Futile or Not? An Interim Analysis Case Study

Ingrid Franklin, Veramed Limited

Rosalind Walley, UCB Pharma

10th October 2017

Contents

I

I

C

P

S

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 ≥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

- Interi[illegible]tility
- Interi[illegible]icacy
- Interi[illegible]mple Size Adjustment

- No Interim Analysis

Initial Decision:

- NOT to include an interim

No recruitment concerns

+

Increased Budget

veramed

ucb

Team Request for Interim Analysis

Why:

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

Statistician's Role:

- **Work with study team to:**
  - Create appropriate rule
  - Calculate its operating characteristics

veramed

ucb

PLANNING AN INTERIM *AFTER STUDY START*

veramed

ucb

Creating a Decision Rule

Aim of Rule: Stop study early if drug is inefficacious

- Basic operating characteristics

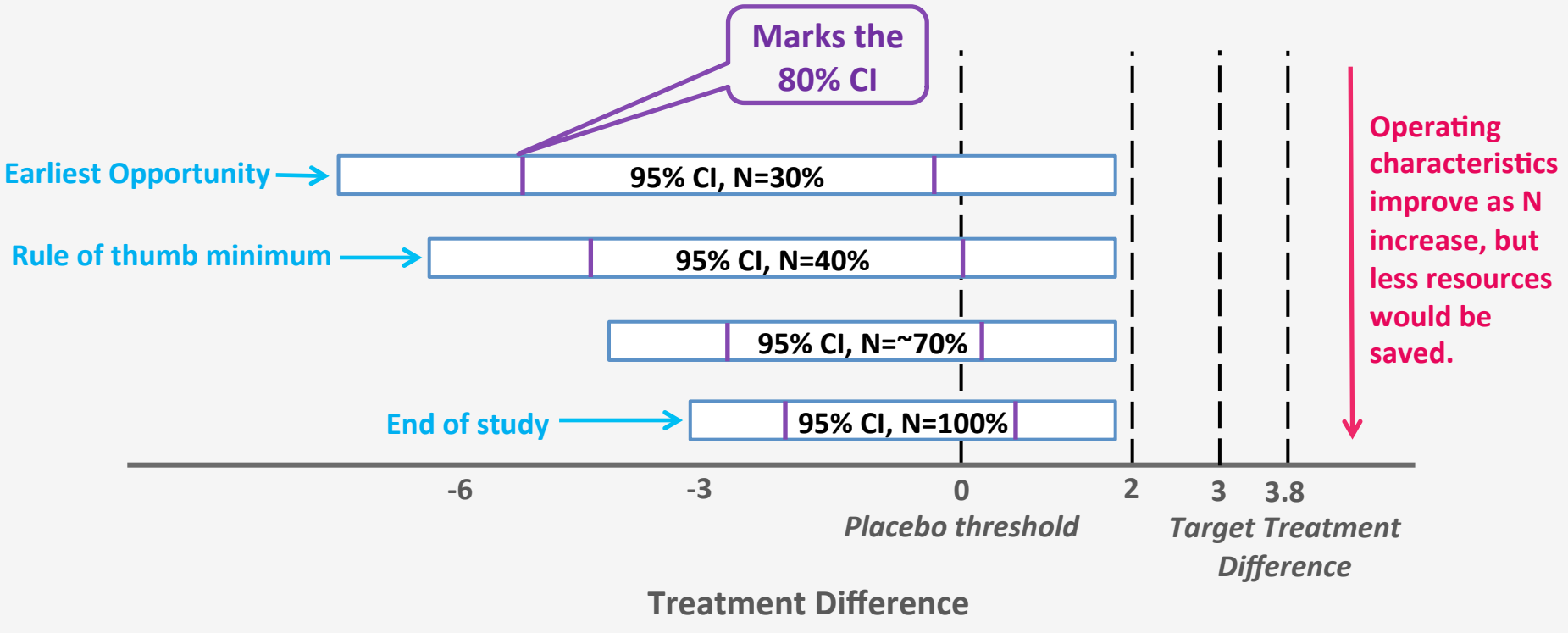
  - Probability of stopping a bad drug at interim 
  - Probability of stopping a good drug at interim 
  - Overall false negative rate 

