Estimands and Their Estimators – How to Align Them in a Coherent Way?

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Quantitative Sciences
Janssen R&D, Johnson & Johnson
Missing Data

His wifen is not working today.
Estimands and Estimators?

“It sort of makes you stop and think, doesn’t it.”
Outline

• ICH E9(R1) Trial Planning Framework

• Case Study:
  • Intercurrent events
  • Estimands
  • Estimators
  • Simulation investigation

• Summary
ICH E9(R1) - Trial Planning Framework

- Objectives
- Estimands
- Design
- Estimators/Analyses (Primary + Sensitivity)
Estimand

Defined by the following components:

- Population
- Variable
- Intercurrent events and their corresponding strategies
- Summary measure

*Not all intercurrent events need to use the same strategy*
ICH E9(R1) Identified Strategies of Addressing Intercurrent Events

- Treatment Policy
- Composite
- Hypothetical
- Principal Stratum
- While on treatment / Prior to the Intercurrent Event
Case Study: Alzheimer Long-Term Prevention Trial

• Objective:

To determine superiority of drug vs placebo in slowing cognitive decline in asymptomatic subjects at risk for developing Alzheimer’s dementia.
Potential Intercurrent Events

Considered in this example:

- Treatment discontinuation (Trt DC)
- Study discontinuation (Study DC)
- Missed visits and/or cognitive data collection leading to intermediate missing in efficacy measurements (Inter Missing)
- Initiation of Alzheimer disease therapy (Initiation of ADT)

Other potential intercurrent events (not covered):

- Treatment adherence
- Death
Study Design

1:1 Randomization

Screening

Drug

Placebo

4.5 years (54 months) Double Blind (DB) Phase

Primary time point

Primary efficacy measure: cognitive scale collected over time in the DB phase
Estimand 1: Treatment and Study DC

Population: as defined by the inclusion-exclusion criteria of the study
Variable: change from baseline to Month 54 in the cognitive measure

Intercurrent events and corresponding strategies:

<table>
<thead>
<tr>
<th>Estimand</th>
<th>Trt DC</th>
<th>Study DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Treatment Policy</td>
<td>Hypothetical*</td>
</tr>
</tbody>
</table>

*Need to specify the hypothetical scenario

Summary measure: mean treatment difference
Treatment Policy Strategy for Trt DC

• The variable observed value is of interest regardless of whether the subject has discontinued treatment
  • In general, regardless of whether the intercurrent event has occurred
• Captures the effect attributable to assignment to the treatment group
• Important for many types of studies
• Appropriate estimators?
Hypothetical Scenarios for Study DC

What would have happened if subjects who discontinued the study had instead, after discontinuation:

- **H-MAR**: similar efficacy as the subjects who did not discontinue the study
  - Treatment completers
  - Subjects who discontinued the treatment but NOT the study
- **H-Control**: efficacy as determined by the control group
  - E.g. Similar efficacy relative to control as at the time of dropout – disease modifying setting
- **H-RD**: similar efficacy as the subjects who discontinued the treatment but NOT the study (retrieved dropout subjects)
Mean On-Treatment Change from Baseline

Mean Response vs. Month for Treatment Comparison

- **Mean On-Treatment Change from Baseline**

- **Active**

- **Placebo**
Simulation Scenarios for Treatment Discontinuation

<table>
<thead>
<tr>
<th>Case</th>
<th>Group</th>
<th>Mean Total %TrtDC</th>
<th>Mean %TrtDC AE</th>
<th>Mean %TrtDC Other</th>
<th>Mean %TrtDC LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>c1a</td>
<td>drug</td>
<td>30.1</td>
<td>15.0</td>
<td>10.0</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>31.3</td>
<td>15.0</td>
<td>10.0</td>
<td>6.3</td>
</tr>
<tr>
<td>c1b</td>
<td>drug</td>
<td>36.1</td>
<td>21.0</td>
<td>10.0</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>31.3</td>
<td>15.0</td>
<td>10.0</td>
<td>6.3</td>
</tr>
<tr>
<td>c1c</td>
<td>drug</td>
<td>42.1</td>
<td>27.0</td>
<td>10.0</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>31.3</td>
<td>15.0</td>
<td>10.0</td>
<td>6.3</td>
</tr>
</tbody>
</table>

TrtDC = Treatment Discontinuation  
AE = Adverse event  
Other = Other reasons of TrtDC  
LOE = Lack of Efficacy
Study DC and %Retrieved Dropout

- Study DC
  - Could occur at or after Trt DC
  - Leads to missing values for the variable

- % Retrieved Dropout = %subjects, out of all subjects who DC the treatment, who have a retrieved end of study value
Simulation Scenarios for Study Discontinuation

