

Dynamic Treatment Strategies in Crohn's Disease: Real-Time Evaluation

Presented at the NIH/AHRQ Conference on
Methodological Challenges in Comparative Effectiveness Research, Bethesda, MD
December 3, 2010

Marshall M. Joffe

Associate Professor of Biostatistics

Center for Clinical Epidemiology and Biostatistics

Department of Biostatistics and Epidemiology

University of Pennsylvania School of Medicine

mjoffe@mail.med.upenn.edu

Outline

- Problems:
 - Defining questions of clinical interest
 - Confounding by variables affected by treatment
 - Performing analyses in real time

Questions of clinical interest

- Strategies for using biologics for children with Crohn's disease
 - Key question: how best to time initiation of biologics
 - Strategies defined in terms of timing
 - Compare strategies
 - Find optimal strategy
- Ideally, randomized trial comparing all strategies of interest
 - Expensive
 - Time-consuming

Types of strategies

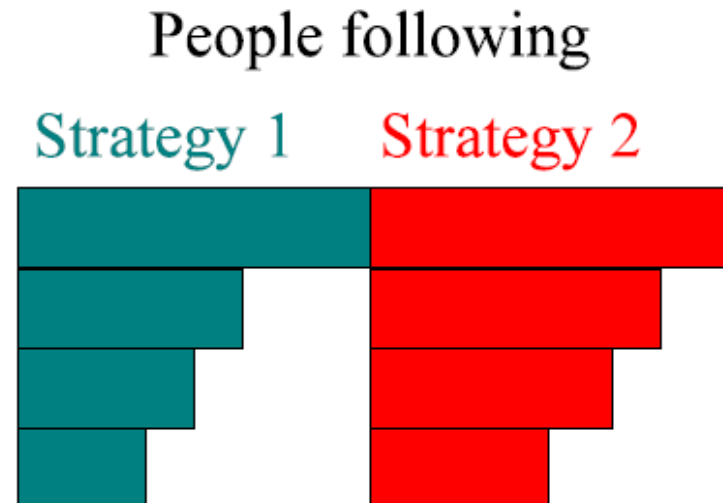
- Top-down biologics:
 - Anti-TNF α at diagnosis
- Rapid step-up to biologics
 - Anti-TNF α within 6 months
- Late step-up to biologics
 - Anti-TNF α 6-12 months
- Thiopurines only
- No biologics/thiopurines
- Decision on treatment course specified
 - Strategies do not adapt to clinical course

Adaptive/dynamic strategies

- Allow treatment decisions to depend on clinical course
 - e.g., start anti-TNF α if current therapies appear to have failed
 - Use disease activity scale as indicator/trigger
 - Options
 - If disease activity above threshold level, initiate anti-TNF
 - If disease activity rises given amount above baseline, initiate
- Analogous to protocols in randomized trials

Comparison of approaches

- Standard
 - Compare people following both strategies
 - Possibly control for confounders at some point
 - Subjects completing strategy unrepresentative of population
- New
 - Compare what would happen to same people under both approaches



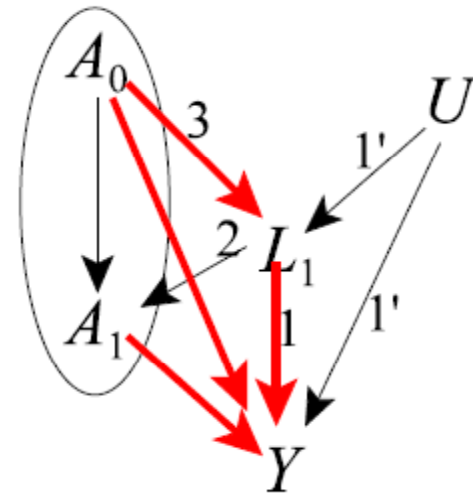
Evaluation/estimation

- Use marginal structural models/inverse probability weighting
- Controls for confounding of effect of treatment strategy by variables affected by strategy
 - e.g, disease activity at intermediate time points
- Conventional methods (e.g., regression) biased whether or not control for intermediate variable
- Explain graphically

Graph of setting

- Interested in effect of strategy
- Characteristics of covariate (L_1)
 - 1 or 1': independent predictor of outcome
 - 2: influences subsequent treatment
 - 3: influenced by prior treatment
- 2 and (1 or 1'): covariate confounder
 - Must control
- 3 and 1: covariate intermediate
 - Should not control

A_0, A_1 : treatment at times 0,1
 L_1 : covariate at time 1
 U : other covariate
 Y : outcome



Conditions for Valid Estimation

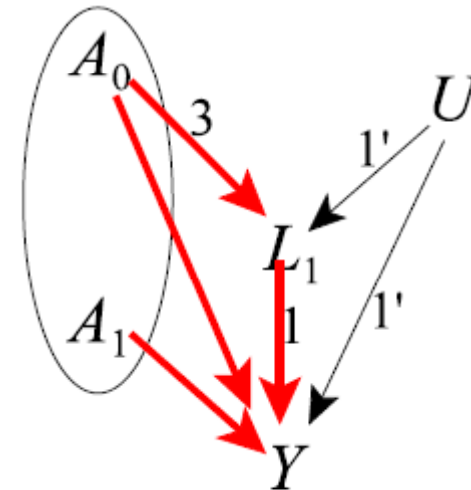
- No unmeasured confounding variables
 - Requires measurement of variables which
 - Influence treatment decisions AND
 - Independent predictors of outcome
 - Integrated system assists with this
 - Ask physicians about what influences treatment decisions
 - Already done: Modified Delphi
 - Can be updated
 - Make certain that information on determinants completely collected at every encounter
 - Don't unnecessarily dichotomize continuous covariates during data collection
 - » May interfere with ability to control confounding

