Analysis Of Effectiveness And Cost-effectiveness In Patient Registries

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Aim of the Workshop

Provide practical guidance on suitable statistical approaches to registry data with the particular focus on estimating the ***effectiveness*** and ***cost-effectiveness*** of treatment methods.

$1.1 Billion (!!) federal spending in "comparative effectiveness"

Developed by the Special Interest Group on Patient Registries - Data Management and Analysis Subgroup

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Outline

- Background & Issues
  - Mike Novotny
- Analysis of effectiveness
  - Maria Malmenäs
- Analysis of cost-effectiveness
  - Marg Hux
- Q&A

Background and Issues

In the Analysis of Comparative Effectiveness and Cost-Effectiveness in Patient Registries

Defining a Registry

Prospective observational study of subjects with certain shared characteristics, that collects ongoing and supporting data over time on well-defined outcomes of interest for analysis, reporting

Potential for Treatment Comparisons

Product Registry
Pharmaceutical; Biologic; or, Device.

Safety Registry
Increasing due to:
Pharma/ Biotech initiatives;
FDA and EMEA mandates.

Disease Registry
Subset of target, accessible, and intended population.

Registry Objectives

Preliminary Analyses:

- Profile population
- Evaluate natural history of disease
- Assess burden and cost of illness
  - Patient Reported HRQoL, Satisfaction, and loss of work productivity/activity
  - Resource use: office visits/contacts, urgent/emergency care, hospitalizations
- Can continue throughout study

Long-term Analyses:

- Identify practice patterns
  - Treatment
  - Quality of care
- Measure long-term outcomes
  - Survival (or time to other event)
  - Rate of events
  - Freedom from hospitalization (or other event)
  - Clinical worsening
  - Clinical improvement

Comparative effectiveness and cost-effectiveness

There can be many Analysis Goals

- Multiple objectives and study endpoints
- Varied / changing stakeholders throughout the study

Understand the clinical settings and the data

Develop *a priori* analysis plan for an analysis goal

Key differences from Randomized Study

	Randomized Trial	Registries
Patients	Small, homogeneous group	Large, heterogeneous group
Treatments	Used as intended	Used as per normal clinical care
	Restricted concurrent treatments and comorbidities	No restrictions on concurrent treatments and comorbidities
Follow-up	Comparatively short and fixed	Extended and variable
	Rigid visit and dosing schedule	Visit and dosing schedule as per normal clinical care
	Efficacy in highly controlled setting	*Effectiveness* in the real-world

Controlled trial data vs. "Take whatever comes" data

- Efficacy and safety measured according to strict protocols result in (somewhat) controlled and orderly data
- Real world utilization measured according to less strict protocols results in much less orderly data

Issues for registry data analysis

- Data collection
  - Missing data allowed
  - Misclassification
  - Post-enrollment case report form modifications
    - e.g. adding or changing variables
- Variable and long follow-up
  - No set visit schedule
    - Important variables may not be collected at all visits
- Treatments are chosen specific for patients
  - Newer, more expensive therapies may be chosen for most ill patients
  - Centres with more extensive treatment may use newer therapies
  - Bias

Established guidelines

Design and Implementation of Registries

- AHRQ, Registries for Evaluating Patient Outcomes: a user's guide (April, 2007)
- ISPOR Patient Registry Special Interest Group (in progress)

Reporting / publishing evidence

- STROBE – **ST**rengthening the **R**eporting of **OB**servational studies in **E**pidemiology (October, 2007)

Regulatory authorities - pharmacoepidemiology and pharmacovigilance

- FDA, EMEA, ENCePP (**E**uropean **N**etwork of **Ce**ntres for **P**harmacoepidemiology and **P**harmacovigilance, in progress)

GRACE Principles – **G**ood **R**ese**A**rch for **C**omparative **E**ffectiveness Observed (August, 2008)

Conclusion

No comprehensive guidelines for analysis of Registry data

Comparative Effectiveness

based in Patient Registries

ISPOR Patient Registry Special Interest Group (SIG)
Design & Operations Working Group's Data Management & Analysis Team

Approaches to Analysis

- Long and variable patient follow-up
- No fixed assessment schedule
- Longitudinal Analyses
  - Change Scores
  - Repeated measures analyses
  - Logistic and linear regression models
  - Time to event models (survival analyses)
- Cross Sectional Analyses
  - Snapshot of the data
    - at one point in time
    - At one point in course of disease

Greater challenges in the analysis than RCT data

Rothman KJ, Greenland S. Modeling Longitudinal Data. In Modern Epidemiology, 2nd Ed. 1998.

