Statistically Speaking Lecture Series

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Interim Analyses in Clinical Trials: An inside "Look"

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Biostatistics at NU

Overview

Division of Biostatistics (Chief: Denise Scholtens),
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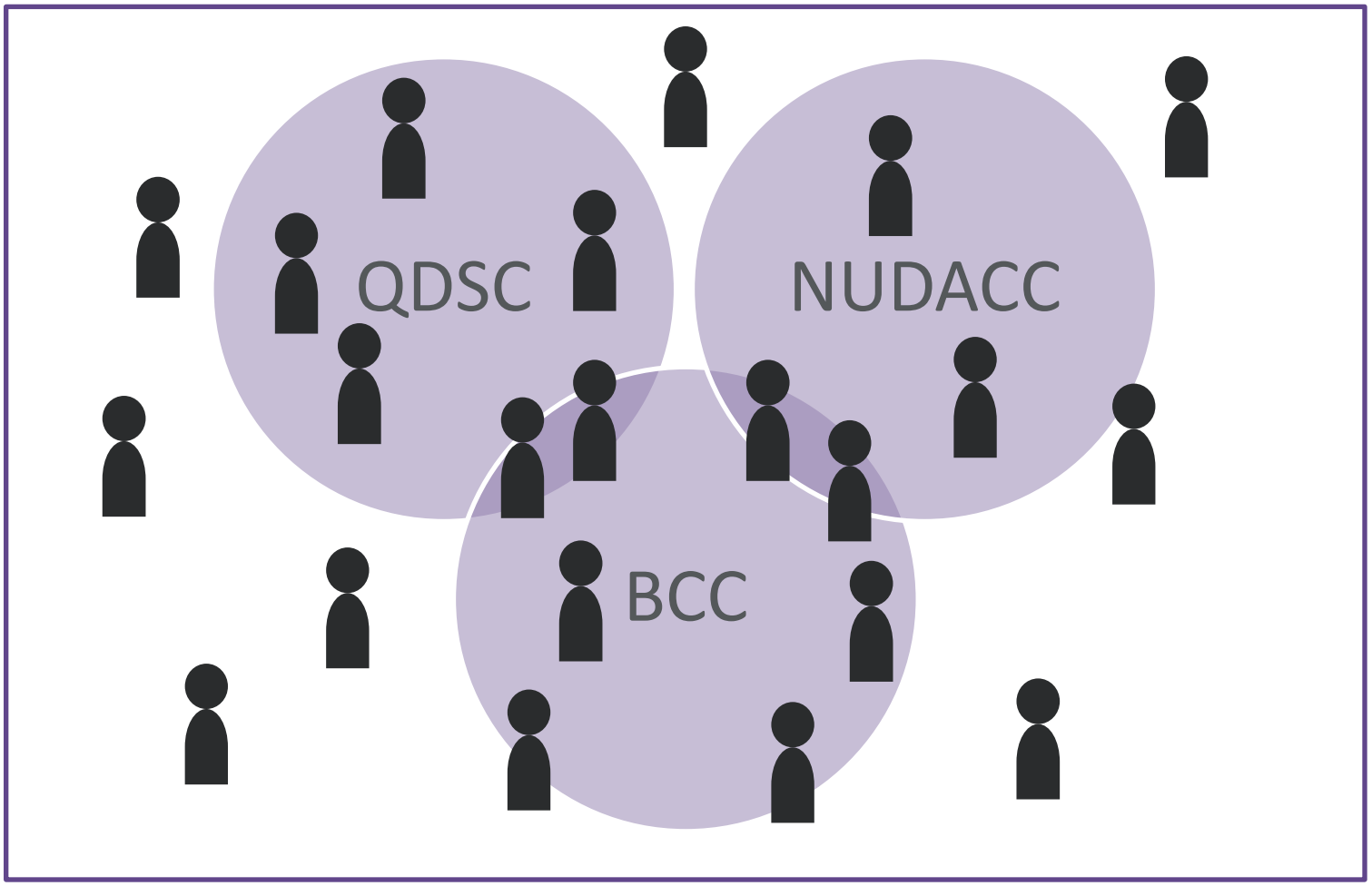

Biostatistics Centers and Cores

Overview

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Biostatistics Collaboration Center (BCC)

- Supports **non-cancer** research at NU
- Initial 1-2 hour consultation subsidized by FSM Research Office
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Disclaimer:

The views presented today are our own. They do not represent those of the statistical community nor those of Northwestern University at large.

We have no relevant conflicts of interest.

Inspired by a manuscript under review with Journal of Clinical and Translational Science

Coauthor: Dr. Alex Kaizer at University of Colorado

Goals for today

- Clarify what we often mean by “interim analysis” and “interim monitoring”

- Review types of common interim analysis methods and discuss reasoning/use cases for each
  - Efficacy
  - Futility
  - Safety
  - Sample size re-estimation

- Questions and Answers / Open Discussion

Interim Monitoring vs. Analysis

These terms are often confused + there are a lot of variations of meaning even within each overarching topic

- For purposes of our discussion…
- Interim **monitoring**:
  - **Processes** and **systems** important for study conduct and reporting
  - **Data integrity** and general cleanliness = primary focus
  - There is almost always an **ethical/safety component** when we talk about human subjects' research

Interim Monitoring vs. Analysis

These terms are often confused + there are a lot of variations of meaning even within each overarching topic

- For purposes of our discussion…

- Interim **analysis**:
  - Referring to **statistical <u>tools</u>** used to **guide** study design modifications (most often revolving around recruitment targets) – "go/no-go", stopping bounds, adding arms, removing arms, sample size re-estimation, etc.
  - **<u>Need not involve a formal hypothesis test (often does, not always!)</u>**

Reasoning for interim monitoring + analyses

Interim monitoring

Ensuring trial conduct according to protocol, **efficiently** and ethically

- Consent verification
- Data quality checks
- Process measures – screening rates, dropout rates, adherence, etc.
- **Safety** and major event reporting – adverse events, deviations, etc.

Findings on interim monitoring help drive study conduct decisions.

Interim analysis

Ensuring the study is set up for success (it addresses the research question + is equipped to address the research question) with an adequate risk-benefit profile

- Making **efficient** use of participant time, data, and general resources
- Continual assessment of **safety** signals

Findings on interim analysis help drive study design considerations.

Title: Guidance on interim analysis methods in clinical trials

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- The term "interim analysis" in clinical trials has multiple meanings.
- In general, interim analyses help **guide decisions on overall clinical trial** modifications, specifically those pertaining to the study sample size or recruitment targets
- We often encounter a lot of confusion and misunderstanding when it comes to interim analysis

Table 1. Summary of Interim Analysis Types

	Explanation	Justification for Use
Efficacy	• Early termination of a trial that is **showing promising results** • **Control of type I error** through group sequential methods or alpha spending functions	• Usually for longer, larger studies and later phases of research • **Ethical imperative for a promising treatment to reach the entire target clinical population**
Futility	• Early termination of a trial that **is not likely to achieve the intended objective** (e.g., little chance of finding a "significant" treatment effect at the end of the study) • Employed through group sequential methods, error spending functions, conditional power, or predictive power	• **Reduces costs, resources, and patient burden** for a trial with a low probability of "success" • Usually for mid-late phase studies • Helpful in the context of recruitment and retention challenges
Safety	• **Early termination** (or pausing) of a trial **for safety concerns** • Should be coupled with efficacy analyses to evaluate the benefit-to-risk ratio	• Incorporated across all phases of research • **Particularly important for vulnerable populations and high-risk interventions** with more "serious" outcomes (e.g., death)
Sample size re-estimation	• Reassessment of the sample size required to **ensure adequate power** using updated information from interim trial data • Can be blinded or unblinded • May not necessarily spend alpha	• Allows for **interim look at assumptions** (standard deviations, event rates, correlations, etc.) • May be particularly useful for mid-late phase studies

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Efficacy

Interim analysis for efficacy

- Involves a statistical hypothesis test evaluating one arm over another
- If there is a “large enough” signal early on in the study, it may be ethically imperative and most efficient to stop the study early
- Threshold for sufficient evidence is subject to debate and topic of statistical research and literature
- We cannot simply use a “statistically significant” finding to guide this decision…

Interim analysis for efficacy

- Recall: **type I error** = probability of finding a significant result [usually $p<0.05$] when in fact we should not, as there is no effect

- The more times we "look" at the data (i.e., conduct statistical tests), the more likely we are to find a significant result (i.e., make a type I error)

