DIFFERENT METHODS FOR MODELLING SEVERE HYPOGLYCAEMIC EVENTS: IMPLICATIONS FOR EFFECTIVENESS AND COST-EFFECTIVENESS ANALYSES

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Severe hypoglycaemia

- Can occur in people with diabetes who take insulin and other anti-diabetic treatments.
- Diabetic emergency which can lead to seizures, coma or death.
Background

- Clinical trials report severe hypoglycaemic events in different ways

Risk

No. of patients experiencing event out of Total number randomised

Rate

No. of events for given total exposure
• **NICE guideline on Type 1 Diabetes in adults (NG17, 2015 update)**

• **Intervention:** Basal Insulin Regimens

• **Data:** 20 trials reporting severe hypoglycaemic events
  - 12 reported both risk and rate of events
  - 4 only reported risk
  - 4 only reported rate

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Network Meta-analysis (NMA)

- Combines all available evidence
- Produces estimates of the **relative effects** of each intervention compared to every other in a network
- Different data types modelled in different ways
NMA models for adverse events

Risk
- Binomial with \textbf{logit} link
- Binomial with complementary log-log (\texttt{clog-log}) link

Rate
- \textbf{Poisson} with log link

Based on the approach and code provided in the NICE Decision Support Unit’s Technical Support Documents 2 on evidence synthesis\textsuperscript{2}
Shared parameter model

- Combines risk and rate data
  - Binomial with **clog-log** link for risk data
  - **Poisson** with log link for rate data
Question No. 1

• 4 models:
  • Binomial with logit link
  • Binomial with clog-log link
  • Poisson with log link
  • Shared parameter model

• What impact does choice of model have on relative effectiveness results?
Network plot – Risk data

Glargine Once

Detemir once/twice

NPH once/twice

NPH Once

Degludec Once

NPH Twice

Detemir Once

Detemir Twice
Glargine Once
Detemir once/twice
NPH once/twice
NPH Once
Degludec Once
NPH Twice
Detemir Once
Detemir Twice
Network plot – Rate data
Network plot – Shared parameter model

- Glargine Once
- NPH Once
- Degludec Once
- Detemir Once
- NPH Twice
- Detemir Twice
- NPH once/twice
- Detemir once/twice
Relative effects
Question No. 2

What impact does modelling the risk or the rate have on the costs and QoL outputs of economic models?

Risk

Rate
Cost-effectiveness analysis

• Requires **absolute probabilities** of events

Relative effects from NMA
combined with
probability of event on reference arm
gives
**absolute probabilities**
Baseline probability

- Probability of having a hypoglycaemic event on baseline treatment (Glargine once) calculated separately in single-arm meta-analyses using three different models
  - Binomial with logit link
  - Binomial with cloglog link
  - Poisson with log link
## Baseline Probability

<table>
<thead>
<tr>
<th>Model</th>
<th>Mean Baseline Probability</th>
<th>95% CrI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logit</td>
<td>0.07</td>
<td>0.04 – 0.13</td>
</tr>
<tr>
<td>Clog-log</td>
<td>0.17</td>
<td>0.06 – 0.34</td>
</tr>
<tr>
<td>Poisson</td>
<td>0.29</td>
<td>0.07 – 0.7</td>
</tr>
</tbody>
</table>
### Absolute probabilities of having a hypoglycaemic event (at one year)

<table>
<thead>
<tr>
<th></th>
<th>Logit</th>
<th>Cloglog</th>
<th>Poisson</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% Crls</td>
<td>Mean</td>
</tr>
<tr>
<td>Detemir Once</td>
<td>0.04</td>
<td>(0.01 - 0.11)</td>
<td>0.1</td>
</tr>
<tr>
<td>Detemir Once/Twice</td>
<td>0.04</td>
<td>(0.01 - 0.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>NPH Once</td>
<td>0.06</td>
<td>(0.01 - 0.17)</td>
<td>0.15</td>
</tr>
<tr>
<td>Glargine (Once)</td>
<td>0.07</td>
<td>(0.04 - 0.12)</td>
<td>0.17</td>
</tr>
<tr>
<td>NPH Once/twice</td>
<td>0.08</td>
<td>(0.04 - 0.16)</td>
<td>0.2</td>
</tr>
<tr>
<td>Degludec Once</td>
<td>0.09</td>
<td>(0.03 - 0.18)</td>
<td>0.21</td>
</tr>
<tr>
<td>Detemir Twice</td>
<td>0.12</td>
<td>(0 - 0.71)</td>
<td>0.26</td>
</tr>
<tr>
<td>NPH (Twice)</td>
<td>0.14</td>
<td>(0 - 0.75)</td>
<td>0.29</td>
</tr>
</tbody>
</table>
## Expected costs (£)*

