Guidance for key issues of design and analysis of observational studies

Causal inference at work

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for the TG7 Group on causal inference

The special challenges of causal inference

- Stating the `what if' question (clearly)
  - Impact of A versus B; total effect or
  - Direct versus indirect effects (what is kept fixed?)
  - In what target population (direct versus indirect standardization, treatment effect on the treated or…)
  - Over which time frame

- E.g. `The effect of binary treatment'

  - Intention to treat effect
  - Per protocol effect
  - As treated effect

- **Assumptions** determine the question we answer

The special challenges of causal inference

- Stating the `what if' question (clearly)
- Clarifying the `data' (**seen and unseen) structure**
- **Two levels of models** & assumptions involved:

A. Causal model in terms of `potential outcomes'
   - how actions change potential outcome distributions

B. Models for the `observed data law': association models
   - How observed outcome distributions change over observed `actions'

- Models **linking A. with B**. with **untestable assumptions**
  - Instrumental variable assumption
  - No unmeasured confounders assumption

Special Challenges

- Beginning:
  - Stating the question
  - Bring structure in real and potential data
- Middle: propose models
  - Formulate and justify assumptions, study design
    - No unmeasured (time-varying) confounders
    - Instrumental variables
  - Derive estimators
  - Conduct sensitivity analysis for (un)testable assumptions
- End: Draw conclusion, careful (!) reporting
- The next step: Validate?

Needed: A common language/translators

- Graphs (DAGS) Judea Pearl
- Potential/counterfactual outcomes (degrees of…)
  - Outcome regression
  - Propensity score adjustment
  - Double robust approaches
  - Principle strata

  Rubin et al. and Robins et al.
- Observed data law only. Dawid P.

Problems are well recognized

- `Myth, Confusion, and Science in Causal Analysis' J. Pearl (SIM, technical report, May 2009)

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- Causal effects in clinical and epidemiological studies via potential outcomes: Concepts and analytical approaches. Little and Rubin, Annu Rev Public Health. 2000;21:121-45.

In this article we review an approach to making such inferences via potential outcomes. In this approach, the causal effect is defined as a comparison of results from two or more alternative treatments, with only one of the results actually observed.

- `Principal Stratification — a Goal or a Tool?' J.Pearl, IJB, 2011

… ***invite response to clarify*** *the value of principal stratification in estimating causal effects of interest.*

Some recent Responses…

- Propensity scores: From naive enthusiasm to intuitive understanding. Williamson, E; Morley, R; Lucas, A; Carpenter, J. SMMR, 21: 273-293, 2012.

*Propensity score methods **remain controversial** and there is no consensus as to when, if ever, they should be used in place of traditional outcome regression models.*

- `Colon Cancer Survival With Herbal Medicine and Vitamins Combined With Standard Therapy in a Whole-Systems Approach: Ten-Year Follow-up Data Analyzed With Marginal Structural Models and Propensity Score Methods'. McCulloch, Broffman and van der Laan, Mark; et al. Integrative Cancer Therapies, 10: 240-259, 2011

`Gold standard' of randomized trials

- `Do observational studies using propensity score methods agree with randomized trials? A systematic comparison of studies on acute coronary syndromes'. Dahabreh et al. European Heart Journal, 2012

- *`Observational data for comparative effectiveness research: An **emulation of randomised trials** of statins and primary prevention of coronary heart disease'*, Dahabreh, Roderiguez, Cantero, Logan and Hernan. SMMR 2011, [AND in `Diabetes care', 2012]
  - Pragmatic versus explanatory trials (blinding, selection)
    - Intention to treat effect
    - Per protocol effect
    - As treated effect

New and more ambitious questions/designs

- Dynamic treatment regimes
- Optimal dynamic treatment regimes
- Mediation analysis

Account for post-entry or post-treatment initiation variables, including g-estimation methods, targeted maximum likelihood estimation, and principal stratification…

Team of collaborators needed

- **Statistical** and **subject matter experts** (clinical, public health policy, pharmaco-epi, pharmaco-economic,…)

- Statisticians from the different Schools:

  Pearl-Robins-Rubin-…

  - Inner circle (less wedded to one approach)
  - Outer circle (to find some common ground)

- Links with (all !) other Topic Groups

What we hope to achieve in a divided world:

- We should understand and respect each other
- We should agree on sound principles
  - e.g. Adjust for confounders, not colliders
- Establish some ground rules
- Provide a guide map: classes of questions with options
- There may be choices left and uncertainties to be resolved (clearly indicated what and why)
- May agree to disagree on certain points/preferences – as long as it is clear what those points are

`**Standards for Causal Inference Methods** in Analyses of Data from Observational and Experimental Studies in Patient-Centered Outcomes Research' (2012)

For: Patient-Centered Outcome Research Institute Methodology Committee

Prepared by: Joshua J Gagne, Jennifer M Polinski, Jerry Avorn, Robert J Glynn, John D Seeger,

B. Main findings

many existing guidance documents mention topics in causal inference, **few provide clear guidance for using these methods.**

… we developed additional minimum standards largely de novo, based on primary methodological literature and on Our own expertise in causal inference methods (Standards 3, 6, and 7)

not intended to help researchers decide among methods, but rather to help researchers implement methods in a rigorous, transparent manner that facilitates causal interpretations of PCOR and promotes their transparent communication.

Standards for Causal Inference Methods …

Next steps

Comprehensive reviews of major classes of methods (e.g., methods to address baseline confounding, methods to address time-varying confounding) are needed **to understand** how these methods are being used in PCOR and CER **and to establish best practices**.

Methods for dealing with time-dependent confounding (SIM, 2012)

Daniel, RM ; Cousens, SN ; De Stavola, BL; Kenward, MG ; Sterne, JAC

Robins and colleagues have proposed several alternative methods that, provided certain assumptions hold, avoid the problems associated with standard approaches.

They include the g-computation formula, inverse probability weighted estimation of marginal structural models and g-estimation of structural nested models.

`In this tutorial, we give a description of each of these methods, exploring the links and differences between them and ***the reasons for choosing one over the others in different settings'****. Copyright (c) 2012*

TO DO

- Review the reviews

- Provide worked out examples [with more than one approach and balanced evaluation for types of questions]
  - Look at what/how other approaches would have fared
  - Strengths and weaknesses for particular types of questions
  - Involve `simurealizations' (realistic data generating model that need not match simpler analysis model)

Types of questions + approaches list

Types of conclusions:evidence requirement or caution

- Agreement on guidance would be major achievement
- Build bridges: language, meaning, approach
- Provide a road map with options

Please join !

- Come to Room B206
- Email: Els.goetghebeur@ugent.be

My own motivation:

Want it for me, my consultants, my students, life long learning

Please join !

- Statistical and subject matter experts (clinical, public health policy, pharmaco-economic,…)
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