Appendix A: Updated Effectiveness Search (Response to D1)

Identification of studies

The following databases were searched (with service providers):

- Medline (OvidSP)
- Medline In-Process & other non-indexed citations (OvidSP)
- Embase (OvidSP)
- Cochrane Libraries

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)

Exact details of the search strategy are provided in table A1.

Table A1: Search Strategy for Effectiveness Studies

Date of search:
The search in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) was conducted on 13 December 2012.

The searches in EMBASE and Cochrane Library were both conducted on 12 December 2012.

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 Cochrane Library encompassed all citations through to the date of the search (12 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	1 or 2 or 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	5 or 6 or 7	16124
9	4 and 8	642
10	randomised controlled trial.pt.	345443

11	controlled clinical trial.pt.	85970
12	randomised.ab.	260170
13	placebo.ab.	142373
14	clinical trials as topic.sh.	164147
15	randomly.ab.	189638
16	trial.ti.	111963
17	10 or 11 or 12 or 13 or 14 or 15 or 16	826598
18	exp animals/ not humans.sh.	3823020
19	17 not 18	763859
20	9 and 19	153
21	limit 20 to English language	137

* Lines 10-19 are derived from the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format. (Available at: http://handbook.cochrane.org/; Box 6.4d)

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	1 or 2 or 3	9323
5	(rifaximin-α or rifamycin or xifaxan or refero or targaxan or tixteller or xifaxanta or redactive or 80621-81-4 or 88747-56-2).tw,rn.	3614
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	5 or 6 or 7	20450
9	4 and 8	1169
10	exp animal/	13634032
11	exp animal-experiment/	1148122
12	nonhuman/	3469399
13	10 or 11 or 12	14516412
14	exp human/	11014295
15	human-experiment/	249143
16	14 or 15	11014970
17	13 and 16	11014468
18	13 not 17	3501944
19	9 not 18	1132
20	Random*.tw. or placebo*.mp. or double-blind*.tw.	875175
21	19 and 20	265
22	limit 21 to English language	242

23	from 22 keep 1-242	242

* The search filter in line 20 is taken from: Wong SSL, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc. 94;1:41-47. The strategy utilised is that which best optimises sensitivity and specificity (Table 3 in the publication).

Cochrane 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	181

Study selection

Table A2 summarises the eligibility criteria for inclusion in the systematic review.

The patient population targeted was defined by the decision problem (adults who have had prior episodes of HE and are currently in remission), in accordance with the summary of product characteristics (SmPC) (rifaximin-α is for the reduction in recurrence of episodes of overt HE in patients ≥ 18 years of age). 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.

Study design was limited to RCTs and linked open-label extension studies, matching the designs of the pivotal rifaximin-α studies pertaining to the decision problem. Studies were limited to English language only. No publication date limits were applied as lactulose has been used to treat HE for nearly 50 years.

To select appropriate studies, de-duplicated citations were screened at the abstract level by a single reviewer, after which a second reviewer re-screened the excluded studies to ensure that none were wrongly excluded. Full-text versions (if available) were retrieved for the citations that were not excluded in this initial (abstract-level) screening, and were subsequently screened by the same reviewers. 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 A2: Eligibility criteria for inclusion in the systematic review

