Comparing Adaptive Designs and the Classical Group Sequential Approach to Clinical Trial Design

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Plan of talk

1. Objectives of Adaptive Designs
2. Objectives of Group Sequential Tests
3. Case Study 1: Sample size re-estimation
4. Case Study 2: Switching to a patient sub-population
5. Conclusions

References:

"Adaptive and non-adaptive group sequential tests", Jennison and Turnbull, *Biometrika* (2006).

"Adaptive seamless designs: Selection and prospective testing of hypotheses", Jennison and Turnbull, *Journal of Biopharmaceutical Statistics* (2007).

1. Objectives of Adaptive Designs

Ordinarily, in a clinical trial one specifies at the outset:

Patient population,

Treatment,

Primary endpoint,

Hypothesis to be tested,

Power at a specific effect size.

Adaptive designs allow these elements to be reviewed during the trial.

Because . . . there may be limited information to guide these choices initially, but more knowledge will accrue as the study progresses.

Adaptive Designs

Adaptive methods can enable mid-study modifications, including:

Changing ***sample size*** in response to estimates of a nuisance parameter

- Changing ***sample size*** in response to interim estimates of the effect size

Switching the ***primary endpoint***

- Switching to a ***patient sub-population***

Changing the ***null hypothesis*** (e.g., switching from a superiority trial to a non-inferiority trial)

Treatment selection (combining dose-selection in Phase II and a confirmatory Phase III trial)

Adaptive Designs

Adaptation must be carried out in a way which ***protects type I error*** probability.

Specialised methods have been developed to do this,

Some adaptive approaches offer a high degree of flexibility.

Adaptive procedures should achieve their objectives ***efficiently***.

A critical appraisal of an adaptive method needs a full specification of the rules that will be applied,

Then, properties such as power and expected sample size can be calculated, often by simulation.

Overall properties of a likely implementation are relevant, even if investigators intend to behave “flexibly”.

2. Objectives of Group Sequential Tests

In a Group Sequential design, accumulating data are monitored regularly.

The study stops as soon as there is sufficient evidence to reach a conclusion.

Group sequential designs are available for testing a null hypothesis against a one-sided or two-sided alternative.

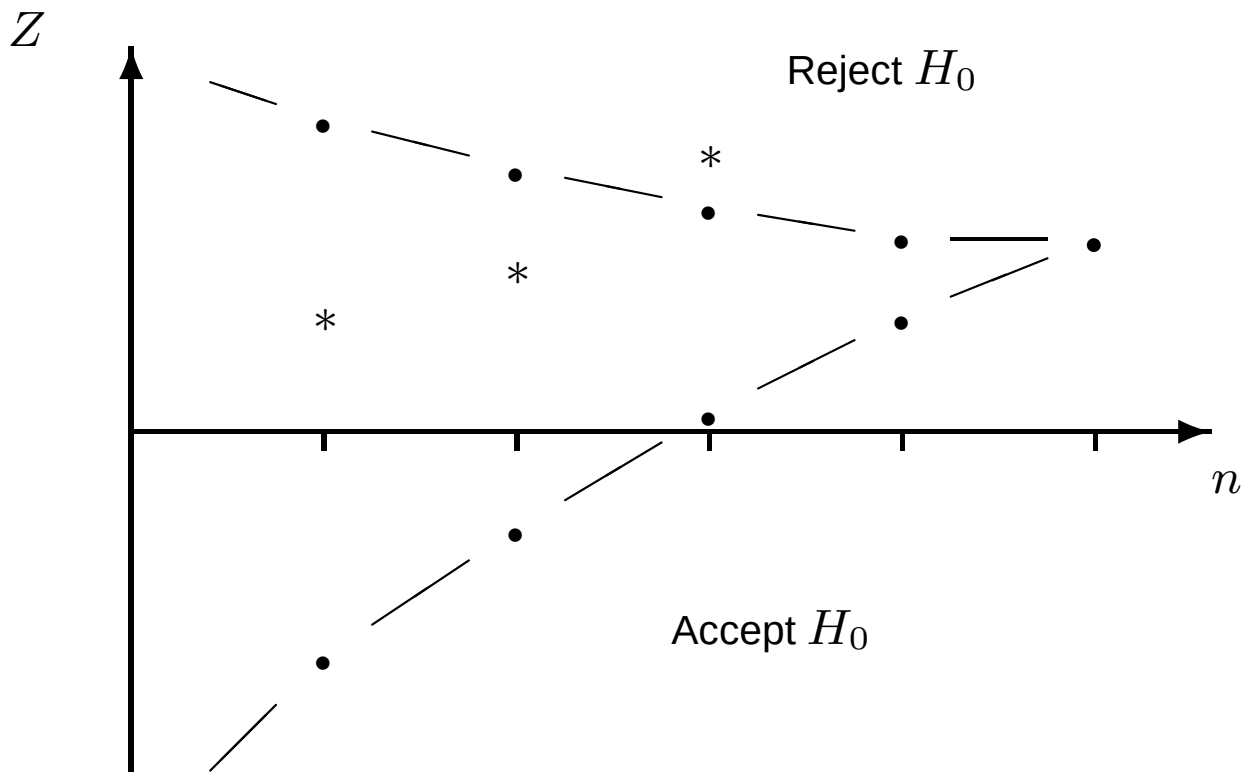
Early termination may be for a positive result (success) or a negative outcome (stopping for futility).

