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2022 NICTC Workshop:

Interim Analyses of Clinical Trials: Practical Considerations

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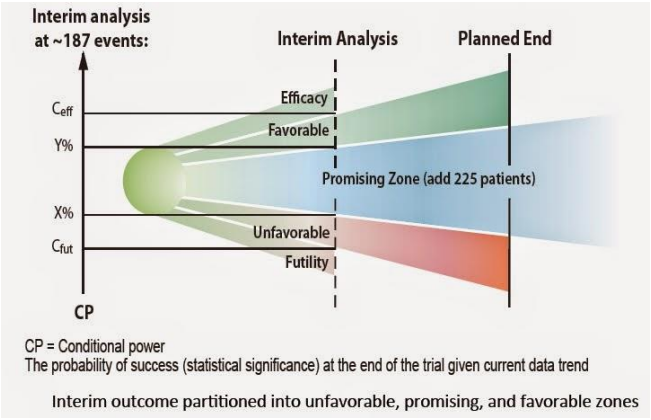
Learning Objectives

- Identify the different types of interim analyses
- Identify the who, what, when, why, and how of conducting interim analyses
- Identify how to incorporate practical considerations into interim analysis decision making

Interim Analyses in Clinical Trials: What, Why, When, How and Who



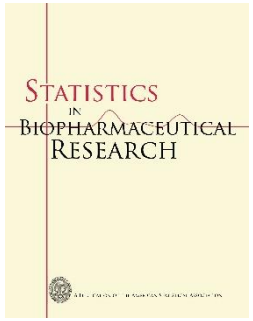
Guidance for Industry

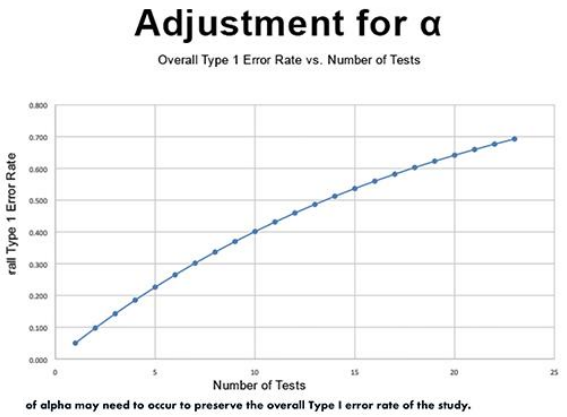
E9 Statistical Principles for Clinical Trials

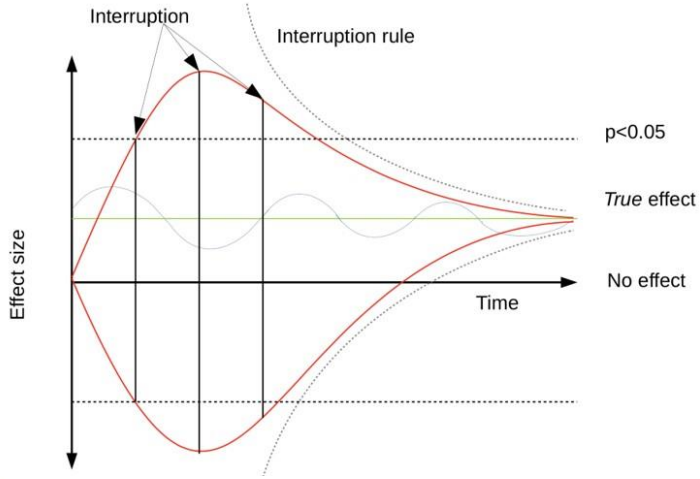
Contains Nonbinding Recommendations

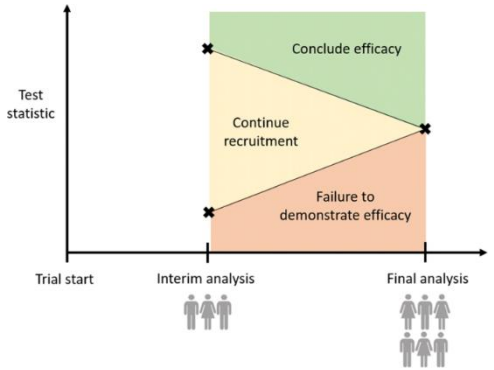
Guidance for Clinical Trial Sponsors

Establishment and Operation of Clinical Trial Data Monitoring Committees









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What?

