
Critical Assessment of Economic Evaluations and Cost – Effectiveness Models

Part 9

Critical Assessment of Economic Evaluations

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Critical Assessment

- Is the methodology employed in the study appropriate and are the results valid?
- If the results are valid, are the data applicable to my setting and useful for my purpose(s)?

Elements of a Sound Economic Evaluation

- Was a well-defined question posed in an answerable form?
 - Did the study examine both the costs and effects of the service, program, or technology?
 - Did the study involve a comparison of alternatives? Was the alternative appropriate (placebo, usual care)?
 - Was a viewpoint for the analysis stated and was the study placed in a particular decision-making context?

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Elements of a Sound Economic Evaluation

- Was a comprehensive description of the competing alternatives given?
 - Were any important alternatives omitted? (placebo vs. usual care)
 - Should a do-nothing alternative have been included?

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Elements of a Sound Economic Evaluation

- Was effectiveness established?
 - Was the appropriate effectiveness measure used? Surrogates or disease endpoints? Was a QALY used?
 - Was effectiveness established through an RCT? If so, was the RCT designed to reflect real world practice and enroll real world patients?

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Elements of a Sound Economic Evaluation

- Was effectiveness established?
 - Was effectiveness established through an overview of the literature (meta-analysis)?
 - Were observational or nonrandomized studies or assumptions used to report effectiveness? If so, what are the potential biases?

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Elements of a Sound Economic Evaluation

- Were all the important and relevant costs and consequences for each alternative identified?
 - Was the range wide enough for the research question?
 - Did it cover all relevant viewpoints? (societal vs. managed care)
 - Were capital and overhead costs included? Were patient costs included (co-payments, time costs, productivity effects)?

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Elements of a Sound Economic Evaluation

- Were costs and consequences measured accurately and in appropriate physical units?
 - Were any of the identified resource units omitted from analysis?
 - Were there any special circumstances that made evaluation difficult (joint production)? How were these handled?

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Elements of a Sound Economic Evaluation

- Were costs and consequences valued correctly?
 - Were the sources of all values clearly identified? Market prices? Whose outcome values? (patients, physicians, general public)
 - How were nonmarket goods (volunteer time, donated space) valued?

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Elements of a Sound Economic Evaluation

- Were costs and consequences adjusted for differential timing?
 - Were costs and consequences that occur in the future adjusted to reflect differential timing? Time preference? Inflation? Project risk?
 - Were both costs and outcomes discounted?
 - Was justification given for the discount rate selected?

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Elements of a Sound Economic Evaluation

- Was an incremental analysis of costs and consequences of alternatives performed?
 - Were the additional costs generated by one alternative over another compared to the additional effects, benefits, or utilities gained?

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Elements of a Sound Economic Evaluation

- Was allowance made for uncertainty in the measurements and estimates of costs and consequences?
 - If data were stochastic, were appropriate statistical analyses performed?
 - If data were deterministic, were appropriate sensitivity analyses performed?
 - Were study results sensitive to changes in the values (or model assumptions)?

Elements of a Sound Economic Evaluation

- Did the presentation and discussion of study results include all issues of concern to users?
 - Were the conclusions to the study based on a presentation of a cost and consequences table or were they based on an index or ratio of costs to consequences? If a ratio, were they interpreted correctly?
 - Were the results compared to those of others who have investigated the same question? If so, were allowances made for possible differences in study methodology?

Elements of a Sound Economic Evaluation

- Did the presentation and discussion of study results include all issues of concern to users?
 - Did the authors discuss the generalizability of the results to other settings and populations?
 - Did the authors discuss issues of implementation, such as feasibility of adopting the preferred program?

Further Readings

- BMJ Working Party on Economic Evaluation. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313:275-283.
- Canadian Coordination Office for Health Technology Assessment (CCOHTA). Guidelines for the Economic Evaluation of Pharmaceuticals II: Canada. 1997. CCOHTA, Ottawa.

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Further Readings

- Commonwealth of Australia. Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee: Including Economic Analysis. 1994. Department of Health and Community Services, Canberra.
- Weinstein MC and Stason WB. Foundations for cost-effectiveness analysis for health and medical practices. NEJM 1977;296:716-721.