An efficient design ***reduces average sample size*** or time to a conclusion while protecting the type I error rate and maintaining the desired power.

The group sequential design must be specified in a trial's protocol.

Group Sequential Tests

A group sequential test can be represented by a stopping boundary:



Group Sequential Tests

Some flexibility and adaptability is available in group sequential designs.

Error spending tests

Error spending designs offer a flexible way to deal with unpredictable group sizes.

Information monitoring

In the general theory of sequential tests, what really matters is the observed *information* for a treatment effect.

Designing a trial so that information will reach a pre-specified level is an effective approach when nuisance parameters affect the sample size needed to meet the power condition.

Implementation

There is a wide literature on the theory and practice of group sequential tests and a range of software products to help implement these methods.

Case study 1: Sample size modification to increase power

Investigators may start out optimistically and design a trial with power to detect a large treatment effect. Interim data may then suggest a smaller effect size — still clinically important but difficult to demonstrate with the chosen sample size.

- An adaptive design can allow sample size to be increased during the trial, ***rescuing*** an under-powered study.
- Some would advocate this approach as a way to "let the data say" what power and sample size should be chosen.
- Or, a ***group sequential design*** can achieve a desired power curve and save sample size through early stopping when the effect size is large.

Questions:

Is there a down-side to the "wait and see" approach?

How are the adaptive and group sequential approaches related?

Sample size modification to increase power

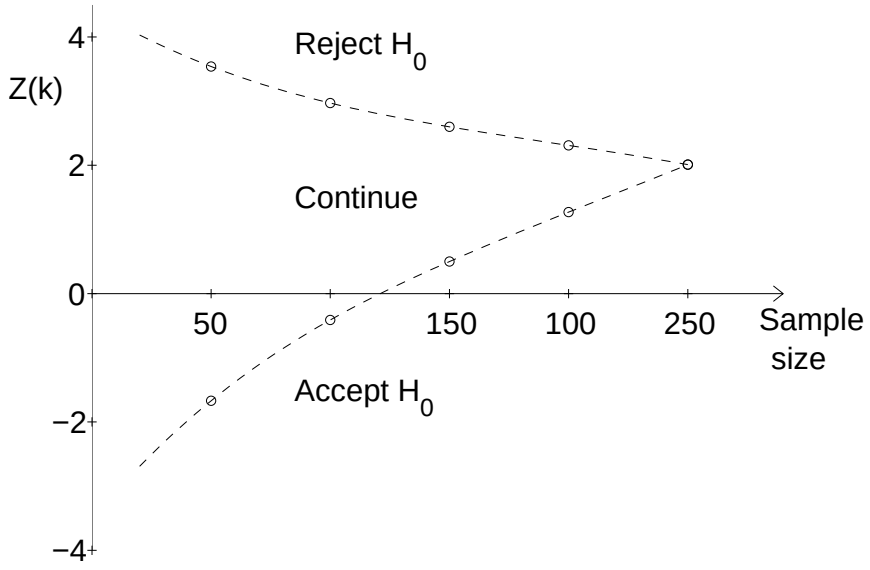
Example *(Jennison & Turnbull, Biometrika, 2006, Ex. 2)*

