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

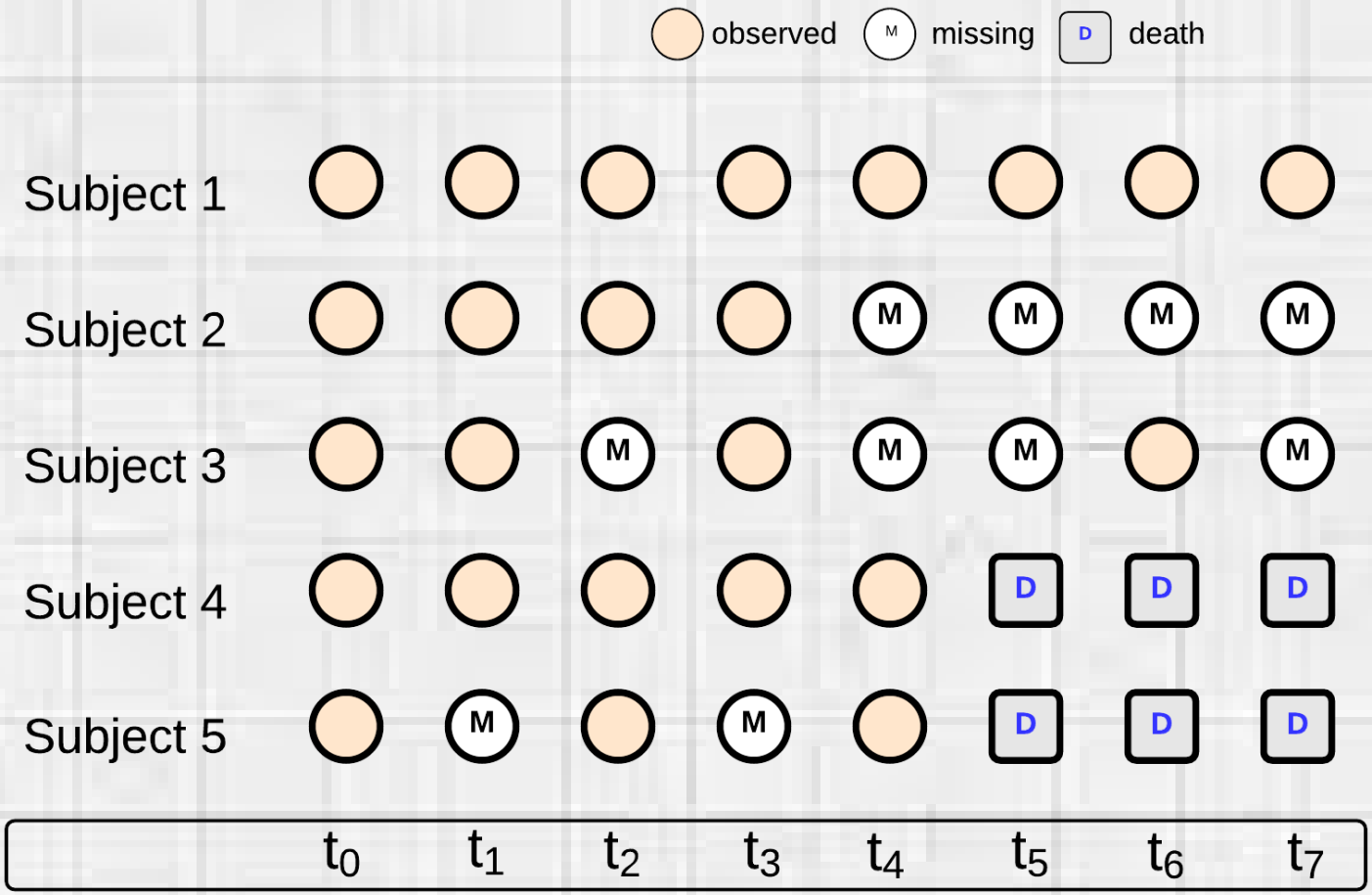
To introduce a software that implements the proposed method

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



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 ($\Delta_K = 1$)
  - τ_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
- $\overline{Y}_k$: $(Y_0, \ldots, Y_k)$

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

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B. F. Kurland, L. L. Johnson, B. L. Egleston, and P. H. Diehr. Longitudinal data with follow-up truncated by death: match the analysis method to research aims.
Statistical Science, 24(2):211–222, 2009

Conditional model

- Unconditional models not appropriate

$$E(Y_k) = E(Y_k|\Delta_k = 1)P(\Delta_k = 1) + \underbrace{E(Y_k|\Delta_k = 0)}_{\textit{undefined}} P(\Delta_k = 0)$$

- Conditional models evaluate treatment effects at a specific time t_k
  - fully conditioning on survival time L
  - or partially conditioning on survival status Δ_k
- Issue: Selection bias introduced in treatment effect estimation since survival is a post-randomization covariate

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M. Shardell and R. R. Miller. Weighted estimating equations for longitudinal studies with death and non-monotone missing time-dependent covariates and outcomes.
Statistics in Medicine, 27:1008–1025, 2008

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*

A Lawrence Gould, Mark Ernest Boye, Michael J Crowther, Joseph G Ibrahim, George Quartey, Sandrine Micallef, and Frederic Y Bois. Joint modeling of survival and longitudinal non-survival data: current methods and issues. report of the dia bayesian joint modeling working group. *Statistics in medicine*, 2014

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*

Dionne L Price and Yan Wang. Commentary on joint modeling of survival and longitudinal non-survival data: current methods and issues.
Statistics in medicine, 34(14):2200–2201, 2015

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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C. E. Frangakis and D. B. Rubin. Principal stratification in causal inference. *Biometrics*, 58(1):21–29, 2002

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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P. Diehr, D. L. Patrick, S. Hedrick, M. Rothman, D. Grembowski, T. E. Raghunathan, and S. Beresford.

