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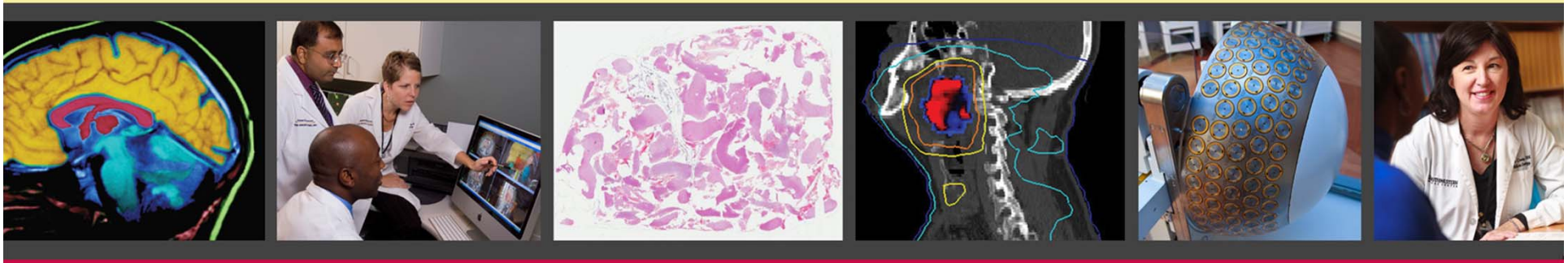

Comparison of Futility Monitoring Methods Using RTOG Clinical Trials

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Futility Monitoring

- Definition: Monitoring for early determination that trial results will not be in favor of H_1
- Of interest when interim analyses show lack of benefit
- Can be complex decision, require multiple methods (see case study: Dignam et al 1998)
- When monitoring for futility, it is important to
  - Protect against increasing type II error, since early negative trends may be due to chance
  - Distinguish inefficacy (i.e., futility) from harm

Futility Monitoring Methods:

- Conditional power: Lan, et al. 1982
- Asymmetric group sequential methods (GSM):
- DeMets & Ware 1980, 1982, Whitehead, et al. 1983, Pampallona et al. 1994, Chang et al. 1998
- Repeated confidence intervals (RCI): Jennison & Turnbull, 1984, 1989, 2000
- Testing to reject H_1 at stringent alpha (Fleming et al. 1984)
- Bayesian predictive power/probabilities: Spiegelhalter, et al. 1986
- Recent proposal: Linear Inefficacy boundary (LIB20): Freidlin, Korn & Gray, 2010

Metric for Efficacy in Survival Data

- Logrank statistic after d^{th} ordered event is:

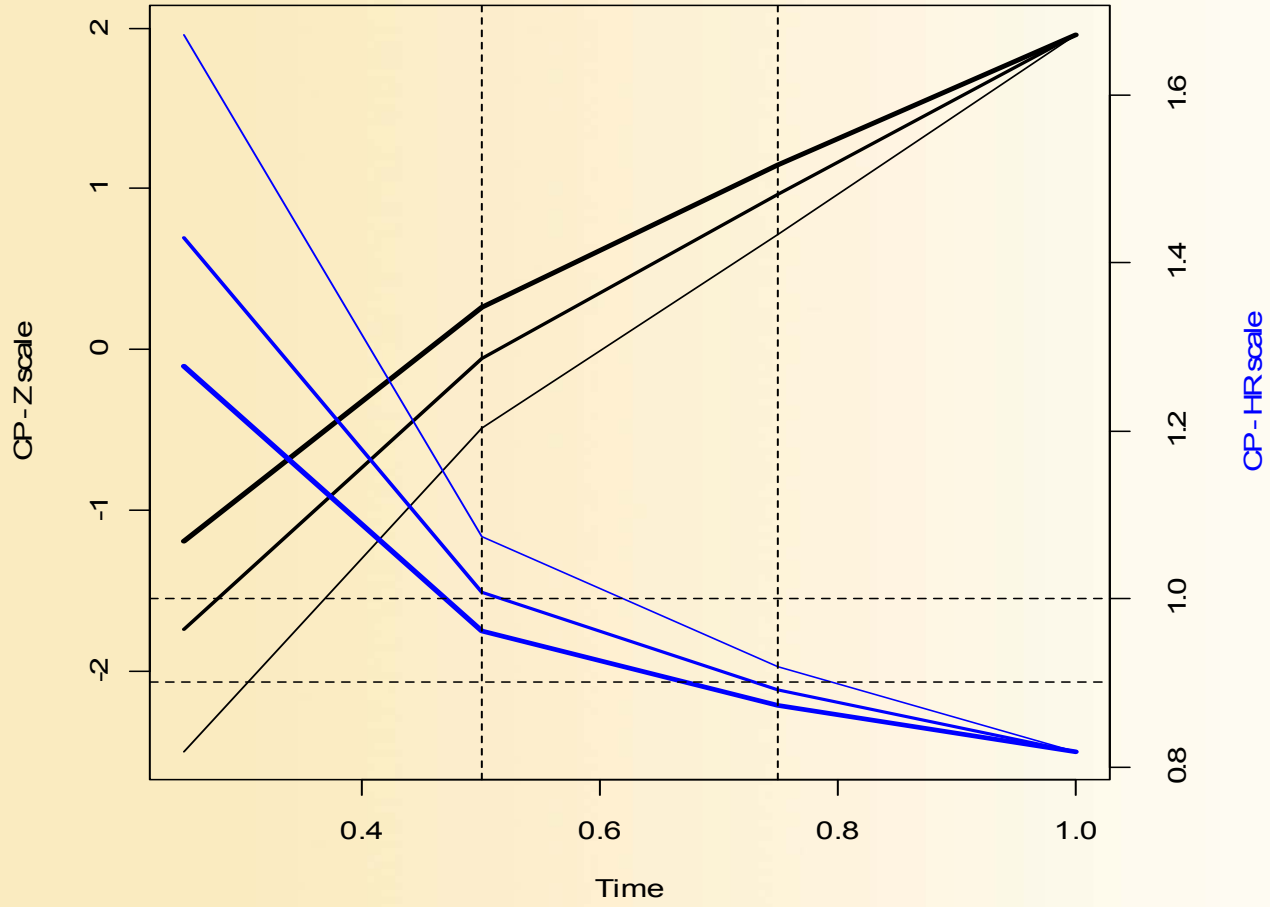
$$Z_d(t) = \sum_{i=1}^{d} (O_i - E_i) / \sqrt{I_d}$$

