Global Sensitivity Analysis for Studies with Intermittent Missing Data and Death

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Objectives

**Part I: Review**
To review issues and common analysis methods for death-truncated data

**Part II: Method**
To learn about a composite endpoint based approach

**Part III: Software**
To introduce a software that implements the proposed method
Part I: Review
General setting

- Consider a two-armed randomized clinical study
- The goal is to evaluate the efficacy of a treatment
- Outcomes scheduled to be measured at pre-specified post-randomization time points
- Subjects at (high) risk of death
- Outcomes unobserved due to loss to follow-up, withdrawal of consent, out-of-window visits, death, etc.
Scenarios of unobserved outcomes

Subject 1

Subject 2

Subject 3

Subject 4

Subject 5

- $t_0$, $t_1$, $t_2$, $t_3$, $t_4$, $t_5$, $t_6$, $t_7$
**Notation**

- \( T = 0, 1 \): treatment assignment
- \( Y_0 \): baseline measure at \( t_0 \)
- \( Y_1, \ldots, Y_K \): functional outcomes at \( t_1, \ldots, t_K \)
- \( Z = g(Y_0, \ldots, Y_K) \): primary functional endpoint
  - e.g. \( Z = Y_K, Z = Y_K - Y_0 \)
  - only defined when \( \Delta_K = 1 \)
- \( L \): survival time
- \( \Delta_k = I(L > t_k) \): survival status at \( t_k \)
- For survivors (\( \Delta_K = 1 \))
  - \( \tau_k \): missingness indicator of \( Y_k \) (1: observed, 0: missing)
  - \( S = (\tau_1, \ldots, \tau_K) \): missing pattern
  - \( Y_{obs} = \{ Y_k : \tau_k = 1, k \geq 1 \} \): observed functional outcome
  - \( Y_{mis} = \{ Y_k : \tau_k = 0, k \geq 1 \} \): missing functional outcome
- \( X \): baseline covariates
- \( \bar{Y}_K : (Y_0, \ldots, Y_K) \)
Data truncated by death

- **Distinction** exists between missing data and data truncated by death
- **Missing data**: exist but not collected
- **Data truncated by death**: does not exist and undefined
- Missing data imputation methods generally **not applicable** for data truncated by death
Common analysis methods

- Evaluate treatment effects **conditional** on survival
- **Joint** modeling survival and functional outcomes
- Evaluate **causal** treatment effects for principal stratum
- **Composite** endpoint combining survival and functional outcomes

Conditional model

- Unconditional models not appropriate

\[ E(Y_k) = E(Y_k | \Delta_k = 1) P(\Delta_k = 1) + E(Y_k | \Delta_k = 0) P(\Delta_k = 0) \]

- Conditional models evaluate treatment effects at a specific time \( t_k \)
  - fully conditioning on survival time \( L \)
  - or partially conditioning on survival status \( \Delta_k \)

- **Issue**: Selection bias introduced in treatment effect estimation since survival is a post-randomization covariate

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Joint model

- Comprised of **two linked sub-models**
  - survival process
  - longitudinal outcome process
- Introduce a set of common latent **random effects** shared by the two sub-models
- **the survival process serves as informative censoring for the longitudinal process**
- **the longitudinal measures can inform the underlying process for survival**

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Joint model

- Allows trajectories of longitudinal outcome after death, not scientifically meaningful
- **assumptions are made regarding the distributions as well as the interrelationships between the longitudinal and event-time data**
- **the models may be most useful as sensitivity analyses, germane exploratory analyses, or informative secondary analyses**

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Dionne L Price and Yan Wang. Commentary on joint modeling of survival and longitudinal non-survival data: current methods and issues.
**Principal stratification**

- Focused on the cohort of subjects who would have survived under either treatment arm, i.e. the principle stratification with respect to survival

\[ \{ \Delta_k(1) = \Delta_k(0) = 1 \} \]