Interim analysis for efficacy

Type I error illustration for hypothetical null effect trial

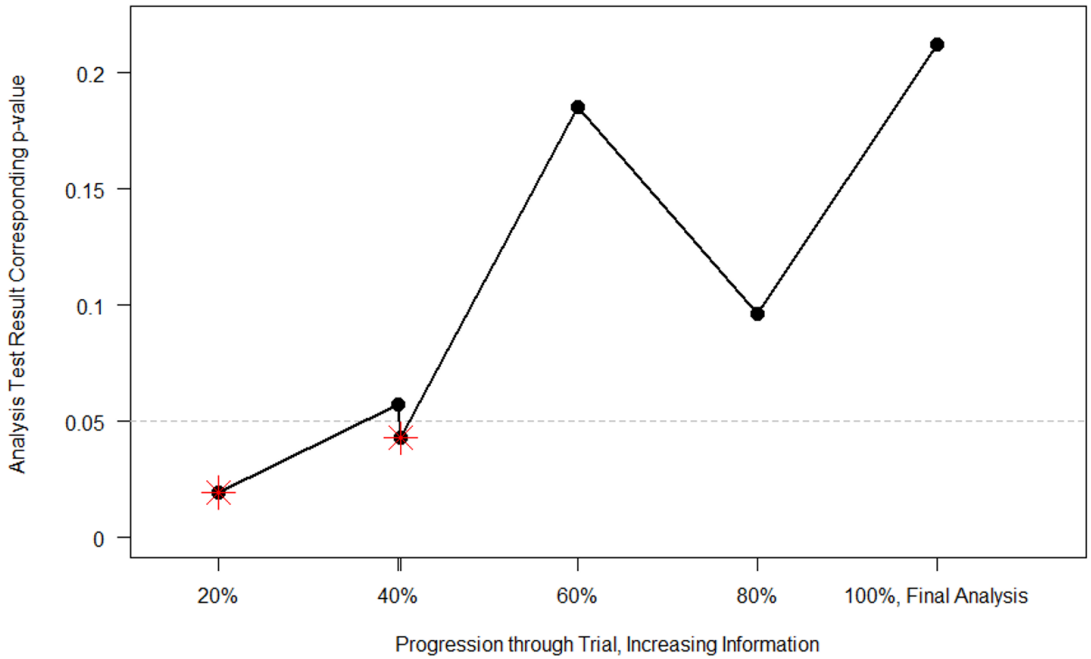
- Consider a hypothetical, two-arm clinical trial
- Binary outcome = “success” of intervention
- Plan to conduct a statistical test at the 5% level of significance

- We can simulate no underlying difference between the two study arms
  - Assume p(success) = 0.30 across arms
  - N=355 planned per arm
  - Simulate under null (H0)
  - IF we conduct a statistical test and find $p<0.05$, we are making a type I error

- There are countless ways the test statistic could “behave” over the course the study, but consider one hypothetical scenario…

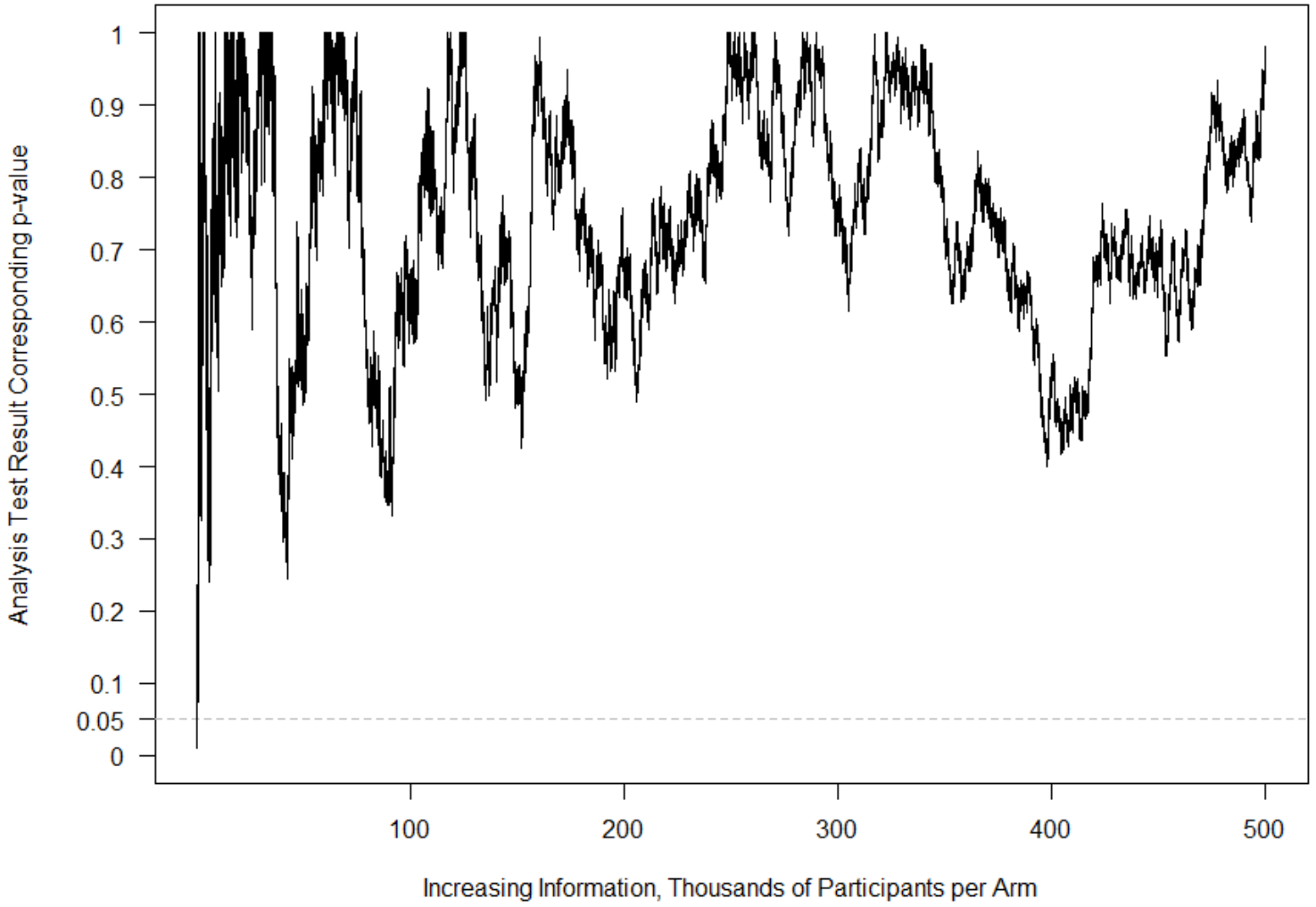
Interim analysis for efficacy

Type I error illustration for hypothetical null effect trial



% of Participants Enrolled with Outcome Data Observed	20%	40%	41%**	60%	80%	100%
N per Arm	71	142	143	213	284	355
p-value	**0.019**	**0.057**	**0.042**	0.185	0.096	0.212
Arm 1 Successes	11	29	29	49	73	93
Arm 2 Successes	24	44	45	62	92	109
Difference in Successes (N)	13	15	16	13	19	16
Difference in Proportions	0.183	0.105	0.112	0.061	0.067	0.045
****between 40-41%, included for illustrative purposes**						

