

Biost 524:
Design of Medical Studies

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Lecture 3:
Overview of Clinical Trial Design

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Lecture Outline

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- Goal: Minimizing Bias and Variability
- Defining the Target Population
 - Disease
 - Patient population
- Defining the Intervention(s)
- Missing Data - Prevention

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Goal of Clinical Trial Design

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Minimizing Bias and Variability

Where am I going?

- Establishing the medical value of a new treatment proceeds through a series of investigations in human volunteers
- We thus want to be able to
 - ensure that we answer the important scientific question efficiently
 - minimize number of patients, calendar time, and cost.

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Clinical Trials

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- Goal:
 - Discovery and adoption of new beneficial treatments or diagnostic methods
- Experimentation in human volunteers to investigate a new treatment, preventive agent, or diagnostic method
 - Safety: Do adverse effects outweigh any benefit?
 - Efficacy: Can treatment beneficially alter disease?
 - Effectiveness: Would adoption of the treatment help population's health?

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Optimality Criteria

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- A good procedure will
 - Minimize “false positives”
 - Any treatment recommended for adoption will have a high probability of being a truly effective therapy
 - Minimize “false negatives”
 - Any truly effective therapy will have a high probability of being recommended for adoption
 - Be highly safe and ethical
 - Minimize the number of patients exposed to inferior treatments while investigations proceed
 - Be efficient
 - Minimize costs (patients, calendar time, money)

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Common Statistical Approach

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- Design an RCT to answer relevant question
 - Treatment, patient population, intervention, comparator, outcome
 - There is an underlying probability of our hypotheses being correct: “Prevalence of effective therapies”
- Fix probability of making wrong decisions
 - Erroneously decide against status quo < 2.5%
 - But: erroneously decide against status quo 2.5%
- Design trial to fix sensitivity of study
 - Power: High probability to detect beneficial treatment

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PV+ and PV- of RCT

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- Relationship to type I error, power, and prevalence of truly effective therapies

$$PVP = \frac{Power \times Prev}{Power \times Prev + (Type\ I\ err) \times (1 - Prev)}$$

$$PVN = \frac{(1 - Type\ I\ err) \times (1 - Prev)}{(1 - Type\ I\ err) \times (1 - Prev) + (1 - Power) \times Prev}$$

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Common Pitfalls of Studies

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- Data driven hypotheses
 - Multiple comparisons
 - Over-fitting of data
- Poor selection of subjects, outcomes
- Noncomparability of treatment groups

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Issues: Bias

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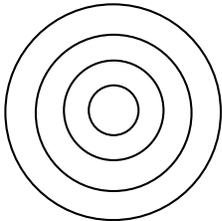
- A biased study is one that will systematically tend to estimate a treatment effect that is not correct
 - across replicated experiments (frequentist bias), or
 - with a large sample size (consistency)
- N.B.: The definition of bias is very much dependent upon what we wish we were estimating
 - How are we going to generalize our results?

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Issues: Bias

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Target - Truth

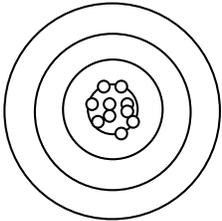


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Issues: Bias

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•If we had many replications



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Issues: Bias

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What we see ...

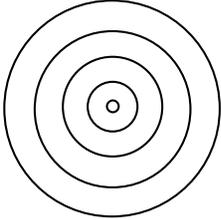


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Issues: Bias

.....

What we hope ...

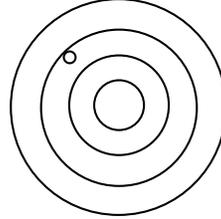


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Issues: Bias

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But it might be ...

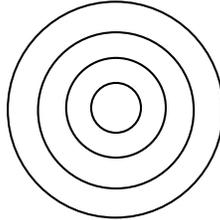


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Issues: Bias

.....

Or it might be ...



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Sources of Bias

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- Attributing an observed difference to a particular treatment
 - Disease
 - Misclassification, overly restrictive
 - Patients
 - Insufficiently or overly restrictive
 - Intervention
 - Administered incorrectly, improper restriction of ancillary treatments
 - Comparator
 - Irrelevant comparator, treatment groups not similar
 - Outcomes
 - Irrelevant outcome, measurements differ by group ¹⁶

Comparator – Example

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- Comparator – Example (RFA HL 11-036)
 - Patients predicted to receive massive transfusions
 - Plasma : Platelets : RBCs
 - 1:1:1
 - 1:1:? Where “?” is 2 or 3
 - Standard highly variable, lab guided

