TRANSFERABILITY OF THE RESULTS FROM MULTINATIONAL TRIALS

Henry Glick, PhD
University of Pennsylvania School of Medicine
Leonard Davis Institute of Health Economics
Amgen Economics Advisory Board
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MULTINATIONAL TRIALS

• Multinational trials are the norm for the evaluation of new medical therapies
  – Speed the development process
  – Broaden the representativeness of the patients who receive the therapy
  – Familiarize clinical decision makers with the therapy prior to its approval by regulatory agencies such as the FDA

HETEROGENEOUS ECONOMIC CONDITIONS

• Recent trend toward inclusion of countries with heterogeneous economic conditions
  – Reduce the cost of the trials
  – ? Increase event rates ?

ECONOMICS AND INTERNATIONAL TRIALS

• There has been a growing trend to incorporate economic evaluations within these trials
• The information developed from these evaluations is intended to inform decision makers about the value for the cost of new drugs and technologies
OUTLINE

• Problems in interpreting economic results from multinational trials?
• Bad solutions to the problem
• Which is more important, country-specific medical service use or price weights?
• Two analytic approaches for the evaluation of transferability
  – Heart failure example
• General comments

NOT PESSIMISTIC!

INTERPRETING ECONOMIC RESULTS FROM MULTINATIONAL TRIALS?

• The Problem:
  – There has been growing concern that the pooled (i.e., average) economic results from multinational trials may not be reflective of the results that would be observed in individual countries that participated 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; practice patterns (i.e., medical service use); and absolute and relative prices for this service use (i.e., price weights)
• Thus decision makers may find it difficult to draw conclusions about the value for the cost of the therapies that were evaluated in multinational trials

DIFFERING MORBIDITY/MORTALITY PATTERNS

• Concerns about transferability may arise due to variations in underlying morbidity/mortality patterns in different countries
  – e.g., cost-effectiveness of cholesterol-lowering agents may vary if underlying risk for CHD differs
• Potential sources
  – Naturally occurring differences
  – Differences in disease identification and treatment
  – Variation in severities of disease of enrolled patients between countries (e.g., cream-skimming or reverse cream-skimming)
DIFFERING PRACTICE PATTERNS

• Concerns about transferability may arise due to variations in practice patterns in different countries
  – Effectiveness of intervention may be related to the other care received by the patient
    • e.g., therapies can be complementary with other care (i.e., more effective when combined with care), and thus less cost-effective in settings that use less other care
    • Alternatively, therapies can be substitutes for other care (i.e., more effective when not combined with other care), and thus more cost-effective in settings that use less other care

DIFFERING PRACTICE PATTERNS (II)

• Practice pattern may affect and be affected by relative price
  – There is (limited) evidence that practice styles vary in the face of differing relative prices
    • If an intervention either substitutes for or is complimentary with intensive care, one would expect its effectiveness to vary when relative prices of hospital units vary by country

DIFFERING PRACTICE PATTERNS (III)

NOTE: While a commonly expressed concern is that protocols dramatically affect and homogenize treatment patterns, in a number of trials in which I’ve been involved, practice variation has been observed across countries

DIFFERING PRICE WEIGHTS

• Probably the most frequently cited reason for lack of transferability, with possibly the smallest impact on the results of the study

<table>
<thead>
<tr>
<th>Country</th>
<th>Price Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46,818</td>
</tr>
<tr>
<td>2</td>
<td>57,636</td>
</tr>
<tr>
<td>3</td>
<td>53,891</td>
</tr>
<tr>
<td>4</td>
<td>69,145</td>
</tr>
<tr>
<td>5</td>
<td>65,800</td>
</tr>
<tr>
<td>Overall</td>
<td>45,892</td>
</tr>
</tbody>
</table>

BAD SOLUTIONS

• Use trial-wide clinical results, trial-wide medical service use, and price weights from one country
  – e.g., to tailor the results to the U.S., just use U.S. price weights, and conduct the analysis as if all participants were treated in the U.S.
• Use trial-wide clinical results and use costs derived from the subset of patients treated in the country
• Ignore the fact that clinical and economic outcomes may influence one another (cost affects practice which affects outcome; practice affects outcome which affects cost)

PRICES VS SERVICES?