Illustration of test statistic behavior with increasingly large sample sizes



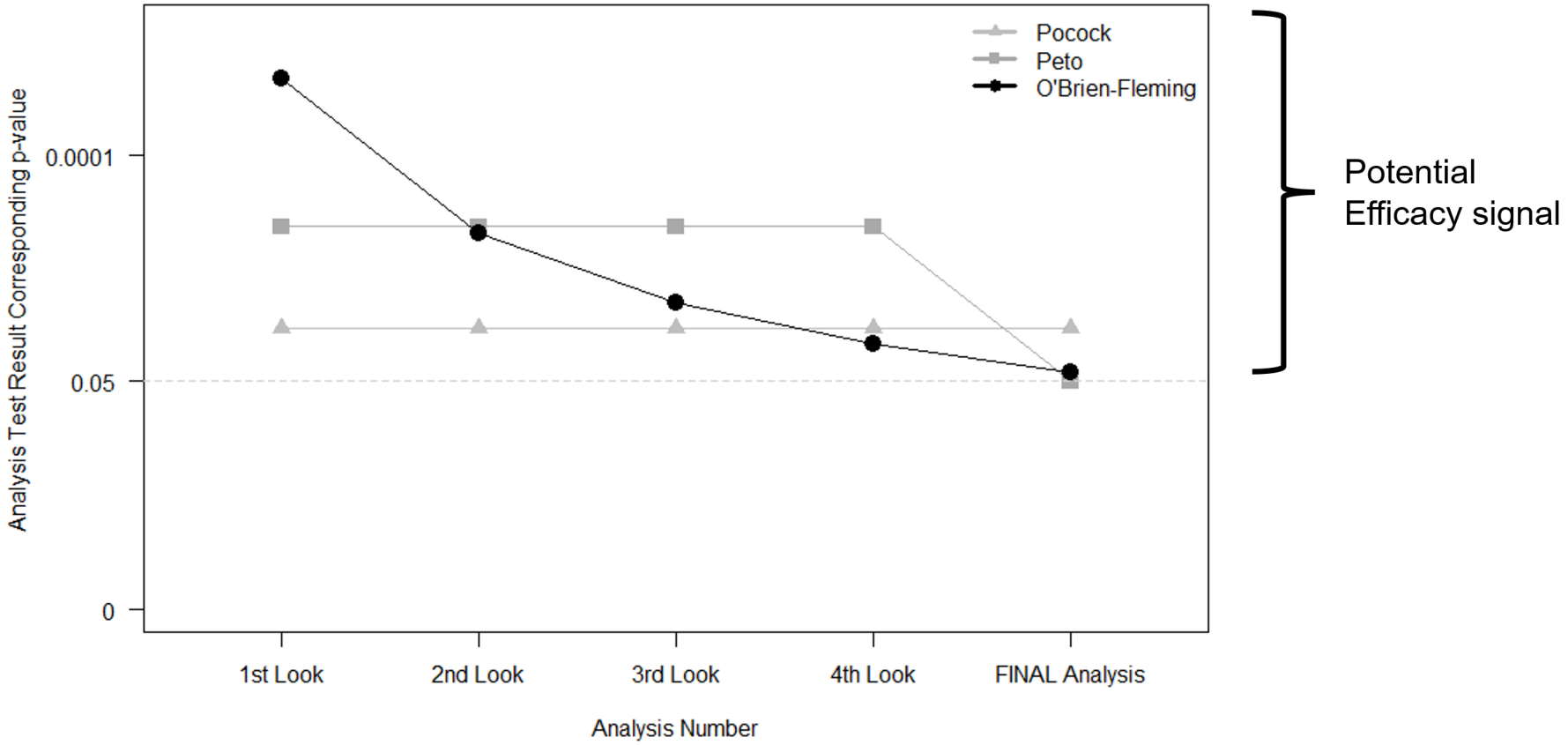
Interim analysis for efficacy

- Recall: type I error = probability of finding a significant result [usually $p<0.05$] when in fact we should not as there is no effect
- The more times we "look" at the data (i.e., conduct statistical tests), the more likely we are to find a significant result (type I error)
- Utilize **methodology to control type I error** with repeated looks at the data
- These methods help us decide whether the results at an interim analysis are **"significant enough" to warrant early stopping**

Interim analysis for efficacy

Common methods for controlling type I error

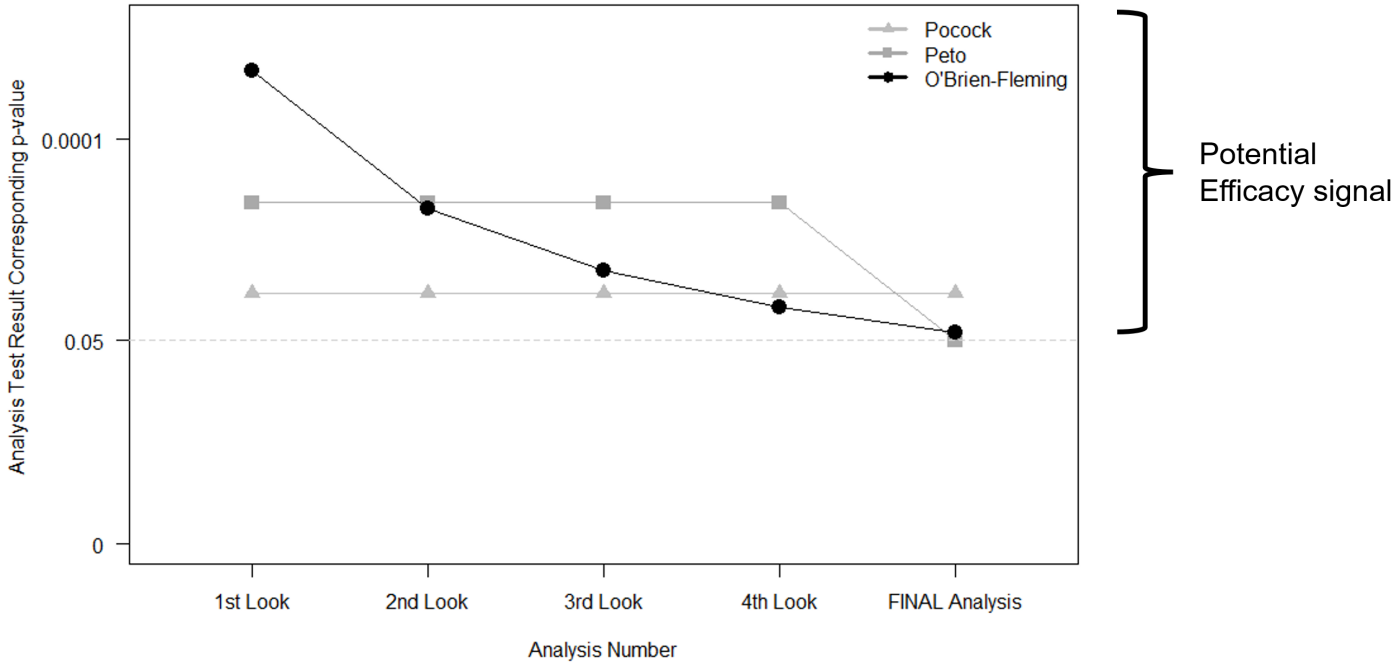
- Another two-arm hypothetical trial
- 4 interim looks + 1 final analysis
- Typical “group sequential” stopping bounds look like this…



Interim analysis for efficacy

Common methods for controlling type I error

- **Pocock** bounds have a constant threshold (p<0.016) for all 5 analyses
- **Peto** bounds have a stringent (p<0.001) threshold for the first 4, then uses p<0.05 at the end
- **O'Brien-Fleming** (perhaps most common) – stringent thresholds early on, and increasingly less stringent as time goes on; final analysis uses p<0.04



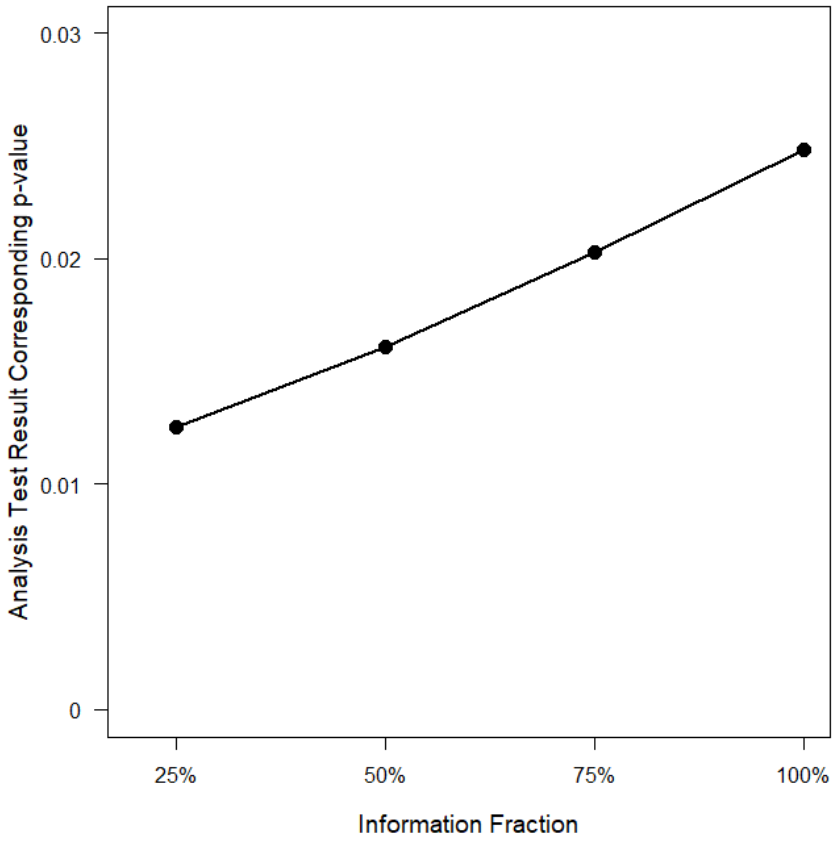
Interim analysis for efficacy

- Note: “alpha spending functions” incorporate these ideas but allow for more flexibility
- Can accommodate different ways of “spending” type I error (differing weights), and the timing of analyses needed not be evenly spaced
- Sometimes these terms “group sequential” and “alpha spending” are used interchangeably since they are so closely linked

