

# PHARMACOECONOMICS

Wyeth Global Positioning Program  
November 2005

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## WHAT IS THE PROBLEM PHARMACOECONOMICS ADDRESSES?

"Because of growing pressure on the healthcare budget in The Netherlands, appropriate justification of current expenditures and future investments in public healthcare are becoming increasingly important...."

"It is anticipated that international pharmaceutical companies will increasingly invest in pharmacoeconomics while government staff will become more experienced in appraising the dossiers, thus resulting in an upward momentum in the quality and usability of pharmacoeconomic data...."

"From the Dutch government's perspective, the use of pharmacoeconomic evaluation in reimbursement decision-making should offer a true opportunity for pharmaceutical companies to present the added value for money of new drugs."

Oostenbruggen, et al. Penny and Pound Wise. Pharmacoeconomics from a Government Perspective. Pharmacoeconomics. 2005;23:219-26



## AGENDA

- Economic messages
- Basic Concepts
- Cost-Effectiveness Analysis
- Sampling Uncertainty
- Special Topics
- Discussion



## ECONOMIC MESSAGES

- Economic studies may convey a number of potential messages, which depend in part on the:
  - The disease and therapy under evaluation
  - The other therapies that are available to treat the condition
  - Interests of regulatory bodies, providers, payers, and patients
- Primary economic message
  - The therapy is good value for the cost.



### ECONOMIC MESSAGES (CONT.)

- Other messages
  - The disease poses a substantial burden to society in terms of morbidity, mortality, costs, and quality of life (QOL)
  - Therapy reduces this burden
- Could devote an entire workshop to each topic



### STUDY DESIGNS FOR SUPPORTING ECONOMIC MESSAGES

- Many different potential study designs are available to support these different messages
  - Clinical trials, decision analytic models, and observational studies can be used to support messages about value for the cost
  - Decision analytic models and observational studies to support messages about disease burden



### WHAT DATA / WHEN

- Phase I and II: Incidence and prevalence-based cost of illness
  - Incidence-based - lifetime costs of the disease for a cohort with incident disease
  - Prevalence-based - costs of disease during a given time period for prevalent cases
- Preplanning for phase III economic studies
- Cost / Efficacy studies in clinical trials
  - Provides economic data for registration, pricing, and early use



### WHAT DATA / WHEN: POST MARKETING STUDIES

- Cost / Effectiveness studies in usual care
  - Comparisons made in more realistic settings with more realistic protocols against comparators of interest to individual decision makers
  - Allow decision makers to assess whether results from phase III trials are generalizable to usual care
- Post marketing surveillance studies
  - Observational data to evaluate costs, effectiveness, and adverse experiences related to the drug



### GOOD VALUE FOR THE COST

- Cutting edge evaluation of the value for the cost supported by an evaluation from a randomized trial that included economic outcomes as primary or secondary endpoints of the trial
  - Short-term economic impacts directly observed; longer term impacts potentially projected by use of decision analysis
  - Reported results include point estimates and confidence intervals for estimates of incremental costs, outcomes, and comparison of costs and effects
  - Impact of sensitivity analysis judged by its impact on both the point estimates and the confidence intervals of the ratios



### EXAMPLE

Analysis	Point Estimate	95% CI
Incremental Costs	-713	-2123 to 783
Incremental QALYs	0.13	0.07 to 0.18
Cost-Effectiveness Ratios		
Principal Analysis	Dominates	Dom to 6650
Survival benefit		
-33%	Dominates	Dom to 9050
+33%	Dominates	Dom to 5800
Hospitalization costs		
-50%	Dominates	Dom to 5300
+50%	Dominates	Dom to 8400
Drug costs		
-50%	Dominates	Dom to 4850
+50%	Dominates	Dom to 8750
Discount rate		
0%	Dominates	Dom to 6350
7%	Dominates	Dom to 7000



### SELECTED COUNTRIES WITH NATIONAL GUIDELINES FOR ECONOMIC ASSESSMENT

Australia	Italy
Baltic countries	Netherlands
Belgium	New Zealand
Canada	Norway
Denmark	Poland
England & Wales	Portugal
Finland	Russian Federation
France	Scotland
Germany	Spain
Hungary	Sweden
Ireland	Switzerland
Israel	

