Attrition in Randomized Controlled Clinical Trials

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Funded, in part, by NIH Grant MH60447

Attrition in RCTs

- Describe the Problem
- Strategies for Analyses of Incomplete Data
- Application
- Recommendations

Goals of RCT Design

- Minimize bias in estimate of treatment effect
- Maintain type I error
- Sufficient statistical power
- Feasible and Applicable

RCT Design

- Randomized group assignment
- Double-blinded assessments
- Control or comparison groups

Problems with Attrition

Attrition interferes with RCT goals.

It can compromise randomization and balance among groups...

- Biased estimate of the treatment effect

- Smaller N reduces statistical power
- Limited generalizability

Dropout Rates

Antidepressant RCT's submitted to FDA

(Khan, 2000, *AGP*)

	PLA	Investigational	Active
4 week	37%	25%	43%
5 week	38%	38%	--
6 week	41%	38%	36%
8 week	36%	36%	38%

45 RCTs N > 19,000 subjects ; mean: 37%

Dropout Rates

- Antipsychotic RCT's submitted to FDA (Khan, 2001, *AJP*)
- 7 RCTs; 1920 subjects
- Mean dropout rate at 6 weeks:
  - Placebo: **64%**
  - Investigational: **50%**
  - Active comparator: **56%**

Dropout Rates

FDA Review of Pediatric Antidepressants and Suicidality
(Hammad, 2004)

	PLA	Investigational	Active
MDD	28%	24%	-
Anxiety	37%	35%	-
OCD	29%	30%	44%

24 RCTs N > 4000 subjects; mean: 32%

Dropout Rates

FDA PDAC Review: 2002
Acamprosate Pivotal Trials

- 4 RCTs

- **Acamprosate: 45% dropout**
- **Placebo 55% dropout**

Dropout Rates

- Geriatric antidepressant RCT's: 1990-2003
- 22 RCTs
- Mean dropout rate: 30%

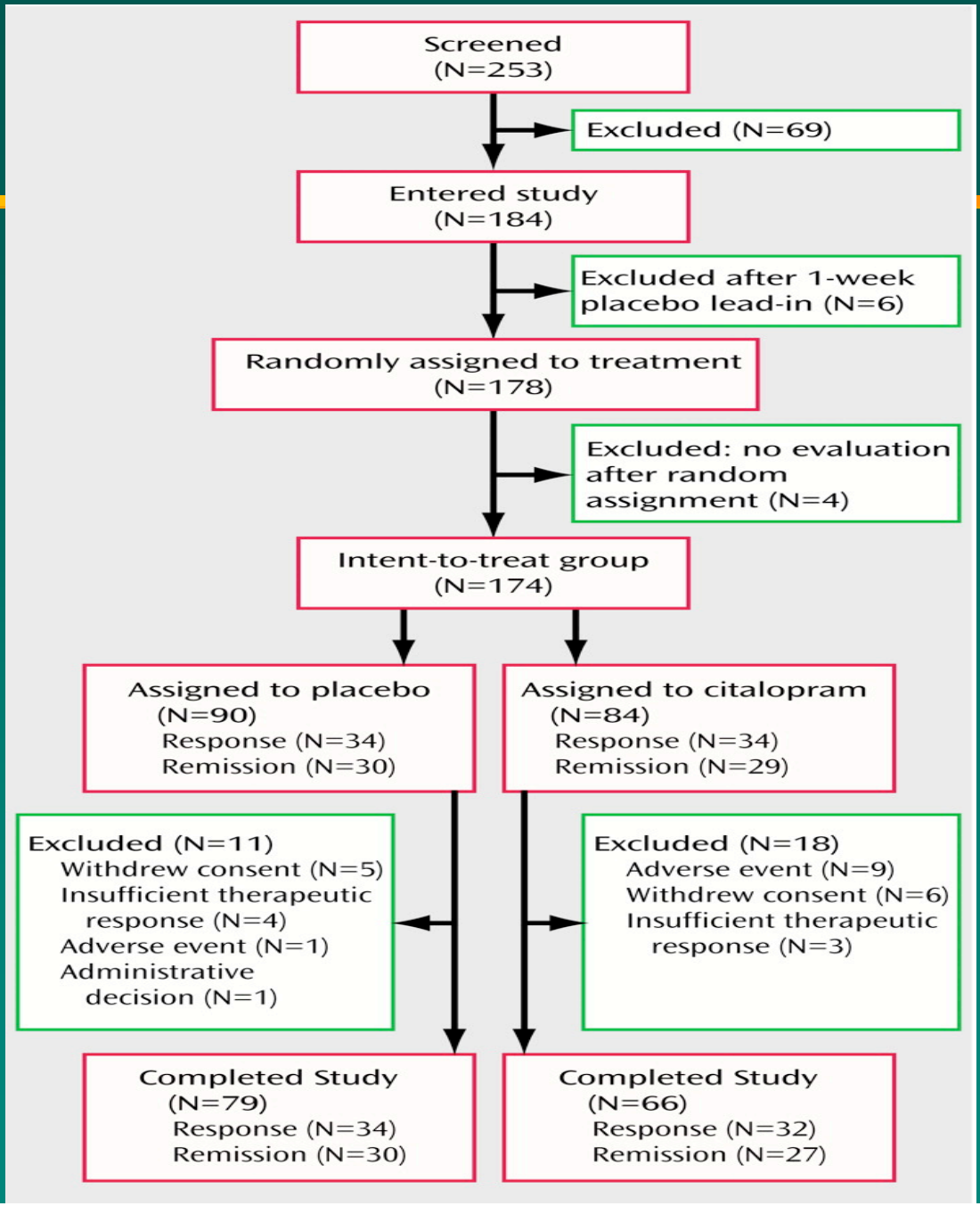
(Heo, unpublished)

