Global Sensitivity Analysis for Studies with Intermittent Missing Data and Death

Global Sensitivity Analysis of Randomized Trials
with Missing Data Workshop

January 12, 2015

Objectives

- To review issues and common analysis methods for death-truncated data
- To learn about a composite endpoint based approach for intermittent missingness and death data analysis
- To introduce a web application that implements the proposed method

{ Review }

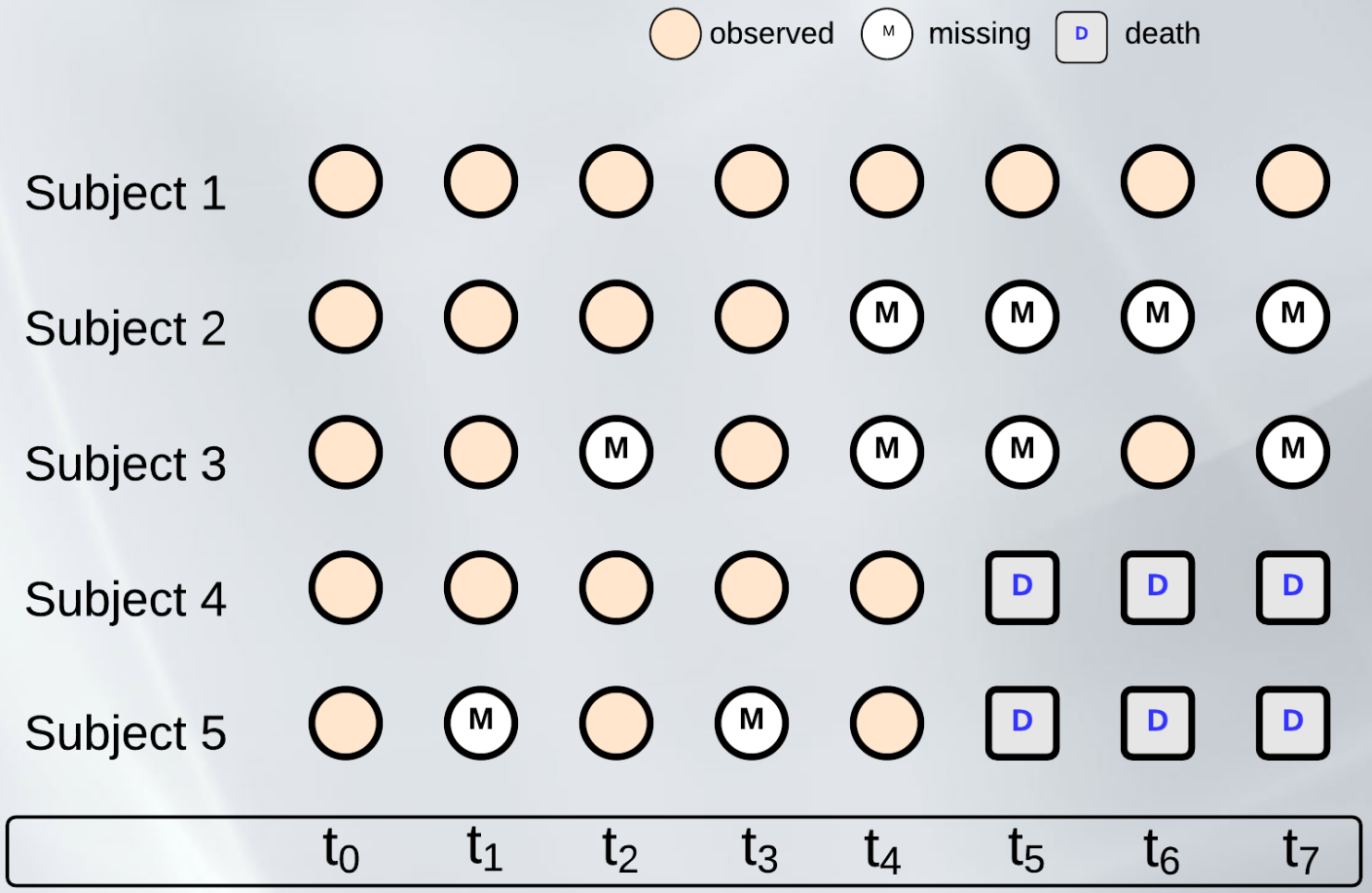
Outline

- Introduction
- Conditional model
- Joint model
- Principal stratification
- Composite endpoint

General setting

- Consider a randomized clinical study
- Goal: to evaluate the efficacy of a treatment
- Outcomes scheduled to be measured at pre-specified time points after randomization
- Subjects at (high) risk of death
- Issue: clinical evaluations unobserved due to
  - lost to follow up
  - withdraw of consent
  - out-of-window visit
  - death

Scenarios of unobserved outcomes



Data truncated by death

- Fundamental 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

Four major groups:

- 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

Notation

- $T = 0, 1$: treatment assignment
- Y_0: baseline measure at t_0
- $Y_1, \ldots, Y_K$: post-randomization outcomes at $t_1, \ldots, t_K$
- L: survival time
- $\Delta_k = I(L > t_k)$: survival status at 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 $\Delta_K = 1$
- X: baseline covariates
- $\overline{Y}_k$: $(Y_0, \ldots, Y_k)$

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Conditional model

- Unconditional model not appropriate

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

- Evaluate treatment effects at a specific time t_k
  - fully conditioning on survival time $L = t_k$
  - or partly conditioning on being alive at t_k (i.e. $\Delta_k = 1$)
- 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

B. F. Kurland and P. J. Heagerty. Directly parameterized regression conditioning on being alive: analysis of longitudinal data truncated by deaths. *Biostatistics*, 6(2):241–258, 2005

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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
- Issue: allows trajectories of longitudinal outcome after death, not scientifically meaningful

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A. A. Tsiatis and M. Davidian. Joint modeling of longitudinal and time-to-event data: An overview. *Statistica Sinica*, 14, 2004

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Potential outcome

For subject i

- $Y_i(0)$: what would have been observed if the subject had been treated with $T = 0$
- $Y_i(1)$: what would have been observed if the subject had been treated with $T = 1$
- $(Y_i(0), Y_i(1))$: potential outcome
- $Y_i(1) - Y_i(0)$: causal effect of treatment versus control

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Donald B Rubin. Estimating causal effects of treatments in randomized and nonrandomized studies. *Journal of Educational Psychology*, 66(5):688, 1974