- Assess *survivor average causal effect (SACE)* defined as

\[ SACE_k = E( Y_k(1) - Y_k(0) | \Delta_k(1) = \Delta_k(0) = 1 ) \]

- Useful for understanding the mechanistic effect of treatment on clinical outcomes

- **Issue:** whether a subject belongs to the “survivor” stratum unknown

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Composite endpoint

- A composite endpoint consists of multiple single endpoints
- For death truncated data, mix both the survival $L$ and the functional outcome $Z$
- Simple and useful if
  - the goal is to evaluate the treatment effect on both the functional outcome and survival
  - the composite endpoint can be ordered in a meaningful way
- **Issue:** effects of treatment on survival and on the functional outcome cannot be easily separated

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Including deaths when measuring health status over time.  
*Medical Care*, 33:AS164 – AS172, 1995
PART II: METHOD
To propose a **composite endpoint approach** that handles both deaths and intermittent missing data among subjects alive at the assessment times.
Outline

- Goal
- Ranking
- Treatment effect
- Benchmark missing data assumptions
- Sensitivity analysis
- Bivariate case (example)
- Imputation
- Case study
- Summary
Assume no missing data at this time
Assume that higher values of $Z$ denote better outcomes
Consider two subjects $i$ and $j$

Subject $i$ ranked better than $j$ if
- both alive at $t_K$ ($\Delta_{i,K} = \Delta_{j,K} = 1$) and $Z_i > Z_j$
- both dead at $t_K$ ($\Delta_{i,K} = \Delta_{j,K} = 0$) and $L_i > L_j$
- subject $i$ alive at $t_K$ and subject $j$ dead at $t_K$

Subject $i$ ranked the same as $j$ if
- both alive at $t_K$ ($\Delta_{i,K} = \Delta_{j,K} = 1$) and $Z_i = Z_j$
- both dead at $t_K$ ($\Delta_{i,K} = \Delta_{j,K} = 0$) and $L_i = L_j$
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Treatment effect

Treatment effect is measured by the probability that the rank for a random individual with $T = 0$ is less than the rank of a random individual with $T = 1$ minus the probability that the rank for a random individual with $T = 0$ is greater than the rank of a random individual with $T = 1$. 
Treatment effect

- $R$: rank of a subject among all the study participants
- $R^{(0)}$: rank for a random subject on $T = 0$
- $R^{(1)}$: rank for a random subject on $T = 1$
- The treatment effect is measured by

$$\theta = P(R^{(1)} > R^{(0)}) - P(R^{(1)} < R^{(0)})$$
Why not $\theta^* = P(R^{(1)} > R^{(0)})$?

Let $\delta$ be the probability that two subjects are ranked the same.

Then, $\theta = 2\theta^* - 1 + \delta$.

Under the null hypothesis of no treatment effect:
- $\theta = 0$ regardless of $\eta$
- $\theta^* = (1 - \eta)/2$

The definition of $\theta$ handles ties.
Estimation of $\theta$

In the absence of missing data, estimate $\theta$ by

$$\hat{\theta} = \frac{1}{n_0 n_1} \sum_{i: T_i = 0} \sum_{j: T_j = 1} \{I(R_i < R_j) - I(R_i > R_j)\}$$

where $n_0 = \sum_i (1 - T_i)$ and $n_1 = \sum_i T_i$
Variance of $\hat{\theta}$

\[
\text{Var}(\hat{\theta}) = \left(\frac{1}{n_0 n_1}\right)^2 \left(\sum_{i=1}^{n_0} \sum_{j=1}^{n_1} \{I(R_i < R_j) + I(R_j < R_i)\}\right)
\]

\[+ \frac{n_0 - 1}{n_0} \sum_{i=1}^{n_0} \sum_{i' = 1, i \neq i'}^{n_0} \sum_{j=1}^{n_1} \{I(R_i < R_j, R_i' < R_j) + I(R_i > R_j, R_i' > R_j)
- I(R_i < R_j, R_i' > R_j) - I(R_i > R_j, R_i' < R_j)\}\]

