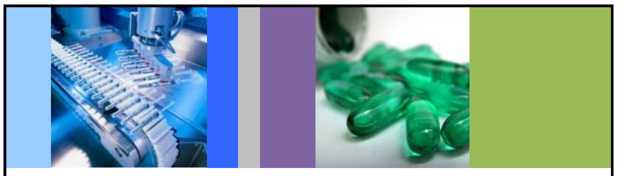

Alternative implementations of Whitehead's methodology for blinded sample size reassessment in survival studies

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Outline

- Background and notation
- Problem description
- The naive approach
- Whitehead's framework
- Possible alternative implementations
- Comparison between alternative implementations using simulations

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Survival clinical trial

- Endpoint: time to ("bad") event
- Two treatment groups: Experimental (E) and Control (C)
- Fixed treatment duration period of length T
- 1:1 randomization ratio
- Proportional hazard ratio assumption - for all t>0:

$$\theta = -\log\left[h_E(t)/h_C(t)\right] = -\log\left[-\log S_E(t)\right] + \log\left[-\log S_C(t)\right]$$

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Sample size and power

For testing $H_0:\theta=0$ vs. $H_1:\theta=\theta_R$

The needed number of events is $\mathrm{e} = \dfrac{4\cdot\left(z_{\alpha/2}+z_\beta\right)^2}{\theta_R^2}$

The required sample size is $N = \dfrac{2\cdot \mathrm{e}}{1\text{-}\mathrm{S_E}(T)+1-\mathrm{S_C}(T)}$

Example

$$\alpha=0.05, 1-\beta=0.83, \theta=\log 0.696 \quad\Rightarrow\quad \mathrm{e}=260$$

$$S_C(2)=0.7 \quad\Rightarrow\quad N=1000$$

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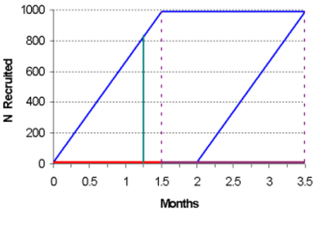
Study flow and problem



Recruitment period: 1.5 years. Overall study duration: 3.5 years.

1.25 years from study beginning, 80 events have been observed.

Are we going to reach 260 events?

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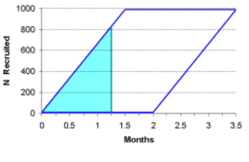
The naïve approach

Assumption: N of events is proportional to exposure



$S_{par} = \text{Overall exposure} = 2\cdot 1000 = 2000\ PY$

$S_{tri} = \text{Exposure so far} = 0.5\cdot 1.25\cdot 833 \approx 521 PY$

$\Rightarrow \text{Expected N of events} \approx 60\cdot\dfrac{2000}{521} \approx 230$

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Whitehead's framework*

- Estimate the overall survivor function from the blinded data
- Construct **illustrative** survival functions for treatment groups consistent with assumed treatment effect and observed overall survival
- Check whether trial is likely to produce number of events needed

Whitehead emphasizes that the procedure is blinded, since the survival function constructed in the second step "are illustrative survival functions, and not estimates, θ itself has not been estimated from the data and the appropriateness of the proportional hazards model has not been assessed".

But…How is the second step implemented?

*Whitehead (2001), *Drug Information Journal*, Vol. 35, 1387–1400

Implementation 1* - Whitehead et. al.

- Estimate $\hat{S}_P(T)$
- Solve the system for $\hat{S}_E(T),\ \hat{S}_C(T)$:

$$\begin{cases} \hat{S}_P(T) = 0.5\cdot\left[\hat{S}_E(T)+\hat{S}_C(T)\right] \\ \theta_R = -\log\left[-\log\left\{\hat{S}_E(T)\right\}\right]+\log\left[-\log\left\{\hat{S}_C(T)\right\}\right] \end{cases}$$

- Use $\hat{S}_E(T),\ \hat{S}_C(T)$ to estimate the expected number of events at T

*Whitehead et. al. (2001), Statistics In Medicine 20: 165-176

Implementation 1 (cont.)

Estimation of $\hat{S}_P(T)$

- Suppose mid-review is to be performed at time R (R<T)
- For various t_i<=R, i=1,…,k and for t=T, compute

$$S_P(t_i) = 0.5\cdot\left[S_E(t_i)+S_C(t_i)\right]$$

- Let Φ be the average difference between the anticipated $S_P(t_i)$ and the new $\hat{S}_P(t_i)$ values on the complementary log-log scale for i=1,…,k. That is

$$\phi = \frac{1}{k}\sum_{i=1}^{k}\left[-\log\left\{-\log\hat{S}_P(t_i)\right\}+\log\left\{-\log S_P(t_i)\right\}\right]$$

- Using Φ, estimate $\hat{S}_P(T)$ by

$$-\log\left[-\log\hat{S}_P(T)\right] = -\log\left[-\log S_P(T)\right]+\phi$$

How is the second step implemented?