Data truncated by death

- $\Delta_k(t)$: potentical survival status at t_k if treated with $T = t$ ($t = 0, 1$)
- With randomization,

$$Y_k(0), Y_k(1), \Delta_k(0), \Delta_k(1) \perp\!\!\!\perp T$$

- Recall: conditional methods estimates

$$\begin{aligned} &E(Y_k|\Delta_k = 1, T = 1) - E(Y_k|\Delta_k = 1, T = 0) \\ &\quad = E(Y_k(1)|\Delta_k(1) = 1) - E(Y_k(0)|\Delta_k(0) = 1) \end{aligned}$$

- Groups $\{\Delta_k(1) = 1\}$ and $\{\Delta_k(0) = 1\}$ not the same if treatment has impact on survival
- Selection bias introduced

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

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Composite endpoint

- Primary endpoint: defined as a composite or a mix of both the survival L and the functional outcome Z
- Simple and useful if the composite endpoint
  - is of clinical interest
  - can be ordered in a meaningful way
- Issue: effects of treatment on survival and on the functional outcome cannot be 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

{ PROPOSAL }

Outline

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

Goal

To propose a composite endpoint approach that handles boh 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
- Consider two subjects i and j with composite endpoints $(L_i, \Delta_K Z_i)$ and $(L_j, \Delta_K Z_j)$, respectively

Ranking

- $\Delta_{K,i} = \Delta_{K,j} = 1$
  - $Z_i > Z_j$: subject i ranked better than subject j
  - $Z_i < Z_j$: subject j ranked better than subject i
  - $Z_i = Z_j$: subjects i and j ranked the same
- $\Delta_{K,i} = \Delta_{K,j} = 0$
  - $L_i > L_j$: subject i ranked better than subject j
  - $L_i < L_j$: subject j ranked better than subject i
  - $L_i = L_j$: subjects i and j ranked the same
- $\Delta_{K,i} = 1$, $\Delta_{K,j} = 0$
  - subject i ranked better than subject j
- $\Delta_{K,i} = 0$, $\Delta_{K,j} = 1$
  - subject j ranked better than subject i

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Treatment effect

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

- 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 $T = 1$
- θ:
  - treatment effect quantification
  - target of inference
  - $\theta = 0$ if no treatment effect
- Hypothesis:

$$H_0 : \theta = 0 \quad \text{vs.} \quad H_A : \theta \neq 0$$

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
- Clinically easier to be interpreted
- Necessary supplement to the primary rank analysis

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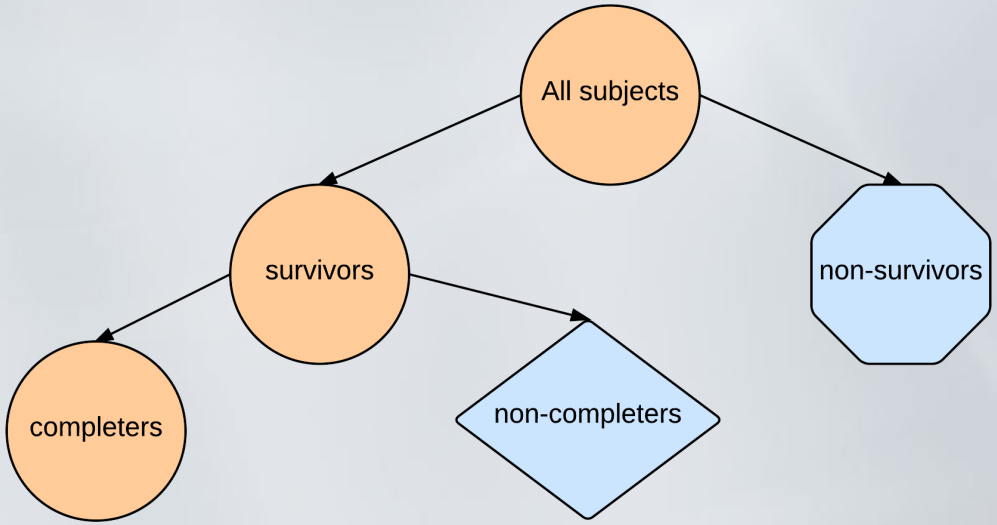
Missingness



- For subjects alive at the end of the study ($\Delta_K = 1$)
  - 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
- To determine ranks
  - sufficient to impute Y_{mis} for subjects with $\Delta_K = 1$

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

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

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

  - $\mu_{k,t}$: 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

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

- $\epsilon_{k,t} \sim F_{k,t}$
  - $F_{k,t} = N(0, \sigma_{k,t}^2)$ 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

