Statistical Challenges within Health Economics and Health Technology Assessment

Claire Watkins
Statistical Science Director

FMS 25-Year Anniversary Meeting
24th-25th Oct 2012
Overview
Health Economics and Health Technology Assessment

Definitions and key concepts

Health Economic Models

Statistical Challenges

Examples

Summary

Disclosure statement: Claire Watkins is an employee of AstraZeneca LP. The views and opinions expressed herein are my own and cannot and should not necessarily be construed to represent those of AstraZeneca or its affiliates
What is Health Economics (HE)?

A branch of **economics** concerned with issues related to efficiency, effectiveness, value and behaviour in the production and consumption of **health and health care**
What is Health Technology Assessment (HTA)?

Health technology is an intervention to/for:

• Promote health
• Prevent, diagnose or treat disease
• Rehabilitation
• Long-term care

Assessment Process

• Evaluate evidence for use of health interventions
• Examine implications and value of medical technology in healthcare
Overlap between HE and HTA

Health Economics

Health Technology Assessment
Some National HTA agencies

NICE, SMC, GBA, CADTH, HAS, PBAC, SBU
The right question for regulators may not be the right question for payers

Can it work?

Does it work?

Is it worth it?
Standard RCTs may not be able to answer the right question for payers

• Philosophy of most payers: “Better an approximate answer to the right question than a precise answer to the wrong question”

• Leads to MODELLING using evidence from many sources
  - RCTs
    • Multiple sponsors, treatments, even other diseases
    • Extrapolation or mapping or simulation common
  - Observational clinical data (trials or databases)
  - Cost data

• Submission is still EVIDENCE BASED
  - Just considers a wider net of evidence than a regulatory submission
  - Requirement for robustness remains
Some Types of Economic Analysis
Different payers have different requirements

- Cost effectiveness analysis
- Cost utility analysis
- Cost-benefit analysis
- Cost minimisation analysis
- Budget impact analysis
A typical health economic model: State Transition Model (cohort based)

- **Alive, Healthy**
  - New treatment: Outcome 1 (P1)
  - Current treatment: Outcome 2 (P2)

- **Alive, Sick**
  - New treatment: Outcome 3 (P3)
  - Current treatment: Outcome 4 (P4)

- **Dead**
Input Parameters in a Cost Utility Model

The input parameters for a cost utility model are…….

- Transition probabilities between health states
- Utility of each health state
- Cost of each health state

These parameters can be treated in 2 ways……

1. Deterministic
   - Assumed to be fixed

2. Probabilistic
   - Assumed to be random, with an associated distribution
Incremental Cost-Effectiveness Ratio (ICER)

\[
\text{ICER} = \frac{\text{Cost}_A - \text{Cost}_B}{\text{Outcome}_A - \text{Outcome}_B}
\]

\(A = \text{new treatment}\)
\(B = \text{current treatment}\)

Measured in QALYs for a Cost-Utility Analysis
What is a QALY?
Calculating QALYs

1 QALY = 1 year of healthy life for one person

- Initial QALY loss due to side effects
- New treatment
- Current treatment

QALYs gained

Length of life (years)

Health-related quality of life

Initial QALY loss due to side effects

New treatment

Current treatment

QALYs gained
The Cost-Effectiveness Plane

Current treatment dominates

New treatment more effective but more costly

New treatment less costly but less effective

New treatment dominates
The Cost-Effectiveness Plane

Deterministic

ΔC (new vs current)

Current treatment dominates

New treatment more effective but more costly

New trt 1

WTP threshold

New trt 2

ΔE

New treatment less costly but less effective

New treatment dominates
The Cost-Effectiveness Plane
Probabilistic

$\Delta C$ (new vs current)

WTP threshold

Current treatment dominates

New treatment more effective but more costly

New treatment less costly but less effective

New treatment dominates
Cost-Effectiveness Acceptability Curve (CEAC)
Statistical challenges/opportunities in HE & HTA

Lots of room for statistical improvements!

- Methods and models developed by statistical/mathematical experts
- But may be applied formulaically by non-experts
  - Low awareness of assumptions
  - Little appreciation of implications
  - Lack of ability to adapt to new situations

- Combining multiple data sources
  - IPD from sponsor RCTs
  - Summary stats from literature RCTs
  - Observational data
  - Utility data
  - Cost data

- Non-standard data
  - Costs, ICER, extrapolation

- Differing perspectives
  - Health economist asks statistician for analyses to use as model inputs
Differing perspectives?