Thrombectomy for Stroke in the Public Health Care System of Brazil

Martins SO, Mont'Alverne F, Rebello LC, et al. Thrombectomy for stroke in the public health care system of Brazil. *New England Journal of Medicine*. 2020;382(24):2316-2326

- Randomized stroke patients to standard-of-care (SOC) or SOC + mechanical thrombectomy
- Proposed interim analysis using information from 90-day follow-up
- Primary outcome = modified Rankin scale (measure of disability) at 90 days



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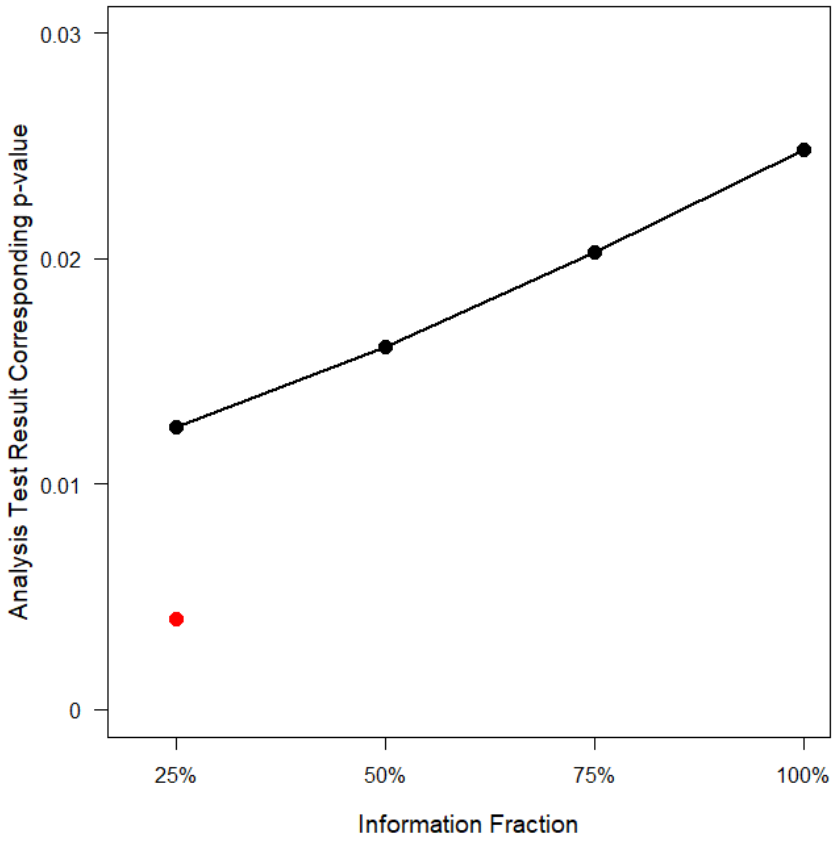
- Results at first interim analysis (N=174):
  - OR = 2.24 (1.30, 3.88) p-value = 0.004, in favor of thrombectomy
- Data and Safety Monitoring Board (DSMB) recommended early stopping
- At time of early termination, N=221 had been randomized and were included in final analyses
  - OR = 2.28 (1.41, 3.69) p-value = 0.001



Interim Analysis for Efficacy: Implications

- Controlling type I error in any trial is important
- Things get more complicated if we plan to incorporate interim analyses for efficacy
- Group sequential methods and alpha spending functions allow researchers a tool to maintain control over type I error

- In the example trial, investigators were able to address their research question with fewer participants than planned → more efficient use of participant time and study resources
  - This is the heart of the reasoning behind these analyses
  - Caveat – intervention being studied should be in later stages (e.g., phase III clinical trial) of development; must consider the big picture

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Futility

Futility Analyses

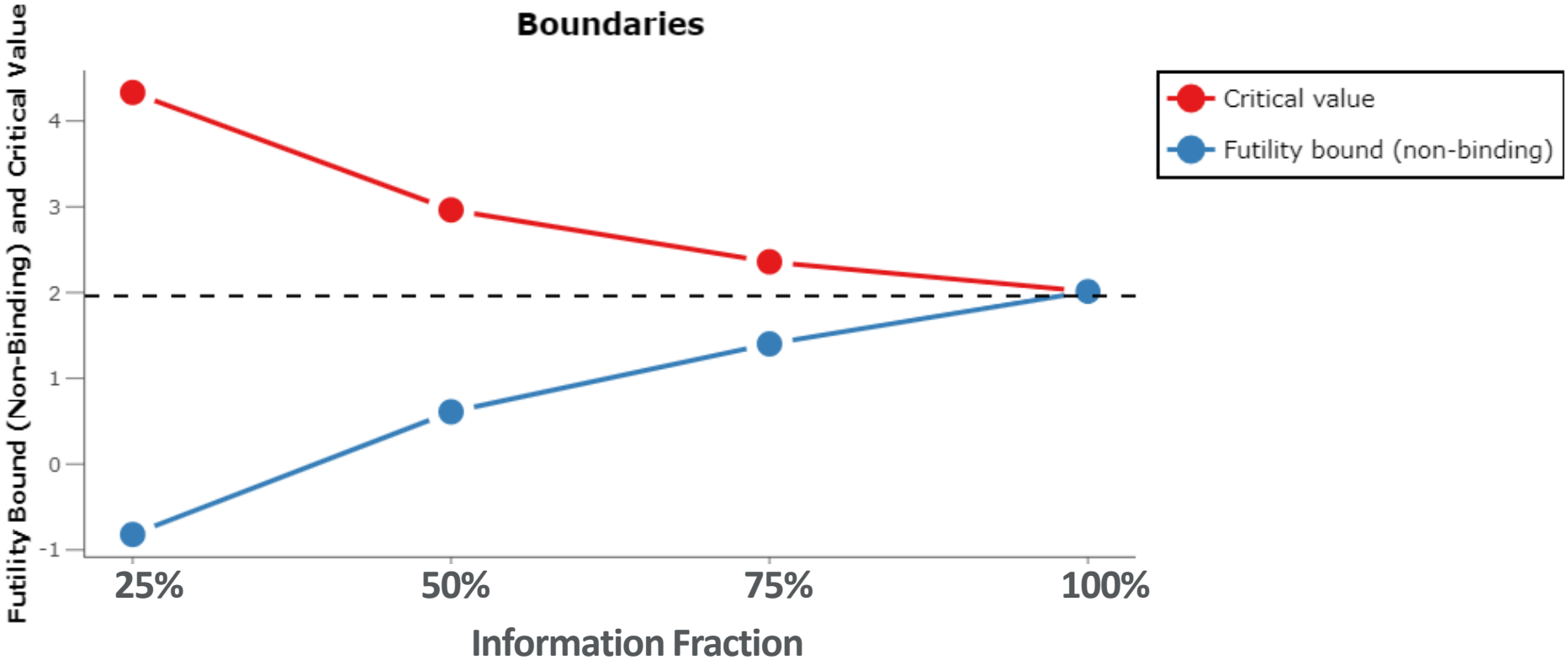
- Stopping a trial for futility suggests that observing a statistically significant result at the end of the study is unlikely
- This can **increase efficiencies** with respect to cost, resources, and participant burden
- There are similar methods to the group sequential methods for futility (or error spending functions)

Figure 1 A futile action can never achieve its goals.

Kite S, Wilkinson S. Beyond futility: to what extent is the concept of futility useful in clinical decision-making about CPR? Lancet Oncol. 2002 Oct;3(10):638-42. doi: 10.1016/s1470-2045(02)00878-1. PMID: 12372726.

