Cost Effectiveness Analysis Alongside Randomized Clinical Trials

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Henry Glick
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Overview
1. Lecture 8:00
   1. Rationale and motivation
   2. Trial Design Issues
   3. Data elements: measures of cost and outcome
   4. Database design and management
   5. Analysis
   6. Reporting the results
2. Case Studies 9:45
   1. SWOG 5909
   2. Tirilazad SAH trial
   3. EPHESUS
3. Discussion Questions 11:30
4. Closing 12:00

Rationale
Joint RCT + CEA Studies

- Internal validity
- Efficiency
- Timeliness
Cautions

• External validity threats
  – Trial population vs. “typical” patients
  – Clinical care within a trial
    • Protocol-induced procedures
    • Motivated trial subjects
    • Skills of investigators.
    • Intensity of monitoring.
  – Endpoints (intermediate vs. disease outcomes)
  – Trial time horizon vs. disease history
• Burden of collecting economic data
  – Sample size and power
• Different purposes for RCT vs. CEA
  – “Does it work” vs. “Is it good value?”

Sample Selection for a Migraine Study

Trial Design
4 Constraints, 4 Considerations

• Product Cycle
• Endpoints
• Follow-up period
• Audience
Study Objectives

- Clinical Trial
  - H₀: μₐ = μₐ versus an alternative H₁: μₐ = μ₉, where μ is a clinical outcome of interest (e.g., blood pressure) and a and b are the competing interventions
- Incremental cost-effectiveness
  - R = incremental cost-effectiveness ratio
  - ΔC = difference in costs
  - ΔW = difference in effects

Issues for Power Calculations

- What hypothesis are we testing?
- Are formulas available to estimate sample size for a joint clinical/economic trial?
  - How precise are they?
- Where does one turn to obtain data to populate such formulas?
- What to do when prior data are unavailable?

Searching for Power

\[ L_{CE} \leq \frac{\Delta C}{\Delta W} \leq U_{CE} \]

\[ \Delta W \]

\[ \frac{1 - \alpha}{2} = 0.025 \]
Hypotheses for a clinical trial evaluating cost-effectiveness

- **H_0**: \( R = R_{\text{max}} \) versus **H_1**: \( R < R_{\text{max}} \)
  - \( R \) is the incremental cost-effectiveness of the experimental intervention
  - \( R_{\text{max}} \) is a pre-specified threshold

- What value for \( R_{\text{max}} \)?
  - Budgetary factors usually dictate the number of subjects that can be enrolled in the trial.
  - Solve for \( R_{\text{max}} \) using accepted levels of power \((1-\beta)\) and significance \((\alpha)\).

Power Calculations

Crib Notes

- **Fieller’s**: Simple algebra, but be sure to correctly interpret counterintuitive confidence intervals
  - Need to specify correlation between \( \Delta C \) and \( \Delta E \)
- **Bayes’**: Relatively simple, but many (especially clinical trialists) don’t like Bayes Theorem
  - Need to specify correlation between \( \Delta C \) and \( \Delta E \)
- **Bootstrapping**:
  - Very robust, but computationally intense
  - Don’t need to specify correlation between \( \Delta C \) and \( \Delta E \) (because it is directly estimated)

Correlation between \( \Delta C \) and \( \Delta E \)

Point Estimate CER: $27,500
Means and S.D.s identical
Correlations: 0.95; -0.95

\begin{table}
\begin{tabular}{|c|c|c|c|}
\hline
\( \Delta C \) & \( \Delta E \) & CER & Incremental QALYs \\
\hline
\$9,500 & \$9,500 & $27,500 & \\
\$6,200 & \$6,200 & $22,870 & \\
\$27,500 & \$27,500 & $11,545 & \\
\$46,200 & \$46,200 & $93,500 & \\
\hline
\end{tabular}
\end{table}
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

<table>
<thead>
<tr>
<th></th>
<th>Δ</th>
<th>SE</th>
<th>T</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>20</td>
<td>776</td>
<td>0.26</td>
<td>0.98</td>
</tr>
<tr>
<td>QALY</td>
<td>.04</td>
<td>.022</td>
<td>1.786</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Power and the Joint Outcome (2)

- 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

Data Elements
Tracking Costs and Outcomes

“You can’t always get what you want… but get what you need”
Tracking Resource Use: Considerations