Mean %Missing at Year 4.5

<table>
<thead>
<tr>
<th>Case</th>
<th>Group</th>
<th>Mean Total %TrtDC</th>
<th>0%SDC (100% Retrieved)</th>
<th>20%SDC (80% Retrieved)</th>
<th>50%SDC (50% Retrieved)</th>
<th>80%SDC (20% Retrieved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>c1a</td>
<td>drug</td>
<td>30.1</td>
<td>0</td>
<td>6.0</td>
<td>15.1</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>31.3</td>
<td>0</td>
<td>6.3</td>
<td>15.7</td>
<td>25.0</td>
</tr>
<tr>
<td>c1b</td>
<td>drug</td>
<td>36.1</td>
<td>0</td>
<td>7.2</td>
<td>18.1</td>
<td>28.9</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>31.3</td>
<td>0</td>
<td>6.3</td>
<td>15.7</td>
<td>25.0</td>
</tr>
<tr>
<td>c1c</td>
<td>drug</td>
<td>42.1</td>
<td>0</td>
<td>8.4</td>
<td>21.1</td>
<td>33.7</td>
</tr>
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<td>0</td>
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</table>

TrtDC = Treatment Discontinuation
SDC = Study Discontinuation
X% SDC = X% of the subjects who discontinue treatment, who also discontinue the study at some time point
Treatment Retrieved Dropouts: Off-Treatment Response – Scenario 1

Scenario 1: Retain mean treatment difference at treatment discontinuation but continue with placebo slope
Estimators to be Evaluated

H-MAR:
- **MMRM** – mixed effect model for repeated measures
- **MAR_DC** – Standard Multiple Imputation (MI) Regression
  - With indicator of treatment discontinuation in the imputation model

H-Control:
- **CIR** – Copy Increment from Reference MI

MISTEP SAS macro developed by James Roger and shared through DIA missing data working group site at [http://www.missingdata.org.uk](http://www.missingdata.org.uk); Figure from O’Kelly & Davis short course at the 2015 ASA Biopharmaceutical Workshop
Estimators to be Evaluated (Continued)

H-RD:

• **RD_SUBSET** – Standard Multiple Imputation (MI) Regression on the subset of subjects who did not complete treatment
  – PROC MI, MONOTONE REGRESSION
  – Treatment indicator in the imputation model

• **RD_TRT** – Stepwise MI with different sets of parameters for each pattern: on and off treatment
  – MISTEP SAS macro developed by James Roger and shared through DIA missing data working group site at http://www.missingdata.org.uk
**Estimated Mean Bias for Mean Treatment Difference: Scenario 1**

<table>
<thead>
<tr>
<th>Case</th>
<th>%TrtDC Pbo</th>
<th>%TrtDC Drug</th>
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</thead>
<tbody>
<tr>
<td>c1a</td>
<td>31.3%</td>
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<tr>
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The diagram shows the mean bias for treatment difference across different % retrieved dropout for scenarios c1a, c1b, and c1c. The methods compared are cir, mar_dc, mmrm, rd_subset, and rd_trt.

**Legend:**
- cir
- mar_dc
- mmrm
- rd_subset
- rd_trt
Estimated Mean Standard Error for Mean Treatment Difference: Scenario 1

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Estimated Power Scenario 1

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</tr>
</tbody>
</table>

Method:
- cir
- mar_dc
- mmrm
- rd_subset
- rd_trt
Treatment Retrieved Dropouts: Off-Treatment Response – Scenario 2

Scenario 2: Different post-treatment response by reason of treatment discontinuation
Estimators to be Evaluated

H-MAR:
- MMRM
- MAR_DC

H-Control (by Reason):
- BY_REASON – MI by reason of discontinuation: CR for AE, J2R for LOE, CIR for Other*

H-RD:
- RD_SUBSET
- RD_TRT_DCREASON: Stepwise MI with different sets of parameters for each pattern: On-treatment, discontinued treatment due to AE, LOE, or Other
  - MISTEP SAS macro developed by James Roger

*CR = Copy Reference; J2R = Jump to Reference; CIR = Copy Increment from Reference
Estimated Mean Bias for Mean Treatment Difference: Scenario 2

<table>
<thead>
<tr>
<th>Case</th>
<th>%TrtDC Pbo</th>
<th>%TrtDC Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>c1a</td>
<td>31.3%</td>
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<tr>
<td>c1b</td>
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</table>
Estimated Mean Standard Error for Mean Treatment Difference: Scenario 2

<table>
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<tr>
<th>Case</th>
<th>%TrtDC Pbo</th>
<th>%TrtDC Drug</th>
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</tr>
</tbody>
</table>

- **Case c1a**
- **Case c1b**
- **Case c1c**

**Graph Details:**
- **Mean Standard Error for Treatment Difference**
- **% Retrieved Dropout**
- **Method:**
  - by_reason
  - mar_dc
  - mmrm
  - rd_subset
  - rd_trt_dcreason
Estimated Power Scenario 2

