Missing Data:
Fundamental Considerations
&
A Brief History of Research

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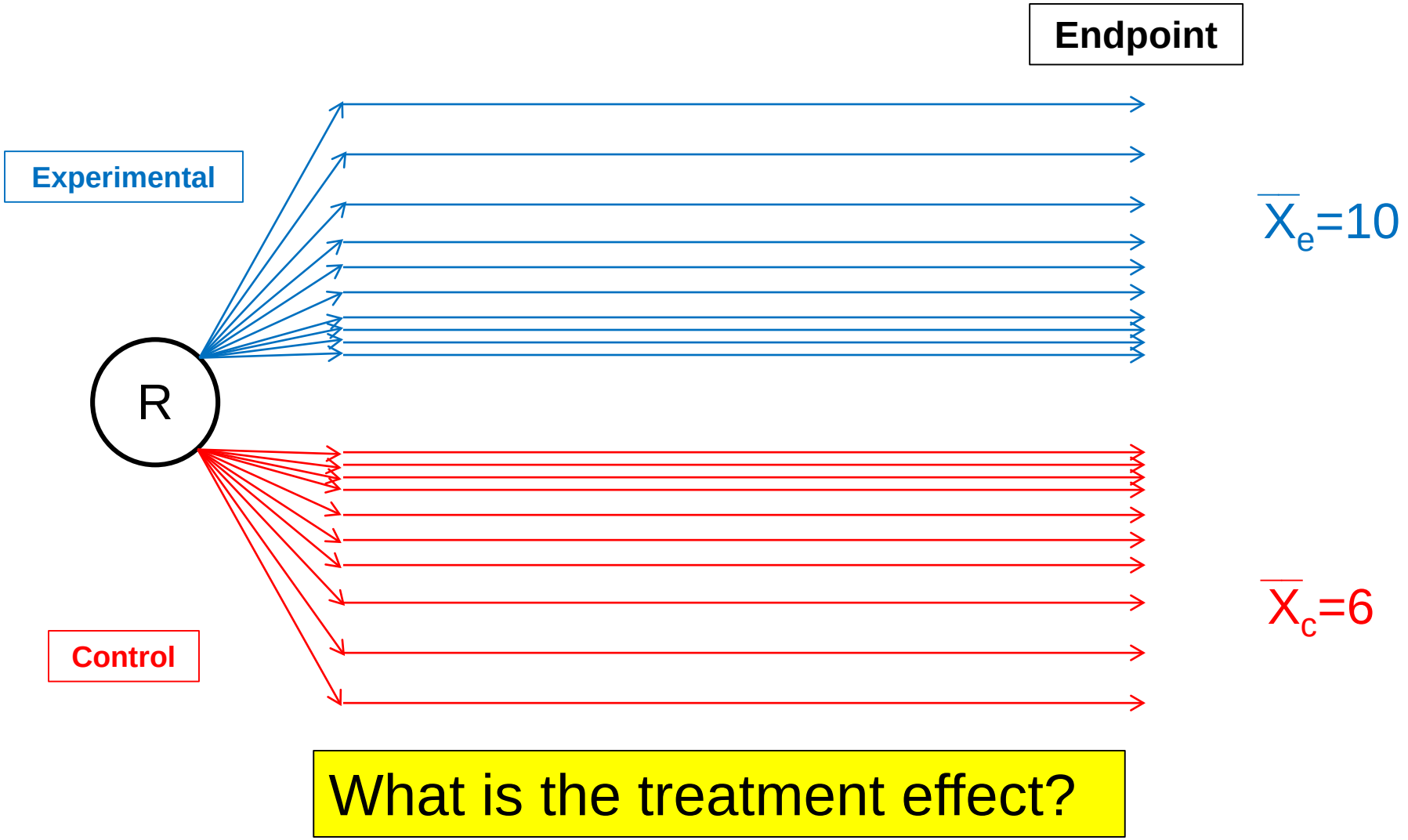
Outline