- $Z(t)$ is logrank test at information time $t = d/D$ events

- When $\theta = \log \lambda \to 0$, $Z_d(t) \sim N(\theta\sqrt{I_d}, 1)$

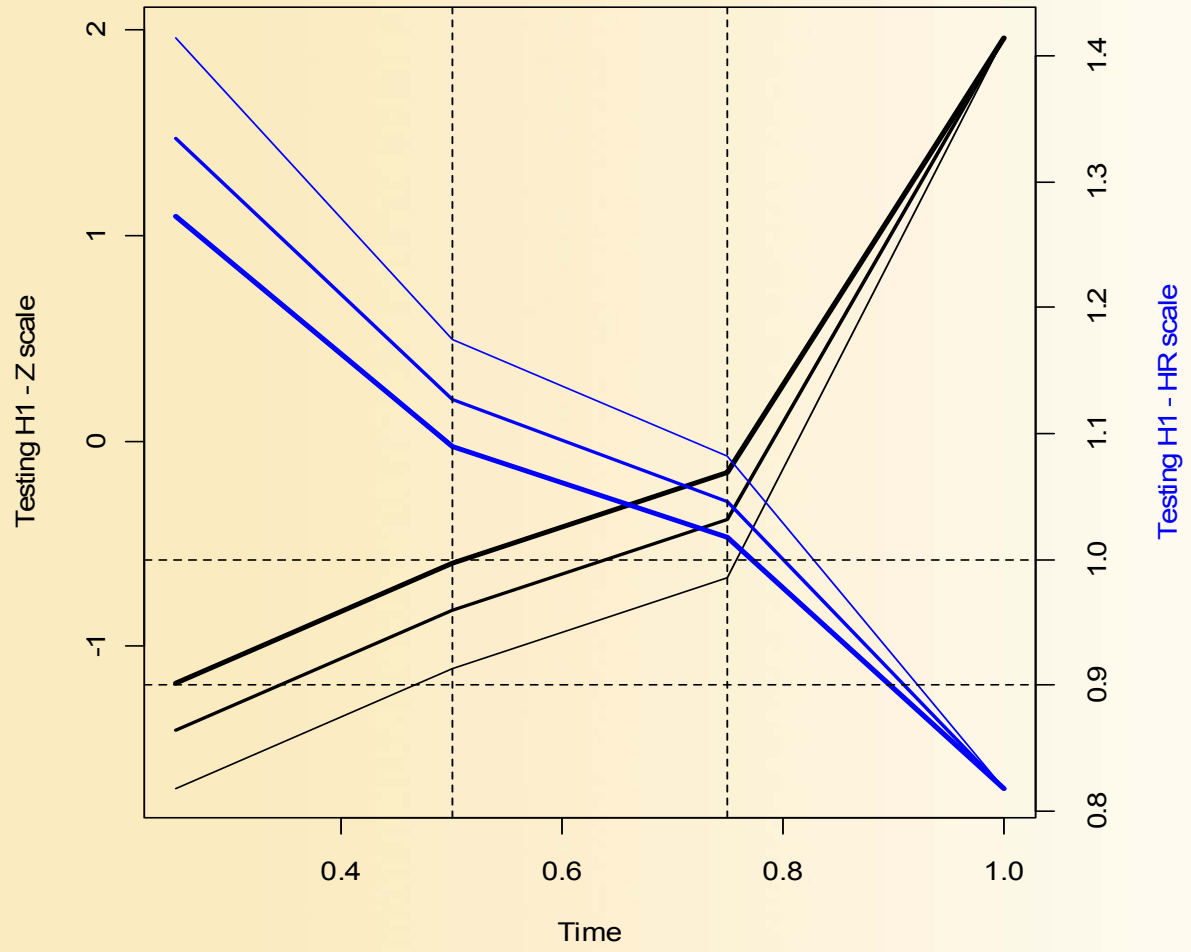
Futility Rules: Conditional Power Boundaries

- $P[Z(t=1) \geq Z_\alpha | Z(t), \theta] = 1 - \Phi\{\frac{|Z_\alpha - Z(t)\sqrt{t} - \theta(1-t)|}{\sqrt{1-t}}\}$