- 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



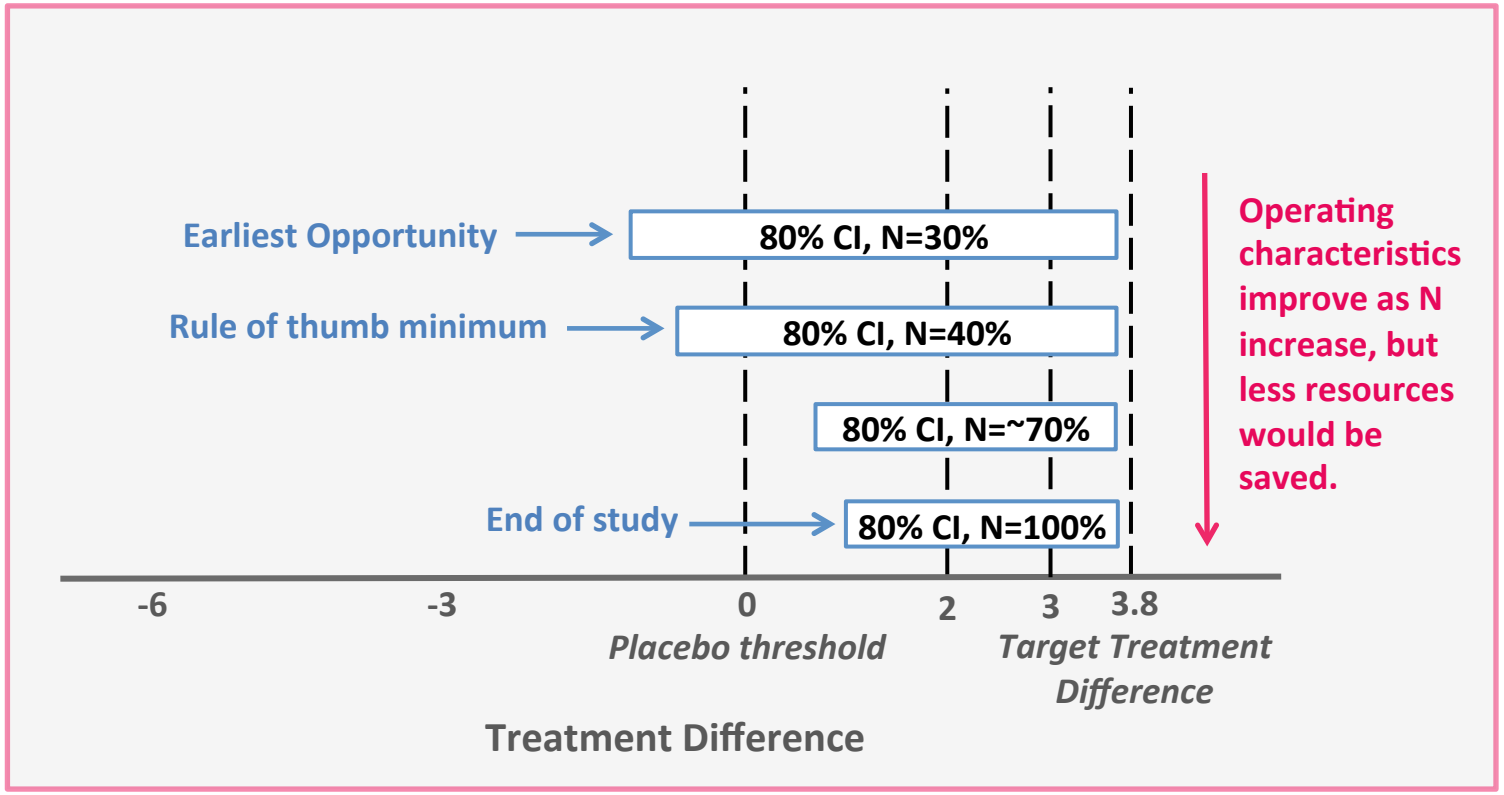
- **Rule:** If 80% CI upper limit < 2, study may be stopped for futility – too stringent!

veramed

ucb

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

veramed

ucb

Calculating Operating Characteristics

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

1. Simulate individual subject primary endpoint data for 10,000 studies
2. Calculate mean and variance of subjects per arm at study-end (N=100%)
3. Calculate mean and variance of subjects per arm at interim (N<100%)
4. Calculate CIs for mean for each simulated study
5. Define threshold used in interim analysis rule
6. Calculate overall α, β, and operating characteristics
7. Repeat for interim scenarios for different total N