\[+ \frac{n_1 - 1}{n_1} \sum_{i=1}^{n_0} \sum_{i' = 1, j \neq j'}^{n_1} \sum_{j=1}^{n_1} \{I(R_i < R_j, R_i < R_j') + I(R_i > R_j, R_i > R_j')
- I(R_i < R_j, R_i > R_j') - I(R_i > R_j, R_i < R_j')\}\]

\[+ \frac{(n_0 - 1)(n_1 - 1)}{n_0 n_1} \sum_{i=1}^{n_0} \sum_{j=1}^{n_1} \sum_{i=1, i \neq i'}^{n_0} \sum_{j=1, j \neq j'}^{n_1} \{I(R_i < R_j) - I(R_j < R_i)\}^2 \right) - \hat{\theta}^2\]
Quantiles

- Quantiles (e.g. median) of the composite endpoint, \((L, \Delta_K Z)\), may further quantify the treatment effect
- More straightforward for interpretation
- Necessary supplement to the primary rank analysis
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To determine ranks, need to impute $Y_{mis}$ for non-completers
**Benchmark assumptions**

\[ f(Y_{mis} | \Delta_K = 1, Y_{obs}, Y_0, X, T, S = s) = f(Y_{mis} | \Delta_K = 1, Y_{obs}, Y_0, X, T, S = 1) \quad \forall s \neq 1 \]

- **1**: a \( K \) dimensional vector of 1’s
- **\( S = 1 \)**: “completers”
- **Complete case missing value (CCMV) restrictions applied** to the missing data patterns for patients alive at \( t_K \)

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## CCMV vs MAR

<table>
<thead>
<tr>
<th></th>
<th>$j = 1$</th>
<th>$j = 2$</th>
<th>$j = 3$</th>
<th>$j = 4$</th>
</tr>
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<td>$S = 1$</td>
<td>$p_1(y_1)$</td>
<td>$p_1(y_2</td>
<td>y_1)$</td>
<td>$p_1(y_3</td>
</tr>
<tr>
<td>$S = 2$</td>
<td>$p_2(y_1)$</td>
<td>$p_{\geq 2}(y_2</td>
<td>y_1)$</td>
<td>$p_2(y_3</td>
</tr>
<tr>
<td>$S = 3$</td>
<td>$p_3(y_1)$</td>
<td>$p_{\geq 2}(y_2</td>
<td>y_1)$</td>
<td>$p_{\geq 3}(y_3</td>
</tr>
<tr>
<td>$S = 4$</td>
<td>$p_4(y_1)$</td>
<td>$p_{\geq 2}(y_2</td>
<td>y_1)$</td>
<td>$p_{\geq 3}(y_3</td>
</tr>
</tbody>
</table>
Data transformation

- For imputation, it is important to utilize an approach that respects bounds on the functional outcomes.
- Failure to do so can result in non-sensical imputations.
- May consider a data transformation

\[
Y_k^\dagger = \phi(y_k) = \log \left\{ \frac{y_k - B_L}{B_U - y_k} \right\},
\]

where \((B_L, B_U)\) denote the lower and upper bound of \(Y\).
- There is a one-to-one mapping

\[
f(\bar{Y}_K | \Delta_K = 1, Y_0, X, T, S = 1) = h(\bar{Y}_K^\dagger | \Delta_K = 1, Y_0, X, T, S = 1) \left| \prod_{k=1}^{K} \frac{d\phi(Y_k)}{dY_k} \right|
\]
Modeling strategy

- Sequential factorization

\[
f(\overline{Y}_K|\Delta_K = 1, Y_0, X, T, S = 1) = \prod_{k=1}^K f(\overline{Y}_k|\Delta_K = 1, \overline{Y}_{k-1}, X, T, S = 1)
\]

- Specify

\[
Y_k|\overline{Y}_{k-1}, Y_0, X, T = t, S = 1 = \mu_{k,t}(\overline{Y}_{k-1}, X; \alpha_{k,t}) + \epsilon_{k,t}
\]