<http://www.ispor.org/PEguidelines/index.asp>



### INFLUENCE OF ECONOMIC EVALUATIONS

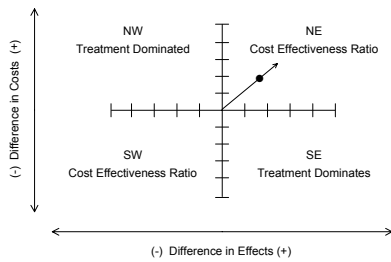
- Number of studies reporting the influence of economic evaluations on healthcare decision making

Degree of influence	"Micro"	"Meso"	"Macro"
	Physicians	MCOs, P&T committees, etc.	Nat decis makers, Hlth auth, Central formul, etc.
Minor	2	6	12
Moderate	4	3	6
Major	1	6	1
N, studies	8	20	22
N, respondents	3766	1430+	1159+

van Velden ME et al. Economic evaluations in healthcare programmes and decision making. *Pharmacoeconomics*. 2005;23:1075-82.



## COST-EFFECTIVENESS PLANE (I)



## TYPES OF ANALYSIS

- Cost-identification / cost-minimization
  - Estimates costs of an intervention, but not benefits
  - Appropriate when two therapies of equal efficacy are compared
- Cost-effectiveness analysis
  - Estimates costs and outcomes of intervention, but the two are measured in different units
  - When the outcomes are measured in QALYs or utilities, referred to as cost-utility analysis



## TYPES OF ANALYSIS (CONT.)

- Cost-benefit analysis
  - Estimate costs and benefits in the same (usually monetary) units



## TYPES OF COSTS

- Direct: medical or nonmedical
- Time costs: Lost due to illness or to treatment
- Intangible costs
- Types of costs included in an analysis depend on what is affected by illness and its treatment and what is of interest to decision makers
  - e.g., the Australian Pharmaceutical Benefits Scheme has indicated it is not interested in time costs



## COST-EFFECTIVENESS ANALYSIS

- Basic adoption formulation:

– Adopt if one can be confident that:

$$\frac{\text{Costs}_1 - \text{Costs}_0}{\text{Outcomes}_1 - \text{Outcomes}_0} = \frac{\Delta C}{\Delta Q} < R_c^*$$

– where  $R_c^*$  = maximum acceptable cost-effectiveness ratio (e.g., 50,000 per QALY)



## WHAT VALUE $R_c$ ?

- There is no general agreement on  $R_c^*$ , the maximum acceptable cost-effectiveness ratio
  - Can differ among decision makers
  - A single decision maker might consider use of different maximum acceptable cost-effectiveness ratios depending on other features of the decision problem



## NET MONETARY BENEFIT

- A composite measure (part cost-effectiveness, part cost-benefit analysis), usually expressed in dollar terms, that is derived by rearranging the cost-effectiveness decision rule:

$$(\Delta Q R_c^*) - \Delta C > 0$$

- Proposed primarily because it overcomes statistical problems that arise when estimating ratios



## NET MONETARY BENEFIT (CONT.)

- Advantages
  - Confidence intervals always defined; facilitates power calculations, allows patient-level statistical tests of value for the cost for specific values of maximum acceptable cost-effectiveness ratio, and facilitates calculation of the "value of information" statistic
- Disadvantages
  - Given there is little agreement about the maximum acceptable cost-effectiveness ratio, the estimate of NMB and its confidence interval for any one  $R_c$  is unlikely to provide sufficient information for policy decisions



## COST-EFFECTIVE DRUG PRICING

- If a drug is effective, there is some price at which it will be cost-effective
- Maximum price one can charge for drug 1 if one is to satisfy a maximum acceptable cost-effectiveness ratio:

$$p_{\max} = \frac{R_c^* \Delta Q + p_0 D_0 - \Delta OC}{D_1}$$

where  $p_{\max}$  = the maximum price that can be charged for drug 1;  $R_c^*$  = maximum acceptable cost-effectiveness ratio;  $\Delta Q$  = the difference in effectiveness;  $p_0$  = the price of the alternative drug;  $D_0$  = the quantity of alternative drug dispensed for the patient;  $\Delta OC$  = the difference in costs other than drug acquisition associated with the two drugs; and  $D_1$  = the quantity of drug 1 dispensed for the patient



## SAMPLING UNCERTAINTY

- An acceptable point estimate may not be sufficient evidence for adoption
  - A decision maker might ask "how certain are you that the therapy represents good value?"
- We use the data used in the evaluation to provide a measure of the precision of our estimates in the light of sampling uncertainty