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Evaluating Cost-Effectiveness Models

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The Decision

- 2 drugs for osteoporosis-related fracture prevention
- Drug A
 - 20% ↓ vertebral fractures
 - 75% ↓ hip fractures
 - 1 month supply = \$125
- Drug B
 - 50% ↓ vertebral fractures
 - 65% ↓ hip fractures
 - 1 month supply = \$100

*All data from large, multicenter RCT's published in leading clinical journals

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Which Drug on the Formulary?

- a) Drug A
- b) Drug B
- c) Both
- d) Neither

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What are we preventing?

- Average Cost of Fracture
 - Vertebral: \$ 1,100
 - Hip: \$25,000

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An Alternative Presentation

	Vertebral		Hip	
	RFR	APR	RFR	APR
Drug A	20%	1.5%	75%	0.38%
Drug B	50%	1.0%	65%	0.33%

*Assumes vert fx 1/50 and hip fx 1/500 over 10 year timeframe

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In Other Words...

- NNT, Drug A
 - 67 patients to prevent 1 vert. fx.
 - 263 patients to prevent 1 hip. fx.
- NNT, Drug B
 - 100 patients to prevent 1 vert. fx.
 - 303 patients to prevent 1 hip. fx.

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Cost per fracture avoided

- Drug A
 - \$1.0 M per vertebral fx.
 - \$3.9 M per hip fx.
- Drug B
 - \$1.2 M per vertebral fx.
 - \$3.6 M per hip. fx.

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What have we done?

- Brought relevant data to the question
 - Different data sources
 - Different studies
- Integrated data to facilitate decision making
- You just did a model!

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Why Models?

- Clinical trials \neq health plan outcomes
 - Need to see how product will change health of members and cost of care
- Models are a systematic, structured aid to formulary decision making
 - Makes choices and tradeoffs explicit
 - Can see how key assumptions influence overall outcomes

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Model Problems

- Unregulated
- Methods not standardized
- Plenty of room for gaming

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Recipe List (for Disaster): 1 Pharmaceutical Company Model

- 1 cup evidence
- 1/4 cup complex mathematics
- 1/2 cup marketing
- 2 teaspoons handwaving (AKA expert opinion)

Directions: Mix well until ingredients are indistinguishable. Some P&T committees may find half-baked models more palatable than fully cooked.

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Key Elements of a Good Model

- Structure
- Data
- Outputs

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Checklist for Good Models: Structure

- Transparent
- Disease progression model
- Relevant timeframe
- Appropriate treatment pathways
- Good math

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Checklist for Good Models: Data

- Data quality is critical
 - Clinical
 - Epidemiologic
 - Cost
 - Quality of Life

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Checklist for Good Models: Outputs

- Face validity
 - Do the results make intuitive sense?
- Scientific validity
 - Publication in a quality peer-reviewed journal?

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Uncertainty in Models

- A well constructed model may still produce results with a great deal of uncertainty
- Like clinical data, uncertainty in CE models must be known before making policy decisions

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What are sources of uncertainty?

- Model structure (Structure)
 - vary structure
- Model parameters (Data)
 - vary parameters
- Modelling process (Outputs)
 - vary analyst!

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Quality of Uncertainty Evaluation in Published Models, 1992

- 24% failed to consider uncertainty at all
- 38% had inadequate sensitivity analyses
- 14% provided a good account of uncertainty

Briggs and Sculpher, Health Economics
1995;4:355 18

Evaluating Uncertainty: Simple sensitivity analysis

- One-way
 - One parameter in the model is varied to examine the effect on the results
 - E.g., as the effectiveness of a drug increases, the cost-effectiveness should also increase

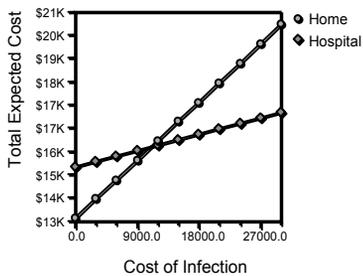
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Sensitivity Analysis

- Sensitivity analysis can be an extremely powerful tool for evaluating:
 - “correctness” of model
 - assumptions in model
 - uncertainty in model due to data uncertainty
 - validity of conclusions

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Sensitivity Analysis on Cost of Infection



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Limitations of one way sensitivity analysis