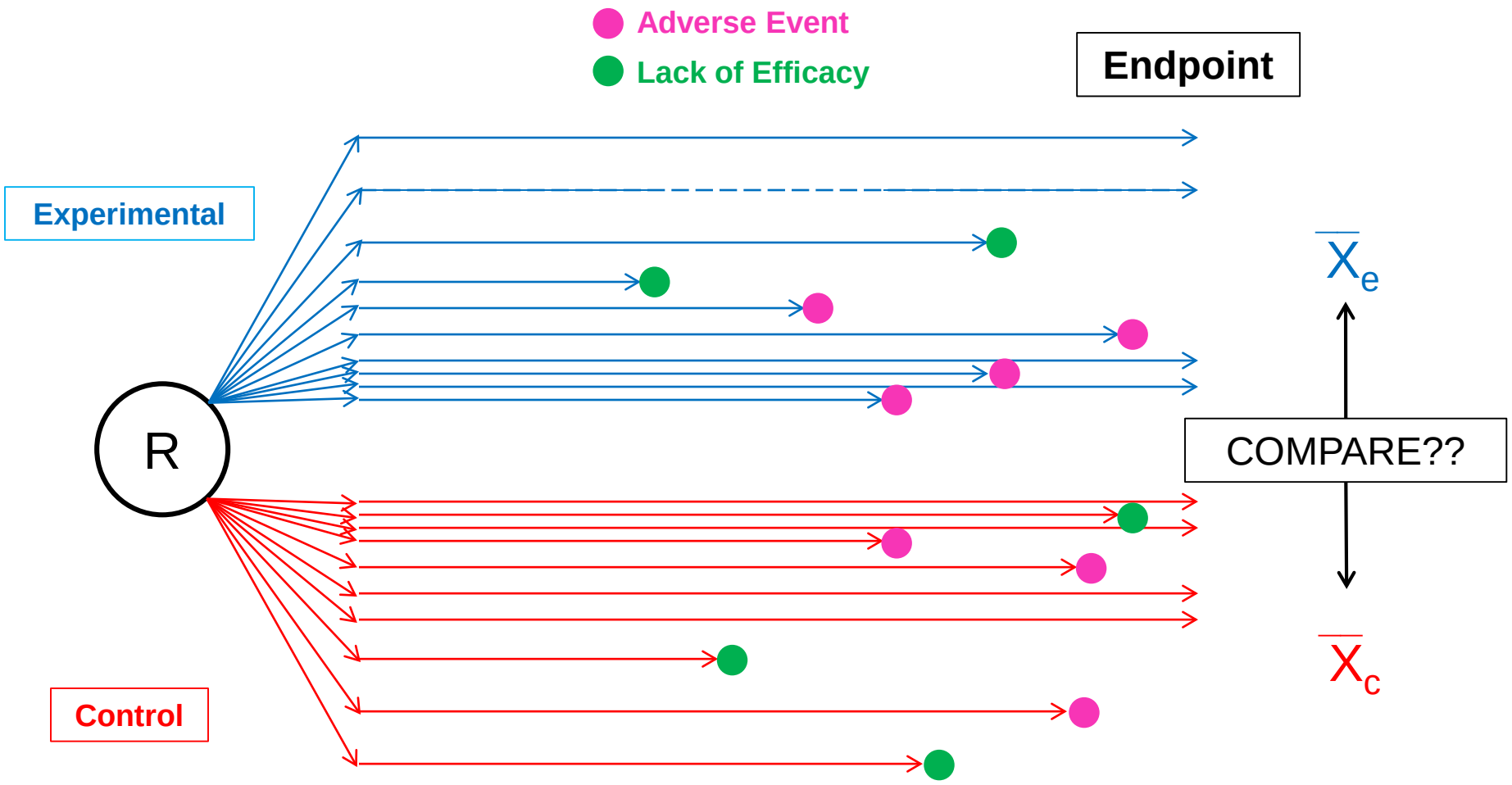
- Overview of the problem
- History of research
- History of industry practice
- A brief look ahead

Randomized Clinical Trials



What is the treatment effect?

Randomized Clinical Trials



PROBLEM: Missing Data

Starting Point

- **Missing data undermines randomization, the lynchpin of inferences in confirmatory trials**
  - **Bias & loss of power**
- **Definition and meaning of missing value / data is situation dependent** *Drug Information Journal*. 2009; 43(4): 403-408.
  - **Loss to follow up in depression trial = missing information**
  - **Death from heart attack in a trial to prevent heart attack = incomplete data but no loss of info**

Research History

1970s and 1980s

- Ad hoc approaches to create balanced data with easy computations
  - OC, LOCF, BOCF
- Definition of missing data mechanisms
  - MCAR MAR MNAR
- Development of MAR-based analyses
  - Multiple Imputation, Likelihood-based repeated measures, (IPW later)

Key Publications

- Maximum Likelihood
  - Harville, D. A. (1977), JASA, 72, 320–338.
  - Hartley, H. O. and Rao, J. N. K. (1967), Biometrika, 54, 93–108.
  - Jennrich, R. I. and Schluchter, M. D. (1986). *Biometrics* 42(4): 805–820.

- Multiple Imputation and missing data mechanisms
  - Rubin DB. Biometrika 1976;63(3),581–592.