An interim analysis is simply an analysis of the data before data collection has ‘completed’, i.e. before the pre-specified criteria for a planned ‘final’ analysis have been met:

- number of events observed
- number of patients achieving a set period of observation
- fixed timepoint
- etc

“Adaptive” Trial Design*

Why?

- An option to stop the trial for:

1. Safety

- spare patients overwhelming or excessive adverse events or non-beneficial treatment (risk:benefit ratio; ethical conduct)

2. Efficacy/Superiority

- expedite declaration of benefit ("superiority") thereby saving resources and maximizing impact (NDA, change of SOC)

3. Futility (or benefit or of trial conduct)

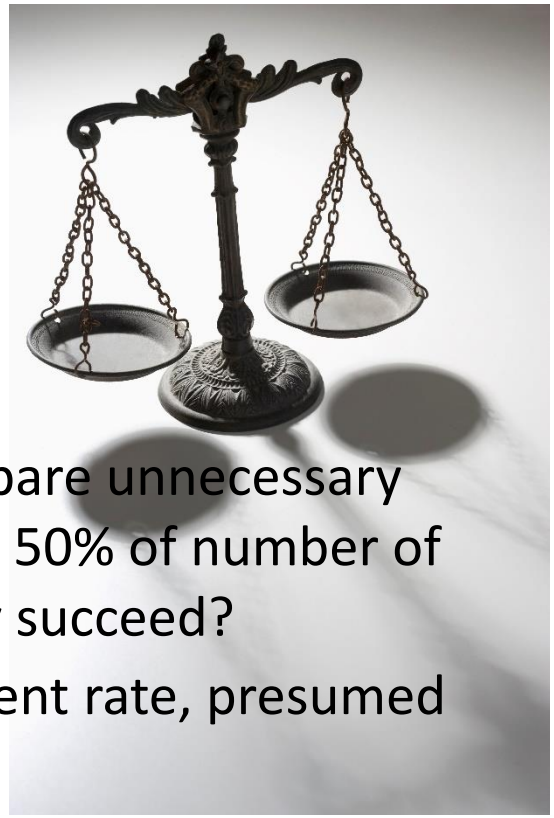
- recognize logistical or practical impediments ($)

Why?

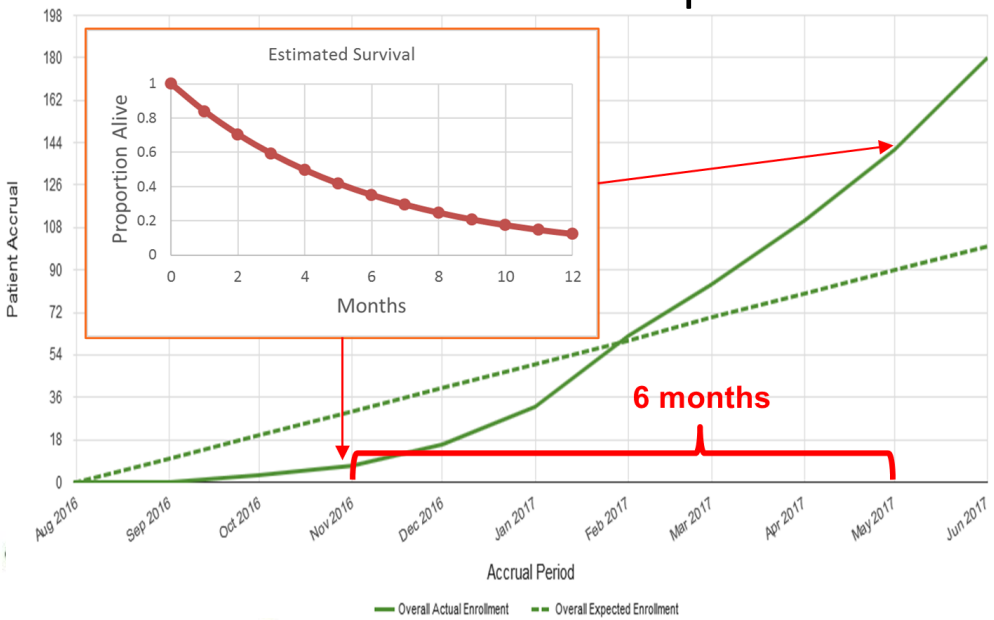
- An opportunity to re-estimate the sample size
  - pursue encouraging results (e.g. phase 2/3; SSR – VALOR Trial)
  - response adaptive randomization or enrichment