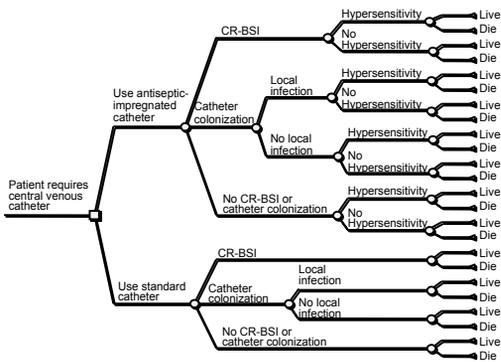
- Analyst selects
 - the parameters that are varied
 - the range of variation
- Interactions between parameters not captured
- Generally underestimates uncertainty

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Sensitivity Analysis Example: Cost-effectiveness of Antiseptic-impregnated central venous catheters

Veenstra et al. *JAMA* 1999;282:554-560

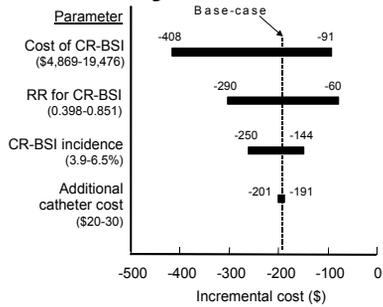
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Results

	Costs	CR-BSI	Death
Antiseptic Catheter	\$336	3.0%	0.45%
Standard Catheter	\$532	5.2%	0.78%
Difference	-\$196	-2.2%	-0.33%

One-way sensitivity analyses: Costs



Real-world example:

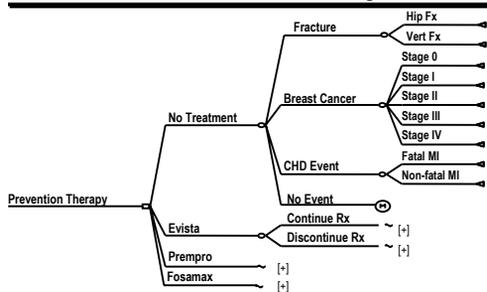
Cost-effectiveness of osteoporosis therapies

Osteoporosis Model Overview

- **Subjects: postmenopausal women**
 - prevention
 - treatment
- **Three therapies compared**
 - Hormone replacement therapy (HRT)
 - Alendronate (Fosamax)
 - Raloxifene (Evista)
- **Outcomes:**
 - hip fracture
 - coronary disease
 - breast cancer
- **Funding source:** Eli Lilly

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Structure Treatment Pathways



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Structure

Disease progression and time horizon?

- 6 year timeframe:
 - appropriate for osteoporosis?
 - relevant for decision makers?
- Clinical trials have been ~ 3 years
- ...timeframe of analysis is reasonable given course of disease, clinical data, and decision-maker's perspective

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Structure

Models clinical practice?

- All relevant treatment options?
 - Residronate, calcium, vit D not modeled
- Patient discontinuation accounted for
- ...model structure is reasonable representation of clinical pathways

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Structure

Endpoints relevant to decision making?

- Does not follow "U.S. Panel on Cost-Effectiveness Guidelines", e.g., cost/QALY
 - Quality and quantity of life is important but hard to conceptualize
- Endpoints are generally clinically and economically important, BUT
 - Model "outcomes" (CEA denominator) are events
 - MI, vertebral fracture, hip fracture, breast cancer

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Grouping Events in Numerator

- A problem if
 - (1) all endpoints receive equal weight in the denominator
 - (2) some events less important clinically than others
 - vertebral fracture = breast CA?
 - (3) The less important endpoints (vert fx) are influenced more by the drug than the important endpoints (hip fx >> breast CA)

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Structure

Calibrated to population-based evidence?

- Difficult...
 - 2 therapies are new technology
 - population-based (non-RCT) studies.
 - 1 therapy (HRT) never studied with RCT

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Structure

Transparency?

- No peer-reviewed publication or technical report
- Can actually go to model itself...