- What is available?
  - Medical chart abstracts
  - Health insurance claims
- What resources drive the difference between treatment and control?
  - Drug costs, hospital days, etc.
- Who will collect the information?
  - Patients
  - Study site personnel

CEA End Point Considerations

- Audience
  - Regulatory
  - Clinical
- Clinical trial endpoints
  - Intermediate vs. final
  - Ad hoc vs. summary measures
- Follow-up period
- Available resources
CHANCE BOARD

<table>
<thead>
<tr>
<th>Choice A</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfect Health</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
</tbody>
</table>

For the rest of your life you:
- Think, remember and talk clearly
- Get around with some difficulty
- Perform self care with some difficulty
- Are in severe physical pain or discomfort

EuroQol questionnaire (EQ-5D)

MOBILITY
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

SELF-CARE
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework family or leisure activities)
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

PAIN/DISCOMFORT
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

ANXIETY/DEPRESSION
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

Database Design and Management

- Integrate collection and management of the economic data fully with the clinical CRFs
- Don’t forget the consent forms!
  - Include permission to collect economic data, particularly when:
    - Gathered from third party databases
    - Includes pre- and/or post-trial records
- Identifiers to link databases
Take Home Points
Trial Design
• Effectiveness trials preferred to efficacy
• Avoid intermediate endpoints and short follow-up
• Describe power and ability to test hypotheses, given the trial sample size
• Disaggregate clinical endpoints used in economic evaluations

Take Home Points:
Trial Design
• Obtain health state utilities directly from the study population
• Track all key healthcare resources use by patients participating in the trial
• Valuation of intermediate endpoints discouraged

Analysis
• Guiding Principles
• Trial Cost Analysis
• Analysis Issues for Outcomes
• Missing Data
• Modeling beyond the time horizon of the trial
• Summary Measures
• Uncertainty
• Identifying and addressing threats to external validity/generализability
• Subgroup Analysis
Analysis: Guiding Principles - 1

- A Data Analysis Plan (DAP) should be developed prior to unblinding.
  - Tests of hypotheses for resource use, cost, and/or cost-effectiveness should be pre-specified in DAP.
  - Regression or other multivariable analyses can be used to correct for imbalances or improve power but variables and other factors (e.g., stepwise criteria) should be included in the DAP.
  - If appropriate, subgroup analyses or use of non-ITT samples should be included in the DAP.
  - Analyses not specified in the DAP should be identified as post-hoc or exploratory in subsequent reports.
  - Methods used should be transparent to relevant audiences.

Analysis: Guiding Principles - 2

- Basic analytic approaches should be applied consistently for each pharmacoeconomic measure.
  - The same time horizon should be used for costs and outcomes within an analysis (although multiple analyses with different time horizons can be done).
  - A within-trial analysis should be conducted, even when modeling beyond the time horizon of the trial is planned.
  - Future costs and benefits should be discounted (when included in summary measures such as the CE ratio).
  - An assessment of uncertainty due to sampling variability and sensitivity analyses around key parameter assumptions should be conducted.
  - Missing and/or censored data should be addressed in the analysis.
  - Use frequentist vs. Bayesian techniques per trial design.

Trial cost analysis - 1

- In most cases, calculate total cost for each patient as the sum of utilization costs (quantity times unit cost for each resource type).
  - Methods that involve censoring may require variations on this approach.
  - Ensure that unit cost estimates match resource quantities measured.
  - In multinational trials, use PPP-adjusted exchange rates to get costs in a common currency.
- Review/describe characteristics of the total cost and key resource utilization data
  - Distribution; nature of data
  - May wish to analyze key resource quantities, e.g., hospital LOS.
Trial cost analysis - 2

• Sources for costs should be listed
  – E.g., Medicare reimbursements, country price lists
  – Methods for imputing unit costs, if needed, should be described
  – Include key unit costs in a table or appendix to report
• The objective of the cost analysis is to measure differences between means
  – Transformation/re-transformation or robust methods may be appropriate to handle significant deviations from normality
  – Medians may be analyzed but should not used in CE ratios

