Appendix B: Updated Cost effectiveness Search (Response to D3)

Identification of studies

The following databases were searched (with service providers):

- Medline (OvidSP)
- Medline In-Process & other non-indexed citations (OvidSP)
- Embase (OvidSP)
- EconLIT (OvidSP)
- NHS EED (http://onlinelibrary.wiley.com/cochranelibrary/search/)

In addition, research abstracts were searched for the 2011 and/or 2012 annual meetings of the following organizations:

- European Association for the Study of the Liver (EASL)
- United European Gastroenterology (UEG)
- American Gastroenterological Association (AGA)
- American Association for the Study of Liver Diseases (AASLD)

Of note, a single systematic review strategy encompassed searches for cost-effectiveness studies and resource identification, measurement, and valuation studies.

Exact details of the search strategy are provided in table B1.

Table B1: Search Strategy for Cost-effectiveness Studies

Date of search: December 13, 2012

The date span of the search:

The search in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) encompassed all citations from 1946 through the date of the search (13 Dec 2012).

The search in EMBASE encompassed all citations from 1988 to 2012 week 49.

The search in Ovid EconLIT encompassed all citations from 1961 through the date of the search (13 Dec 2012).

The search of NHS EED encompassed all citations through the date of the search (13 Dec 2012).

Medline Search Strategy:

SEARCH #	SEARCH TEXT	HITS
1	Hepatic Encephalopathy/	8505
2	(encephalopath* adj2 (hepatic or hepatocerebral or portosystemic or portal-systemic)).tw.	5350
3	(hepatic adj1 (stupor* or coma*)).tw.	1571
4	or/1-3	11000
5	(Rifaximin-α or rifamycin or Xifaxan or refero or targaxan or tixteller or xifaxanta or redactiv or 80621-81-4 or 88747-56-2).tw,rn.	1851
6	(Lactulose or generlac or kristalose or enulose or constulose or duphalac or lactugal or normase or amivalex or 4618-18-2).tw,rn.	2760
7	(Neomycin or mycifradin or neo-fradin or neo-tab or nivemycin or fradiomycin or 11004-65-2 or 1404-04-2 or 1405-10-3 or 8026-22-0).tw,rn.	11763

8	or/5-7	16124
9	4 and 8	642
10	economics/	26673
11	exp "costs and cost analysis"/	170635
12	economics, dental/	1863
13	exp "economics, hospital"/	18505
14	economics, medical/	8512
15	economics, nursing/	3899
16	economics, pharmaceutical/	2393
17	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*).ti,ab.	412409
18	(expenditure* not energy).ti,ab.	16680
19	value for money.ti,ab.	861
20	budget*.ti,ab.	17532
21	or/10-20	533578
22	((energy or oxygen) adj cost).ti,ab.	2677
23	(metabolic adj cost).ti,ab.	723
24	((energy or oxygen) adj expenditure).ti,ab.	15460
25	or/22-24	18184
26	21 not 25	529450
27	letter.pt.	786560
28	editorial.pt.	323629
29	historical article.pt.	291541
30	or/27-29	1387864
31	26 not 30	502401
32	animals/	5112318
33	humans/	12758117
34	32 and 33	1381898
35	32 not 34	3730420
36	31 not 35	474116
37	9 and 36	16
38	limit 37 to English language	15

*Lines 10-36 are from the published NHS EED filter: (http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html)

EMBASE Search Strategy:

SEARCH #	SEARCH TEXT	HITS
1	Hepatic Encephalopathy/	7854
2	(encephalopath* adj2 (hepatic or hepatocerebral or portosystemic or portal-systemic)).tw.	5787
3	(hepatic adj1 (stupor* or coma*)).tw.	416
4	or/1-3	9323
5	(Rifaximin-α or rifamycin or Xifaxan or refero or targaxan or tixteller or xifaxanta or redactiv or 80621-81-4 or 88747-56-2).tw,rn.	3613
6	(Lactulose or generlac or kristalose or enulose or constulose or duphalac or lactugal or normase or amivalex or 4618-18-2).tw,rn.	5371
7	(Neomycin or mycifradin or neo-fradin or neo-tab or nivemycin or fradiomycin or 11004-65-2 or 1404-04-2 or 1405-10-3 or 8026-22-0).tw,rn.	12409