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Confounding Bias

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- The treatment groups being compared differ with respect to other important (measured or unmeasured) variables that are predictive of outcome
 - Systematic confounding
 - Process of assigning treatments tends to create groups that are dissimilar
 - Patient or provider preference
 - Time trends in diagnosis, treatment
 - Stochastic (conditional) confounding
 - No systematic trends, but we got unlucky this time

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Ascertainment Bias

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- Assessment of outcomes differs across treatment groups
 - Method of measurement
 - Clinical versus subclinical triggers for assessment
 - Frequency of measurement
 - Adverse events leading to higher surveillance
 - Impact on minima, maxima, time to event
 - Misclassification
 - Accuracy and/or precision of measurement affected by treatment (e.g., tumor growth vs inflammation)

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Effect Modification Bias

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- Treatment effect varies across subgroups
 - Can lead to appearance of confounding if subgroup membership differs across treatment groups
 - Also leads to problems in generalizing effectiveness to eventual treated population

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Reporting Bias

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- Tendency to report results agreeing with preconceived notions
 - Publication bias in literature
 - Selection of historical results to get most favorable outcomes
 - Multiple comparison issues in selecting primary outcomes
 - Multiple comparison issues in selecting summary of outcome distributions
- Increases type I error substantially
 - See last class

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For Each Outcome Define “Tends To”

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- In general, the space of all probability distributions is not totally ordered
 - There are an infinite number of ways we can define a tendency toward a “larger” outcome
 - This can be difficult to decide even when we have data on the entire population
 - Ex: Is the highest paid occupation in the US the one with
 - the higher mean?
 - the higher median?
 - the higher maximum?
 - the higher proportion making \$1M per year?

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Statistical Issues

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- Need to choose a primary summary measure or multiple comparison issues result
- Example: Type I error with normal data

– Any single test:	0.050
– Mean, geometric mean	0.057
– Mean, Wilcoxon	0.061
– Mean, geom mean, Wilcoxon	0.066
– Above plus median	0.085
– Above plus Pr ($Y > 1$ sd)	0.127
– Above plus Pr ($Y > 1.645$ sd)	0.169

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Statistical Issues

.....

- Need to choose a primary summary measure or multiple comparison issues result
- Example: Type I error with lognormal data

– Any single test:	0.050
– Mean, geometric mean	0.074
– Mean, Wilcoxon	0.077
– Mean, geom mean, Wilcoxon	0.082
– Above plus median	0.107
– Above plus Pr ($Y > 1$)	0.152
– Above plus Pr ($Y > 1.645$)	0.192

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Issues: Variability

- Even when unbiased, studies that are conducted with low precision present a problem
 - Decreased power leads to decreased positive predictive value of statistically significant results (Phase III)
 - The same number of patients spread across multiple small studies increases the number of statistically significant studies
 - 10,000 pts in 10 studies: Expect 0.25 false positive
 - 10,000 pts in 400 studies: Expect 10 false positive

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Statistical Design Issues

- Variability of measurements decreased by
 - Homogeneity of patient population
 - Precise definition of treatment(s)
 - Appropriate choice of clinical, statistical endpoints
 - High precision in measurements
 - Appropriate sampling strategy
- NB: But first and foremost, the RCT must be relevant

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Lecture Outline

- Goal: Minimizing Bias and Variability
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Defining the Target Population

Inclusion / Exclusion Criteria

Where am I going?

- Patients are the fundamental "material" of our scientific experiment
- We thus want to be able to
 - have a clear definition of the disease we are targeting,
 - exclude patients for whom the risk of RCT is high and
 - for whom the likelihood of successfully completing the RCT is low.

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Scientific Basis

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- A patient population for whom
 - An improved treatment is desired
 - There is no contraindication to the use of the investigational treatment
 - The investigational treatment might reasonably be expected to work
 - Furthermore: the degree of benefit is expected to be nearly the same for all subgroups of patients that can be identified beforehand

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Clinical basis

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- For clinical utility, the definition of the target population must be based on information commonly available prior to start of treatment
 - Definitions based on diagnostic criteria available only after some delay should be avoided
 - e.g., bacterial culture is often only available 24 hours after start of therapy
 - Definitions based on diagnostic tests that are not routinely available should be avoided
 - genetic profile?
 - clinical utility versus basic science

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Target Population

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- Patient population should generally reflect clinical basis as closely as possible
 - Exception: when it is ethical to conduct a clinical trial to answer a basic science question
- Additional concerns in clinical trial setting
 - Clinical equipoise among choice of all possible treatment assignments
 - Conservatism in using untested treatments
 - Patients' compliance with heightened surveillance in a clinical study

