An experience in implementing the Promising Zone sample size re-estimation methodology in a phase 3 oncology study

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Outline

- Study background
- Design options
- Selection of sample size re-estimation method
- Promising zone method
- Sample size calculations
- Regulatory authority interactions

Study background

- Device study, in oncology
  - Randomised control trial
  - Open-label
  - Time-to-event primary endpoint
  - Primary objective to obtain FDA marketing approval

- Study was ongoing
  - In early stages
  - No adaptive features

- Uncertainty in estimated treatment effect size
  - Published literature suggests treatment effect size may depend on aetiology, and other aspects of the disease

Study design options

- **Option 1**: Leave as is
  - But what if estimated treatment effect size is incorrect?
  - Considered too risky
- **Option 2**: Reduce treatment effect size and include interim analyses
  - Up-front commitment to large study
  - Considered to provide insufficient flexibility
- **Option 3**: Maintain treatment effect size and include unblinded sample size re-estimation
  - Predicted enrolment rates examined to ensure enrolment would not need to be suspended
  - Considered to offer sufficient flexibility

Sample size re-estimation methods

- **Solutions to preserve Type I error**
  - Combination of p-values before and after interim analysis
    - Pre-specify combination function
  - Preserve conditional Type I error
    - Set conditional Type I error for re-designed trial = conditional Type I error of current study design
  - Weighted statistics (Cui, Hung and Wang, 1999)
    - Down weights contribution of sample after interim analysis
      - Contradicts premise that “all patients are equal”

Cui L, Hung HM, Wang SJ (1999). Modification of sample size in group sequential clinical trials. *Biometrics*; 55:853–7

Promising Zone method (Mehta and Pocock, 2011)

- **Overview**
  - Size of increase in sample size based on interim analysis results
  - Allowed only when interim results fall into the 'Promising zone'
    - Promising zone is defined based on conditional power
- **Advantages**
  - Uses conventional test statistics
  - Equally weighted observations
  - Sample size increased only when interim results are 'promising' (cf Option 2)
- **Disadvantage**
  - Spuriously positive interim analysis results could lead to sample size not being increased, resulting in an underpowered study

Mehta, C. R. and Pocock, S. J. (2011), Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statist. Med., 30: 3267–3284. doi: 10.1002/sim.4102

Promising Zone method

- **Type I error preservation**
  - Let $CP_1 = P_{Z1}(Z_2 > c_2 \mid Z_1 = z_1)$
    - be the conditional power at first interim analysis
    - conditional probability of rejecting the null hypothesis at the final analysis given the interim results and the pre-planned sample size
  - For $CP_1 \geq 0.5$, the sample size may be increased and final analysis conducted using the conventional statistic, without inflating Type I error
  - In fact, Type I error preservation holds for CP_1 slightly less than 0.5, (eg, ≥ a lower boundary = CP_{min}), in a design specific manner

