Calculating and Presenting Conditional Power at Interim Looks for an Adjudicated Time to Event Outcome

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Sponsored By: **National Heart Lung and Blood Institute (NHLBI)**

TOPCAT Trial

- TOPCAT : International double-blind RCT comparing spironolactone to placebo for patients with heart failure symptoms and preserved ejection fraction
- Primary outcome: Time from randomization to first occurrence of
  - Heart Failure Hospitalization
  - Aborted Cardiac Arrest
  - Cardiovascular Death
- These components all undergo adjudication

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Unconditional Power

- Depends on parameters such as
  - Sample size
  - Accrual timeline and length of additional follow-up
  - Assumed event rates in each treatment group
  - Assumed loss rates
- Does not depend on outcome data observed during the actual study

Conditional Power

- Calculated at an interim look
- Assesses the probability of reaching a statistically significant treatment group difference by the end of the study
- Does take into account currently observed study data
- Makes assumptions about event rates for remainder of study

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Conditional Power

- Two most common ways of calculating conditional power:
  - Assume observed rates in each treatment arm continue for remainder of study
  - Assume future event rates in each treatment arm are the rates used in designing the study

Adjudication of Outcomes

- Many multi-site studies have an independent Clinical Endpoints Committee (CEC)
- CEC adjudicates whether each reported event meets study criteria for the outcome
- At end of study, only events meeting study criteria are included in primary analysis

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Issue for Conditional Power Calculation

- Adjudication takes time!
- At the interim look, some reported events still pending adjudication
- “Observed” event rates in the treatment groups are not fully known at the time conditional power is calculated

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Simulation Approach for Estimating Conditional Power

- For each replication…
- Randomly decide which pending events to count as actual events
- Randomly select future event and censoring times
- Calculate if significant difference at end of study

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Simulation Approach for Estimating Conditional Power

- Repeat simulation many times
- Estimated conditional power = percentage of simulated studies in which a statistically significant difference is found
- If true percentage is 85%, need 5000 replications for confidence interval width +/- 1%

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Hypothetical Study for Examples

- Designed for 85% power if true 3-year event rates are 20% in Control group and 16% in Active group
- 2 year accrual, 2 additional years follow-up
- 3-year loss rate 10%
- Interim looks at 1/3 and 2/3 information

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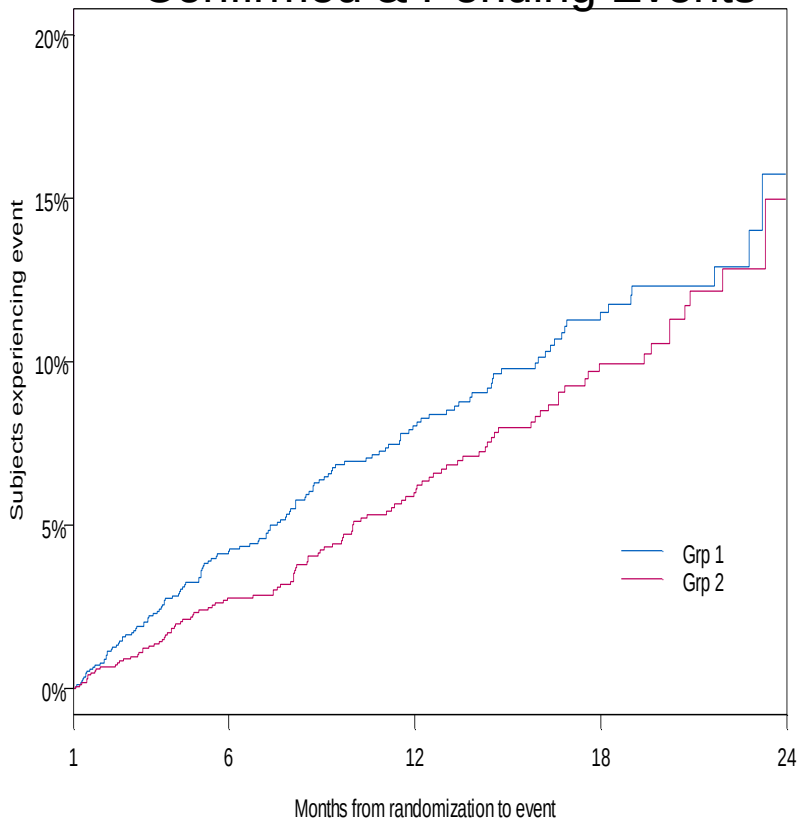
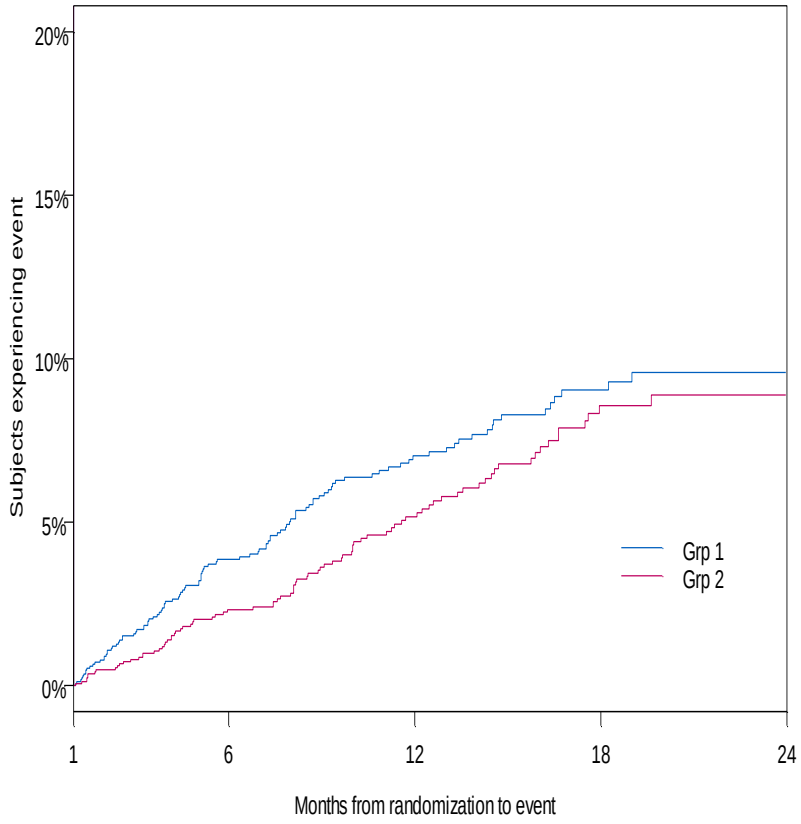
Example 1: Kaplan-Meier Plots at 1st Interim Look
(NOT actual TOPCAT data)