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Transparency: model inputs

Summary of Key Model Assumptions	
Cost of Fractures	Y0
Hip (Age 55)	\$ 26,740
Cost of Drugs	
Prempro	
Cost of Side Effects	
Prempro	\$200.00
Cost of MI	
Fatal	\$ 27,595.00
Non-fatal	\$ 47,347.00
Cost of Breast Cancer	
Stage III	\$ 91,451.00
Stage IV	\$ 49,099.00
Fracture Prevention Efficacy (RF)	
Hip (Age 55)	
Prempro	0.75
Edista	1
Fosamax	0.75
CHD Prevention Efficacy (RF)	
Breast Cancer Effects (RF)	
Continuation Rates	

Transparency: model inputs

55 Year Old Women	No Treatme
YEAR 0	
Percentage Full Compliance:	100.0000%
Probability of Hip Fracture:	0.0632%
Probability of Vert Fracture	0.1500%
Probability of Fatal MI:	0.1000%
Probability of Nonfatal MI:	0.2600%
Prob Stage 0 Breast Cancer:	0.0420%
Prob Stage I Breast Cancer:	0.1232%
Prob Stage II Breast Cancer:	0.0868%
Prob Stage III Breast Cancer:	0.0168%
Prob Stage IV Breast Cancer:	0.0112%

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Model transparency

- *For those who have access to the model*, it is reasonably transparent
 - no hidden components

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Cost data (first year)

- Breast cancer
 - \$31,451 Stage III
 - \$43,099 Stage IV
- Hip fracture
 - \$26,740
- MI
 - \$27,585 fatal
 - \$47,347 non-fatal

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Data

Valid Evidence? *Breast cancer*

- RCT, N = 7705 women with osteoporosis
- 60 mg or 120 mg raloxifene vs. placebo
- RR breast cancer = 0.24 (0.13-0.44)
- RR ER+ BrCA 0.10 (0.04-0.24)
- RR ER- BrCA 0.88 (0.26-3.0)
- Good evidence (from one study) on clinical endpoint

JAMA 1999;281:2189

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Data:

Valid Evidence? *Fracture*

- Same trial (MORE)
- RR vertebral fracture 0.7 (0.5-0.8) for 60 mg, 0.5 (0.4-0.7) for 120 mg
- RR non-vertebral fracture 0.9 (0.8-0.11)
- RR hip fracture 1.1 (0.6-1.9)
- But 2% increase in hip BMD (P<0.001)
- Surrogates are significant, but clinical and economic endpoint is not

JAMA 1999;282:637 41

Data

Valid Evidence? *CVD*

- Model assumptions:
 - Raloxifene 60 or 120 mg, HRT, or placebo*
 - LDL-C ↓ 12% raloxifene, 14% HRT
 - HDL-C ↑ -- raloxifene, 11% HRT
- Lipid profile influences risk of coronary events

JAMA 1998;279:1445 42

Data

Valid Evidence? CVD and HRT

- Large studies now question the value of HRT in reducing the risk of coronary endpoints despite favorable lipid effects*
- Impact of raloxifene's favorable lipid effects on risk of coronary disease is unknown

*See:
HERS study. JAMA 1998;280:605
NEJM 2000;343:522

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Data:

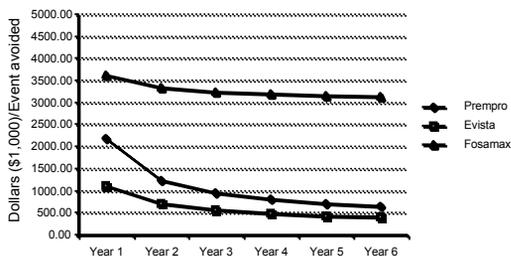
Valid Evidence? CVD and raloxifene

- May not be reasonable to assume CV benefit from raloxifene or HRT

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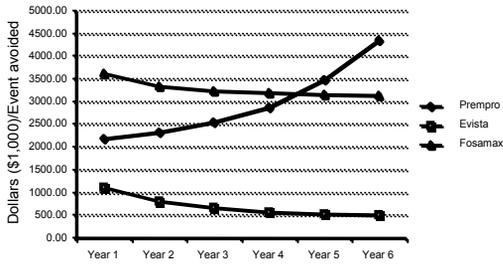
Outputs

Scenario 1: BrCA, HipFx, CVD



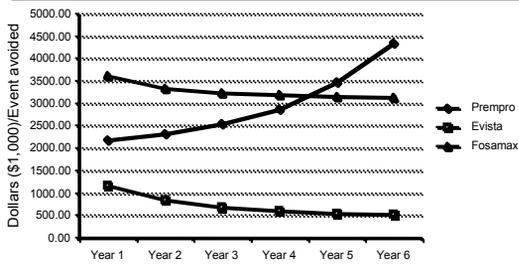
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Scenario 2: No CVD Benefit