Reasons for Attrition

- Symptom worsening*
- Adverse events*
- Symptom improvement*

- Subject burden
- Subject withdrew consent
- Administrative decision

CONSORT Diagram: Flow of participants through stages of RCT.



Roose et al; AJP 2004

Analysis of Incomplete Data

- **Missing data introduce bias**
- **Extent of bias is a function of**
  - Dropout rate
  - Association of dropout and unobserved outcome

Prevent Loss of Subjects

Reduce subject burden

- Telephone calls
- Home visits
- More accessible assessments (e.g., IVR)

➢ Ethical guidelines protect subjects

 Guarantee subject's right to exit

Should Protocol Deviation Censor Patient Data? **(Lavori, 1992)**

- **Attempt to continue assessments for the entire course of the RCT, regardless of protocol adherence**

  e.g., Subject drops out in week 2, assess for entire 6 weeks of RCT.

- If attrition is related to efficacy or safety…

  ⇒ Truncation of assessment confounds attrition, efficacy & safety

Neuropsychopharmacology, 1992; 6:39-42

Three general approaches to missing data
(Little, 1998)

- **Analyze complete cases only**
- **Impute data**
- **Analyze incomplete dataset**

Handling of Missing Outcomes in Published RCTs
(Wood et al, *Clinical Trials* 2004; 1:368-376)

- 71 RCTs in *BMJ*, *Lancet*, *NEJM*, and *JAMA* *July-Dec*, 2001
- 89% RCTs reported Ss were missing primary outcome
- Of RCTs with missing outcome
  - 65% performed complete case analyses
    - 46% of had repeated assessments, but excluded Ss with data

