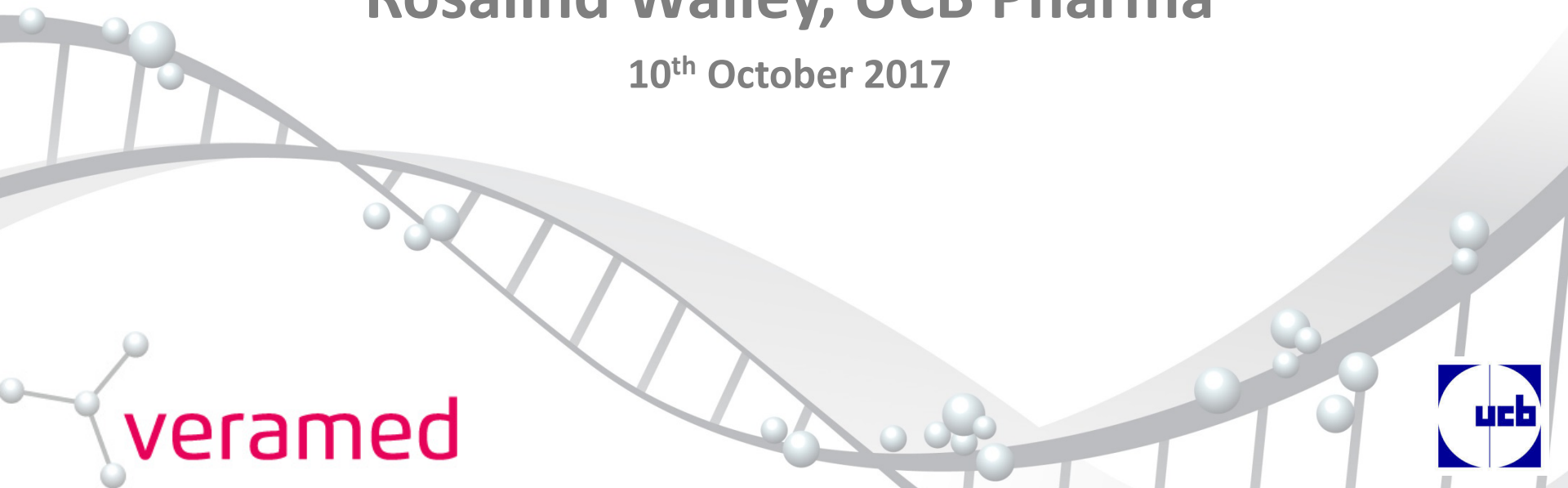


Futile or Not? An Interim Analysis Case Study

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Interim Analysis Defined

Interim Analysis: *Analysis of the data conducted before data collection has been completed, which may result in a study adjustment*

Rules of Thumb

- Must be pre-specified
- Conduct when $\geq 40\%$ subjects have completed

Interim Concerns

- Increased type I error rate (interim for efficacy)
- Increased type II error rate (interim for futility)

ICH E9 – A study should only be stopped early for:

- Ethical reasons
- Unacceptable power

Case Study Introduction

Study Overview:

- Phase II study. Rare disease.
- **Primary Endpoint:** Treatment difference at Week 12 (End of treatment) in disease activity score - continuous.
- **Double-Blind, Parallel Group Design:**
 - Placebo vs Treatment (1:1 randomisation)

Null hypothesis: *There is no difference in disease activity score between the placebo and the treatment groups at week 12.*

Classical Frequentist Sample Size Calculation:

Treatment Difference at Week 12	SD	False +ve Rate	Power	n per arm (Total N)
3.8	5	5%	80%	29:29 (58)

Interim Analysis Options

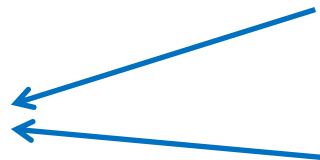
- Interim  Effectiveness
- Interim  Efficacy
- Interim  Sample Size Adjustment
- No Interim Analysis



Initial Decision:

- NOT to include an interim

No recruitment concerns
+
Increased Budget





- Concern about wasting resources
- Senior management request formal interim to assess *for futility*