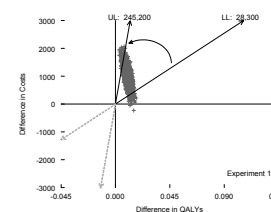


## COMMON MEASURES OF SAMPLING UNCERTAINTY

- Confidence intervals for cost-effectiveness ratios
- Confidence intervals for net monetary benefit
- Acceptability curves



## CONFIDENCE INTERVALS FOR COST-EFFECTIVENESS RATIOS



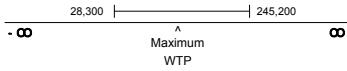
\*  $\Delta C = 1000$ ;  $SEC = 324$ ;  $\Delta Q = 0.01$ ;  $SEQ = 0.001929$ ;  $\rho = -.7102$ ;  $DOF = 498$

- Decision threshold: Is the cost-effectiveness ratio less than  $R_c^*$

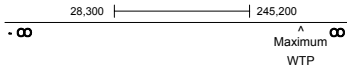


## CONFIDENCE STATEMENTS FOR EXPERIMENT 1

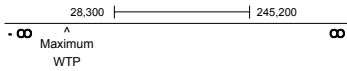
- 1) Not confident A differs from B



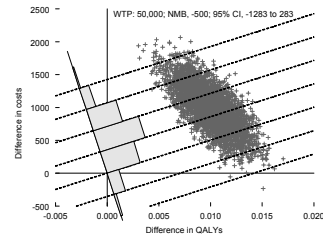
- 2) Confident A cost-effective compared to B



- 3) Confident B cost-effective compared to A



## CONCEPTUALIZING A CONFIDENCE INTERVAL FOR NMB

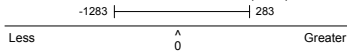


- Decision threshold: Is the difference greater than 0?

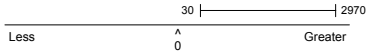


## CONFIDENCE STATEMENTS FOR EXPERIMENT #1

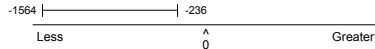
- 1)  $\lambda = 50,000$ : Not confident A differs from B (A - B)



- 2)  $\lambda = 250,000$ : Confident A net beneficial compared to B



- 3)  $\lambda = 10,000$ : Confident B net beneficial compared to A

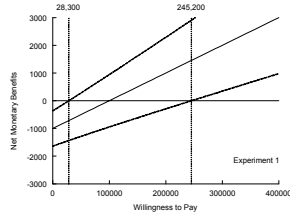


## CONFIDENCE STATEMENTS FOR EXPERIMENT #1 (CONT.)

- One must calculate separate CI for each policy-relevant maximum acceptable cost-effectiveness ratio
- CI -- and resulting policy inference -- derived for a single Rc (e.g., 50,000) may have little in common with CI -- and resulting policy inference -- derived for other values of Rc (e.g., 10,000 or 250,000)



### CONFIDENCE INTERVALS FOR NMB

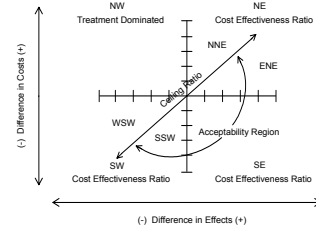


- What conclusions would you draw about one's maximum acceptable cost-effectiveness ratio and one's confidence in adopting or rejecting drugs A and B?



### QUANTIFYING UNCERTAINTY USING ACCEPTABILITY CURVES

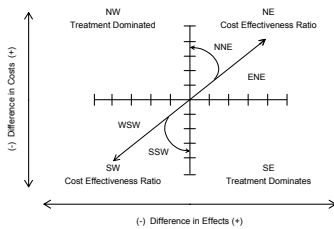
- Evaluation of the acceptability criterion is based on the probability that the estimated ratio falls below a specified  $R_c$



- The acceptability criterion is defined on the cost-effectiveness plane as a line passing through origin with a slope defined by  $R_c$ . Points from the cost/effect distribution falling in quadrants ENE, SE, and SSW satisfy the criterion



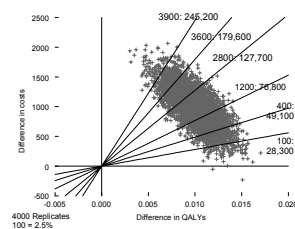
### ALTERNATIVE ACCEPTABILITY CRITERIA



- Given that there is no agreed upon maximum acceptable cost-effectiveness ratio for use in hypothesis testing of cost-effectiveness ratios, we routinely estimate the probability of acceptability over the range of possible positive values of willingness to pay