- Whitehead et. al. (2001) proposed a method that assumes some knowledge (that can be empirical) of $S_E(t)$ *and* $S_C(t)$
- *Other alternatives assume that each of* $S_E(t)$ *and* $S_C(t)$ *depend on a single parameter,* λ_E and λ_C, *respectively, and that* θ *can be expressed by these two parameters.*
- *The exponential survival function and its extension, the Weibull survival function , are examples for such survival function.*
- *Throughout the rest of the presentation I will use exponential survival for illustration:*

$$S_E(t) = e^{-\lambda_E\cdot t}\qquad S_C(t) = e^{-\lambda_C\cdot t}\qquad \theta_R = -\log\left(\lambda_E/\lambda_C\right)$$

Implementation 2 – estimate λ_C from KM curve

- If that time to event is exponentially distributed, then

$$S_P(t) = 0.5\cdot\left(e^{-\psi\cdot\lambda_C\cdot t}+e^{-\lambda_C\cdot t}\right),\ \text{where } \psi = e^{-\theta}$$

- Let $\hat{S}_P(t)$ be the pooled Kaplan-Mayer estimator
- Obtain estimates $\hat{\lambda}_{C,i}$ by solving for various t_i<=R, (i=1,…,k):

$$\hat{S}_P(t_i) = 0.5\cdot\left(e^{-\psi\cdot\lambda_C\cdot t_i}+e^{-\lambda_C\cdot t_i}\right)$$

- Estimate λ_C by $\hat{\lambda}_C = \frac{1}{k}\sum_{i=1}^{k}\hat{\lambda}_{C,i}$

Implementation 3 - estimate λ_C from mean time to event

- Estimate μ_P, the mean time to event in the pooled population
- Solve the set of equations to obtain estimates for λ_E and λ_C

$$\begin{cases} \mu_P = 0.5\cdot\left(1/\hat{\lambda}_E + 1/\hat{\lambda}_C\right) \\ \psi = \hat{\lambda}_E/\hat{\lambda}_C \end{cases}$$

Implementation 4 - estimate λ_C from mixed likelihood function

- If subject *i* is randomized to group X (X is T or C) then the likelihood for this subject is:

$$L_{i,X}(\lambda_X \; ; t_i, d_i) = \lambda_X(t_i)^{d_i} S_X(t_i)$$

- Since it is not known to which group the subject belongs, the likelihood for this subject will be

$$L_{M,i}((\lambda_P, \lambda_E) ; t_i, d_i) = 0.5 \cdot \left[\lambda_E(t_i)^{d_i} S_E(t_i) + \lambda_C(t_i)^{d_i} S_C(t_i)\right]$$

- Then the overall likelihood function is

$$L((\lambda_E, \lambda_C) ; (t_i, d_i), i = 1, \ldots, N) = \prod_{i=1}^{N} 0.5 \cdot \lambda_C^{d_i} \cdot \left[\psi^{d_i} \cdot e^{-\lambda_C \cdot \psi \cdot t_i} + e^{-\lambda_C \cdot t_i}\right]$$

Implementation 5 - estimate λ_C from likelihood of pooled survival?

- Recall that $S_P(t) = 0.5 \cdot \left(e^{-\psi \cdot \lambda_C \cdot t} + e^{-\lambda_C \cdot t}\right)$
- Then the pooled hazard function is

$$\lambda_P(t) = \frac{\lambda_E \cdot e^{-\lambda_E \cdot t} + \lambda_C \cdot e^{-\lambda_C \cdot t}}{e^{-\lambda_E \cdot t} + e^{-\lambda_C \cdot t}} = \frac{\psi \cdot \lambda_C \cdot e^{-\psi \cdot \lambda_C \cdot t} + \lambda_C \cdot e^{-\lambda_C \cdot t}}{e^{-\psi \cdot \lambda_C \cdot t} + e^{-\lambda_C \cdot t}}$$

- Let t_i be event or censoring time, d_i censoring indicator. Then an MLE for λ_C can be derived from the likelihood function

$$L_P(\lambda_C \; ; (t_i, d_i), i = 1, \ldots, N) = \prod_{i=1}^{N} \lambda_P(t_i)^{d_i} S_P(t_i)$$