• When addressing transferability of data from other countries, Australian, Canadian, and British guidelines for cost-effectiveness primarily discuss variability in price weights and medical service use
• All 3 request that local price weights be used in evaluations submitted to the government
  – At least one has a preferred schedule
• All 3 also recognize that medical service use in other countries may not reflect their medical service use
  – None provide specific instructions for addressing the latter issue

TRANSFERABILITY OF RESULTS FROM 44 MULTINATIONAL STUDIES

• Drummond and colleagues reviewed the "main causes of variation in study results from place to place"
• Conducted a literature review using OHE-HEED and NHSEED to identify 46 European studies with inter-country comparisons
  – In current presentation, 2 studies omitted because they had "detailed data from only one country, with negligible information about other countries"

CLASSIFICATION BY EXTENT OF "GENERALIZABILITY"

• Classification “based on size of difference in results and importance for decision-making”
  – More generalizable: Observed differences in ICERS unlikely to change adoption decision
  – Less generalizable: Observed differences in ICERS likely to change adoption decision
REVIEW RESULTS

Authors’ conclusion: "...the amount of variation you find depends on the amount the analyst allows (in study design or analysis)"

PRW only PW & RU PW, RU, & EP

0 5 10 15 20 25
Number of studies

More generalizable

Less generalizable

Source: Drummond MF. Are the results of economic evaluations generalizable? iHEA 4th World Congress.

PRICE WEIGHTS VS OTHER VARIATION *

<table>
<thead>
<tr>
<th>Trial-Wide Effects</th>
<th>Country Specific Costs and Effects</th>
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<tbody>
<tr>
<td></td>
<td>Price Weights</td>
</tr>
<tr>
<td>Country</td>
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</tr>
<tr>
<td>Overall</td>
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</tr>
</tbody>
</table>

† Country-specific resource use
** New therapy dominates

A SECOND EXPERIMENT

One problem with last experiment is that when we assessed price weights alone, we multiplied them times trial-wide medical service use; when we assessed country-specific medical service use, the Ns for each mean were the Ns from each country

When one subdivides a larger group into smaller groups, one expects variability to grow!

DESIGN OF SECOND EXPERIMENT

Used data from 2 RCTs to design a different experiment in which the N’s per country and per treatment group were maintained

1) To assess the relative contribution of price weights, we randomly assigned patients to countries’ price weights and assessed results for each set of price weights (pseudo-countries based on prices)

2) To assess the relative contribution of service use, we randomly assigned countries’ price weights to participants in each country and assessed results for each set of countries’ participants (pseudo-countries based on medical service use)
**INTERPRETING SECOND EXPERIMENT**

- If results from all countries shrink towards a common mean, suggests variable that is held constant (e.g., groups of price weights) isn’t that important
- If results from all countries have patterns of variability similar to what was observed in the trial, suggests variable that is held constant (e.g., practice pattern) is important
- Complexity of relationship between price and service use may lead to other patterns of results

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**POTENTIAL PROBLEM FOR INTERPRETATION**

- When we calculate the costs of patients who were all treated in each country together (i.e., when we randomize price weights), what look like country-specific effects may be due to differences in either practice pattern or severity of illness
  - Used multivariable analysis in an attempt to control for differences in severity that may exist between countries

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**EXPERIMENT 2A**

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost Difference ($)</th>
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</thead>
<tbody>
<tr>
<td>EU1</td>
<td>-2000</td>
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<tr>
<td>EU2</td>
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</tr>
<tr>
<td>EU3</td>
<td>2000</td>
</tr>
<tr>
<td>EU4</td>
<td>4000</td>
</tr>
<tr>
<td>EU5</td>
<td>6000</td>
</tr>
<tr>
<td>EU6</td>
<td>8000</td>
</tr>
<tr>
<td>EU7</td>
<td>10000</td>
</tr>
</tbody>
</table>

**EXPERIMENT 2B**

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost Difference ($)</th>
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<tbody>
<tr>
<td>LA1</td>
<td>-2000</td>
</tr>
<tr>
<td>EU6</td>
<td>-1500</td>
</tr>
<tr>
<td>EU7</td>
<td>-1000</td>
</tr>
<tr>
<td>NA1</td>
<td>-500</td>
</tr>
<tr>
<td>EU8</td>
<td>0</td>
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<tr>
<td>EU9</td>
<td>500</td>
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<tr>
<td>EU10</td>
<td>1000</td>
</tr>
<tr>
<td>EU11</td>
<td>1500</td>
</tr>
<tr>
<td>EU12</td>
<td>2000</td>
</tr>
</tbody>
</table>

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![Graphs of Experiment 2A and Experiment 2B](image-url)
TAKE HOME MESSAGES FROM EXPERIMENTS

• Unlikely that multiplication of trial-wide service use times a country’s price weights provides information about the likely impact of the therapy when it is used in that country
  – In general, dramatically shrinks estimates for all countries to a common result

TAKE HOME MESSAGES (cont.)

