Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction

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ABSTRACT

Objective Chronic heart failure with reduced ejection fraction (HF-REF) represents a major public health issue and is associated with considerable morbidity and mortality. We evaluated the cost-effectiveness of sacubitril/valsartan (formerly LCZ696) compared with an ACE inhibitor (ACEI) (enalapril) in the treatment of HF-REF from the perspective of healthcare providers in the UK, Denmark and Colombia.

Methods A cost-utility analysis was performed based on data from a multinational, Phase III randomised controlled trial. A decision-analytic model was developed based on a series of regression models, which extrapolated health-related quality of life, hospitalisation rates and survival over a lifetime horizon. The primary outcome was the incremental cost-effectiveness ratio (ICER).

Results In the UK, the cost per quality-adjusted life-year (QALY) gained for sacubitril/valsartan (using cardiovascular mortality) was £17 100 (£20 400) versus enalapril. In Denmark, the ICER for sacubitril/valsartan was Kr 174 000 (£22 600). In Colombia, the ICER was COP$39.5 million (£11 200) per QALY gained. Deterministic sensitivity analysis showed that results were most sensitive to the extrapolation of mortality, duration of treatment effect and time horizon, but were robust to other structural changes, with most scenarios associated with ICERS below the willingness-to-pay threshold for all three country settings. Probabilistic sensitivity analysis suggested the probability that sacubitril/valsartan was cost-effective at conventional willingness-to-pay thresholds was 68%–94% in the UK, 84% in Denmark and 95% in Colombia.

Conclusions Our analysis suggests that, in all three countries, sacubitril/valsartan is likely to be cost-effective compared with an ACEI (the current standard of care) in patients with HF-REF.

INTRODUCTION

Chronic heart failure with reduced ejection fraction (HF-REF) represents a major public health issue and is associated with considerable morbidity and mortality. Globally, heart failure (HF) affects an estimated 26 million people and is responsible for 1%–2% of hospitalisations in the USA and Europe.1 HF as a primary diagnosis accounts for approximately 2% of the UK National Health Service (NHS) annual budget,2 and up to 4% of healthcare expenditure if hospitalisations with HF as a secondary diagnosis and nursing home admissions are considered.2

The ACE inhibitor (ACEI) enalapril was the first treatment shown to reduce the risk of hospitalisation and death in patients with HF-REF; ACEIs remain the first-line therapeutic option in these patients.3,4 Despite this and several other therapeutic advances in the field, individuals with HF-REF remain at high risk of hospitalisation and death and experience poorer health-related quality of life (HRQL) than age-matched and gender-matched individuals in the general population.6,9

Sacubitril/valsartan (formerly LCZ696) is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI). The Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial was a multinational, Phase III, prospective, double-blind, randomised active-controlled trial, comparing the effects of sacubitril/valsartan and enalapril on mortality and morbidity, in addition to standard of care, in patients with chronic HF-REF.9 PARADIGM-HF demonstrated that, compared with enalapril, treatment with sacubitril/valsartan significantly reduced the composite primary outcome of cardiovascular (CV) death or HF hospitalisation, and both components of this composite, by approximately 20%.10

As the drug acquisition cost of sacubitril/valsartan is higher than that of an ACEI, reimbursement by national payers requires an estimation of expected costs and benefits in order to determine value for money. This study assesses the cost-effectiveness of sacubitril/valsartan versus enalapril from three perspectives: the UK, the Danish and the Colombian healthcare systems.

METHODS

Consistent with UK and Danish guidance,11 the England and Wales National Heart Failure Audit (2013) found that 73% of patients discharged with HF-REF were treated with ACEI,11 while 18% were treated with an angiotensin receptor blocker (ARB). Therefore, enalapril was selected as the base case comparator in this economic analysis.