- However, this approach is equivalent to the previous one

Simulated study design

- 2 arm placebo control study: 500 subjects per arm
- Fixed treatment duration: 2 years
- Recruitment period: 1.5 years
- Blinded design review at 1.25 years
- Design review assumptions:
  - Time to event is exponential
  - $S_c(2)$=0.7, ψ=0.7 => 260 events are expected

Simulation model

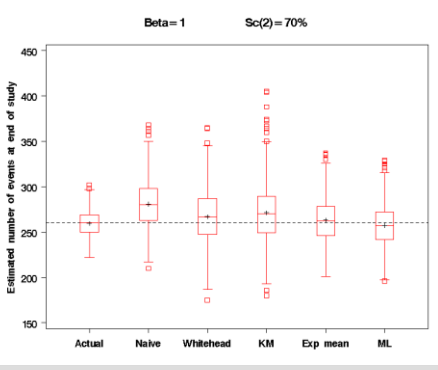
- Time to event ~ Weibull(λ,β)
  - Survival function: $S(t) = \exp\{-(\lambda t)^{\beta}\}$
  - Hazard function $h(t) = \lambda\beta(\lambda t)^{\beta-1}$
- Proportional hazard: $\beta_E = \beta_C = \beta \quad , \quad \lambda_E = \lambda_C \cdot \psi^{1/\beta}$

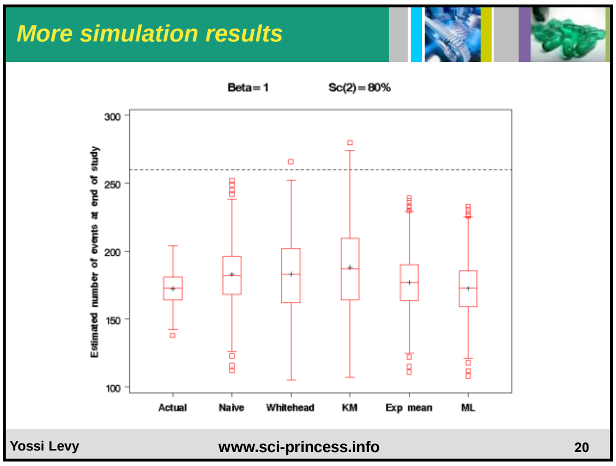
Simulation scenarios

9 scenarios:

- Weibull shape parameter (β):
  - β =0.5 (decreasing hazard)
  - β =1 (constant hazard – exponential)
  - β =2 (increasing hazard)
- $S_C(2)$ =% of subjects not experiencing event in control group (determining λ_C)
  - 80% (inactive population)
  - 70% (assumed population)
  - 60% (active population)

Simulation results – the good news





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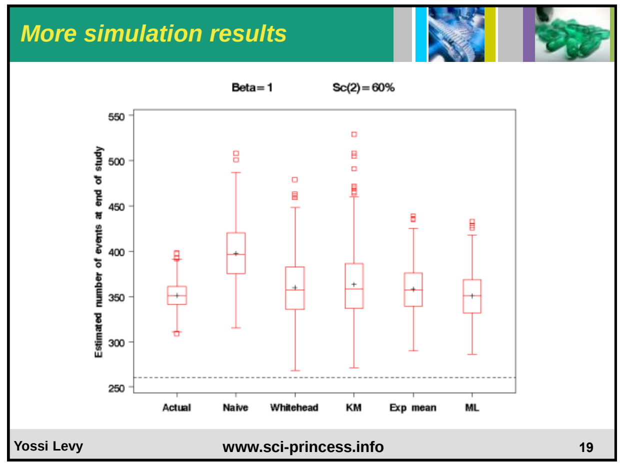

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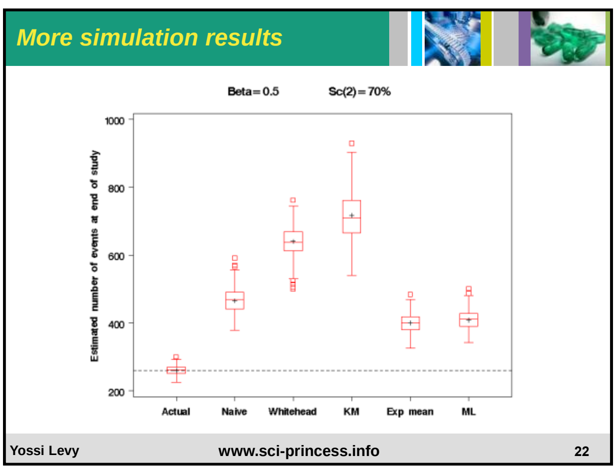

