Comparative efficacy and effectiveness via meta-analysis – Health economics approach

Jeroen Jansen PhD
Chief Scientist – Evidence Synthesis & Decision Modeling

jeroen.jansen@precisionxtract.com
Cost-effectiveness analysis

NMB = QALYs * WTP - Costs
Decision modeling for cost-effectiveness analysis

- An individual study hardly ever provides information regarding all aspects informing the cost-effectiveness decision of the competing interventions
- Decision models are mathematical frameworks that integrate relevant evidence and provide estimates of resource use and outcomes associated with competing interventions
Decision modeling: Evidence synthesis & extrapolation

- Evidence synthesis
  - Relative treatment effects over time
  - Outcomes over time with standard of care / natural history
  - Relationship between surrogate and clinical endpoints
  - Relationship between clinical and economic endpoints

- Extrapolation
  - beyond the time horizon, interventions, outcomes, and settings observed in the available individual studies
Example research question

*What is the cost-effectiveness of available interventions for the xth line treatment of tumor type y?*
This is what we want: comparative effectiveness estimates

Areas under the progression free survival (PFS) and overall survival (OS) curves multiplied with corresponding utilities to obtain the expected QALYs with each of the interventions of interest.
This is what we have

- A set of randomized controlled trials each comparing a subset of the interventions of interest
- Limited follow-up (15-50 months)
Steps

1. Meta-analysis of *absolute effect* with reference treatment A; “real-world” data
2. *Network meta-analysis* to obtain *relative treatment effects* for each intervention relative to A; randomized controlled trials
3. Extrapolation of 1 and 2 over time
4. Apply extrapolated relative treatment effects to extrapolated absolute effect of A to obtain absolute effects for all interventions
Baseline model

Meta-analysis of available data

Extrapolation

Overall survival
Progression free survival

Follow-up in months

PFS & OS
Meta-analysis - random effects model

\[ \hat{\theta}_s \sim \text{Normal}(\theta_s, \hat{\sigma}_s^2) \]

\[ \theta_s \sim \text{Normal}(\theta, \tau^2) \]
Baseline model – meta-analysis of parametric survival functions

- **Weibull**
  \[
  \ln(h_s(t)) = \theta_{0,s} + \theta_1 \ln(t)
  \]
  \[\theta_{0,s} \sim \text{Normal}(\theta_0, \tau^2)\]

- **Fractional polynomial**
  \[
  \ln(h_s(t)) = \begin{cases} 
  \theta_{0,s} + \theta_1 t^{p_1} + \theta_2 t^{p_2} & p_1 \neq p_2 \\ 
  \theta_{0,s} + \theta_1 t^p + \theta_2 t^p \ln(t) & p = p_1 = p_2
  \end{cases}
  \]
  with \(t^0 = \ln(t)\)
  \[\theta_{0,s} \sim \text{Normal}(\theta_0, \tau^2)\]
Network meta-analysis for relative treatment effects
Network meta-analysis for relative treatment effects

\[ d_{bk} = d_{Ak} - d_{Ab} \]

Assumption: No differences in effect-modifiers between studies indirectly compared
Network meta-analysis for relative treatment effects

\[ \hat{\delta}_{sa} \sim \text{Normal}(\delta_{sa}, \hat{\sigma}_{sa}^2) \]

\[ \delta_{sa} \sim \text{Normal}\left(d_{1k_{sa}} - d_{1k_{s1}}, \tau^2\right) \]
Network meta-analysis for relative treatment effects