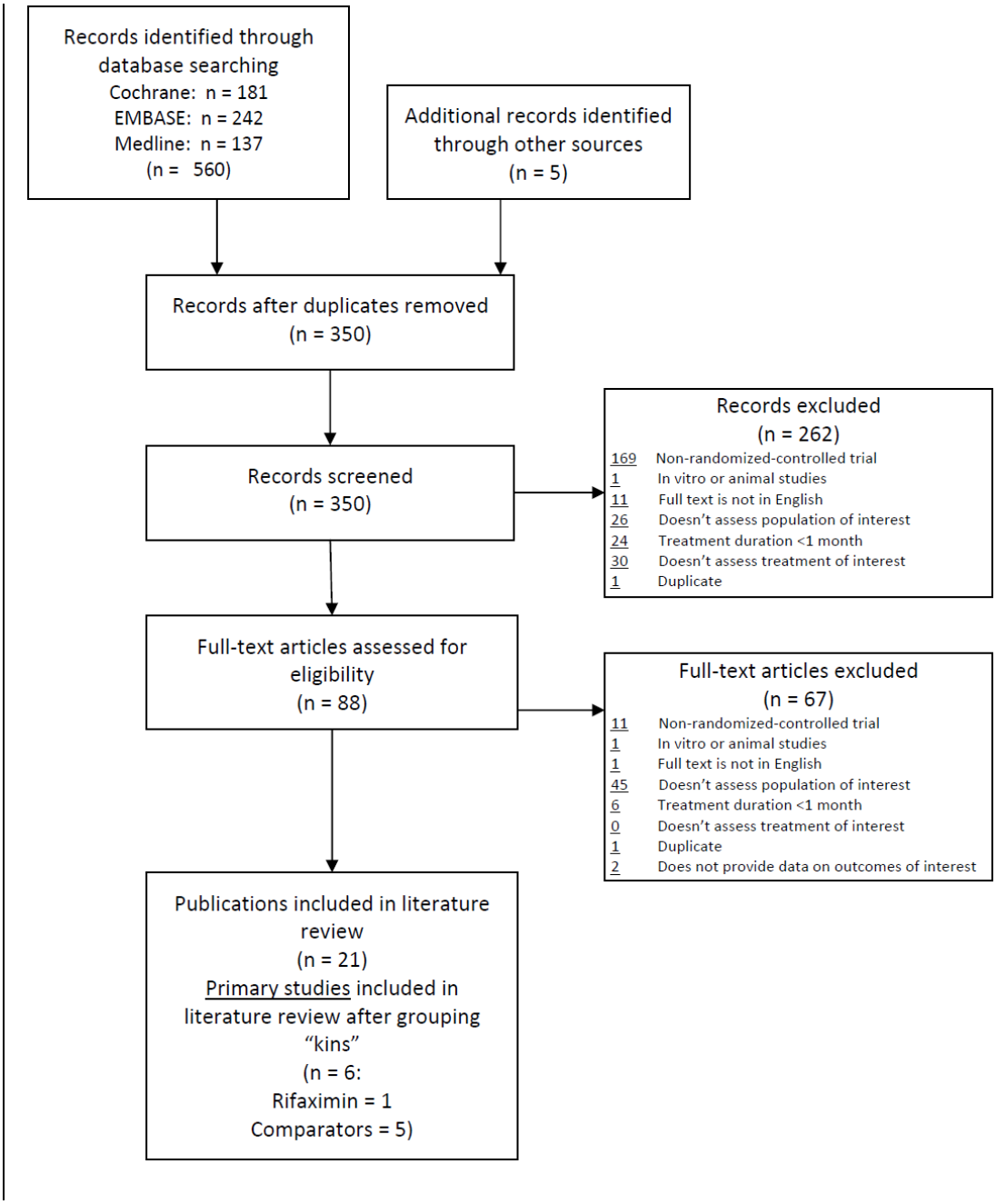
	Clinical effectiveness

Inclusion criteria	• RCT (linked open-label extensions of included RCTs also included)
	• Studies including adult patients with prior history of HE documented or inferred and currently in remission
	• Studies with at least one arm evaluating any of the interventions of interest, i.e., rifaximin-α, lactulose, neomycin, neomycin + lactulose
	• Studies with a treatment duration of at least 1 month
	• Studies reporting at least one of the outcomes of interest, i.e.,
	  ○ Disease progression to more severe grade of HE
	  ○ Frequency of hospitalisation and/or time to next hospitalisation
	  ○ Frequency of recurrent acute episodes of HE and time to next episode
	  ○ Mortality
	  ○ AEs of treatment
	  ○ HRQL
	• English language