Trial cost analysis - 3

• Methods - univariate
  – T tests, one way ANOVA (parametric)
  – Bootstrapping, randomization tests (non-parametric)
• Methods - multivariate
  – Ordinary least square regression
  – Box-Cox transformations
  – Generalized linear models
  – Two-stage analyses
    Often best to use several types and compare
• Guidance/warnings in selecting analysis options

Analysis issues for outcomes

• Methods should be transparent
  – Consistent with product labeling (for drugs)
  – Use technical level appropriate to data, but more complex methods may need to be compared to simpler methods for some decision-makers
  – Use of surrogate markers within accepted clinical norms
• Analytic techniques should be appropriate to:
  – Type of variable (dichotomous, categorical, continuous, duration, censored, etc.)
  – Type of endpoint (end-of-treatment comparison, change from baseline, area under curve, longitudinal, etc.)
• Analysis of means or event probabilities are most typical for use in cost-effectiveness ratios
Missing data

- Missing data are inevitable
  - Ex: missing patient surveys, survey item nonresponse, utilization data
  - Missing at random less of a problem than not at random
- Report summary statistics for missing data
  - amount of missingness (costs and outcomes)
  - whether missing data likely to be MCAR, MAR, or NIM
- Describe method for addressing missing data, including software packages used
  - E.g., imputation techniques, weighting, pattern mixture models
  - State whether method for the CEA differs from the method used for the clinical trial
- Report whether main outcomes utilized imputed values
  - If imputation substantially alters the results, the alternative outcome should be reported in an appendix

Modeling beyond the time horizon of the trial

- Important when long-term costs or outcomes are altered by treatment, or only surrogate endpoints captured during trial
  - Justify any extension of treatment effects beyond trial
- Ground the model on data from the trial
  - e.g., use parametric survival models from the trial, especially if treatment continuing
- When modeling post-treatment outcomes based on non-trial data, match patient characteristics closely
  - preferably based on multivariable models
- Report effects of long-term health care costs not directly related to treatment
- Calculate CE ratios at several time points, both within trial (outcomes trials) and beyond
  - the “trajectory” of CE ratios may be informative

CE Ratios at Several Time Points

<table>
<thead>
<tr>
<th>Years of Follow-up</th>
<th>Point Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within the trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Dominated 168,884 to Dominated</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>282,857</td>
<td>45,577 to Dominated</td>
</tr>
<tr>
<td>3</td>
<td>73,529</td>
<td>Dominates to Dominated</td>
</tr>
<tr>
<td>4</td>
<td>12,074</td>
<td>Dominates to Dominated</td>
</tr>
<tr>
<td>5</td>
<td>15,258</td>
<td>Dominates to 122,772</td>
</tr>
<tr>
<td>Longer term projection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>12,246</td>
<td>Dominates to 42,263</td>
</tr>
<tr>
<td>15</td>
<td>8,578</td>
<td>Dominates to 26,721</td>
</tr>
<tr>
<td>20</td>
<td>7,320</td>
<td>681 to 21,841</td>
</tr>
</tbody>
</table>
Summary measures

A variety of summary measures can be used to combine costs and consequences (C&C):

- **Ratio measures**
  - cost-effectiveness and cost-utility ratios
- **Difference measures**
  - net monetary benefits and cost-benefit measures
- **Probability measures**
  - characterize the likelihood the incremental costs and benefits fall in a particular region of the CE plane

Summary measures should be based on incremental analyses of treatments being compared

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Uncertainty - 1

- Sampling (stochastic) and other sources of variability exist in estimates
- Addressing sampling uncertainty:
  - Around both within-group means group and between-group differences in means
  - Construct 95% confidence intervals for individual endpoints, and for CE ratios
  - For CE ratios: Fieller theorem method or bootstrap; CI possibly undefined
  - Cost-acceptability curves are recommended
    - Fieller method, bootstrap, or net monetary benefit C.I's

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Uncertainty - 2

- Addressing non-stochastic uncertainty
  - Sensitivity analysis, e.g., parameter assumptions; when both are present, show revised CI's within scenarios
  - Probabilistic sensitivity analysis now recommended by NICE
- Imputation-related uncertainty
  - Report results from different imputation methods
  - Consider bootstrapping entire imputation and estimation process
Identifying and addressing threats to external validity/generalizability