Conditions for Valid Estimation (2)

- Positive probability of staying on regime given covariate history
 - If strategy never used for subset of patient experience, cannot evaluate
 - Examples
 - If anti-TNF α never given at diagnosis for patients with low disease activity, cannot evaluate regime: “Top-down biologics”
 - If anti-TNF α never given when PCDAI $<$ 10, cannot evaluate regime: “Initiate biologics as soon as PCDAI exceeds 5”
 - Don’t want to include variables that are extremely good predictors of treatment but do not predict outcome
 - e.g., suppose that physician determines treatment given covariate history, not associated with outcome
 - Would not want to adjust for physician as confounder

Inverse probability weighting

- Idea: each subject who stays on regime at time t represents
 - Self; and
 - Subjects otherwise comparable who did not stay on regime
- Mimics sequential randomized trial
 - Covariates do not affect treatment
 - Effect of treatment unconfounded
 - Apply standard methods in weighted pseudopopulation



Steps for implementing analysis

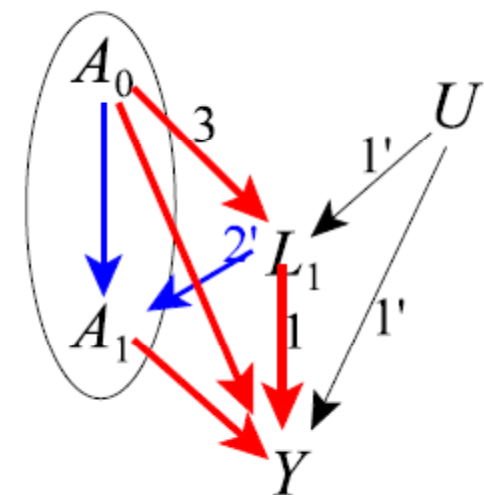
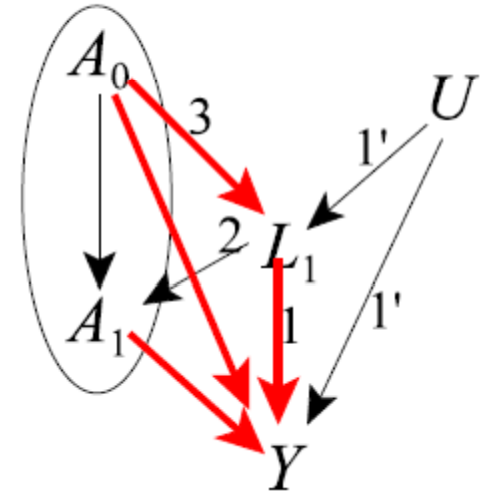
- Fit model for (repeated) treatment at t as function of covariate history, prior treatment history
- Compute probability of remaining on regime at t given history
- Multiply probabilities together for all times
- Weights: inverse of product of probabilities
- Create weighted pseudopopulation
- Use weighted version of standard approaches for estimating expected outcome under regime
- Compare outcomes under different regimes

Dynamic regimes: evaluation

- Several differences:
 - Individual subject's observed treatment consistent with multiple regimes
 - e.g., subject who has PCDAI < 10, no biologics throughout follow-up; consistent with
 - “No biologics”
 - “Initiate therapy when PCDAI > 10”
 - “Clone” subject: contributes as many observations as the number of regimes consistent with treatment history
 - Above example: subject contributes to both regimes
 - Account necessary for variance of contrasts

Dynamic regimes: evaluation (2)

- Link between covariate history and subsequent treatment
 - Not broken
 - Changed
 - Deterministic function of history



Evaluation in real time

- Challenge:
 - Analyses using inverse probability weighting, marginal structural models more difficult, time-consuming than standard analyses
- Speed up analyses after first one
 - Perhaps use same predictors, treatment in subsequent evaluation
 - Consider automated algorithms/machine learning, especially for treatment assignment models
- Feedback within system
 - Regimes feasible at outset may become infeasible to evaluate later as practice patterns change
 - Consider evaluating new aspects/dimensions of treatment choice over time

Feedback/Quality Improvement

- Standardization of treatment decisions: goal/danger
 - Goal: after analysis, want to avoid treatment decisions determined to be suboptimal
 - More uncertainty here than in randomized trials, because of uncertainty of ability to completely control confounding
 - Danger: do not want to completely standardize decisionmaking
 - Makes it difficult to compare standardized protocol with other possibilities within database
 - Middle course
 - Identify suboptimal regimes as result of analysis; discourage use (perhaps with automated implementation)
 - Do not attempt to standardize within region of clinical equipoise

References

- **Robins JM, Hernán MA . (2009).** In: [Estimation of the causal effects of time-varying exposures.](#) Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G, eds. New York: Chapman and Hall/CRC Press, 2009
- **Cain, Lauren E.; Robins, James M.; Lanoy, Emilie; Logan, Roger; Costagliola, Dominique; and Hernán, Miguel A. (2010)** "When to Start Treatment? A Systematic Approach to the Comparison of Dynamic Regimes Using Observational Data," *The International Journal of Biostatistics*: Vol. 6 : Iss. 2, Article 18.
DOI: 10.2202/1557-4679.1212
Available at: <http://www.bepress.com/ijb/vol6/iss2/18>