Including All
Confirmed & Pending Events



Including Only
Confirmed Events



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What are the “Observed” Outcome Data?

- Counting all confirmed & pending events, projected 3-year rates 22.5% in Group 1, 18.6% in Group 2
- Counting only confirmed events, projected 3-year event rates 18.6% in Group 1, 15.1% in Group 2
- What do we assume has happened so far?

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Randomly Choose “Observed” Data

- For each subject with confirmed outcome, count as true event
- For each subject lost from study with no confirmed or pending outcome, count as censored on loss date
- For each subject with “pending” status, randomly decide whether to analyze the pending event as confirmed or not confirmed, using “confirmation proportion” from assigned treatment group

Confirmation Proportions in Example 1

- Treatment Group 1 (n=1715)
  - 109 with confirmed events, 25 with pending events, 24 with events not meeting criteria
  - 109/133 or 82.0% of adjudicated events met the criteria
- Treatment Group 2 (n=1714)
  - 87 with confirmed events, 22 with pending events, 19 with events not meeting criteria
  - 87/106 or 82.1% of adjudicated events met the criteria

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Simulate Future Data – Enrolled Subjects

- For each subject still in study, but with no reported event being treated as confirmed
  - Randomly choose time from data freeze to actual event (Can use either best estimates of observed rates, or pre-specified rates)
  - Randomly choose time from data freeze to loss date
  - Calculate follow-up time based on minimum of event date, loss date, or end date for entire study
  - If event date occurs first, analyze as actual event
  - Otherwise, analyze as censored

Simulate Future Data – Future Subjects

- For each subject yet to be enrolled
  - Choose enrollment date based on accrual projections
  - Randomly choose time from enrollment to actual event
  - Randomly choose time from enrollment to loss date
  - Calculate follow-up time based on minimum of event date, loss date, or end date for study
  - If event date occurs first, analyze as actual event
  - Otherwise, analyze as censored

Example 1, 5000 Replications

Assumed 3-year event rates during remainder of study	Group 1	Group 2	Estimated Conditional Power
Best estimates of event rates continue forward	21.8%	18.0%	84.5%
Group 1 is Control, initial assumptions apply	20%	16%	88.9%
Group 2 is Control, initial assumptions apply	16%	20%	9.4%

- If DSMB does not want to know whether Group 1 is Control or Experimental, must report both line 2 and line 3
- Otherwise, could give away which group is Control, based on how the design assumption affects conditional power

