

TRIAL-BASED ECONOMIC EVALUATIONS: CAN THEY STAND ALONE?

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SHORT ANSWER: "CAN TRIAL-BASED EVALUATIONS STAND ALONE"

- Under the right circumstances, YES
 - In common parlance: the evidence from within the trial can be so compelling that we don't need more evidence
 - In VOI-terms: the VOI calculated from the truncated results within a trial can be so low that it doesn't justify calculating a "more complete" estimate of VOI
- But who said they are supposed to?
 - Like the clinical evidence developed from trials, the economic evidence can stand alone or be synthesized

OUTLINE

- Parallels with clinical studies
- Attributes that increase the likelihood that a single trial's data will be sufficient
- Two (of a number of) concerns about data from trials
 - What is the likelihood that the cost-effectiveness ratio observed in the trial describes longer term therapy?
 - How transferable are the pooled results from multinational trials?
- Concluding comments

PARALLELS WITH CLINICAL STUDIES (I)

- Does a single clinical trial provide sufficient evidence for the clinical adoption decision?
 - NO. The US FDA requires 2 well designed, etc, trials
- Are clinical adoption decisions made based on two trials?
 - YES, even though there may be other evidence one could subject to synthesis

PARALLELS WITH CLINICAL STUDIES (II)

- Reporting an experiment VS research synthesis
 - When clinical trial reports are published, they rarely combine data from the trial with prior data to yield a synthesis of all current information
 - Some of the other speakers here today have conducted economic studies alongside trials such as the Heart Protection Study (Lancet. 2002;360: 7-22), EUROPA (Lancet. 2003;362:782-8), and ATLAS (Circulation. 1999;100:2312-8)
 - * In neither the clinical nor the economic evaluations were syntheses reported (e.g., no forest plots, etc.)
- Why should the reporting requirements for the economic effects observed in trials differ from the reporting requirements for clinical effects observed in trials?

ATTRIBUTES THAT INCREASE THE LIKELIHOOD THAT A SINGLE TRIAL'S DATA WILL BE SUFFICIENT

- Has reasonable comparators (e.g., a therapy currently deemed cost-effective)
- Adopts final outcomes like death, disability, and QALYs
- Collects data on a sufficiently broad set of medical services, in a broad range of delivery settings, among all or a random sample of trial participants
- Is adequately powered
- Does not overly proscribe medical care
- Has sufficiently long follow-up / observes a sufficient fraction of participants' life courses (e.g., if more than 50% of population has died by the end of the trial)
- Enrolls a reasonably representative sample of the patient population who will receive the drug
- Collects data to assess / improve transferability
- Observes a sufficiently large or small treatment benefit

WHAT CAN GO WRONG

- In a forthcoming review of economic evidence from 8 reports on the cost-effectiveness of from 6 trials of second-generation antipsychotics, we concluded that they provided little information supporting cost-effectiveness
- Problems included:
 - Use of inappropriate statistical tests and reporting of inappropriate moments of the distribution
 - Inadequate efforts to quantify sampling uncertainty
 - Lack of statistical power
 - Failure to adequately address problems arising from missing data
 - Lack of an intention-to-treat analysis
 - Follow-up that was too short to sufficiently measure economic (and clinical?) outcomes

Polsky D, Doshi JA, Bauer MS, Glick HA. Clinical trial-based cost-effectiveness analyses of antipsychotics. Am J Psychiatry. In press.

CONCERNS ABOUT DATA FROM TRIALS (I)

TIME HORIZON: WHAT IS THE LIKELIHOOD THAT THE COST-EFFECTIVENESS RATIO OBSERVED IN THE TRIAL DESCRIBES LONGER TERM THERAPY?

- When a trial follows participants for a time-limited period (e.g., 2 or 3 years), but the therapy will be taken for lifetime, one should consider the likelihood that the cost-effectiveness ratio observed in the trial will describe longer term therapy
- To address this uncertainty one should conduct:
 - A within-trial analysis: Evaluates what was observed during the trial
 - A longer-term projection: By use of a decision model, projects beyond the period of observation

STRENGTHS AND WEAKNESSES

- Within-trial analysis and longer term projections have opposing strengths/weaknesses:
 - We are more certain of what was observed during the trial, but follow-up may be too short to capture the most important impacts of the therapy
 - We are less certain about the projection beyond the trial, but this projection attempts to quantify what may be the most important impacts of the therapy
- Homerun: Evidence of cost-effectiveness within the trial; no evidence of lack of cost-effectiveness in decision models

WITHIN-TRIAL ANALYSIS

- Even if one decides that the primary analysis will be a projection beyond the period of observation, one should still evaluate the costs and outcomes that were observed during the trial
 - In such a within-trial evaluation, one should maintain the same time horizons for costs and outcomes observed in the trial (e.g., if follow-up for the trial was for one year, then costs and effects should be measured for one year)
- Not always easy to demonstrate cost-effectiveness in a within-trial analysis
 - e.g., no within-trial analysis of cholesterol-modifying therapy has demonstrated reasonable cost-effectiveness
 - But there are areas of medicine, such as severe heart failure, in which demonstrated cost-effectiveness during 2-4 year trials has routinely translated into cost-effectiveness in lifetime projections

