Choosing Interim Sample Sizes in Group Sequential Designs

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Group Sequential Designs

- The number of patients isn't set in advance but is determined by a rule that is a function of cumulative data.
- Data is analyzed at pre-determined points during the experiment, and a decision is made to stop and draw a conclusion regarding the study's objective or continue collecting data.
- Typically, the decision rule at each interim analysis takes the form of a hypothesis test, and emphasis in the design is placed on maintaining the overall type I error rate in the presence of (potentially) multiple tests.
- The expected sample size may be substantially decreased the while controlling overall type I error and power.

Popular Uses

- Group sequential designs (GSDs) allow studies to stop earlier for efficacy or futility at pre-planned interim analysis times.

- GSDs can indicate studies should be stopped for unexpectedly high toxicity rates.

A simple illustrative example with a single interim analysis

Let Z_1 and Z_2 be independent N(θ,1),

but Z_2 is observed only when $Z_1 \leq 1.96$.

- **In study design,** the stopping decision is unknown and the design's characteristics should be evaluated based on the overall distribution of $\hat{\theta}$ where both stopping options are possible.
- **Data analysis** should be based on

$\widehat{\theta_1} =$ MLE given experiment stopped with Z_1; or

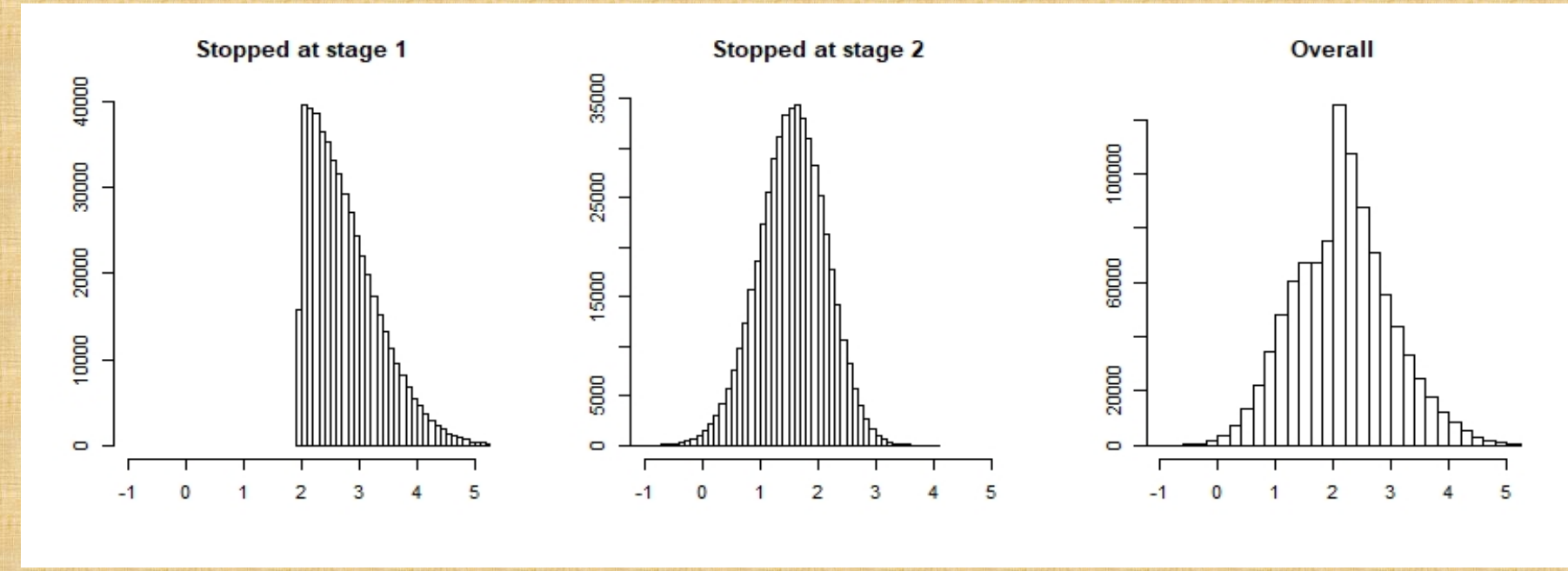
$\widehat{\theta_2} =$ MLE given experiment continued to include Z_2.