Including deaths when measuring health status over time.
Medical Care, 33:AS164 – AS172, 1995

Part II: Method

Outline

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

Goal

To propose a composite endpoint approach that handles both deaths and intermittent missing data among subjects alive at the assessment times

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Ranking

- Assume no missing data at this time
- Assume that higher values of Z denote better outcomes

Ranking

- 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

$$\theta = P(R^{(1)} > R^{(0)}) - P(R^{(1)} < R^{(0)})$$

Treatment effect

- Why not $\theta^* = P(R^{(1)} > R^{(0)})$?
- Let δ 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 η
  - $\theta^* = (1 - \eta)/2$
- The definition of θ handles ties

Estimation of θ

In the absence of missing data, estimate θ by

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

where $n_0 = \sum_i (1 - T_i)$ and $n_1 = \sum_i T_i$

Variance of $\widehat{\theta}$

$$
\begin{aligned}
&\mathrm{Var}(\widehat{\theta}) \\
&= \left(\frac{1}{n_0 n_1}\right)^2 \left(\sum_{i=1}^{n_0}\sum_{j=1}^{n_1} \{ \mathrm{I}(R_i < R_j) + \mathrm{I}(R_j < R_i) \} \right. \\
&\quad + \frac{n_0 - 1}{n_0} \sum_{i=1}^{n_0} \sum_{i'=1, i\neq i'}^{n_0} \sum_{j=1}^{n_1} \{ \mathrm{I}(R_i < R_j, R_{i'} < R_j) + \mathrm{I}(R_i > R_j, R_{i'} > R_j) \\
&\qquad\qquad - \mathrm{I}(R_i < R_j, R_{i'} > R_j) - \mathrm{I}(R_i > R_j, R_{i'} < R_j) \} \\
&\quad + \frac{n_1 - 1}{n_1} \sum_{i=1}^{n_0} \sum_{j=1}^{n_1} \sum_{j'=1, j\neq j'}^{n_1} \{ \mathrm{I}(R_i < R_j, R_i < R_{j'}) + \mathrm{I}(R_i > R_j, R_i > R_{j'}) \\
&\qquad\qquad - \mathrm{I}(R_i < R_j, R_i > R_{j'}) - \mathrm{I}(R_i > R_j, R_i < R_{j'}) \} \\
&\quad \left. + \frac{(n_0 - 1)(n_1 - 1)}{n_0 n_1} \sum_{i=1}^{n_0} \sum_{j=1}^{n_1} \sum_{i=1, i\neq i'}^{n_0} \sum_{j=1, j\neq j'}^{n_1} \{ \mathrm{I}(R_i < R_j) - \mathrm{I}(R_j < R_i) \}^2 \right) - \widehat{\theta}^2
\end{aligned}
$$

Quantiles

- Quantiles (e.g. median) of the composite endpoint, $(L, \Delta_K Z)$, may further quantify the treatment effect
- More straight forward for interpretation
- Necessary supplement to the primary rank analysis

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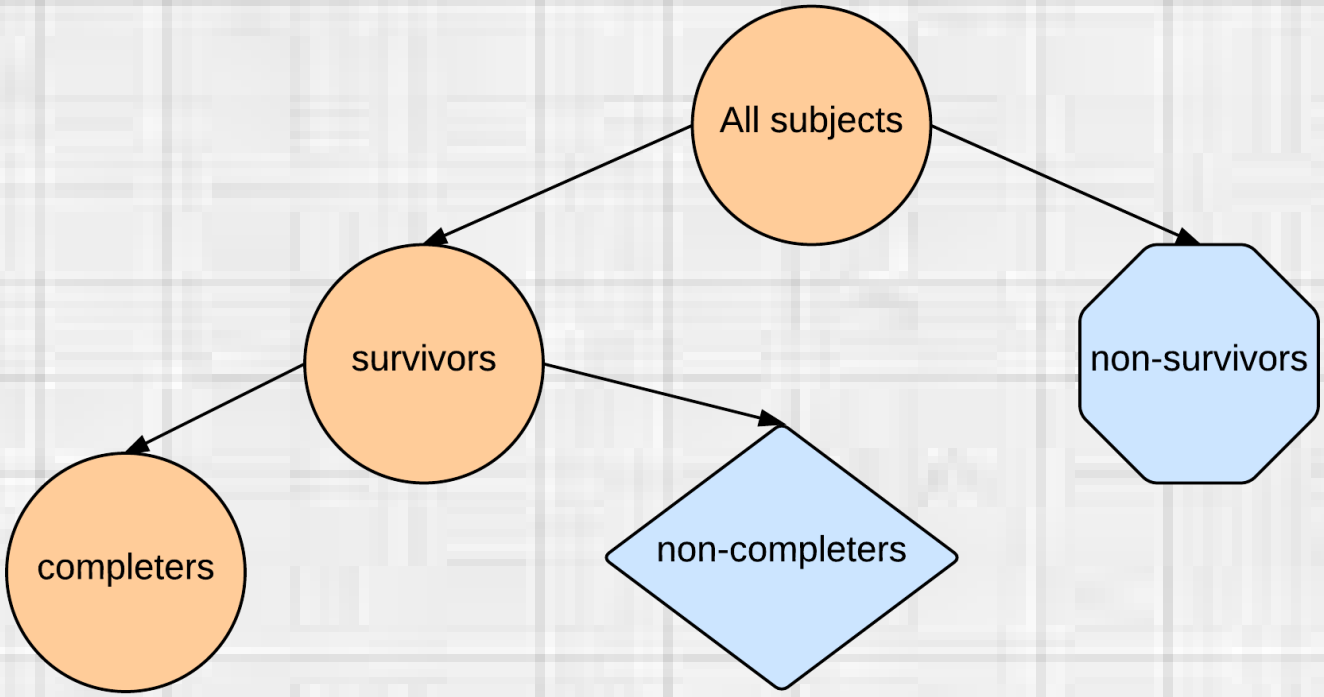
Missingness



To determine ranks, need to impute Y_{mis} for non-completers

Benchmark assumptions

$$f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T, S = s)$$
$$= f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T, S = \mathbf{1}) \qquad \forall s \neq \mathbf{1}$$

- $\mathbf{1}$: a K dimensional vector of 1's
- $S = \mathbf{1}$: "completers"
- Complete case missing value (CCMV) restrictions applied to the missing data patterns for patients alive at t_K

Roderick JA Little. Pattern-mixture models for multivariate incomplete data. *Journal of the American Statistical Association*, 88(421):125–134, 1993

CCMV vs MAR

	$j=1$	$j=2$	$j=3$	$j=4$
$S=1$	$p_1(y_1)$	$p_1(y_2\|y_1)$	$p_1(y_3\|y_1,y_2)$	$p_1(y_4\|y_1,y_2,y_3)$
$S=2$	$p_2(y_1)$	$p_{\geq 2}(y_2\|y_1)$	$p_2(y_3\|y_1,y_2)$	$p_2(y_4\|y_1,y_2,y_3)$
$S=3$	$p_3(y_1)$	$p_{\geq 2}(y_2\|y_1)$	$p_{\geq 3}(y_3\|y_1,y_2)$	$p_3(y_4\|y_1,y_2,y_3)$
$S=4$	$p_4(y_1)$	$p_{\geq 2}(y_2\|y_1)$	$p_{\geq 3}(y_3\|y_1,y_2)$	$p_4(y_4\|y_1,y_2,y_3)$

