.22	-2254

* Expert panel (see Table 2.3). Annual probability of progression from CC- to DC was obtained by multiplying probability of progression from CC+ to DC.

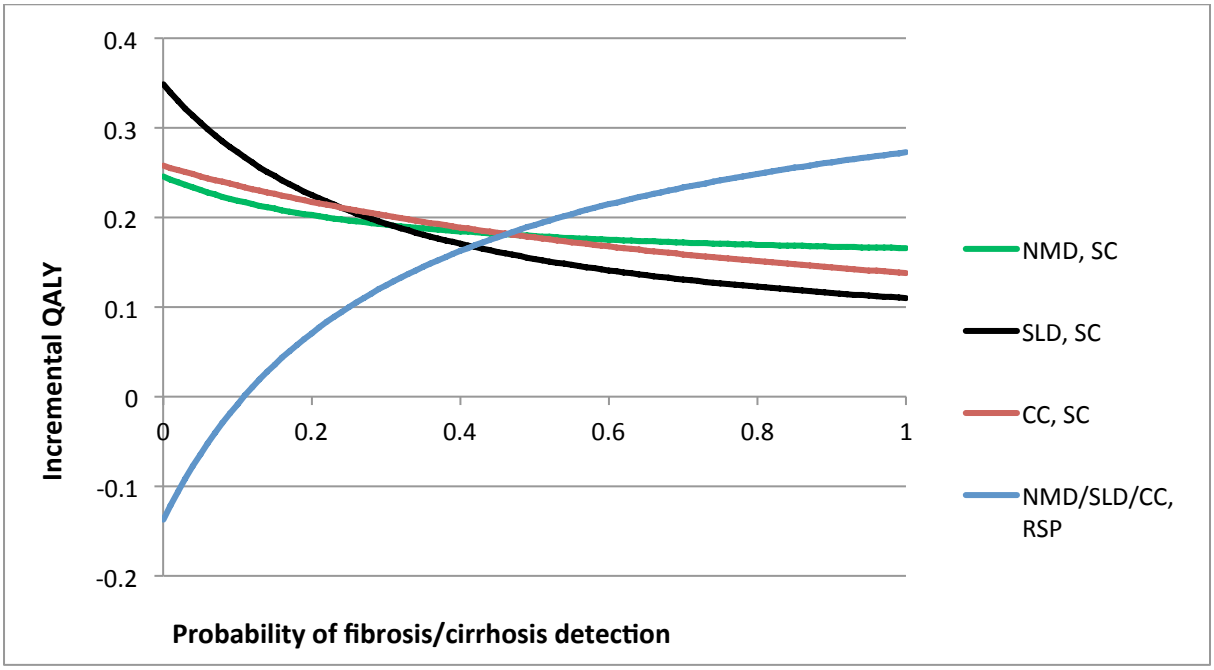
** Expert panel (see Table 2.3). Annual probability of death from CC- was obtained by multiplying probability of death from CC+.
*** Expert panel (see Table 2.3). Annual probability of HCC from CC- was obtained by multiplying probability of HCC from CC+.
**** Notation: 14.8 / 9.2 / 5.7 / 3.6 reflects stage 0 to 1, stage 1 to 2, stage 2 to 3, and stage 3 to 4 mean times of progression in years, respectively.

To test the impact of the input parameters obtained from the RSP feasibility study, a wider one-way sensitivity analysis for the probabilities of identifying/detecting NMD/SLD/CC was conducted, to explore how incremental costs and QALYs contributed to overall cost-effectiveness, when changing these detection probabilities. Figures 5.1, 5.2, and 5.3 show incremental cost, effect, and ICER, respectively, for all possible values of these probabilities. From Figure 1 we know that the life-time incremental cost increases with detection probability in the RSP and decreases with detection probabilities in SC. This suggests that the direct impact of better diagnostic accuracy in RSP, compared to SC, on fibrosis/cirrhosis management cost exceeds the lifetime cost savings due to earlier detection and treatment of fibrosis/cirrhosis. However, the health benefits of earlier detection upon RSP, when compared to SC, are clear - both higher probability of detection NMD/SLD/CC in RSP and lower detection probabilities in SC lead to higher incremental QALY (Figure 2), RSP vs. SC. Excluding less favourable case of worse health state at lower costs (and negative ICERs upon RSP being dominant), ICER is stable around 1,700-2,200 £/QALY for the probability of NMD/SLD/CC detection in RSP ranging from 20% to 100% (Figure 5.3).