Beta spending function

One-sided test with efficacy and futility stopping bounds



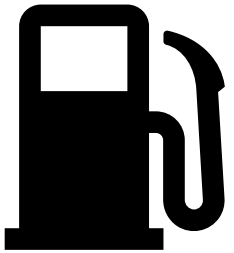
The Stroke and Hyperglycemia Insulin Network Effort (SHINE)

Johnston KC, Bruno A, Pauls Q, et al. Intensive vs Standard Treatment of Hyperglycemia and Functional Outcome in Patients With Acute Ischemic Stroke: The SHINE Randomized Clinical Trial. JAMA. 2019;322(4):326-335. doi:10.1001/jama.2019.9346

- Randomized trial to evaluate **efficacy of intensive glucose control** during ischemic stroke (N=1400)
- **Non-binding futility thresholds** using error spending function approach
- **4th interim analysis** (N=1151), trial was **stopped for futility**
- Final results: no significant difference in proportion with 90-day favorable outcome between groups **(20.5% vs. 21.6%)**

Interim Analysis Sample Size	P-value Futility Threshold
500	0.949
700	0.896
900	0.652
1100	0.293

Conditional Power



- Probably a bit more common are **conditional power or predictive power** approaches…
- In general: power = probability(reject null | some assumption with respect to true underlying effect)

		True	
		Null is True (No Difference)	Null is not True (Difference)
Test	Reject Null	Type I Error	**Power**
	Fail to Reject Null	Confidence	Type II Error

- **Conditional power** = probability(reject null | **data observed up to this point in the trial** and assumption with respect to effect)

Conditional Power

- Based on…
  - Information fraction (how far we are through the trial)
  - Current test statistic – from interim analysis
  - **Assumption of effect at end of trial**
    - Current trend
    - H1 (from beginning of trial)
    - H0 or null effect
  - If this calculated conditional power is low (usually below 20%, 15%, 10%), then we might consider stopping a study

Predictive Power

- Bayesian alternative to conditional power
- Likelihood of demonstrating treatment efficacy at the end of the study
- Estimated by…
  - Updating prior assumptions with observed data
  - Average conditional power over this distribution
- Avoids having to assume a specific treatment effect (as in the conditional power approach)

Vesnarinone in Heart Failure Trial (VEST)

Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. N Engl J Med 1998;339:1810–1816.

- Patients with heart failure randomized to placebo or Vesnarinone
- Primary outcome: All-cause mortality
- Sample size calculations:
  - 20% 1-year mortality in placebo
  - Power to detect 30% reduction (0.2-0.2*0.3 = 0.14)
  - Sample size of 3618 would provide 90% power

Friedman LM, Furberg CD, DeMets DL, Reboussin D, Granger GB. *Fundamentals of Clinical Trials*. Fifth Edition. 2015.

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  - Sample size of 3618 would provide 90% power

But the trial was not stopped early – due to external trial information

Table 17.2 Conditional power for the Vesnarinone in Heart Failure Trial (VEST) [129]

	Information fraction		
RR	0.50	0.67	0.84
0.50	0.46	<0.01	<0.01
0.70	0.03	<0.01	<0.01
1.0	<0.01	<0.01	<0.01
1.3	<0.01	<0.01	<0.01
1.5	<0.01	<0.01	<0.01

RR = relative risk

Considered a range of effects:
-Beneficial effects: 0.5-0.7
-Null effect: 1.0
-Negative trends: 1.3-1.5

Friedman LM, Furberg CD, DeMets DL, Reboussin D, Granger GB. *Fundamentals of Clinical Trials*. Fifth Edition. 2015.

Futility Analysis: Implications

- Incorporating a futility assessment can **increase efficiency of the trial**, allowing trials that are unlikely to meet their objectives to stop early ultimately reducing costs, preserving resources, and limiting patient burden

- Particularly in large clinical trials or vulnerable patient populations, an interim futility assessment may be essential to **prevent patients from being unnecessarily randomized to ineffective treatments**

- Despite common misconceptions, an interim analysis incorporating a futility assessment **alone does not inflate the type I error**

- It can, however, have **implications on type II error**, reducing the overall power of the study by stopping early

Stopping a study early

For efficacy or futility

- Potential to pose challenges in interpretations – smaller than expected sample size decreases precision around treatment effect estimates
- Subgroup analyses and analyses examining heterogeneity of intervention effects will inevitably suffer (they are typically underpowered already)

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Safety

Interim analysis for safety

- Note: all clinical studies (regardless of phase) should incorporate safety monitoring

- It is impossible to foresee all potential safety issues ahead of time, and **safety analyses are seldom adequately powered**

- Unanticipated safety issues should merit consideration for early stopping; for example,
  - **Serious** and **unanticipated** events or event rates
  - Events that are **related and unexpected**

Interim analysis for safety

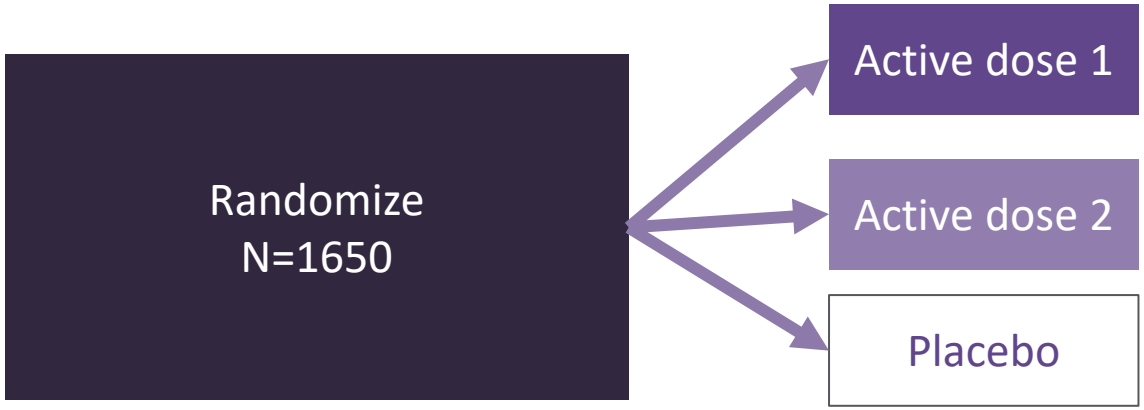
- Discussion on formal interim safety analyses should consider the **benefit-to-risk assessment**: i.e., it **should be paired with an interim efficacy analysis**

- **Context is key** in this assessment…. *For example, a cardiovascular secondary prevention trial to prevent subsequent myocardial infarction may have the expectation of some myocardial infarction events, whereas it may be extremely concerning to observe the same events in a behavioral intervention in a generally healthy population.*

The EARLY Trial

Sperling R, Henley D, Aisen PS, et al. Findings of efficacy, safety, and biomarker outcomes of atabecestat in preclinical Alzheimer disease: a truncated randomized phase 2b/3 clinical trial. JAMA neurology. 2021;78(3):293-301

- Randomized phase 2b/3 trial assessing effects of atabecestat in preclinical Alzheimer's disease
  - 3 arms (2 doses of active intervention + placebo)
  - Double-blind
  - Primary outcome: change from baseline in cognitive composite score
- **Plan:**
  - N=1650 across 143 sites
  - Interim analysis for futility
  - NO formal interim efficacy analyses



The EARLY Trial

Safety and tolerability monitored throughout study

- Treatment-emergent adverse events
- Vital signs
- Serial MRIs
- Clinical laboratory results

0%

33%

N=557

100%

N=1650

- Safety concerns
- Serious elevation in liver enzymes
- Unexpected
- Related to dosage

Benefit

Risk

The study terminated early due to unacceptable safety profile

Interim analysis for safety: Implications

- Monitoring safety outcomes and adverse events is crucial for **maintaining study integrity and protecting study participants**

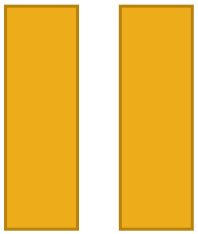
- Decision to stop a trial early for safety concerns should generally be made in the context of the **benefit-to-risk ratio**
  - No "one size fits all" approach to assessing benefit-to-risk ratio

Remember: **Context is key** in this assessment…. *For example, a cardiovascular secondary prevention trial to prevent subsequent myocardial infarction may have the expectation of some myocardial infarction events, whereas it may be extremely concerning to observe the same events in a behavioral intervention in a generally healthy population.*

Interim analysis for safety: Implications

- Safety monitoring may raise concerns about **multiple "looks"** at the data
  - When coupled with efficacy analysis, incorporate conservative alpha-spending approach

- Safety concerns may warrant a **temporary pause** to further assess causality – consider whether to pause vs. completely terminate the study