- An opportunity to modify the trial design
  - true adaptive trial designs (e.g platform, basket, etc)

When?



- **<u>Pre-specified</u>** (time or trigger); more than 1?
- Timing, timing, timing… Need to balance valid and accurate decisions against expediency and efficiency:
  - e.g. if an interim <u>futility</u> analysis is designed to spare unnecessary accrual and patient treatment AND is planned at 50% of number of events required for final analysis… can it actually succeed?
  - depends on estimated unknowns: underlying event rate, presumed accrual rate and accrual pattern.



- a rapidly accruing trial with a time-to-event analysis (e.g. disease progression or survival) in a moderate or relatively good prognosis population may not! – e.g. CO.26
- must factor in analysis timelines

When?

- Suppose for CO.26 we wish to conduct an interim analysis at 50% of events (75 deaths on study) and we 'observe' this occurs in our electronic database on May 1st when 130 patients are enrolled
- But… data submission is not complete for all sites and much of the data is unreviewed = add 3 months for cleaning and collation, with database locked and sent to statistician on August 1st
- Statistician takes two weeks to perform IA and prepare report which he sends to the DSMC on August 15th
- DSMC polls for availability and sets meeting on September 15th where they note the p-value is 0.043

Should they recommend to stop the trial? What if p-value was 0.013? How many patients are left to be recruited? How many deaths have occurred in the interim?

How?

- Trial assessed against pre-specified metrics according to pre-planned design:
  - Safety: deaths on trial, SAEs, rates of higher grade AEs, AEs of special interest/significance, etc.
  - Futility of Conduct: accrual rate, patient compliance, loss-to-follow-up, withdrawal of consent, observed event rate and pattern, etc.

  - Efficacy/Superiority: statistical significance of outcome measure
  - Futility of Effect: statistical significance of outcome measure

