Appendix I: Supplementary Analyses Suggested in the ERG Critique of Norgine Addendum to Rifaximin-α 550mg NICE STA

<table>
<tr><th>Section of Norgine Addendum</th><th>ERG Critique</th><th>Norgine Response</th></tr>
<tr><td>Section 4.2
Page 17</td><td>For example, it is not clear why the Akaike Information Criteria (AIC) or Bayesian Information Criterion (BIC) were not presented. Finally, the Gamma distribution should have been included in the analysis for the sake of completeness.</td><td>
AIC/BIC have been calculated as suggested. The rank order of the candidate distributions presented in the Addendum is unchanged. An alternative parameterisation method for the Gompertz (“cure” method) distribution consistent with the statistical application used to generate the parameter estimates (Stata) was ranked higher than the original Gompertz model (R) goodness of fit estimation presented in the Addendum.
RFHE3001 C_1 to O_1 transition
<table>
<tr><th>Model</th><th>Obs</th><th>ll(model)</th><th>AIC</th><th>BIC</th></tr>
<tr><td>lognormal</td><td>299</td><td>-748.68</td><td>1499.36</td><td>1503.09</td></tr>
<tr><td>"cure" gompertz</td><td>299</td><td>-749.02</td><td>1500.05</td><td>1503.78</td></tr>
<tr><td>loglogistic</td><td>299</td><td>-752.93</td><td>1507.87</td><td>1511.60</td></tr>
<tr><td>weibull</td><td>299</td><td>-755.58</td><td>1513.16</td><td>1516.89</td></tr>
<tr><td>exponential</td><td>299</td><td>-758.56</td><td>1519.11</td><td>1522.84</td></tr>
<tr><td>"original" gompertz</td><td>299</td><td>-758.56</td><td>1519.11</td><td>1522.84</td></tr>
</table>
Choice of distribution curve fitting the covert to first-observed BOHE (C_1 to O_1) has little impact on ICER ((range £18,946 [weibull] to £20,829 [lognormal])).
Time constraints prevented exploration of all possible parametric modelling options. We do not believe the gamma distribution would significantly affect the ICER.
</td></tr>
<tr><td>Section 4.3
Page 20</td><td>AIC BIC for RFHE 3002</td><td>
RFHE3002new C_2 to O_2 transition
<table>
<tr><th>Model</th><th>Obs</th><th>ll(model)</th><th>AIC</th><th>BIC</th></tr>
<tr><td>lognormal</td><td>102</td><td>-377.20</td><td>754.40</td><td>754.40</td></tr>
<tr><td>"cure" gompertz</td><td>102</td><td>-377.56</td><td>755.11</td><td>755.11</td></tr>
<tr><td>loglogistic</td><td>102</td><td>-377.80</td><td>755.60</td><td>755.60</td></tr>
<tr><td>weibull</td><td>102</td><td>-381.78</td><td>763.57</td><td>763.57</td></tr>
<tr><td>exponential</td><td>102</td><td>-388.57</td><td>777.14</td><td>777.14</td></tr>
<tr><td>"original" gompertz</td><td>102</td><td>-388.57</td><td>777.14</td><td>777.14</td></tr>
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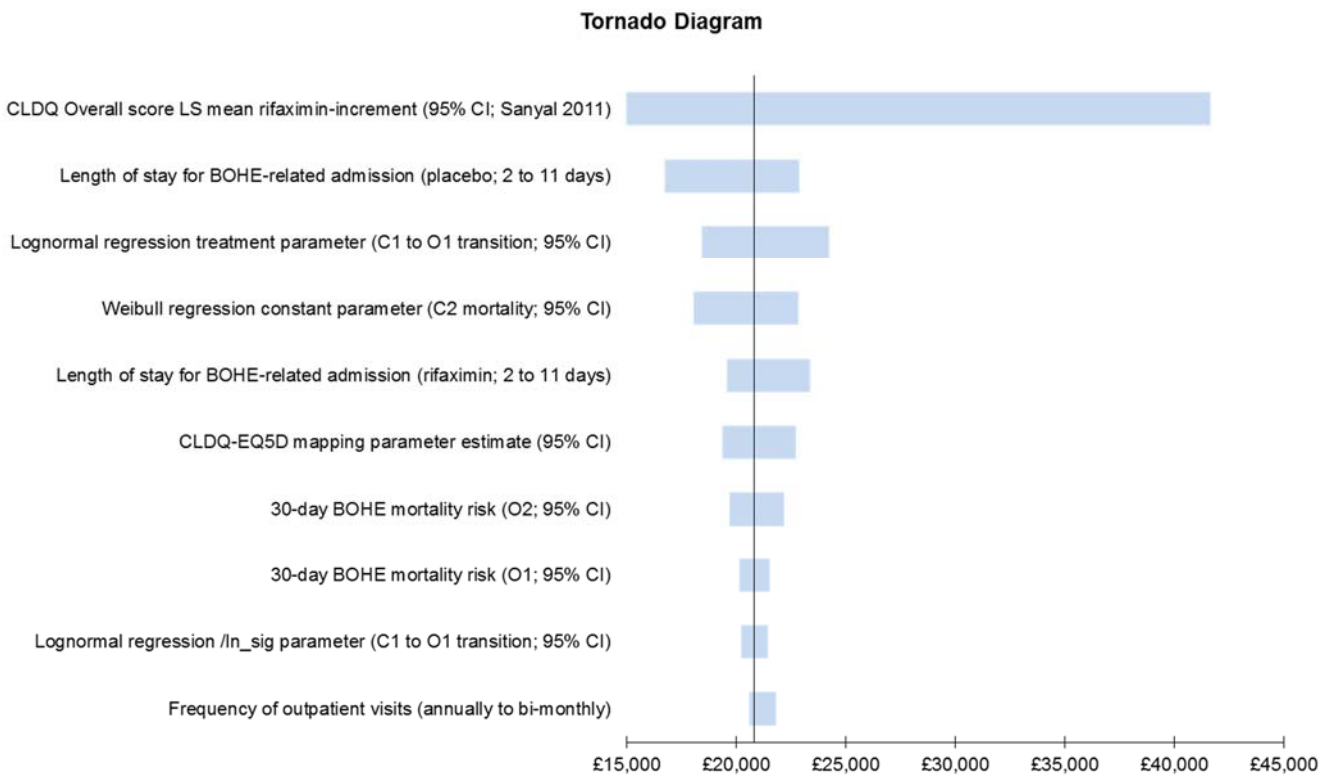
<table>
<tr>
<td>Section 5
Page 26</td>
<td>Norgine did not present a Tornado diagram of their revised model</td>
<td>