A. Threats due to "artificiality" of trials
- Clinical trials have high internal, but lower external validity
- Threats to external validity come from:
  - Protocol-driven utilization, especially when it affects outcomes
  - Unrepresentative recruiting centers
  - Unrealistic inclusion and exclusion criteria
  - Monitored compliance
- Address these issues
  - Prospectively:
    - Trial design phase (i.e., make the trial more naturalistic)
  - Retrospectively:
    - Sensitivity analyses (e.g., to assess impact to protocol-driven utilization)
    - Regression analyses (e.g., to allow for estimating effects on different populations)

B. Threats due to international differences
- Unit costs, practice patterns, outcomes, etc., may differ across countries in int'l trials
  - Pooled results not representative of any one country
  - Sample size not large enough to analyze countries separately
  - Many countries, however, want data representative of their own systems
- Approaches
  - Hypothesis tests of homogeneity of results across countries
  - Multivariable regressions to adjust for gross country effects
  - Multi-level random effects model with shrinkage estimators

Subgroup analysis
- Dangers of spurious sub-group effects well known
- Yet economics requires a marginal approach
  - Subgroup analysis vital to decision-makers
- Care should be taken to employ robust methodology for subgroups
  - Splitting of data/stratification should be avoided
  - Focus should be on testing treatment interactions on the absolute scale, or absence of interaction in relative treatment effects
  - Justification for choice of scale
Reporting the Results

- Adhere to minimum reporting standards for all economic analyses*
- Include a general description of the clinical trial and key clinical findings
- Distinguish economic data collected as part of the trial versus data not collected as part of the trial

*See USPSTF 1996, Drummond et al BMJ 1996

Reporting the Results

- Report the amount of missing data
  - If imputation methods are used, describe them
- Describe methods used to construct and compare costs and outcomes, and to project costs and outcomes beyond the trial period

Reporting the Results

- Include summaries of resource use, costs, and outcome measures, including point estimates and measures of uncertainty
- Report results for the time horizon of the trial, and for projections beyond the trial (if conducted)
- Use graphical displays for results not easily reported in tabular form
  - e.g., cost-effectiveness acceptability curves, joint density of incremental costs and outcomes
Reporting the Results

<table>
<thead>
<tr>
<th>Effectiveness data</th>
<th>Resource utilization and costs</th>
<th>Incremental cost-effectiveness</th>
<th>Other analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective data should always be presented (discounted and undiscounted)</td>
<td>All resource utilization should always be presented (undiscounted)</td>
<td>An ICER with confidence intervals should be included</td>
<td>Other analyses, eg. regression analysis, to test drivers of costs and effectiveness are also important</td>
</tr>
<tr>
<td>If QALYs are used, the QALY weights and the LYS should be reported separately</td>
<td>Unit costs (prices) should be included</td>
<td>Other techniques, eg. responsiveness and acceptability curves, can also be included</td>
<td>Further analyses, eg. to address the internal validity, are also recommended</td>
</tr>
<tr>
<td>Cost data should be presented (per year and aggregated), separated by drug, other health care, and productivity costs (all discounted)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case Example 1

Economic Analysis of SWOG 9509: Vinorelbine/Cisplatin versus Paclitaxel/ Carboplatin for Advanced Non-small Cell Lung Cancer

Scott Ramsey1, Carol Moinpour1, Laura Lovato1, Karen Kelley2, Cary Presant3

1Fred Hutchinson Cancer Research Center
2University of Colorado Health Sciences Center
3Los Angeles Oncology Institute/St. Vincent Medical Center
**SWOG 9509: PC vs VC**

Untreated Patients with Stage IIIb and IV NSCLC

<table>
<thead>
<tr>
<th>Randomized</th>
<th>Paclitaxel 225 mg/m² + Carboplatin AUC 6 q 3 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vinorelbine 25 mg/m² + Cisplatin 100 mg/m² q 4 wks</td>
</tr>
</tbody>
</table>

**Economic Analysis Alongside SWOG 9509**

- Research question:
  - For patients with advanced non-small cell lung cancer:
    - Estimate the cost-effectiveness of vinorelbine + platinum vs. paclitaxel + carboplatin

**Overview**

- Perspective:
  - Health insurer responsible for direct medical costs
- Time horizon:
  - Cost and outcomes over the duration of observation (25 months)
- Outcomes:
  - Life expectancy (cost/life-year gained)
  - Disease specific QOL (no utilities)
Funding