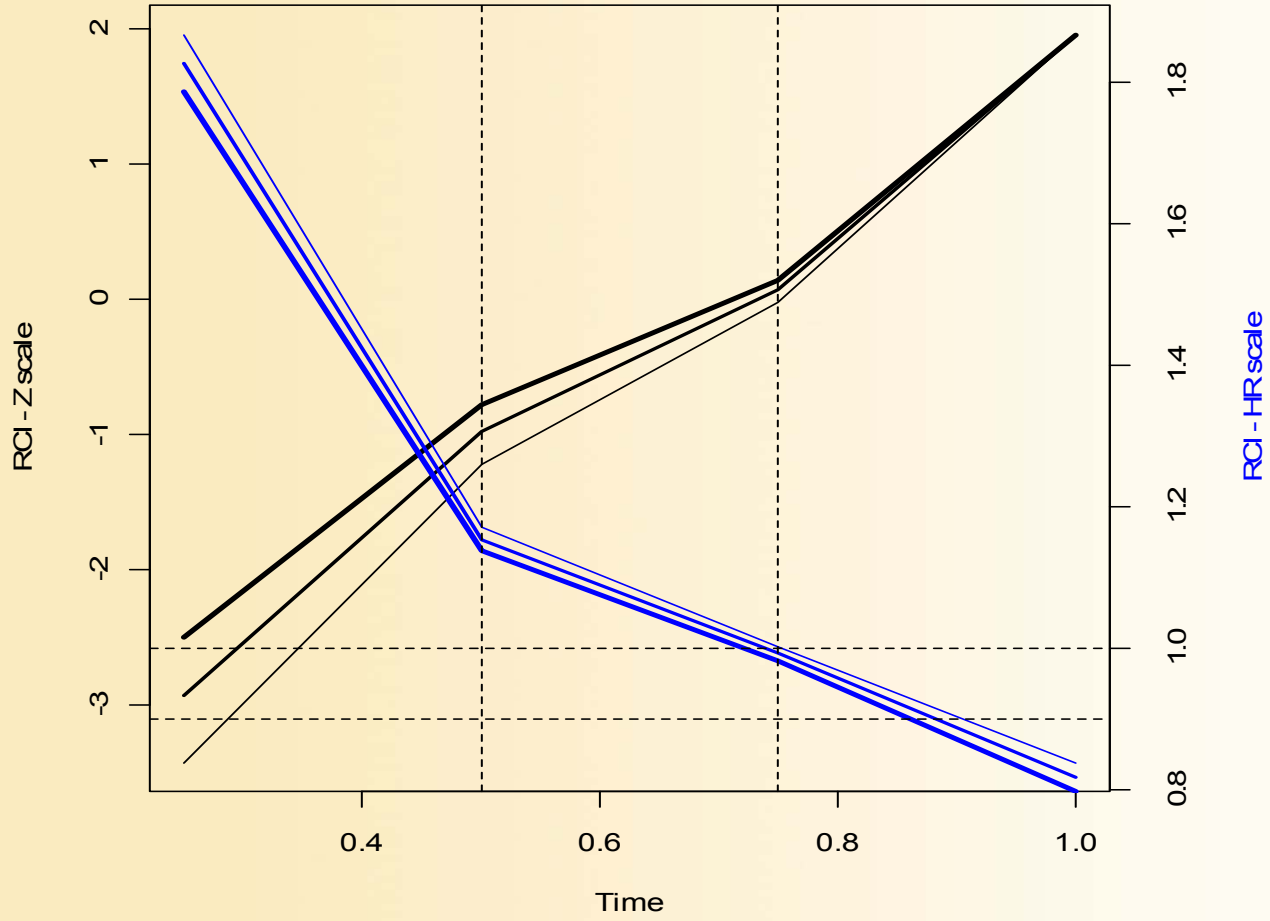
Futility Rules: Testing H_1

- $b = Z_\alpha + \log(\lambda) * \sqrt{d/4}$, α=0.001, 0.0025, 0.005



Futility Rules: Repeated Confidence Intervals

- $Z(t) + C_{OBF} * SE < \theta(t)$



Problems With Current Rules

Freidlin & Korn (2002, 2009) addressed futility stopping in several circumstances:

- Experimental arm is better, smaller effect than H_1 target
- Conditional power is not low
- Time-dependent treatment effect (non-PH)

Some Observations/Recommendations:

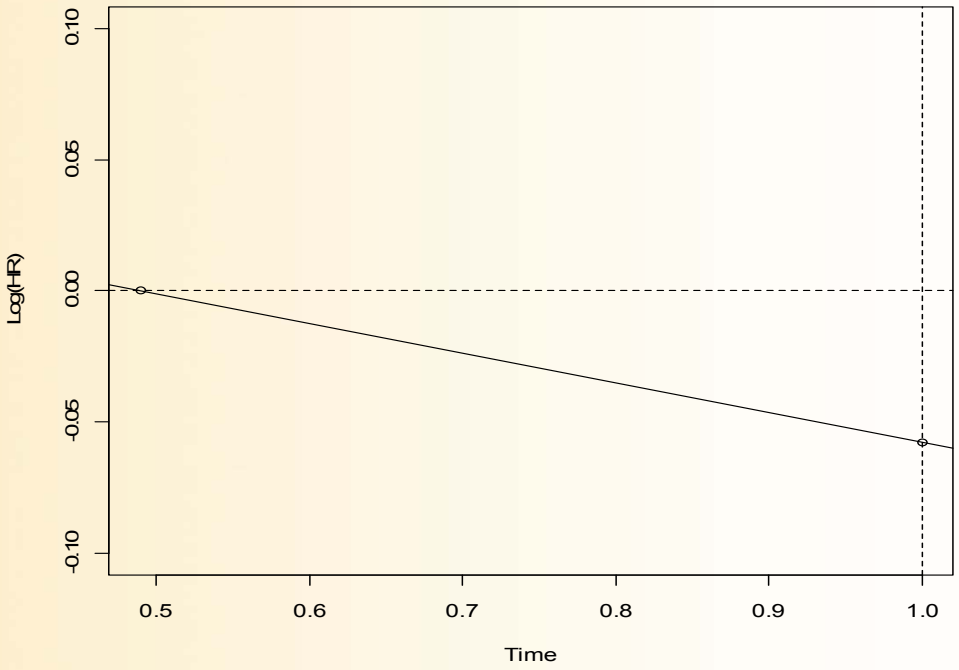
- Aggressive futility monitoring for highly toxic regimens vs. placebo
- Conservative monitoring when treatment is historically effective elsewhere, or may have delayed effect
- Overly aggressive rules stop when there is benefit (Ex. HR = 0.80)

Also:

- RCI and testing against H1 too conservative mid-trial
- Conditional power too aggressive towards end of trial