Reasons for Potential Bias

- Registry data has lack of randomization
  - Treatments self-selected by physicians for specific patients
  - Study sites have different treatment protocols
- Selection Bias
  - Groups may be imbalanced on important risk factors for outcome

Control of bias is an important factor in ensuring valid comparative analyses

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Explore and Understand the Data

- Become familiar with the data
  - Important for interpretation
  - Descriptive analyses, distributions, relationships
- Anticipate potential bias
  - At the time of design potential factors related to the outcome and to treatment choice must be identified and collected
  - Clinician input

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Example – Registry for an enzyme deficiency disease

- World wide observational study
  - To understand the long-term effectiveness and safety of enzyme replacement treatment on the clinical course of Fabry disease
  - To understand the natural history of the disease

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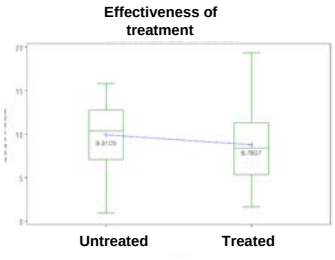
Without considering other factors, treated patients appear to have worse outcomes



However, treated patients have worse status on important risk factors

- Based on a summary measure of risk for poor outcome
  - age, disease severity, gender
- Therefore, the initial comparison is biased

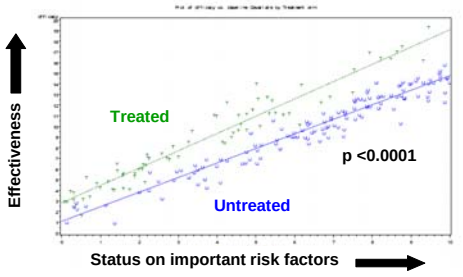
Methods of Dealing with Bias

- Covariate analysis
- Matching
- Prognostic Stratification
- Propensity scoring

Covariate Analysis

- Example Methods
  - Analysis of Covariance (ANCOVA)
  - General linear model (GLM)
  - Logistic regression analysis

Treated patients show better outcomes after adjustment for covariates



After adjusting for age, disease severity, gender etc

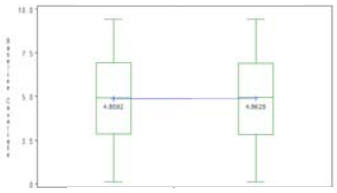
Matching

- Example Methods
  - Pair wise matching (1:1),
  - Several controls to a case(1:m)
  - Several cases to one control (m:1)
- Analysis
  - Matched-paired t-test, signed rank test, mixed model etc

Even with a substantial reservoir of controls, numbers may decrease considerably over time

Status on important risk factors after matching

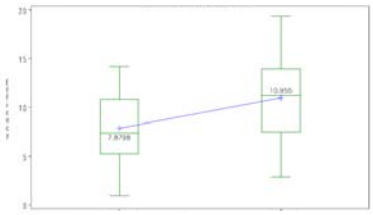
Baseline covariates



Untreated Treated

Treated patients have better outcomes than their matched controls

Effectiveness of treatment



Untreated Treated

Prognostic Stratification

- Summary measure of risk for outcome
  - Combination of several risk factors
  - Used as one single covariate or matching variable
  - Many variables to select and combine best prognostic factors
  - Can be developed in one dataset, used subsequently
- Preceding examples of stratified analysis and matching used a prognostic variable
  - status on important risk factors
  - Included age, disease status, gender

Propensity Scoring

- Summary measure - probability of treatment group assignment
  - Combination of several predictors
  - Can accommodate more than two treatment conditions.

Step 1: Remove patients with no chance of getting both therapies

Step 2: Conduct analysis to create propensity scores
- Identify probability of being assigned one treatment group vs. another at the outset of a non-randomized study

Step 3: Divide into groups (or retain as a continuous propensity score)
  - Strong propensity to be given a certain treatment;
  - Moderately strong propensity to be given treatment;
  - Moderately strong propensity against being given treatment;
  - Strong propensity against being given treatment;

Step 4: Conduct analysis:
- Use subgroups or adjust for propensity to mimic a randomized trial

Conclusion

The methodological challenges in registry data of effectiveness come from the lack of randomization to treatment, which leads to concern about bias

Control of bias may be obtained by design and/or analysis

Cost-Effectiveness Analyses

based in Patient Registries

Cost-Effectiveness

Estimate cost/savings for additional benefit compared to alternative treatment in real world use

- Compare to currently used alternatives
- In patients who will actually use the therapy
- No restrictions on physician practice
- Fixed timeframe sufficient to include consequences and downstream costs
  - summary aggregate measures

Disease registries are an attractive setting to evaluate cost-effectiveness

- Longer follow-up than available with RCTs
- All treatment monitoring and management of downstream consequences are usual care
  - No protocol-driven visits and assessments
- Patients more heterogeneous than RCT
- Treatments chosen by physicians and patients

Challenges with estimating Cost-Effectiveness based in Registry data

- Follow-up usually very variable
  - Difficult to choose one consistent fixed time
  - Right censoring of data
- Choosing treatment alternatives / comparator
- Heterogeneous patients - disease stages
  - Identify the population of interest within the full population
- Treatments selected specific for the patients
  - Great potential for confounding and bias

