Inference in Randomized Trials with Death and Missingness

SISCR Shortcourse

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July 26, 2016

HT-ANAM 302 Study

- Anamorelin is a drug developed for the treatment of cancer cachexia and anorexia.
- HT-ANAM 302 was a randomized, double-blind, placebo-controlled Phase III study designed to evaluate the efficacy of anamorelin in patients with advanced non-small cell lung cancer.
- Lean body mass (LBM) was 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%)

Central Question

How should data from studies like HT-ANAM 302 be analyzed to evaluate the effect of treatment on the functional outcome?

Key Issue

- Distinction between missing data and data truncated by death
  - Missing data: exist but not collected
  - Data truncated by death: does not exist and undefined
- Can't just treat as a missing data problem.

Common Approaches

1. Evaluate treatment effect on functional outcome conditional on survival
   - Conditioning on post-baseline factor
2. Joint modeling survival and functional outcomes
   - Allows extrapolation of outcomes after death
3. Principal stratification
   - Applies to a subset of patients who are not identifiable at baseline
4. Composite endpoint combining survival and functional outcomes
   - May be hard to separate effect on function.

Bottom Line

NO PERFECT SOLUTIONS

Not a fan of Approaches 1 and 2.

Goal

To construct a composite endpoint approach that handles both death and missing data

Notation

- $T = 0, 1$: treatment assignment
- X vector baseline covariates
- Y_0: baseline functional measure at t_0
- $Y_1, \ldots, Y_K$: functional outcomes at $t_1, \ldots, t_K$
- L: survival time
- $A_k = I(L > t_k)$: survival status at t_k
- $Z = g(Y_0, \ldots, Y_K)$: primary functional endpoint
  - e.g. $K = 2$, $Z = (Y_2 + Y_1)/2 - Y_0$
  - only defined when $A_K = 1$

Composite Outcome

Finite-valued random variable U which assigns a score to each patient such that

- each patient who dies prior to t_K is assigned a score according to their survival time (L), with shorter survival times assigned lower scores
- each patient who survives past t_K is assigned a score (higher than those who died prior to t_K) according to their functional status (Z), with lower functional status assigned lower scores.

Only the ordering of U is important, not the actual score assignments.

Mathematical Definition

- Let $W = L$ if $A_K = 0$ and $W = Z$ if $A_K = 1$
- U is a function of (A_K, W)
- U is defined such that
  - For all $\omega \in \Omega$, $U(\omega) < c$ when $A_K(\omega) = 0$
  - For all $\omega, \omega' \in \Omega$

$$
\begin{array}{ll}
U(\omega) < U(\omega') & \text{if } A_K(\omega) = A_K(\omega'), W(\omega) < W(\omega') \\
U(\omega) > U(\omega') & \text{if } A_K(\omega) = A_K(\omega'), W(\omega) > W(\omega') \\
U(\omega) = U(\omega') & \text{if } A_K(\omega) = A_K(\omega'), W(\omega) = W(\omega') \\
U(\omega) < U(\omega') & \text{if } A_K(\omega) = 0, A_K(\omega') = 1 \\
U(\omega) > U(\omega') & \text{if } A_K(\omega) = 1, A_K(\omega') = 0.
\end{array}
$$

Ranking examples

- $A_{K,i} = A_{K,j} = 1$
  - $Z_i > Z_j$: 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
- $A_{K,i} = A_{K,j} = 0$
  - $L_i > L_j$: 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
- $A_{K,i} = 1$, $A_{K,j} = 0$
  - subject i ranked better than subject j
- $A_{K,i} = 0$, $A_{K,j} = 1$
  - subject j ranked better than subject i

Treatment Effect

Treatment effect (θ) is measured by the probability that the outcome for an individual with $T = 0$ is less than the outcome of an individual with $T = 1$ minus the probability that the outcome for an individual with $T = 0$ is greater than the outcome of an individual with $T = 1$

- $\theta = 0$ under the null
- $\theta > 0$ favors $T = 1$; $\theta < 0$ favors $T = 0$
- First part: Mann-Whitney
- Second part: needed to handle ties

Can also compare the treatment-specific quantiles of U.

Estimation of θ

In the absence of missing data,

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

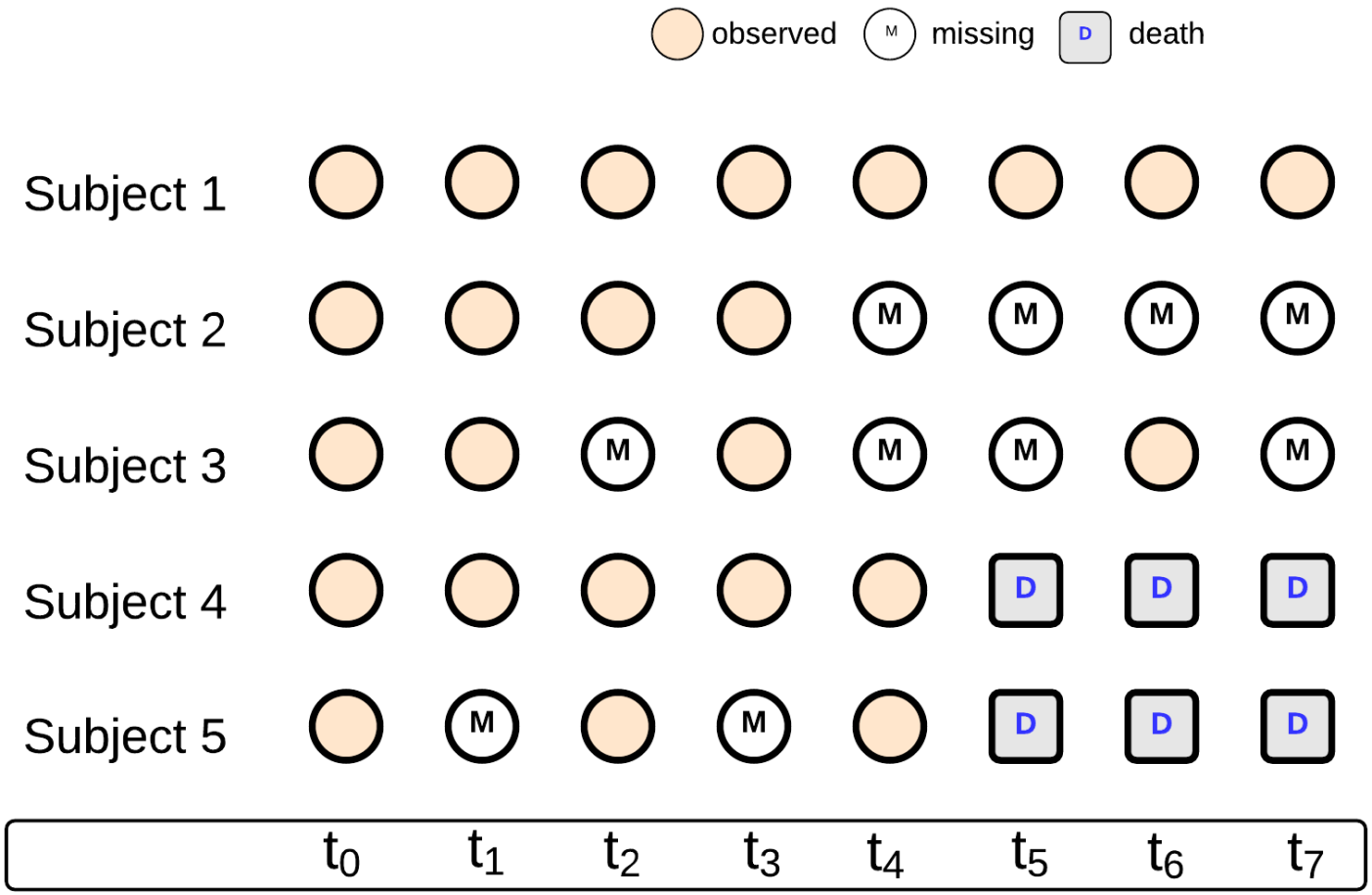
where $n_0 = \sum_i (1 - T_i)$ and $n_1 = \sum_i T_i$.