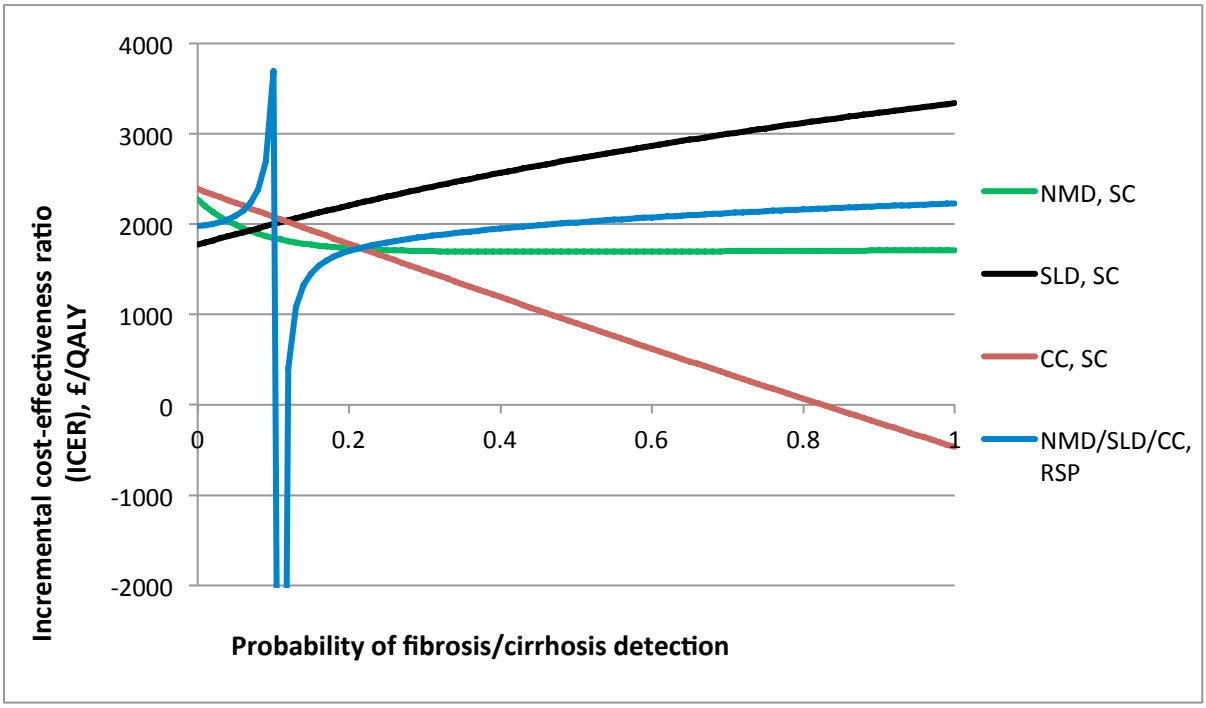
Supplementary Figure 5.1. Incremental cost as the function of the probability of fibrosis/cirrhosis detection in RSP and SC



Supplementary Figure 5. 2. Incremental QALY as the function of the probability of fibrosis/cirrhosis detection in RSP and SC



Supplementary Figure 5.3. Incremental cost-effectiveness ratio (ICER) as the function of the probability of fibrosis/cirrhosis detection in RSP and SC


4000
3000
2000
1000
0
-1000
-2000
0
0.2
0.4
0.6
0.8
1
Incremental cost-effectiveness ratio (ICER), £/QALY
Probability of fibrosis/cirrhosis detection
NMD, SC
SLD, SC
CC, SC
NMD/SLD/CC, RSP

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