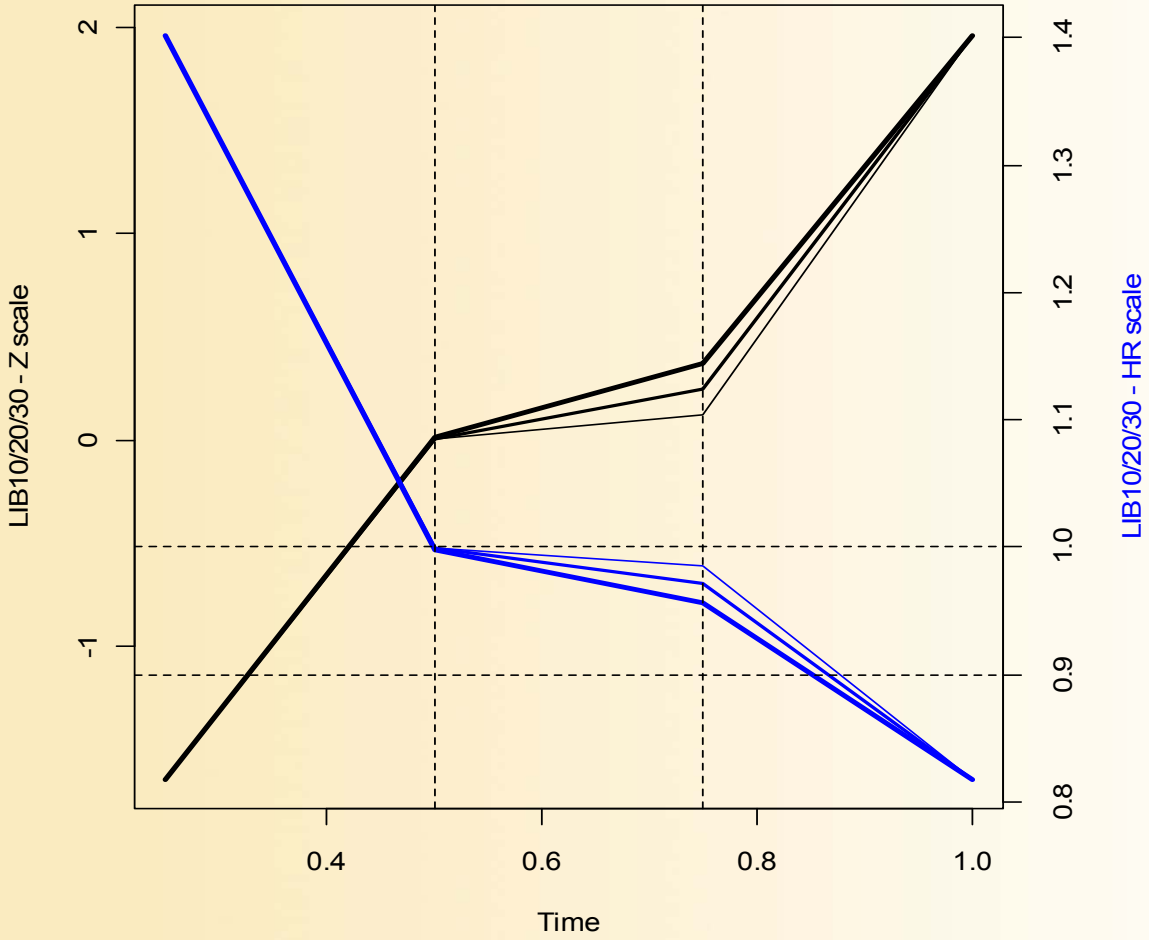
LIB20 - Freidlin, Korn & Gray 2010

- $t_0 = \left(\frac{C_{0.975}}{C_{1-\alpha/2}+C_{1-\beta}}\right)$
- $0.20 * \log\theta_A \frac{(C_{1-\frac{\alpha}{2}}+C_{1-\beta})^2 t - C_{0.975}^2}{(C_{1-\frac{\alpha}{2}}+C_{1-\beta})^2 - C_{0.975}^2}$



- Timely stopping if therapy is harmful or there is no tangible benefit
- Simulation results show that designs with LIB20 will need less patients and shorter duration under H_0 and minor loss of power ($\leq 1\%$) under H_1
- Wieand et al. 1994

LIB10/20/30


LIB10/20/30 - Z scale
2
1
0
-1
0.4
0.6
0.8
1.0
Time
1.4
1.3
1.2
1.1
1.0
0.9
0.8
LIB10/20/30 - HR scale

Comparing Futility Rules using RTOG Trials

- Reported RTOG phase III trials since 1990 (12 trials, 17 comparisons)
- Multiple disease sites
- Total number of events (if not given) calculated using type I, II error rates in protocol
- Multiple comparisons adjusted
- Logrank tests used for all time to event endpoints
- Upper boundary
- Analysis schedules:
  1. Six/Seven looks: 0.25, (0.40), 0.50, 0.60, 0.70, 0.80, 0.90, 1
  2. Three looks: 0.25, (0.40), 0.50, (0.70), 0.75, 1
  3. One look: 0.5, 1

Calculation of Savings

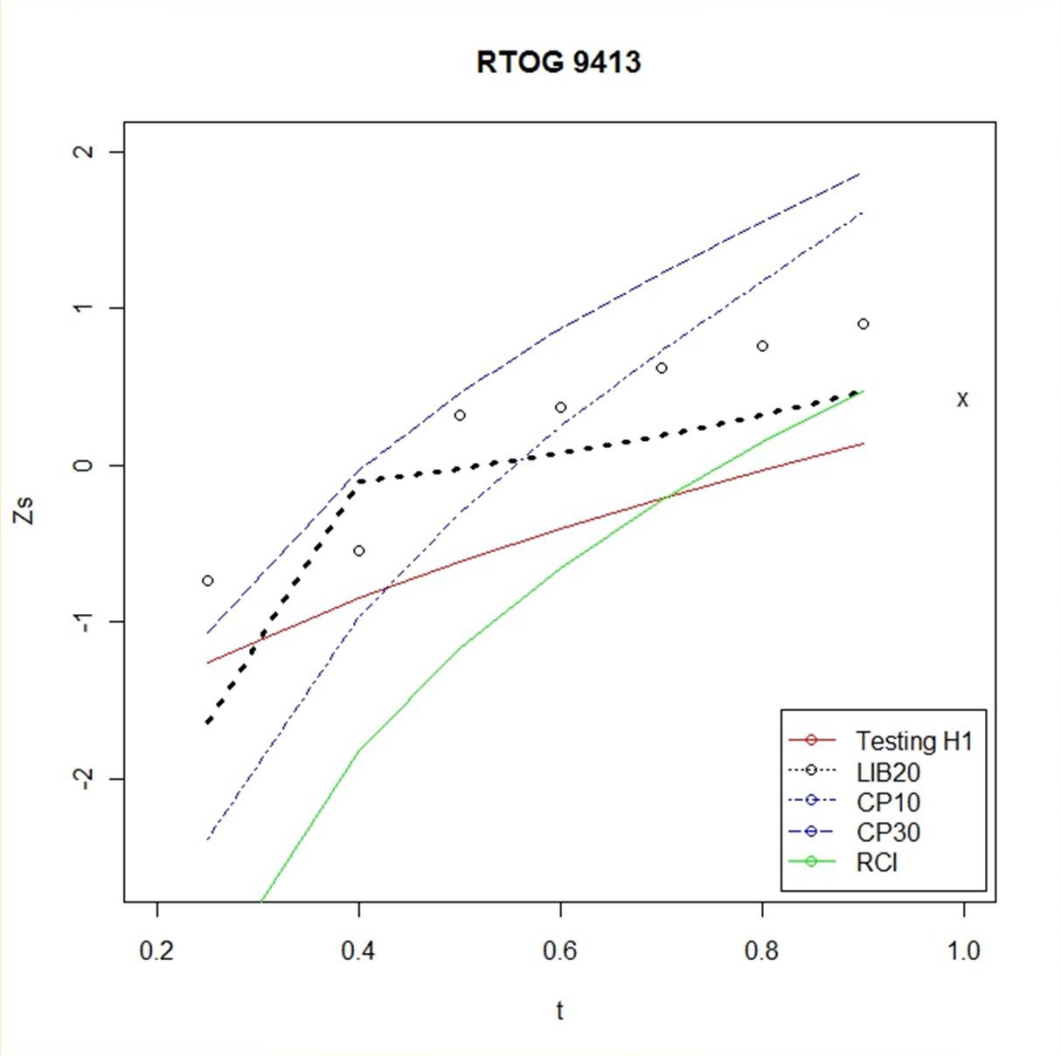
- For each trial and boundary if stop due to futility then
  1. Calculate observed study duration
  2. Calculate number of observed events
  3. Calculate current sample size