• Joint sponsorship by the manufacturers of the competing products
  – Navelbine (Glaxo Wellcome)
  – Taxol (BMS)

Tracking Health Care Resource Use: Issues

• Multiple study sites with widely varying billing records
• Chemotherapy administered in outpatient and inpatient settings
• Need to track both present and future cancer-related health care
  – hypothesis: initial therapy may affect long term health care utilization*


Tracking Health Care Use: Issues

• More than 60 participating study sites across the United States
• Not feasible to collect patient insurance records
• Detailed resource use forms very burdensome
Tracking Health Care Use: Solution

- Discussed resource issues with trial clinical practices committee
- Limit health care utilization tracking to:
  - Very expensive items (e.g., hospital days, CT scans, growth factors)
  - Resources that might vary greatly between treatment arms (e.g., anti-nausea medications)
- CRA training sessions
  - Study leaders met with site staff to address potential issues that might arise when tracking care outside the SWOG institution and to identify solutions
- Two resource forms created:
  - first 6 months of the study
  - a form tracking most protocol and nonprotocol resource use
  - month 6 through the end of the observation period
  - less detailed second form tracking the most costly resources consumed from
- Additional resources secured for site CRAs to fill out forms

<table>
<thead>
<tr>
<th>Resource category</th>
<th>Includes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical procedures</td>
<td>Chest x-ray, MRI of chest, MRI of abdomen, MRI of brain, chest CT, abdomen CT, brain CT, bone scan, bone x-ray, audiogram, electrocardiogram, thoracentesis, and laboratory tests</td>
</tr>
<tr>
<td>Supportive care</td>
<td>Antiemetics (5-HT3 antagonists and others), bone pain therapy, antibiotics (infusion only), growth factors (e.g., G-CSF/rhG-CSF, GM-CSF/lenograstim, GM-CSF/hirudin)</td>
</tr>
<tr>
<td>Blood products delivery</td>
<td>Red blood cells and platelets</td>
</tr>
<tr>
<td>Protocol chemotherapy</td>
<td>Inpatient (ICU vs. non-ICU) and outpatient</td>
</tr>
<tr>
<td>Drug</td>
<td>Chemo given each cycle</td>
</tr>
<tr>
<td>Nonprotocol therapy</td>
<td>2nd and 3rd line chemotherapy and radiation therapy</td>
</tr>
<tr>
<td>Days/Visits</td>
<td>Emergency room visits, hospital days (ICU and non-ICU), home-based hospice, hospital-based hospice, nursing home stay, home care visits, and physician officer/pain service visits</td>
</tr>
</tbody>
</table>

Protocol and Nonprotocol Resource Use

Protocol Related
- Chemotherapy
- Administration
  - Inpatient
  - Outpatient

Non Protocol
- Medical imaging procedures
- Blood products
- Supportive care medications
- Non-protocol therapy
  - Radiation
  - 2nd and 3rd line chemotherapy
- Medical care days
  - Outpatient & ER visits
  - Inpatient days
  - Hospice days
Price Weights

<table>
<thead>
<tr>
<th>Resource</th>
<th>Valuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital days (ICU, non-ICU, ER visits)</td>
<td>National survey (Millman and Robertson)</td>
</tr>
<tr>
<td>Medication costs</td>
<td>Average Wholesale Price (Red Book)</td>
</tr>
<tr>
<td>Nursing home care</td>
<td>National survey (Millman and Robertson)</td>
</tr>
<tr>
<td>Office visits, physician fees</td>
<td>Medicare fee schedule</td>
</tr>
<tr>
<td>Radiology, laboratory, outpatient procedures</td>
<td>Medicare fee schedule</td>
</tr>
</tbody>
</table>

Cost Analysis

- Kaplan Meier Sample Average Estimator
  - 95% CIs using method of Lin et al.