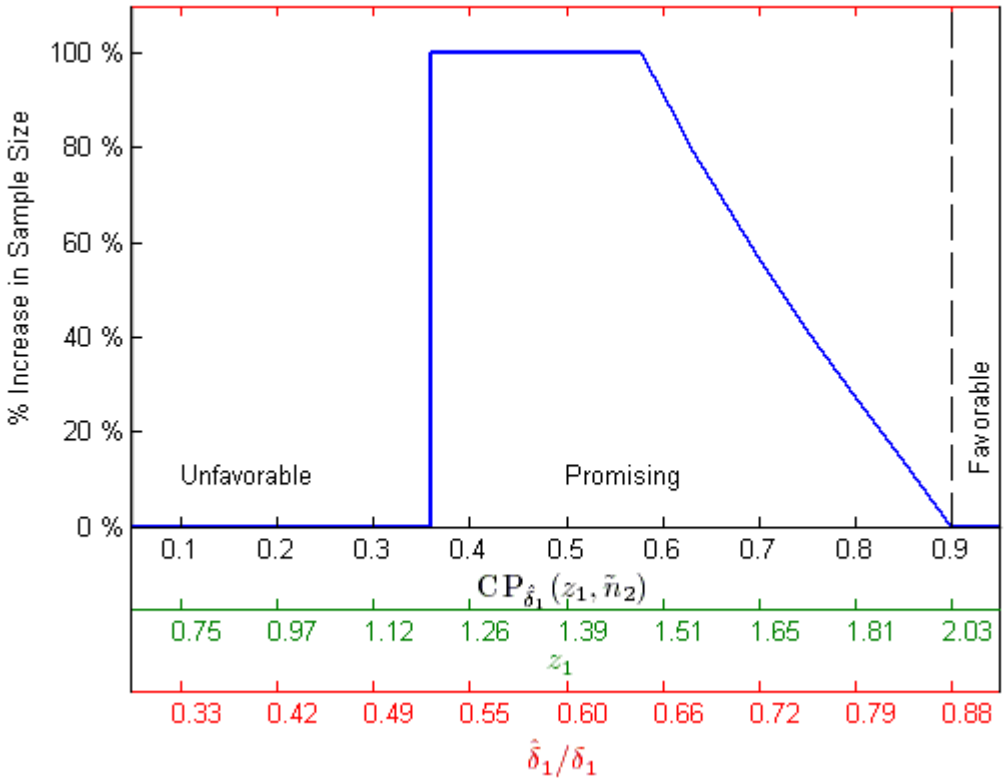
Promising Zone method

Design Adaptation Zones

Unfavourable: $CP_1 < CP_{min}$	→ Maintain sample size
Promising: $CP_{min} < CP_1 < 1 - \beta$	**→ Increase sample size**
Favourable: $CP_1 \geq 1 - \beta$	→ Maintain sample size

Promising Zone method

Figure 1. Partitioning of Interim Result into Zones($\dagger$) and % Sample Size Increase in Each Zone: An Illustrative Example where $n_{max}/n_2 = 2$, $n_1/n_2 = 0.5$, one-sided $\alpha = 0.025$, and $1 - \beta = 0.9$.



Source: Mehta, C. R. and Pocock, S. J. (2011), Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statist. Med., 30: 3267–3284. doi: 10.1002/sim.4102

Promising Zone method

- **Some slight modifications**
  - Decision to only allow 'fixed' sample size increase
    - Rather than 'sliding scale' approach
    - Due to possibility of treatment effect size being back-calculated
  - Inclusion of non-binding futility boundary
  - Sample size re-estimation performed at second interim analysis

Design Adaptation Zones at 2nd interim analysis

Futility	$CP_2 < CP_{fut}$	→ Stop for futility
Unfavourable	$CP_{fut} < CP_2 < CP_{min}$	→ Maintain sample size
Promising	$CP_{min} < CP_2 < 1 - \beta$	→ Increase sample size
Favourable	$CP_2 \geq 1 - \beta$	→ Maintain sample size
Efficacy	Efficacy boundary crossed	→ Stop for efficacy

Sample size calculations

- Computations performed in SAS PROC SEQDESIGN and EAST

- Timing of interim analyses and alpha spending options discussed with team
  - Based on predicted enrolment rates to ensure enrolment would not need to be suspended
  - Sufficient power to stop early for efficacy if treatment effect is large
    - Power family alpha spending methods considered
      - O'Brien-Fleming (ρ = 0.5)
      - Pocock (ρ = 0)
      - Other values of ρ

	OBF	ρ=0.25	Pocock
Number of events	202	208	222
Number of patients	332	342	365
Timing	46	47	47
Power for Δ=6mo	0.55	0.61	0.66
Power for Δ=8mo	0.68	0.73	0.78
Power for Δ=10mo	0.79	0.83	0.86

