Estimand Framework in Oncology Drug Development: Challenges and Opportunities

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Disclaimers

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.
- I have nothing to disclose

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Outline

- Objectives
- Definitions
- Causal Inference
- Treatment Switching (Cross-Over)
- Beyond Efficacy
- Next Steps

Objectives

Patient Objective

Treatment outcomes with adequate utility

- Therapy efficacy and safety
- Quality-of-life
- Physical, psychological, and social functioning
- Financial toxicity

Regulatory Objective

Substantial evidence

- adequate and well-controlled investigations
- drug will have the effect… prescribed, recommended, or suggested in the labeling

Structured risk-benefit assessment framework

- a consistent and systematic approach to the discussion and regulatory decision-making
- communication of the benefits and risks of new drugs

Title 21. FOOD AND DRUGS Chapter 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT Subchapter V. DRUGS AND DEVICES Part A. Drugs and Devices Section 355. New drugs

Definitions

Estimand

The target of estimation to address the scientific question of interest posed by the trial objective.

1. Population of interest
2. Variable (or endpoint) of interest
3. Specification of how intercurrent events are reflected in the scientific question of interest
4. Population-level summary for the variable

Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Key Considerations for Intercurrent Events

- Time to premature treatment discontinuation and the observed assessments for the primary endpoint before and after treatment discontinuation
- The extent of the use of effective rescue medical products after treatment discontinuation or at any other postbaseline times
- Time to follow-up discontinuation

Strategies for Addressing Intercurrent Events

Treatment Policy: "The occurrence of the intercurrent event is irrelevant"

Composite: "intercurrent event is integrated with one or more other measures of clinical outcome"

Hypothetical: "a scenario is envisaged in which the intercurrent event would not occur"

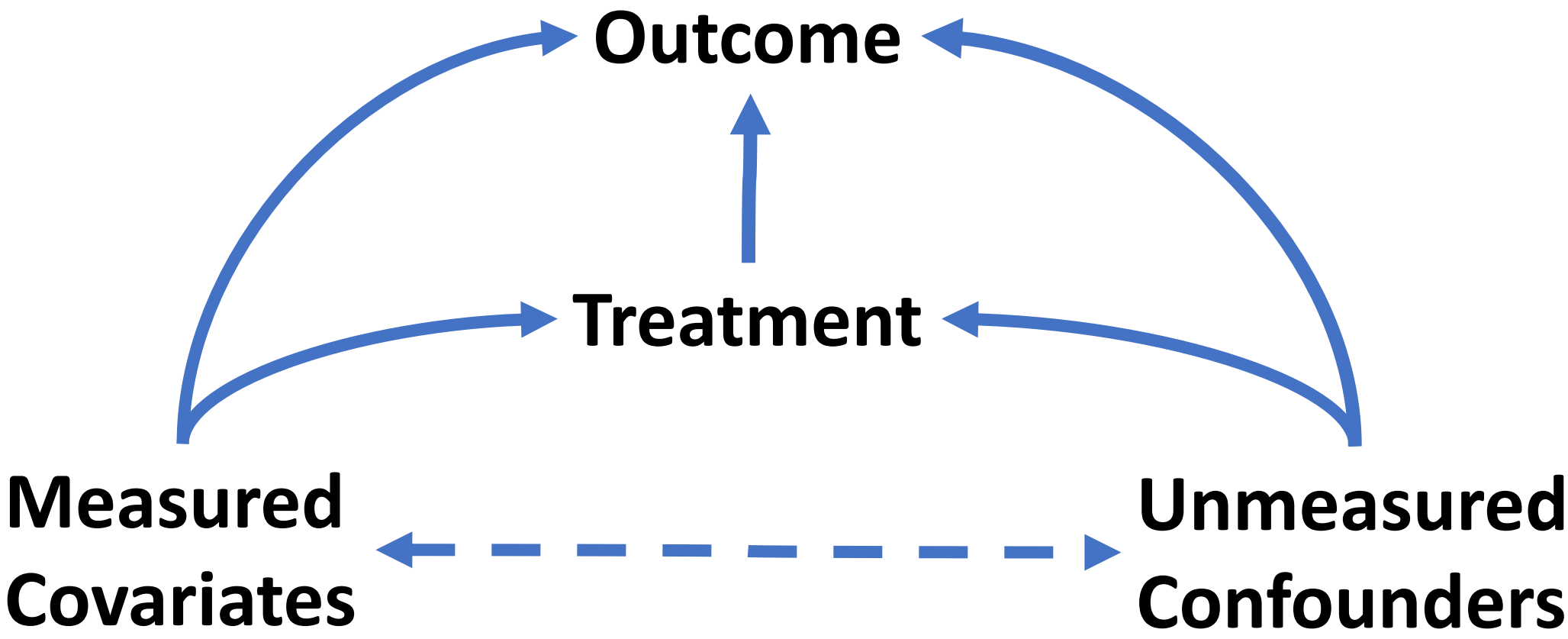
Principal Stratum: "principal stratum in which an intercurrent event would not occur."