We start with a group sequential design with 5 analyses,

testing H_0: $\theta \leq 0$ against $\theta > 0$ with

one-sided type I error probability $\alpha = 0.025$ and

Initial design: power $1 - \beta = 0.9$ at $\theta = \delta$.



Sample size modification to increase power

Suppose, at analysis 2, a low interim estimate $\hat{\theta}_2$ prompts investigators to consider the trial's power at effect sizes below δ, where power 0.9 was originally set:

Lower effect sizes start to appear plausible,

Conditional power under these effect sizes, using the current design, is low.

Applying the method of Cui, Hung and Wang (*Biometrics*, 1999)

Sample sizes for groups 3 to 5 are multiplied by a factor γ.

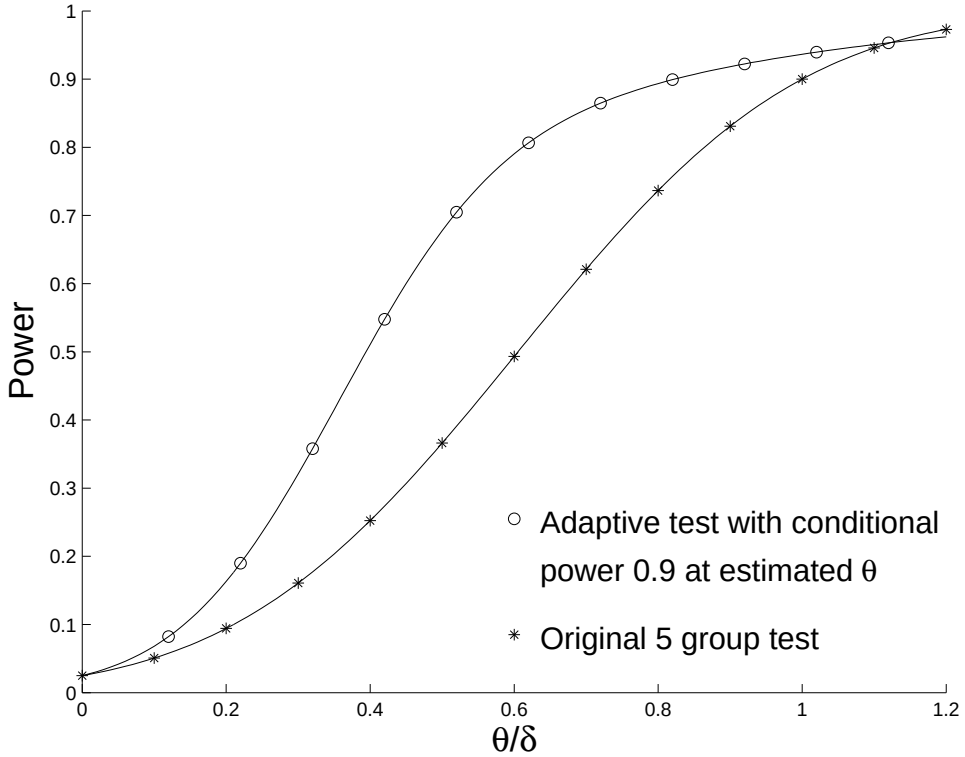
Sample sums from these groups are down-weighted by $\gamma^{-1/2}$. This gives the same variance as before but the mean is multiplied by $\gamma^{1/2}$.