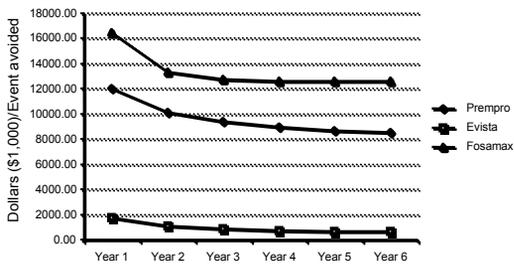
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Scenario 3: No CVD, No Hip Fx for Raloxifene



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Scenario 4: No CVD, No HipFx for raloxifene, No vert. fx. No BrCa for HRT



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Conclusion

- Raloxifene CE not sensitive to efficacy estimates for HipFx or CVD
 - Impact on breast CA “drives” the model
- If one accepts the clinical inputs and projections:
 - Cost-effectiveness of raloxifene may be as good as or better than alendronate or HRT

Evaluating Cost-Effectiveness Models

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Evaluation Costs – Effectiveness Models

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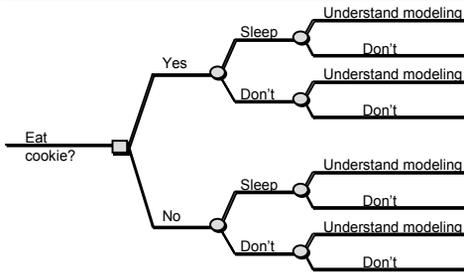
Criteria for Good Model Transparency

1) Model Structure

- Graphical representation of model process
- Should be disease-based
- Should be interpretable by clinicians

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Figure 1: Model Structure



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Model Transparency

2) Model Inputs

- Probabilities and Costs
- Sources of Data
- Range of Data

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Table 1: Model inputs

Parameter	Estimate	Range	Source
Prob. sleeping if cookie	0.10	0.05-0.15	Sullivan
Prob. sleeping if no cookie	0.20	0.15-0.20	Ramsey
Prob. understanding models if asleep	0.25	0.15-0.35	Veenstra
Prob. understanding models if not asleep	0.85	0.70-1.00	Watkins
Cost of cookie	\$1.00	\$0.50-\$1.50	Evans

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Model Transparency

3) Model Assumptions

- Explicit list provided

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Table 2: Model Assumptions

- Cookies are good
- Data from Sullivan et al is relevant to your population
- Cookies purchased from Cookies.Com
- You are not already asleep

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Model Transparency

4) Outputs

- Costs and outcomes presented separately
- Difference in costs and outcomes presented separately
- Incremental cost-effectiveness ratios

$$\frac{\text{Cost}_{\text{TxB}} - \text{Cost}_{\text{TxA}}}{\text{Effect}_{\text{TxB}} - \text{Effect}_{\text{TxA}}}$$

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Table 3: Results

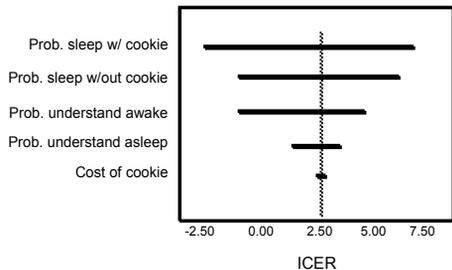
	Total Cost	Chance of understanding modeling
Cookie strategy	\$1,010.00	0.70
o Cookie strategy	\$1,009.50	0.50
Difference	\$0.50	0.20
Incremental Cost-Effectiveness Ratio (ICER)	\$2.50 to get one person to understand modeling	

Model Transparency

5) Sensitivity Analysis

- One-was sensitivity analysis run on all parameters
- Data presented in a "Tornado Diagram"

Figure 2: Tornado Diagram



Modeling example 2: DMARDS for Rheumatoid Arthritis

- RA:
 - Progressive, disabling disease
 - Requires long-term therapy with potentially toxic medications
- Major morbidities:
 - joint replacements, rehabilitation, and long-term institutionalization
- Treatment issue:
 - Monitoring costs can often account for 40-70% of the total costs of a medication, depending on the drug

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RA Therapy Question:

- Are newer, more costly therapies more cost-effective for RA than existing therapies? Specifically, will they:
 - Improve quality of life?
 - Produce significant lifetime cost savings by
 - Reduce monitoring costs?
 - Reducing expensive services such as joint replacements, rehabilitation, and long-term institutionalization?