While on Treatment: "response to treatment prior to the occurrence of the intercurrent event is of interest."

Intent-to-Treat (ITT) Principle

- All randomized patients
- Preservation of the initial randomization
  - Helps to prevent some bias
  - Provides a “secure foundation for statistical tests”

Causal Inference


Outcome
Treatment
Measured
Covariates
Unmeasured
Confounders

Randomization

- Causal RR: P(Y(TRT)=CR) / P(Y(CTRL)=CR)
- Observed RR: P(CR|TRT) / P(CR|CTRL)
- Randomization: (Y(CTRL), Y(TRT)) ⫫ TRT
- TRT = treatment
- CTRL = control
- CR = Complete Response
- PD = Progressive Disease
- ⫫ = Independent

Group	Y	Y(CTRL)	Y(TRT)
CTRL	CR	CR	?
CTRL	PD	PD	?
CTRL	PD	PD	?
TRT	CR	?	CR
TRT	CR	?	CR
TRT	PD	?	PD

Which causal inference framework?

- “Some form of counterfactual reasoning, such as the “potential outcomes” approach championed by Rubin, appears unavoidable, but this typically yields “answers” that are sensitive to arbitrary and untestable assumptions.” (Dawid et al., 2016)
- What is identifiable and estimable? (Greenland and Robins, 2009; Maclaren and Nicholson, 2019)

Hidden Causal Assumptions Lead to Erroneous Causal Claims

- Treatment randomization allows identification of the marginal Y(TRT) and Y(CTRL) distributions (Rubin, 1978).
- Treatment randomization does not identify the joint potential-outcome (Y(TRT), Y(CTRL)) distribution (e.g. Dawid, 2000).
- No complete (Y(TRT), Y(CTRL)) pair is observed. We cannot verify harm, benefit, or no effect in any individual from the data alone.
- We only observe marginal averages over these individuals (e.g. Greenland et al., 2019).