8	or/5-7	20449
9	4 and 8	1169
10	health-economics/	18617
11	exp economic-evaluation/	181789
12	exp health-care-cost/	175899
13	exp pharmacoeconomics/	141778
14	or/10-13	395195
15	(econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*).ti,ab.	467778
16	(expenditure* not energy).ti,ab.	18198
17	(value adj2 money).ti,ab.	1109
18	budget*.ti,ab.	18440
19	or/15-18	485766
20	14 or 19	708812
21	letter.pt.	677019
22	editorial.pt.	390937
23	note.pt.	538924
24	or/21-23	1606880
25	20 not 24	630389
26	(metabolic adj cost).ti,ab.	651
27	((energy or oxygen) adj cost).ti,ab.	2354
28	((energy or oxygen) adj1 expenditure).ti,ab.	16643
29	or/26-28	19012
30	25 not 29	626533
31	exp animal/	13634032
32	exp animal-experiment/	1148122
33	nonhuman/	3469399
34	(rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.	3121425
35	or/31-34	14573590
36	exp human/	11014295
37	exp human-experiment/	249143
38	36 or 37	11014970
39	35 and 38	11014476
40	35 not 39	3559114
41	30 not 40	581245
42	9 and 41	75
43	limit 42 to English language	70

*Lines 10-41 are from the published NHS EED filter (http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html)

EconLIT Search Strategy:

SEARCH	SEARCH TEXT	HITS
1	hepatic encephalopathy [Including Limited Related Terms]	55
2	hepatocerebral encephalopathy [Including Limited Related Terms]	54
3	portosystemic encephalopathy [Including Limited Related Terms]	54
4	portal-systemic encephalopathy [Including Limited Related Terms]	54
5	hepatic stupor [Including Limited Related Terms]	4
6	hepatic coma [Including Limited Related Terms]	7

7	or/1-6	64

NHS EED Search Strategy:

SEARCH #	SEARCH TEXT	HITS
#1	MeSH descriptor: [Hepatic Encephalopathy] explode all trees	323
#2	encephalopath* and (hepatic or hepatocerebral or portosystemic or portal-systemic or portal systemic)	857
#3	hepatic and (stupor* or coma*)	205
#4	#1 or #2 or #3	987
#5	Rifaximin-α or rifamycin or Xifaxan or refero or targaxan or tixteller or xifaxanta or redactiv or 80621-81-4 or 88747-56-2	182
#6	Lactulose or generlac or kristalose or enulose or constulose or duphalac or lactugal or normase or amivalex or 4618-18-2	706
#7	Neomycin or mycifradin or neo-fradin or neo-tab or nivemycin or fradiomycin or 11004-65-2 or 1404-04-2 or 1405-10-3 or 8026-22-0	579
#8	#5 or #6 or #7	1395
#9	#4 and #8 in Economic Evaluations	2

Study selection

Table summarises the eligibility criteria for studies identified in the systematic review of cost-effectiveness and resource use studies.

Patients with HE comprised the target population, in accordance with the decision problem. Patients were not required to have had prior episodes of HE or be in remission, as it was anticipated that cost-effectiveness or resource use studies would be less likely to specify patients to this level of detail. Furthermore, broader criteria were deemed appropriate for this search as methodological characteristics and input sources of any study identified may be relevant to the de novo model prepared as part of this submission.

Specific interventions were similarly not considered to be criteria for inclusion, as the methodology and inputs of any study identified, regardless of comparators, may be relevant to the de novo model.

A criterion of “treatment duration ≥ 1 month” was used to help differentiate the use of study drug for reduction in recurrence of episodes of overt HE from the treatment of an actual overt episode.

Studies were limited to English language.

To select appropriate studies, de-duplicated were screened at the abstract level by one reviewer. Full-text versions (if available) were retrieved for the citations that were not excluded in this initial screening, and were subsequently screened by the same reviewer. Those studies that were not excluded at the full-text level were included in the review. Two additional levels of reviewers were available for consultation if a rationale for inclusion or exclusion was not immediately identified.