The Tornado diagram shows the effect of the major changes to model inputs at their respective mean values.
</td>
</tr>
<tr>
<td>Section 6
Page 28</td>
<td>Two different distributions (log-normal and Weibull) were used to fit RFHE3002 data. Further steps should have been taken in assessing the goodness of fit of the different distributions. For example, Akaike Information Criteria (AIC) or Bayesian Information Criterion (BIC) could have been presented. Finally the Gamma distribution should have been included in the analysis for the sake of completeness.</td>
<td>
RFHE3002 C_1 to death
<table>
<tr><th>Model</th><th>Obs</th><th>ll(model)</th><th>AIC</th><th>BIC</th></tr>
<tr><td>lognormal</td><td>321</td><td>-219.92</td><td>439.85</td><td>439.85</td></tr>
<tr><td>"cure" gompertz</td><td>321</td><td>-220.98</td><td>441.95</td><td>441.95</td></tr>
<tr><td>loglogistic</td><td>321</td><td>-221.12</td><td>442.24</td><td>442.24</td></tr>
<tr><td>weibull</td><td>321</td><td>-221.36</td><td>442.72</td><td>442.72</td></tr>
<tr><td>exponential</td><td>321</td><td>-221.40</td><td>442.80</td><td>442.80</td></tr>
<tr><td>"original" gompertz</td><td>321</td><td>-221.40</td><td>442.80</td><td>442.80</td></tr>
</table>
</td>
</tr>
</table>

RFHE3002 C_2 to death

Model	Obs	ll(model)	AIC	BIC
weibull	205	-160.09	320.17	320.17
loglogistic	205	-160.27	320.55	320.55
lognormal	205	-160.49	320.98	320.98
"cure" gompertz	205	-160.88	321.76	321.76
exponential	205	-160.95	321.9	321.9
"original" gompertz	205	-160.95	321.9	321.9