Aside: Power, P-value and Errors

Sample

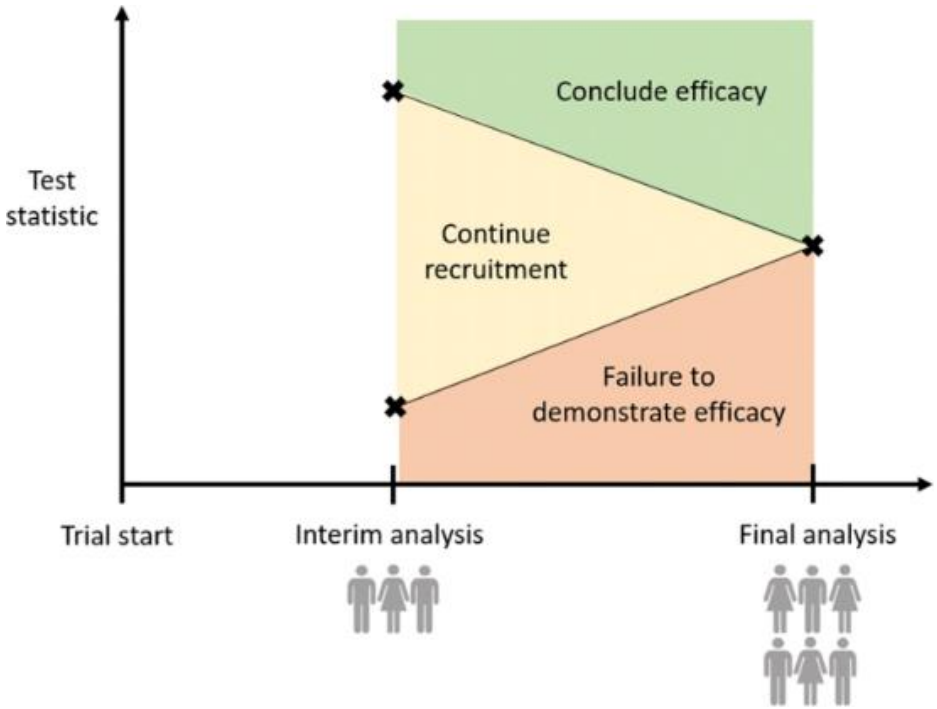
Results of Statistical Analysis

State of Nature (Reality) **UNKNOWN**

	No Effect	Effect
No Effect	✓ 'Accept' null hypothesis when it is true	Type II (β) error 'Accept' null hypothesis when it is false
Effect	Type I (α, p) error Reject null hypothesis when it is true	✓ Reject null hypothesis when it is false

Considerations for Statistical Analyses

- Superiority/Futility interim analyses have a Type I and Type II error rate, respectively each time they are performed and when these are performed early in the trial (i.e. with limited data/events available), the thresholds for declaring benefit or futility must be very large/small to minimize chance of error.
- We also need to preserve the 'trial level' of statistical significance (aka overall Type I Error Rate)
  - Adjustment/spending of alpha for repeated measures and timing of interim statistical analyses relative to final analysis (Pocock, Haybittle-Peto, O'Brien-Fleming, Lan-Demets etc)



Considerations for Statistical Analyses

- E.g. I need to observe 375 events (d) to detect a HR=0.75 with 80% power and 2-sided alpha of 5% in an adjuvant colorectal cancer trial.

$$H_0 : \Delta = 1 \; vs \; H_a : \Delta = \frac{\lambda_c}{\lambda_e} \neq 1$$

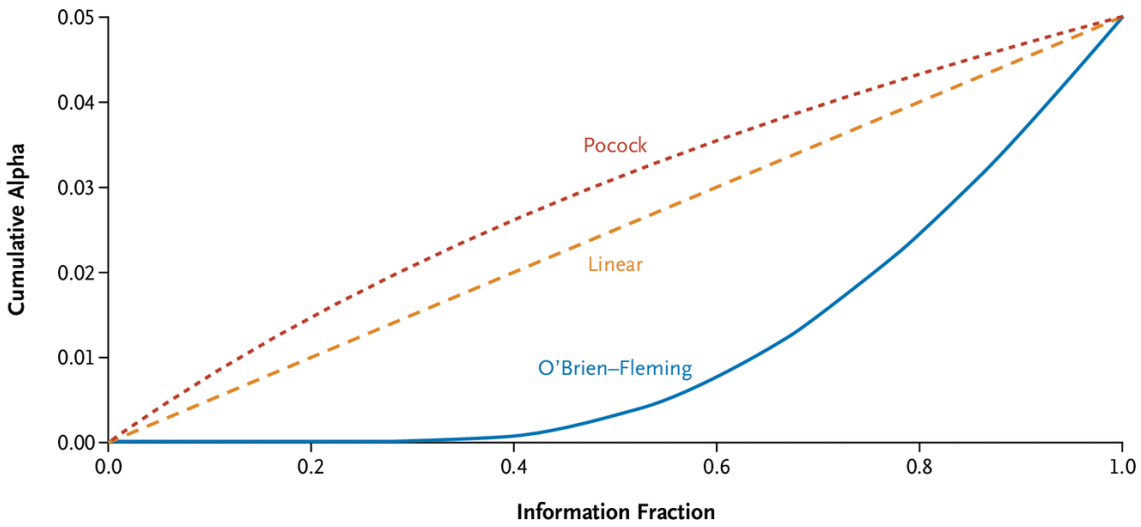
Statistical Significance

$$d = \frac{2\left(z_{\alpha/2} + z_{1-\beta}\right)^2}{\left(\ln \Delta\right)^2}$$