Exponential tilting

- Exponential tilting model

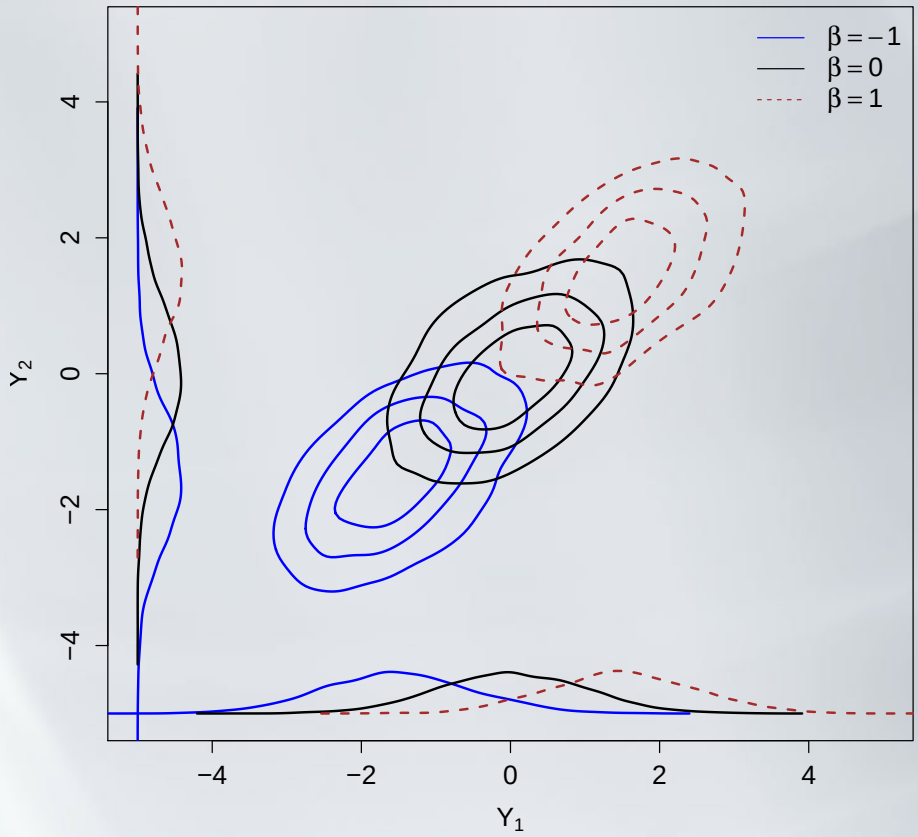
$$f'(y) \propto e^{\beta y} f(y)$$

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

Example: Exponential tilting

- Close form can be derived for multivariate normal,
  - $Y \sim N(\mu, \Sigma)$
  - $Y' \sim N(\mu + \Sigma\beta, \Sigma)$
- Example:

$$Y \sim N\left(0, \begin{bmatrix} 1 & 0.5 \\ 0.5 & 1 \end{bmatrix}\right)$$



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

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

Sensitivity analysis assumptions

- Let $Z = Y_1 + Y_2$
- Assumptions

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

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

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

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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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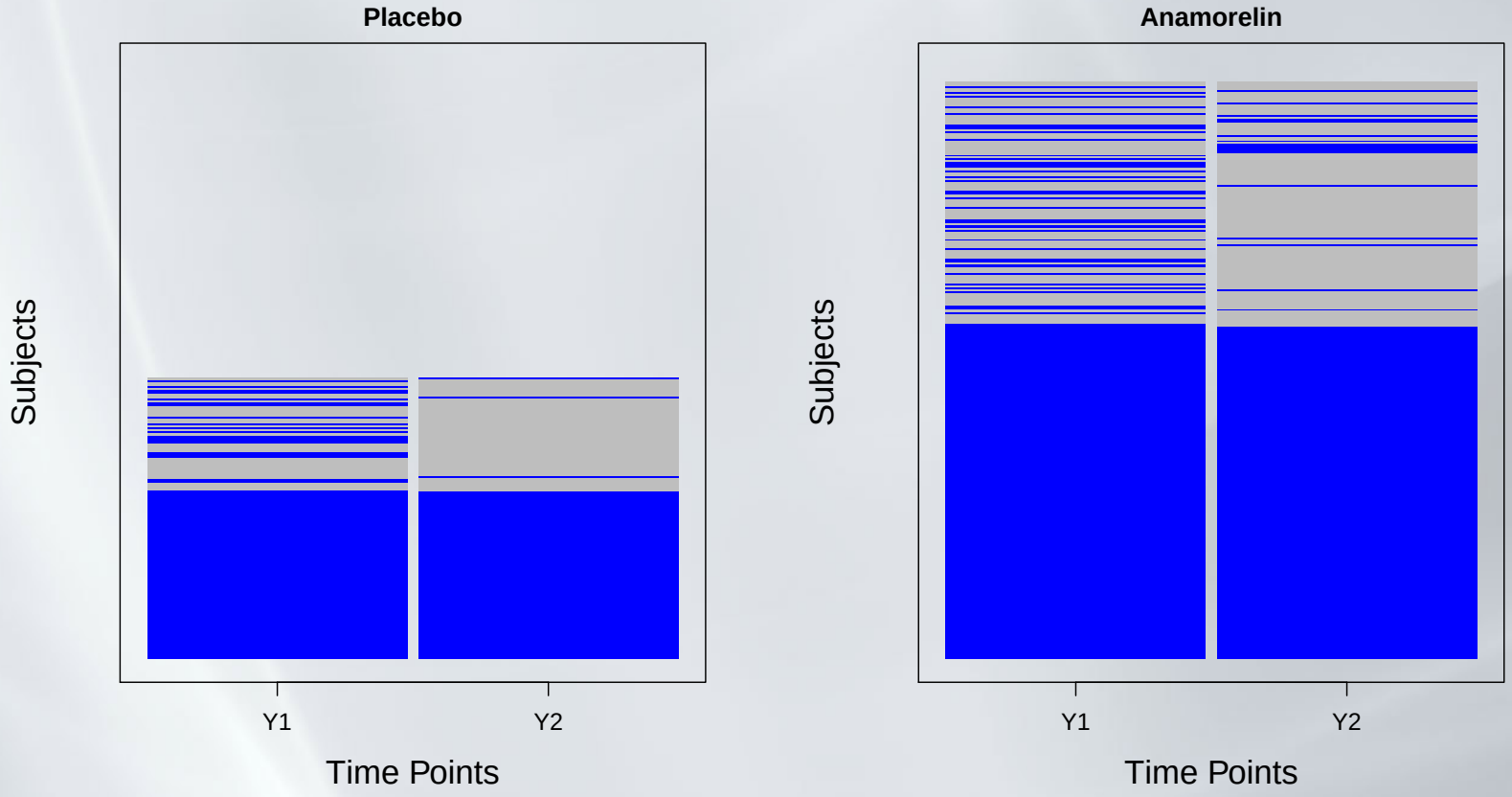
HT-ANAM 302 study

- 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: $Z = \frac{(Y_2+Y_1)}{2} - Y_0$

