Challenges when conducting economic evaluation alongside clinical trials: experience of economic appraisal in cardiovascular disease

Andrew Briggs
University of Glasgow
Borislava Mihaylova
University of Oxford

Issues and challenges

• Role of ‘within trial’ analysis
• Extrapolating results over time
• Importance of sub-group effects
• Role of the ‘single trial’ evaluation
• Will use two ‘single trial’ economic evaluations as examples

Example 1:
Cost-effectiveness of simvastatin

• Recently published within-trial analysis
• Based on Heart Protection Study
  – ‘Big, simple’ trial design (20,000+ patients)
  – 40mg simvastatin versus placebo
  – Primary endpoint ‘major vascular event’
  – 5-year mean follow up
• Extrapolation model (in preparation)

Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R on behalf of the Heart Protection Study Collaborative Group

Role of ‘within trial’ analysis

• HPS trial
  – Primary outcome ‘major vascular event’
  – Follow-up five years
• Team took the view that reporting the data was important: i.e. ‘within trial CEA’
  – Makes no sense to report cost-per life year?
  – Cost per MVE avoided
  – Cost per vascular death averted
• But roundly criticised by reviewers!

Stability of CEA over time

Importance of CE subgroups

I. Standard approach to CE alongside trials
   Overall CE for trial, for example:

   4S (4444) £5,502 per a life-year gained
   WOSCOPS (6595) £13,995 per a life-year gained
   LIPID (9014) £7,695 per a life-year gained

II. Within subgroup analysis

   4S diabetes subgroup £3,200 per a life-year gained

Multivariate range of risk (5-year MVE risk)

Quintiles of vascular risk

| Monovariate* | 12% | 18% | 22% | 28% | 42% |

*Cox proportional hazards model estimates the 5-year risk of MVE with baseline prior vascular disease or diabetes, age, sex, LDL and HDL cholesterol, midpoint of SBP and DBP, smoking status, creatinine and statin allocation as covariates.

Assessing subgroup effects reliably

- Analyses in different subgroups indicate:
  - Similar relative reduction in vascular events
  - Similar relative reduction in costs of vascular events
  - Similar absolute difference in statin treatment cost

- Hence, cost-effectiveness for subgroups estimated by applying overall treatment effects to placebo event rates and costs observed in each subgroup

Results: Within subgroup and constant relative/absolute impact

Example 2:
Cost-effectiveness of perindopril

- Based on EUROPA study*
  - 'Big, simple' trial design (12,000+ patients)
  - 8mg perindopril versus placebo
  - Primary endpoint 'CV death or nonfatal MI/CA'
  - 4.2-year mean follow up
- Extrapolation model (in preparation)


EUROPA extrapolation model
Other evidence on ACE inhibitors

- Myriad of evidence relating to effectiveness and cost-effectiveness of ACE inhibitors
- In particular PEACE trial:
  - Similar trial
  - Different patients / different health system
  - Different ACE Inhibitor/dose
  - No significant effect
- Currently much debate about reconciling EUROPA & PEACE
  - Should we attempt a ‘synthesis’?

Role of ‘single trial’ models

- Relevance of trial-based CEA questioned for decision making
- In CVD, extrapolation over time is necessary
  - Continued role for ‘within trial’ analysis to be clear about the ‘evidence base’
- Large trials have the ability to inform modelling assumptions
  - Sorts of single trial appraisal presented represent a ‘hybrid’?
- Use of external evidence is challenging
  - Single trial analysis is ‘clean’
  - Can be pooled (if correctly reported)?

Challenges for evidence synthesis modelling

- Practical
  - Task can be huge, not always realistic for single research team
- Methodological
  - Synthesis methods not fully worked out
  - Structural assumptions of decision models can be key, but rarely tested
- Therefore continued role for ‘single trial’ analyses as distinct pieces of work