The simple example continued

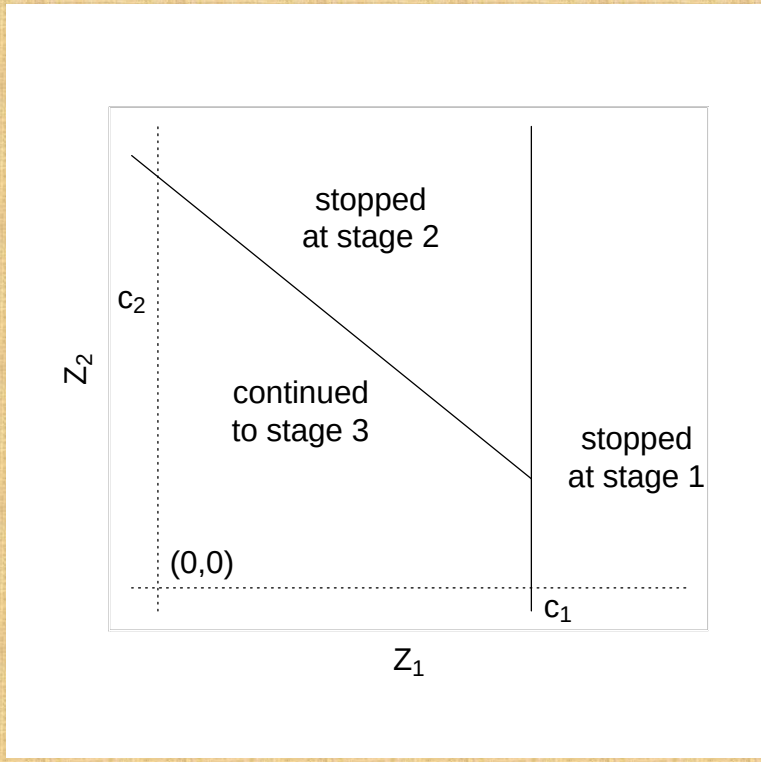
- If Z_1>1.96, the MLE of θ is $\widehat{\theta_1} = Z_1$,
- If $Z_1 \leq 1.96$, the MLE of θ is $\widehat{\theta_2} = (Z_1 + Z_2)/2$.
- Unconditionally, the MLE $\hat{\theta}$ of θ is

$$\hat{\theta} = I(Z_1 > 1.96)\widehat{\theta_1} + I(Z_1 \leq 1.96)\widehat{\theta_2}.$$

