

# Guidance for key issues of design and analysis of observational studies

## Causal inference at work

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# The special challenges of causal inference

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- 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

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- 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

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- 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

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- 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

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

## Problems are well recognized

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

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- 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

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- `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

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- 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

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- **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:

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- 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)**

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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 ...

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## 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)

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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

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- 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 `simrealizations' (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 !

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- Come to Room B206
- Email: [Els.goetghebeur@ugent.be](mailto:Els.goetghebeur@ugent.be)

My own motivation:

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

# Please join !

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