- Three groups based on final p values: trials we would not want to stop ($p<0.1$, n=3), neutral ($0.1<p<0.2$, n=3) and stop for sure ($P>0.2$, n=11)

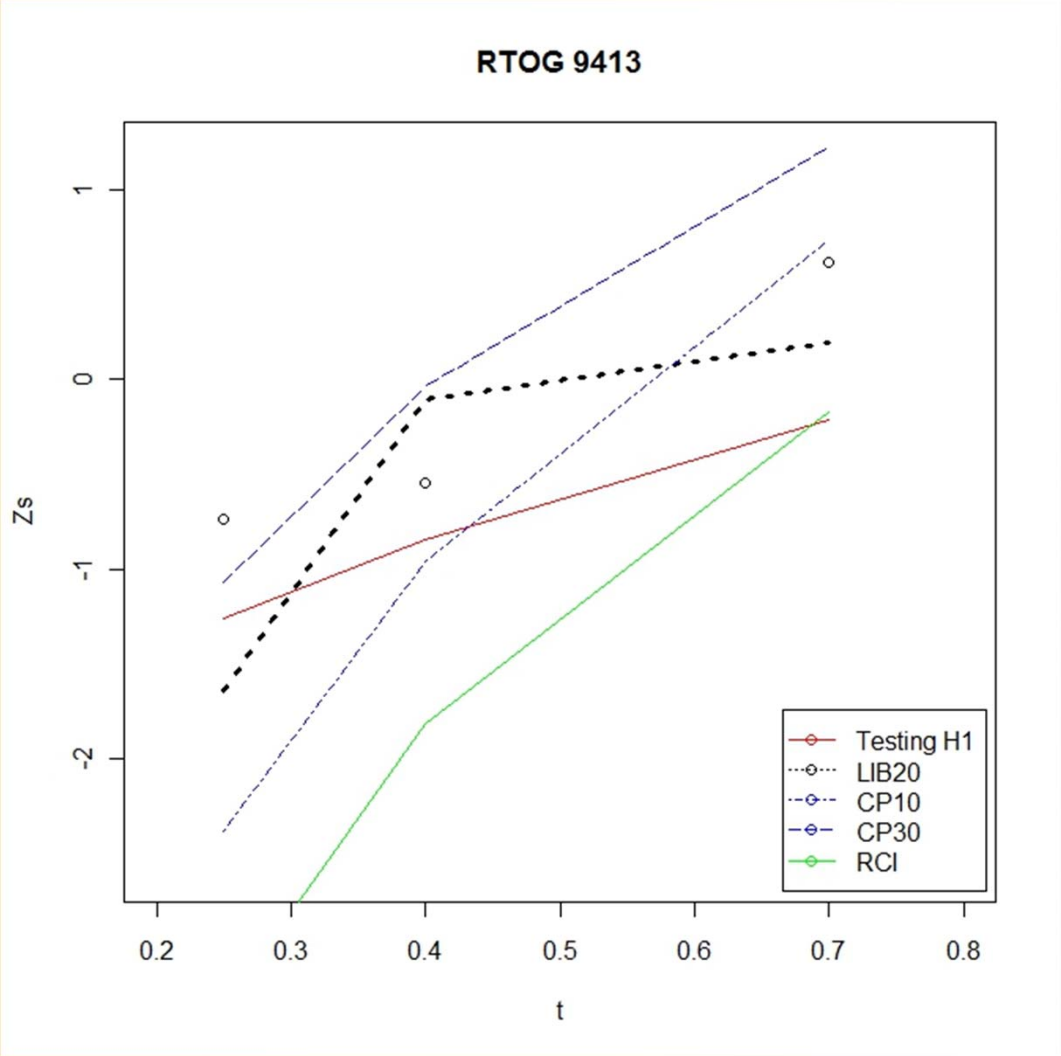
- For all trials in one group given an analysis schedule

- Savings=1- $\frac{\sum_{i=1}^{k} Observed}{\sum_{i=1}^{k} Planned}$ for each rule