Measured and Unmeasured Covariates

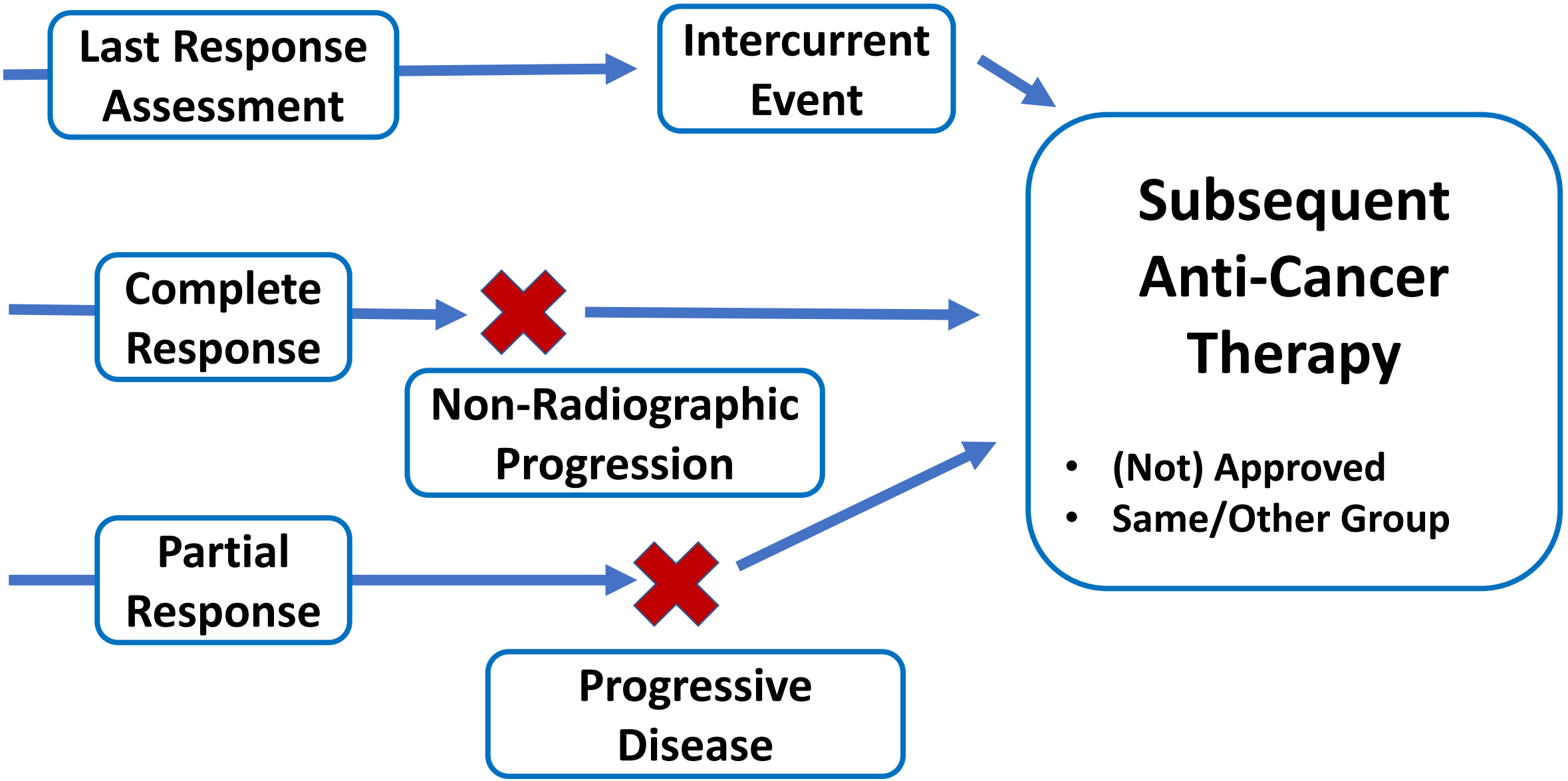
Can we identify relevant covariates?

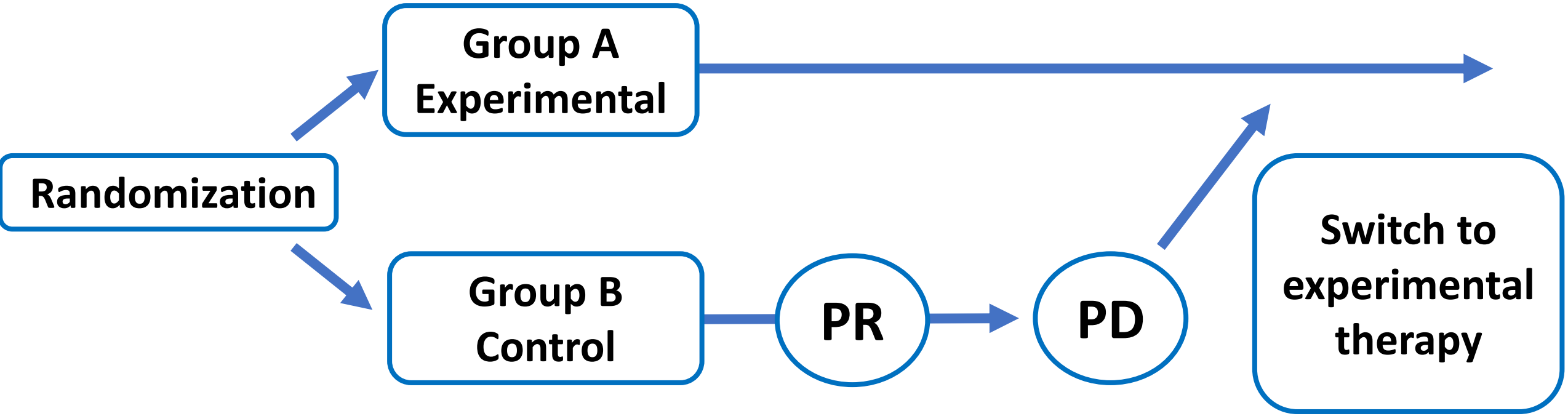
- Measured covariates must be sufficient to block all backdoor paths from treatment to outcome (Pearl, 2009).
- Adjusting for all measured covariates is not the answer: adjusting for factors affected by the exposure may introduce bias (e.g. Weinberg, 1993).