Using the new weighted sample sum in place of the original sample sum maintains the type I error rate and increases power.

We choose the factor γ to give conditional power 0.9 **if $\boldsymbol{\theta}$ is equal to $\hat{\boldsymbol{\theta}}_{\mathbf{2}}$**, with the constraint $\gamma \leq 6$ so sample size can be at most 4 times the original maximum .

Sample size modification to increase power

Re-design has raised the power curve at all effect sizes.



Overall power at $\theta = \delta/2$ has increased from 0.37 to 0.68.

Sample size modification to increase power

Reasons for re-design arose purely from observing $\hat{\theta}_2$. A group sequential design responds to such interim estimates — in the decision to stop the trial or to continue.

Investigators could have considered at the design stage how they would respond to low interim estimates of effect size.

If they had thought this through and chosen the above adaptive procedure, they could also have examined its overall power curve.

Assuming this power curve were acceptable, how else might it have been achieved?

An alternative group sequential design

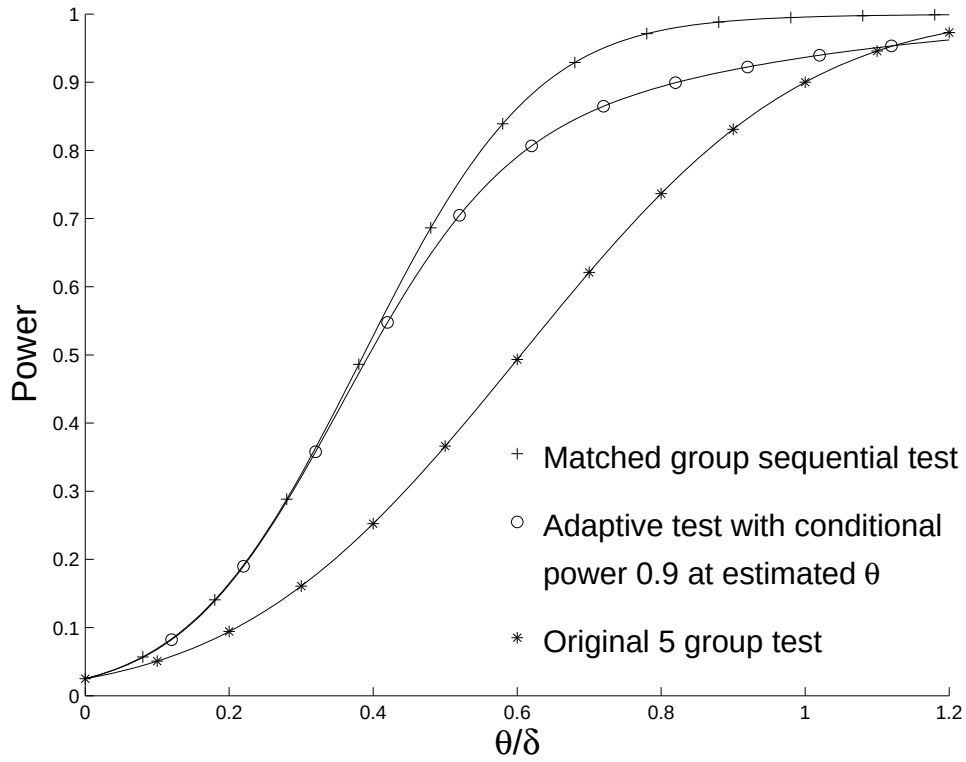
Five-group designs matching key features of the adaptive test can be found.

To be comparable, power curve should be as high as that of the adaptive design.

Can expected sample size be lower too?