- IPW
  - Robins, J.M., Rotnizky, A., and Zhao, L.P. (1994) JASA 89, 846–866.
  - Robins, J.M., Rotnitzky, A., and Zhao, L.P. (1995) JASA 90, 106-121.

~1990s

- **Development of MNAR-based methods**
  - **Shared-parm model:** Wu MC, Carroll RJ. Biometrics 1988; 44:175–188. 21
  - **Pattern mixture model:** Little RJA. JASA. 1993;88(421):125–134.
  - **Selection model:** Diggle PD, Kenward MG. Appl. Sta 1994;43,49–93.
- **Some criticism, but continued use of simple, ad h methods as primary analysis in clinical trials**

2000s

- Proliferation of simulation studies comparing MAR methods with simple, ad hoc methods
  - Multiple, independent investigations in simulated and real data, b industry, academia, and regulatory agencies
- Growing awareness that simple, ad hoc methods are not broadly “conservative”
- Growing debate about appropriate choices for the primary analysis
- Developed wide spread awareness of need for sensitivity analyses

2010s

- Development and refinement of estimand ideas
- New Analytic Methods
  - Multiple-imputation based approaches for sensitivity and for certain primary estimands
  - Likelihood-based analogs to the newer MI-based approaches
  - Other Approaches (trimmed mean)
- Some refocusing on need to reduce missing data

Evolution of Industry Practice

Pre - 2000

- **Analyses tended to be simple and ad hoc, a hold-over from the era when computing power limited options**
- **Post-randomisation events dealt with implicitly by choices made about data collection and statistical analysis**
- **These choices defined the scientific question**
- **ICH E9 guidance 1998**

ICH E9 and ITT

"The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject

2000-2010

- **ITT influenced handling of missing data**
  - **ITT intended to define analysis sets, not as a means to address missing data. ICH E10 states need for rescue is an endpoint.**
  - **What if key scientific questions are about the initially randomized treatments?**
- **Industry moved away from simple, ad hoc approaches toward MAR-based approaches**
- **Missing data an important topic at conferences and in regulatory-industry interactions**

2000-2010 (continued)

- **NRC Expert panel: 18 recommendations**
  - **Set clear objectives & define causal estimands**
  - **Maximize adherence**
  - **Sensible primary analysis supported by plausible sensitivity analyses**

2010-Present

Consequences of NRC Report

- Estimands are important
  - Link between objectives and analysis. The definition and proper handling of missing data depend on the estimand
- Methods research
  - Sensitivity analyses becoming routine, straight-forward approaches to assessing consequences of departures from MAR
- Greater, but still probably not enough, emphasis on prevention
- ICH E9 R1 Addendum

Process Chart to Implement 3 Pillars

- **Objectives**
  - **Decisions to be made drive objectives, which drives choice of estimands…**
- **Estimands (what is to be estimated)**
- **Design**
- **Analysis**
- **Sensitivity**
- **Iterative process**

Different Decisions & Perspectives

Stakeholders	Types of Clinical Trials
• Regulators • Payers • Physicians • Patients • Sponsors	• Exploratory vs. confirmatory vs. post-approval • Short-term vs. long-term treatment • Symptomatic treatment vs. disease modification • Efficacy vs. safety • In-patient vs out-patient

Defining Estimands

- **Population**
- **Endpoint**
- **Summary measure**
- ***How to account for inter-current events***
  - **Post-randomization events that may be related to treatment & outcome**
    - **Discontinuation of intervention +/- study**
    - **Addition of, or switching to rescue medication**
    - **Death**

Example Data

Visit	1	2	3	4	5	6	7	8
1	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X
5	X	X	X	X	X	X	.	.
6	X	X	X	X	.	.	.	.

X = observed on initially randomized treatment

X = observed on rescue medication

X = observed on no medication

. = not observed

Five Methods of Dealing with Inter-Current events

- **1) Treatment policy (ITT) – ignore inter-current events**
- **2) Composite - modified definition of the variable (or the summary measure) with inter-current event(s) a component of the outcome**
  - **NRI, mNRI, assign band rank to patients with inter-current event**
- **3) Hypothetical - specific hypothetical conditions of interest, e.g.**
  - **Outcome if patient had not stopped / switched treatment**
  - **Outcome if patients could be followed without treatment (reference based controlled imputations.**

Five Methods of Dealing with Inter-Current events (continued)

- **4) Principal strata - restrict population of interest to the stratum of patients in which an inter-current event would not have happened.**
- **5) While on treatment - values of the variable in those patients up to the time of the inter-current event in all patients**