• While there is evidence that price weights matter, among countries with similar levels of economic development, accounting for differences in medical service use appears to be more important than differences in price weights
• Limited evidence that when working with dramatically different price weights (e.g., from the developing and the developed world), price weight differences more important (see LA1 in experiment 2B)

TAKE HOME MESSAGES (cont.)

• Should perform experiment in more trials -- particularly those with evidence of heterogeneity -- to evaluate consistency of these findings across trials

TWO ANALYTIC APPROACHES TO TRANSFERABILITY

• Two approaches -- which rely principally on data from the trial to address these issues -- have made their way into the literature
  – Hypothesis tests of homogeneity (Cook et al.)
  – Multi-level random-effects model shrinkage estimators
HYPOTHESIS TESTS OF HOMOGENEITY

• Evaluate the homogeneity of the results from the different countries
  – If there is no evidence of heterogeneity (i.e., a nonsignificant p-value for the test of homogeneity), and if one believes the test was powerful enough to rule out economically meaningful differences in costs, then one cannot reject that the pooled economic result from the trial applies to all of the countries that participated in the trial
  – If there is evidence of heterogeneity, then the method indicates one should not use the pooled estimate to represent the result for the individual countries, but this method is less clear about the result that should be used instead

SEPARATE HOMOGENEITY EVALUATIONS FOR COSTS AND EFFECTS?

• Homogeneity of a therapy’s effects on costs and outcomes need not guarantee the homogeneity of the resulting cost-effectiveness ratios or net monetary benefit (NMB) associated with the therapy
• Statistical tests of the clinical endpoints of trials often based on relative measures such as odds ratios
• Economic outcomes are the result of absolute differences
• Heterogeneity in absolute treatment effects (a difference) can occur when there are large country-to-country differences in underlying rates of events and a constant multiplicative treatment effect (i.e., homogeneity in relative treatment effects)

EXAMPLE

• Suppose you had data from two trials
  
<table>
<thead>
<tr>
<th>Country</th>
<th>( p_{lo}^{*} )</th>
<th>OR*</th>
<th>( p_{ac} )</th>
<th>OR†</th>
<th>( p_{ac} )</th>
<th>Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial #1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.5</td>
<td>0.111</td>
<td>0.099</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.5</td>
<td>0.053</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.05</td>
<td>1.0</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial #2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.72</td>
<td>0.153</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.5</td>
<td>0.053</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.05</td>
<td>&lt;1.0</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† \( p_{ac} = (p_{lo} \times OR) / ((p_{lo} \times OR) + (1-p_{lo})) \)
EVALUATING HOMOGENEITY OF VALUE FOR THE COST

• The complexities related to assessing the homogeneity of the country-specific cost-effectiveness / NMB by evaluating the homogeneity of the country-specific treatment effects on cost and effects suggest an alternative approach:
  – Estimate country-specific NMB and evaluate its homogeneity directly

EVALUATING HOMOGENEITY OF VALUE FOR THE COST (cont.)

• One would use the more precise pooled (average) ratio / NMB for the overall study to represent these countries’ ratios only if:
  1) It appears that there is no country-by-ratio (country-by-NMB) interaction and
  2) The minimum detectable difference was small enough to be economically important
• In what follows, I am focus on homogeneity of NMB

TESTS OF HOMOGENEITY

• Evaluation of homogeneity of clinical outcomes common
  – Similarity of treatment effect in men and women; young and old; more and less severely ill
• Heterogeneity of treatment effects is called an interaction between treatment and the variable which was used to create the subsets (e.g., a treatment-by-country interaction)
• A number of methods are available for assessing homogeneity
  – e.g., F or $X^2$ tests to assess significance of a set of country-by-outcome interaction terms

GAIL AND SIMON TESTS OF HOMOGENEITY

• Gail and Simon have proposed two tests to determine whether results are inconsistent in both direction and magnitude or whether they are consistent in direction but not in magnitude
  – Qualitative or crossover interaction: The treatment effect is positive in some countries and negative in other countries (i.e., inconsistent in both direction and magnitude)
  – Non-crossover interaction: There is variation in the magnitude of the effect, but not in its direction. Peto has termed the latter type of interaction a quantitative interaction
INTERPRETATION OF QUALITATIVE INTERACTION

• A finding of qualitative interaction suggests:
  – For the clinical outcome, treatment is effective in some countries and ineffective in others
  – For the cost outcome, treatment saves money in some countries and adds costs in others
  – For NMB, treatment has an NMB greater than 0 in some countries and less than 0 in others