*Assuming a cost of £333 per severe hypoglycaemic event, estimated from Hammer et al*3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Logit</th>
<th></th>
<th>Cloglog</th>
<th></th>
<th>Poisson</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CrIs</td>
<td>Mean</td>
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<td>Mean</td>
<td>95% CrIs</td>
</tr>
<tr>
<td><strong>Detemir Once</strong></td>
<td>13.29</td>
<td>(2.97 - 36.83)</td>
<td>34.21</td>
<td>(6.88 - 97.52)</td>
<td>123.8</td>
<td>(13.21 - 323)</td>
</tr>
<tr>
<td><strong>Detemir once/twice</strong></td>
<td>14.41</td>
<td>(4.17 - 34.16)</td>
<td>38.16</td>
<td>(9.81 - 97.26)</td>
<td>66.91</td>
<td>(10.31 - 201.7)</td>
</tr>
<tr>
<td><strong>NPH Once</strong></td>
<td>20.42</td>
<td>(4.38 - 57.71)</td>
<td>51.11</td>
<td>(10.14 - 145)</td>
<td>110.4</td>
<td>(18.24 - 287.6)</td>
</tr>
<tr>
<td><strong>Glargine Once</strong></td>
<td>22.65</td>
<td>(11.76 - 39.04)</td>
<td>56.14</td>
<td>(22.35 - 112.6)</td>
<td>95.59</td>
<td>(22.34 - 233.5)</td>
</tr>
<tr>
<td><strong>NPH once/twice</strong></td>
<td>28.08</td>
<td>(12.17 - 53.85)</td>
<td>68.36</td>
<td>(24.27 - 144.5)</td>
<td>134.6</td>
<td>(27.28 - 302.8)</td>
</tr>
<tr>
<td><strong>Degludec Once</strong></td>
<td>29.63</td>
<td>(11.53 - 61.19)</td>
<td>71.1</td>
<td>(23.44 - 156.8)</td>
<td>102.7</td>
<td>(18.24 - 287.6)</td>
</tr>
<tr>
<td><strong>Detemir Twice</strong></td>
<td>41.67</td>
<td>(0.35 - 237.9)</td>
<td>87.82</td>
<td>(1.13 - 332.8)</td>
<td>126.7</td>
<td>(1.43 - 333)</td>
</tr>
<tr>
<td><strong>NPH Twice</strong></td>
<td>47.37</td>
<td>(0.44 - 251.1)</td>
<td>97.82</td>
<td>(1.43 - 333)</td>
<td>128.3</td>
<td>(1.55 - 333)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Logit</td>
<td>Cloglog</td>
<td>Poisson</td>
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<td>Mean</td>
<td>95% Crls</td>
</tr>
<tr>
<td>Glargine Once</td>
<td>-0.001</td>
<td>(-0.001, 0)</td>
<td>-0.002</td>
<td>(-0.004, -0.001)</td>
<td>-0.003</td>
<td>(-0.008, -0.001)</td>
</tr>
<tr>
<td>NPH Twice</td>
<td>-0.002</td>
<td>(-0.009, 0)</td>
<td>-0.004</td>
<td>(-0.012, 0)</td>
<td>-0.005</td>
<td>(-0.012, 0)</td>
</tr>
<tr>
<td>Detemir Once</td>
<td>0.000</td>
<td>(-0.001, 0)</td>
<td>-0.001</td>
<td>(-0.004, 0)</td>
<td>-0.004</td>
<td>(-0.012, 0)</td>
</tr>
<tr>
<td>Detemir Twice</td>
<td>-0.001</td>
<td>(-0.009, 0)</td>
<td>-0.003</td>
<td>(-0.012, 0)</td>
<td>-0.005</td>
<td>(-0.012, 0)</td>
</tr>
<tr>
<td>Degludec Once</td>
<td>-0.001</td>
<td>(-0.002, 0)</td>
<td>-0.003</td>
<td>(-0.006, -0.001)</td>
<td>-0.004</td>
<td>(-0.01, -0.001)</td>
</tr>
<tr>
<td>NPH Once</td>
<td>-0.001</td>
<td>(-0.002, 0)</td>
<td>-0.002</td>
<td>(-0.005, 0)</td>
<td>-0.004</td>
<td>(-0.01, -0.001)</td>
</tr>
<tr>
<td>NPH once/twice</td>
<td>-0.001</td>
<td>(-0.002, 0)</td>
<td>-0.002</td>
<td>(-0.005, -0.001)</td>
<td>-0.005</td>
<td>(-0.011, -0.001)</td>
</tr>
<tr>
<td>Detemir once/twice</td>
<td>-0.001</td>
<td>(-0.001, 0)</td>
<td>-0.001</td>
<td>(-0.004, 0)</td>
<td>-0.002</td>
<td>(-0.007, 0)</td>
</tr>
</tbody>
</table>

*Assuming a disutility of -0.012 taken from NICE guideline on Diabetes*
Conclusion

• Important to ensure absolute probabilities of events are not being underestimated, particularly in health economic models where small differences can have a considerable impact on results.

• Care should be taken to choose an appropriate outcome measure when synthesizing data on repeated events for use in an economic model.
References


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