Missing Data

- R_k: missing data indicator (defined when $A_k = 1$)
- $S = (R_1, \ldots, R_K)$ (defined when $A_K = 1$)
  - $Y_{obs}^{(s)} = \{Y_k : R_k = 1, k \geq 1, S = s\}$
  - $Y_{mis}^{(s)} = \{Y_k : R_k = 0, k \geq 1, S = s\}$
  - Z is unobserved when $S \neq \mathbf{1}$.

To estimate θ, need to impute Z or equivalently $Y_{mis}^{(s)}$ for $s \neq \mathbf{1}$

Observed Data



Missing Data Assumptions

$$f(Y_{mis}^{(s)} | A_K = 1, Y_{obs}^{(s)}, Y_0, X, T, S = s)$$
$$\propto \exp(\beta_T Z) \underbrace{f(Y_{mis}^{(s)} | A_K = 1, Y_{obs}^{(s)}, Y_0, X, T, S = \mathbf{1})}_{\text{Reference Distribution}}$$

for all $s \neq \mathbf{1}$,

- β_T is a treatment-specific sensitivity parameter.
- $\beta_T = 0$ (i.e., benchmark assumption) reduces to the complete case missing value (CCMV) restrictions applied to the missing data patterns for patients alive at t_K.
- CCMV is different than missing at random (MAR) assumption.

- $K = 2$, $Z = (Y_1 + Y_2)/2 - Y_0$.
- $\beta'_T = 2\beta_T$

$$f(Y_2|A_2 = 1, Y_1, Y_0, X, T, S = (1,0)) \propto \exp(\beta'_T Y_2) \underbrace{f(Y_2|A_2 = 1, Y_1, Y_0, X, T, S = \mathbf{1})}_{\text{Reference Distribution}}$$

For subjects alive at t_2, who are observed at time t_1, who share the same functional measure at t_1 and who share the same baseline factors, the distribution of Y_2 for those whose functional measure at t_2 is missing is, when $\beta'_T > 0$ (< 0), more heavily weighted toward higher (lower) values of Y_2 than those whose functional measure at t_2 is observed.

$$f(Y_1|A_2 = 1, Y_2, Y_0, X, T, S = (0,1))$$
$$\propto \exp(\beta_T' Y_1) \underbrace{f(Y_1|A_2 = 1, Y_2, Y_0, X, T, S = \mathbf{1})}_{\text{Reference Distribution}}$$

For subjects alive at t_2, who are observed at time t_2, who share the same functional measure at t_2 and who share the same baseline factors, the distribution of Y_1 for those whose functional measure at t_1 is missing is, when $\beta_T' > 0$ (< 0), more heavily weighted toward higher (lower) values of Y_1 than those whose functional measure at t_1 is observed.

$$f(Y_1, Y_2|A_2 = 1, Y_0, X, T, S = (0,0))$$
$$\propto \exp\left(\beta_T'(Y_1 + Y_2)\right) \underbrace{f(Y_1, Y_2|A_2 = 1, Y_0, X, T, S = \mathbf{1})}_{\text{Reference Distribution}}$$

For subjects alive at t_2 and who share the same baseline factors, the joint distribution of Y_1 and Y_2 for those whose functional measures at t_1 and t_2 are missing is, when $\beta_T' > 0$ (< 0), more heavily weighted toward higher (lower) values of Y_1 and Y_2 than those whose measures are fully observed.

- Ignore conditioning on Y_0 and X and suppose $f(Y_1, Y_2|A_2 = 1, T, S = \mathbf{1})$ is multivariate normal with mean $(\mu_{T,1}, \mu_{T,2})$ and variance-covariance matrix

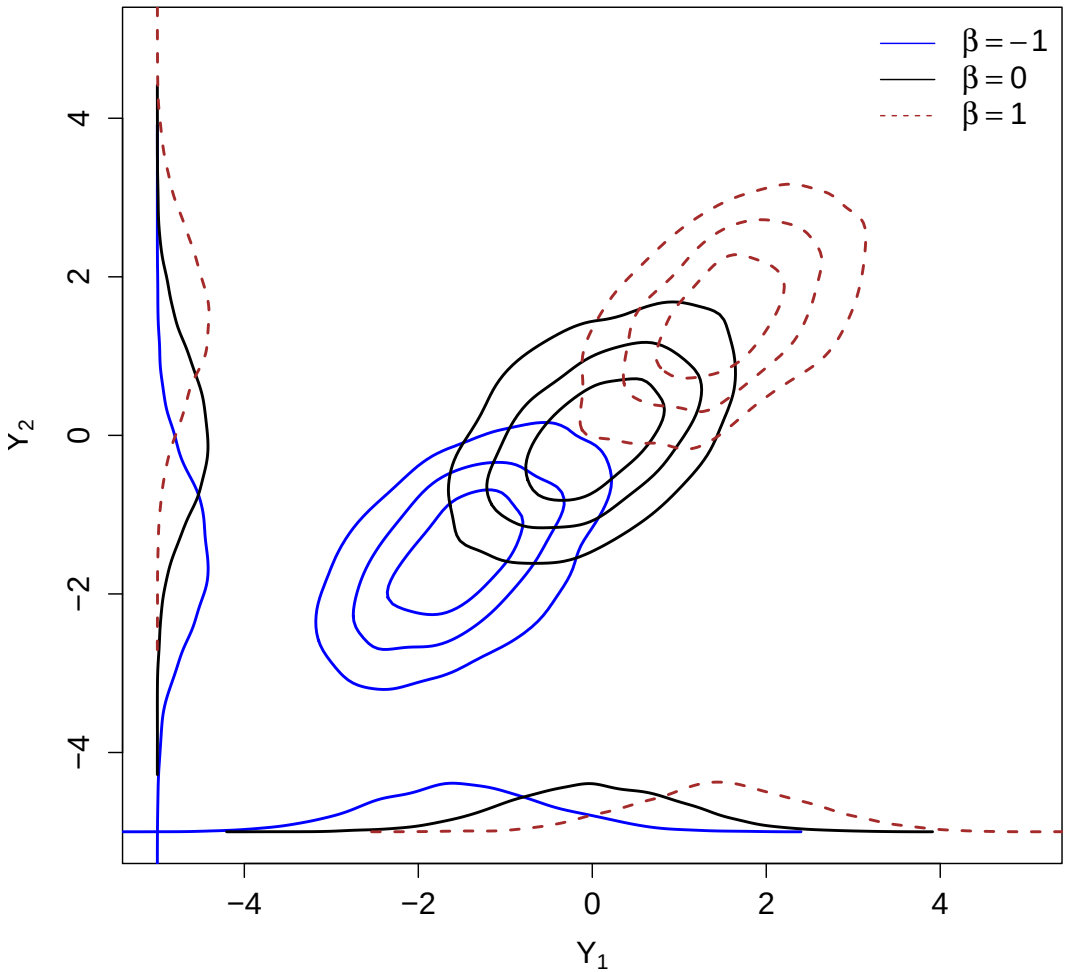
$$\Sigma_T = \begin{bmatrix} \sigma^2_{T,1} & \rho_T \sigma_{T,1} \sigma_{T,2} \\ \rho_T \sigma_{T,1} \sigma_{T,2} & \sigma^2_{T,2} \end{bmatrix}$$

- $f(Y_2|A_2 = 1, Y_1, T, S = (1, 0))$ is normal with mean $\mu_{T,2} + \beta'_T(1 - \rho^2_T)\sigma^2_{T,2} + \rho_T \frac{\sigma_{T,2}}{\sigma_{T,1}}(Y_1 - \mu_{T,1})$ and variance $(1 - \rho^2_T)\sigma^2_{T,2}$
- $f(Y_1|A_2 = 1, Y_2, T, S = (0, 1))$ is normal with mean $\mu_{T,1} + \beta'_T(1 - \rho^2_T)\sigma^2_{T,1} + \rho_T \frac{\sigma_{T,1}}{\sigma_{T,2}}(Y_2 - \mu_{T,2})$ and variance $(1 - \rho^2_T)\sigma^2_{T,1}$

HT-ANAM 302 Study

- $f(Y_1, Y_2|A_2 = 1, T, S = (0,0))$ is multivariate normal with mean $(\mu_{T,1} + \beta'_T\sigma^2_{T,1} + \beta'_T\rho_T\sigma_{T,1}\sigma_{T,2}, \mu_{T,2} + \beta'_T\sigma^2_{T,2} + \beta'_T\rho_T\sigma_{T,1}\sigma_{T,2})$ and variance-covariance matrix Σ_T.
- If $\rho_T > 0$, then the means increase linearly in β'_T
- β'_T has no impact on the variances and covariances.
- $\beta'_T > 0$ ($\beta'_T < 0$) implies that the non-identified distributions have more (less) mass at higher values than their reference distributions.