- Costs for treatment arms were compared with a 2-sided t-test

- In secondary analyses, important cost components compared after adjustment for multiple comparisons (Bonferroni method)
SWOG 9509: PC vs VC
Quality of Life Analysis at 13 weeks

<table>
<thead>
<tr>
<th></th>
<th>VC (N = 55)</th>
<th>PC (N = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>Stable</td>
<td>36%</td>
<td>37%</td>
</tr>
<tr>
<td>Declined</td>
<td>45%</td>
<td>46%</td>
</tr>
</tbody>
</table>

SWOG 9509: PC vs VC
Quality of Life Analysis at 25 weeks

<table>
<thead>
<tr>
<th></th>
<th>VC (N = 30)</th>
<th>PC (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>37%</td>
<td>28%</td>
</tr>
<tr>
<td>Stable</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td>Declined</td>
<td>40%</td>
<td>39%</td>
</tr>
</tbody>
</table>

p=NS

Analysis Issue 1
No Difference in Survival, QOL

- CEA changed to Cost-Minimization Analysis
  - Consider outcomes to be comparable for both therapies
  - Goal: identify least costly therapy
Analysis Issue 2
• During the trial, we noted that an unexpectedly high proportion of patients were receiving salvage chemotherapy in both arms of the study (190/408 patients).
• Took additional steps to determine treatment costs for these services.
• Identified all who received salvage therapy. Of that group, we randomly selected 57 patients for a detailed chart audit (24 patients in the vinorelbine plus cisplatin arm and 33 patients in the carboplatin plus paclitaxel arm; budgetary limitations prevented full sampling).
• Study coordinator reviewed charts for that group of patients to identify the type of salvage therapy received, dosing schedules, and duration of therapy.
• Applied the proportions of patients receiving specific sequences of salvage therapy in the sample to the total number of patients in each treatment arm who had salvage therapy.

Analysis Issue 3: Missing Data

<table>
<thead>
<tr>
<th>Form</th>
<th>Response Rate</th>
<th>Number Submitted</th>
<th>% Submitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Month</td>
<td>444</td>
<td>396</td>
<td>89%</td>
</tr>
<tr>
<td>25 Week</td>
<td>363</td>
<td>301</td>
<td>83%</td>
</tr>
<tr>
<td>13 Month</td>
<td>280</td>
<td>202</td>
<td>72%</td>
</tr>
<tr>
<td>18 Month</td>
<td>152</td>
<td>89</td>
<td>59%</td>
</tr>
<tr>
<td>25 Month</td>
<td>66</td>
<td>24</td>
<td>36%</td>
</tr>
</tbody>
</table>

Resource Utilization Form Response Rates

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Vinorelbin + Cisplatin</th>
<th>Carboplatin + Paclitaxel</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>90</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>84</td>
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<td>12</td>
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<td>18</td>
<td>74</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>24</td>
<td>61</td>
<td>47</td>
<td>54</td>
</tr>
</tbody>
</table>
### Overall Average Costs, Per Participant

<table>
<thead>
<tr>
<th>Resource</th>
<th>Cis + Vinorelbine (N=186)</th>
<th>Carbo + Paclitaxel (N=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Procedures*</td>
<td>$2,637</td>
<td>$3,161</td>
</tr>
<tr>
<td>Blood Products</td>
<td>$166</td>
<td>$182</td>
</tr>
<tr>
<td>Supportive Care Meds</td>
<td>$4,804</td>
<td>$4,339</td>
</tr>
<tr>
<td>Prot Chemo Deliv*</td>
<td>$2,199</td>
<td>$1,007</td>
</tr>
<tr>
<td>Prot Chemo Drug*</td>
<td>$5,069</td>
<td>$16,732</td>
</tr>
<tr>
<td>Non-Protocol Therapy</td>
<td>$8,372</td>
<td>$7,037</td>
</tr>
<tr>
<td>Medical Care Days/Visits</td>
<td>$9,964</td>
<td>$11,062</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$33,209</strong></td>
<td><strong>$43,522</strong></td>
</tr>
</tbody>
</table>

* = Significant p value

### Cost analysis example: SWOG study projections

![Graph showing average costs over time](image)

*Fig. 1: Estimate of mean cumulative costs 2 years after randomization (dashed line = carboplatin plus paclitaxel; solid line = vinorelbine plus cisplatin). Costs are from a model to account for medical care spending. The costs in year 3 are discounted at 3%, whereas all other expenses are discounted to year 0. Vertical bars represent 95% confidence intervals for individual intervals.*