- \(\mu_{k,t}\): mean function, e.g.

\[
\mu_{k,t}(\overline{Y}_{k-1}, X; \alpha_{k,t}) = \alpha_{k,t,0} + \alpha_{k,t,1} \overline{Y}_{k-1} + \alpha_{k,t,2} Y_0 + \alpha_{k,t,3} X
\]

- \(\epsilon_{k,t}\): residuals
Estimation

- $\alpha_{k,t}$: estimated using least square estimator

$$
\hat{\alpha}_{k,t} = \arg\min \left\{ \sum_{i=1}^{n} I(T_i = t) \Delta_{K,i} \left( \prod_{k=1}^{K} \tau_{k,i} \right) \epsilon_{k,t,i}^2 \right\}
$$

- $\epsilon_{k,t} \sim F_{k,t}$
  - $F_{k,t} = N(0, \sigma_{k,t}^2)$ under normality assumption
  - $F_{k,t}$ estimated by kernel density estimator, e.g.

$$
\hat{f}_{k,t}(x) \propto \sum_{i=1}^{n} I(T_i = t) \Delta_{K,i} \left( \prod_{k=1}^{K} \tau_{k,i} \right) \phi \left( \frac{x - \epsilon_{k,t,i}}{h} \right)
$$

where $h$ is the bandwidth
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Sensitivity analysis

- Benchmark assumptions (CCMV) untestable
- **Sensitivity analysis** essential to evaluate the robustness of inferences to deviations from benchmark assumptions

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Exponential tilting

- Exponential tilting model
  \[ f'(y) \propto e^{\beta y} f(y) \]

- Constructs a neighborhood of distributions \( f'(y) \)
  - centered around benchmark distribution \( f(y) \)
  - indexed by (sensitivity) parameter \( \beta \)

- Closed form can be derived for (multivariate) normal distribution
  - \( Y \sim N(\mu, \Sigma) \)
  - \( Y' \sim N(\mu + \Sigma \beta, \Sigma) \)
Example: Exponential tilting

\[ Y \sim N \left( 0, \begin{bmatrix} 1 & 0.5 \\ 0.5 & 1 \end{bmatrix} \right) \]
Dimension of sensitivity parameters

- Recall: benchmark assumptions

\[
f(Y_{mis}|\Delta K = 1, Y_{obs}, Y_0, X, T = t, S = s) \\
= f(Y_{mis}|\Delta K = 1, Y_{obs}, Y_0, X, T = t, S = 1)
\]

- Sensitivity parameters typically introduced as follows:

\[
f(Y_{mis}|\Delta K = 1, Y_{obs}, Y_0, X, T = t, S = s) \\
\propto \exp\{\beta_{t,s}Y_{mis}\}f(Y_{mis}|\Delta K = 1, Y_{obs}, Y_0, X, T = t, S = 1)
\]

- Sensitivity parameters $\beta_{t,s}$
  - depends on treatment and missing pattern
  - dimension too high
  - difficult to set sensitivity analysis scenarios
  - difficult to interpret and summarize results
Sensitivity analysis assumption

\[
f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T = t, S = s) \\
\propto \exp\{\beta_t Z\} f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T = t, S = 1)
\]

- \(Z\): primary endpoint, clinical interest
- \(\beta_t\): treatment specific, dimension 2 regardless of \(K\)
- \(\beta_t = 0\): benchmark assumptions
- \(|\beta_t|\): distance (in the units of \(Z\)) from benchmark assumptions
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### Benchmark assumptions

<table>
<thead>
<tr>
<th></th>
<th>( S )</th>
<th>( \tau_1 )</th>
<th>( \tau_2 )</th>
<th>( Y_1 )</th>
<th>( Y_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( s_1 )</td>
<td>0</td>
<td>0</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>( s_2 )</td>
<td>0</td>
<td>1</td>
<td>x</td>
<td>( y_2 )</td>
<td></td>
</tr>
<tr>
<td>( s_3 )</td>
<td>1</td>
<td>0</td>
<td>( y_1 )</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>( s_4 )</td>
<td>1</td>
<td>1</td>
<td>( y_1 )</td>
<td>( y_2 )</td>
<td></td>
</tr>
</tbody>
</table>