Operating Characteristics of Possible Rules

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

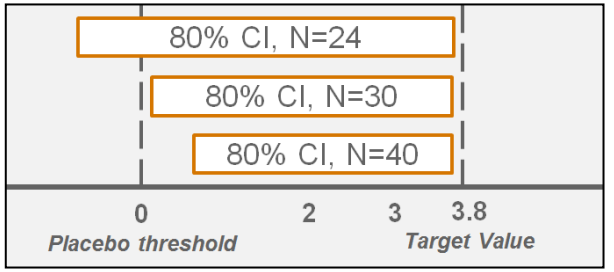
N %	N	CI	Probability of stopping a bad drug		Probability of stopping a good drug	
30%	18	95%	32%	12%	3%	<1%
30%	18	80%	61%	32%	10%	<1%
40%	24	95%	45%	16%	3%	<1%
40%	24	80%	72%	38%	10%	<1%
~70%	40	95%	66%	24%	3%	<1%
~70%	40	80%	87%	48%	10%	<1%

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

veramed

ucb

Final Interim Rule



Difference to placebo at Week 12

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

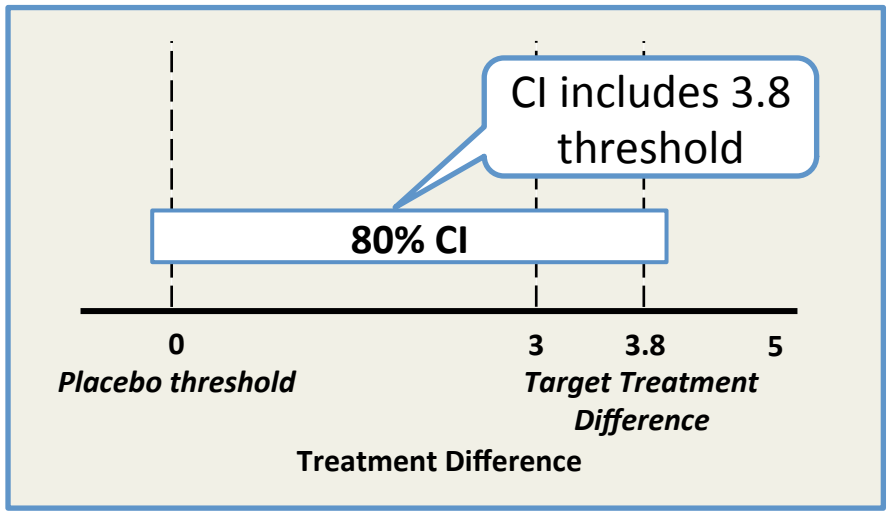
Risk of ignoring the rule

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

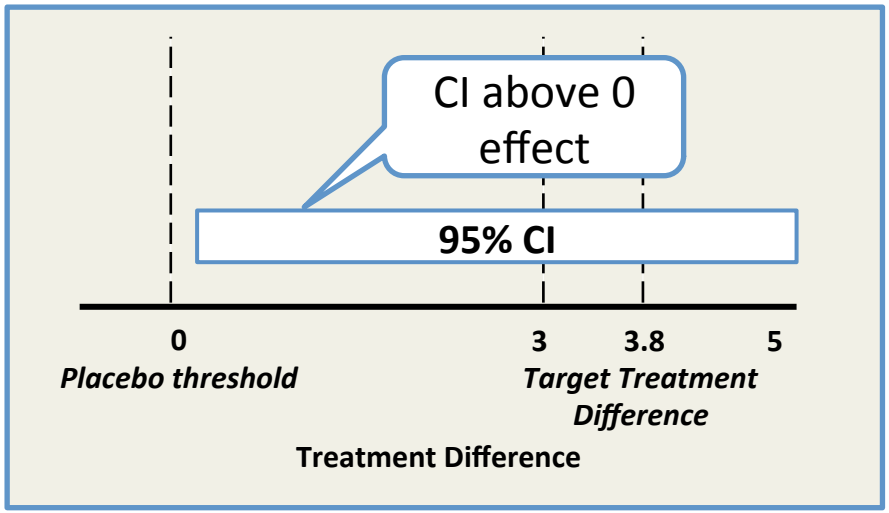
Impact of Interim on Overall Probability of Success

- **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

veramed

ucb

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

Acknowledgements

R

.for this study

Disclaimer:

Pharma employee and holds stock and stock options. Ingrid Franklin is an

.e

veramed

ucb