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 tranformation

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

where (B_L, B_U) denote the lower and upper bound of Y

- There is a one-to-one mapping

$$f(\overline{Y}_K|\Delta_K = 1, Y_0, X, T, S = \mathbf{1}) =$$

$$h(\overline{Y}_K^{\dagger}|\Delta_K = 1, Y_0, X, T, S = \mathbf{1}) \left|\prod_{k=1}^{K} \frac{d\phi(Y_k)}{dY_k}\right|$$

Modeling strategy

- Sequential factorization

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

- Specify

$$Y_k|\overline{Y}_{k-1}, Y_0, X, T = t, S = \mathbf{1}$$
$$= \mu_{k,t}(\overline{Y}_{k-1}, X; \boldsymbol{\alpha}_{k,t}) + \epsilon_{k,t}$$

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

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

  - $\epsilon_{k,t}$: residuals

Estimation

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

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

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

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

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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Panel on Handling Missing Data in Clinical Trials; National Research Council. *The Prevention and Treatment of Missing Data in Clinical Trials*.
The National Academies Press, 2010.
ISBN 9780309158145.
URL http://www.nap.edu/openbook.php?record_id=12955

Exponential tilting

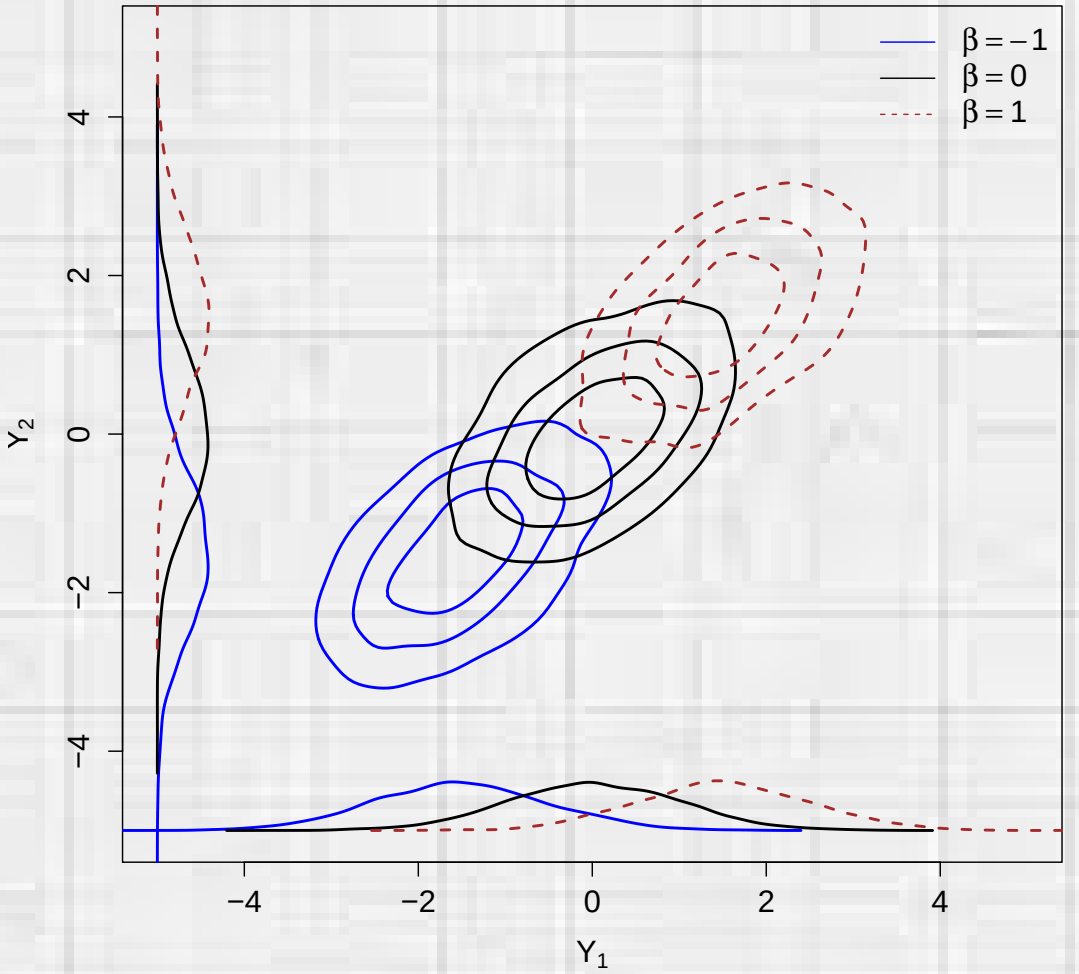
- Exponential tilting model

$$f'(y) \propto e^{\beta y} f(y)$$

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

$$f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T = t, S = s) = f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T = t, S = \mathbf{1})$$

- Sensitivity parameters typically introduced as follows:

$$f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T = t, S = s) \propto \exp\{\beta_{t,s} Y_{mis}\} f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T = t, S = \mathbf{1})$$

- 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

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

- Z: primary endpoint, clinical interest
- β_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

S	τ_1	τ_2	Y_1	Y_2
s_1	0	0	x	x
s_2	0	1	x	y_2
s_3	1	0	y_1	x
s_4	1	1	y_1	y_2

Assumptions:

$$
\begin{aligned}
&f(Y_2, Y_1 | \Delta_2 = 1, Y_0, X, T, S = (0,0)) \\
&\qquad = f(Y_2, Y_1 | \Delta_2 = 1, Y_0, X, T, S = \mathbf{1}) \\
&f(Y_1 | \Delta_2 = 1, Y_2, Y_0, X, T, S = (0,1)) \\
&\qquad = f(Y_1 | \Delta_2 = 1, Y_2, Y_0, X, T, S = \mathbf{1}) \\
&f(Y_2 | \Delta_2 = 1, Y_1, Y_0, X, T, S = (1,0)) \\
&\qquad = f(Y_2 | \Delta_2 = 1, Y_1, Y_0, X, T, S = \mathbf{1})
\end{aligned}
$$