Section 6
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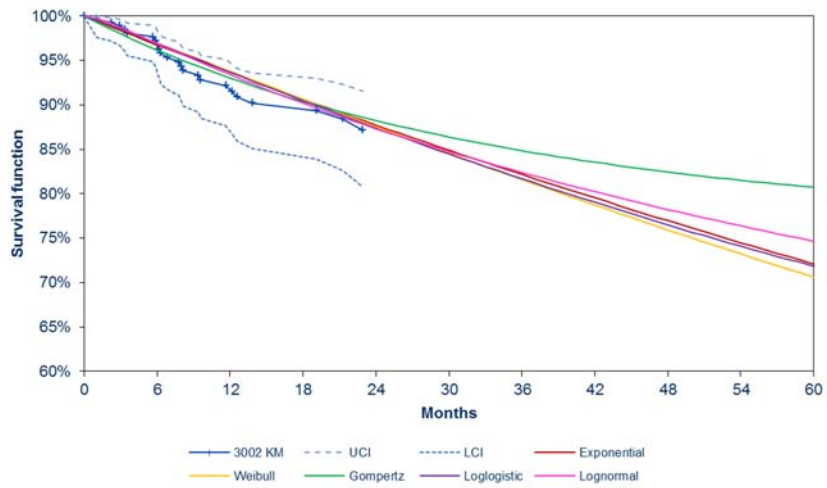
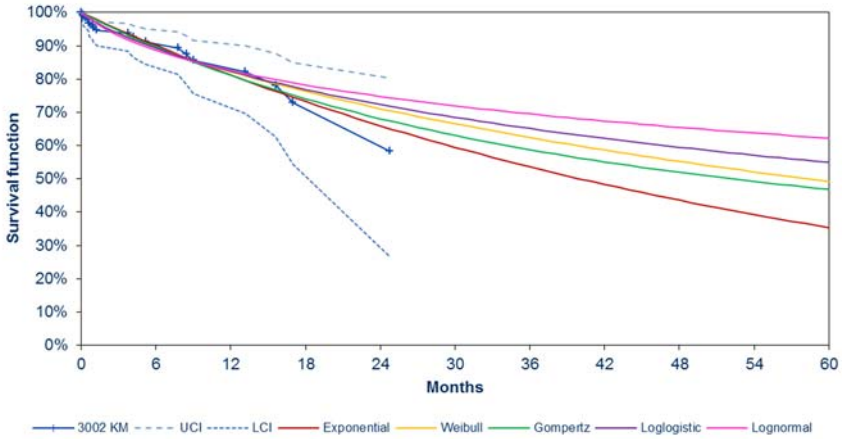
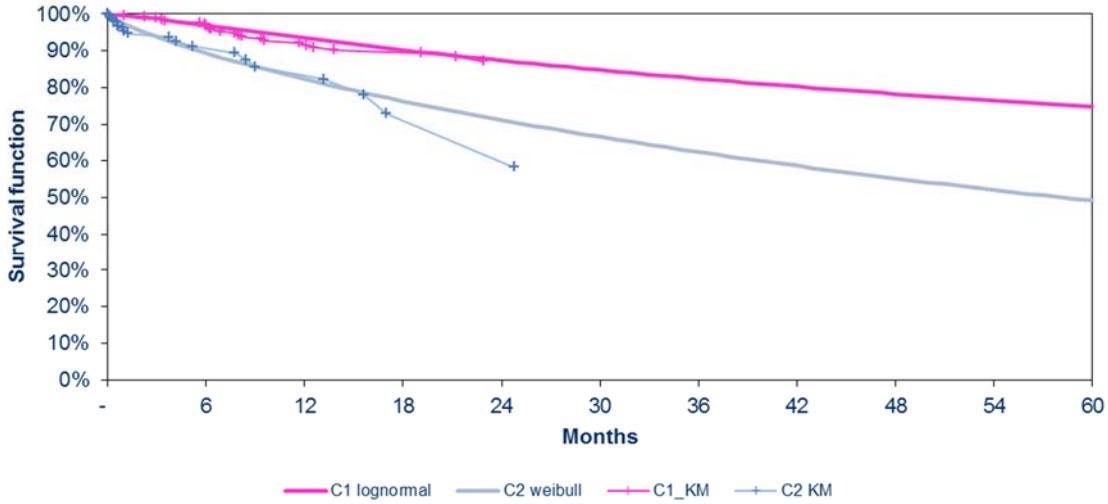
Even though Norgine used RFHE3002 data to model mortality in the economic model, KM curves were not provided on time to death from both covert states. Furthermore, the Excel model did not contain the necessary data to allow the ERG to plot such curves. Therefore, in this case, providing different distributions fitted to the RFHE3002 study mortality data would be meaningless as there are no KM curves for visual comparison.

Covert mortality



Subsequent covert mortality



Best fit models for C_1 and C_2 mortality