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Documentation

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- Precise definition of target patient population is crucial
 - Scientific:
 - Materials and methods of scientific experiment
 - Clinical:
 - Generalization of safety outcomes
 - Generalization of efficacy outcomes

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Inclusion / Exclusion Criteria

- Inclusion / exclusion criteria define target population
- Source of patients also of great interest for generalizability
 - Primary care versus tertiary care centers' patient populations
 - Regional differences in possible effect modifiers
 - environmental exposures
 - genetic factors

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Conceptual Framework

- Population of patients with disease
 - Definition of disease by cause vs signs / symptoms
- Subpopulation with disease targeted by intervention
 - I 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

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Ideal

- The study sample should look like a random sample from the subpopulation of all diseased patients who would ultimately be judged suitable for the intervention.
 - Negligible impact of restrictions due to clinical trial procedures
 - Negligible impact of restrictions due to locale of clinical trial
 - High participation rate by eligible patients

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Safety Considerations

- In conduct of clinical trial may want to exclude some patients
 - Need to consider whether at-risk patients should be exposed to unproven therapy
 - Pregnancy
 - Children
 - Liver, renal, heart disease
 - Elderly

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Safety Considerations

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- Generalizing study results: Efficacy vs effectiveness
 - Treatment may have to be delivered to a population larger than studied
 - Diagnostic procedures after approval may be less rigorous
 - Time requirements: Definition of gram negative sepsis
 - “Diagnostic creep”
 - If some disease has no treatment, then there may be tendency to diagnose a disease that does
 - Gram negative sepsis, non VT/VF cardiac arrest
- Off-label use

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Inclusion / Exclusion Criteria

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- Inclusion criteria:
 - Definition of ultimate target population
- Exclusion criteria:
 - Exceptions required for clinical trial setting
- Above definitions based on ideal.
 - In fact, the safety and efficacy of the investigation treatment will only have been established in patients meeting both inclusion and exclusion criteria

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Inclusion Criteria

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- Objective criteria of disease
 - Strive for common clinical definitions
 - Minimize subjective criteria
- Measures of severity of disease that might preclude inclusion in target population
 - mild disease might not be of interest
 - severe disease might not be ethical

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Inclusion Criteria

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- Subgroups of interest
 - E.g., age: adult vs children (though avoid unnecessary restriction)
 - E.g., not candidate for surgery or having failed other treatments
- Contraindications to treatment
 - Ideally, only if ultimate labeling of treatment would include such contraindications
 - E.g., liver disease, renal disease, diabetes

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Exclusion Criteria

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- Contraindications to treatments in clinical trial setting
 - E.g., safety concerns with new drug that might lead to compliance issues with unproven efficacy
 - E.g., contraindication to comparison treatment
 - E.g., language barriers
- Requirements for evaluation of treatment outcome
 - E.g., lack of measurable disease
 - E.g., inability to make clinic visits
 - E.g., simultaneous participation in other clinical trials

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Exclusion Criteria

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- Requirements for compliance to protocol
 - E.g., not passing a run-in period
 - (but need to avoid lessening generalizability)
- Requirements for ethical investigation
 - unwillingness or inability to provide informed consent

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Comments re Specification

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- Criteria for inclusion / exclusion should consider
 - Methods of measurement
 - Need for and impact of multiple measurements
 - effect of more frequent surveillance
 - possible contradictory measurements
 - Time frames for all criteria
 - usually stated relative to randomization

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Defining the Intervention(s)

.....
Complete Definition of the Intervention

Where am I going?

- The RCT will ultimately compare outcomes across populations receiving different treatments
- We thus need a prespecification of the interventions, including
 - the nominal intervention,
 - dose modifications, and
 - ancillary prophylactic or rescue treatments.

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Treatment Strategies

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- In human experimentation, we never test a treatment
 - We may not ethically force people to continue a therapy
 - It may not be medically advisable to even want a patient to continue
 - Patients may discontinue a therapy due to headache
 - If forced to continue, those patients may have CVA
- Instead we test a treatment strategy
 - We prescribe an initial treatment
 - Patients may also receive ancillary treatments
 - These may be precipitated by experimental therapy
 - Patients may progress to other therapies

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Definition of Treatments

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- Full description
 - Formulation of treatment
 - Dose, administration, frequency, duration
 - Rules for responsive dosing (e.g., insulin)
 - Include plans for
 - Treatment of adverse events
 - Dose reduction
 - Dose discontinuation
 - Ancillary treatments
 - Prescribed vs allowed vs prohibited
 - (Distinguish safety issues from efficacy issues)