Modeling

$$
\begin{aligned}
&f(Y_1, Y_2 | \Delta_2 = 1, Y_0, X, T = t, S = \mathbf{1}) \\
&\quad = \underbrace{f(Y_1 | \Delta_2 = 1, Y_0, X, T = t, S = \mathbf{1})}_{\text{model 1}} \\
&\quad\quad \times \underbrace{f(Y_2 | \Delta_2 = 1, Y_1, Y_0, X, T = t, S = \mathbf{1})}_{\text{model 2}}
\end{aligned}
$$

Sensitivity analysis assumptions

- Let $Z = Y_1 + Y_2$
- Assumptions

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

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Numerical sampling

- Goal: to draw samples of Y_{mis} for each individual with $\Delta_K = 1$ and $S \neq \mathbf{1}$ from

$$f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T, S = s) \propto \exp(\beta_T Z) f(Y_{mis}|\Delta_K = 1, Y_{obs}, Y_0, X, T, S = \mathbf{1})$$

- 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 Metroplis-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 Σ

Sampling steps

4. Calculate the acceptance ratio as

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

where Z' and $Z^{(j-1)}$ are the primary functional endpoints with data (Y_{obs}, Y'_{mis}) and $(Y_{obs}, Y^{(j-1)}_{mis})$, respectively

Sampling steps

5. Accept $Y_{mis}^{(j)} = Y'_{mis}$ with probability $\min(1, a)$ and $Y_{mis}^{(j)} = Y_{mis}^{(j-1)}$ with probability $1 - \min(1, a)$
6. Repeat Steps 2-5 until the Markov chain converges
7. Draw random samples from the set $\{Y_{mis}^{(j_0)}, Y_{mis}^{(j_0+1)}, \ldots\}$ 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 $S \neq \mathbf{1}$
- Create M complete datasets
- For each complete dataset m, estimate θ by $\widehat{\theta}_m$
- Overall estimator of θ

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

- Confidence intervals constructed by non-parametric bootstrap

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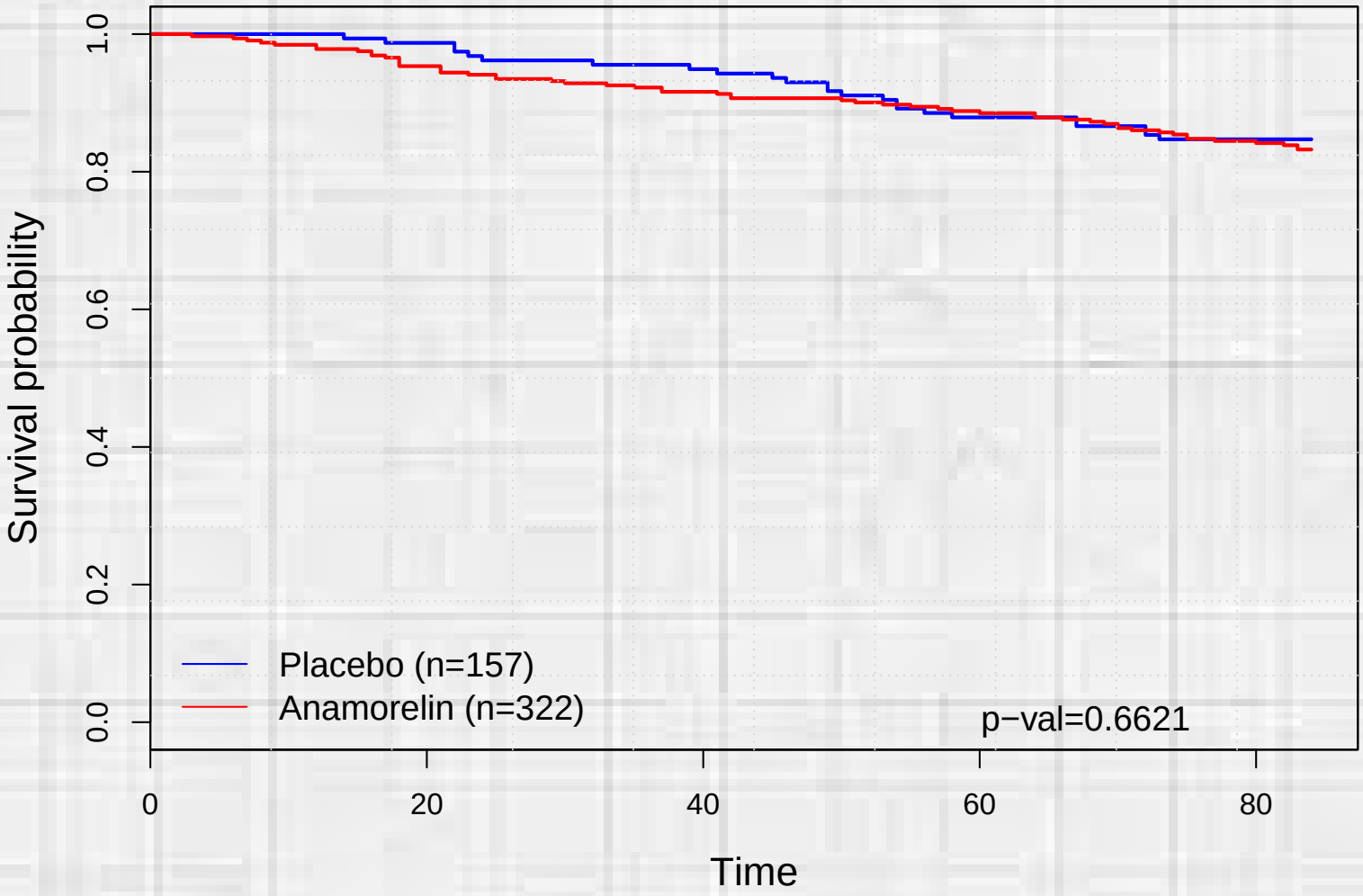
HT-ANAM 302 study

- 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

	Placebo $n = 157$	Anamorelin $n = 322$
Died Prior to Wk 12	24 (15.3%)	54 (16.8%)
Survivors with complete data	93 (59.2%)	185 (57.5%)
Survivors missing only Wk 6	3 (1.9%)	17 (5.3%)
Survivors missing only Wk 12	17 (10.8%)	31 (9.6%)
Survivors missing both Wks 6, 12	20 (12.7%)	35 (10.9%)

Survival


Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
Placebo (n=157)
Anamorelin (n=322)
p−val=0.6621
0
20
40
60
80
Time