Strategies for Incomplete Data

Analyze Complete Cases Only

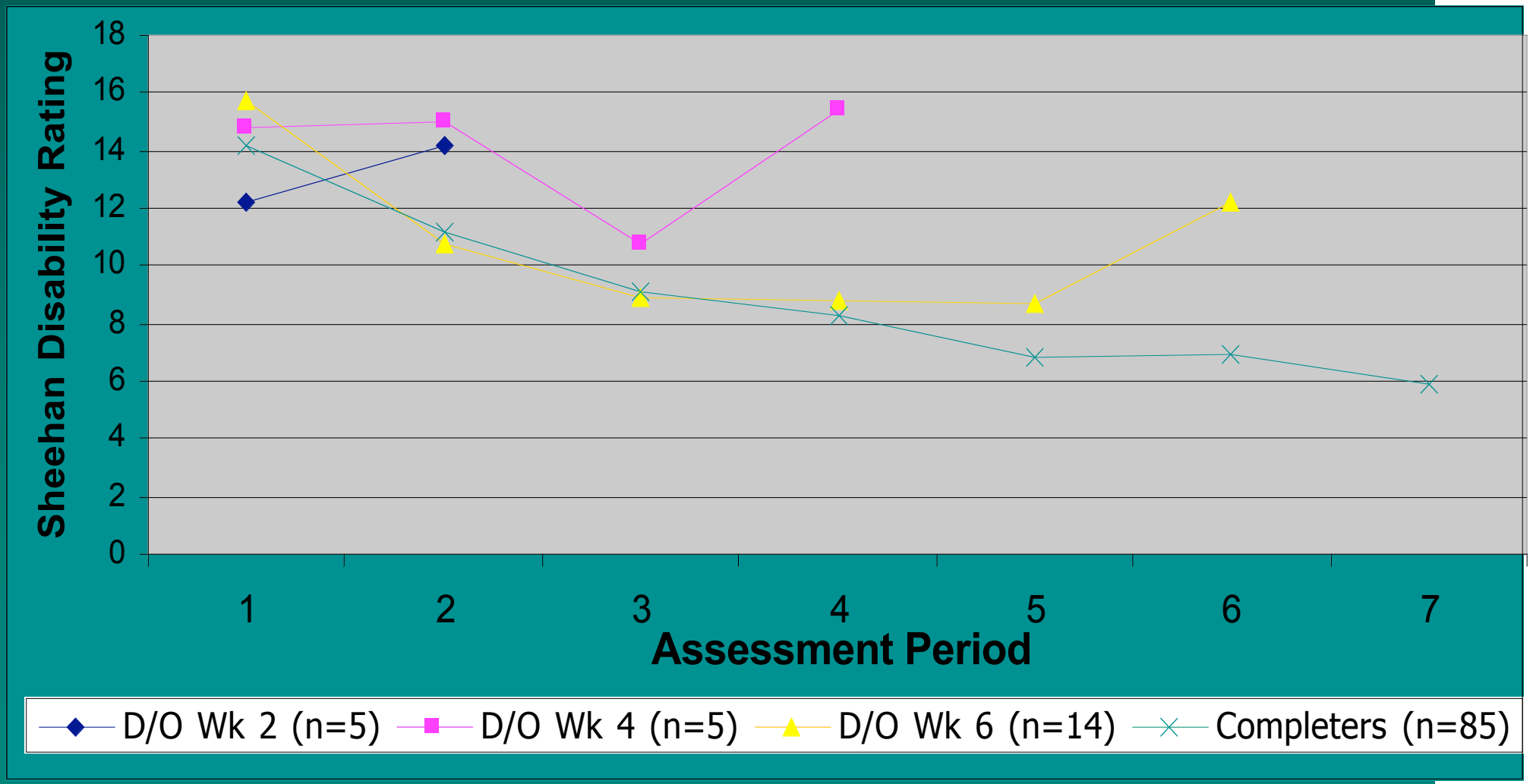
- Assumes data are Missing Completely at Random (MCAR):
  - Missingness does not depend on the dependent variable (*observed* or *unobserved* measures)
  - Assumes dropout is unrelated to efficacy (or safety)
  - Difficult to verify

Evaluating Assumption of MCAR

- Examine MCAR:
  - Compare subjects with and without missing data
  - Compare completers and dropouts
  - Among completers: Compare treatment groups

  - Comparisons are feasible for observed measures (e.g., baseline variables)
  - Not feasible for missing assessments

RCT for Panic & MDD: Course of Dropouts



Three general approaches to missing data
(Little, 1998)