- Create appropriate rule
- Calculate its operating characteristics

PLANNING AN INTERIM AFTER STUDY START

Creating a Decision Rule

Aim of Rule: Stop study early if drug is inefficacious

➤ Basic operating characteristics

Probability of stopping a bad drug at interim



Probability of stopping a good drug at interim



Overall false negative rate



➤ Further details to consider before final rule is chosen

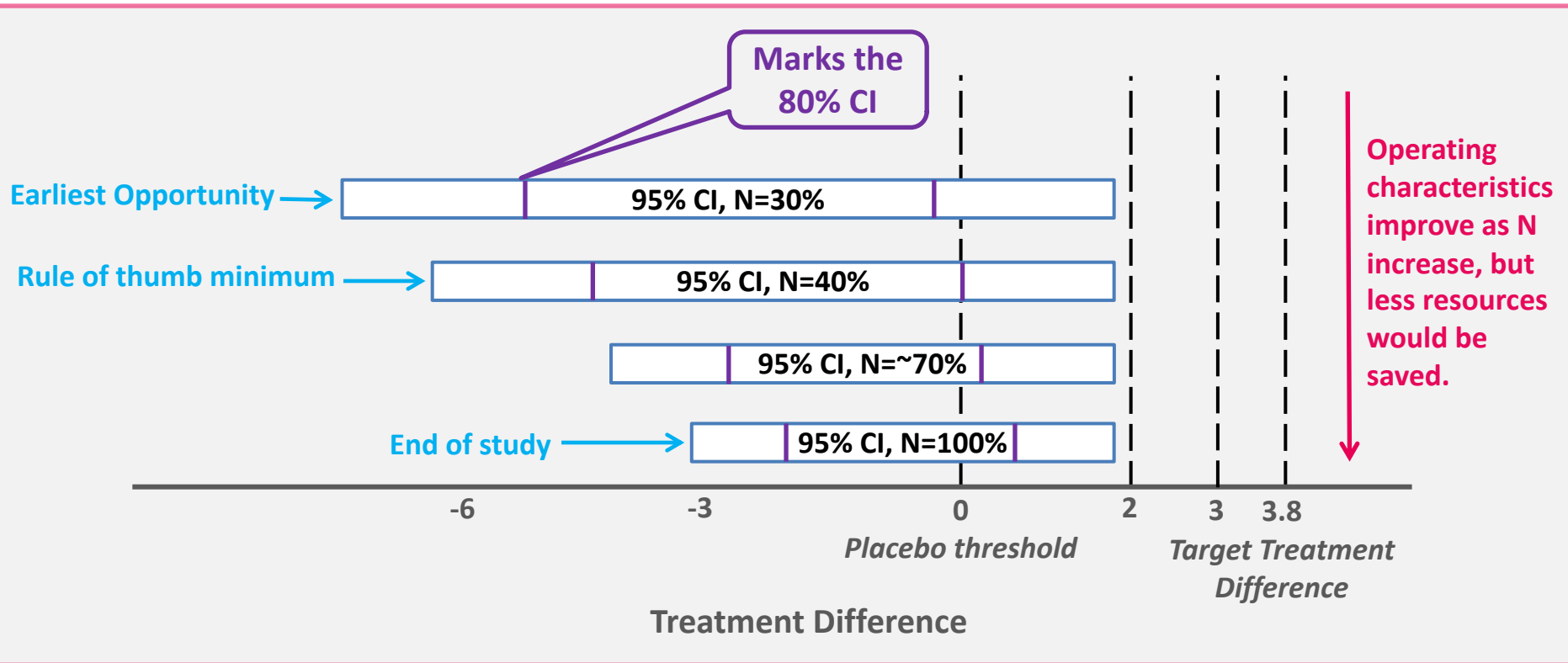
Probability a bad drug *would have been successful* at study-end