Power

Difference/Effect

- If I plan to conduct two interim analyses for superiority when 1/3 and 2/3 of these events have occurred (0.33 and 0.67 information fraction) and I want to use the Lan-DeMets error spending function approach using an O'Brien-Fleming stopping boundary to control for alpha of 5% at the end of the study, then my available alpha at each analysis is:
  1. 0.0004 at 125 events
  2. 0.0129 at 250 events
  3. 0.0367 at 375 events
  - Meaning the observed benefit would need to be enormous at the first interim analysis for me to declare superiority.



Considerations for Statistical Analyses

- There is a cost to pay (in terms of alpha spending) for each interim efficacy analysis… meaning that the alpha left for final analysis is <0.05 and therefore a p-value also <0.05 but above the residual alpha (e.g. 0.0367 in prior example) can NOT be declared statistically significant.
- To some extent this may be mitigated where a slightly larger final sample size than calculated for alpha=5% is used… but that somewhat defeats the purpose of an interim analysis.
- This cost 'may' be avoided if a surrogate measure is used in the context of a decision-point interim analysis (e.g. PFS for phase 2 of phase 2/3 trial with primary endpoint of OS or to continue cohort in an adaptive trial design).

Who?

- If you are asking, the answer is … **NOT YOU!**
- The use of an independent Data and Safety Monitoring Committee (DSMC) is consistent with (although not mandated by) ICH and GCP principles and guidance provided by regulatory authorities (FDA, Health Canada, EMU) as well as expectations of funding agencies (CIHR).
- Ensures integrity of the trial through unbiased decision-making, permitting Trial Committee Members and Principal Investigators to remain blinded to interim outcome data.
- CCTG maintains a standing DSMC composed of experts in clinical trial design, statisticians, bioethicists, and experienced clinical investigators who are without corporate or financial relationship to an industry sponsor nor are active investigators for any study in question.

What if an Interim Analysis Stops the Trial?

- Futility of Benefit:
  1. Stop further accrual
  2. Expeditiously inform collaborating organizations (e.g. other Cooperative Groups), supporting Pharma partners (… potential SEC Press Release), Investigators, Patients, Research Ethics Boards and Regulatory Authorities (as appropriate)
  3. Unblind as appropriate (Patients, Investigators, Yourself)
  4. Consider whether patients that are apparently benefiting clinically may continue on treatment and how that decision will be made
  5. Consider whether or how trial should continue and/or statistical analysis should be revised, e.g. patients to remain in follow-up per-protocol with additional efficacy analyses as data matures?

What if an Interim Analysis Stops the Trial?

- Superiority/Efficacy:
  1. Stop further accrual (?)
  2. Expeditiously inform collaborating organizations (e.g. other Cooperative Groups), supporting Pharma partners (… potential SEC Press Release), Investigators, Patients, Research Ethics Boards and Regulatory Authorities (as appropriate)
  3. Unblind as appropriate (Patients, Investigators, Yourself)
  4. Consider whether patients that were enrolled to the control arm should be permitted to "cross-over" to receive the beneficial therapy? Criteria for crossing over – eligibility? timeline? sufficient IMP?
  5. Consider whether or how trial should continue and/or statistical analysis should be revised, e.g. patients to remain in follow-up per-protocol with additional efficacy analyses as data matures?
  6. Rapid presentation/publication, press releases?, NDA?