

UC Irvine Data Science Initiative Short Course

# Experimental Design

## The Key to Reliable & Reproducible Science

Lecture 4:  
Missing Data

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# Ultimate Goal

- ▶ Reporting a scientific experiment
  - Overall goal
  - Specific aims
  - Materials and Methods
    - Patients, dosing, adherence to monitoring
  - Results
    - Disposition, compliance, adverse events, outcomes
  - Conclusions

# Materials

- ▶ Role of data
  - Eligibility criteria are usually broad
  - Need to describe the population actually sampled
  - Need to describe how the sample might differ from the ultimate target population
    - (Limitations to include in the Discussion)

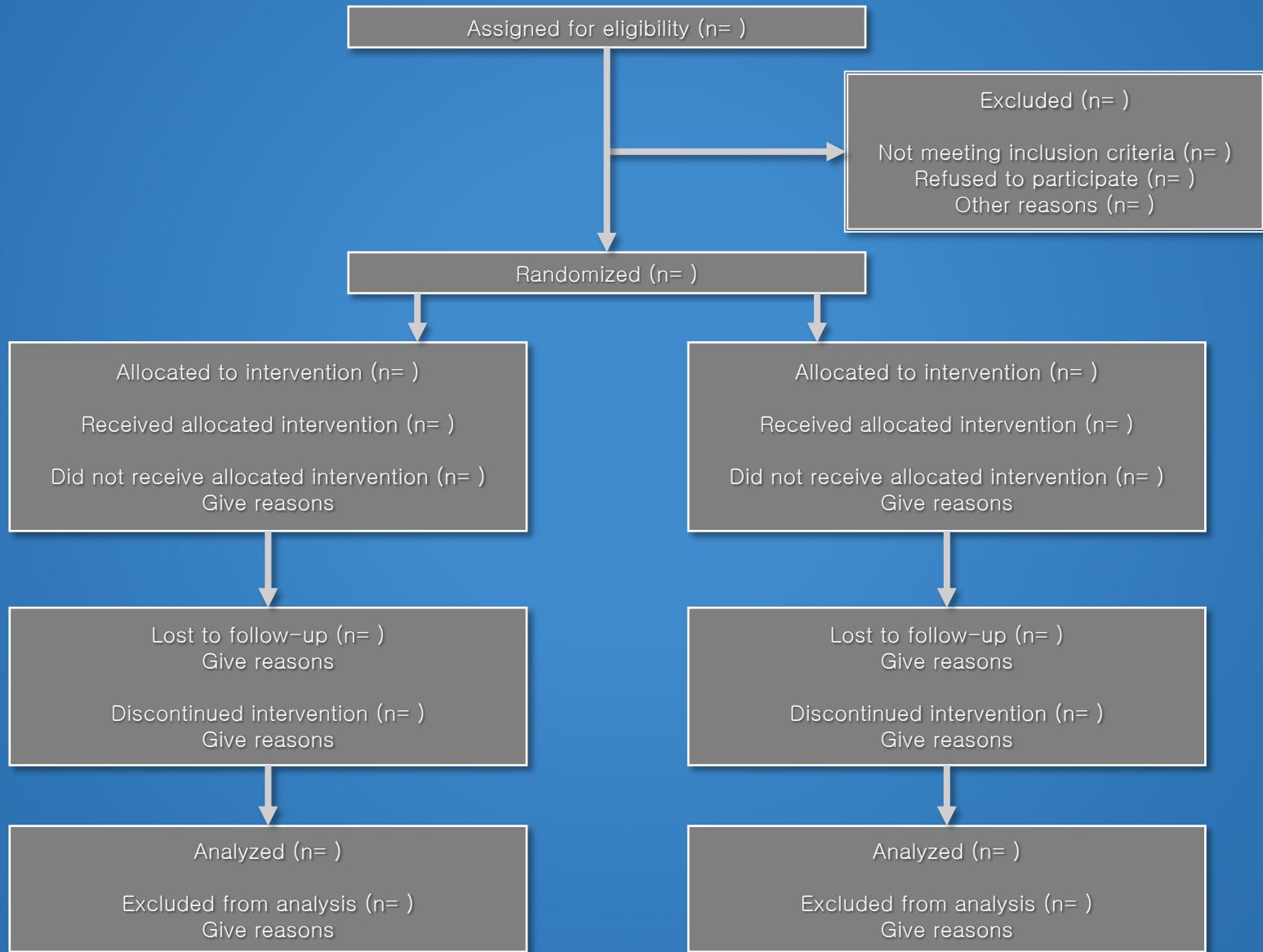
# Conceptual Framework

- ▶ Population of patients with disease
  - Defining of disease by cause vs. signs / symptoms
- ▶ Subpopulation with disease targeted by intervention
  - Some argue “Disease” is really defined by treatment
- ▶ Subpopulation eligible for study accrual
  - Restricted due to general clinical trial setting
- ▶ Eligible patients from which sampled
  - Restricted due to specific clinical trial (location, time)
- ▶ Study sample
  - Restricted due to willingness to participate
- ▶ Analysis sample
  - Data collection

# Generalizability

- ▶ CONSORT: Consolidated Standards of Reporting Trials
  - Evidence based, minimum standards
  - Report flow of patients from screening to collection of primary outcomes
    - Screened
    - Enrolled
    - Randomized
    - Completed

# CONSORT Diagram



# Run-in Data

- ▶ Some clinical trials involve a run-in
  - Placebo: All patients take placebo
    - Washout vs. assessing compliance
    - Patients may be blinded to existence of run-in