Baseline covariates

Covariates	Levels
ECOG	0:$\{0, 1\}$, 1:$\{2\}$
AGE	0:≤ 65, 1:> 65
GENDER	0:M, 1:F
BMI	0:≤ 18.5, 1:> 18.5
WEIGHT LOSS [1]	0:$\leq 10\%$, 1:$> 10\%$
Y0	Continuous

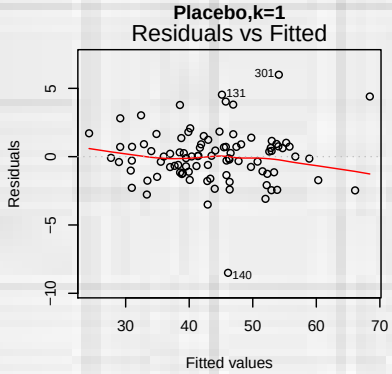
[1] in prior 6 months

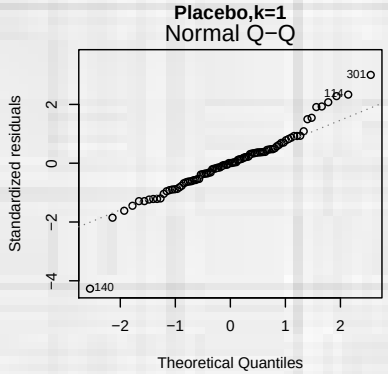
Modeling

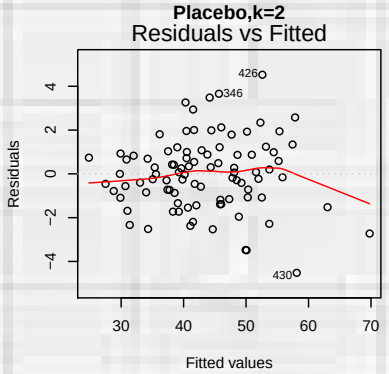
Specify $\mu_{k,t}(\overline{Y}_{k-1}, X; \alpha_{k,t})$ as follows:

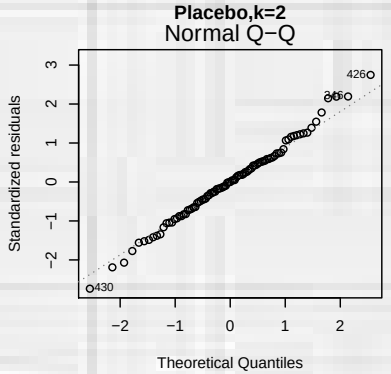
$$\begin{aligned}
\mu_{1,t,i} &= \alpha_{1,t,1} + \alpha_{1,t,2} Y_{0,i} + \alpha_{1,t,3} ECOG_i + \alpha_{1,t,4} AGE_i \\
&\quad + \alpha_{1,t,5} G_i + \alpha_{1,t,6} BMI_i + \alpha_{1,t,7} WL_i \\
\mu_{2,t,i} &= \alpha_{2,t,1} + \alpha_{2,t,2} Y_{0,i} + \alpha_{2,t,3} ECOG_i + \alpha_{2,t,4} AGE_i \\
&\quad + \alpha_{2,t,5} G_i + \alpha_{2,t,6} BMI_i + \alpha_{2,t,7} WL_i \\
&\quad + \alpha_{2,t,8} Y_{1,i}
\end{aligned}$$