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Special Issues

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- Ultimately, the scientific credibility of the clinical trial stems from our ability to assign a treatment to the participants
 - Ideally we do this in a random fashion
 - At a given point in time, we can only assign a strategy
 - Competing risks may make treatment impossible
 - Intervening events may change indications
 - Informed consent can be withdrawn
 - We must avoid ruining the comparisons of strategies
 - Naïve attempts to compare “treatment” may ruin our ability to assess what really can be tested

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Ramifications

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- Possible actions on progression
 - Stay the course
 - “Progression” dichotomizes a continuous process
 - Treatment may be delaying that process
 - Advance to other therapies
 - Ideally the same for both treatment arms
 - Cross-over to other arm (unidirectional)
 - Sometimes motivated to increase sample treated
 - A huge scientific mistake but
 - Ethics sometimes demands it

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Can There Be Noncompliance?

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- Experimentally: NO
 - By definition, all patients are following intent to treat
 - Clearly addresses effectiveness questions
 - If efficacy had been our goal:
 - Exclude noncompliant patients as much as possible prior to randomization
 - Increase sample size to deal with attenuation

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Can There Be Noncompliance?

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- Safety: MAYBE
 - We do have to worry that adherence to treatment strategy may change after reporting efficacy
 - We will only have tested safety under the compliance actually achieved
 - Measuring compliance is important for interpretation

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Ramifications

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- An important distinction needs to be made between
 - “Stopping study drug”
 - This may happen due to
 - Adverse events
 - Progression
 - Study burden
 - While we hope for high compliance
 - Badgering patients to remain on therapy can lead to worse adverse events or the quitting the study
 - In the event of stopping study drug, all follow-up of primary outcomes should proceed as planned
 - “Withdrawing consent”
 - No further data will be available

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Missing Data

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- Ideal:

“Just say no.”

(Nancy Reagan)

- Real life:

“Missing data happens”

(Bumper Sticker-
rough translation)

- Quote from a students' thesis:

“Each variable and participant will
be inspected for missing data”

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Types of Missing Data

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- Ignorable

- We can safely throw out the cases with missing data without biasing our results

- Nonignorable

- Omitting cases with missing data leads to erroneous conclusions

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Solutions?

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“If certain girls don't look at you
It means that they like you a lot
If other girls don't look at you
It just means they're ignoring you
How can you know, how can you know?
Which is which, who's doing what?
I guess that you can ask 'em
Which one are you baby?
Do you like me or are you ignoring me?”

Dan Bern, “Tiger Woods”

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Sad Facts of Life

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“Bloodsuckers hide beneath my bed”

“Eyepennies”, Mark Linkous (Sparklehorse)

- Typically, nothing in your data can tell you whether missing data is ignorable or nonignorable

- You just have to deal with what you worry about
- At the time of study design, plans should be made
 - Do the best that you can to prevent it!
 - Sensitivity analyses? Imputation? Ignore?

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Missing Data – Prevention

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- Be creative in avoiding missing data
 - HIVNET 012 (Fleming, Ann Intern Med, 2011, 154, 113)
 - ? % @ week 14-16
 - ? % @ month 18

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Missing Data – Prevention

.....

- Be creative in avoiding missing data
 - HIVNET 012 (Fleming, Ann Intern Med, 2011, 154, 113)
 - 97.1% @ week 14-16
 - 95.5% @ month 18

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Missing Data – Prevention

.....

- Be creative in avoiding missing data
 - HIVNET 012 (Fleming, Ann Intern Med, 2011, 154, 113)
 - 97.1% @ week 14-16
 - 95.5% @ month 18
 - Project I (Milburn et al., J Adol, 2005, 28, 263)
 - 3, 6 and 12 months follow-up
 - ? US
 - ? AU

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Missing Data – Prevention

.....

- Be creative in avoiding missing data
 - HIVNET 012 (Fleming, Ann Intern Med, 2011, 154, 113)
 - 97.1% @ week 14-16
 - 95.5% @ month 18
 - Project I (Milburn et al., J Adol, 2005, 28, 263)
 - 3, 6 and 12 months follow-up
 - 83%, 88%, 83% US
 - 76%, 84%, 86% AU

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Missing Data – Prevention

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- Distinguish between
 - “off study treatment”
 - “off study”
- Inactive patient
 - Continue follow-up without treatment if acceptable to patient
- Informed consent
 - Neg effect of incomplete data
- Increase in sample size
 - More precise (biased) estimates

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Missing Data – Prevention

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- Protocol
 - Performance standards
- Investigators
 - Committed to continue follow-up without treatment if acceptable to patient
- Oversight process / DSMB

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