  - Active: All patients take experimental therapy
    - Allows randomized comparison of efficacy in patients actually taking drug
      - Randomized withdrawal of drug (among “responders”?)
      - Usually patients aware of run-in
    - Assess tolerability of AEs
    - Assess compliance

# Retention

- ▶ Everything else is done correctly, but lack of retention can ruin everything
  - Missing data is dangerous
- ▶ Missingness Mechanisms
  - MCAR
  - MAR
  - MNAR

# The solution?

## ► LOCF

- This is a problem in superiority trials
- If patients stop taking experimental intervention it is likely because it is not working, causing AE, “causing” other issues
  - Do NOT want to make experimental intervention look better than it likely is
    - LOCF bad, BOCF bad, worse case isn’t the solution
    - Imputation better, but not the solution

# HIVNET 012

- ▶ ACTG 076 – in 1993 stopped because 65% reduction in mother-to-child transmission of HIV
  - Using AZT during 2<sup>nd</sup> and 3<sup>rd</sup> trimesters of pregnancy
  - During labor and delivery (IV administration)
  - To infant 6 weeks thereafter
  - Problem: deliver that or triple drug therapy was not possible
  - 1997 (standard: triple drug therapy)
    - Reduction infection rates by 99% (25% to 1%)
    - Unavailable in developing country settings

# HIVNET 012

- ▶ Single oral dose nevirapine to mother at labor and delivery and single oral dose to infant was
  - Convenient
  - Feasible
  - Affordable
  - Would it work?
    - Substantially reduce transmission
- ▶ Fleming:
  - Need to reduce missingness
  - High retention to have interpretable results
  - Have to follow infants 18 months after birth
    - Prevent becoming infected during breast feeding
    - Get them through the risk
  - Follow at least 95%