Numbers in the table above are for illustration purposes only

FDA interactions

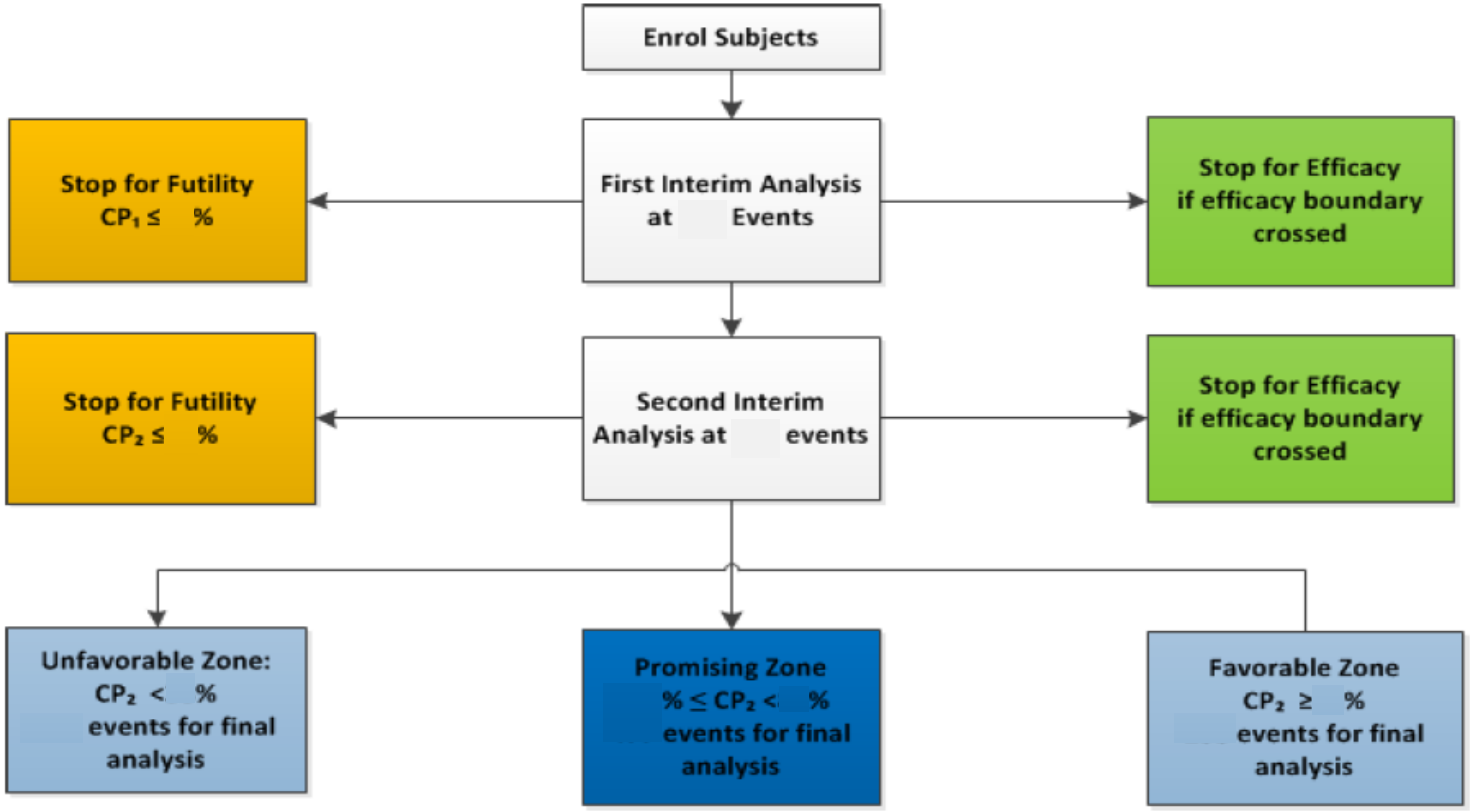
- Protocol amendment submitted to FDA
  - Conditional approval
    - *To mitigate the introduction of operational bias into this open-label study, please have operational procedures in place to ensure that the IDMC does not reveal unblinded interim results to study investigators per the recommendations given in Mehta and Pocock (Stat. Med., 2011).*
    - *You need to specify your adaptive method more clearly and justify it. For example, with your method, what values for the conditional power cause the sample size to increase or not increase? Also do the similarities between your method and Mehta and Pocock's method imply that your method controls the type 1 error?*

FDA interactions

- IDMC charter includes the following to minimize operational bias:
  - Unblinded CRO statistician and statistical programmer(s), who are not otherwise be involved in the study, will perform the interim analyses
  - IDMC members required to maintain strict confidentiality of study data
    - Not share any study data or information about the study with any individual external to the IDMC, including study investigators and Sponsor staff involved in operational aspects of the study
  - Fixed sample size increase allowed (vs 'sliding scale' approach)
  - Procedure mapped out for notifications to be followed by IDMC if recommendation to stop study or to increase sample size