Example: Exponential tilting



Modeling

Need to specify of a model for

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

- To respect bounds, define

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

- $Y_k^\dagger = \phi(Y_k)$ and $\overline{Y}_k^\dagger = (Y_1^\dagger, \ldots, Y_k^\dagger)$.
- One-to-one mapping between

$$h(\overline{Y}_K^\dagger | A_K = 1, Y_0, X, T, S = \mathbf{1})$$

and

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

.

Modeling

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

- Posit a model for each component of the product.

Modeling

$$h(Y_k^\dagger | A_K = 1, \overline{Y}_{k-1}^\dagger, Y_0, X, T = t, S = \mathbf{1})$$
$$= h_{k,t}(Y_k^\dagger - \mu_{k,t}(\overline{Y}_{k-1}^\dagger, Y_0, X; \boldsymbol{\alpha}_{k,t}))$$

- $\mu_{k,t}(\overline{Y}_{k-1}^\dagger, Y_0, X; \boldsymbol{\alpha}_{k,t})$ is a specified function
- $\boldsymbol{\alpha}_{k,t}$ is an unknown parameter vector
- $h_{k,t}$ is an unspecified time/treatment-specific density function.

Estimation

- The parameter vectors $\boldsymbol{\alpha}_{k,t}$ can be estimated by minimizing the least squares objective function

$$\sum_{i=1}^{n} I(T_i = t) A_{K,i} \left(\prod_{k=1}^{K} R_{k,i} \right) \{ Y_{k,i}^{\dagger} - \mu_{k,t}(\overline{Y}_{k-1}^{\dagger}, Y_0, X; \boldsymbol{\alpha}_{k,t}) \}^2$$

- The density function $h_{k,t}$ can be estimated by kernel density estimation based on the residuals $\{ Y_{k,i}^{\dagger} - \mu_{k,t}(\overline{Y}_{k-1,i}^{\dagger}, Y_{0,i}, X_i; \widehat{\boldsymbol{\alpha}}_{k,t}) : T_i = t, A_{K,i} = 1, R_{1,i} = \ldots, R_{K,i} = 1, i = 1, \ldots, n \}$
- $f(\overline{Y}_K | A_K = 1, Y_0, X, T, S = \mathbf{1})$ is estimated by

$$\prod_{k=1}^{K} \widehat{h}_{k,t}(Y_k^{\dagger} - \mu_{k,t}(\overline{Y}_{k-1}^{\dagger}, Y_0, X; \widehat{\boldsymbol{\alpha}}_{k,t})) \left| \frac{d\phi(Y_k)}{dY_k} \right|.$$

Imputation/Estimation

- For each individual i alive at t_K and who is in a stratum $s \neq \mathbf{1}$ and treatment t, impute the missing functional outcomes by drawing (using Metropolis-Hastings algorithm) from the density that is proportional to

$$\exp(\beta_t Z)\widehat{f}(Y_{mis}^{(s)} | A_K = 1, Y_{obs}^{(s)} = Y_{obs,i}, Y_0 = Y_{0,i}, X = X_i, T = t, S = \mathbf{1})$$

- Draw M copies of the missing functional outcomes to create M complete datasets.
- For each complete dataset m, estimate θ by $\widehat{\theta}_m$.
- Overall estimator of θ is $\tilde{\theta} = \frac{1}{M}\sum_{m=1}^{M}\widehat{\theta}_m$.
- Confidence intervals can be constructed by non-parametric bootstrap

Sampling steps

1. Set $j = 0$. Choose arbitrary initial values for $Y_{mis}^{(s)}$, denoted by $Y_{mis}^{(s,0)}$. Let $Z_i^{(0)}$ be the primary functional endpoint with data $(Y_{obs,i}, Y_{mis}^{(s,0)})$.
2. Set $j = j + 1$
3. Generate $Y_{mis}^{(s)'}$ from a (multivariate) Gaussian distribution with mean $Y_{mis}^{(s,j-1)}$ and variance Σ. Let Z_i' be the primary functional endpoint with data $(Y_{obs,i}, Y_{mis}^{(s)'})$.

Sampling steps

4. Calculate the acceptance ratio as

$$
\begin{aligned}
a &= \frac{\exp\{\beta_t Z_i'\}\widehat{f}(Y_{mis}^{(s)'} | A_K = 1, Y_{obs,i}, Y_{0,i}, X_i, T = t, S = \mathbf{1})}{\exp\{\beta_t Z_i^{(j-1)}\}\widehat{f}(Y_{mis}^{(s,j-1)} | A_K = 1, Y_{obs,i}, Y_{0,i}, X_i, T = t, S = \mathbf{1})} \\
&= \frac{\exp\{\beta_t Z_i'\}\widehat{f}(Y_{mis}^{(s)'}, Y_{obs,i} | A_K = 1, Y_{0,i}, X_i, T = t, S = \mathbf{1})}{\exp\{\beta_t Z_i^{(j-1)}\}\widehat{f}(Y_{mis}^{(s,j-1)}, Y_{obs,i} | A_K = 1, Y_{0,i}, X_i, T = t, S = \mathbf{1})}
\end{aligned}
$$

Sampling steps

5. Accept $Y_{mis}^{(s)'}$ with probability $\min(1, a)$ and $Y_{mis}^{(s,j-1)}$ with probability $1 - \min(1, a)$. Let $Y_{mis}^{(s,j)}$ be the accepted value.
6. Repeat Steps 2-5 until the Markov chain converges
7. Draw random samples from the set $\{Y_{mis}^{(s,j_0)}, Y_{mis}^{(s,j_0+1)}, \ldots\}$ as the imputed missing values, where j_0 corresponds to the number of burn-in

Simulation scenarios

- Considered two post-baseline functional assessments at t_1 and t_2
- Scenario I
  - Focused on evaluating the impact of survival and functional status among survivors
  - Assume no missing data among survivors
- Scenario II
  - Focused on evaluating the impact of missing data and the proposed sensitivity analysis strategy
  - Assume no deaths

Data generation

- Draw Y_0 from standard normal distribution.
- Given T and Y_0, draw L_1 from an exponential distribution with mean $1/\exp(\lambda_{T,0} + \lambda_{T,1} Y_0)$. If $L_1 < t_1$, set $L = L_1$ and stop.
- Given T and Y_0, draw Y_1 from a normal distribution with mean $\mu_T + \gamma_T Y_0$, and variance 1.
- Given T and $\overline{Y}_1$, draw L_2 from an exponential distribution with mean $1/\exp(\lambda_{T,0} + \lambda_{T,1} Y_1)$. If $L_2 < t_2 - t_1$, set $L = L_2 + t_1$ and stop.
- Given T and $\overline{Y}_1$, draw Y_2 from a normal distribution with mean $\mu_T + \gamma_T Y_1$ and variance 1.