Probability a good drug *would have been successful* at study-end

Number of subjects saved if study is stopped

Possible Interim Decision Rule

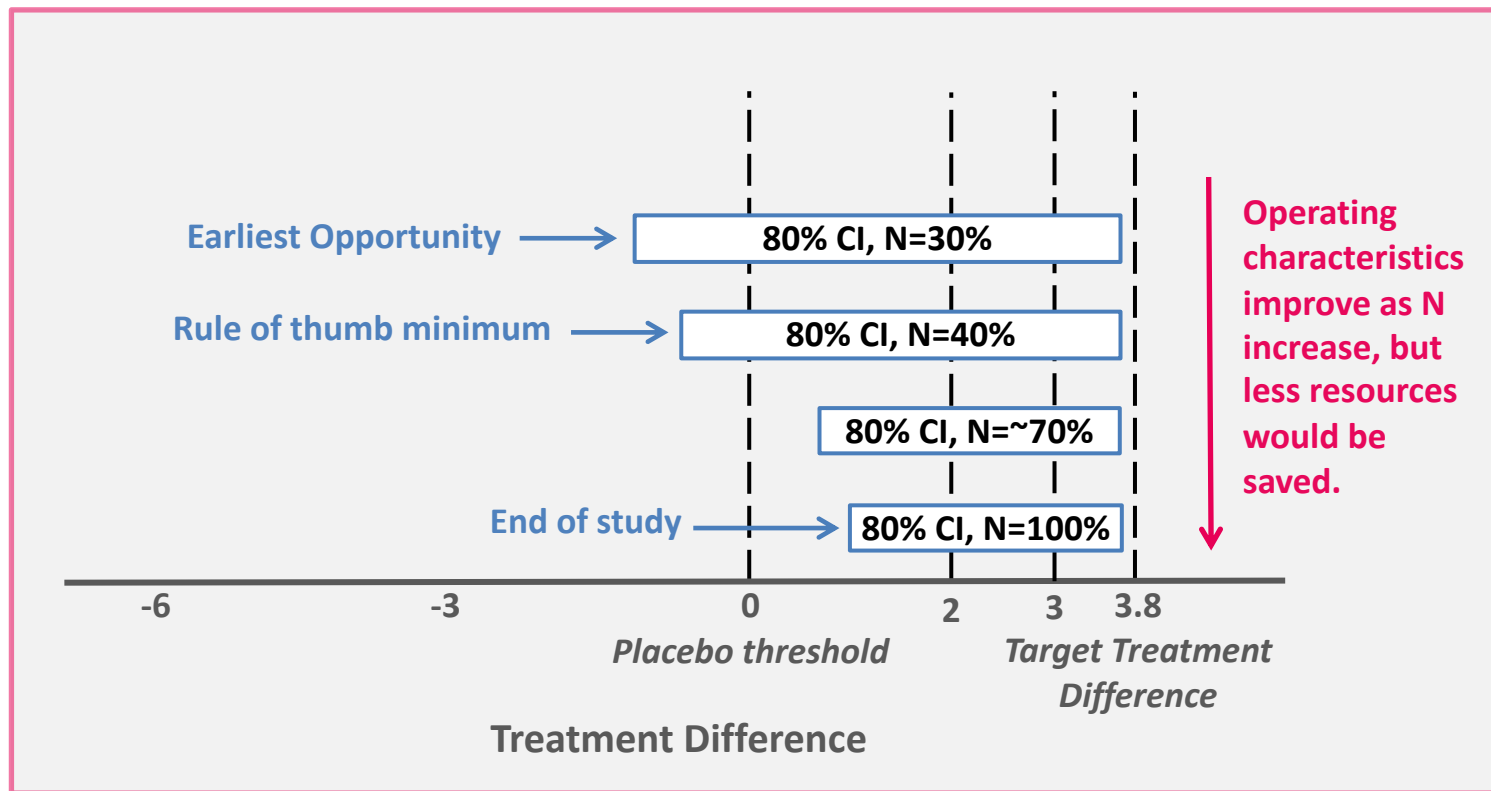
- Rule: If 95% CI upper limit < 2, study may be stopped for futility
- Too stringent



- Rule: If 80% CI upper limit < 2, study may be stopped for futility – too stringent!