Comparing Futility Rules - Example



Comparing Futility Rules - Example



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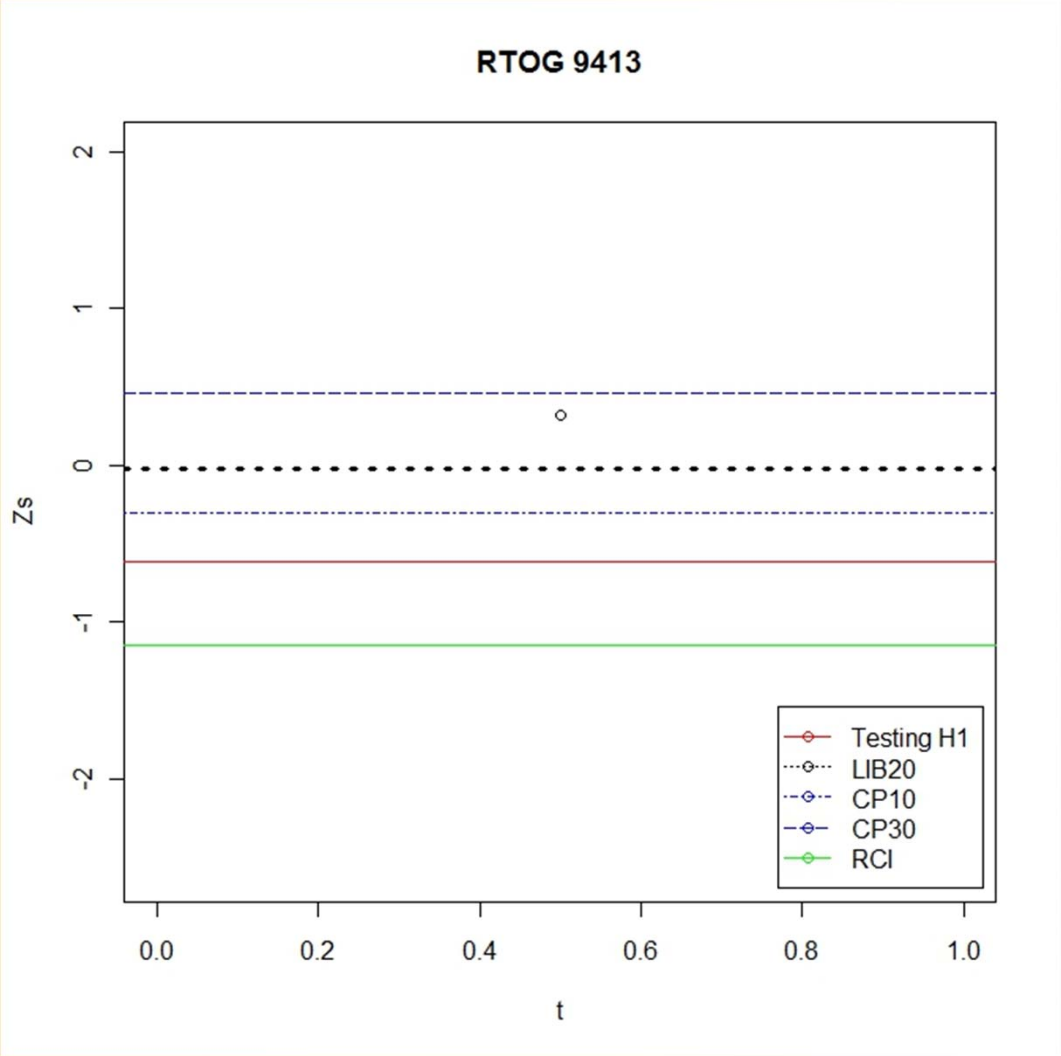
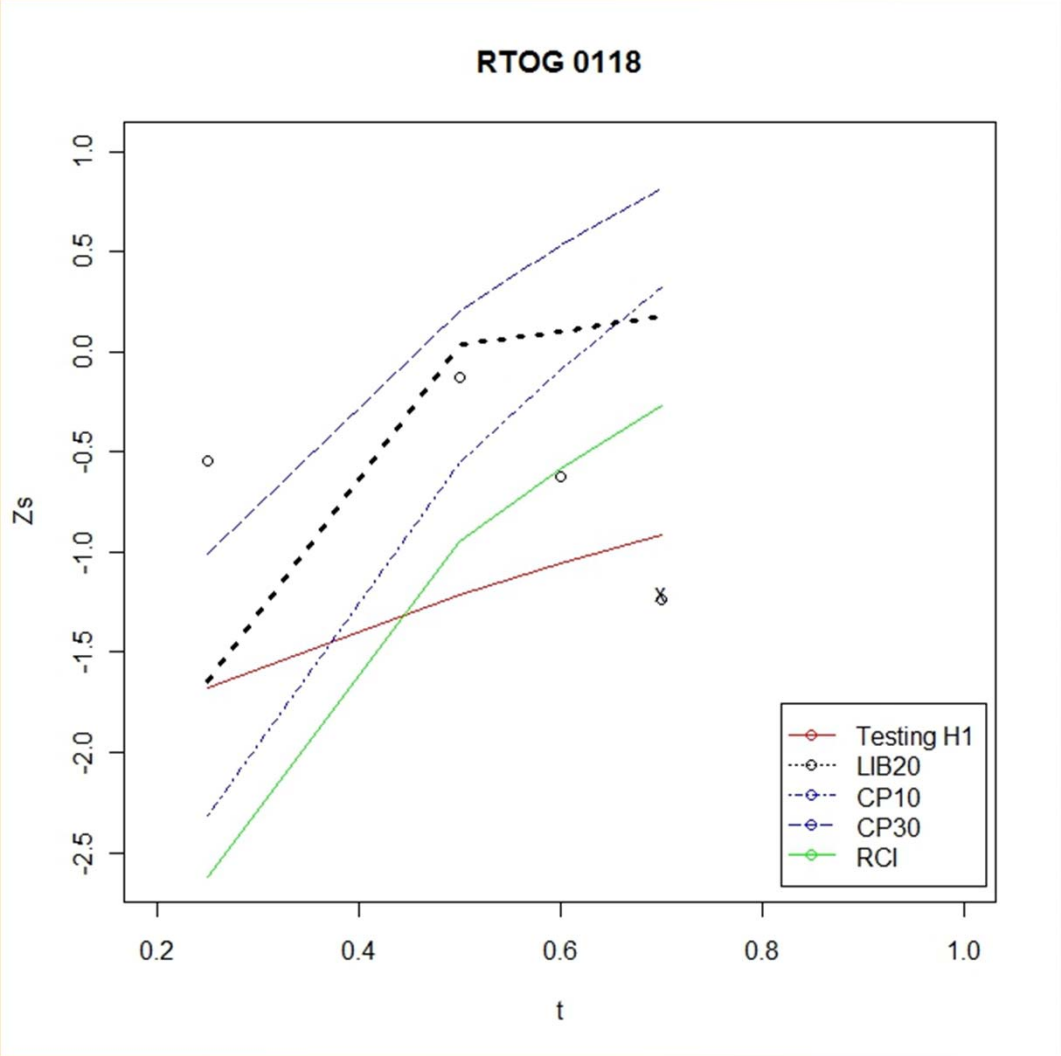
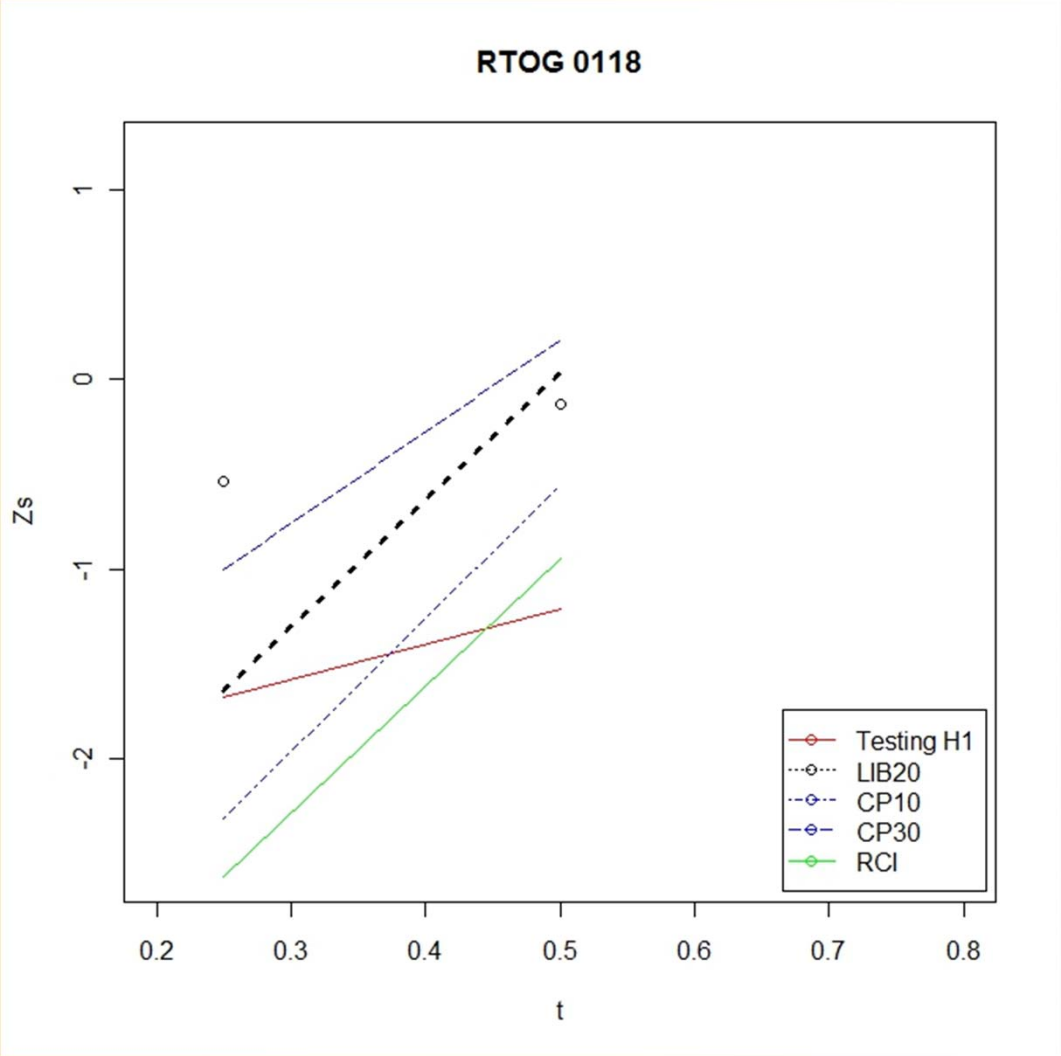