**Assumptions:**

\[
f(Y_2, Y_1|\Delta_2 = 1, Y_0, X, T, S = (0, 0)) = f(Y_2, Y_1|\Delta_2 = 1, Y_0, X, T, S = 1)\]

\[
f(Y_1|\Delta_2 = 1, Y_2, Y_0, X, T, S = (0, 1)) = f(Y_1|\Delta_2 = 1, Y_2, Y_0, X, T, S = 1)\]

\[
f(Y_2|\Delta_2 = 1, Y_1, Y_0, X, T, S = (1, 0)) = f(Y_2|\Delta_2 = 1, Y_1, Y_0, X, T, S = 1)\]
Modeling

\[ f(Y_1, Y_2 | \Delta_2 = 1, Y_0, X, T = t, S = 1) = f(Y_1 | \Delta_2 = 1, Y_0, X, T = t, S = 1) \]

\[ \times f(Y_2 | \Delta_2 = 1, Y_1, Y_0, X, T = t, S = 1) \]

[Proposal] Bivariate case (example)
Sensitivity analysis assumptions

- Let $Z = Y_1 + Y_2$
- Assumptions

$$f(Y_2, Y_1 | \Delta_2 = 1, Y_0, X, T = t, S = (0, 0))$$
  $$\propto \exp\{\beta_t(Y_1 + Y_2)\} f(Y_2, Y_1 | \Delta_2 = 1, Y_0, X, T, S = 1)$$

$$f(Y_1 | \Delta_2 = 1, Y_2, Y_0, X, T, S = (0, 1))$$
  $$\propto \exp\{\beta_t Y_1\} f(Y_1 | \Delta_2 = 1, Y_2, Y_0, X, T, S = 1)$$

$$f(Y_2 | \Delta_2 = 1, Y_1, Y_0, X, T, S = (1, 0))$$
  $$\propto \exp\{\beta_t Y_2\} f(Y_2 | \Delta_2 = 1, Y_1, Y_0, X, T, S = 1)$$
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Numerical sampling

- Goal: to draw samples of $Y_{mis}$ for each individual with $\Delta_K = 1$ and $S \neq 1$ from
  
  $$f(Y_{mis}\mid \Delta_K = 1, Y_{obs}, Y_0, X, T, S = s) \propto \exp(\beta_T Z) f(Y_{mis}\mid \Delta_K = 1, Y_{obs}, Y_0, X, T, S = 1)$$

- Close form only available when
  - $\mu_{k,t}$: linear
  - $\epsilon_{k,t}$: normally distributed
  - $Z = g(Y_0, \ldots, Y_K)$: linear

- Numerical sampling necessary in general

- Propose to apply a random-walk Metropolis-Hastings algorithm
Sampling steps

1. Set $j = 0$. Choose arbitrary initial values for $Y_{mis}$, denoted by $Y_{mis}^{(0)}$. Let $Z^{(0)}$ be the primary functional endpoint with data $(Y_{obs}, Y_{mis}^{(0)})$

2. Set $j = j + 1$

3. Generate $Y_{mis}'$ from a (multivariate) Gaussian distribution with mean $Y_{mis}^{(j-1)}$ and variance $\Sigma$
4. Calculate the acceptance ratio as

$$ a = \frac{\exp\{\beta_T Z'\} f(Y'_\text{mis} | \Delta_K = 1, Y_{\text{obs}}, Y_0, X, T, S = 1)}{\exp\{\beta_T Z^{(j-1)}\} f(Y^{(j-1)}_{\text{mis}} | \Delta_K = 1, Y_{\text{obs}}, Y_0, X, T, S = 1)} $$