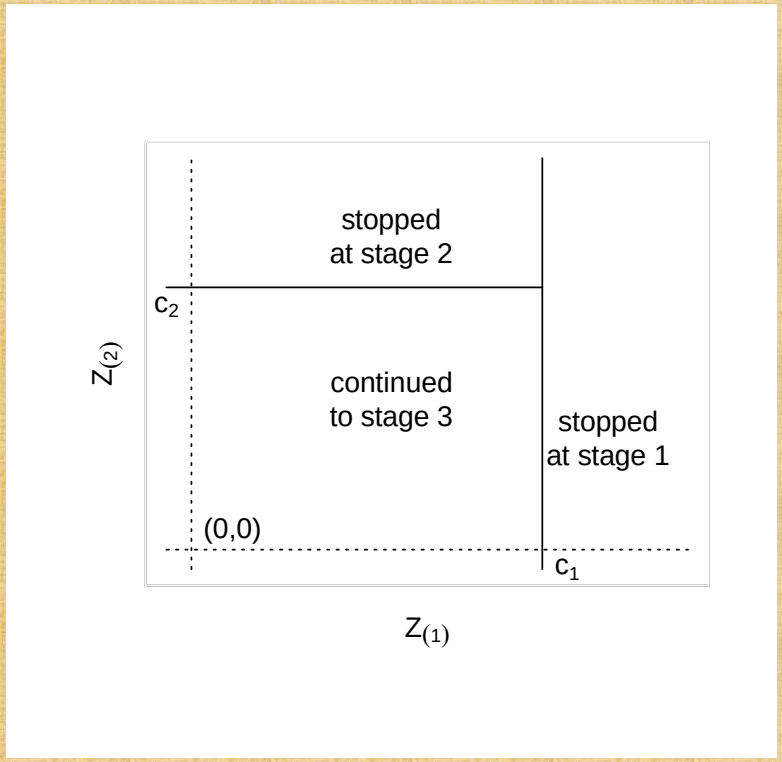
Distributions of the MLE



Support for A Three Stage GSD



Stage-Specific Test Statistics



Cumulative Test Statistics

Pocock's One-Sided 3-Stage GSD

- Suppose a new treatment needs to be tested against a historically established level.

- $Overall\ Testing\ Goal$: $H_0: \theta = 0$ *versus* $H_A: \theta = \theta_A = 1$

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The alternative hypothesis is defined on a standardized scale (mean divided by standard deviation): $\theta = 1$. The use a standardized scale (effect size) eliminates a need to estimate a nuisance parameter (standard deviation) and separates this from the design problem.

- Set $\alpha = \Pr(\text{reject } H_0 \text{ at } 1,2, \text{or } 3) = 0.05$

Pocock's *α−spending function* has the same critical values at all interim analyses

This implies equal sample sizes at each stage:

$$m = m_1 = m_2 = m_3 = \frac{1}{3}n;$$

- $Define\ the\ cumulative\ test\ statistic\ Z_{(k)} = \frac{1}{\sqrt{2mk\sigma^2}}(\sum_{i=1}^{mk} X_i)$, $k = 1,2,3$

where X_i is the observed difference between the outcome and control of the ith subject.

Stop with Z_k if $z_k > C_p$=1.9922, $k = 1,2$

Slide 8

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Pocock Stopping Probabilities
(SAS Output)

θ	**Stage 1** $n_1 = 244$	**Stage 2** $n_2 = 488$	**Stage 3** $n_3 = 732$
0.0000	**0.02318**	**0.03866**	**0.05000**
0.5000	0.11289	0.22628	0.32918
1.0000	0.33343	0.62094	**0.80000**
1.5000	0.63698	0.91735	0.98455

First row gives **α**-spending function.

Sample sizes found to achieve 80% power at $H_A : \theta = 1$

Group Sequential Design Defined by Ordered Alternatives (SOA)

- Tarima and Flournoy (2019) suggested *simultaneously* targeting constant power against *multiple* ordered alternatives.

- E.g., with α=0.05, choose interim sample sizes to secure 80% statistical power at all three H_A: θ =0.3, θ =0.2, and θ =0.1 regardless of when stopping occurs.

- We used **equal** stage-specific rejection probabilities (0.0172) under H_0: θ =0.0.

- Sample sizes for interim analyses: n_1=98, n_2=196, n_3=772,
- stage-specific critical values: c_1=2.12, c_2=2.02 c_3=2.02.

SOA's Rejection Probabilities by Stage

and Expected Sample Sizes using $\alpha_1 = \alpha_2 = \alpha_3 = 0.0172$.

θ	Pr(Reject at k=1)	Pr(Reject at k≤2)	Pr(Reject at k≤3)	E(N)
0.0	0.0179	0.0337	**0.0509**	750.83
0.1	0.1320	0.3019	**0.7990**	585.18
0.2	0.4473	**0.7985**	0.9998	268.24
0.3	**0.8007**	0.9868	1.0000	125.17