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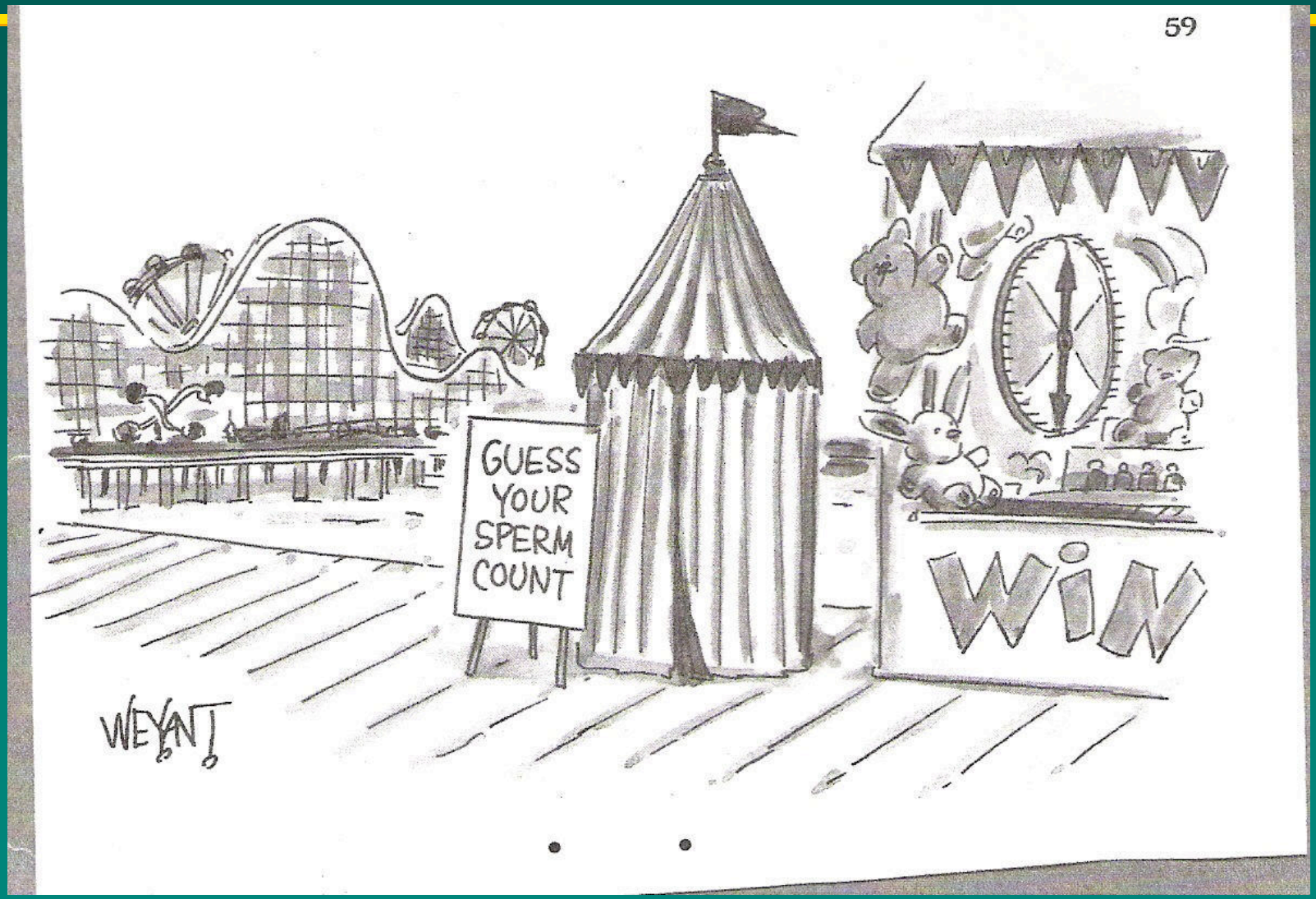
Imputation



Strategies for Incomplete Data: **Imputation**

Single Imputation

- **Last Observation Carried Forward (LOCF)**
  - A crude imputation that assumes
    - No change after dropout
  - Does not estimate any population parameter

- **Worst Observation Carried Forward**
  - Assumes dropout due to worsening symptoms

Strategies for Incomplete Data: **Imputation**

Multiple Imputation

- Imputes data for each missing value to create complete data
- Generate several data sets in this way.
- Conduct standard analysis on each data set.
- Pool results across data sets.
- Incorporates *uncertainly* of imputed data

Three general approaches to missing data
(Little, 1998)

- Analyze complete cases only
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- **Analyze incomplete dataset**

Strategies for Incomplete Data

Analyze Incomplete Data

Survival Analysis

Mixed-effects models

Model Missingness Mechanism

Survival Analysis:
Time to Response

- **Includes some data from all subjects**
- **Estimates cumulative response rates during trial**

- **Assumptions**
  - **Once classified a *responder*, subject will not revert to *non-responder* status (during trial)**
  - **Dropout is not related to outcome.**

Mixed-Effect Models

- Use available data without completely excluding subjects with some missing data
- Include varying # of observations per subject
- Account for within-subject changes over time
- Assumption: Ignorable dropout.

Ignorable Dropout

Dropout is explained by covariates and/or earlier measures of outcome

With ignorable dropout, likelihood-based models (mixed-effects models) can be used for valid inference.