$$ \frac{\exp\{\beta_T Z'\} f(Y'_\text{mis} | \Delta_K = 1, Y_{\text{obs}}, Y_0, X, T, S = 1)}{\exp\{\beta_T Z^{(j-1)}\} f(Y^{(j-1)}_{\text{mis}} , Y_{\text{obs}} | \Delta_K = 1, Y_0, X, T, S = 1)} $$

where $Z'$ and $Z^{(j-1)}$ are the primary functional endpoints with data $(Y_{\text{obs}}, Y'_\text{mis})$ and $(Y_{\text{obs}}, Y^{(j-1)}_{\text{mis}})$, respectively.
5. Accept \( Y^{(j)}_{mis} = Y'_{mis} \) with probability \( \min(1, a) \) and 
\( Y^{(j)}_{mis} = Y^{(j-1)}_{mis} \) with probability \( 1 - \min(1, a) \)

6. Repeat Steps 2-5 until the Markov chain converges

7. Draw random samples from the set \( \{ Y^{(j_0)}_{mis}, Y^{(j_0+1)}_{mis}, \ldots \} \) as the imputed missing values, where \( j_0 \) corresponds to the number of burn-in
Multiple imputation

- Draw $M$ copies $Y_{mis}$ for each individual with $\Delta_K = 1$ and $S \neq 1$
- Create $M$ complete datasets
- For each complete dataset $m$, estimate $\theta$ by $\hat{\theta}_m$
- Overall estimator of $\theta$

$$\tilde{\theta} = \frac{1}{M} \sum_{m=1}^{M} \hat{\theta}_m$$

- Confidence intervals constructed by non-parametric bootstrap
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HT-ANAM 302 study

- Randomized, double-blind, placebo-controlled Phase III study
- Intent-to-treat population: advanced non-small cell lung cancer subjects
- To evaluate the efficacy of drug anamorelin
- Functional outcome lean body mass (LBM) scheduled to be measured at baseline ($Y_0$), 6 weeks ($Y_1$) and 12 weeks ($Y_2$)
- Primary functional endpoint: $Z = \frac{(Y_2 + Y_1)}{2} - Y_0$
## Death and missingness

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 157$</td>
</tr>
<tr>
<td>Died Prior to Wk 12</td>
<td>24 (15.3%)</td>
</tr>
<tr>
<td>Survivors with complete data</td>
<td>93 (59.2%)</td>
</tr>
<tr>
<td>Survivors missing only Wk 6</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>Survivors missing only Wk 12</td>
<td>17 (10.8%)</td>
</tr>
<tr>
<td>Survivors missing both Wks 6, 12</td>
<td>20 (12.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Anamorelin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 322$</td>
</tr>
<tr>
<td>Died Prior to Wk 12</td>
<td>54 (16.8%)</td>
</tr>
<tr>
<td>Survivors with complete data</td>
<td>185 (57.5%)</td>
</tr>
<tr>
<td>Survivors missing only Wk 6</td>
<td>17 (5.3%)</td>
</tr>
<tr>
<td>Survivors missing only Wk 12</td>
<td>31 (9.6%)</td>
</tr>
<tr>
<td>Survivors missing both Wks 6, 12</td>
<td>35 (10.9%)</td>
</tr>
</tbody>
</table>
Survival

Survival probability

Placebo (n=157)
Anamorelin (n=322) p−val=0.6621

Time

Survival probability

Placebo (n=157)
Anamorelin (n=322) p−val=0.6621

Time
## Baseline covariates

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG</td>
<td>0: {0, 1}, 1: {2}</td>
</tr>
<tr>
<td>AGE</td>
<td>0: ≤ 65, 1: &gt; 65</td>
</tr>
<tr>
<td>GENDER</td>
<td>0: M, 1: F</td>
</tr>
<tr>
<td>BMI</td>
<td>0: ≤ 18.5, 1: &gt; 18.5</td>
</tr>
<tr>
<td>WEIGHT LOSS(^1)</td>
<td>0: ≤ 10%, 1: &gt; 10%</td>
</tr>
<tr>
<td>Y0</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