### Treatment-Related Service Expenditures*

*(Inpt, Outpt, Home Care)*

<table>
<thead>
<tr>
<th>Resource</th>
<th>Cisplatin + Vinorelbine (N=186)</th>
<th>Carboplatin + Paclitaxel (N=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiemetics (5HT3 Antagonists)</td>
<td>$2,358</td>
<td>$2,783</td>
</tr>
<tr>
<td>Growth factors</td>
<td>$654</td>
<td>$536</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>$2,743</td>
<td>$2,654</td>
</tr>
</tbody>
</table>

*Average expenditure per enrollee in each arm
Use of Hospital and Outpatient Services During Protocol Chemotherapy*

<table>
<thead>
<tr>
<th>Resource</th>
<th>Cisplatin + Vinorelbine</th>
<th>Carboplatin + Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>InPt, ICU days</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>InPt, Non-ICU days</td>
<td>0.77</td>
<td>0.35</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>10.56</td>
<td>4.70</td>
</tr>
</tbody>
</table>

*Averages per enrollee in each arm

Non-Protocol Health Care Utilization*

<table>
<thead>
<tr>
<th>Resource</th>
<th>Cisplatin + Vinorelbine</th>
<th>Carboplatin + Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER Visits</td>
<td>0.68</td>
<td>0.71</td>
</tr>
<tr>
<td>Office Visits</td>
<td>1.95</td>
<td>3.01</td>
</tr>
<tr>
<td>Hospital days</td>
<td>2.48</td>
<td>3.11</td>
</tr>
<tr>
<td>Nursing home days</td>
<td>2.35</td>
<td>2.00</td>
</tr>
<tr>
<td>Hospice days</td>
<td>8.62</td>
<td>9.21</td>
</tr>
</tbody>
</table>

*Averages per enrollee in each arm

Case Example 2
Tirilazad Study

• Phase 3 trial of tirilazad mesylate in acute treatment of subarachnoid hemorrhage (for up to 14 days post-SAH)
• Multinational RCT in 11 countries:
  – 9 EU + Australia and New Zealand
  – 1023 patients total, across 3 dose groups + vehicle (placebo)
  – In-hospital drug treatment w/ 3 mo. follow-up
  – Primary outcomes: Clinical vasospasm
  – Secondary outcomes: Survival, Glasgow Outcome Scale score (5-pt scale)
• Glick et al, IJTAHC, 1998

Tirilazad Study: Trial Design Issues

• Economic analysis not part of original protocol (1991)
  – Were asked to design econ analysis just as trial was starting
• Surgical procedures, diagnostic tests, non-investigational medications, 3-month residence already being collected as part of protocol
• Selected random sample of centers from which to collect days by unit type (ICU, etc.) during initial hospital stay
  – But some refused, others volunteered
• Not allowed to collect more detail on care between hospital discharge and 3-month visit

Tirilazad Study: Resource costing

• Units costs collected by local health economists in 6 countries (covering 84% of patients)
• Held 3 meetings to design, discuss, and review cost data collection
• Unit costs for most common surgical procedures were collected; costs for less common procedures then estimated using OLS regression employing Medicare RVS measures as predictors (see Schulman et al, 1998)
• Averages of the six countries’ unit costs were used for the other five countries
• Translated into US $ using PPP adjustments
**Tirilazad Study: Missing data**

- Length of stay by unit type (intensive care, regular ward, etc.) in hospital only available for 60% of patients; determined they were not randomly selected (mortality rate different across those collecting data and those not collecting data, p<.01)
- Developed 3 pairs of regressions to estimate LOS in each unit based on patient, disease & treatment characteristics; used them to estimate LOS by unit type when it was missing (still blinded to tx group), separately for men and women

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**Tirilazad Study: Cost analysis**

**Hospital cost by category**

![Hospital cost by category](chart)

- Tested differences in costs within hospital and at 3 months using ANOVA for comparisons of 4 dose groups and t-tests for pairwise comparisons
- Predicted cost differences due to treatment using OLS regression (explanatory variables identified by stepwise selection)
  - Also estimated log cost regression with smearing retransformation, but it did not improve ability to predict costs
- Daily residence costs assessed at 3 months
  - Mean costs by treatment group compared separately using ANOVA

