Caveats of Randomized Clinical Trials for Economic Analysis

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That infamous fourth hurdle…

Quality  Safety  Efficacy  Reimbursement and pricing

Market Authorisation  Fourth Hurdle Market Access

Health Economics data
Requirements for economic data for market access

- **Ontario and Australia**: mandatory for reimbursement
- **UK**: required for products subject to NICE appraisal
- **Netherlands**: mandatory only for drugs that request a premium price
- **Portugal**: selective request from government for reimbursement
- **Finland**: mandatory submission for reimbursement
- **Sweden**: setting up NICE-equivalent
- **Italy, Spain**: needed more and more
- **France**: economic dossier explicit component of application for reimbursement and pricing
- **Belgium**: economic dossier required > 2002
- **US**: required by some MCOs
“Fourth hurdle” impact

- Increased sensitivity to economic evaluations -- proliferation of methodological guidelines
- Increased need for transparent economic evaluations
- Data accepted for registration purposes scrutinized differently by “market access” decision-makers
- Separation of clinical from economic benefits of new interventions no longer realistic
- Implications for strategy for data collection strategy and prioritization of studies within clinical development programs
Summary market access criteria across Europe

- **Efficacy - safety - tolerability**
  - principal basis for reimbursement
  - perception of superiority to relevant comparator determinant of price premium/parity decision

- **Cost comparisons**
  - Cost per average daily dose of competitors taken as benchmark
  - Explicit or implicit comparison with other European prices for product

- **Economic impact on health care system**
  - Need to demonstrate acceptable impact on clinical practice
  - Budget impact and cost offsets -- mostly in retail drugs budget

- **Unmet medical need and innovation**
  - less critical factors
Interdependence of European drug prices

- Reference to other EU prices
- No reference

- Average BE, FR, GER, UK
- Average of 3 lowest prices in basket of 9 (Swe, Fin, DK, Ger, BE, Aus)
- Minimum price UK or maximum DK, FR, GER, NL, UK
- Average DK, FIN, FR, GER, NL, NOR, SWE, UK
- Minimum FR, IT, SP
- Average FR, IT

- Weighted EU average
- EU median
- EU average
- EU average
- All EU prices
- Lowest EU price
What payers look for in registrational data

**Trial design**
- Representative trial population?
- Subsets of patients who will benefit more than others?
- Relevant comparators?

**Dose ranging studies**
- Likely standard dose?
- Percentage of patients who will be treated at each dose level?
- Likelihood of dose/cost escalation in clinical practice?

**Duration of effect**
- Efficacy vs. effectiveness
- Translation of trial results into long-term benefits

**Ratings scales**
- Clinical relevance of an improvement on included rating scales?

**Side effects**
- Impact of side effects on overall patient management eg compliance, GP visits, etc?
- Economic impact of side-effects?
What is NICE?

• The National Institute for Clinical Excellence
• Established in 1999
• Objective: “faster access to modern treatments in England and Wales”
• Selective appraisal of products or technologies based on established criteria (high cost impact or inappropriate use within the National Health Service)
• “4th hurdle” in a system of free pricing and locally-driven reimbursement decisions
Components to a NICE submission

- Clinical effectiveness
- Cost-effectiveness
- Impact on the health care service
The NICE precedent

- Relenza for the prevention of flu (GlaxoSmithkline)
- Appraised after drug had received market approval from Medicines Control Agency
- Product deemed unacceptable on the basis of unconvincing clinical effectiveness data
  - no clear demonstration of benefit in the elderly
  - inadequate subgroup analyses
In the world of NICE

- Clinical efficacy is no longer enough
- Health Economics is no longer a luxury, but a requirement
- Global development programs are expected to serve as vehicles for HE data collection
- The value of evidence being provided needs to be ascertained early.
NICE needs for economic data

• Rigorously conducted economic analyses that allow to ascertain the relationship between costs and outcomes of therapies.
• Ideally, cost-effectiveness analyses mirror pivotal trial designs
• Result: A “complete” clinical and economic story based on RCTs performed in highly experimental settings.
Impact of NICE

- Informal relationships with other national HTA agencies
- Appraisals close to launch may impact on pricing & reimbursement negotiations in EU and beyond
- A Euro-NICE unlikely, however general culture of cost-containment prevalent throughout Europe
- Web-disclosed NICE decisions may have trickle effect
- More stringent requests for demonstration of clinical benefits in relevant populations -- “niching”
NICE requirements that will influence trial design

Need for relevant comparator
Different comparators needed for registration and market access/payors
• Local standard treatment/usual care
• Most recently launched product of same class
• Cheapest and most effective alternative

⇧ Compromise solution necessary in multinational trials
NICE requirements that will influence trial design

Need for more representative trial populations

• Relax entry criteria to generate more typical patient mix
• Allow for comorbidities
• Increase sample sizes
• May increase enrolment trials if recruitment is more complex
NICE requirements that will influence trial design

Need for long-term demonstration of benefit

• Final as opposed to intermediary outcomes
• Longer trial duration to allow for collection of complete data
• Increased trial costs
• Longer period of evaluation, hence longer development timelines
NICE requirements that will influence trial design

**Need for local data**

- Multinational Phase III trials are not powered for individual country assessments
- Clinical data obtained over pooled trial population -- acceptable external validity
- Trial-derived resource use multiplied by local unit costs
NICE requirements that will influence trial design

**Demonstration of benefit in relevant subgroups**
- Larger sample sizes needed
- Powering of study more explicit and complex
  - disease severity
  - patient populations (elderly, male/female, …)
  - disease subtypes
- Gives rise to equity concerns
- Possible outcome: niching of product
Limitations of randomized controlled trials