EXAMPLE, TEST OF HOMOGENEITY

• Data drawn from a randomized, double blinded, placebo controlled trial evaluating a drug for severe heart failure
• A total of 1663 patients enrolled in 16 countries were used in our analysis
  – Five countries enrolled more than 100 patients (N’s = 130, 372, 382, 236, and 254)
  – The remaining 11 countries enrolled 289 patients (80 from the developing world and 209 from the developed world)

INTERPRETATION OF QUANTITATIVE INTERACTION

• A finding of qualitative interaction suggests:
  – For the clinical outcome, treatment is effective (ineffective) in all countries, but differs in the degree of its effectiveness (ineffectiveness)
  – For the cost outcome, treatment saves (costs) money in all countries, but differs in the degree of savings (costs)
  – For NMB, treatment is net monetary beneficial (non-net monetary beneficial) in all countries, but differs in its magnitude

COSTING

• Costs estimated for hospitalization, active drug therapy, and ambulatory care
• Price weights for hospitalizations obtained from 4 countries that enrolled more than 100 patients, and 1 that enrolled fewer
• Used average of price weights collected from 4 developed countries to value medical service use in 7 developed countries for which they were unavailable
• Used price weights collected from 1 developing country to value medical service use in 3 developing countries for which they were unavailable
ANALYSES

• All results are based on nonparametric bootstrap analyses for the pooled data and for the country-specific data
  – We report a pooled result, results for four countries that enrolled more than 100 patients and for which price weight data are available, and results for a category made up of the remaining 11 countries (N = 525)
  – Results reported for costs, QALYs and NMB

RESULTS REPORTED FOR NMB

• We report:
  – NMB and 95% CI for three ceiling ratios, $20,000, $50,000, and $80,000
  – Probability that NMB is greater than 0 for ceiling ratios ranging from 0 to $100,000 (acceptability curves)
  – Statistical tests of the homogeneity of NMB between the four individual countries for which the analyses were performed and the remaining pool of countries

Pooled and Country-Specific Estimates of Incremental Costs and QALYS

<table>
<thead>
<tr>
<th>Country</th>
<th>Costs Mean</th>
<th>95% CI</th>
<th>QALYs Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled</td>
<td>-847</td>
<td>-2015 to 316</td>
<td>0.08</td>
<td>0.04 to 0.12</td>
</tr>
<tr>
<td>C1</td>
<td>-802</td>
<td>-4895 to 2872</td>
<td>0.09</td>
<td>-0.02 to 0.22</td>
</tr>
<tr>
<td>C2</td>
<td>-932</td>
<td>-2647 to 654</td>
<td>0.08</td>
<td>0.01 to 0.16</td>
</tr>
<tr>
<td>C3</td>
<td>-2457</td>
<td>-6056 to 945</td>
<td>0.06</td>
<td>-0.03 to 0.14</td>
</tr>
<tr>
<td>C4</td>
<td>-452</td>
<td>-3195 to 2606</td>
<td>0.15</td>
<td>0.05 to 0.25</td>
</tr>
<tr>
<td>Other</td>
<td>283</td>
<td>-1243 to 1869</td>
<td>0.04</td>
<td>-0.01 to 0.10</td>
</tr>
</tbody>
</table>

Tests for interaction
Qual: p > 0.50
Quant: p = 0.65

Pooled and Country-Specific Estimates of Net Monetary Benefit For Selected Ceiling Ratios

<table>
<thead>
<tr>
<th>Cntry</th>
<th>Costs $20,000 Mean</th>
<th>95% CI</th>
<th>QALYs $20,000 Mean</th>
<th>95% CI</th>
<th>Costs $50,000 Mean</th>
<th>95% CI</th>
<th>QALYs $50,000 Mean</th>
<th>95% CI</th>
<th>Costs $80,000 Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled</td>
<td>2429</td>
<td>1157 to 3793</td>
<td>4801</td>
<td>2741 to 6953</td>
<td>7174</td>
<td>4171 to 10,3</td>
<td>7174</td>
<td>4171 to 10,3</td>
<td></td>
<td></td>
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<tr>
<td>C1</td>
<td>2570</td>
<td>-1959 to 7432</td>
<td>5224</td>
<td>-1521 to 13,073</td>
<td>7877</td>
<td>-1876 to 19,7</td>
<td>7877</td>
<td>-1876 to 19,7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>2509</td>
<td>400 to 4743</td>
<td>4876</td>
<td>768 to 8697</td>
<td>7242</td>
<td>1118 to 13,0</td>
<td>7242</td>
<td>1118 to 13,0</td>
<td></td>
<td></td>
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<tr>
<td>C3</td>
<td>3583</td>
<td>26 to 7445</td>
<td>5271</td>
<td>67 to 10,849</td>
<td>6990</td>
<td>-557 to 14,1</td>
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<tr>
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<td>3407</td>
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<td>-1639 to 788</td>
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<td>-1639 to 788</td>
<td></td>
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</tr>
</tbody>
</table>