A systematic review of economic evaluations of chronic HF treatments was performed to inform
the design of the economic evaluation. The health states most frequently employed were ‘alive’ and ‘dead’, with outcomes such as hospitalisation or New York Heart Association (NYHA) functional class distribution considered in the ‘alive’ state. Therefore, a decision-analytic model was developed with ‘alive’ and ‘dead’ health states to estimate costs and benefits over the population lifetime, with hospitalisation rates, HRQL (evaluated using the EuroQol-5 Dimension (EQ-5D) index score) and adverse event (AE) rates included in the ‘alive’ health states (figure 1).

A 1-month cycle length with half-cycle correction was employed. Costs and benefits beyond 1 year were discounted at rates of 3.5%, 3% and 5% for the UK, Danish and Colombian settings, respectively, according to local guidelines.11–13

The risks of events were estimated, dependent on patients’ baseline characteristics (reported previously)10 14 and treatment (sacubitril/valsartan or ACEI), through multivariable regression models. Outcomes were estimated for each patient in PARADIGM-HF and results presented as the expected costs and benefits across the patient cohort. Cost-effectiveness was estimated for all a priori defined subgroups in PARADIGM-HF by averaging across the members of the relevant subgroup. The primary model outcome was the incremental cost-effectiveness ratio (ICER), expressed as the cost per quality-adjusted life-year (QALY) gained, reported to the nearest 100 currency units. The ICERs for each setting were compared with country-specific cost-effectiveness thresholds, as listed in table 1.

Deterministic and probabilistic sensitivity analyses were performed to test parameter uncertainty in the model; the methods are provided in the online Supplementary file 1.

All statistical analyses were performed using Stata V.13.15 The cost-effectiveness model was built in MS Excel.

Table 1  ICER and cost-effectiveness thresholds in the settings considered in the cost-effectiveness model

<table>
<thead>
<tr>
<th>ICER comparison per setting</th>
<th>Cost-effectiveness threshold/QALY gained</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>£20 000 (EUR 23 862)*</td>
<td>NICE†</td>
</tr>
<tr>
<td></td>
<td>£30 000 (EUR 35 793)*</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>Kr250 000 (EUR 33 624)†</td>
<td>National drug reimbursement committee</td>
</tr>
<tr>
<td>Colombia</td>
<td>COP$52.4 million (EUR 15 975)$§</td>
<td>Colombian HTA guidance12</td>
</tr>
</tbody>
</table>

* Exchange rate used: 1 GBP=1.19 EUR.
‡ Exchange rate used: 1 DKK=0.13 EUR.
§ Exchange rate used: COP$1=0.0003 EUR, equivalent to three times Colombian GDP.14
COP, Colombian peso; DKK, Danish kroner; EUR, Euro; GBP, British pound sterling; GDP, gross domestic product; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; Kr, Danish kroner; QALY, quality-adjusted life-year.
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Table 2  Summary of differences between models

<table>
<thead>
<tr>
<th>Component</th>
<th>UK</th>
<th>Denmark</th>
<th>Colombia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>PARADIGM-HF</td>
<td>Reweighted</td>
<td>PARADIGM-HF</td>
</tr>
<tr>
<td>Analysis type</td>
<td>Patient-level analysis</td>
<td>Patient-level analysis</td>
<td>Patient-level analysis</td>
</tr>
<tr>
<td>Mortality</td>
<td>CV mortality from PARADIGM-HF+life tables</td>
<td>CV mortality from PARADIGM-HF+life tables</td>
<td>CV mortality from PARADIGM-HF+life tables</td>
</tr>
<tr>
<td>EQ-5D tariff</td>
<td>Dolan</td>
<td>Wittrup-Jensen</td>
<td>Dolan</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>considered in the base case?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CV, cardiovascular; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure.

AEs used were those reported in the primary analysis of PARADIGM-HF. A constant rate of AEs was assumed over the model time horizon.

Health-related quality of life

The EQ-5D tariff published by Dolan was applied to EQ-5D responses collected in PARADIGM-HF to generate utility values for each patient for the UK setting. The tariff published by Wittrup-Jensen et al was applied to the Danish setting. As there is no Colombian EQ-5D tariff, the Dolan tariff was applied in the Colombian setting.