THE STATISTICIAN

THE HEALTH ECONOMIST
Differing perspectives?

THE STATISTICIAN

THE HEALTH ECONOMIST
In reality: Overlap of Quantitative disciplines
Common ground: Data analysis for evidence-based decisions
Evidence Synthesis
Meta-Analysis and Network Meta-Analysis

Direct comparison
Indirect comparison
Mixed treatment comparison

Trt difference $d_{AB}^{dir}$
Variance $V_{AB}^{dir}$

$d_{AB}^{indir} = d_{AC}^{dir} - d_{BC}^{dir}$
$V_{AB}^{indir} = V_{AC}^{dir} + V_{BC}^{dir}$

Synthesise direct and indirect

Additional assumptions vs standard MA

Just because multiple trials exist it does not mean that it is appropriate to pool them for analysis! Sutton 2008

Further info: Jones, Pharm Stat 2011 (10) 523-531
Example: MTC NMA of doublet chemotherapies in 1<sup>st</sup> line NSCLC

Overall survival hazard ratios from Bayesian MTC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>95% Credible Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel/Carboplatin</td>
<td>1.00</td>
<td>-- baseline treatment --</td>
</tr>
<tr>
<td>Paclitaxel/Cisplatin</td>
<td>0.91</td>
<td>0.80 - 1.04</td>
</tr>
<tr>
<td>Docetaxel/Carboplatin</td>
<td>1.03</td>
<td>0.80 - 1.32</td>
</tr>
<tr>
<td>Docetaxel/Cisplatin</td>
<td>0.94</td>
<td>0.78 - 1.14</td>
</tr>
<tr>
<td>Gemcitabine/Carboplatin</td>
<td>0.95</td>
<td>0.73 - 1.23</td>
</tr>
<tr>
<td>Gemcitabine/Cisplatin</td>
<td>0.92</td>
<td>0.81 - 1.04</td>
</tr>
<tr>
<td>Vinorelbine/Carboplatin</td>
<td>ND</td>
<td>ND - ND</td>
</tr>
<tr>
<td>Vinorelbine/Cisplatin</td>
<td>1.08</td>
<td>0.90 - 1.28</td>
</tr>
</tbody>
</table>

Source: NICE website, gefitinib appraisal, manufacturer submissions
Extrapolating data beyond the trial period

- QALYs use mean survival to reflect a lifetime horizon
- Parametric modelling needed (unless very mature data)
  - Standard distributions (exponential, Weibull, generalised Gamma, Gompertz, log-logistic, log-normal)
  - Piecewise or flexible models
  - Fit to all data with treatment covariate, or each arm separately
- Use a logical and critical approach for model selection (NICE DSU TSD14)
Real World Evidence (Observational data)
Study Design and Analysis

• A big problem:
  Two treatment groups were not comparable **before** the start of treatment.
due to imbalanced covariates between two treatment groups.
• So, direct treatment comparisons are invalid.
• Adjust for confounding covariates: matching, stratification, regression, propensity score
Example: Nested Case-Control Study
Interstitial Lung Disease in Japanese NSCLC patients

Cohort investigation

Registration of 3166 previously treated NSCLC patients (basic data)

Patients treated with gefitinib
Patients treated with chemotherapy

Onset of ILD, diagnosed by investigators

Follow up for 12 weeks per regimen

Naive cumulative incidence: 3.9% vs 2.0%
OR 2.35 [1.56-3.52]

Case-control Study

Register as provisional case

Randomly select 4 control patients without ILD

CRB Review

Confirmed cases (122) & controls (574) as case-control study data-set (detailed data)

Kudoh et al, 2008
Adjusted odds ratios for risk factors for ILD

Chemotherapy

- Gefitinib: Adjusted OR 3.23 [1.94-5.40]

- ≤54 yrs
- ≥ 55 yrs

PS
- 0
- 1
- 2-3

<0.5y since diag

- 0.5-<1y since diagnosis
- ≥1y since diagnosis

No concurrent cardiac disease

Concurrent cardiac disease

No pre-exg pulmonary emph

Mild pulmonary emphysema

Mod pulmonary emphysema

Severe pulmonary emphysema

ILD risk greater for blue characteristic  ILD risk greater for green characteristic
Conclusions

• Statistics plays a pivotal role in health economics and health technology assessment