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Sample Size Re-estimation

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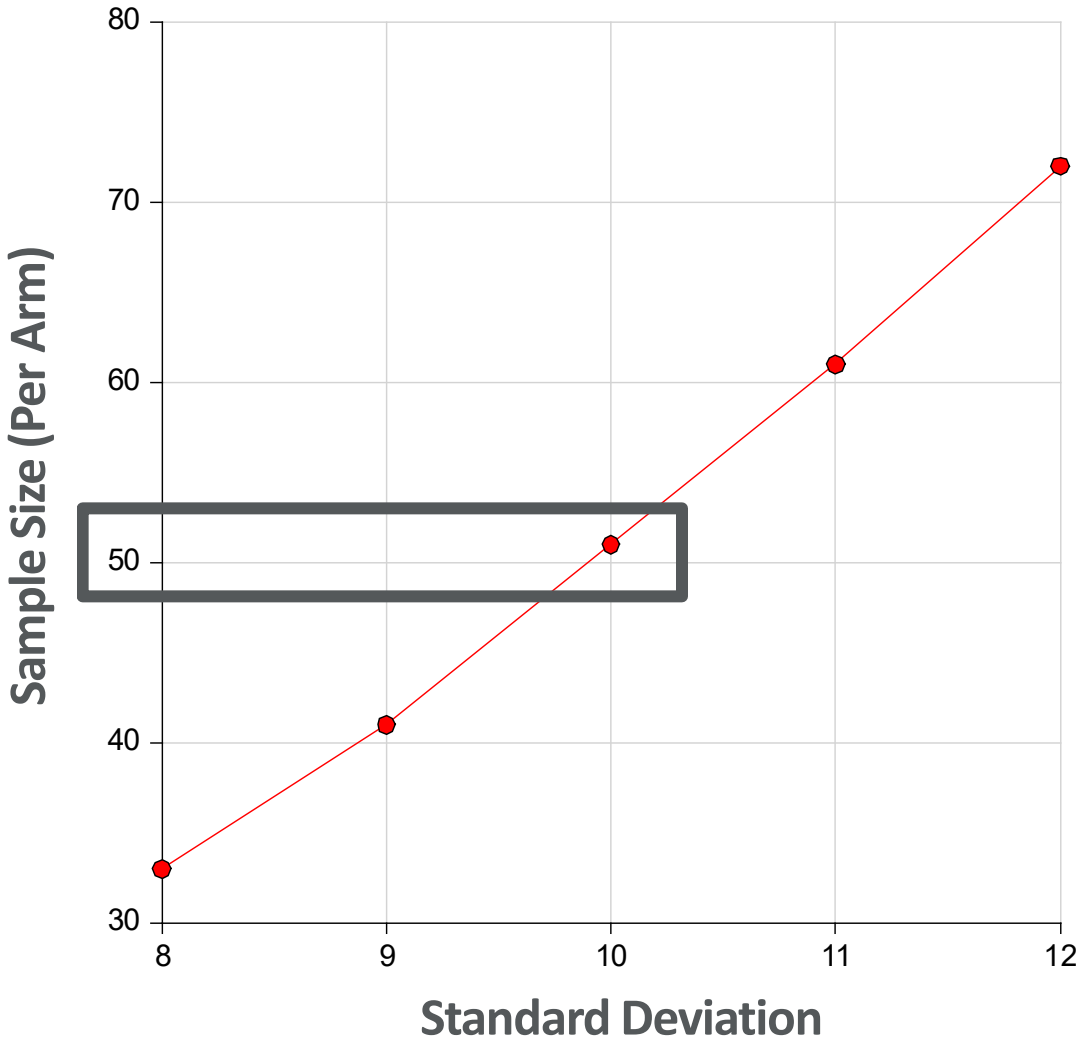
Sample size re-estimation

- Designed to modify the planned sample size based on the accumulating data
- Accounts for **uncertainty when conducting power calculations** during the initial planning of the study



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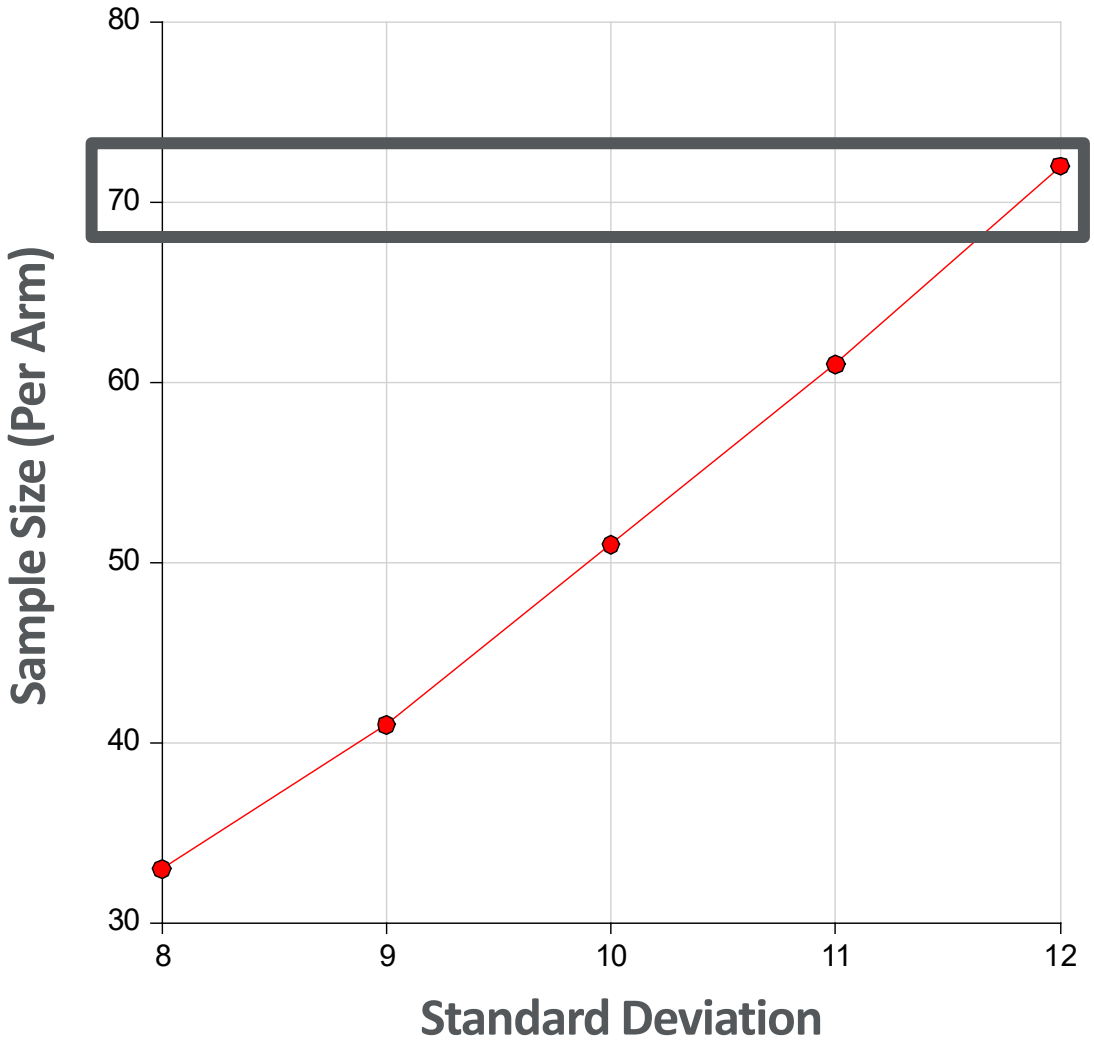
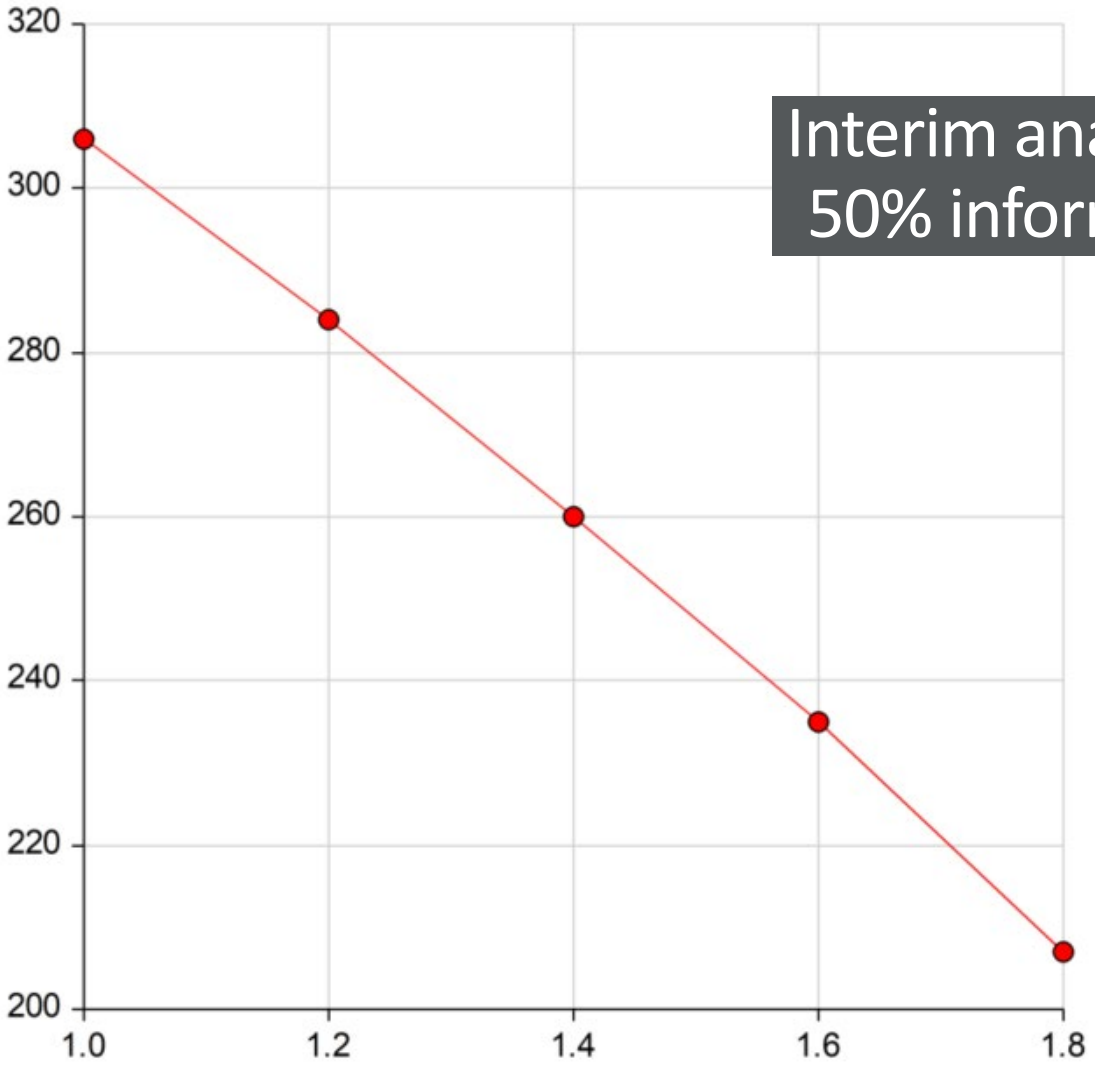