<table>
<thead>
<tr>
<th>Case</th>
<th>%TrtDC Pbo</th>
<th>%TrtDC Drug</th>
</tr>
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<tbody>
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<td>42.1%</td>
</tr>
</tbody>
</table>

method
- by_reason
- mar_dc
- mmrm
- rd_subset
- rd_trt_dcreason

% Retrieved Dropout

Power (%)
Simulation Investigation Findings

- On and off mean treatment trajectories are expected to be different:
  - MAR models lead to bias
  - Bias could be improved if MMRM replaced by MI that accounts for treatment discontinuation in the imputation model

- Control-based MI or other type of MI could work very well if off-treatment mean trajectory is understood

- Retrieved dropout (RD) MI analyses:
  - Improvement in bias as compared to MAR models but increase in SE for lower %RD
  - When low %RD, the “right” RD model could improve both bias and the variability

Keep subjects in the study!
## Estimands – Treatment Policy for Trt DC

<table>
<thead>
<tr>
<th>Estimand</th>
<th>Trt DC</th>
<th>Study DC</th>
<th>Inter Missing</th>
<th>Main Estimator</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Treatment Policy</td>
<td>Hypothetical: H-Control</td>
<td>Hypothetical: H-MAR</td>
<td>-MAR MI for intermediate missing-control-based MI</td>
</tr>
</tbody>
</table>

**Note:**
- **H-Control** refers to the hypothetical control group.
- **H-MAR** refers to the hypothetical missing-at-random group.
- **Missing** indicates the handling of missing data.
- **Main Estimator** specifies the method used for handling missing data.
### Estimands – Treatment Policy for Trt DC (Cont. 1)

<table>
<thead>
<tr>
<th>Estimand</th>
<th>Trt DC</th>
<th>Study DC</th>
<th>Inter Missing</th>
<th>Main Estimator</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Treatment Policy</td>
<td>Hypothetical: H-Control</td>
<td>Hypothetical: H-MAR Other Option?</td>
<td>-MAR MI for intermediate missing -Control-based MI</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Hypothetical: H-RD</td>
<td></td>
<td>-MAR MI for intermediate missing -MI based on retrieved dropouts (RD_SUBSET, RD_TRT)</td>
</tr>
</tbody>
</table>
### Estimands – Treatment Policy for Trt DC (Cont. 2)

<table>
<thead>
<tr>
<th>Estimand</th>
<th>Trt DC</th>
<th>Study DC</th>
<th>Inter Missing</th>
<th><strong>Initiation of AD therapy (ADT)</strong></th>
<th>Main Estimator</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Trt Policy</td>
<td>Hypothetical H-RD</td>
<td>Hypothetical H-MAR</td>
<td>NA</td>
<td>-MAR MI for intermediate missing -MI based on retrieved dropouts (RD_TRT)</td>
</tr>
<tr>
<td>3</td>
<td>Treatment Policy</td>
<td></td>
<td></td>
<td><strong>Treatment Policy</strong></td>
<td>-MAR MI for intermediate missing -MI based on retrieved dropouts, with patterns of *On trt *Off trt+no ADT *Off trt + ADT (expanded RD_TRT model)</td>
</tr>
</tbody>
</table>
Hypothetical Example: Initiation of AD Therapy

![Graph showing the comparison between active and placebo treatments over time. The graph plots mean response against month. The active treatment line is green and the placebo treatment line is red. The graph shows a downward trend for both treatments, with the active treatment line consistently below the placebo line, indicating a better response.]
### Estimands – Treatment Policy for Trt DC (Cont. 3)

<table>
<thead>
<tr>
<th>Estimand</th>
<th>Trt DC</th>
<th>Study DC</th>
<th>Inter Missing</th>
<th>Initiation of AD therapy (ADT)</th>
<th>Main Estimator</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Trt Policy</td>
<td>Hypothetical H-RD</td>
<td>Hypothetical H-MAR</td>
<td>NA</td>
<td>-MAR MI for intermediate missing -MI based on retrieved dropouts (RD_TRT)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>Hypothetical -worsening vs subjects who don’t initiate ADT</td>
<td>-MAR MI for intermediate missing -MI based on retrieved dropouts (RD_TRT)</td>
</tr>
</tbody>
</table>
Sensitivity Estimators

• Change/Stress-test the assumptions of main estimator

Examples:

• Estimator for a different hypothetical scenario for study discontinuation

• Delta worsening adjustment (potentially with a tipping point finding)
Summary

• Complex framework of selecting estimands and estimators
  – Multiple intercurrent events that need to be addressed by different strategies
  – Availability of reliable estimators for certain strategies?
• Need for:
  – clear estimand definitions
  – aligned estimators
• Simulation investigation:
  – Estimator selection can have a strong impact on the estimates of the treatment effect
  – Similar operating characteristics for all estimators for high %Retrieved
  – Act to reduce preventable missing