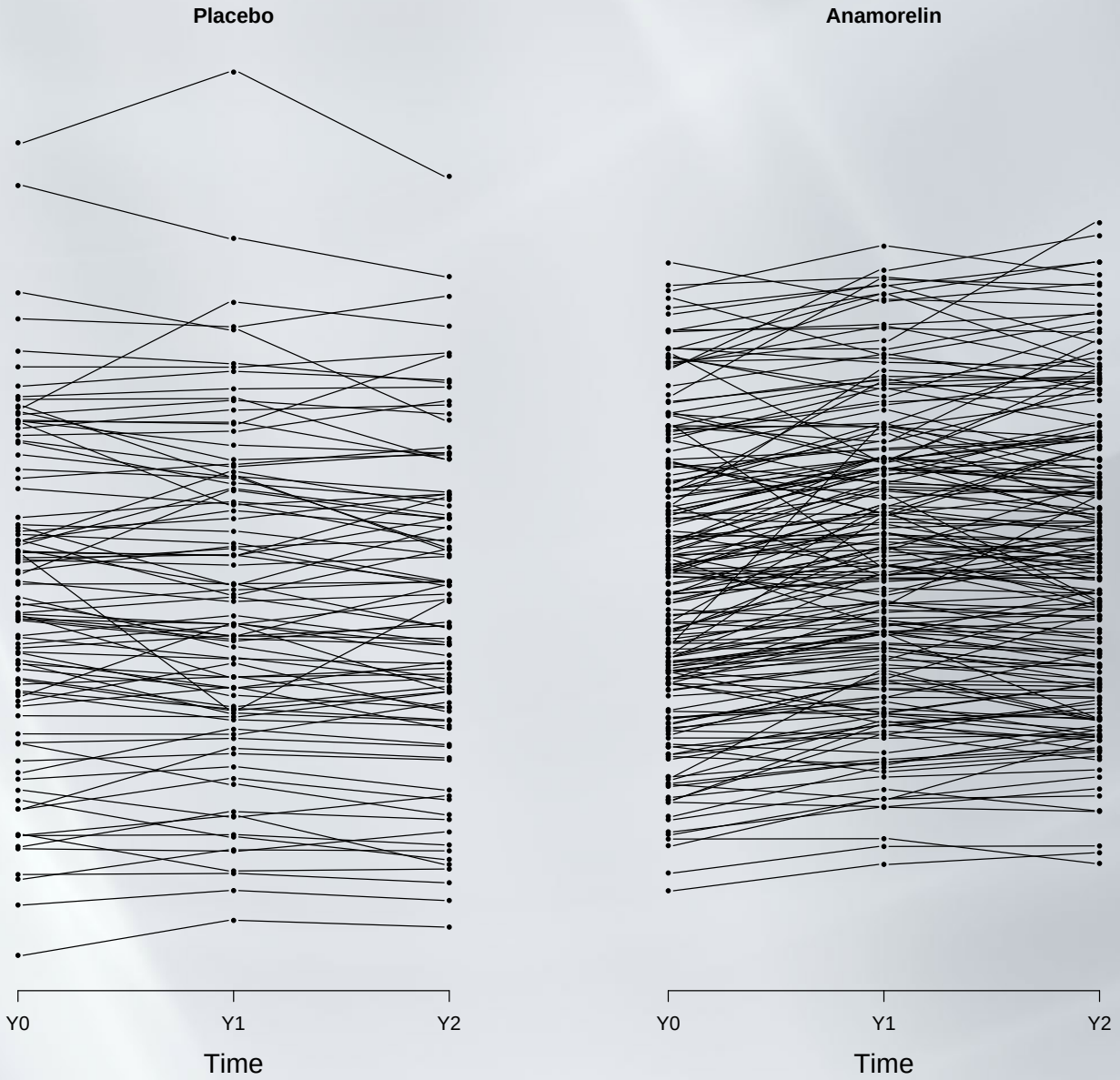
Death and missingness

	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%)