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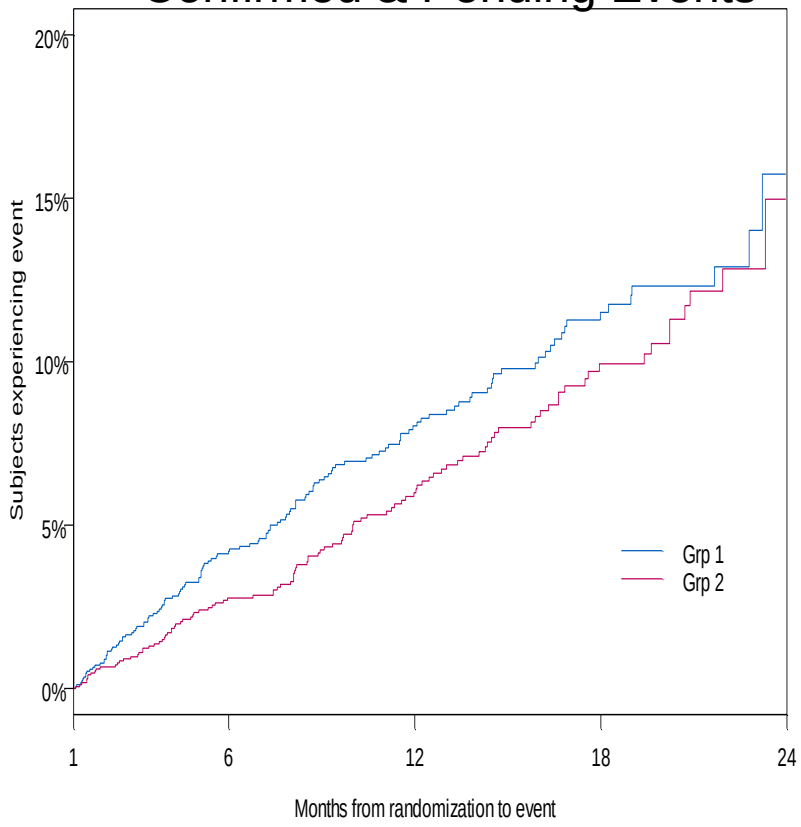
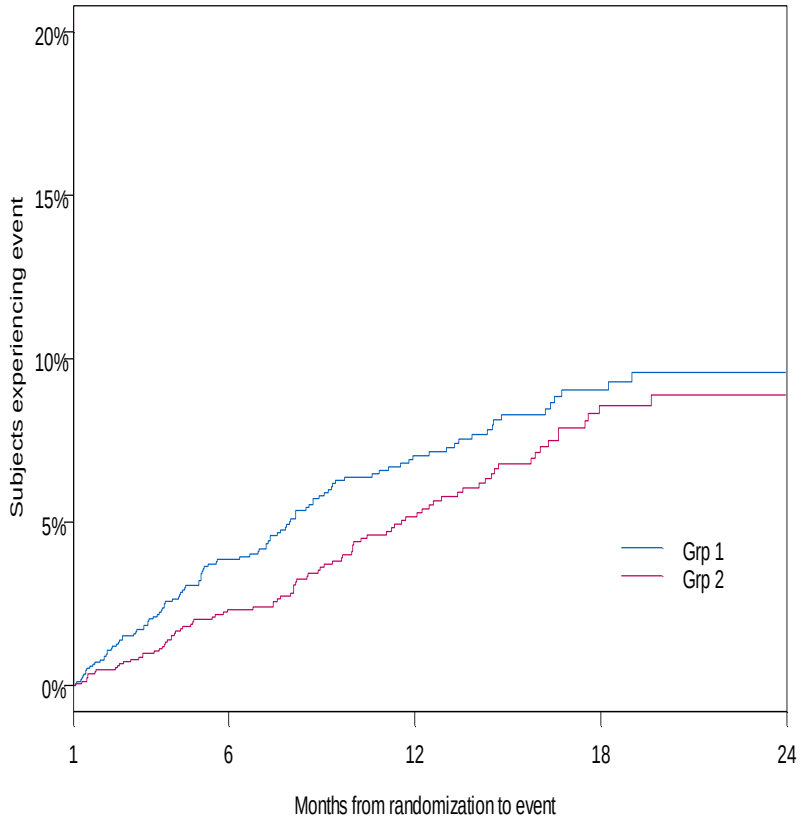
Example 1: Kaplan-Meier Plots at 1st Interim Look
(NOT actual TOPCAT data)