Data generation

- Given T and $\overline{Y}_2$, draw S from multinomial distribution with

$$P[S = s | T, \overline{Y}_2] = \frac{\exp(\mu'_{T,s} + \beta_T Z)}{1 + \sum_{s' \neq \mathbf{1}} \exp(\mu'_{T,s'} + \beta_T Z)}, \quad s \neq \mathbf{1}$$

and

$$P[S = \mathbf{1} | T, \overline{Y}_2] = \frac{1}{1 + \sum_{s' \neq \mathbf{1}} \exp(\mu'_{T,s'} + \beta_T Z)}.$$

Scenario I results

	Death Rate			True	Sample	Estimation		Rate	
$\lambda_{1,1}$	$T=0$	$T=1$	μ_1	θ	Size	$\widehat{\theta}$	MSE*	Rej*	Cov*
1.3	0.188	0.230	0.0	-0.056	200	-0.060	5.5	0.092	0.978
					500	-0.054	2.9	0.186	0.938
		0.293	0.5	0.088	200	0.085	7.1	0.198	0.944
					500	0.086	2.5	0.358	0.958
	0.354	0.388	0.0	-0.051	200	-0.053	6.7	0.104	0.936
					500	-0.046	2.7	0.154	0.956
		0.463	0.5	0.007	200	0.007	7.6	0.072	0.928
					500	0.006	2.6	0.042	0.960
1.0	0.188	0.188	0.0	-0.001	200	0.002	6.9	0.050	0.952
					500	0.004	2.7	0.048	0.958
		0.236	0.5	0.178	200	0.181	7.5	0.602	0.932
					500	0.177	2.7	0.934	0.946
	0.354	0.354	0.0	0.000	200	-0.003	6.1	0.032	0.974
					500	0.000	2.7	0.058	0.944
		0.418	0.5	0.080	200	0.079	7.2	0.180	0.946
					500	0.084	2.7	0.352	0.948
0.7	0.188	0.151	0.0	0.051	200	0.047	6.4	0.090	0.960
					500	0.053	2.4	0.174	0.952
		0.180	0.5	0.265	200	0.269	5.8	0.924	0.954
					500	0.262	2.7	0.996	0.944
	0.354	0.315	0.0	0.054	200	0.051	6.3	0.096	0.958
					500	0.053	2.5	0.174	0.964
		0.362	0.5	0.163	200	0.160	6.0	0.518	0.950
					500	0.165	2.7	0.884	0.954

Table: Scenario I Simulation Study Results. MSE*: mean squared error $\times 1000$. Rej*: rejection rate for $H_0 : \theta = 0$. Cov*: bootstrap 95% confidence interval coverage rate. The Death Rates for $T = 0$ are 0.188 or 0.354 corresponding to the study length (t_2) of 0.2 and 0.5, respectively.

Scenario II results

	Missing		True	Sample	Estimation		Rate	
β_1^*	Rate*	μ_1	θ	Size	$\widehat{\theta}$	MSE*	Rej*	Cov*
0	0.21	-0.25	-0.186	200	-0.049	26.8	0.090	0.640
				500	-0.045	23.5	0.146	0.268
	0.15	0.00	0.000	200	0.104	18.4	0.236	0.780
				500	0.110	15.1	0.516	0.476
	0.10	0.25	0.186	200	0.275	14.4	0.906	0.810
				500	0.271	9.5	1.000	0.614
-2	0.21	-0.25	-0.186	200	-0.192	7.1	0.612	0.952
				500	-0.189	2.9	0.928	0.950
	0.15	0.00	0.000	200	-0.014	7.6	0.054	0.952
				500	-0.011	3.1	0.050	0.952
	0.10	0.25	0.186	200	0.180	7.5	0.572	0.950
				500	0.178	2.7	0.928	0.948

Table: Scenario II Simulation Study Results. MSE*: mean squared error $\times 1000$. Rej*: rejection rate for $H_0 : \theta = 0$. Cov*: bootstrap 95% confidence interval coverage rate. β_1^*: sensitivity parameter for $T = 1$. Missing rate*: overall functional endpoint missing rate.

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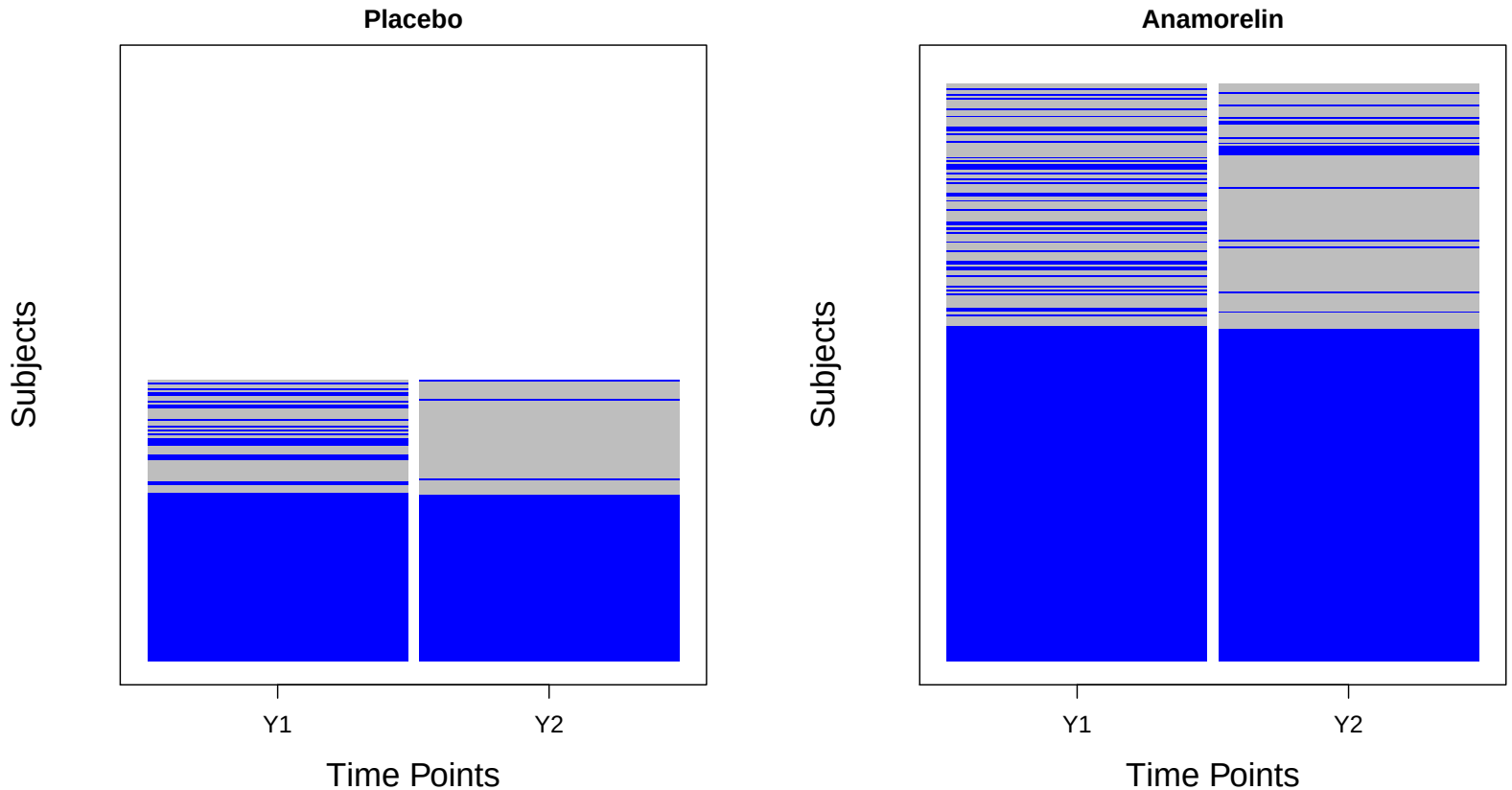
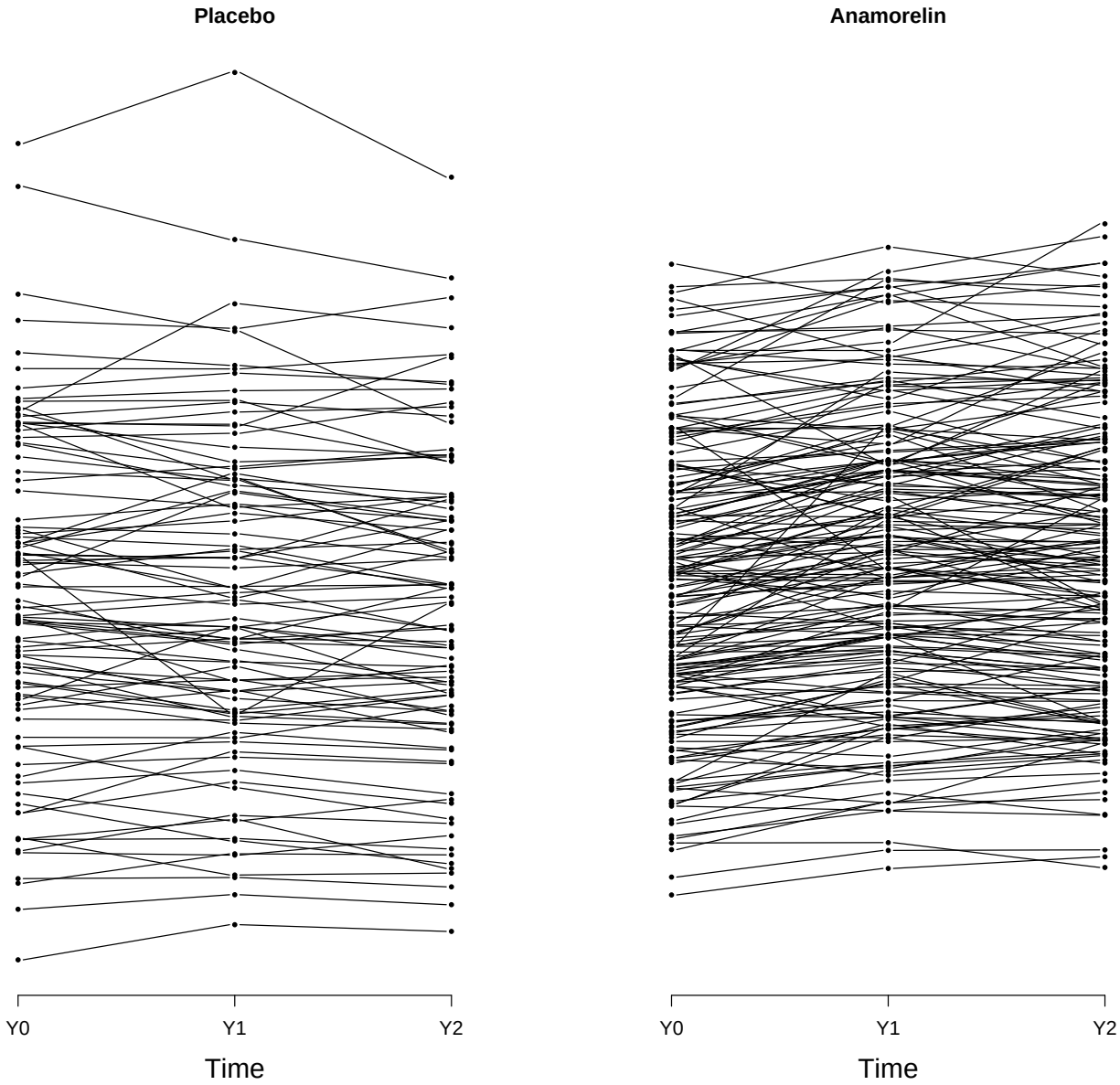
Central Question