• Payers, like regulators, want evidence based submissions

• The type of evidence may differ due to the question
  - Can cast a wider net, but still needs to be robust

• There are many challenges opportunities for statisticians looking to make a positive difference in this rapidly growing area
References

• Arnold R. Pharmacoeconomics: From Theory to Practice (Drug Discovery Series), CRC Press, 2010
• Jones B et al. Statistical approaches for conducting network meta-analysis in drug development. Pharm Stat 2011 (10) 523-531
• NICE website: http://www.nice.org.uk/
• Sutton A et al. Use of Indirect and Mixed Treatment Comparisons for Technology Assessment. Pharmacoeconomics 2008; 26 (9): 753-767
Backup slides
Some key concepts in HE and HTA
Different priorities to regulatory assessment

- Payers as decision makers
- Societal perspective
- Comparative effectiveness
The role of the clinical statistician

Providing evidence to support HTA submissions

• Economic model inputs are often statistical analyses of clinical data

• As with all models, Garbage In = Garbage Out

• The statistician needs to understand what the inputs will be used for
  - The analysis people ask for may not be the one they actually need
    • Strive to understand the underlying question (right answer, wrong question?)
    • Then work together to decide the optimal way to answer it
    • Clearly articulate the assumptions and limitations of different approaches
  - Standard regulatory analyses may not be the most appropriate for payers

• Work as a cross functional team
  - Payer agencies often have health economic, statistical and medical expertise
Economic model - inputs

- Health states (e.g. alive, responding)
- Comparators
- Comparative efficacy and safety (direct and indirect evidence; RCTs and RWE)
- Population and subgroups
- Costs (drug, side effects, resource, etc)
- Simulations
- Lifetime horizon
- Quality weightings (utilities)
Economic model - outputs

Overall cost of treatment

Quality adjusted survival for each comparator (QALYs)

Difference in cost per QALY between comparators

Cost per QALY for each comparator
**Adjusting OS for treatment switches**

- Real life treatment strategies for payers: Experimental *first* vs *never*
- QALY depends on OS
- ITT placebo arm does not reflect real life
- Censoring at switch or analysing *non-switch only* is biased
- Alternatives that aim to reduce bias include:
  - Inverse Probability of Censoring Weighting (IPCW) - weight non-switchers by patient characteristics predictive of switch
  - Rank Preserving Structural Failure Time Models (RSPFT) - estimate counterfactual survival in absence of experimental
- Methods make strong, often untestable assumptions
- Area of active research (Morden 2011, etc)
- **Preferable to avoid switching in study design!**
Example: Pazopanib vs Placebo
Renal Cell Carcinoma, NICE submission

Interim overall survival in treatment-naive population (N=233; E=90)
31/78 (40%) placebo patients crossed over to pazopanib

<table>
<thead>
<tr>
<th>Method</th>
<th>HR (95% CI) from Cox PH model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without covariates</td>
</tr>
<tr>
<td>ITT</td>
<td>0.752 (0.491-1.153)</td>
</tr>
<tr>
<td>Censor at crossover</td>
<td>0.683 (0.426-1.093)</td>
</tr>
<tr>
<td>Crossover as time dependent covariate</td>
<td>0.684 (0.428-1.095)</td>
</tr>
<tr>
<td>IPCW</td>
<td>-</td>
</tr>
<tr>
<td>RPSFT</td>
<td>0.345 (0.086-1.276)</td>
</tr>
</tbody>
</table>

Source: NICE website, pazopanib appraisal, manufacturer submission
Derivation of utilities

Quality values or weights that are placed on different health states

The “Q” in QALY

Statistical aspects of:

- Utility values themselves
  - What value to place on the health states
  - Often want perspective of general population in the payer’s country
  - Requires a well designed value elicitation study
  - Several value sets already available for existing tools, e.g. EQ-5D

- The health states to which they are applied
  - Often collected in the trial
  - Could use existing tools, e.g. EQ-5D
  - Or mapping relationship from another trial
  - One that collected the health state from your trial and the health state you want to map to
  - E.g. FACT-L and EQ-5D, pre-progression and post-progression and EQ-5D

Trial design and quantification of uncertainty are key
Confidentiality Notice

This file is private and may contain confidential and proprietary information. If you have received this file in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this file is not permitted and may be unlawful. AstraZeneca PLC, 2 Kingdom Street, London, W2 6BD, UK, T: +44(0)20 7604 8000, F: +44 (0)20 7604 8151, www.astrazeneca.com