Non-ignorable Dropout

Probability of missing data depends on unobserved outcome data

- Dropout due to unobserved symptom severity, adverse events, or death

- Predictors of dropout are not known/available

Strategies for Non-ignorable Dropout

- Pattern-mixture Model
- Propensity Model

Non-ignorable Dropout

Pattern-mixture model (Little, *JASA*, 1993)

Stratify analyses by pattern of missing data:

WEEK			
1	2	3	4
Obs	Obs	Obs	Obs
Obs	Obs	Obs	Missing
Obs	Obs	Missing	Obs
…			
Obs	Missing	Missing	Missing
Missing	Missing	Missing	Missing

Pattern-Mixture Model

- **Possible missing data patterns: 2^k**
  - **4 weeks: 16 patterns**
  - **Too many missingness patterns: small Ns**
- **Stratify by Phase of RCT Dropout**
  - **(Early, Middle, Late, Completer)**
- **Stratify by Reason for Dropout**
  - **(Lack of efficacy, Side effects, Moved, …)**
- **Pool stratified results**

Mixed-Effects Pattern Mixture

- **6 week RCT for schizophrenia**
- **Mixed-effects pattern mixture model**
- **Covariate: *Dropout* vs. *Completer***

Hedeker D, Gibbons RD. *Psych Methods*, 1997; 2:64-78

Strategies for Incomplete Data

- The distinction between RCTs and observational studies diminishes with attrition
- Dropout is non-randomized, observational aspect of RCT
- Non-equivalent comparison groups:

  Consider observational approaches to adjust for imbalance

Observational Strategy for Non-equivalent Comparison Groups

- Example: Subjects who dropout tend to be more symptomatic.
- A simple strategy to reduce bias:

  Conduct analyses stratified by confounding variable
- Dropout is likely a function of several characteristics
  - symptom severity, # prior episodes, # prior treatment failures
  - With *k* dichotomous variables: 2^k strata

Multi-Variable Stratification

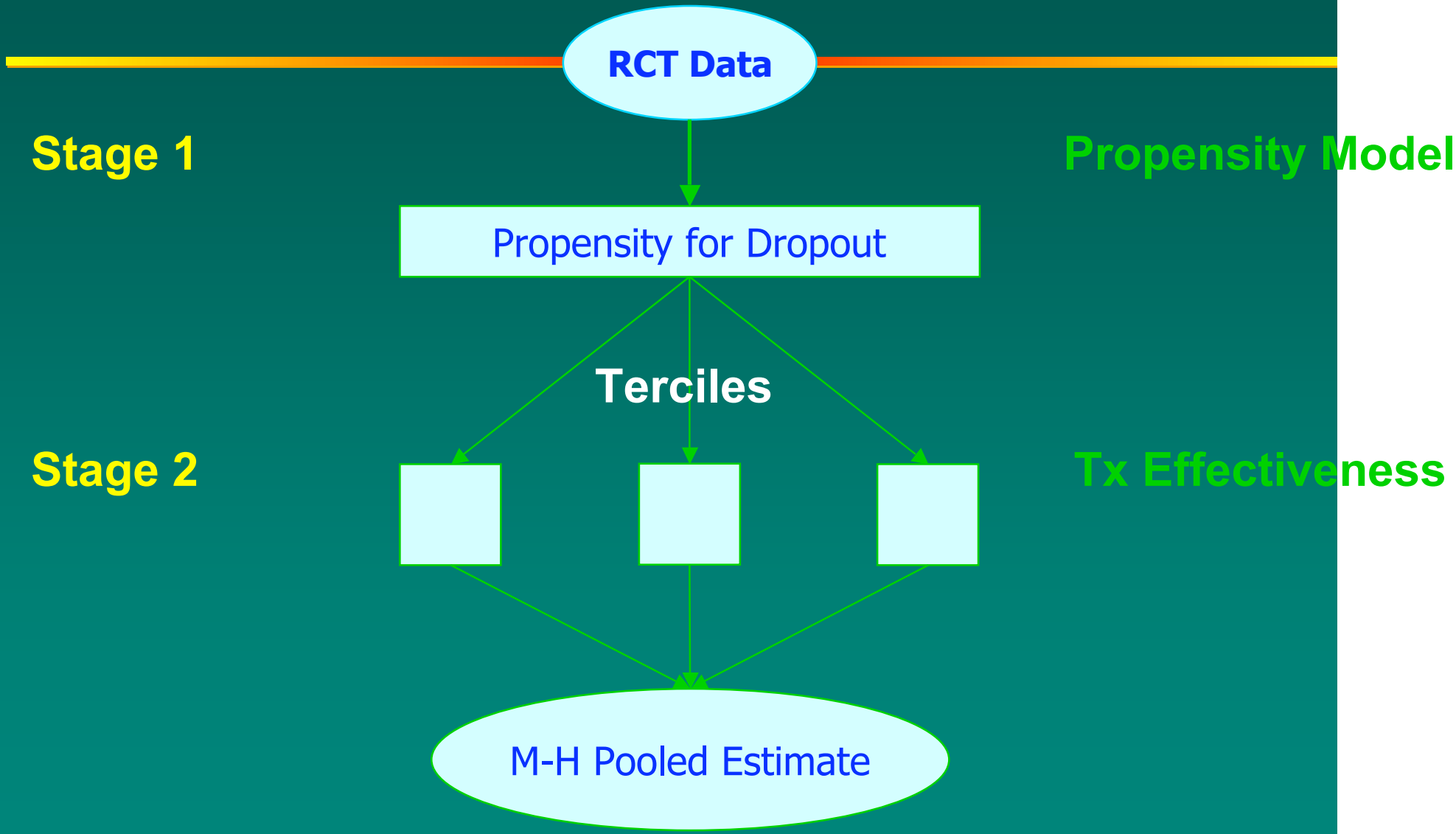
- The *propensity adjustment* is a univariate alternative to multi-variable stratification (Rosenbaum & Rubin, Biometrika 1983)
  - Propensity score: *conditional probability of group membership (ie, dropout) given observed covariates*.
- Propensity score estimated with logistic model.
- Can be used to adjust for:
  - Non-randomized treatment assignment in observational studies
  - Attrition in RCTs.