Unknown Unknowns

- What about unmeasured covariates? What magnitude of association is needed to sufficiently reduce the treatment effect? (e.g. E-values and related methods with minimal assumptions).

Treatment Switching


Last Response Assessment
Intercurrent Event
Subsequent Anti-Cancer Therapy
• (Not) Approved
• Same/Other Group
Complete Response
Non-Radiographic Progression
Partial Response
Progressive Disease


Randomization
Group A
Experimental
Group B
Control
PR
PD
Switch to
experimental
therapy

Study Conduct and Design, Equipoise

- Interim PFS analysis
- Intolerance
- Clinical progression
- Protocol Violations

Some Statistical Methods

- **Censoring**
- **Inverse Probability of Censoring Weighting** (IPCW) (e.g. Robins, 1993)
- **Rank Preserving Structural Failure Time models** (RPSFT) (e.g. Robins and Tsiatis, 1991)
- **Two-stage methods** (e.g. Robins and Greenland, 1994; Yamaguchi and Ohashi, 2004; Latimer et al., 2014)

This is not a comprehensive list.

This is NOT the FDA endorsement of methods listed above.

NICE DSU TECHNICAL SUPPORT DOCUMENT 16: ADJUSTING SURVIVAL TIME ESTIMATES IN THE PRESENCE OF TREATMENT SWITCHING

REPORT BY THE DECISION SUPPORT UNIT

July 2014

"Given the limitations associated with the adjustment methods, the ITT analysis should always be presented."

Consider

- Characteristics of the trial
- The switching mechanism
- The treatment effect
- Data requirements/availability and adjustment method outputs

EMA Guidance on Treatment Switching

13 December 2018
EMA/845963/2018
Human Medicines Research and Development Support Division

Question and answer on adjustment for cross-over in estimating effects in oncology trials

Agreed by Biostatistics Working Party	November 2018
Adoption by CHMP	13 December 2018