A multilevel model of EQ-5D was developed to allow the prediction of EQ-5D dependent on baseline characteristics, hospitalisation, AEs and time since randomisation. A constant decline in EQ-5D common to all patients was assumed as a simplifying assumption, and sacubitril/valsartan was assumed to confer a constant effect at all time points on HRQL.

The effect of hospitalisation on HRQL was captured through the model. These differences are summarised in table 2. The effects of hospitalisation were based on the average doses taken in PARADIGM-HF (enalapril, 18.9 mg/day and sacubitril/valsartan, 375 mg/day).

Cost-effectiveness model

Model structure

All patients started in the ‘alive’ health state and transitions to the ‘dead’ health state were governed by the mortality model. During each cycle, the probability of death was calculated based on the cohort’s baseline characteristics and the time since randomisation. In the ‘alive’ health state, patients were at risk of hospitalisations and AEs.

The model structure was constant across the UK, Denmark and Colombia, but the data used to inform the model differed by country. These differences are summarised in table 2. The UK and Colombian models used the PARADIGM-HF patients as the base case population in the model, whereas the Danish model reweighted the characteristics of the PARADIGM-HF patients to more closely match the Danish patient population in terms of age, gender, ejection fraction and NYHA class. A scenario analysis in which the characteristics of the PARADIGM-HF patients were reweighted to match the UK HF-REF population was also performed (see online Supplementary file 1).

Resource use

Costs included pharmacological therapies, hospitalisations, AEs and background medical management, including general practitioner visits and other outpatient contacts (see online Supplementary file 1). The costs of the ACEI (enalapril) and sacubitril/valsartan were based on the average doses taken in PARADIGM-HF (enalapril, 18.9 mg/day and sacubitril/valsartan, 375 mg/day).

The costs of background therapies were based on recommended doses and utilisation reported in PARADIGM-HF at baseline. The year base cost was 2015.

The cost data used in the model are summarised in the online Supplementary file 1. The resource use for hospitalisations and AEs was assumed to be constant between model arms.

RESULTS

Statistical analysis

Full details of statistical models included in the economic model are provided in the online Supplementary file 1.

The model of CV mortality estimated a HR for sacubitril/valsartan of 0.81 (P<0.001), which was consistent with the primary statistical analysis in PARADIGM-HF. Baseline EQ-5D was a highly significant predictor of CV mortality (P<0.001).

Similarly, the model of all-cause hospitalisation estimated a rate ratio for sacubitril/valsartan of 0.84 (P<0.001). Baseline EQ-5D was again observed to be a highly significant predictor (P<0.001). The predicted average annual rates of all-cause hospitalisation were 0.42 and 0.50 for sacubitril/valsartan and enalapril, respectively, congruent with the results of PARADIGM-HF.

The results varied slightly between Denmark and the UK. This was due to the differing EQ-5D tariffs applied, as baseline EQ-5D was included as an independent variable in all models. However, the treatment effects for sacubitril/valsartan were almost identical in all three countries (see the online Supplementary file 1).

In the UK, the model predicted a mean life expectancy of 9.27 and 8.36 years for sacubitril/valsartan and ACEI, respectively, indicating an additional 0.91 years of life with sacubitril/valsartan treatment. All-cause mortality at year 5 was estimated to be 33% and 38% for sacubitril/valsartan and ACEI, respectively (table 3).