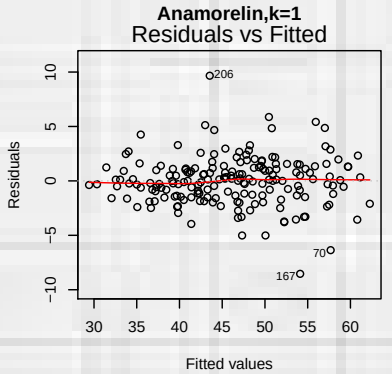
Model fitting diagnosis

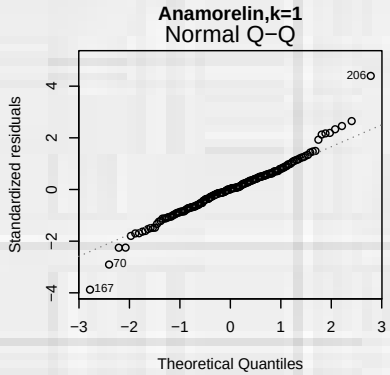


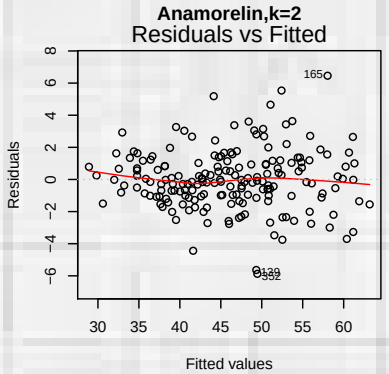


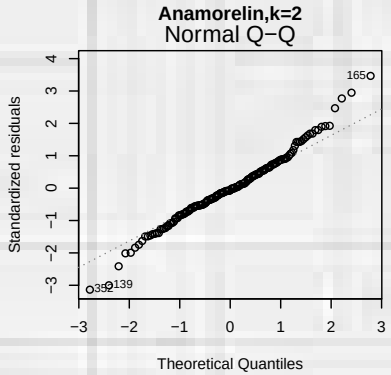












Analysis under benchmark assumptions

- 10 imputed datasets generated
- 200 bootstrap samples

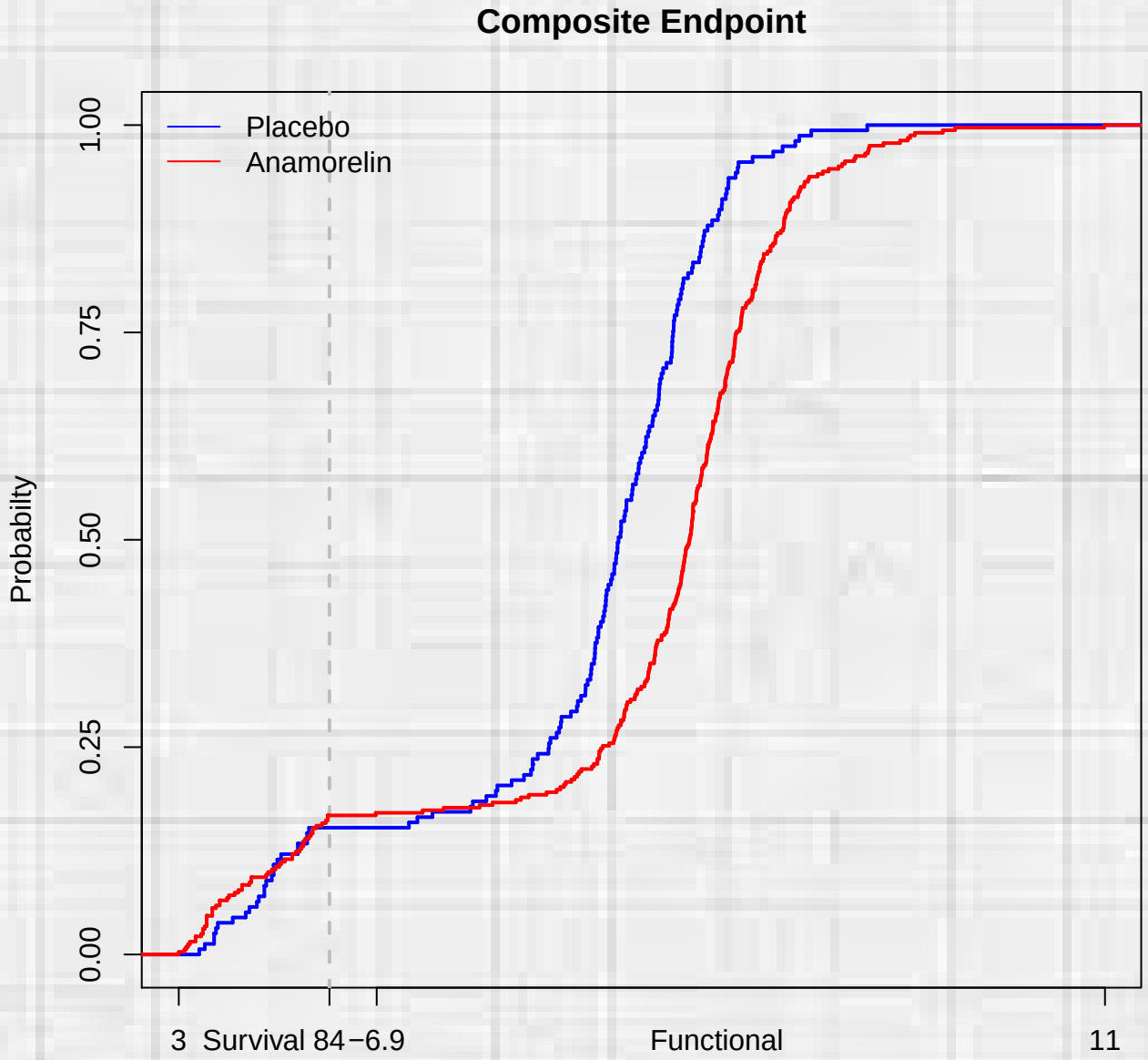
Table: Hypothesis testing

	$\widehat{\theta}$ (95% CI)	p-value
HT-ANAM 302 Study	0.30(0.19,0.40)	< 0.0001

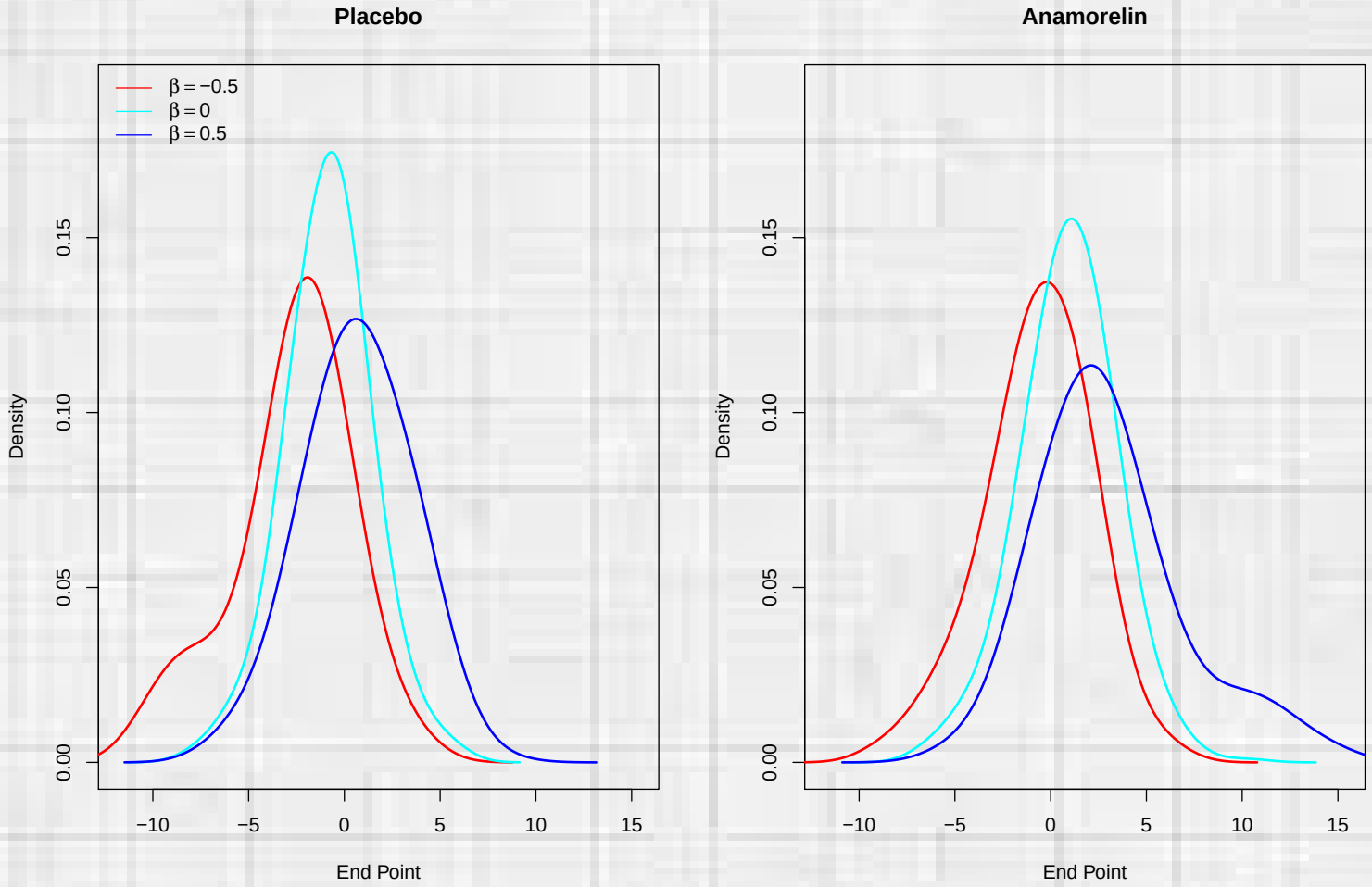
Table: Median

		$\widehat{p}_{50}$ (95% CI)
HT-ANAM 302 Study	Anamorelin	0.67(0.45, 0.89)
	Placebo	-0.92(-1.43,-0.28)