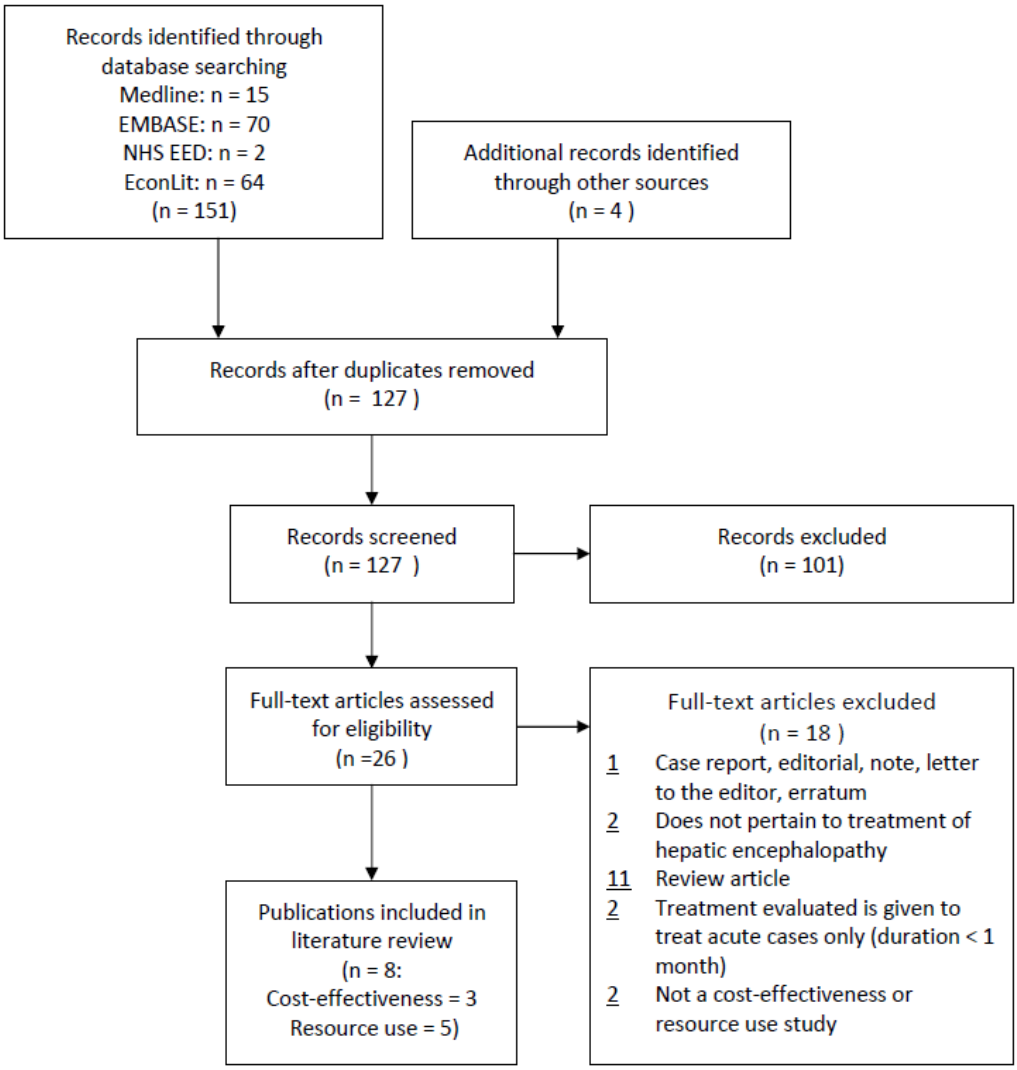
Table B2: Eligibility criteria used in search strategy for cost-effectiveness and resource use studies

	Cost-Effectiveness and Resource Use
Inclusion criteria	• Cost-effectiveness analyses • Resource use or cost of illness studies • Pertains to treatment for the prevention of HE (duration ≥ 1 month)
Exclusion criteria	• Does not pertain to treatment of HE • Case report, editorial, note, letter to the editor, erratum • Review article • Not a cost-effectiveness or resource use (cost of illness) study • Treatment evaluated is given to treat acute cases only (duration < 1 month) • Not in English

A PRISMA flow diagram of the systematic search and screening process is included in **Figure B1:**

In sum, 151 citations were identified in the searches of the Medline, Embase, NHS EED, and EconLit databases, with 4 additional records included from the conference abstract searches. After removing duplicates, 127 records were screened at the abstract level. 101 records were excluded at the abstract level. Of the 26 records that advanced to full-text review, 18 were further excluded, primarily (N = 11) because they were review articles. Ultimately, 8 records fulfilled the inclusion criteria.