Table 3  Model predicted clinical outcomes over lifetime unless otherwise stated

<table>
<thead>
<tr>
<th>Component</th>
<th>ACEI UK</th>
<th>ACEI Denmark</th>
<th>ACEI Colombia</th>
<th>Sacubitril/valsartan UK</th>
<th>Sacubitril/valsartan Denmark</th>
<th>Sacubitril/valsartan Colombia</th>
<th>Incremental UK</th>
<th>Incremental Denmark</th>
<th>Incremental Colombia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy, years</td>
<td>8.36</td>
<td>7.34</td>
<td>7.95</td>
<td>9.27</td>
<td>8.07</td>
<td>8.78</td>
<td>0.91</td>
<td>0.73</td>
<td>0.83</td>
</tr>
<tr>
<td>Number of HF hospitalisations per patient</td>
<td>0.89</td>
<td>0.82</td>
<td>0.85</td>
<td>0.84</td>
<td>0.76</td>
<td>0.79</td>
<td>−0.05</td>
<td>−0.05</td>
<td>−0.05</td>
</tr>
<tr>
<td>Number of CV hospitalisations per patient</td>
<td>2.18</td>
<td>2.01</td>
<td>2.08</td>
<td>2.06</td>
<td>1.88</td>
<td>1.95</td>
<td>−0.13</td>
<td>−0.13</td>
<td>−0.13</td>
</tr>
<tr>
<td>All-cause hospitalisations</td>
<td>3.50</td>
<td>3.22</td>
<td>3.34</td>
<td>3.30</td>
<td>3.01</td>
<td>3.13</td>
<td>−0.20</td>
<td>−0.21</td>
<td>−0.21</td>
</tr>
<tr>
<td>All-cause mortality (%) at year 2</td>
<td>16%</td>
<td>20%</td>
<td>17%</td>
<td>14%</td>
<td>17%</td>
<td>15%</td>
<td>−0.02</td>
<td>−0.02</td>
<td>−0.02</td>
</tr>
<tr>
<td>All-cause mortality (%) at year 5</td>
<td>38%</td>
<td>44%</td>
<td>40%</td>
<td>33%</td>
<td>40%</td>
<td>36%</td>
<td>−0.05</td>
<td>−0.04</td>
<td>−0.04</td>
</tr>
<tr>
<td>All-cause mortality (%) at year 10</td>
<td>66%</td>
<td>72%</td>
<td>68%</td>
<td>60%</td>
<td>67%</td>
<td>63%</td>
<td>−0.05</td>
<td>−0.04</td>
<td>−0.05</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting-enzyme inhibitor; CV, cardiovascular; HF, heart failure.
In Denmark, the predicted mean life expectancy was 7.34 for the ACEI arm and 8.07 for the sacubitril/valsartan arm, a gain of 0.73 years of life. All-cause mortality at year 5 was estimated to be 40% and 44% in the sacubitril/valsartan and ACEI arms, respectively (table 3).

In Colombia, predicted mean life expectancy in the ACEI arm was 7.95 years and in the sacubitril/valsartan arm was 8.78, a gain of 0.83 years. All-cause mortality at year 5 was estimated to be 36% and 40% in the sacubitril/valsartan and ACEI arms, respectively (table 3).

A longitudinal analysis estimated that the EQ-5D scores declined at a rate of 0.008 per year across both arms when using the Dolan tariff and 0.006 per year when using the Wittrup-Jensen tariff. Sacubitril/valsartan was associated with a small but statistically significant positive effect on EQ-5D, compared with enalapril, after adjusting for baseline characteristics (including baseline EQ-5D), hospitalisation, AEs and time. The absolute mean difference in EQ-5D score between treatments, after baseline EQ-5D, hospitalisation, AEs and time. The absolute mean difference in EQ-5D score between treatments, after adjusting for baseline characteristics (including baseline EQ-5D), hospitalisation, AEs and time. The absolute mean difference in EQ-5D score between treatments, after adjusting for baseline characteristics (including baseline EQ-5D), hospitalisation, AEs and time.

**Cost-effectiveness and model outcomes**

**UK setting**

Sacubitril/valsartan treatment led to an additional (discounted) lifetime cost of £8906 per patient. Incremental acquisition costs of sacubitril/valsartan (£8665 per patient) were partly offset by savings attributable to reduced hospitalisation costs (£598 per patient). Sacubitril/valsartan treatment was associated with a QALY gain of 0.52, with a cost per QALY gained of £17 100 (€20 393) (table 4).