Possible Interim Decision Rule

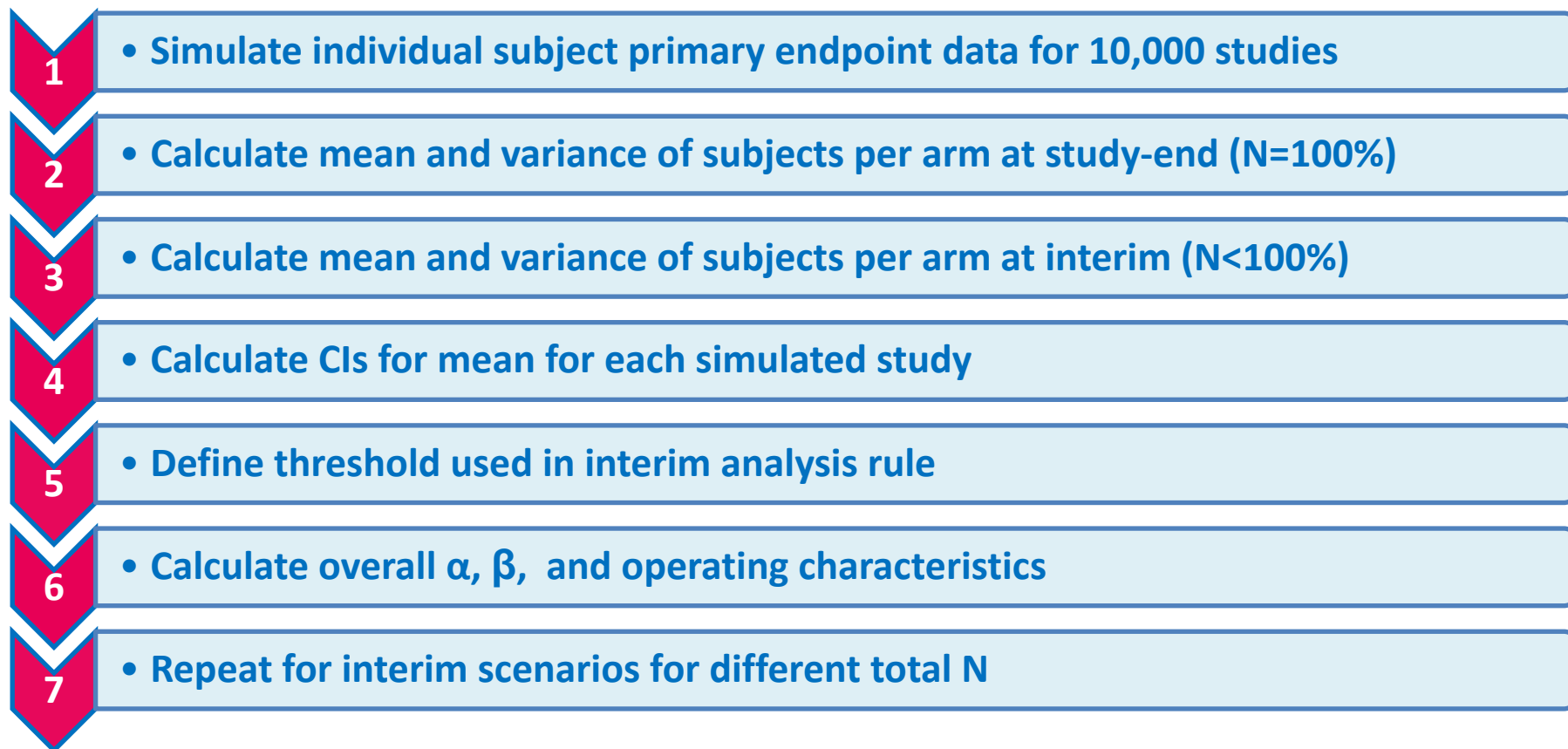
- Rule: If 80% CI upper limit < 3.8, study may be stopped for futility



- Clinically relevant rule - operating characteristics look reasonable visually

Calculating Operating Characteristics

- Check rule has good chance of finding futility if drug is inefficacious
- Aid decision of when to perform interim analysis (N=?)



Operating Characteristics of Possible Rules

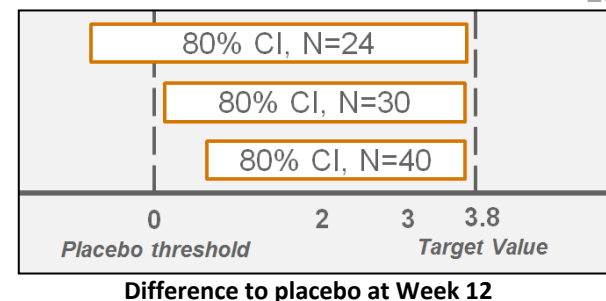
- Rule: Upper CI limit < 3.8 , indicates futility
- Rule: Upper CI limit < 2.0 , indicates futility

N %	N	CI	Probability of stopping a bad drug		Probability of stopping a good drug	
30%	18	95%	32%	12%	3%	$<1\%$
30%	18	80%	61%	32%	10%	$<1\%$
40%	24	95%	45%	16%	3%	$<1\%$
40%	24	80%	72%	38%	10%	$<1\%$
~70%	40	95%	66%	24%	3%	$<1\%$
~70%	40	80%	87%	48%	10%	$<1\%$

- Overall false negative probability increases slightly to 22%
- Low probability of stopping a good drug, therefore negligible impact on overall false negative probability