# You're not at Mayo Clinic

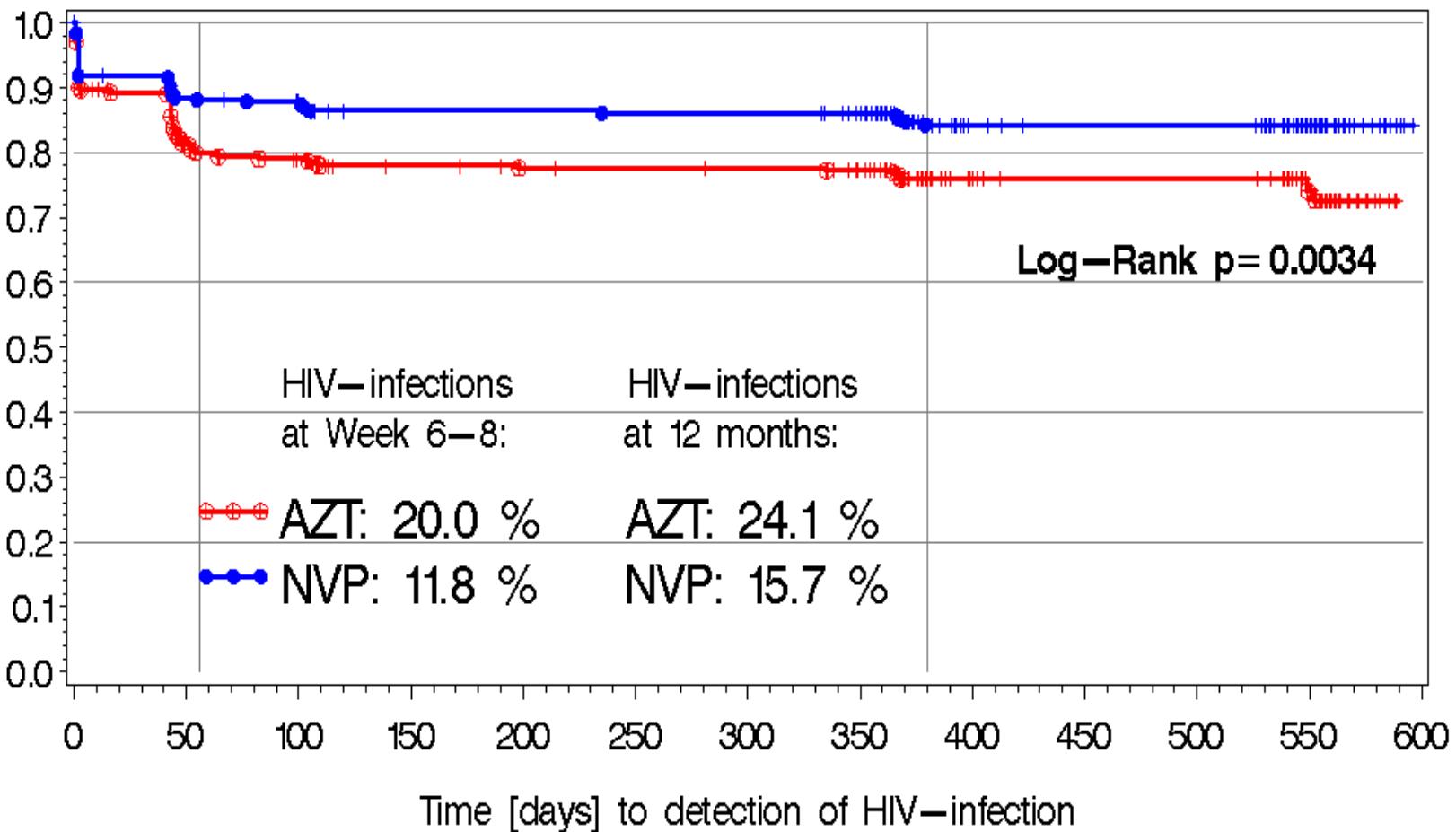
- ▶ Mother infant pairs walking into Old Mulago Hospital in Kampala Uganda
  - Follow 95% infants after 18 months
  - “The fact that it is harder does not make it any less bias inducing. The fact that it is hard to follow these infants doesn’t mean that when you don’t follow it induces less bias than when you are not following a patient at Mayo Clinic. It’s the same bias.” (Fleming)
  - “If something’s worth doing, it’s worth doing it right.” (Fleming’s mentor)
  - Doing it in a way that is interpretable
    - Preventing MTC transmission in developing countries
    - Care clinics 1/3 are already infected (1/3 of infants to become infected)
      - 1/9 of infants will be infected