**Danish setting**

Treatment with sacubitril/valsartan led to a lifetime incremental cost of Kr80 984 and an incremental QALY gain of 0.47, resulting in an ICER of Kr174 000 (€22 620, table 4). The incremental acquisition costs of sacubitril/valsartan (Kr88 540 per patient) were partially offset by a reduction in hospitalisation costs (Kr10 102 per patient).

**Colombian setting**

Sacubitril/valsartan was associated with an incremental lifetime cost of COP$16 723 507 and an incremental QALY gain of 0.42, giving an ICER of COP$39.5 million (€11 200) per QALY gained (table 4). The incremental acquisition costs of sacubitril/valsartan (COP$17 424 660 per patient) were partially offset by a reduction in hospitalisation costs (COP$1 406 331 per patient).

Estimates of cost-effectiveness were consistent across subgroups (detail provided in the online Supplementary file 1).

**Deterministic sensitivity analysis**

In all the three settings, the three most influential parameters were the coefficient for sacubitril/valsartan, the age-squared coefficient and the constant coefficient in the Gompertz model of CV mortality (figure 2).

In the UK setting, the most influential variable was the constant coefficient, which increased the ICER to £26 500 at the upper limit of the 95% CI and decreased it to £12 700 at the lower limit. The coefficient for sacubitril/valsartan, the age-squared coefficient and the constant coefficient in the Gompertz model of CV mortality were the only parameters to produce an ICER over £20 000 (figure 2).

In the Danish setting, the coefficient for sacubitril/valsartan, the age-squared coefficient and the constant coefficient in the Gompertz model of CV mortality were the only three parameters to generate an ICER over Kr250 000. The most influential parameter was the age-squared term in the regression model for CV mortality, which increased the ICER to Kr285 700 at the upper limit and reduced it to Kr116 100 at the lower limit (figure 2).

In the Colonial setting, the constant coefficient for CV mortality was the most influential parameter, which produced an ICER of COP$24.1 million at the lower limit of the 95% CI and an ICER of COP$5.0 million at the upper limit. No parameter produced an ICER above the willingness-to-pay (WTP) threshold of COP$52.4 million (figure 2).

**Probabilistic sensitivity analysis (PSA)**

In the UK, the expected ICER from the PSA was £18 000 (95% CI £8 900 to £34 700). At cost-effectiveness thresholds of £20 000 and £30 000 per QALY gained, the probabilities that sacubitril/valsartan was cost-effective were 68% and 94%, respectively (figure 3).
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<table>
<thead>
<tr>
<th>Health care delivery, economics and global health care</th>
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</table>

- **Denmark**: The expected ICER from PSA was Kr176,700 (95% CI Kr76,200 to Kr367,300). The probability that sacubitril/valsartan was cost-effective at Kr250,000 was 84% (figure 3).

- **Colombia**: The expected ICER from the PSA was COP$33.8 million. The probability of being cost-effective at a WTP threshold of COP$52.4 million (three times the average per capita income) was 95% (figure 3).

- **UK**: The base-case analysis for the UK indicates that sacubitril/valsartan was cost-effective at a WTP threshold of £20,000 per QALY, compared with an ACEI, with an ICER of £17,100. This result was not only mainly driven by reductions in mortality but also by improvements in HRQL and reductions in hospitalisation. The findings of the analysis were robust to changes in most structural assumptions, and a PSA suggested that the probability that sacubitril/valsartan was cost-effective at a WTP threshold of £20,000 was 68%.

Three analyses from the perspective of third-party healthcare payers in the USA have also suggested that sacubitril/valsartan is cost-effective at commonly accepted WTP thresholds.21–23

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**Figure 2** Tornado diagrams. ICER, incremental cost-effectiveness ratio.

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In Denmark, the expected ICER from PSA was Kr176,700 (95% CI Kr76,200 to Kr367,300). The probability that sacubitril/valsartan was cost-effective at Kr250,000 was 84% (figure 3).

In Colombia, the expected ICER from the PSA was COP$33.8 million. The probability of being cost-effective at a WTP threshold of COP$52.4 million (three times the average per capita income) was 95% (figure 3).