Final Interim Rule

- Rule: If upper end of the 80% CI < 3.8, this indicates futility



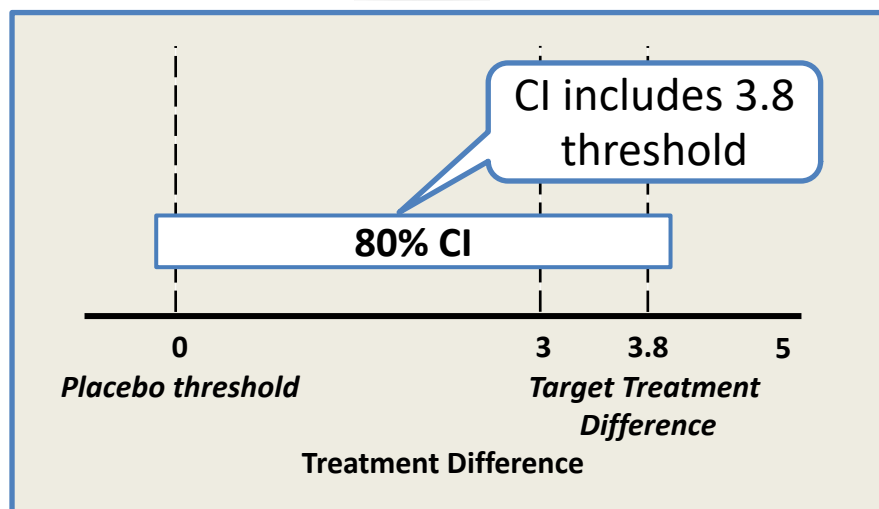
Risk of ignoring the rule

N %	N	CI	Probability of stopping at interim:		Probability of success at study-end if you continue at interim, despite rule indicating you should stop:		Estimated date this could be applied	No. of subjects saved if we stop for futility
			Bad drug	Good drug	Bad drug	Good drug		
40%	24	80%	72%	10%	0.3%	4.4%	Jul-2017	~17
~50%	30	80%	78%	10%	0.3%	3.5%	Sep-2017	~11
~70%	40	80%	87%	10%	0.3%	2.5%	Dec-2017	~2

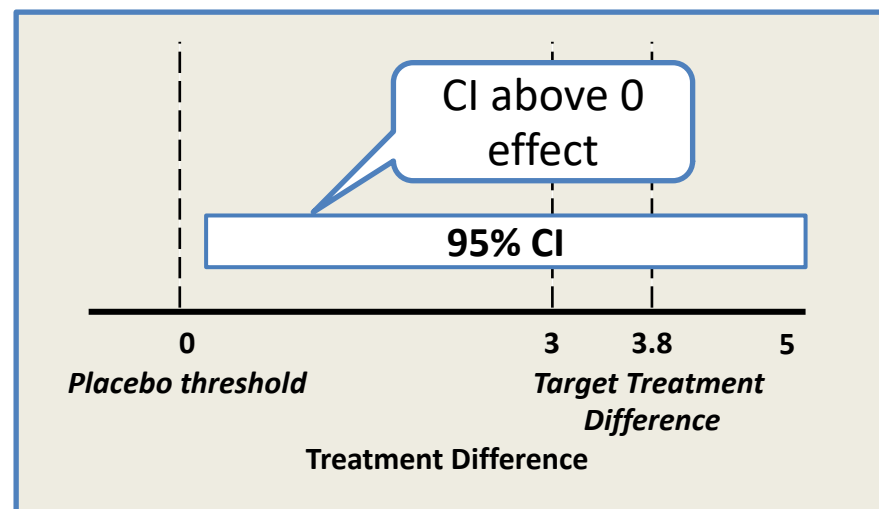
Impact of Interim on Overall Probability of Success

- Reaching Study Success: With an interim, good drugs must pass *two hurdles*

1. At interim



2. At end of study



- If a good drug fails either rule the study is not considered successful
- Extent of impact depends on stringency of interim rule



IMPLEMENTING THE INTERIM ANALYSIS

Interim Rule Chosen... Next Steps



Initial Documentation

- Protocol amendment
- Interim analysis SAP
- Identification of unblinded team



CRO Partnership

- Timeframe
- Budget



Results Presentation

- Key results slides

Summary

In an Ideal World...

- An interim analysis would be planned in the original study design
- However, circumstances can lead to requests for an interim mid-study

Interim Design Process – Statistician's Role

- Work with study team to identify reason for interim
- Present options in a simplistic manner
- Advise appropriate rule based on operating characteristics
- Identify unblinded team and prepare necessary documentation
- Ensure smooth running of interim

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