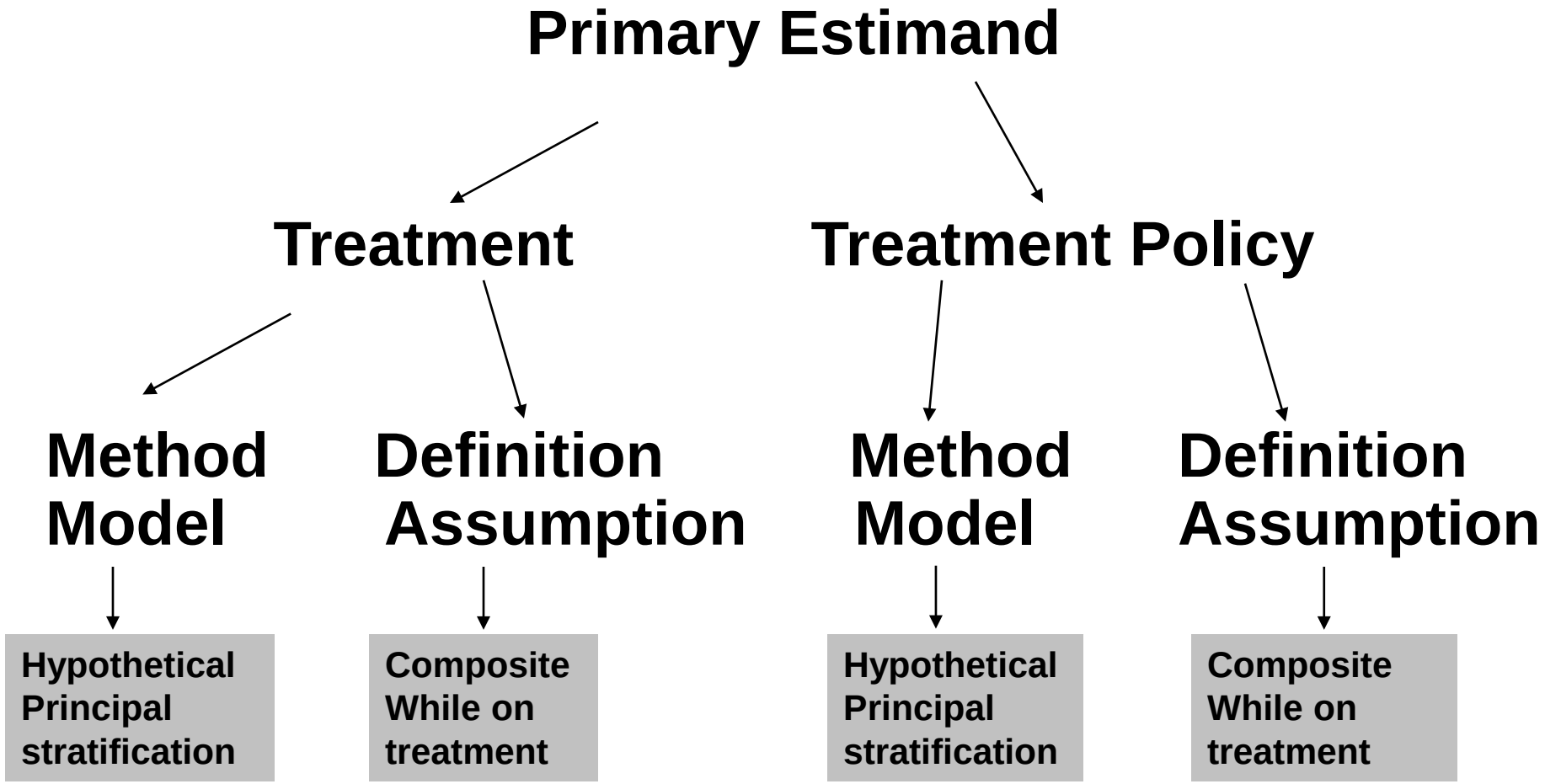
General Categories of Objectives

- **Compare treatment A vs treatment B**
- **Compare treatment policy A vs policy B**
  - **Begin with treatment A vs begin with treatment B**
  - **Treatment A + rescue vs Treatment B + rescue**

General Categories of Estimands

- **Efficacy (de-jure)**
  - **Benefit of the drug when taken as directed**
  - **Hypothetical and Principal Stratification**
- **Effectiveness (de-facto)**
  - **Benefit of the drug as actually taken**
  - **Conceptually, a composite of efficacy and adherence**
  - **Composite and while on treatment**

Analytic Road Map



Summary

- **A work in progress**
- **Much progress in the work**