# Health Visitors

- ▶ Each health visitor had a number of patients assigned
  - Each health visitor had a specific relationship with each patient
  - Developed rapport
    - Cared about well being (theirs) personally
    - Locator info was provided
    - Not just about the research
    - Home visits if acceptable to the mothers
    - Info to contact was made available
    - Proactive (not passive)
    - Education was provided
      - Malaria therapies, and help in a healthcare manner that did not impact study question of single dose nevirapine
    - Recorded everything in a meticulous manner
      - Periodic meetings held by investigators in Kampala
      - Proactive, interactive approach
      - Sharing insights to achieve retention and continue participation of mother infant pairs

# HIV Transmission Through 18 Months

Kaplan-Meier Estimates of Proportion of Infants Free of HIV-Infections



# HIVNET Retention Information

	AZT	Nevirapine	Total
Enrolled	308 100%	311 100%	619 100%
Week 6–8	300 97.4%	304 97.7%	604 97.6%
Week 14–16	300 97.4%	301 96.8%	601 97.1%
Month 12	294 95.4%	300 96.5%	594 95.9%
Month 18	293 95.2%	298 95.8%	591 95.5%
LFU over 18 mos.	4.8%	4.2%	4.5%

# HIVNET 012

- ▶ Preventing 8 infants per 100 from having a morbid life threatening infection
  - Preventing 8 deaths per 100 people
  - With 20% missing, this result could be highly unreliable
  - At a key endpoint 3–4 months
    - <3%
  - At 18 months
    - 4.5% missing
- ▶ Missingness mechanisms
  - MCAR, MAR, MNAR
    - Like you in covariates (imputation?)
      - Tip of the iceberg
        - Usually not known (or recorded) what makes individuals different
    - PREVENT MISSINGNESS

# Limitations to Missing Data Methods

- ▶ Missing data frequently are due to mechanisms that create strong dependent censoring
- ▶ These mechanism can be related to:
  - Occurrence of “off-target” effects of interventions
  - Participant willingness/ability to return for evaluation
- ▶ Covariates that are both known and recorded are usually the tip of the iceberg for the totality of factors that explain important inherent differences between participants with vs. without missing data

# Approaches to Avoid

- ▶ Changing definition of primary endpoint to reduce the risk for missing data if such a change meaningfully compromises the endpoint's clinical relevance
  - Reducing follow-up period (chronic setting)
- ▶ Compromising clinical relevance

# Approaches to Reducing Missing Data

- ▶ Protocols should more clearly distinguish between reasons for taking a patient “off study treatment” (non-adherence) vs. “off study” (non-retention)
- ▶ Follow-up should not be discontinued due to inappropriate characterization of “WD of consent”
- ▶ The informed consent process should more clearly alert patients to the negative impact that incomplete capture of outcomes has on trial integrity and credibility
- ▶ Protocol specified increases in sample sizes to address missing data should be recognized to simply produce more precise biased estimates

# Approaches to Reducing Missing Data

- ▶ Studies should involve only those investigators who are committed to follow all patients until death or capture of all trial outcomes, even if the patients have discontinued randomized treatment or initialized other interventions
- ▶ Protocols should specify performance standards for achieving high quality of trial conduct, including high levels of data capture
- ▶ Creative and effective procedures should be implemented during enrollment and follow-up to enhance achieving pre-specified targeted levels of retention
- ▶ An oversight process should be in place during trial conduct to ensure the achievement of performance standards, including targeted levels of data capture

# To Keep in Mind

- ▶ Role of data
  - Goal / aims ideally determined prior to start of study
  - BUT, the question actually answered is specific to the
    - Subjects actually sampled
    - Methods actually used
    - Data actually gathered
    - Analysis actually performed
  - Generalization of results depends on all of the above

# Overall Course Summary

1. Explain the importance of pre-specifying the primary analysis, including what can happen if the analysis is not pre-specified (i.e., performing multiple “looks”).
2. Explain what is the purpose of randomizing experimental units (e.g., study participants) to an experimental factor (e.g., experimental vs. control intervention), and when is randomization appropriate to implement in an experiment (study).
3. Identify components of different types of experimental designs (e.g., complete / blocked / stratified randomization, cross-over, factorial, non-inferiority) according to the pre-specified primary scientific question of interest for an experiment (study).
4. Explain the best way to handle missing data, and the ways to proactively try to minimize missing data.