Sample size re-estimation

- Approaches facilitate a revised sample size calculation using information for the **ongoing assessment of event rates, the estimation of nuisance parameters** (e.g., the variance of a continuous outcome), or the effect size expected

- Re-estimating a sample size at an interim stage can increase the likelihood of a successful trial, but **may result in a substantial increase** in the needed sample size if the initial sample size **assumptions** were very **different** from what is observed

Sample size re-estimation



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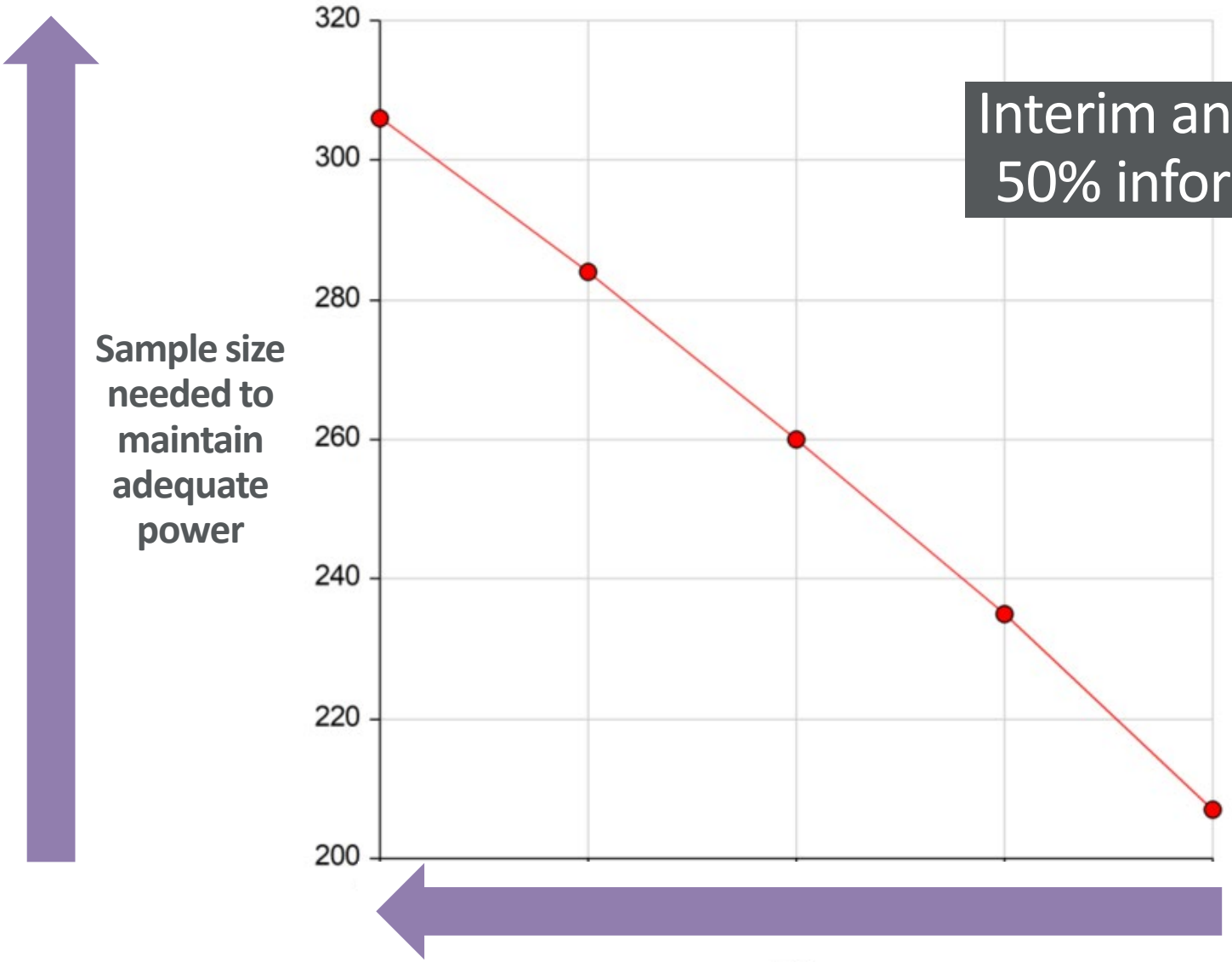

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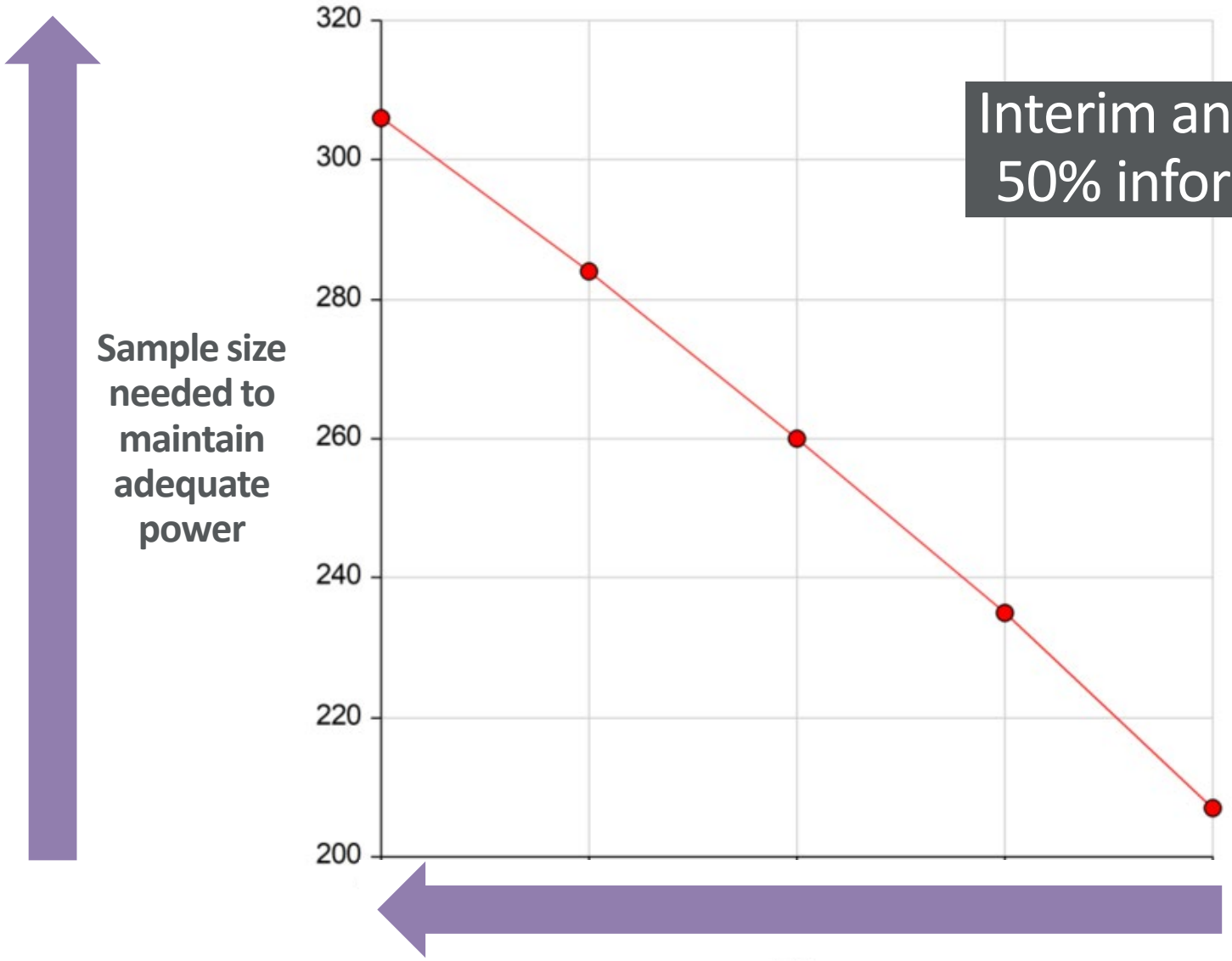