Figure B1: PRISMA flow diagram for cost-effectiveness and resource use systematic review



A summary of each the three cost-effectiveness studies identified in the systematic review can be found in Table B3.

Table B3 Summary list of cost-effectiveness evaluations identified in systematic review

Study	Cost Year	Country Perspective	Summary of model	Patient Population	Effects (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER
Bajaj et al. 2012	2010	US, societal perspective	• Aim of study: To conduct a cost-effectiveness analysis to assess the benefits of different strategies of MHE diagnosis and treatment for reducing motor-vehicle accident (MVA)-related societal costs. • Markov model diagnostic/ treatment strategies: 1. Presumptive treatment (lactulose or rifaximin-α) of all cirrhosis patients 2. Diagnosis by rapid screening using ICT, if positive for MHE followed by treatment (lactulose or rifaximin-α) 3. Diagnosis by SPT battery, if positive for MHE followed by treatment (lactulose or rifaximin-α) 4. Diagnosis by NPE, if positive for MHE followed by treatment (lactulose or rifaximin-α) 5. No MHE diagnosis or treatment • Model specifics: ○ Time-horizon: 5 yr. ○ MHE testing was conducted biannually ○ Clinical inputs: "Empirically derived and literature based estimates of MHE	Simulated cohort of 1,000 cirrhosis patients with compensated liver disease and without OHE, from entry into treatment, through MHE development, and later OHE at which time they exited the modelled cohort.	Presumptive lactulose: 205.94 accidents avoided ICT with lactulose: 202.20 accidents avoided SPT with lactulose: 204.164 accidents avoided NPE with lactulose: 205.94 accidents avoided Presumptive rifaximin-α: 279.49 accidents avoided ICT with rifaximin-α: 274.41 accidents avoided	Presumptive lactulose: $6.3M total cost ICT with lactulose: $4.9M total cost SPT with lactulose: $5.2M total cost NPE with lactulose: $6.9M total cost Presumptive rifaximin-α: $46.9M total cost ICT with rifaximin-α: $36.5M SPT with rifaximin-α: $37.0M NPE with rifaximin-α:	Presumptive lactulose vs. no testing or treatment: $30,469 per accident avoided ICT with lactulose vs. no testing or treatment: $24,454 per accident avoided SPT with lactulose vs. no testing or treatment: $25,470 per accident avoided NPE with lactulose vs. no testing or treatment: $33,742 per accident avoided

			diagnostic tests and treatment parameters and MVA-related parameters" were used. ○ Cost inputs: Societal cost per MVA from national highway and traffic administration data, pharmaceutical costs from 2007 Red Book, value of patient time from Bureau of Labour Statistics. Test costs and patient time for the four diagnostic test options were based on the authors' experience at their home institutions. ○ Discount rate: 3% • Sensitivity Analysis: discount rate at 5%, univariate analyses conducted for all key parameters		SPT with rifaximin-α: 277.07 accidents avoided NPE with rifaximin-α: 279.49 accidents avoided	$31.2M	Presumptive rifaximin-α vs. no testing or treatment: $167,633 per accident avoided ICT with rifaximin-α vs. no testing or treatment: $133,085 per accident avoided SPT with rifaximin-α vs. no testing or treatment: $133,564 per accident avoided NPE with rifaximin-α vs. no testing or treatment: $111,760, per accident avoided
Paul et al. 2012 (abstract)	NR	US, third-party payer's perspective	• Aim of study: The 2007 decision analysis by Huang et al.(91) (1st row of this table) concluded that a 'Rifaximin-α Salvage' strategy reserving Rifaximin-α only for those failing lactulose was most cost-effective. However, more studies,	Hypothetical cohort of 50-year-old patients with overt HE.	Lactulose Monotherapy: 2.1 discounted LY 'Rifaximin-α Salvage': 2.5 LY	Lactulose Monotherapy was least expensive: $61,300 total lifetime combined cost of care	Lactulose Monotherapy was dominated by all Rifaximin-α arms. 'Rifaximin-α