Good News and Bad News

Real world data

Disease-related Cost

- Aggregate cost over a fixed timeframe
  - Does not require fixed assessment schedule
- Identify health resources to include in cost
  - Health resources including
    - treatments, administration, monitoring, management of short term and downstream clinical consequences
  - Unit prices from standard cost sources
    - To a specific cost perspective / country
- Handling of missing / censored data
- Cultural and country differences

Evaluation Timeframe

- Selecting the length of the timeframe
  - Long enough to capture downstream costs, consequences
  - Small amounts of data at the extreme right of the time
- Censored follow-up
  - Patients have 'rolling' enrollment
  - Censoring due to dropout
- Handling of missing / censored data
  - Extrapolate out using average cost prior to censoring
  - Survival methods
  - Extensions of survival methods
    - Cost accumulation can differ across the timeframe

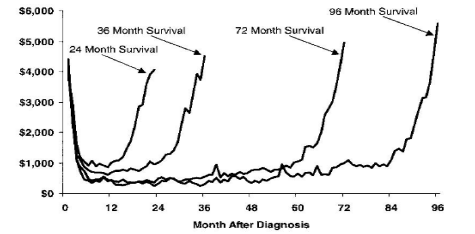
Censoring in the presence of variable pattern of cost across time

- SEER – Medicare Registry data
  - patients with breast cancer
- Censored follow-up
  - Patients begin follow-up at all different times, fixed cutoff for analysis
  - Align cases at entry into the registry
  - Censored with regard to survival - zero cost after death
  - Imputation of cost up until death
- Three phases of cost
  - Initial diagnosis, treatment – fixed 5 months
  - Maintenance / remission period – variable time
  - Terminal care – last 12 months of life

Brown ML, Riley GF, Schussler N, Etzioni R. Estimating Health Care Costs related to cancer treatment from SEER-Medicare data. Medical Care. 40(8):IV104 – IV117.

Imputing Cost after censoring

Breast cancer cost profiles post diagnosis
(Brown et al., 2002)



Brown (2002); Lin DY, Linear regression analysis of censored medical costs Biostatistics 2000. 1: 35-47.

Imputation of cost due to censoring

- Linear regression analysis including
  - Phase of disease (initial, maintenance, terminal care)
  - Monthly intervals within phases
  - Covariate adjustments for age, sex, other variables
  - Estimate cost over the following time based on the observed pattern for patients with data, the censoring
    - Estimate time of death
    - Estimate cost based on the phase
  - Assumed censoring occurred at the end of monthly intervals
- Later work extended
  - Censoring at midpoint of intervals vs. end of intervals
  - Found to minimize the bias

Lin, 2000, 2003; Bang and Tsiatis, 2005, Manning 2008

Choosing treatment alternative

- Ideal
  - Treatment comparator is most common, recommended care
    - May be a mix of therapies
  - Alternatives given to patients who are similar at treatment choice
    - Disease severity, risk of outcome

Issue:

- Treatments chosen to fit the patients
  - More expensive, advanced treatments used for most ill patients
  - Centres with more extensive care may choose the more expensive product
- Real-world treatment usage
  - Switching of treatment groups, concurrent treatments

Comparability of Treatment Groups

- Need to estimate:
  incremental cost,
  incremental effectiveness
- Same challenges as comparative effectiveness
- Same methods to identify and adjust for bias
  - Need to have overlap in the treatment groups with respect to risk factors to be able to adjust for bias.

Example
Bandaging system for burn patients

ICU setting

Sophisticated bandaging system

- Easier to apply
- Can be left on longer (fewer changes)
- Protection from infections, better healing
- Saves nursing time

- Prospective observational registry study to compare
  - Patients treated with usual care
  - Patients treated with new bandaging system

Bandaging system for burn patients - Selecting study sites

Select study sites that use primarily one method

- Expect to find the full range of patient severity
- May be other differences in medical practice, patients
  - ICU that uses new product as standard care
    - Formulary also provides routinely other new products and medicines
    - Also more nursing time to do dressing changes
  - ICU that does not use bandaging system at all
    - Less well funded, limited formulary
    - Higher ratio of patients to staff

Select study sites that use both methods

- Treatment protocol likely to limit new treatment for most ill patients

Conclusion

- Key challenges
  - Constructing aggregate measure of cost over fixed timeframe
    - in the presence of right censoring
  - Ensuring that potential bias is prevented or adjusted for
    - In both costs and effects
    - Need overlap in groups with respect to risk factors to allow adjustment at the stage of analysis
- If not possible to conduct a full cost-effectiveness
  - May estimate costs for states of health
  - Utility associated with states of health
  - Combine with effectiveness / efficacy from randomized comparative trials in modeled comparison

Conclusion
Treatment comparisons using Registry Data

- A careful design of the registry is critical
  - Know your study settings
  - Be aware of potential confounding
  - Collect data to adjust for confounding where possible
- Analysis methods exist to deal with the challenges of registry data
- We have begun describing analysis guidance

Questions / Discussion