Sample size re-estimation

- Two categories: blinded or unblinded
- **Blinded:** used to revise estimation of nuisance parameters (e.g., variance) – often used pooled estimates
- **Unblinded**: based on comparative interim results; ideal when uncertainty about estimates of effect size and nuisance parameters – allows for capturing an effect that may still be clinically meaningful, but differs from original assumption.

Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) Trial

Campbell BC, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. New England Journal of Medicine. 2018;378(17):1573-1582.

- **Non-inferiority randomized** (1:1) trial enrolling patients with ischemic stroke eligible to undergo intravenous thrombolysis and endovascular thrombectomy
- Primary outcome: **Proportion of participants** with restoration of blood flow to >50% of the affected arterial territory
- Initial sample size calculation: **120 participants to provide 80% power**
- Proposed blinded sample size re-estimation at **n=100** using **conditional power** approach

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- Initial sample size calculation: **120 participants to provide 80% power**
- Proposed blinded sample size re-estimation at **n=100** using **conditional power** approach
- Conditional power: **0.52 -> Increased sample size to N=202** to maintain adequate power

Sample size re-estimation: Implications

- Goal to **prevent underpowered** studies

- Be careful as this **may have impact on type I error** without using appropriate methods to control
- What if re-estimated sample size is **not feasible**?
- What if re-estimated sample size is based on an observed effect that is **no longer clinically meaningful**?
- Care should be taken in **how results from interim re-estimation are reported** for ongoing studies -> may be possible to back-calculate the effect size!

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Tying it all together

Table 1. Summary of Interim Analysis Types

	Explanation	Justification for Use
Efficacy	• Early termination of a trial that is **showing promising results** • **Control of type I error** through group sequential methods or alpha spending functions	• Usually for longer, larger studies and later phases of research • **Ethical imperative for a promising treatment to reach the entire target clinical population**
Futility	• Early termination of a trial that **is not likely to achieve the intended objective** (e.g., little chance of finding a "significant" treatment effect at the end of the study) • Employed through group sequential methods, error spending functions, conditional power, or predictive power	• **Reduces costs, resources, and patient burden** for a trial with a low probability of "success" • Usually for mid-late phase studies • Helpful in the context of recruitment and retention challenges
Safety	• **Early termination** (or pausing) of a trial **for safety concerns** • Should be coupled with efficacy analyses to evaluate the benefit-to-risk ratio	• Incorporated across all phases of research • **Particularly important for vulnerable populations and high-risk interventions** with more "serious" outcomes (e.g., death)
Sample size re-estimation	• Reassessment of the sample size required to **ensure adequate power** using updated information from interim trial data • Can be blinded or unblinded • May not necessarily spend alpha	• Allows for **interim look at assumptions** (standard deviations, event rates, correlations, etc.) • May be particularly useful for mid-late phase studies

Considerations for Interim Analyses

- **Pre-specify** as much as possible
- Describe anticipated timing, proposed methodology, pre-specified rules to **guide** decisions
- Timing of analysis can be flexible
- Often specified when some proportion of participants is enrolled and meet a particular study milestone (e.g., 50% of participants completed 6-week follow-up)
- Balance between **maximal information** (later interim analysis) vs. ensuring **adequate time to make any modifications** and reducing potential risk to participants as much as possible

Considerations for interim analysis

- Think about potential logistical implications…if an interim sample size re-estimation is proposed, are there adequate resources to support an increase in sample size if indicated?
- Evaluation of interim analysis results **should not be interpreted in isolation**, but rather in the context of other internal study factors and external contemporaneous issues
- Any interim analysis results and statistical tools are intended to serve as **guidelines**
- **Transparency** in disseminating trial results when interim analyses were conducted is also critical

Tying it all together

- **Interim monitoring** of data quality and integrity ≠ **interim analysis** to guide study design modifications
- Both **require coordination and pre-specification** of protocol and procedural elements to the extent possible
- Monitoring does not have implications for type I error issues; interim analyses can, but it is not always the case
- Remember that there is no "one size fits all" + recommendations should be made with a big picture view

Relying on a Data and Safety Monitoring Board (DSMB)

A minor tangent that is important to consider in interim analyses

- A DSMB is an **independent group of experts** (and potentially patient representative[s]), **appointed by a sponsor/investigator** to **review accumulating clinical trial data** on a regular basis.

- The external DSMB will be instrumental in reviewing these data and any analysis results to **guide recommendations** (remember they are recommendations)

- Interim results should be kept strictly with the DSMB and the unblinded study statistician. Only high-level recommendations from the DSMB and/or modifications to the trial should be communicated to the study team or external entities while the study is ongoing.

DSMB Composition

- Usually 3-5 total members, can be more
  - **Clinical expert in relevant field(s)**
  - **Biostatistician**
  - Basic scientist
  - Regulatory specialist
  - Ethicist
  - Patient representative

DSMB Review Process

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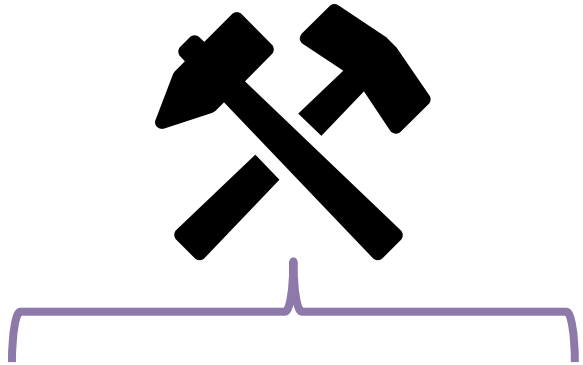
Typically prior to initiation (close in time to initial IRB review)

- Interim review schedules may vary…
- Typically every 6 months
- Usually at least yearly
- Oftentimes guided by study milestones (25%, 50%, etc. recruitment or endpoint goals)
- Be prepared for ad hoc review – e.g., Serious Adverse Events (SAEs) occurrence, related events, blinding issues, conduct issues, etc.

Final review of study findings and reporting plans

DSMB Review Process – Meeting Format



Open Session →	Closed Session →	Executive Session →	Debrief
• **All key parties** involved • Review data in aggregate • Nothing unblinded (if applicable)	• Just **DSMB** + **unblinded members** (usually statistician) • Review interim analyses	• Just **DSMB** members • Not always requested/required	• All key players, as needed • Not always requested/required • DSMB may use to communicate recommendations + summarize discussion

Use caution when discussing decisions based on interim analyses

Thank you for your attention today + please feel free to reach out with comments/questions!

Upcoming *Statistically Speaking* Lectures

Thursday, April 6 12-1pm	Longitudinal Data: Challenges and Opportunities Nathan Gill, PhD, Assistant Professor, Division of Biostatistics, Department of Preventive Medicine *Location: Lurie - Hughes Auditorium & Zoom**

Thank you!

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