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.47</td>
<td>0.22</td>
<td>1.44</td>
<td>1.35</td>
<td>2.90</td>
<td>0.18</td>
<td>0.20</td>
<td>0.21</td>
</tr>
<tr>
<td>(2.25 - 8.89)</td>
<td>(0.11 - 0.45)</td>
<td>(0.78 - 2.66)</td>
<td>(0.69 - 2.63)</td>
<td>(1.28 - 6.55)</td>
<td>(0.09 - 0.36)</td>
<td>(0.1 - 0.41)</td>
<td>(0.1 - 0.44)</td>
</tr>
<tr>
<td>3.09</td>
<td>0.32</td>
<td>1.95</td>
<td>3.91</td>
<td>2.56</td>
<td>0.26</td>
<td>0.29</td>
<td>0.30</td>
</tr>
<tr>
<td>(1.25 - 7.66)</td>
<td>(0.13 - 0.8)</td>
<td>(1.31 - 2.89)</td>
<td>(1.55 - 9.96)</td>
<td>(1.14 - 5.76)</td>
<td>(0.1 - 0.64)</td>
<td>(0.12 - 0.73)</td>
<td>(0.11 - 0.78)</td>
</tr>
<tr>
<td>2.30</td>
<td>0.44</td>
<td>5.66</td>
<td>3.45</td>
<td>2.49</td>
<td>0.34</td>
<td>0.39</td>
<td>0.40</td>
</tr>
<tr>
<td>(1.05 - 5.06)</td>
<td>(1.01 - 1.58)</td>
<td>(2.75 - 11.58)</td>
<td>(1.37 - 8.67)</td>
<td>(1.06 - 5.89)</td>
<td>(0.15 - 0.78)</td>
<td>(0.17 - 0.88)</td>
<td>(0.17 - 0.95)</td>
</tr>
<tr>
<td>0.79</td>
<td>1.26</td>
<td>4.98</td>
<td>3.35</td>
<td>1.16</td>
<td>E</td>
<td>1.03</td>
<td>1.09</td>
</tr>
<tr>
<td>(0.63 - 0.99)</td>
<td>(0.93 - 1.33)</td>
<td>(2.45 - 10.1)</td>
<td>(1.28 - 8.83)</td>
<td>(0.78 - 1.75)</td>
<td>0.88</td>
<td>(0.75 - 1.07)</td>
<td>(0.78 - 1.52)</td>
</tr>
<tr>
<td>0.90</td>
<td>0.69</td>
<td>1.95</td>
<td>3.91</td>
<td>0.88</td>
<td>0.86</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>(0.75 - 1.07)</td>
<td>(1.01 - 1.58)</td>
<td>(2.75 - 11.58)</td>
<td>(1.37 - 8.67)</td>
<td>(0.66 - 1.17)</td>
<td>(0.57 - 1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.92</td>
<td>5.66</td>
<td>4.98</td>
<td>3.35</td>
<td>0.98</td>
<td>0.90</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>(0.66 - 1.29)</td>
<td>(2.45 - 10.1)</td>
<td>(2.28 - 10.43)</td>
<td>(1.28 - 8.83)</td>
<td>(0.67 - 1.42)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Needed for our CEA
Modeled PFS and OS curves by treatment - constant hazard ratios

All curves run ‘parallel’ due to (unrealistic) assumption of constant hazard ratios

Follow-up in months

PFS & OS

Overall survival
Progression free survival
Network meta-analysis – time-varying hazard ratios

- **Weibull**
  \[
  \ln \left( h_{sa} (t) \right) = \theta_{0,sa} + \theta_{1,sa} \ln(t)
  \]
  \[
  \left( \begin{array}{c}
  \theta_{0,sa} \\
  \theta_{1,sa}
  \end{array} \right) = \left( \begin{array}{c}
  \mu_{0,s} \\
  \mu_{1,s}
  \end{array} \right) + \left( \begin{array}{c}
  \delta_{0,sa} \\
  d_{1,1k_s} - d_{1,1k_{s1}}
  \end{array} \right)
  \]
  \[
  \delta_{0,sa} \sim \text{Normal} \left( d_{0,1k_s} - d_{0,1k_{s1}}, \tau^2 \right)
  \]

- **Fractional polynomial**
  \[
  \ln \left( h_{sa} (t) \right) = \begin{cases} 
    \theta_{0,sa} + \theta_{1,sa} t^{p_1} + \theta_{2,sa} t^{p_2} & p_1 \neq p_2 \\
    \theta_{0,sa} + \theta_{1,sa} t^p + \theta_{2,sa} t^p \ln(t) & p = p_1 = p_2
  \end{cases}
  \quad \text{with } t^0 = \ln(t)
  \]
  \[
  \left( \begin{array}{c}
  \theta_{0,sa} \\
  \theta_{1,sa} \\
  \theta_{2,sa}
  \end{array} \right) = \left( \begin{array}{c}
  \mu_{0,s} \\
  \mu_{1,s} \\
  \mu_{2,s}
  \end{array} \right) + \left( \begin{array}{c}
  \delta_{0,sa} \\
  d_{1,1k_s} - d_{1,1k_{s1}} \\
  d_{2,1k_s} - d_{2,1k_{s1}}
  \end{array} \right)
  \]
  \[
  \delta_{0,sa} \sim \text{Normal} \left( d_{0,1k_s} - d_{0,1k_{s1}}, \tau^2 \right)
  \]
Network meta-analysis – time-varying hazard ratios
Extrapolation of relative treatment effects

Hazard Ratio

Follow-up in months
Extrapolation of relative treatment effects
Extrapolation of relative treatment effects
Modeled PFS and OS curves by treatment – time-varying hazard ratios
Key issues to consider

- Target population(s) of interest
  - Subgroups
  - Meta-regression
  - Use of IPD

- Model selection for evidence synthesis
  - Fit to the data
  - Extrapolation
  - Use of external evidence
Summary: Evidence synthesis for cost-effectiveness analysis

- It is the absolute difference between treatments that will determine the value of a treatment

- Assumption: absolute efficacy of a treatment may vary with the study population, the relative effect remains relatively stable

- Evidence synthesis
  - Baseline model: Absolute effect with “standard care” in routine practice
  - Relative treatment effects

- Need for extrapolation
  - Time-horizon
  - Population
  - Setting
  - ....
References
