Impact of Updated Mortality Estimates on the Cost-Effectiveness of Rifaximin for the Treatment of Patients with Overt Hepatic Encephalopathy
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BACKGROUND
Hepatic encephalopathy (HE) is one of the most significant complications of cirrhosis with a substantial economic burden (HE-related hospitalization charges of $7.2 billion in 2009 in the United States) [1,2].

Rifaximin® (Rifaximin) is the only US Food and Drug Administration (FDA)-approved (2010) treatment for the reduction of risk of overt hepatic encephalopathy (OHE).[3]

A cost-effectiveness model by Jesudian AB et al. (2020) demonstrated that rifaximin 1 lactulose (vs. lactulose monotherapy) is cost-effective with a incremental cost-effectiveness ratio (ICER) of $29,161 (2018 US dollar) per quality-adjusted life years (QALY) gained [4].

OBJECTIVE
The objectives of the current study are:

1. To identify updated rifaximin-associated OHE mortality estimates for US patients
2. To conduct scenario analyses to assess the robustness of the Jesudian AB et al. (2020) study ICER estimates (base case), by comparing the base case ICER to the ICER estimates using updated rifaximin-associated OHE mortality identified in objective 1

METHODS
To identify updated (as of 08/22/2022) rifaximin-associated OHE mortality estimates for US patients (objective 1), a targeted literature review (TLR) was conducted:

1. The TLR search was conducted using PubMed (MEDLINE), Ovid MEDLINE, and Ovid Embase databases and the Population Intervention Comparator Outcome (PICO) framework (Table 2) based on a pre-specified inclusion/exclusion criteria (Table 2).
2. Critical appraisal of identified studies was conducted using Cochrane RoB v2.0 (randomized controlled trials), ROBINS-I tool (non-randomized controlled trials), STROBE Checklist (cohort studies and cross-sectional studies).

Table 1: PICO framework for the targeted literature review search

| Population | Patients with overt hepatic encephalopathy
| Comparator | Lactulose or lactulose
| Outcome | Rate of mortality
| PICO | Population, Intervention, Comparator, and Outcome

Table 2: Inclusion and exclusion criteria for targeted literature review search

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<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<td>Parallel-group RCTs</td>
<td>Studies without the relevant outcome, review articles, non-English language articles, letters to the editor, and animal trials</td>
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<td>Studies reporting mortality outcomes</td>
<td>RCT: Randomized Clinical Trial</td>
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Following the TLR, scenario analyses (objective 2) were conducted to assess the impact of updated US mortality estimates (identified from the TLR) on the robustness of the base case model ICER estimates:

1. In the scenario analyses, the impact on the QALY gained was assessed under two scenarios:
   - Assuming no mortality benefits associated with rifaximin
   - Assuming rifaximin-associated US mortality estimates from literature identified from the TLR
2. All the ICERs in the scenario analyses were presented in 2018 USD for comparability with the Jesudian AB et al. (2020) ICER estimates

Table 3: Studies identified in the targeted literature review

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<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Reported mortality</th>
<th>Mortality reported in the base case analysis</th>
<th>Cost modelled for use with the mortality outcomes in the base case analysis</th>
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RESULTS

At the time of the Jesudian AB et al. (2020) cost-effectiveness model development, only Mullen et al. (2014) was available as a source for mortality rates among non-hospitalized HE patients in the US.

Further, the study authors validated the ICER using mortality estimate from Mullen et al. (2014) by comparing to ICER results using mortality estimates reported by Bannister et al. (2016) – a high-quality study that reported mortality estimates among non-hospitalized patients in the United Kingdom [5].

The mortality estimates obtained from Bannister et al. (2016) were similar to that obtained from Mullen et al. (2014) and in the scenario analyses (Figure 1), the results under both scenarios were similar to the base case results from Jesudian AB et al. (2020).

The mortality rates estimated from Bannister et al. (2016) were $29,161 per QALY gained when no mortality benefit associated with rifaximin was assumed (scenarios 1-3).

In scenario analyses (Figure 1), the results under both scenarios were similar to the base case results from Jesudian AB et al. (2020). The mortality estimates from Bannister et al. (2016) were $29,161 per QALY gained when no mortality benefit associated with rifaximin was assumed (scenarios 1-3).

The mortality estimates from Bannister et al. (2016) were $29,161 per QALY gained when no mortality benefit associated with rifaximin was assumed (scenarios 1-3).

DISCUSSION

The mortality estimate for the non-hospitalized population from Mullen et al. (2014) used in the Jesudian AB et al. (2020) study, corroborated well with another high-quality publication (Bannister et al. 2016) and was the best available evidence for US population at the time of the study in 2018-19.

Assuming no rifaximin-associated mortality benefit and using mortality estimates from recent studies in the US population demonstrate that mortality benefit associated with rifaximin use is not a key cost-effectiveness value driver.

Changes in the mortality estimates or assumptions do not significantly impact the ICER of rifaximin for the treatment of OHE presented in Jesudian AB et al. (2020).

The authors critically evaluated quality (RoB 2 tool, ROBINS-I checklist, and STROBE framework, as applicable) of the relevant studies identified in the TLR. Some of these studies do not study Xifaxan® 550 mg BID. There are studies that did not use Xifaxan 550 mg BID according to the US FDA label for the approved indication for HE (i.e. reduction in risk of OHE recurrence) and we cannot speak to the propriety of off-label use of any rifaxim for HE that is not Xifaxan 550 mg BID for the reduction in risk of OHE recurrence.

REFERENCES