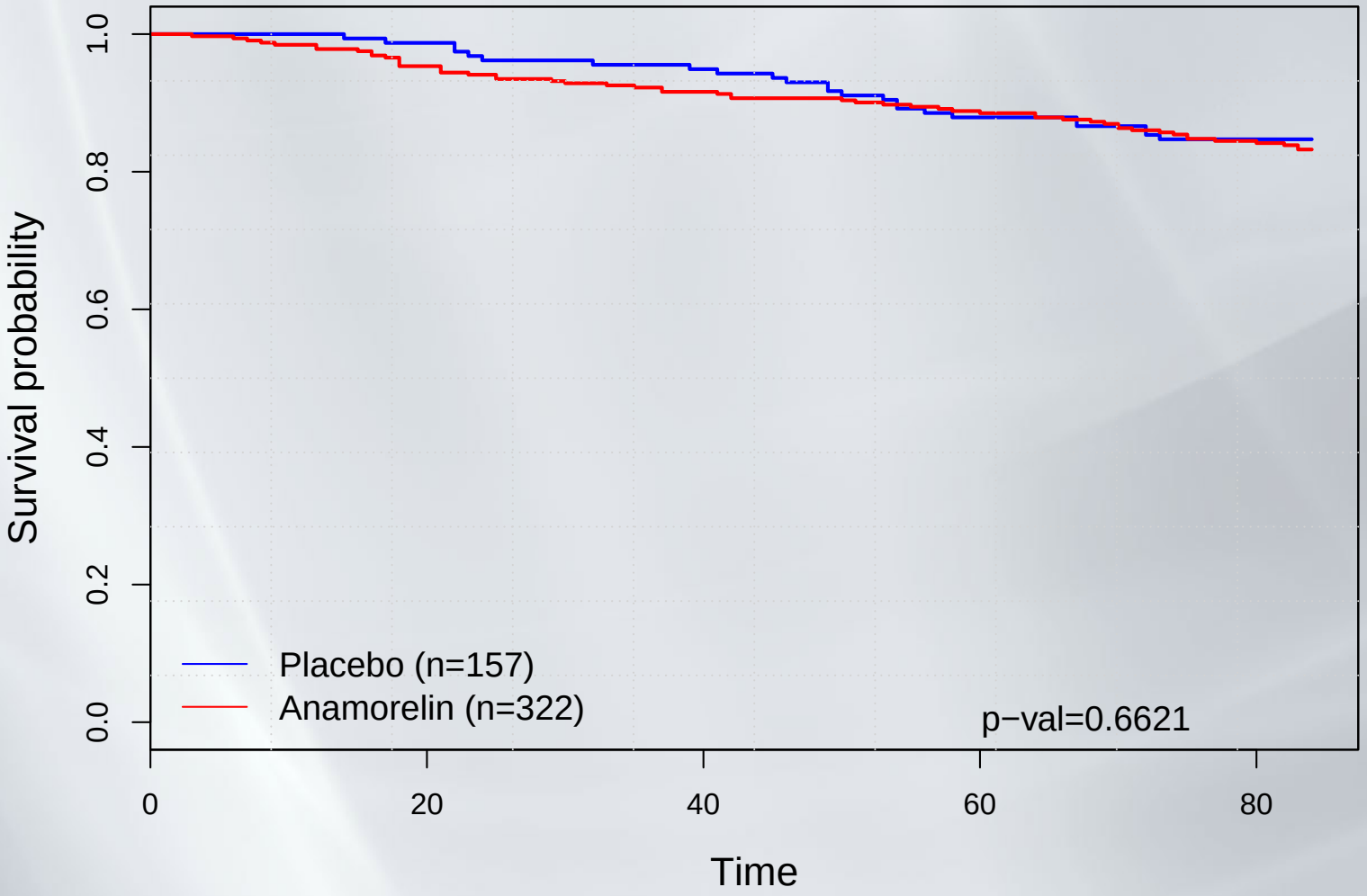
Missing pattern



Completers LBM



Survival


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

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

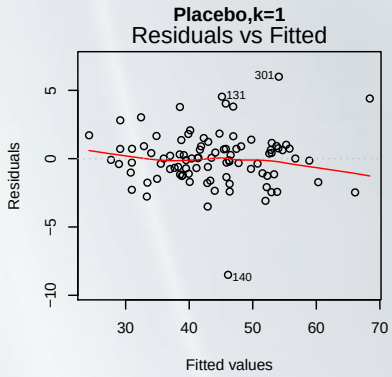
[1] in prior 6 months

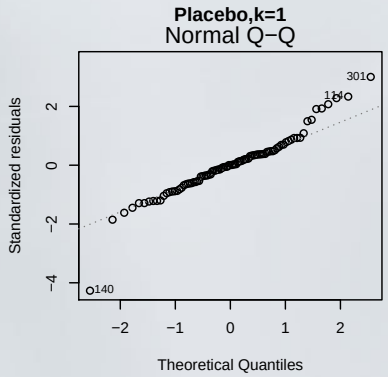
Modeling

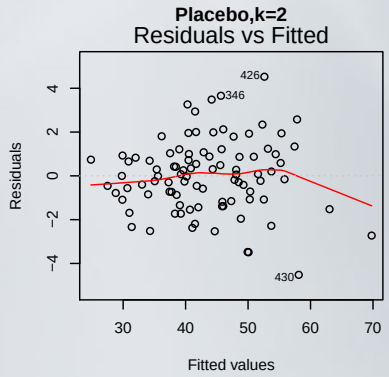
Specify $\mu_{k,t}(\overline{Y}_{k-1}, X; \alpha_{k,t})$ as follows:

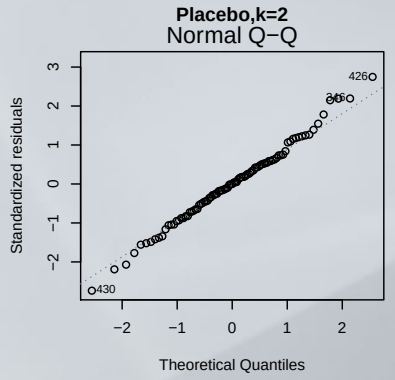
$$\begin{aligned}
\mu_{1,t,i} &= \alpha_{1,t,1} + \alpha_{1,t,2} Y_{0,i} + \alpha_{1,t,3} ECOG_i + \alpha_{1,t,4} AGE_i \\
&\quad + \alpha_{1,t,5} G_i + \alpha_{1,t,6} BMI_i + \alpha_{1,t,7} WL_i \\
\mu_{2,t,i} &= \alpha_{2,t,1} + \alpha_{2,t,2} Y_{0,i} + \alpha_{2,t,3} ECOG_i + \alpha_{2,t,4} AGE_i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