Sample size modification to increase power

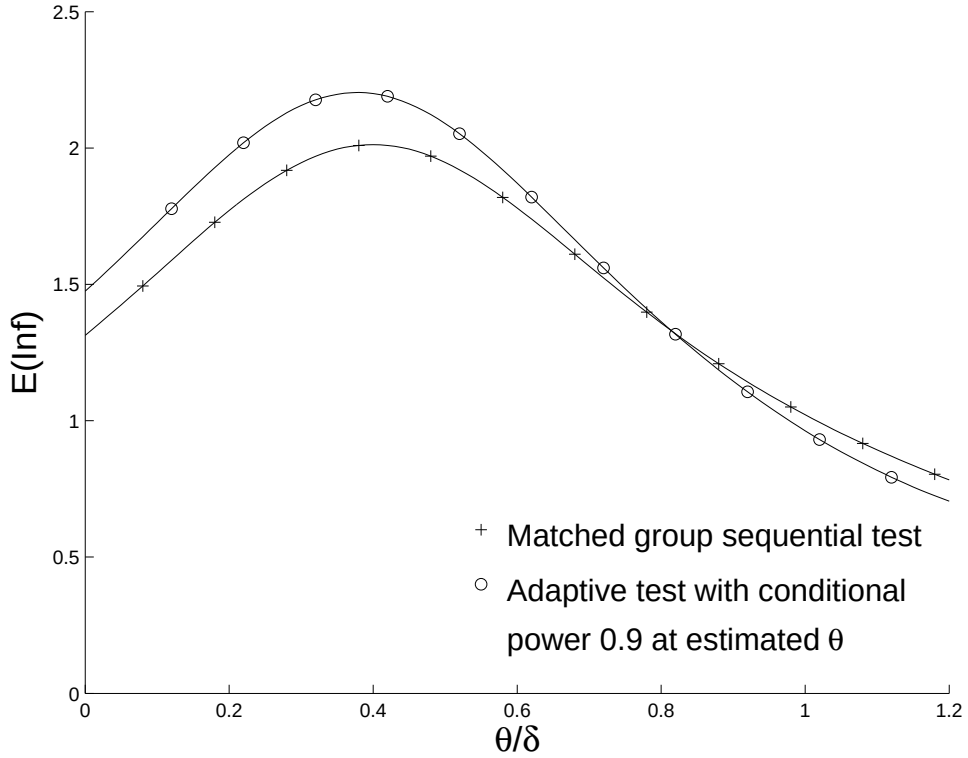
Power of our “matched” group sequential design is as high as that of the adaptive design at all effect sizes — and substantially higher at the largest θ values.



Sample size modification to increase power

The group sequential design has significantly lower expected information than the adaptive design over a range of effect sizes.

The group sequential design has slightly higher expected information for $\theta > 0.8\,\delta$, but this is where its power advantage is greatest.

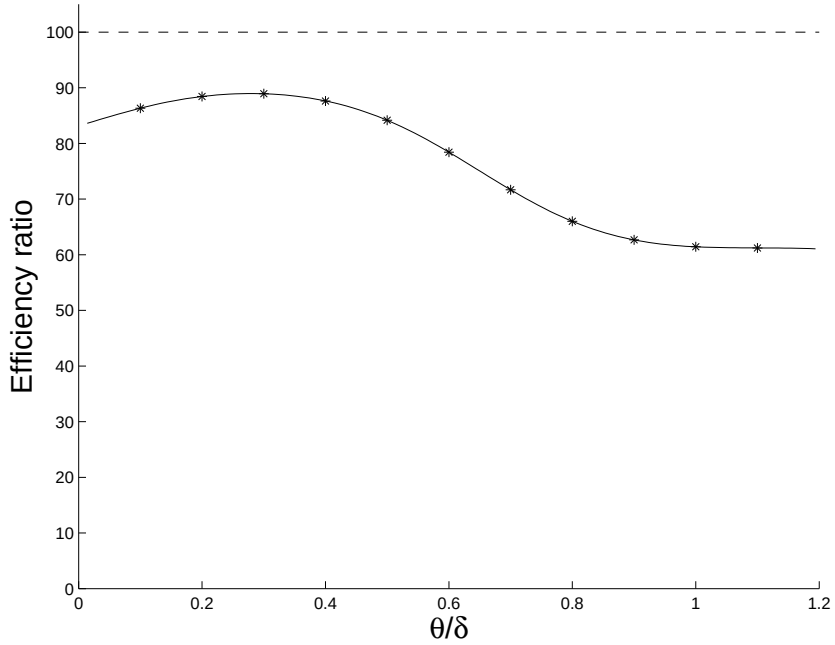


Sample size modification to increase power

Jennison & Turnbull (*Biometrika*, 2006) define an “Efficiency Ratio” to compare expected sample size, adjusting for differences in attained power.