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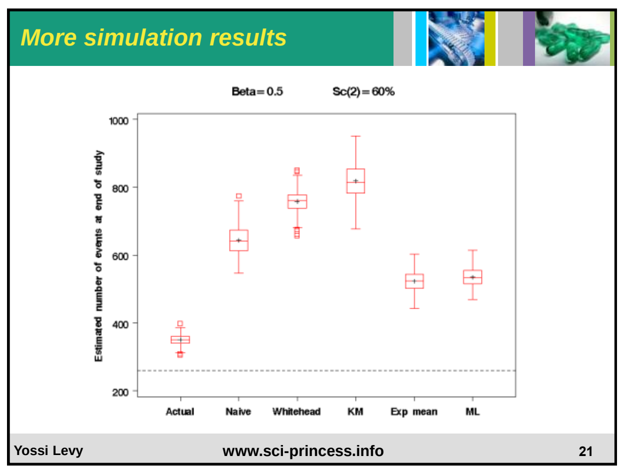

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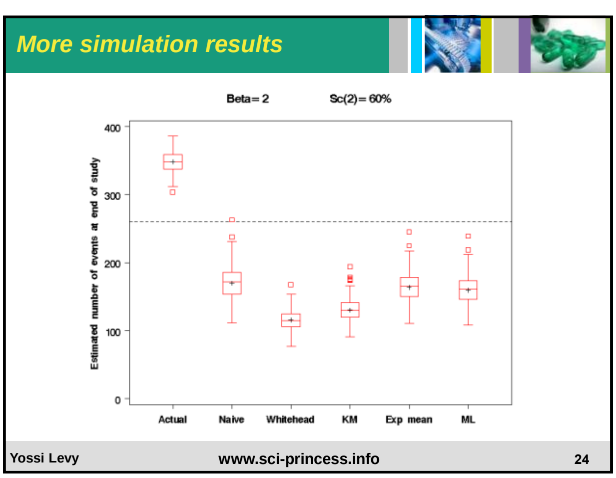

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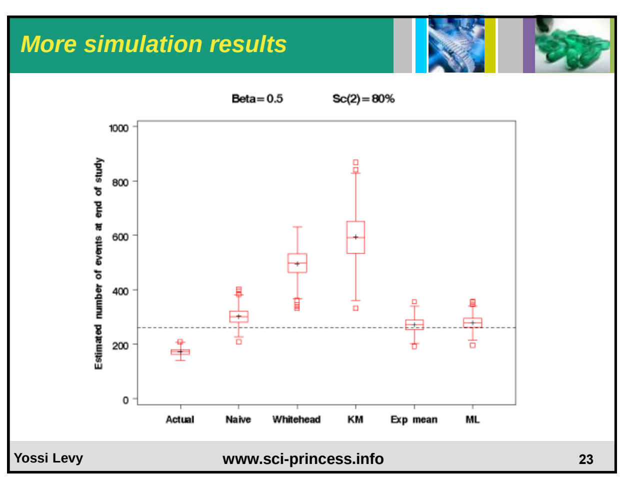

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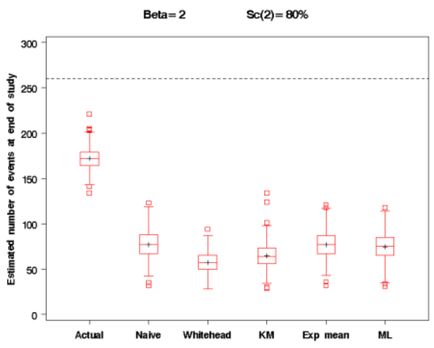
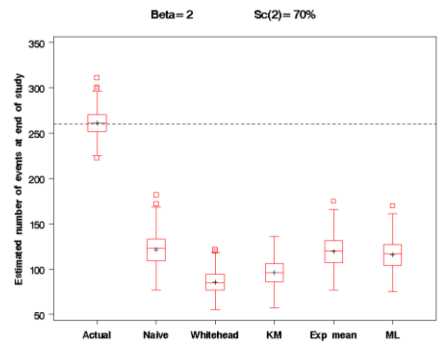
More simulation results



More simulation results



Conclusions

- All approaches generally provide similar results
- If the design underlying distributional assumptions do not hold, then the results of the blinded design review are imprecise