Propensity Adjustment

Propensity score is incorporated in treatment effectiveness analyses:

* Stratification
- Matching
- Covariate adjustment

Propensity for Dropout Adjustment



Application:
RCT for Panic and Depression

- 3 site, 16 week, randomized, double-blind clinical trial:
  alprazolam (N=35) vs. imipramine (N=36) vs. placebo (N=29)
- Subjects met criteria for panic disorder and depression
- Assessments
  baseline and weeks 2, 4, 6, 8, 12, and 16
- Week 16 dropout rates:

  alprazolam (20%) vs. imipramine (17%) vs. placebo (28%)

Stage 1: Propensity Analyses

Cox proportional hazards survival model

- Dependent variable: *time until dropout*
- Independent variables:
  - clinical & demographic variables hypothesized to be related to dropout

Model of *Propensity for Dropout*

Proportional hazards model: ***time until dropout***

Variable	Odds Ratio	(95% CI)
Hamilton Anxiety	1.11	(1.03-1.20)
Anticipatory Anxiety	0.80	(0.65-0.98)

Stage 2: Treatment Effectiveness Analyses

Mixed-effects linear regression model

- Dependent Variable:
  - Repeated Assessment of Sheehan Disability Scale
- Stratified by Propensity Score
- Pool stratified results

Model of Treatment Effectiveness:
Mixed-effects Linear Regression

Treatment dose	*b*	(95% CI)
Placebo	1.00	
Alprazolam	-3.00	(-5.02 to -0.97)
Imipramine	-3.25	(-5.25 to -1.25)

Dependent variable: Sheehan Disability Scale

Results pooled from propensity stratified analyses.

Unadjusted analyses were less precise: std errors 35% larger

Propensity for Dropout in RCTs

- Accounts for dropout with propensity adjustment
  - Reduces bias to the extent that dropout is ignorable based on covariates.
  - Only reduces attrition bias related to variables in propensity model.

Recommendations

RCT Protocol: Prespecify Strategy

"… no universally acceptable methods of handling missing data can be recommended" (*ICH-E9*)

The RCT protocol must specify:

- Planned approaches to missing data
- Sensitivity analyses

Sensitivity Analyses

- Sensitivity analyses evaluate assumptions about dropout and approach to missing data
- Do not rely on results of just one model
- Compare results of various approaches

Predicting Dropout

- Weekly assessment:

How likely is it that you will remain in this study through the next assessment period ?

unlikely **unsure** **very likely**

- **These data could change non-ignorable to ignorable.**

Demirtas H, Schafer JL. Statistics in Medicine, 2003; 22:2553-2575.

Summary

- Attrition can create non-equivalent comparison groups… especially when related to symptoms or side effects.
- Without proper adjustment, estimates of treatment effect will likely be biased.
- Consider data analytic approaches that account for dropout.
- Collect data that predict dropout.

Summary

Design RCTs to Minimize Attrition

Pharma collaborative analyses of *reasons for dropout* could inform future RCT design?

Consider an ethnographic study of circumstances of dropout.

"In a sense, all studies lie on a continuum from irrelevant to relevant with respect to answering a question.

A poorly controlled nonrandomized study conducted on atypical trials is barely relevant, but a small randomized study with much missing data conducted on the same atypical trials is not much better…"

DB Rubin, 1974