FDA interactions

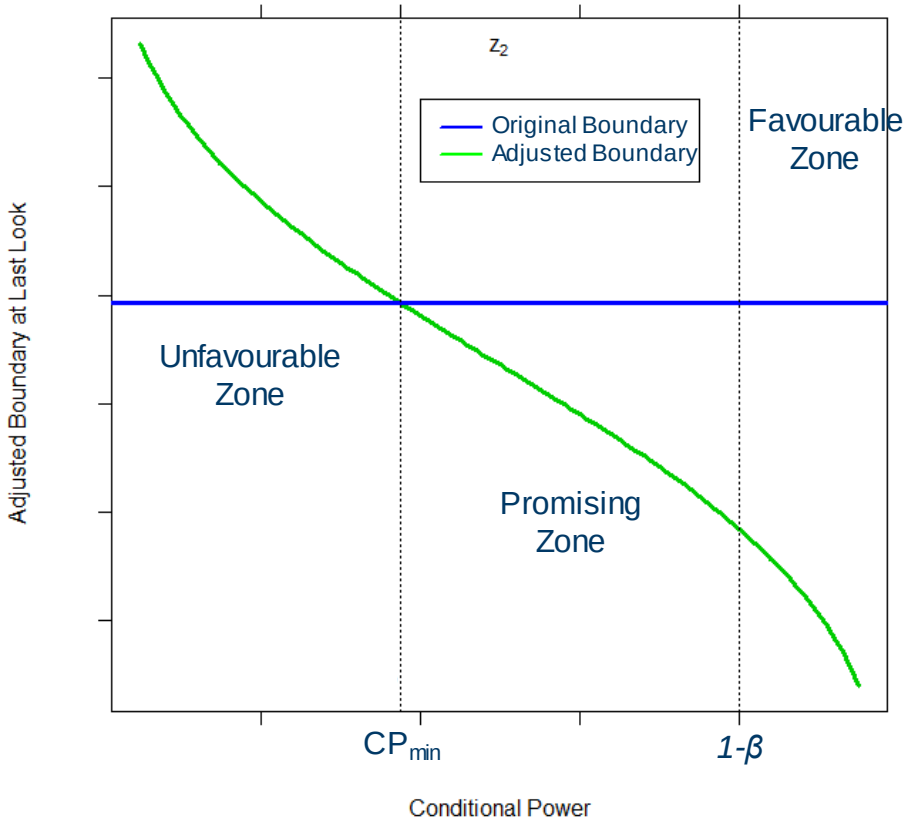
- Responses to FDA



CP_1 = Conditional power at the first interim analysis; CP_2 = Conditional power at the second interim analysis

FDA interactions

- Theoretical explanation of control of Type I error and derivation of CP_{min}



FDA interactions

- Simulation study also conducted
  - Type I error assessment
    - Assuming hazard ratio = 1 and nominal one-sided alpha = 2.5%

Zone	Prob. of entering each zone (%)	Prob. of declaring efficacy (%)	
		Group Sequential Design	Promising Zone Design
Futility	89.9	0	0
Unfavourable	3.8	4.5	4.5
Promising	4	11.9	9.2
Favourable	1.1	27.2	28.2
Efficacy	1.2	100	100
All Trials	**100**	**2.133**	**2.025**

    - Average sample sizes, number of events, study durations also provided

FDA interactions

- Simulation study
  - Type II error assessment also provided to FDA
    - Assuming hazard ratios corresponding to both original and increased sample sizes

Zone	Prob. of entering each zone (%)	Prob. of declaring efficacy (%)	
		Group Sequential Design	Promising Zone Design
Futility	13.6	0	0
Unfavourable	4.7	54.8	55.2
Promising	15.3	74.5	94.8
Favourable	12.5	88.6	89.3
Efficacy	53.9	100	100
All Trials	**100**	**82.2**	**85.4**

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Conclusions

- Sample size re-estimation offered by the promising zone method fitted needs of BTG
- Positive experience with device branch of FDA
  - FDA agreement to change design of an ongoing, open-label study
- Able to show control of Type I error theoretically, but simulation study gave additional assurance
- Our study investigators tell us they like the “Promising Zone” concept!

Questions