Exclusion criteria	• Non RCTS (or linked open-label extension)- Reviews, case reports, observational studies, single armed, letters, editorials, comments
	• In vitro or animal studies
	• Studies in a language other than English
	• Studies assessing populations other than the population of interest (i.e., children, patients without prior episodes of HE, patients during an acute episode of HE)
	• Studies whose treatment duration is <1 month
	• Studies that do not feature a treatment of interest
	• Duplicates
	• Does not provide data on the outcomes of interest, i.e.,
	  ○ Disease progression to more severe grade of HE
	  ○ Frequency of hospitalisation, and/or time until next hospitalisation
	  ○ Frequency of recurrent acute episodes of HE and time to next episode
	  ○ Mortality
	  ○ AEs of treatment
	  ○ HRQL

A PRISMA flow diagram of the systematic search and screening process is included in Figure A1. In sum, 560 citations were identified in the searches of the Medline, Embase, and Cochrane databases, with 5 additional records included from the conference abstract searches. After removing duplicates, 350 records were screened at the abstract level. 262 records were excluded at the abstract level, primarily (N = 169) because they did not pertain to RCTs. Of the 88 records that advanced to full-text review, 67 were further excluded, primarily (N = 45) because the trials did not assess the population of interest. Ultimately, 21 records fulfilled the inclusion criteria, pertaining to 6 primary trials (2 trials were represented by 2 or more records, explaining the discrepancy in total records and total primary trials).

Figure A1: PRISMA flow diagram for RCT systematic review



A summary of the studies included as the primary data sources, together with the associated secondary "kin" data are listed in Table A3.

Table A3: Summary of linked studies and "kin" publications in the review of rifaximin-α RCTs

	RFHE3001 (RCT)	**RFHE3002 (linked open-label extension)**
Primary data source(s)	• Bass et al. 2010 (clinical) • Sanyal et al. 2011 (HRQL) • CSR (unpublished)	• CSR (unpublished)
Secondary ("kin") data sources identified in the systematic review (all are in abstract form only)	• Brown et al. 2009 • Mullen et al. 2009 • Neff et al. 2009 • Sanyal et al. 2009 • Sanyal et al. 2010a • Sanyal et al. 2010b • Younossi et al. 2011	• Poordad et al. 2009 • Frederick et al. 2011 • Mullen et al. 2011 • Bajaj et al. 2012 • Mullen et al. 2012 • Sanyal et al. 2012

Only one RCT was identified that included rifaximin-α in the relevant patient group defined by the decision problem in accordance with the SmPC. This was the RFHE3001 trial, which included a linked open-label extension (RFHE3002). Details can be found in table A4.

Table A4: List of relevant RCTs

Trial	**Intervention**	**Comparator**	**Population**	**Primary study refs.**
RFHE3001	Rifaximin-α 550 mg, taken orally BID*	Placebo*	Outpatients ≥ 18 years with a recent history of recurrent (≥ 2 episodes in the past 6 months), overt HE (Conn score ≥ 2) associated with hepatic cirrhosis or portal hypertension who are currently in remission (Conn score 0 or 1) and have a score of ≤ 25 on the MELD scale.	CSR (unpublished) Bass et al. 2010 (clinical publication Sanyal et al. 2011 (HRQL publication)
RFHE3002 (open-label extension to RFHE3001)	Rifaximin-α 550 mg, taken orally BID	Not applicable	Outpatients ≥ 18 years with a Conn score of 0-2 at baseline, rolled over from RFHE3001 or other clinical trial conducted under IND 59,133 for rifaximin-α or, if not rolled over, with ≥ 1 verifiable episode of HE (Conn score ≥ 2, returning to score of 0 or 1) associated with cirrhosis or portal hypertension within 12 months of screening.	CSR (unpublished)

* Patients were permitted to take concomitant lactulose if necessary. Ultimately, 91.4% of patients in the rifaximin-α arm and 91.2% of patients in the placebo arm (91.3% of all trial patients) received concomitant lactulose for the duration of the trial.