Tests for interaction
Qual: p = 1.00
Quant: p = 0.51
EXAMPLE DISCUSSION

- In the example, we found little evidence of difference in the incremental costs, QALYS, and NMB associated with therapy for severe heart failure among the different countries that were evaluated.
- In this case, one may want to use the more precise trial-wide (i.e., pooled) estimate for each of the countries in the trial.
  - The pooled point estimate suggested that usual care plus active therapy dominated usual care alone, and the upper limit of the 95% confidence interval for the cost per QALY ratio equalled $3865.

EXAMPLE DISCUSSION (cont.)

- Could there be a difference in the country-specific results yet we not be able to detect it?
  - A qualified yes
- The power of the test of homogeneity is low
  - However, except for the result for 11 miscellaneous countries for which price weight data were not available, all of the country-specific evidence suggests that the therapy saved money and increased QALYS.

ESTIMATION

- An alternative to homogeneity tests is to use multi-level random-effects model shrinkage estimation to provide more precise estimates of the country-specific results than are yielded by separate -- and naive -- analysis of each country's costs and effects.
  - Borrow information from the mean estimate to add precision to the country-specific estimates.
  - These methods have the potential added advantage of providing better estimates of the uncertainty surrounding the pooled result than naive estimates of the trial-wide result.
**CURRENT DEBATE**

- "Exchangability"
  - One must make assumptions about whether:
    - The data should be shrunk to a single mean (a predisposition towards homogeneity) or
    - The data from some countries should be shrunk to one mean while the data from others should be shrunk to a second mean (a predisposition towards heterogeneity)

**IS WHAT WE OBSERVE REPRESENTATIVE?**

- These techniques assume that what we observed is a guide to what we did not observe
  - We use evidence of heterogeneity or the lack thereof across countries, practice patterns, levels of illness severity, etc., to determine whether the pooled results are applicable across countries, practice patterns, levels of illness severity, etc.

**IS WHAT WE OBSERVE REPRESENTATIVE? (cont.)**

- Techniques will fail if:
  - What we observed is so transformed by the study protocol that it is not a guide to what we would have observed had the therapy been used outside a trial
  - We desire to know about cost effectiveness in settings or populations that are unlike anything observed in the trial (e.g., the trial was conducted in tertiary care hospitals but the therapy actually will be delivered in community hospitals)
  - **NOTE:** If the heterogeneity test is thought to be inapplicable, that may mean we have no evidence of the therapy’s affect for use in decision analytic models that might be used to assess transferability

**PROBLEMS / POTENTIAL SOLUTIONS**

- Trials often have too few subjects per country
  - Modify designs so that more patients are enrolled in fewer countries
  - If infeasible, pool among similar types of countries, where similarity might be defined based on price weights, event rate in placebo group, etc
  - **Price weights**
    - While one need not obtain price weights for every country that participates in the trial, one should obtain price weights from a subset of countries stratified by level of economic development
TESTS HAVE TOO LITTLE POWER

- Use larger \( \alpha \) levels (e.g., 0.1 or 0.2) and look for larger differences between groups
- Pool across other relevant attributes, e.g.,
  - Characteristics of medical practice (e.g., types of centers and providers); characteristics of reimbursement patterns
  - Ex post: Pool countries with most similar results
- Principle: Given all the tests tend toward a finding of homogeneity, try to identify any evidence of heterogeneity that may exist

SAMPLE SIZE AND SHRINKAGE MODELS

- Shrinkage models may not be as affected by small sample sizes per country (although small sample sizes may again predispose one towards findings of homogeneity)
  - Small sample sizes may make it difficult to determine whether one should shrink to a common mean or to multiple means

TRIALS DON’T PROVIDE INFORMATION FOR COUNTRIES THAT DID NOT PARTICIPATE

- Characterize countries that participated in trials by their practice patterns and match nonparticipating countries to these patterns

CONCLUSIONS

- Issues of transferability are of growing importance as decision makers in more countries desire information about the likely economic impact of the adoption of new therapies
- Historically, have tended to do a poor job of estimation of transferability: price weights likely aren’t the primary source of variability when countries have similar economic conditions
Conclusions (cont.)

• Two recently proposed analytic techniques better address transferability issues
  – Each uses data from the trial to address these issues
  – Trade-off problems with power for problems with exchangability