LONGER-TERM PROJECTION

- To investigate whether the cost-effectiveness ratio observed during the trial is likely to represent the ratio of longer-term therapy, one may also project the results for longer periods
- For projection: Maintain a common time horizon for both costs and effects
 - a number of studies have used the cost difference observed within the trial; argued that the benefits of the therapy extend beyond the trial; and incorporated the benefits from beyond the trial
 - E.g., West of Scotland Coronary Prevention Study
 - * If the therapy has downstream benefits that have not been adequately captured during the trial, it most likely has downstream costs that also have not been adequately captured during the trial

TIME HORIZON FOR PROJECTION

- Given that the longer the projection, the less certain the results, one should make projections for different time horizons
 - Even if the longest time horizon in a lifetime projection is 30-40 years, one may observe that projected long-term cost-effectiveness reaches equilibrium after only 5 or 10 years of projection
- To add face validity to the trajectory of the projected cost-effectiveness ratios:
 - If there is sufficient follow-up during the trial, make estimates for differing lengths of follow-up during the trial (e.g., the first year, the first 2 years, etc.)

COST EFFECTIVENESS RATIO AND 95% CI, 5.5-YEAR
CHOLESTEROL LOWERING TRIAL

| Years of Follow-up/ Projection | Point Estimate | 95% CI |
|-----------------------------------|----------------|------------------------|
| Within the trial | | |
| 1 | Dominated | \$168,884 to Dominated |
| 2 | \$282,857 | \$45,577 to Dominated |
| 3 | \$73,529 | Dominates to Dominated |
| 4 | \$12,074 | Dominates to Dominated |
| 5.5 | \$15,258 | Dominates to \$122,772 |
| Projection beyond the trial | | |
| 10 | \$12,246 | Dominates to \$42,263 |
| 15 | \$8,578 | Dominates to \$6,721 |
| 20 | \$7,320 | \$681 to \$21,841 |

CONCERNS ABOUT DATA FROM TRIALS (II)

TRANSFERABILITY: HOW SHOULD ONE INTERPRET RESULTS FROM MULTINATIONAL TRIALS?

- The Problem:
 - Pooled (i.e., average) clinical and economic results from multinational trials may not be reflective of the results that would be observed in individual countries/centers that participated in the trial
 - * ?More problematic? The results may not be reflective of results that would be observed in countries that did not participate in the trial
 - Similar issues arise for any subgroup of interest in the trial (e.g., more and less severely ill patients)
- Common sources for concern
 - Transnational differences in morbidity/mortality patterns; absolute and relative prices for medical service use (i.e., price weights); and practice patterns (i.e., medical service use)
- Thus decision makers may find it difficult to draw useful conclusions about the value for the cost of the therapies that were evaluated in multinational trials

BAD SOLUTIONS

- Use trial-wide clinical results, trial-wide medical service use, and price weights from one center
- Use trial-wide clinical results and use costs derived from the subset of patients treated in the country
- These approaches ignore the fact that clinical and economic outcomes may influence one another
 - Differences in costs may affect practice patterns, which in turn may affect outcomes
 - Differing practice patterns may affect outcomes, which in turn may affect costs

APPROACHES TO TRANSFERABILITY

- For countries that participated in the trial, two approaches -- which rely principally on data from the trial to address these issues -- are currently making their way into the literature
 - Hypothesis tests of homogeneity
 - Multi-level random-effects model shrinkage estimators
- For countries that did not participate, one might consider the problem of transferability as a case of missing data
 - Solutions to the missing data problem often derive from identifying countries in the trial that are "like" the ones with "missing data," etc....

"EVIDENCE" VS "SOURCE OF DATA"

- Not necessarily a question of either / or
- Should analyze and report economic data from within a trial in a manner similar to analysis and reporting of clinical data
 - Including comments on projection and transferability
- Should also report data in ways that it will be usable for synthesis
 - ISPOR RCT-CEA TASK FORCE: "To facilitate synthesis, report means and standard errors for the incremental costs and outcomes and their correlation"

SOURCES OF DIFFERENCES IN OPINION?

- Differing opinions may be due to differing levels of confidence in decision analysis
 - Those arguing for greater reliance on synthesis may be more confident that decision models / evaluation of second order uncertainty are ready for prime time
 - * There comments seem to have more to do with perceived limitations of trials and less to do with the relative strengths and weaknesses of trials versus models
 - Those arguing for greater reliance on trials may be less confident in these models
- Differing opinions may also be due to the environments the speakers come from
 - In the U.S., economic data aren't used in the same way as it is in the relatively small number of countries that make strong use of economic data

CONCLUSIONS

- Under the right circumstances, a trial-based economic evaluation can stand alone, but more routinely, the evidence from a single trial won't "prove" (or disprove) that a therapy is cost-effective
- Economic data from a single trial should be analyzed and reported in a manner similar to the analysis and reporting of clinical data from a single trial
 - Trial-based economic evaluations provide evidence about cost-effectiveness that should be weighed against other economic evidence (if available)
- To be most useful to decision makers, issues related to time horizon and transferability must be assessed
- Economic data from a trial should be reported in such a way as to facilitate synthesis