**DISCUSSION**

The base-case analysis for the UK indicates that sacubitril/valsartan was cost-effective at a WTP threshold of £20,000 per QALY, compared with an ACEI, with an ICER of £17,100. This result was not only mainly driven by reductions in mortality but also by improvements in HRQL and reductions in hospitalisation. The findings of the analysis were robust to changes in most structural assumptions, and a PSA suggested that the probability that sacubitril/valsartan was cost-effective at a WTP threshold of £20,000 was 68%. Three analyses from the perspective of third-party healthcare payers in the USA have also suggested that sacubitril/valsartan is cost-effective at commonly accepted WTP thresholds.21–23
Our findings were consistent across all three countries. The base-case analysis for Denmark, another high-income country, found that sacubitril/valsartan was cost-effective at a WTP threshold of Kr250 000 per QALY, compared with an ACEI, with an ICER of Kr174 000. The base-case analysis for Colombia, a middle-income country, found that sacubitril/valsartan was cost-effective at a WTP threshold of COP$52.4 million per QALY, with an ICER of COP$39.5 million.

These results are in line with National Institute for Health and Care Excellence (NICE) guidance, which recommends sacubitril/valsartan as a cost-effective option for the treatment of HF-REF in patients who are already taking a stable dose of ACEI or ARB. The key limitation of this analysis was the extrapolation beyond the follow-up of PARADIGM-HF (with median follow-up of 27 months). This is a cause of uncertainty which cannot readily be characterised in sensitivity analysis, but is common to all modelling exercises, particularly in HRQL estimates. However, the assumption of an annual decline in EQ-5D of 0.008 appears consistent with data from other studies; 1-year longitudinal data presented by Berg et al in patients with chronic HF suggests an annual decrease in EQ-5D of 0.006.

PARADIGM-HF was a geographically diverse study, and the patient population may not be generalisable to individual countries. Although there is no evidence that the treatment effect differed across subgroups in PARADIGM-HF, cost-effectiveness is driven by absolute benefit, which is dependent on patients’ absolute risk of events, reflecting their baseline clinical characteristics. If patient characteristics differ between PARADIGM-HF and the HF-REF population in the UK, Denmark or Colombia, then absolute benefit, and therefore
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What is already known on this subject?
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial showed that sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor, was superior to the ACE inhibitor enalapril in reducing the risks of death and heart failure hospitalisation in patients with heart failure with reduced ejection fraction. Published analyses from the perspective of third-party healthcare payers in the USA have suggested that sacubitril/valsartan is cost-effective at commonly accepted willingness-to-pay thresholds.

What might this study add?
We evaluated the cost-effectiveness of sacubitril/valsartan compared with enalapril in the treatment of heart failure with reduced ejection fraction from the perspectives of the UK National Health Service, the Danish healthcare system (high-income countries) and the Colombian healthcare system (middle-income country). We found sacubitril/valsartan to be cost-effective at conventional willingness-to-pay thresholds in all three country settings.

How might this impact on clinical practice?
This analysis, which shows sacubitril/valsartan to be a cost-effective use of resources, should aid decision-makers and may enhance availability of this efficacious treatment for patients with heart failure with reduced ejection fraction.

cost-effectiveness, would be expected to differ too. However, the results of the subgroup and scenario analyses suggest that the conclusions of the base-case analysis would not change to any meaningful extent.

In conclusion, this analysis suggests that sacubitril/valsartan likely represents a cost-effective option in the treatment of HF-REF for the NHS in the UK, the Danish healthcare system and for the Colombian healthcare system.

Correction notice Since this paper has been published online an update has been made to the paragraph Colombian setting. The ICER value of €15 975 has been changed to €11 200.

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Contributors JVM, DT, EH, MRC, AB, MT, JMC, RH and CD contributed to the design of the evaluations. DT, EH, FW and ML were responsible for data collection, development of the economic model and performing the analysis. CD and RH were responsible for overseeing the content. All authors contributed to the writing of the manuscript.

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