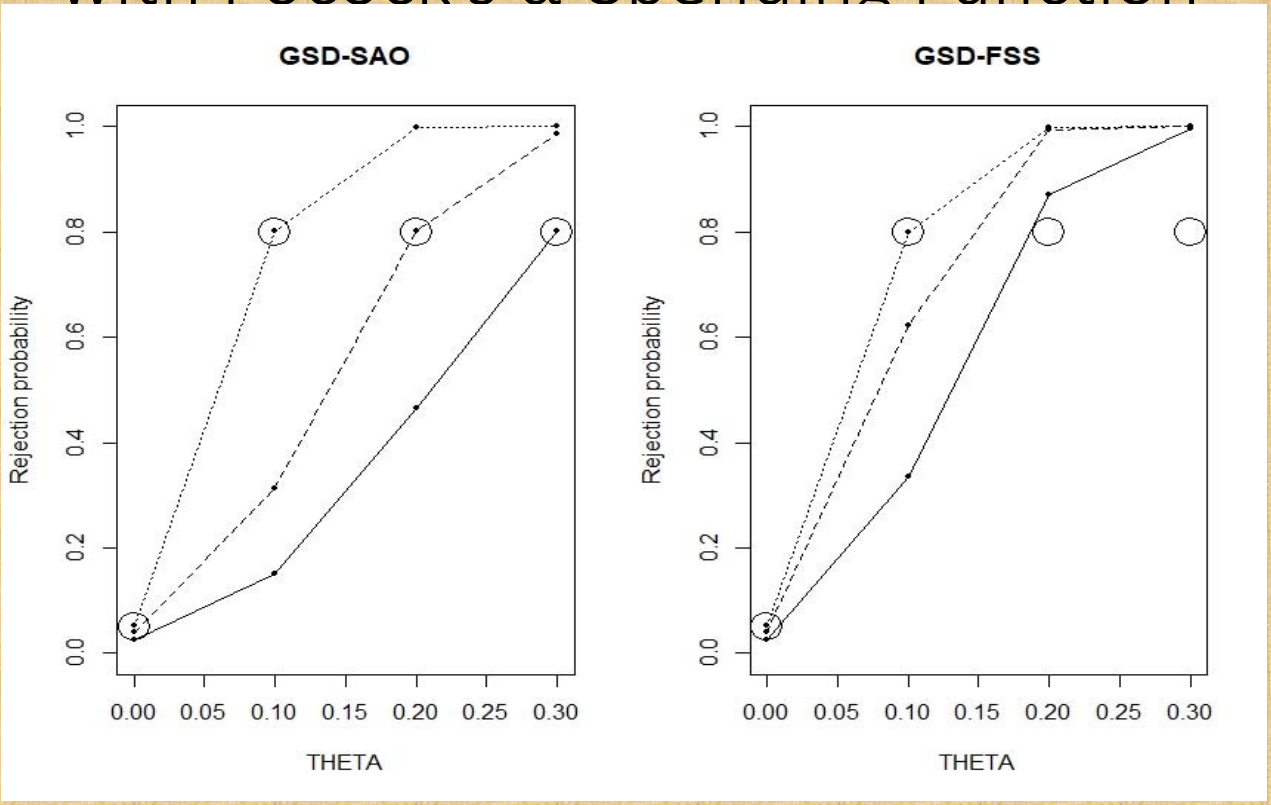
- The SOA design with Pocock's α-spending function has **80% power at each stage**

- Cumulative rejection probabilities 0.0232, 0.0387, 0.0500 are associated with stage-specific rejection probabilities α_1= 0.0232, α_2= 0.0158, and α_3 = 0.0118.

- Interim analyses will be at n_1=90, n_2=205, and n_3=86.
- stage-specific critical values are

  c_1= 1.9921, c_2=2.0216, and c_3=2.1812.
- This leads to **smaller overall expected sample size**

SAO's and Pocock's Cumulative Rejection Probabilities with Pocock's α-Spending Function



α_1= 0.0232
α_2= 0.0158
α_3 = 0.0118

solid line: stage 1
dashed line: stage 2
dotted line: stage 3

Conclusions

1. A possibility of early stopping changes the distribution the MLEs:

   it becomes non-normal.

2. A new group sequential design which controls an overall type 1 error while controlling statistical power at multiple alternatives is proposed.

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