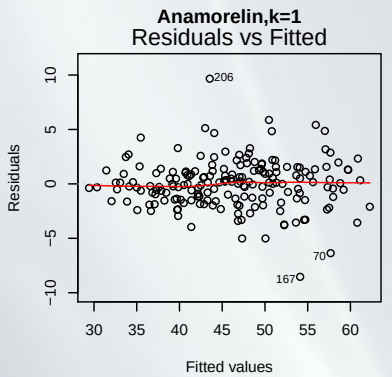
Model fitting diagnosis

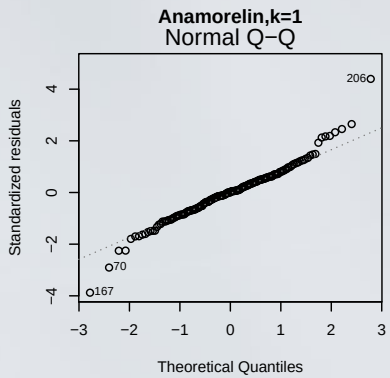


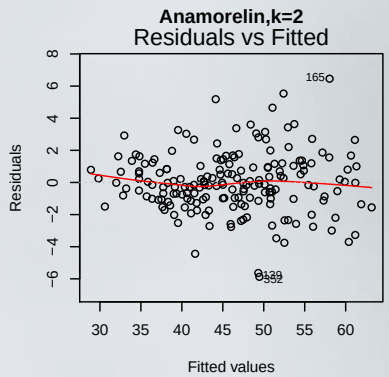


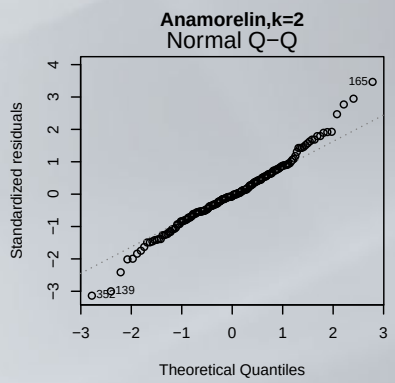












Analysis under benchmark assumptions

- 10 imputed datasets generated
- 200 bootstrap samples

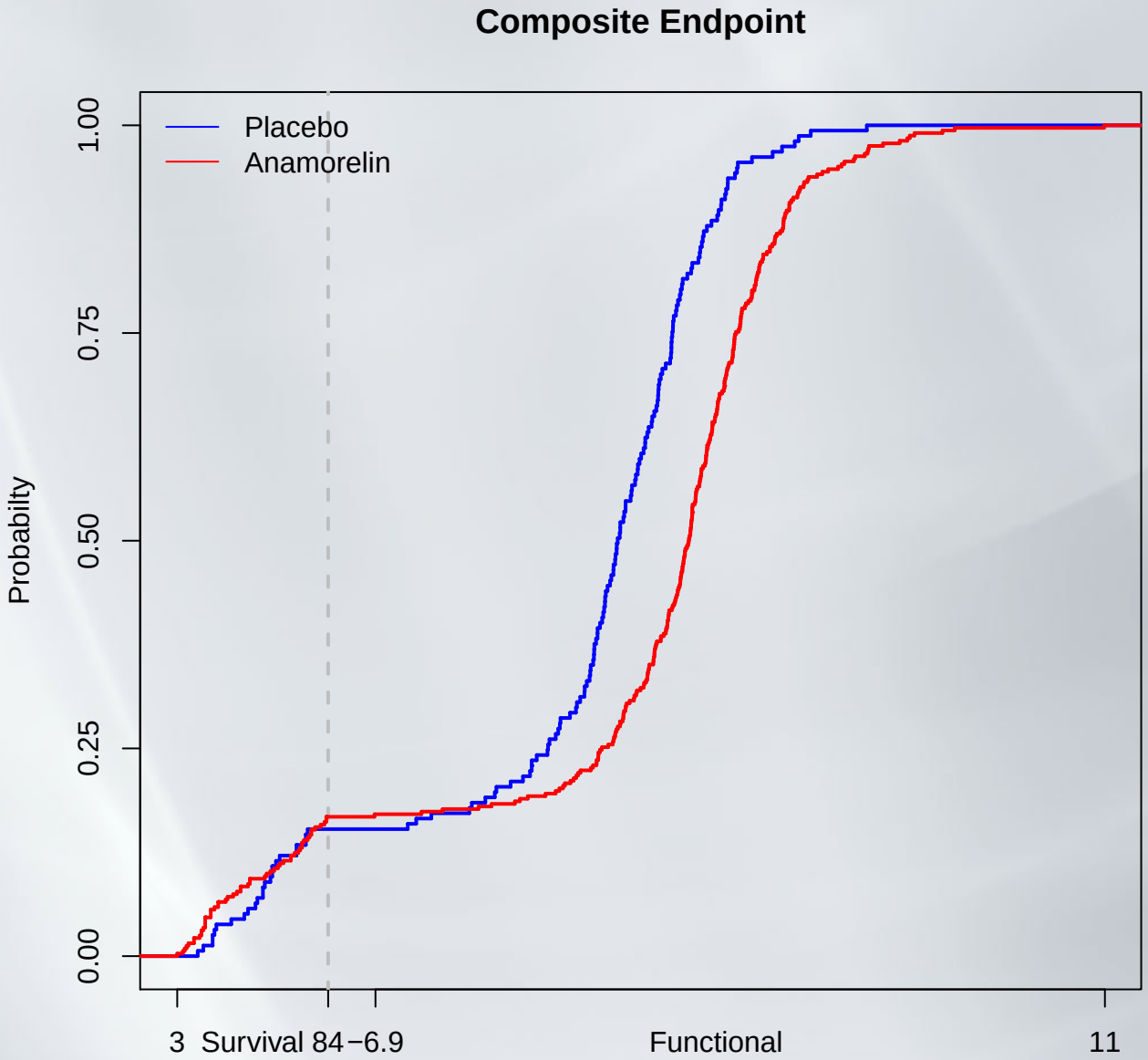
Table: Hypothesis testing

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

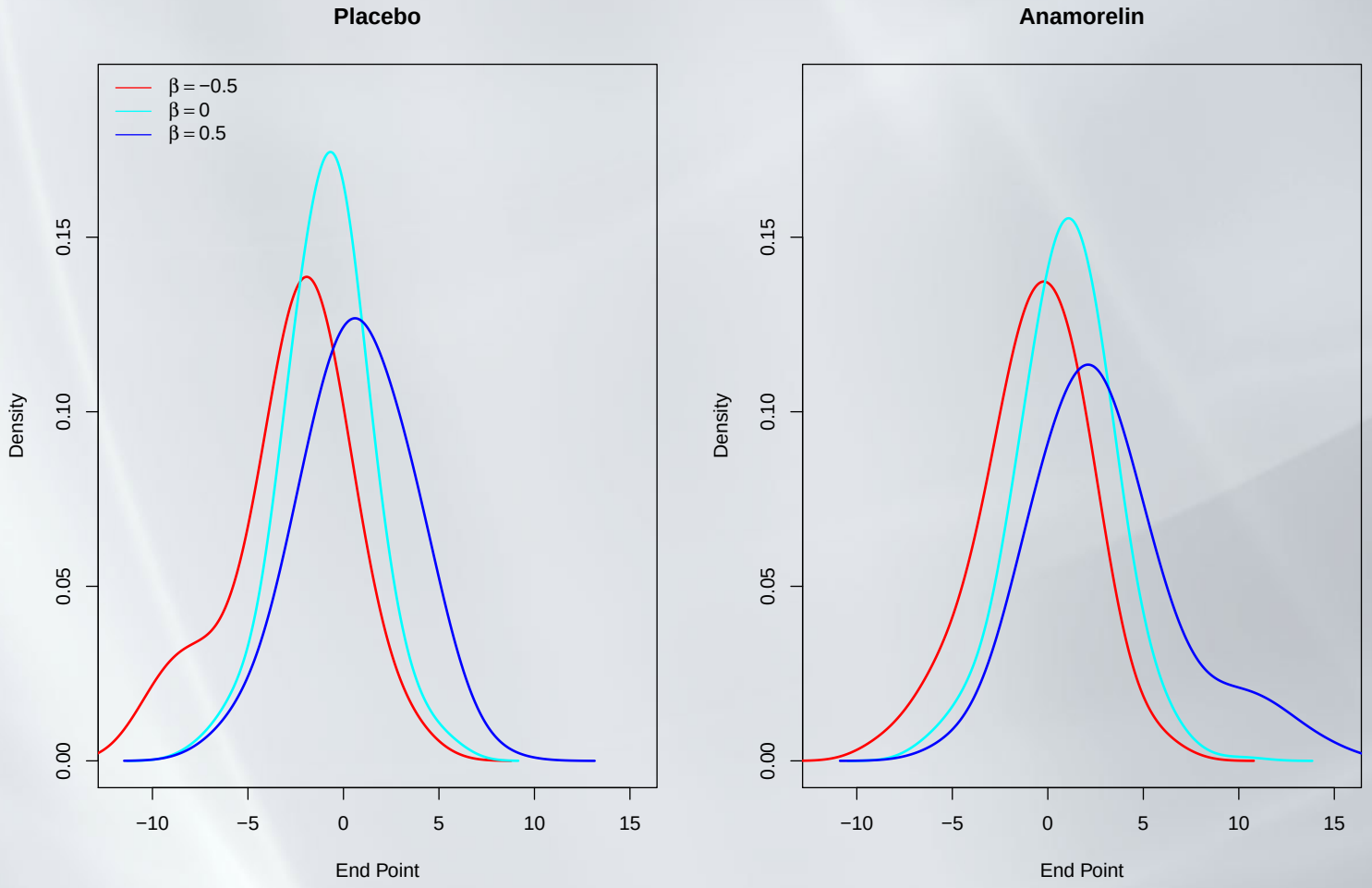