How should data from studies like HT-ANAM 302 be analyzed to evaluate the effect of treatment on the functional outcome?

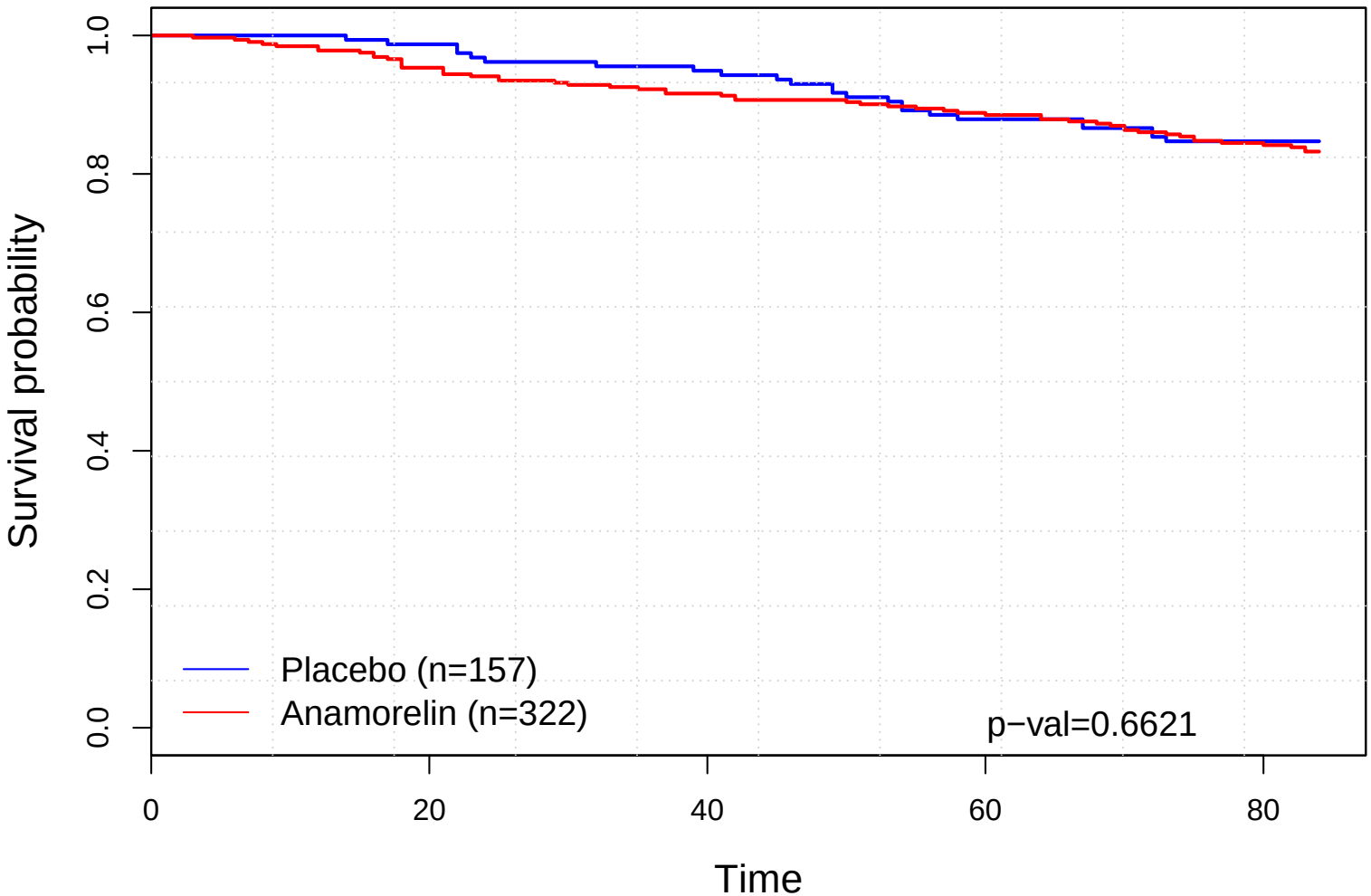
Missing pattern



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

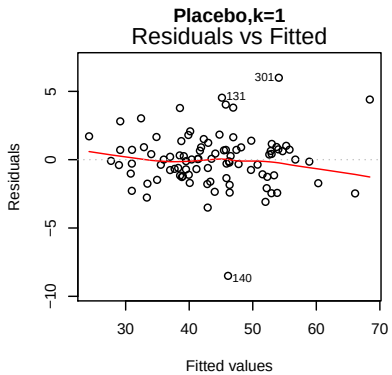
[1] in prior 6 months

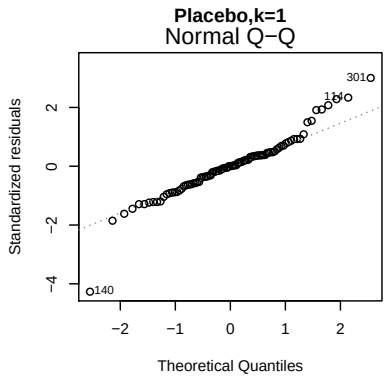
Modeling

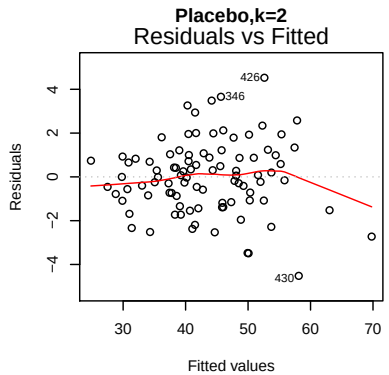
Specify $\mu_{k,t}(\overline{Y}_{k-1}, Y_0, X; \boldsymbol{\alpha}_{k,t})$ as follows:

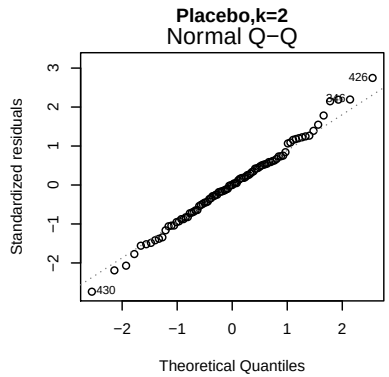
$$\begin{aligned}
\mu_{1,t} &= \alpha_{1,t,1} + \alpha_{1,t,2} Y_0 + \alpha_{1,t,3} ECOG + \alpha_{1,t,4} AGE \\
&\quad + \alpha_{1,t,5} G + \alpha_{1,t,6} BMI + \alpha_{1,t,7} WL \\
\mu_{2,t} &= \alpha_{2,t,1} + \alpha_{2,t,2} Y_0 + \alpha_{2,t,3} ECOG + \alpha_{2,t,4} AGE \\
&\quad + \alpha_{2,t,5} G + \alpha_{2,t,6} BMI + \alpha_{2,t,7} WL + \alpha_{2,t,8} Y_1
\end{aligned}$$

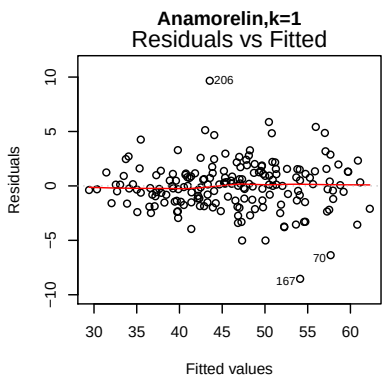
Model fitting diagnosis

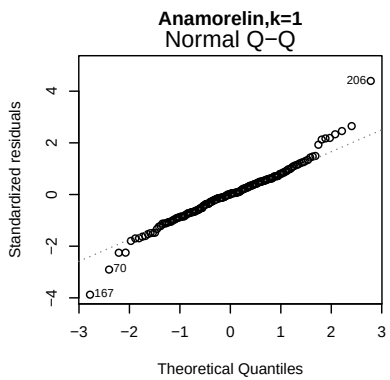


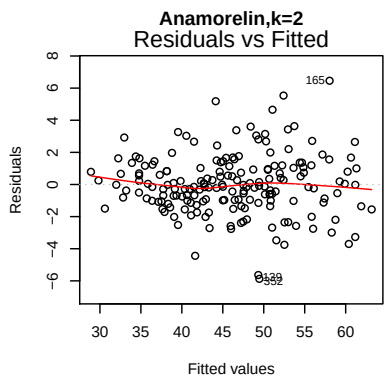


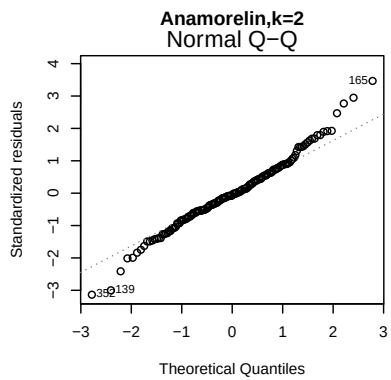