### ALTERNATIVE ACCEPTABILITY CRITERIA (II)

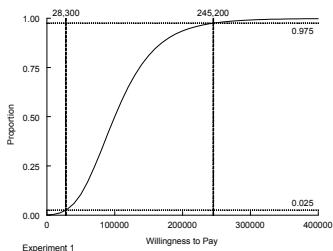


- In experiment 1, the ratio of \$245,200 per QALY saved has the equivalent of a one-tailed p-value less than 0.025 (3900/4000)
  - i.e., 2.5% of the distribution falls above the \$245,200 line)



### ACCEPTABILITY CURVES

- To be  $1-\alpha$  confident that the therapy is or is not acceptable, at  $Rc^*$ , either less than  $\alpha/2$  or more than  $1-(\alpha/2)$  of the density should be acceptable (e.g., to be 95% confident, either less than 2.5% should be acceptable or more than 97.5% should be acceptable)



- What conclusions would you draw about one's maximum acceptable cost-effectiveness ratio and one's confidence in adopting or rejecting drugs A and B?



### TAKE-HOME MESSAGES, MEASURES OF SAMPLING UNCERTAINTY

- If one's primary interest is identifying ranges of willingness to pay where:
  - One can be confident that therapy A is cost-effective compared to B
  - One can be confident that therapy B is cost-effective compared to therapy A, and
  - One cannot be confident that therapy A differs from therapy B

ALL 3 METHODS PROVIDE THE SAME INFORMATION



### TAKE-HOME MESSAGES, MEASURES OF SAMPLING UNCERTAINTY (cont.)

- CI for CER identify the boundaries between these ranges for a specific level of certainty (e.g., 95% CI define the boundaries where one can be 95% certain)
- The advantage of acceptability curves is that they report these boundaries for varying levels of certainty



### EXTENDING ADOPTION CRITERIA TO ACCOUNT FOR SAMPLING UNCERTAINTY

- There is no uniform approach to how decision makers evaluate measures of sampling uncertainty
- If decision makers were to adopt a pharmaceutical decision making paradigm, they might require  $p \leq 0.05$  evidence that a therapy is good value
- NICE isn't being that strict
  - If the point estimate is acceptable but the confidence intervals are wide, they may require more information either before or after approval

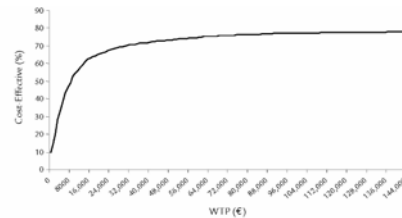


### LEVEL OF CONFIDENCE

- 95% generally accepted outside of economics, e.g. clinical endpoints
- Some discussion that we may not need to be as confident about economic "knowledge" as we do about other knowledge (e.g., 90% confidence?)
  - Concern: If I decide to give up health to save money, wouldn't I want to be confident about the savings?



### IS SAMPLING UNCERTAINTY BEING IGNORED?



- "The predicted cost-effectiveness ratios were well below the threshold values generally considered cost-effective. Adding clopidogrel to aspirin appeared to be cost-effective in this model analysis of patients with unstable CAD undergoing PCI in Sweden."

Lindgren P, Stenestrand U, Malmberg K, Jonsson B. The long-term cost-effectiveness of clopidogrel plus aspirin in patients undergoing percutaneous coronary intervention in Sweden. Clin Therapeutics. 2005;27:100-110.



### SPECIAL TOPIC #1 POWER AND ECONOMIC ANALYSIS

- Prior to the development of the literature that described confidence intervals for cost-effectiveness ratios, common to base sample size on the larger of the sample sizes needed for estimating pre-specified cost and effect differences
  - i.e., what sample sizes are required to identify a \$1000 difference in costs, and to identify a 10% reduction in mortality
- Current sample size methods based on the number of study subjects needed to rule out unacceptably high upper confidence limits for the cost-effectiveness ratio (equivalently, to rule out that the net monetary benefits of the intervention are less than 0)



### SAMPLE SIZE FORMULA

- Sample size for NMB uses the standard formula for continuous variables

$$n = \frac{2 \sigma_{\text{NMB}}^2 (1-R^2) (z_{\alpha/2} + z_{\beta})^2}{\Delta \text{NMB}^2}$$

- where  $\Delta \text{NMB}^2$  equals the square of the difference in mean NMB between the therapies;  $\sigma^2$  equals the variance of NMB; and  $R^2$  = variance explained in OLS (assuming OLS is used to predict the difference)