An old hobby horse for economists

- Focus on intermediary as opposed to long-term outcomes
  - Efficacy vs. effectiveness
  - eg. Cholesterol lowering vs. decreased cardiovascular mortality
- Over-reporting of non-clinically relevant events
  - eg. Protocol-defined MIs may include mild infarcts that would usually require observation only
  - Low-molecular weight heparin prevented mainly distal DVT compared to warfarin, however these as less clinically-relevant than proximal DVT (O’Brien et al, XX)
- Experimental context non-representative of actual practice
  - highly selected patient population
  - cautionary approach due to blinding of therapy
  - high prevalence of specialized centers
Randomized controlled trials and economic analyses

**Kassiner & Angel, NEJM 1994**
- “Bias can compromise even original scientific studies, but…opportunities for introducing bias into economic studies are far greater, given the discretionary nature of model building and data selection in those analyses.”

**Rittenhouse & O’Brien, 1996**
- Randomised controlled trials present a trade-off between internal and external validity for the purposes of economic analysis
  - High internal validity: between-group differences unlikely to be biased
  - Low external validity: treatment conditions untypical of normal practice

**FDA Principles for Review of pharmacoeconomic studies**
- Research to substantiate pharmacoeconomic claims must meet traditional standards for quality
- Thus randomized clinical trial-derived estimates are best source
Deriving economic data from RCTs

“The estimation of economic response to therapy is inevitably confounded in RCTs unless patients are randomized to setting as well as treatment”

(Drummond M. Experimental versus observational data in the economic evaluation of pharmaceuticals. Med Care 1998; 18(2) Suppl)
Deriving economic data from RCTs

**Issues**

- Resource use may be influenced by trial setting
- Cost drivers are closely linked to clinical outcomes
- Protocol bias in treatment of clinical events
  - more intense
  - more cautious
  - more specialized
- Between-treatment group differences may be reliable, however absolute magnitude of effect is not.
Deriving economic data from RCTs

**Solutions**

- Measure *resource precipitating events* within clinical trials
- Derive *resource consequences of precipitating events* from observational data relevant to the desired setting

- Resource use is most likely to be relevant if trial is of pragmatic design.
- Results are more transferable if the health care system to biological response are not shown to vary per setting.
## Pragmatic vs. explanatory trials

<table>
<thead>
<tr>
<th>Explanatory/experimental</th>
<th>Pragmatic/naturalistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrowly-defined population</td>
<td>Broad population</td>
</tr>
<tr>
<td>Randomized, double-blind</td>
<td>Randomization possible</td>
</tr>
<tr>
<td>Rarely <em>a priori</em> specified subgroups</td>
<td>Potential for subgroup analyses</td>
</tr>
<tr>
<td>Specialist setting most common</td>
<td>Setting reflective of actual practice</td>
</tr>
<tr>
<td>Derive efficacy and safety</td>
<td>Derive effectiveness</td>
</tr>
<tr>
<td>Necessary informant of product licensure</td>
<td>Best informant of market access decisions</td>
</tr>
<tr>
<td>Questionable external validity</td>
<td>High external validity</td>
</tr>
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</table>
### Pragmatic vs. explanatory trials (2)

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<tbody>
<tr>
<td>• Hypothesis-driven</td>
<td>• Low construct validity</td>
</tr>
<tr>
<td>• Assumed universality of clinical results</td>
<td>• High transferability of economic results</td>
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<tr>
<td>• Trial design minimizes confounding effects on observed clinical benefits</td>
<td>• Confounding effects difficult to elucidate in observed effects</td>
</tr>
<tr>
<td>• Protocol-induced bias for economic benefits</td>
<td>• Protocol-induced bias minimized for economic benefits</td>
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Pragmatic trials -- issues

• Choice of patients, settings and comparators
• A new bias: the care effect
• Suitable observation period?
• Sample size calculation
  – basis for effect size calculations?
  – differences likely to be smaller than in randomised trials
• Interpretation of results
  – eg. GUSTO trial: 41 000 patients, 4-way comparison
  – difficult to isolate impact of care setting from that of treatment
• Commercial ramifications
Forcing industry to address tough questions

- What data exist to substantiate product claims?
- Which patient subgroups benefit most?
- What impact will the product have on current or future treatment options?
- What is the most appropriate comparator?
- What is the product’s wider impact on the NHS, social services and public health?
- What methods can we use to fill gaps in clinical trial evidence?
Remaining methodological challenges

- Effective allocation of resources or simply cost containment?
- Selective evaluation of evidence for new products -- what about the older ones?
- Using cost/QALYs as a basis for decision-making
- The role of patient-based outcomes in determining the value of new products
- Explicit thresholds for decision-making
Desired state: the ideal allocation of scarce resources

- Need mechanisms to ensure more rapid adoption of clinically and cost-effective technologies
- Need more rapid decline of ineffective technologies that should be replaced by newer and better ones
- Delayed or limited adoption of technologies that lack sufficient evidence of clinical and cost-effectiveness.
The goal of economic evaluation is to aid decision-making

“If you can see that the introduction of a technology will cause problems to decision makers, offer solutions or at least a process by which a solution might be found”

Prof. Ron Akehurst, ScHARR, NICE Appraisals Committee
Conclusions

• Clinical trials pose problems but they remain the gold standard from which one can collect economic data
• Environment is changing to focus beyond registration -- impact on clinical development programs certain
• Implications for data collection strategy -- need to think of multiple audiences and target beyond registration
• Pragmatic trials designs advocated however the science stil needs to be perfected to gain credibility
• Combination of approaches and data sources likely to be future for evaluating value of products.