Comparing Futility Rules - Example



Comparing Futility Rules - Example



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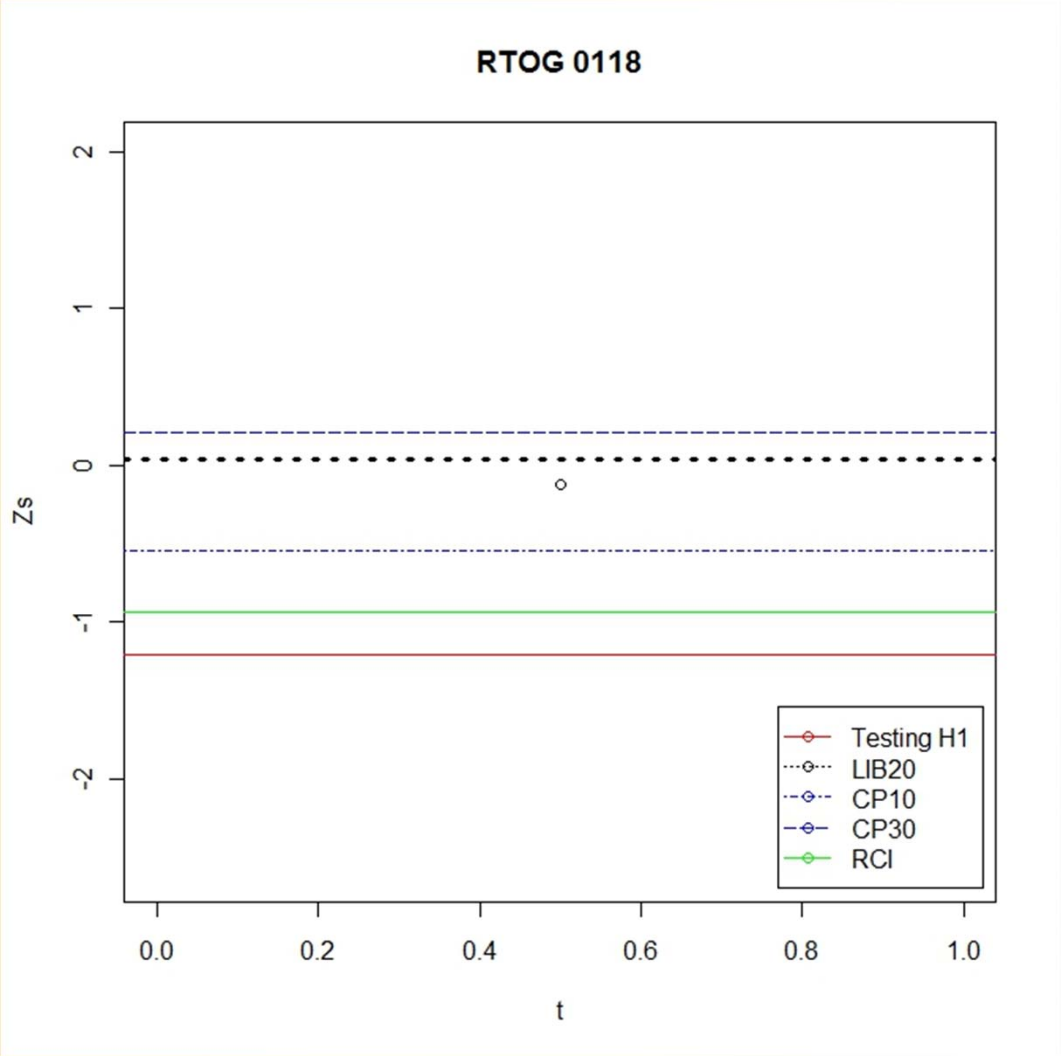