Analysis under benchmark assumptions

- 10 imputed datasets generated
- 200 bootstrap samples

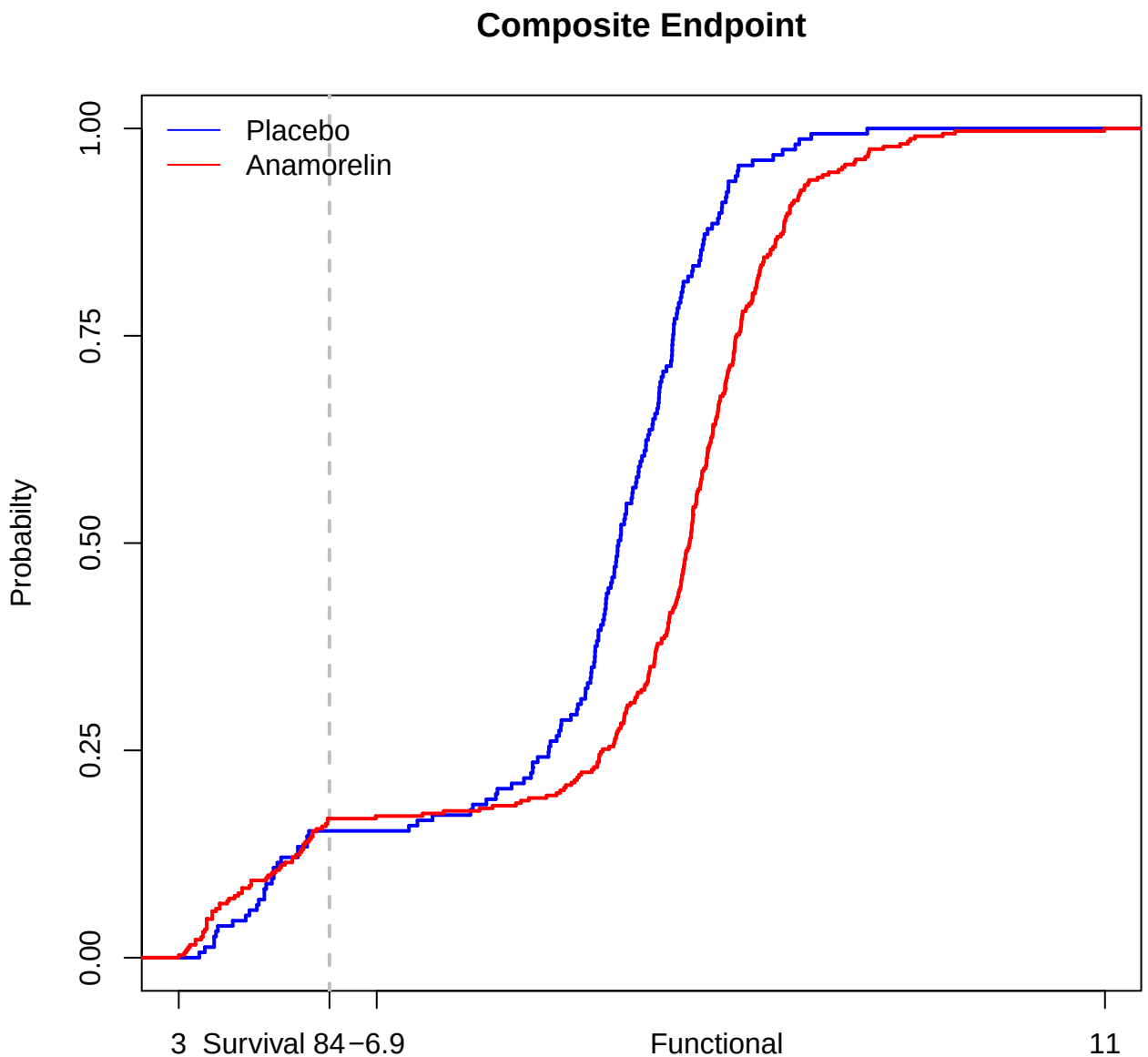
Table: Hypothesis testing

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

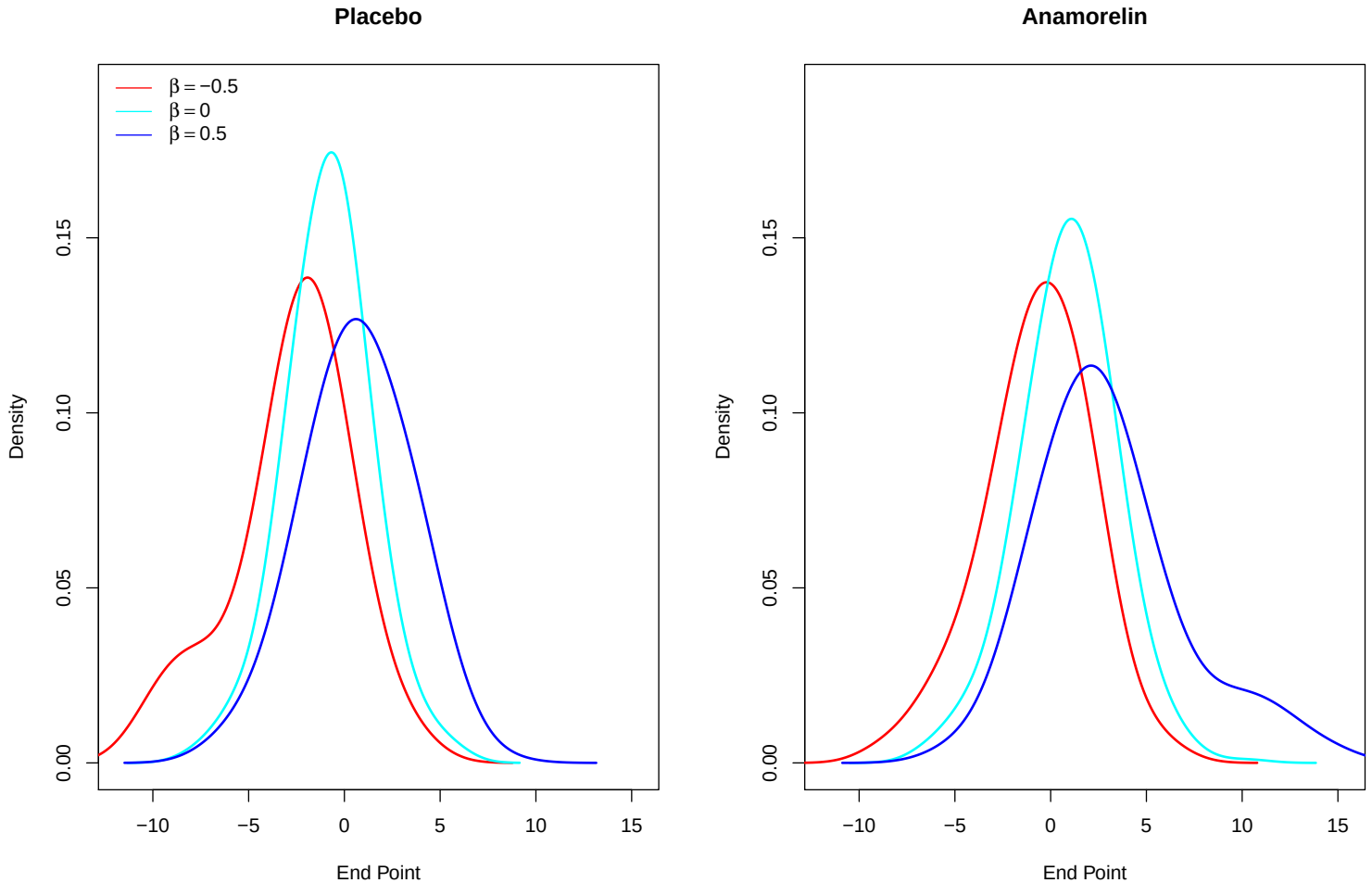
Table: Median

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

Cumulative plot

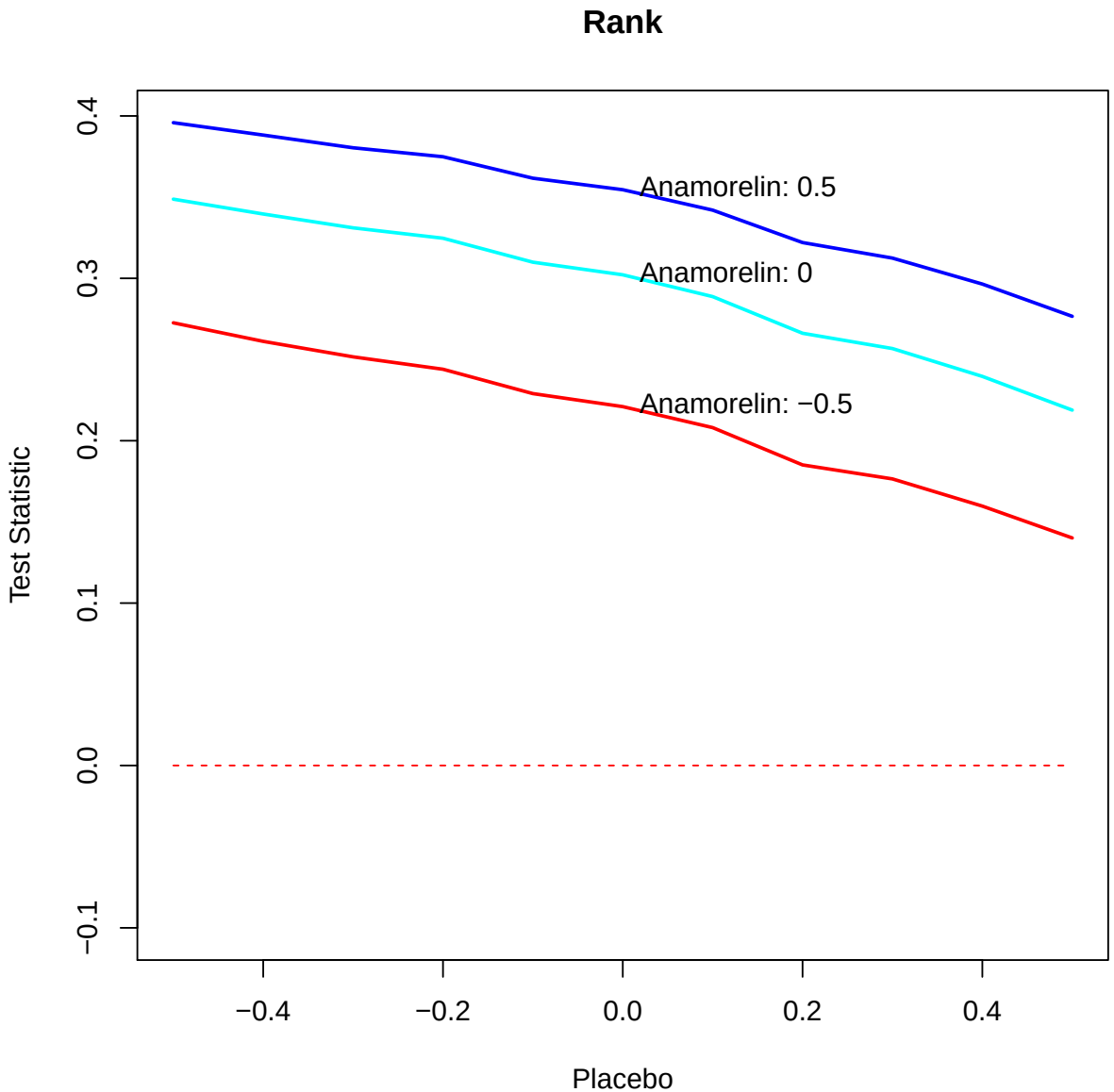


Choice of sensitivity parameters

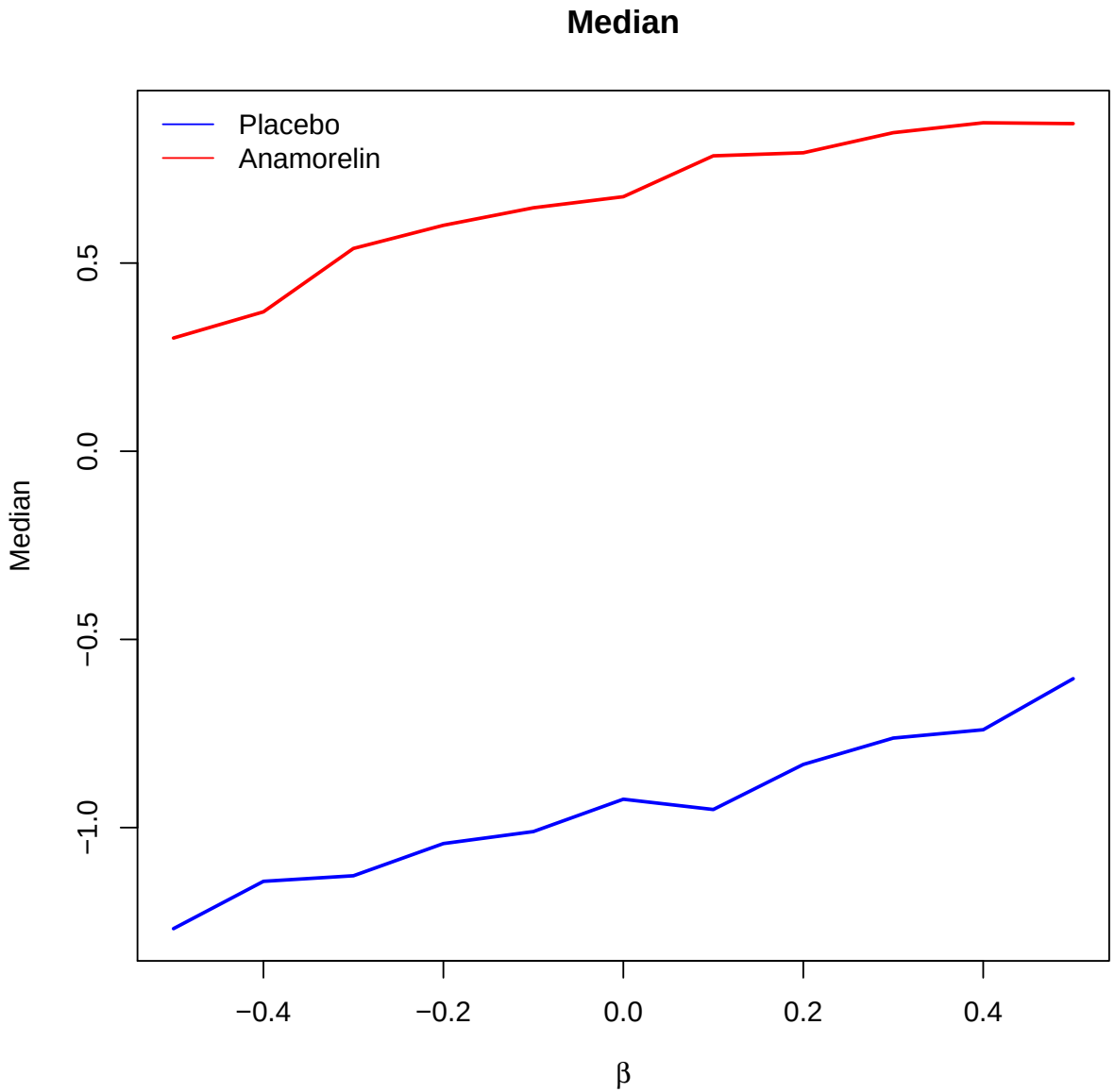


- Change in $E(Z)$ about 1.5 kg at $\beta_T = 0.5$ and $\beta_T = -0.5$
- Set $\beta_T = \{-0.5, -0.4, \ldots, 0, \ldots, 0.5\}$

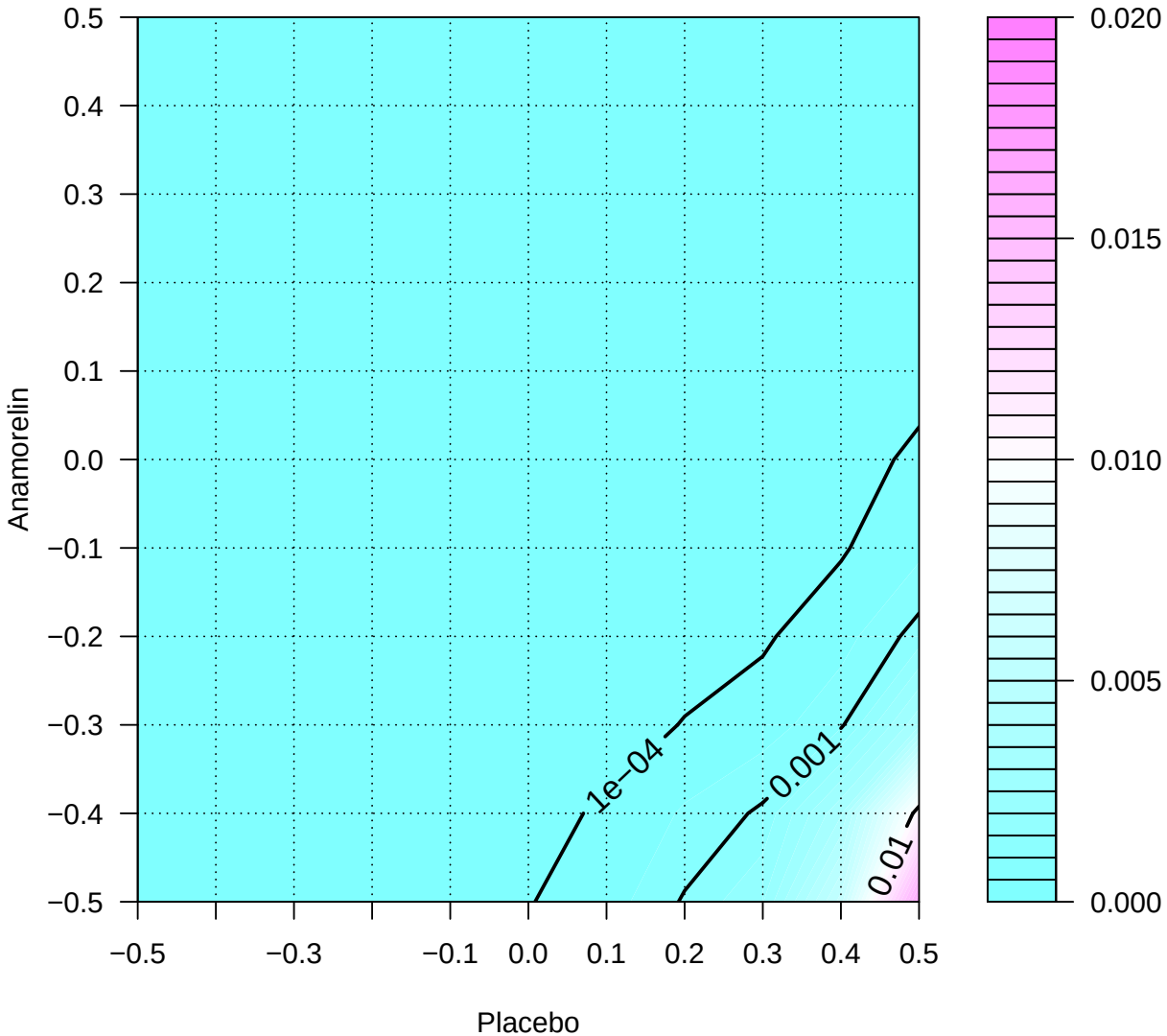
Sensitivity analysis: Rank



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.

Discussion

- Method presumes that death and the functional outcome can be ordered in a scientifically meaningful way.
- Use mixed methods to confirm that ordering is consistent with the health preferences of patient population.
- Ranking scheme is similar to 'untied worst-rank score analysis" for missing data of Lachin (1999).
- The "worst-rank score analysis" ranks all the patients who died ($A_K = 0$) the same and is also commonly used.
- CCMV is a strong benchmark assumption.
- Assumed survival time is always known, need to extend methods to handle censoring.
- R package `idem`