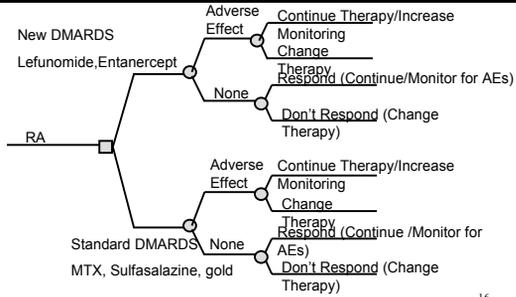
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The Rheumatoid Arthritis Economic Model

- An open Excel spreadsheet
 - Compares therapeutic options for the treatment of RA.
- Developed by G. Singh in response to a request from Regence BlueShield.

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RA Decision Model



Costs

- Drug costs
- Monitoring costs
 - CBC, LFT, etc.
- Adverse event treatment costs
- Morbidity costs
 - Joint replacements, rehabilitation, etc.

Measure of Effectiveness

- HAQ-DI
 - Arthritis-specific measure of disability
- QALY
 - Quality Adjusted Life Years

The Rheumatoid Arthritis Economic Model Database

- Calibrated on 13 years of ARAMIS data
 - Change in HAQ-DI linked to resource use, cost and health state preferences adjusting for confounding risk factors.
 - Ex. The mean annual change in costs for patients who progress from a DI score of 2 to 1 is \$5,600.
 - Changes in HAQ-DI for treatment group only (not change vs placebo).

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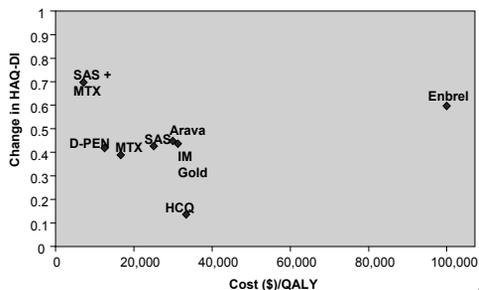
Cost-Effectiveness of Treatments for RA

Improvement in DI	Drug Cost Per Year					
	\$1,000	\$3,000	\$6,000	\$9,000	\$12,000	\$15,000
1	5,000	15,000	30,000	45,000	60,000	75,000
0.9	5,556	16,667	33,333	50,000	66,667	83,333
0.8	6,250	18,750	37,500	56,250	75,000	93,750
0.7	7,143	21,429	42,857	64,286	85,714	107,143
0.6	8,333	24,999	50,000	75,000	100,000	125,000
0.5	10,000	30,000	60,000	90,000	120,000	150,000
0.4	12,500	37,500	75,000	112,500	150,000	187,500
0.3	16,667	50,000	100,000	150,000	200,000	250,000
0.2	25,000	75,000	150,000	225,000	300,000	375,000
0.1	50,000	150,000	300,000	450,000	600,000	750,000

** Bolded Numbers Indicate an Acceptable Cost/QALY
Assumes: Straight line depreciation of benefits over 5 year period

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Outcomes and Cost-effectiveness of Treatments for Rheumatoid Arthritis



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Tricks of the Trade

1) Carefully review the clinical data

- Where did it come from?
 - FDA application?
 - Scientific/clinical journal?
 - Third party database?
 - Expert opinion?

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Tricks of the Trade

2) Looking for Bugs

- Set drug effectiveness to zero
 - are complications, life expectancy, etc. the same?
 - do total costs differ by drug therapy costs?
- Set any probability in the model to 0 or 1
 - Does the model break?

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Tricks of the Trade

3) Results: What happens in the first year after therapy?

- Are the outcomes/costs generated by the model similar to what one would expect based on what the drug is marketed to do?
- Results similar to RCT's?

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Tricks of the Trade

4) Sensitivity analysis:

Which parameters drive the results?

- cost of drug
- cost of complications
- incidence of complications (NNT)
- effectiveness of drug

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Tricks of the Trade

5) Explainability

– Can you explain the results to your spouse?

- The reason(s) why a drug is a good value should not be convoluted

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Summary

- Evaluating economic models is difficult and time consuming
- Focusing on model structure, data, and outputs, and using plenty of sensitivity analyses will make your job easier
- Ask for good presentations of models!
 - A good presentation of a bad model may be better than a bad presentation of a good model

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