\(^1\)in prior 6 months
Specify $\mu_{k,t}(\bar{Y}_{k-1}, X; \alpha_{k,t})$ as follows:

$$
\mu_{1,t,i} = \alpha_{1,t,1} + \alpha_{1,t,2} Y_{0,i} + \alpha_{1,t,3} ECOG_i + \alpha_{1,t,4} AGE_i \\
+ \alpha_{1,t,5} G_i + \alpha_{1,t,6} BMI_i + \alpha_{1,t,7} WL_i
$$

$$
\mu_{2,t,i} = \alpha_{2,t,1} + \alpha_{2,t,2} Y_{0,i} + \alpha_{2,t,3} ECOG_i + \alpha_{2,t,4} AGE_i \\
+ \alpha_{2,t,5} G_i + \alpha_{2,t,6} BMI_i + \alpha_{2,t,7} WL_i \\
+ \alpha_{2,t,8} Y_{1,i}
$$
Model fitting diagnosis

Placebo, k=1
Residuals vs Fitted

Placebo, k=1
Normal Q–Q

Placebo, k=2
Residuals vs Fitted

Placebo, k=2
Normal Q–Q

Anamorelin, k=1
Residuals vs Fitted

Anamorelin, k=1
Normal Q–Q

Anamorelin, k=2
Residuals vs Fitted

Anamorelin, k=2
Normal Q–Q

[Proposal] Case study
Analysis under benchmark assumptions

- 10 imputed datasets generated
- 200 bootstrap samples

Table: Hypothesis testing

<table>
<thead>
<tr>
<th></th>
<th>( \hat{\theta} ) (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT-ANAM 302 Study</td>
<td>0.30(0.19, 0.40)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Table: Median

<table>
<thead>
<tr>
<th></th>
<th>( \hat{p}_{50} ) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT-ANAM 302 Study</td>
<td>Anamorelin: 0.67(0.45,0.89)</td>
</tr>
<tr>
<td></td>
<td>Placebo: -0.92(-1.43,-0.28)</td>
</tr>
</tbody>
</table>
Cumulative plot

Composite Endpoint

Probability

Survival

Functional

3 84 6.9

0.00 0.25 0.50 0.75 1.00

Placebo
Anamorelin

[Proposal] Case study
Change in $E(Z)$ about 1.5 lb at $\beta_T = 0.5$ and $\beta_T = -0.5$

Set $\beta_T = \{-0.5, -0.4, \ldots, 0, \ldots, 0.5\}$

[Proposal] Case study
Sensitivity analysis: Rank

Rank

Test Statistic

Anamorelin: 0.5
Anamorelin: 0
Anamorelin: −0.5
Sensitivity analysis: Median

Median

Placebo
Anamorelin

Median

β
Sensitivity analysis: Contour of p-values

Anamorelin

Placebo

[Proposal] Case study
Conclusion

There is a significant difference between the Placebo and the Anamorelin arms in their composite endpoints of survival and average LBM change. The difference favors the Anamorelin arm.
Outline

- Goal
- Ranking
- Treatment effect
- Benchmark missing data assumptions
- Sensitivity analysis
- Bivariate case (example)
- Imputation
- Case study
- Summary
**Summary**

- Propose a **composite endpoint** approach for evaluating treatment effects in randomized clinical trials with **death** and **missingness**
- Apply complete case missing-variable restrictions (**CCMV**) for handling missing data in survivors
- Apply **exponential tilting** model for sensitivity analysis
- Introduce a parsimonious way of introducing sensitivity parameters
Part III: Software
Web application

- Currently available at
  http://sow.familyds.com/shiny/composite/
- Major components
  - upload study data
  - graphical data presentation
  - generate imputed dataset
  - bootstrap analysis
Recapitulation

- Issues and common analysis methods for death-truncated data
- Proposal: a composite endpoint based approach
- Web-application