Cumulative plot

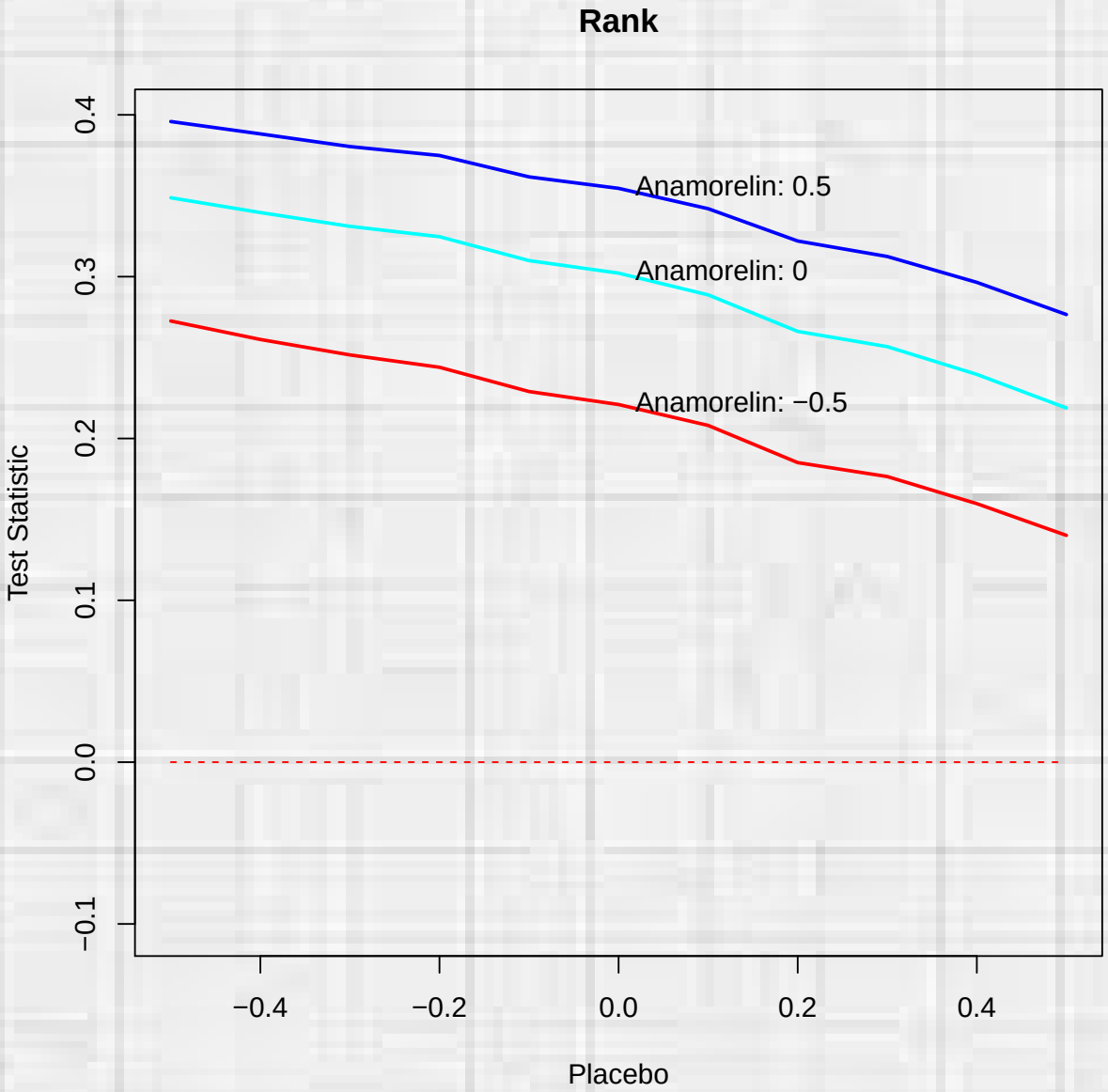


Choice of sensitivity parameters

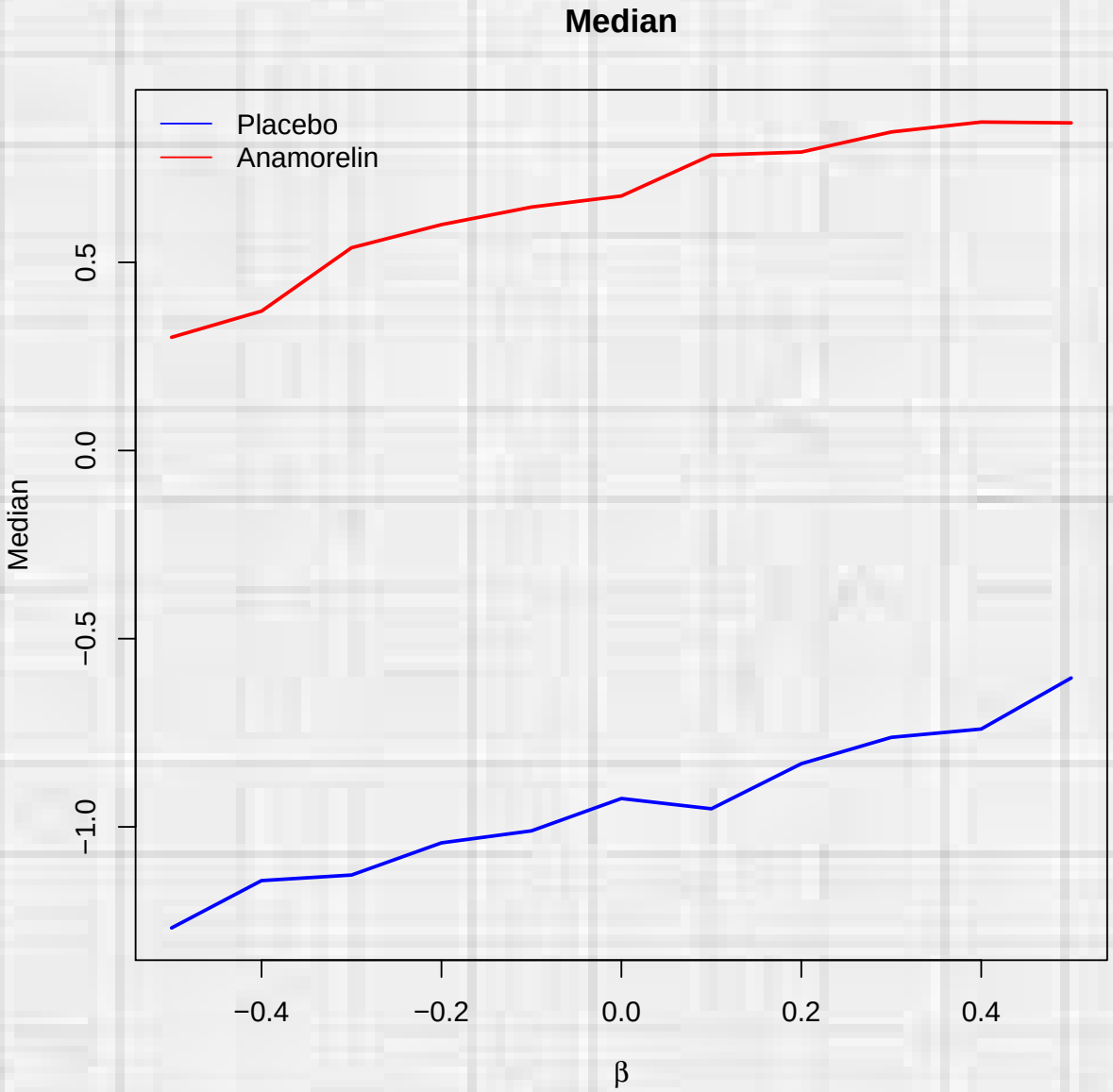


- Change in $E(Z)$ about 1.5 lb at $\beta_T = 0.5$ and $\beta_T = -0.5$
- Set $\beta_T = \{-0.5, -0.4, \ldots, 0, \ldots, 0.5\}$