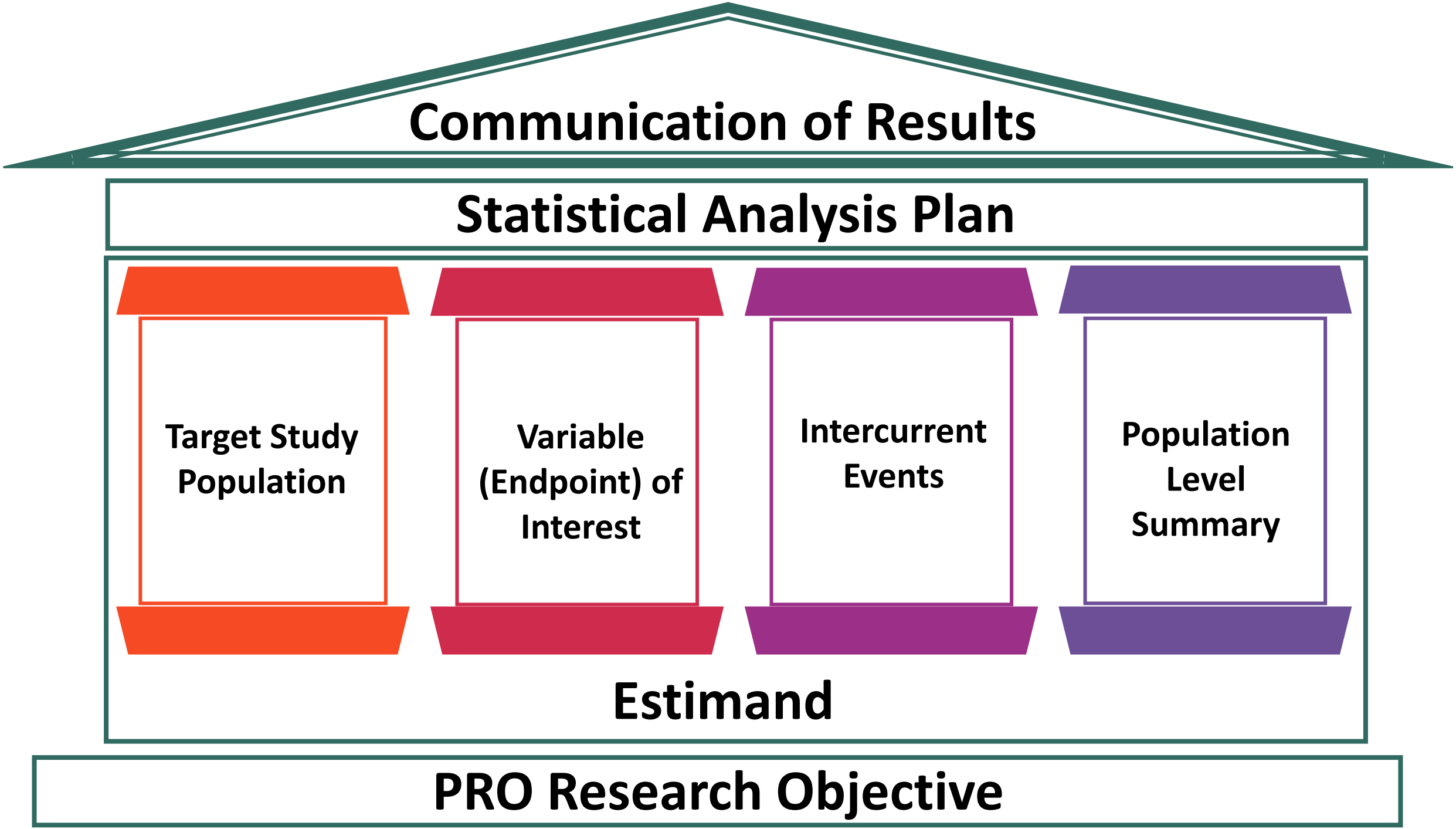
EMA Guidance on Treatment Switching

- Assumptions of the adjustment methods can in principle not be proven to be true
- A positive result from an analysis adjusted for cross-over cannot be used to rescue a trial
- May only be useful for regulatory purposes as supportive or sensitivity analyses

Beyond Efficacy

Beyond Efficacy

- Safety (e.g. Unkel et al., 2018)
- Patient-Reported Outcomes (FDA-ASCO Public Workshop 2019)
- Benefit-Risk
- Real World Evidence


Communication of Results
Statistical Analysis Plan
Target Study Population
Variable (Endpoint) of Interest
Intercurrent Events
Population Level Summary
Estimand
PRO Research Objective

BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING

Draft PDUFA VI Implementation Plan (FY 2018-2022)

Next Steps

ICH E9 R1 Addendum

“gives a framework for discussing certain interesting estimands… but **it is not clear whether methods** for estimating them are **presently practical in a regulatory environment**” (Permutt, 2019)

Transparent Subjectivity

(a) statistical work in which the assumptions and judgments are fully in view, for everyone to consider and critique, and in which sensitivity analysis reveals stability or fragility of conclusions with respect to the assumptions and judgments.

(b) analyses disciplined by both coherence and calibration in a way that helps us, and others working with us, to make good predictions of observables.

Practical Considerations: Pre-Specification

Explicitly specify in protocol and SAP

- Potential intercurrent events
- All censoring and event rules
- Statistical methods for addressing intercurrent events
- All assumptions of statistical methods
- If any assumptions can be assessed and which sensitivity analyses will be used to assess each assumption

Practical Considerations: Causal Inference

- Is the quantify of interest identifiable and estimable?
- What assumptions are needed?
- Is a clinical interpretation of a statistical method output meaningful?
- Can relevant covariates be identified at a design stage?
- Is utility of measuring these covariates favorable?
- How may potential unmeasured covariates change conclusions and interpretation of the results?
- Are regulatory agencies in alignment with the proposed statistical plan?

Practical Considerations: Treatment Switching

- Address treatment switching at the design stage
- Adequately align enrollment in trials intended for accelerated and regular approval
- Explicitly state if treatment switching is allowed and under what conditions in the protocol and SAP
- Ensure adequate data collection to support the proposed analyses
- Minimize protocol violations by investigators

Opportunities

- What is the relevant scientific question? Can existing statistical methods provide results with meaningful clinical interpretation? What scientific questions do existing methods really answer?
- Develop methods that rely on minimal assumptions
- Identify conditions when ITT analysis is suboptimal
- Collaborate with clinicians by disease area to determine:
  - Populations: identify key populations of interest
  - Variables: identify clinically meaningful outcomes
  - Intercurrent events: identify all potential intercurrent events and the best methods to address them