Table: Median

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

Cumulative plot

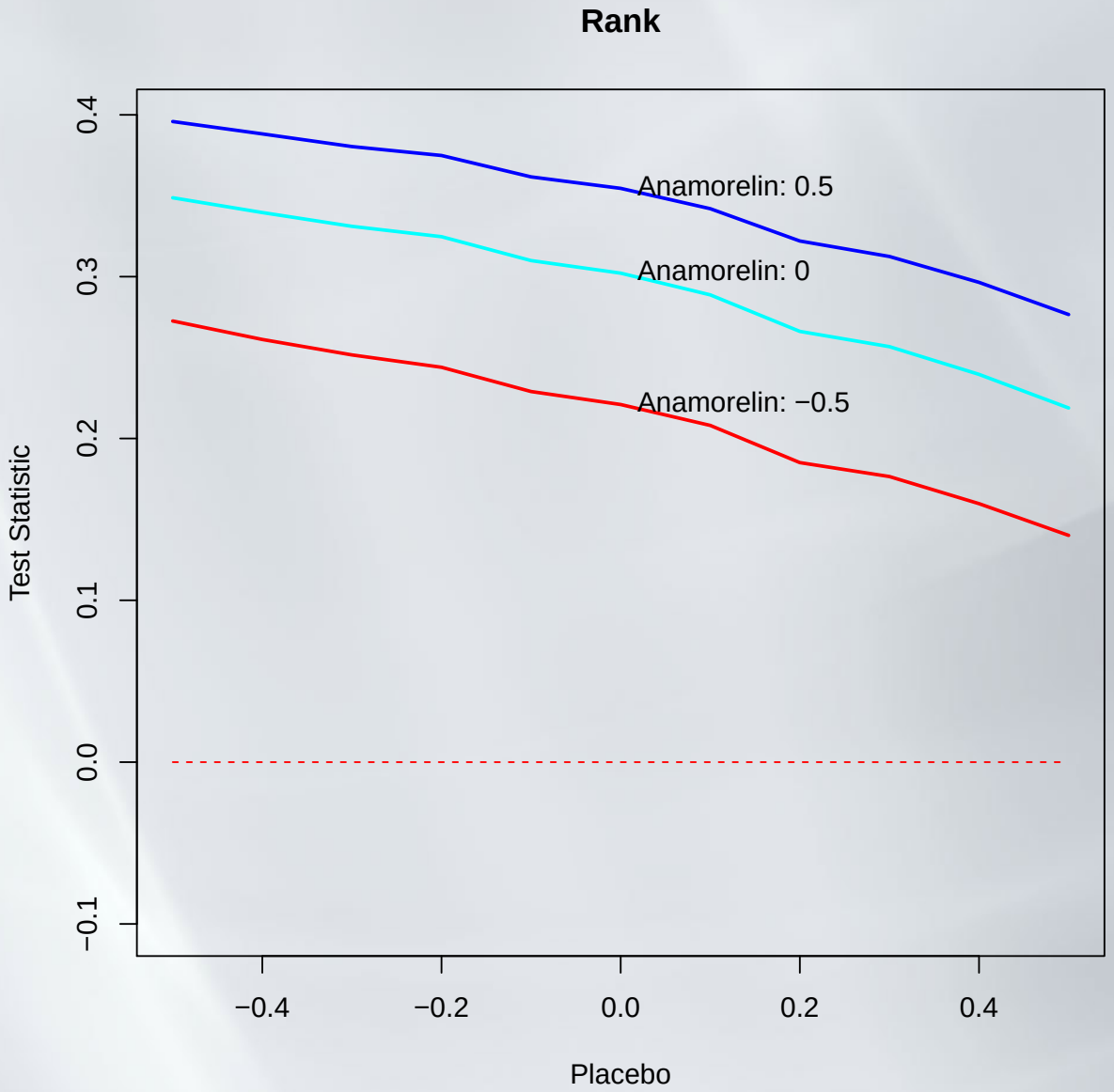


Choice of sensitivity parameters

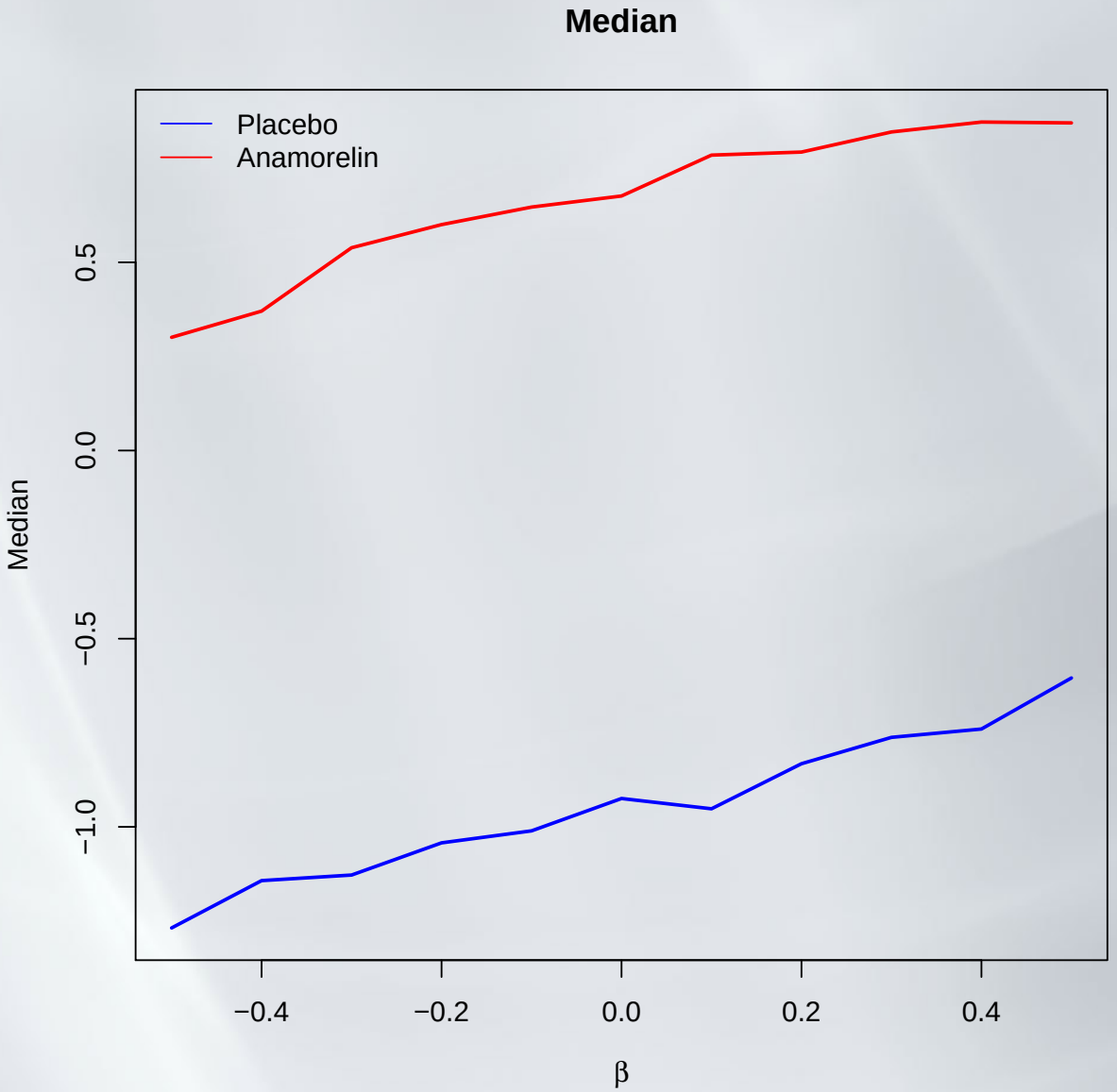


- Change in $E(Z)$ about 1.5 lb at $\beta_T = 0.5$ and $\beta_T = -0.5$
- Set $\beta_T = \{-0.5, -0.4, \ldots, 0, \ldots, 0.5\}$

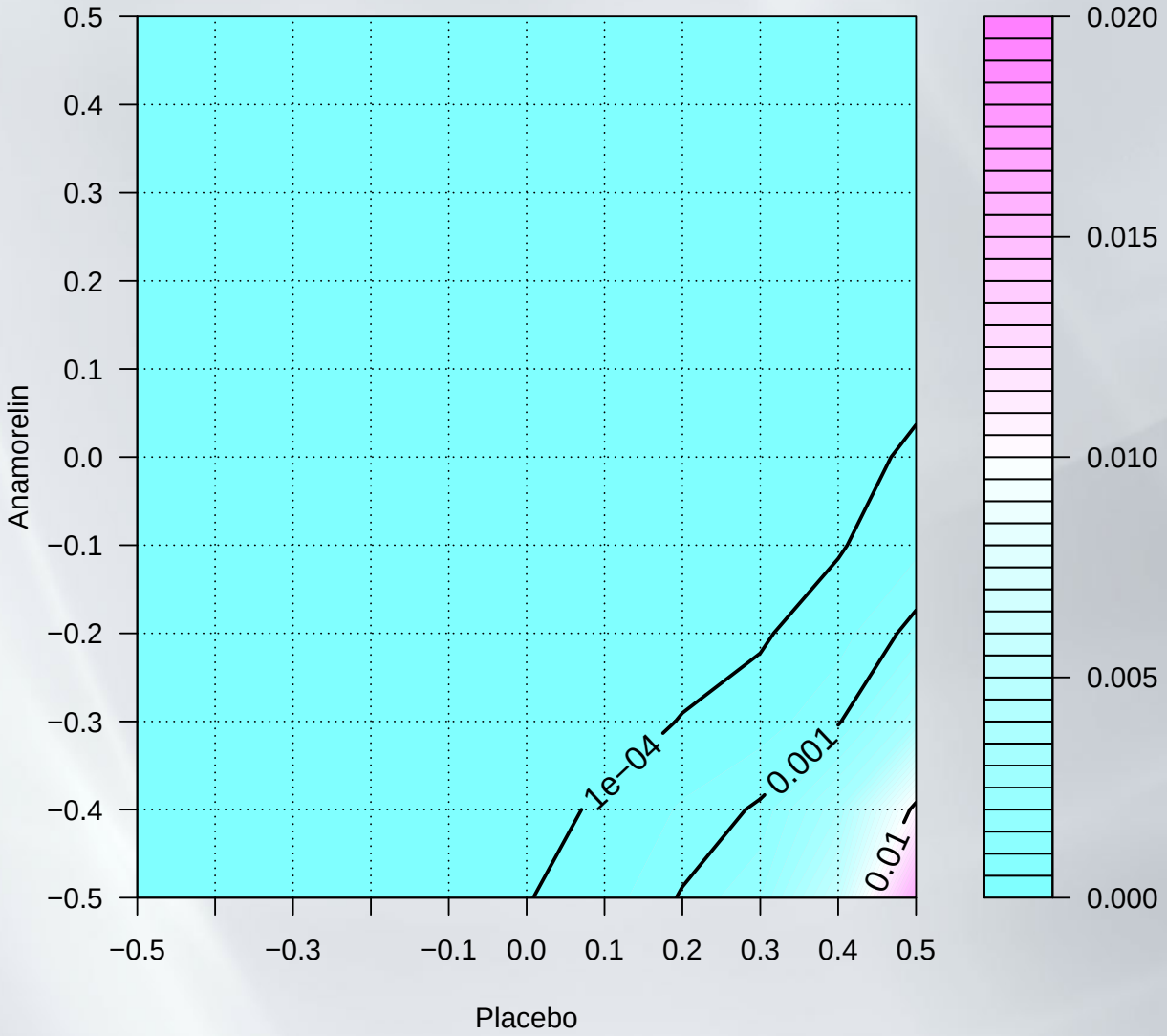
Sensitivity analysis: Rank



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 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

{ SOFTWARE }

Web application

- Currently available at
  `http://sow.familyds.com/shiny/composite/`
- Major components
  - upload study data
  - graphical presentation of the data
  - specify endpoints and imputation model
  - specify ranking rule
  - generate imputed dataset
  - bootstrap analysis

Recapitulation

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

THE END