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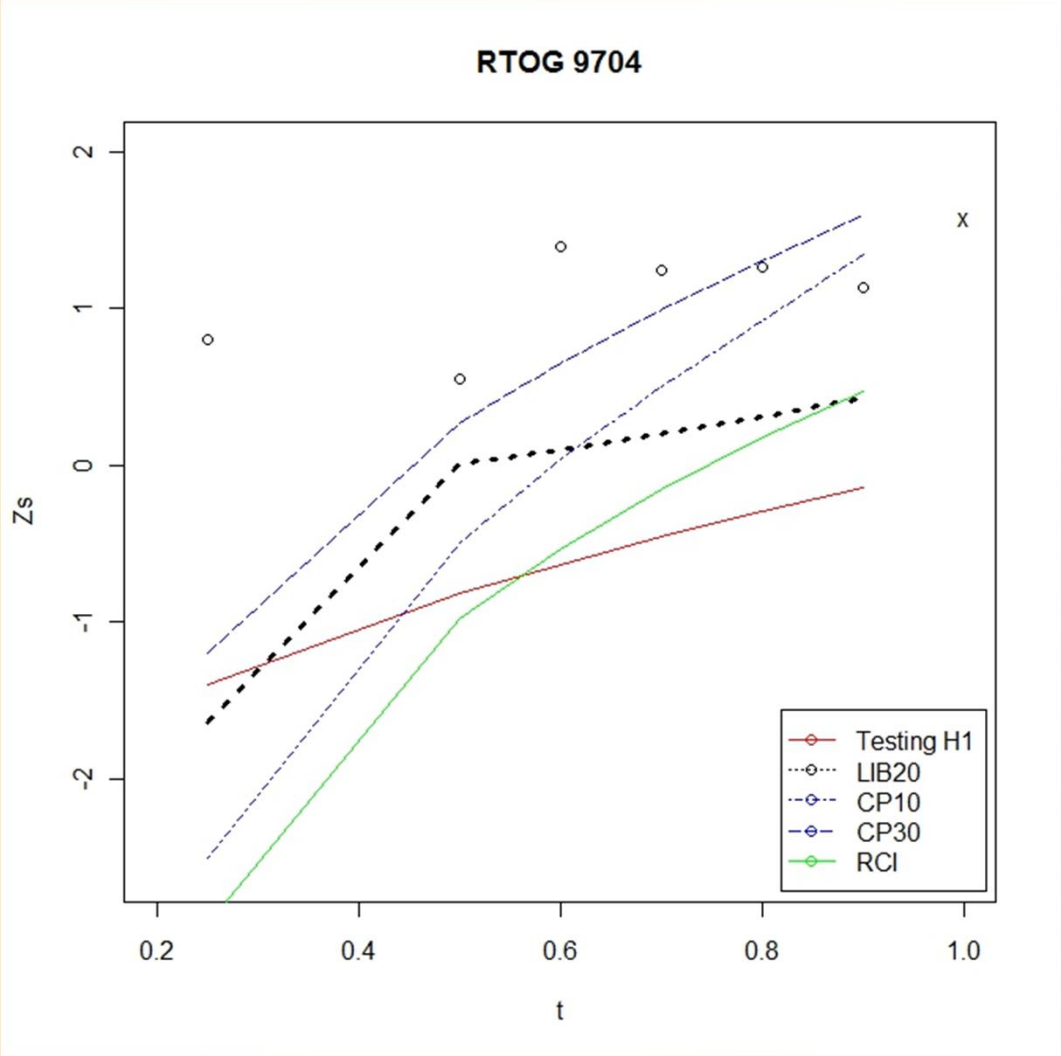

Results

Table 1. Trial time saved, 6/7 looks.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0.158	0.067	0.309	0
Stop yes	0.052	0.238	0.242	0.324	0.163
All trials	0.035	0.189	0.175	0.274	0.110

Table 2. Trial time saved, 3 looks.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0.158	0	0.337	0
Stop yes	0.024	0.220	0.113	0.286	0.138
All trials	0.016	0.177	0.076	0.254	0.093

Table 3. Trial time saved, 1 look.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0	0	0.127	0
Stop yes	0.014	0.146	0.080	0.193	0.014
All trials	0.010	0.099	0.054	0.153	0.010

Results

Table 4. Information time saved, 6/7 looks.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0.2	0.033	0.333	0
Stop yes	0.038	0.256	0.225	0.347	0.121
All trials	0.024	0.200	0.150	0.282	0.077

Table 5. Information time saved, 3 looks.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0.2	0	0.367	0
Stop yes	0.028	0.233	0.108	0.282	0.102
All trials	0.018	0.185	0.069	0.246	0.065

Table 6. Information time saved, 1 look.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0	0	0.167	0
Stop yes	0	0.111	0.047	0.205	0
All trials	0	0.071	0.030	0.161	0

Results

Table 7. Sample size saved, 6/7 looks.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0.252	0	0.270	0
Stop yes	0.006	0.060	0.018	0.062	0.012
All trials	0.004	0.074	0.013	0.078	0.008

Table 8. Sample size saved, 3 looks.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0.252	0	0.284	0
Stop yes	0.006	0.053	0.006	0.045	0.009
All trials	0.004	0.069	0.004	0.067	0.006

Table 9. Sample size saved, 1 look.

	Testing H1	LIB20	CP10	CP30	RCI
Stop no	0	0	0	0	0
Neutral	0	0	0	0.208	0
Stop yes	0	0.011	0.005	0.040	0
All trials	0	0.008	0.004	0.054	0

Discussion

- More frequent monitoring saves more on study duration, number of events and sample sizes
- LIB20 saves more relative to commonly used rules for all analysis schedules
- 10% Conditional power rules have similar savings for frequent monitoring, but conditional power rules are aggressive at the end
- Testing H1 and RCI methods are more conservative
- LIB20 is a rule with good properties across broad applications
  - Lessens patients' exposure to inactive treatment
  - Improves resource utilization
  - Accelerates dissemination of important clinical information

Discussion – Additional Considerations

- Futility rules affect error rates and power –adjust for in sample size
- Futility rules should be formulated based on trial design needs
- Futility stopping must consider other beneficial aspect of the trial
- Futility stopping also depends on study team guidance and DMC input

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