Including All
Confirmed & Pending Events



Including Only
Confirmed Events



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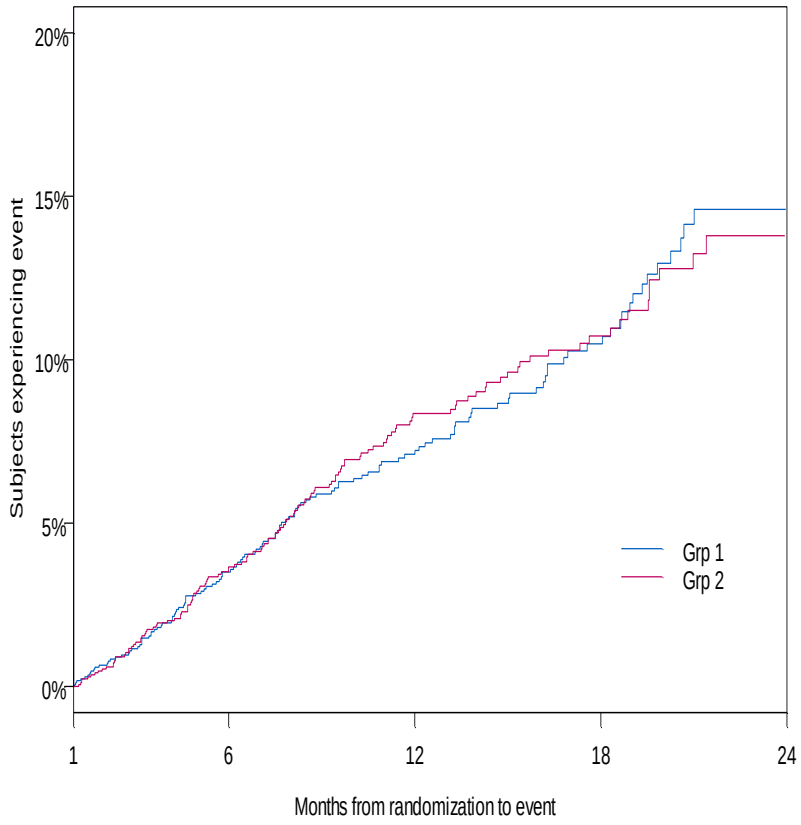
Example 2: Kaplan-Meier Plots at 1st Interim Look
(NOT actual TOPCAT data)

Including All
Confirmed & Pending Events



Including Only
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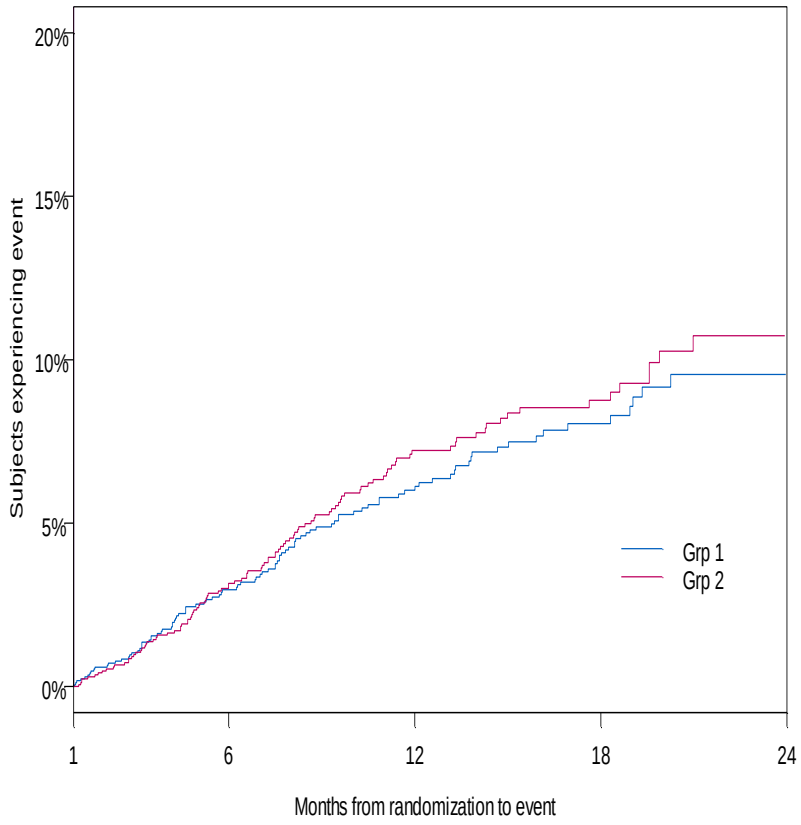

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Example 2, 5000 Replications

Assumed 3-year event rates during remainder of study	Group 1	Group 2	Estimated Conditional Power
Best estimates of event rates continue forward	20.8%	21.2%	2.4%
Group 1 is Control, initial assumptions apply	20%	16%	40.9%
Group 1 is Experimental, initial assumptions apply	16%	20%	54.8%

Approach Can Easily Incorporate…

- Variations in enrollment rates over time
- Subjects not followed until end of entire study (e.g. visits occur every 6 months, and subjects followed only until last scheduled visit)

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Summary

- Adjudication generally is not immediate
- “Observed” data not completely known at time of interim look
- Using confirmation proportions in each group provides estimate of currently “observed” event rates

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Summary

- Simulation approach for outcomes pending adjudication, future outcome events, future censoring
- Can easily incorporate more complicated situations
- For blinded studies, important to provide conditional power for both possible treatment assignments

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