Name	Dr Debbie L Shawcross
Role	NHS Professional
Other role	
Location	England
Conflict	yes
Notes	[redacted]
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Since the last appraisal committee meeting held in October where I served as a Clinical Advisor, I have some additional relevant data to submit for the committee to consider. These are the results of a National Audit of Rifaximin use in 4 UK centres [King's College London, Newcastle, Liverpool and Portsmouth]. This audit included data on 170 patients with hepatic encephalopathy (HE) who were retrospectively studied 1 year prior and up to 1 year following commencement of rifaximin therapy. These "real world data" convincingly demonstrate the efficacy and clinical utility of the drug as a fundamental component of the armamentarium available to clinicians treating patients with HE. A power point presentation summarising the key data arising from this audit will be forwarded to the NICE HQ for review. In essence however, apart from showing a significant reduction in the severity of the HE Conn Score ($p<0.0001$) and hospitalisation rate ($p<0.0001$) following commencement of the drug, the drug also impacted on the trajectory of disease progression in patients who survive >90 days and show significant reductions in the Child Pugh Turcotte, ($p<0.0001$) MELD ($p=0.03$) and UKELD scores ($p=0.02$).
Section 2 (The technology)	The results of the National Audit referred to above show that the drug was extremely well tolerated with only 4/170 patients reporting side effects [diarrhoea which resolved after 7 days, nausea , rigors and rash]. The rigors were likely related to concomitant infection rather than the drug. None of the 170 patients developed Clostridium Difficile infection. What did become apparent from the audit data was that only 30/170 were still on the drug at the last follow up as there were a large number of who dropped out within 3 months of follow up [31% died and 35% were transplanted]. Indeed, there are insufficient data at this time to perform robust 6 and 12 month analyses. This calls into question putting too much weight on the validity of reflecting upon a clinically plausible diminishing mortality benefit with rifaximin over time, excluding mortality benefit in the remission state and the use of a lifetime time horizon to capture all costs and benefits associated with rifaximin although there is no doubt that the greatest benefit of the drug may be obtained in the first 3 months of treatment. Patients listed for transplantation gain the most benefit from the drug.
Section 3 (The manufacturer's submission)	I think the clinical efficacy of rifaximin has never been called into question by the hepatology community but it has been harder to robustly demonstrate the HRQoL and mortality benefits of the drug when considering RFHE3001 and 3002 trial data. I am therefore unclear how requesting estimates of utilities from SF-36 quality-of-life data collected from the RFHE3001 trial and mapped directly to the EQ-5D, using all

	observations in each relevant health state and adjusted for baseline utility will provide any further clarity here. What the national audit does robustly demonstrate is that the reduction in hospital admissions from a mean(SD) of 2.7(3.2) pre-rifaximin to 1(1.8) post; p<0.0001 will have huge cost savings for the NHS. Furthermore, the improvement in Child Pugh, MELD and UKELD in those surviving >90 days will favourably impact on the mortality benefit of the drug way in excess of 10% considering the 2 year survival rate of someone with Child Pugh C disease is 35% compared to B (57%) and A (85%).
Section 4 (Consideration of the evidence)	In addition to my comments above, I think that 2 other key points need to be considered when reaching a FAD. Firstly, with regard to "Equalities considerations and social value judgements", any patient with hepatic encephalopathy (HE) is in my opinion a vulnerable adult. Indeed, patients enrolled into HE trials are considered to lack the capacity to consent and require special dispensation from ethics committees and a nominee to facilitate important clinical decisions. Therefore, denying these patients access to this drug may be adversely impacting on a vulnerable cohort of society who does not have the capacity or access to patient advocate groups to argue on their behalf. Secondly, the burden on carers needs to be considered in any consultation decision. Many of these patients? next of kin have to look after them 24 hours a day and are consequently unable to work or contribute financially otherwise to society. Most patients with cirrhosis and HE are unable to self-care or be employed and are reliant on state benefits compared to those with cirrhosis without HE.
Section 5 (Implementation)	No further comment
Section 6 (Proposed recommendations for further research)	No further comment
Section 7 (Related NICE guidance)	Bearing in mind that further clinical trials are being performed, this date is possibly too remote and I would favour review in 2016.
Section 8 (Proposed date of review of guidance)	
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