### INFORMATION REQUIRED TO ESTIMATE SAMPLE SIZE FOR ECONOMIC EVALUATION

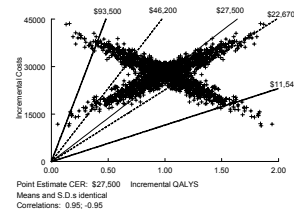
- While the sample size equation above is similar to that for any continuous variable, its error term is complicated by the fact that it includes variances and covariances for costs and effects

$$se^2(NMB) = s_{AC}^2 + R_c^2 s_{\Delta E}^2 - 2 R_c \rho s_{AC} s_{\Delta E}$$

- Basic data for such calculations include the magnitude of the incremental costs and outcomes; the standard errors for the difference in costs and outcomes; and the **correlation between costs and outcomes**



### CORRELATION BETWEEN COSTS AND EFFECTS



- Correlation between costs and effects can have dramatic effects on the confidence interval for the cost effectiveness ratio/NMB and thus on the sample size required to demonstrate value for the cost



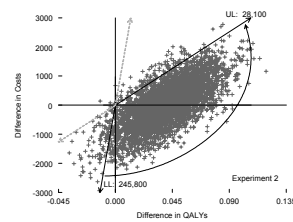
### POWER AND THE JOINT OUTCOME OF COST AND EFFECT

- What would your clinical colleagues conclude about this therapy's clinical effectiveness?
- Your economic colleagues about whether it saves costs

Variable	Mean	SE	T	P-value
Cost	20	776	0.26	0.98
QALY	.04	.0224	1.786	0.07



### POWER AND THE JOINT OUTCOME OF COST AND EFFECT (cont.)



- 95% CI for the cost-effectiveness ratio indicates that for willingnesses to pay ranging between \$28,100 and \$245,800, one can be 95% confident of adoption



**SPECIAL TOPIC #2  
HOW SHOULD ONE INTERPRET  
RESULTS FROM MULTINATIONAL TRIALS?**

- There has been growing concern that the pooled (i.e., average) clinical and economic results from multinational (or multicenter) 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 OF 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
  - 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
- 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)



**IMPACT OF UNIT COSTS VS OTHER  
VARIATION**

Country	Trial-Wide Effects		Country Specific Costs and Effects
	Unit Costs	Country Specific Costs $\square$	
1	46,818	5,921	11,450
2	57,636	91,906	60,358
3	53,891	90,487	244,133
4	69,145	93,326	181,259
5	65,800	**	**
Overall	45,892	45,892	45,892

\* Wilke RJ, et al. Estimating Country-Specific Cost- Effectiveness from Multinational Clinical Trials. Health Economics. 1998;7:481-93.

$\square$  Country-specific resource use  $\times$  Country-specific unit costs  
 \*\* New therapy dominates



## TWO APPROACHES TO TRANSFERABILITY

- 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

Cook JR, Drummond M, Glick H, Heyse JF. Assessing the appropriateness of combining economic data from multinational clinical trials. *Statist. Med.* 2003; 22:1955-76.

- Multi-level random-effects model shrinkage estimators

Manca A, Rice N, Sculpher JM, Briggs AH. Assessing generalisability by location in trial-based cost-effectiveness analysis: the use of multilevel models. *Health Econ.* 2005;14:471-485.



## HYPOTHESIS TESTS OF HOMOGENEITY

- Evaluate the homogeneity of the results from the different countries
  - If there is no evidence of heterogeneity, and if the test was powerful enough to rule out economically meaningful differences in costs, then 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 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



## ESTIMATION

- The second method uses 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



## DISCUSSION

- Because of growing pressure on healthcare budgets, justification of current expenditures and future investments in public healthcare are becoming increasingly important
  - Cost-effectiveness analyses are one means of justifying these expenditures
  - Justification often depends on demonstration that the value for the cost falls below a maximum acceptable cost-effectiveness ratio ( $Rc^*$ )



### DISCUSSION (cont.)

- Decision makers may also be interested in one's confidence level that the therapy represents good value
- Confidence intervals for cost-effectiveness ratios, confidence intervals for net monetary benefits, and acceptability all provide information about these confidence levels
- Evaluation of confidence level complicated by the fact:
  - Decision makers may not agree on the maximum acceptable cost-effectiveness ratio
  - Decision makers may not agree on how confident one must be before adoption