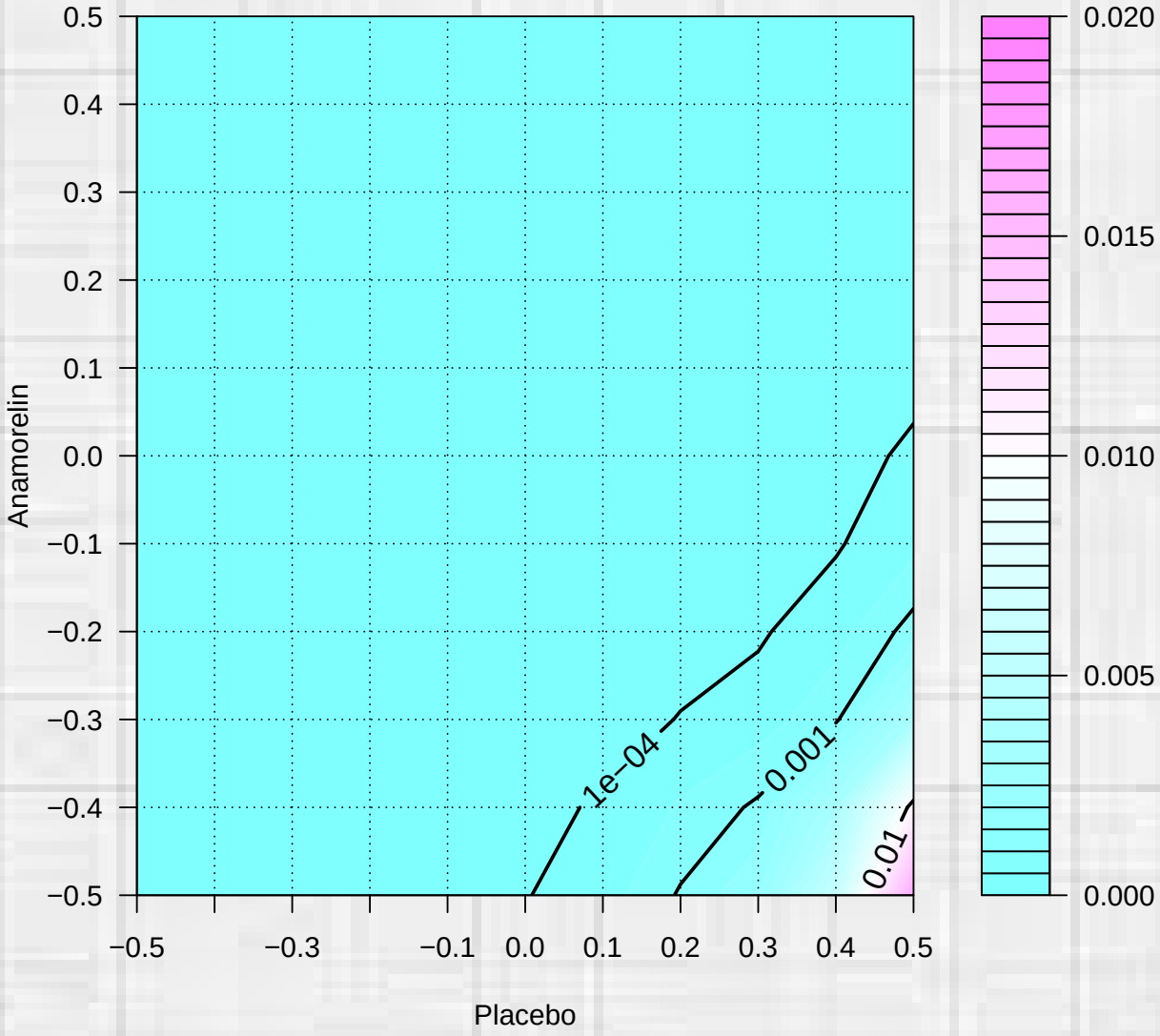
Sensitivity analysis: Rank



Sensitivity analysis: Median



Sensitivity analysis: Contour of p-values



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

THE END