			notably the large multi-centre trial by Bass et al.(1) (RFHE3001) have been published since then. In this setting, a re-analysis of the cost-effectiveness of four competing strategies including newly available data and updated costs was performed. • Patients distributed to four treatment strategies: 1. Lactulose Monotherapy 2. Rifaximin-α Monotherapy 3. Rifaximin-α and Lactulose Combination 4. 'Rifaximin-α Salvage'= initiation with lactulose and crossover to rifaximin-α in case of inadequate response or intolerance to lactulose (Since previously used agents such as neomycin, and lactitol are no longer widely used, they were excluded, as was the "do nothing" strategy from the previous Huang et al. model) • Patients then entered Markov model with: ○ Time-horizon: 6 months (to be consistent with Bass et al. trial) ○ Clinical and HRQL Inputs: Probability estimates were derived from a systematic literature review to identify RCTs of HE with follow-up >4 weeks			Rifaximin-α Monotherapy was most expensive: $65,800 total lifetime combined cost of care	Salvage' was the overall dominant strategy

			○ Cost Inputs: Management costs for a patient with cirrhosis and HE from Medicare and the Red Book • Sensitivity Analysis: Each probability estimate was varied over a wide range.				
Huang et al. 2007	2006	US, third-party payer perspective	• Aim of study: To perform a decision analysis to measure the cost-effectiveness and managed care budget impact of the trade-off between the improved therapeutic benefits of rifaximin-α in HE and its increased cost compared to competing therapies, which have more therapeutic disadvantages but are less expensive. • Decision node distributing patients to six treatment strategies: 1.'Do Nothing' 2. Lactulose Monotherapy 3. Lactitol Monotherapy 4. Neomycin Monotherapy 5. Rifaximin-α Monotherapy 6. 'Rifaximin-α Salvage'= upfront lactulose with crossover to rifaximin-α if poor response or intolerance to lactulose • Patients then entered Markov model with: ○ Time-horizon: 10 yr. ○ Cycle length: 1 yr.	Hypothetical cohort of 50-year-old patients with cirrhosis and HE. 50% of the cohort had subclinical HE, and the remainder had overt HE.	'Do Nothing': 2.8 QALYs Lactulose Monotherapy: 4.2 QALYs (estimated from a chart) Lactitol Monotherapy: 3.7 QALYs (estimated from a chart) Neomycin Monotherapy: 4.1 QALYs (estimated from a chart) Rifaximin-α Monotherapy: 5.0 QALYs (estimated from a chart)	'Do Nothing': $67,700 (estimated from a chart) Lactulose Monotherapy: $56,967 Lactitol Monotherapy: $61,800 (estimated from a chart) Neomycin Monotherapy: $59,100 (estimated from a chart) Rifaximin-α Monotherapy: $75,671 'Rifaximin-α Salvage': $61,000 (estimated from a chart)	'Rifaximin-α Salvage' vs. Lactulose Monotherapy: $2,315 (2.5th and 97.5th percentile, $995, $4,816) per QALY-gained Rifaximin-α Monotherapy vs. Lactulose Monotherapy: $20,553 per QALY-gained Lactulose monotherapy dominated "do nothing," lactitol monotherapy, and neomycin monotherapy, while Rifaximin-α monotherapy was

			○ Clinical and HRQL inputs: Base-case treatment-related and cirrhosis-related health state probability point estimates were derived from a systematic review of MEDLINE. When multiple studies supported an individual point estimate a weighted mean was calculated according to sample size. When available, pre-existing meta-analyses were used. ○ Cost inputs: Doctor services and procedures from coding book, pharmaceutical costs from 2006 Red Book, and health state costs from a 1997 study by Bennett et al. 1997(92) inflated to 2006 ○ Discount rate: 3% • Sensitivity Analysis: % of patients with either overt or subclinical HE was varied from the base- case 50/50, and multivariable sensitivity analysis		'Rifaximin-α Salvage': 5.3 QALYs		dominated by the "Rifaximin-α salvage" treatment strategy.

Abbreviations: HE = hepatic encephalopathy; ICER = incremental cost-effectiveness ratio; ICT = inhibitory control test; MHE = minimal hepatic encephalopathy; MVA = motor vehicle accident; NPE = neuropsychological exam; NR = not reported; OHE = overt hepatic encephalopathy; QALY = quality-adjusted life year; SPT = standard psychometric test.