---

**Tirilazad Study: Cost analysis - 2**

- Tested differences in costs within hospital and at 3 months using ANOVA for comparisons of 4 dose groups and t-tests for pairwise comparisons
- Predicted cost differences due to treatment using OLS regression (explanatory variables identified by stepwise selection)
  - Also estimated log cost regression with smearing retransformation, but it did not improve ability to predict costs
- Daily residence costs assessed at 3 months
  - Mean costs by treatment group compared separately using ANOVA
Tirilazad Study: Hospital Cost Regressions

<table>
<thead>
<tr>
<th>Sample as a Whole</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coef</td>
<td>P</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mg/kg/d</td>
<td>0.03</td>
<td>0.37</td>
</tr>
<tr>
<td>2 mg/kg/d</td>
<td>-330</td>
<td>-244</td>
</tr>
<tr>
<td>0.6 mg/kg/d</td>
<td>-897</td>
<td>-1091</td>
</tr>
<tr>
<td>Other covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R²</td>
<td>0.31</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Tirilazad Study: Analysis of outcomes

- Used secondary clinical outcome, mortality, as primary economic outcome
- Used multivariable logistic regression to estimate treatment effect on mortality
  - Not exactly same estimate as clinical study reported, but close, and well within CI
  - Treatment showed a significant survival difference overall between 6 mg and vehicle, primarily among male patients (post-hoc analysis); was no survival difference for lower doses
- Also assessed daily employment value at 3 months for those employed or classified as homemakers
  - Shown as separate economic outcome from cost analysis

<table>
<thead>
<tr>
<th>Sample as a Whole</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CI</td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mg/kg/d</td>
<td>0.41</td>
<td>.23-.72</td>
</tr>
<tr>
<td>2 mg/kg/d</td>
<td>1.09</td>
<td>.66-1.79</td>
</tr>
<tr>
<td>0.6 mg/kg/d</td>
<td>.78</td>
<td>.47-1.31</td>
</tr>
<tr>
<td>Other covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C statistic</td>
<td>0.844</td>
<td></td>
</tr>
</tbody>
</table>
Tirilazad Study: Summary measures

Selected in-trial endpoints – 3 month costs and mortality – for use in principal summary measure

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost difference</td>
<td>$2,695</td>
<td>$6,058</td>
<td>$1,238</td>
</tr>
<tr>
<td>Mortality difference</td>
<td>.091</td>
<td>.225</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cost per death averted</td>
<td>$29,615</td>
<td>$26,924</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Tirilazad Study: Uncertainty

- Bootstrap analysis of ICER was conducted
- 95% CI from comparison between 6 mg Tir and vehicle:
  - For all patients, ICER range was from tirilazad having an ICER of $9,189 per death averted to tirilazad being dominated on costs and mortality.
  - For men, the ICER ranged from $4,300 to $54,600 per death averted.

Tirilazad study: Modeling past the trial

Actual life expectancies of SAH survivors was not well-known, so LE from 0.5 to 25 years was projected
Top two lines: Cost/QALY (top) and Cost/LYR for all 6 mg pats vs. vehicle
Bottom two lines: Cost/QALY (higher) and Cost/LYS for all male 6 mg pats vs vehicle
Utility of survivors based on HUI measure at 3 months; costs for survivors based on cost of long-term care observed at 3 months
Tirilazad study: Sensitivity to country-specific results cost per death averted, 3 methods

<table>
<thead>
<tr>
<th>Country</th>
<th>Price</th>
<th>Specific</th>
<th>Costs †</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46,818</td>
<td>5,921</td>
<td>11,450</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>57,636</td>
<td>91,906</td>
<td>60,358</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>53,891</td>
<td>90,487</td>
<td>244,133</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>69,145</td>
<td>93,326</td>
<td>181,259</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>65,800</td>
<td>**</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>45,892</td>
<td>45,892</td>
<td></td>
</tr>
</tbody>
</table>

† Country-specific resource use = Country-specific price weights
** New therapy dominates

Tirilazad Study: 8 Years Later, What Would We Change?
- Generally stands the test of time
- For ICU stay, use count model rather than OLS; also use censored data method rather than direct imputation
- Use a general linear model (GLM) for the estimation of cost
  - Log OLS with common smearing retransformation a mistake, given heteroscedasticity
- Include ICU analysis in bootstrap
- Assess the impact of sensitivity analysis on the confidence interval for the cost-effectiveness ratio
- Estimate CI for the cost/LYS and cost/QALY ratios

Selected References