By this measure, the adaptive design is up to 39% less efficient than the non-adaptive, group sequential alternative.

Efficiency ratio of adaptive design vs group sequential test



Sample size modification to increase power

We have found similar inefficiency relative to group sequential tests in a wide variety of proposed adaptive designs.

Paradoxically, adaptive designs should have an advantage from the extra freedom to choose group sizes in a response-dependent manner.

Jennison & Turnbull (*Biometrika*, 2006) show that adaptation can lead to gains in efficiency over non-adaptive group sequential tests — but the gains are very slight.

Moreover, sample size rules based on conditional power are far from optimal, hence the poor properties of adaptive designs using such rules.

Conclusion:

Specify power properly at the outset, then

Group sequential designs offer a simple and efficient option.

Case study 2: Switching to a patient sub-population

A trial protocol defines a specific target population.

Suppose it is believed the treatment may be effective in a certain sub-population, even if it is ineffective in the rest of the population.

Enrichment: Focusing recruitment on a sub-population

At an interim analysis, the options are:

Continue as originally planned, or

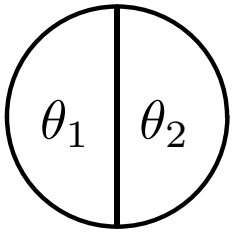
Restrict the remainder of the study to a sub-population.

This choice will affect the licence a positive outcome can support.

The possibility of testing several null hypotheses means a multiple testing procedure must be used.

Enrichment: Example

Sub-population 1 (proportion λ_1)



Sub-population 2 (proportion λ_2)

Overall treatment effect is $\theta = \lambda_1\theta_1 + \lambda_2\theta_2$.

We may wish to test:

- The null hypothesis for the full population, H_0: $\theta \leq 0$ vs $\theta > 0$,
- The null hypothesis for sub-population 1, H_1: $\theta_1 \leq 0$ vs $\theta_1 > 0$,
- The null hypothesis for sub-population 2, H_2: $\theta_2 \leq 0$ vs $\theta_2 > 0$.

Multiple testing procedures

Suppose k null hypotheses, H_i: $\theta_i \leq 0$ for $i = 1, \ldots, k$, are to be considered.

A procedure's ***family-wise error rate*** under a set of values $(\theta_1, \ldots, \theta_k)$ is

$$Pr\{\text{Reject } H_i \text{ for some } i \text{ with } \theta_i \leq 0\} \;=\; Pr\{\text{Reject any true } H_i\}.$$

The family-wise error rate is controlled strongly at level α if this error rate is at most α for all possible combinations of θ_i values. Then

$$Pr\{\text{Reject any true } H_i\} \leq \alpha \quad \text{for all } (\theta_1, \ldots, \theta_k).$$

With such strong control, the probability of choosing to focus on the parameter θ_{i*} and then falsely claiming significance for null hypothesis H_{i*} is at most α.

Closed testing procedures (Marcus et al, *Biometrika*, 1976)

For each subset I of $\{1, \ldots, k\}$, we define the intersection hypothesis

$$H_I = \cap_{i \in I} H_i.$$

We construct a level α test of each intersection hypothesis H_I: this test rejects H_I with probability at most α whenever all hypotheses specified in H_I are true.

Closed testing procedure

The simple hypothesis H_j: $\theta_j \leq 0$ is rejected if, and only if, H_I is rejected for every set I containing index j.

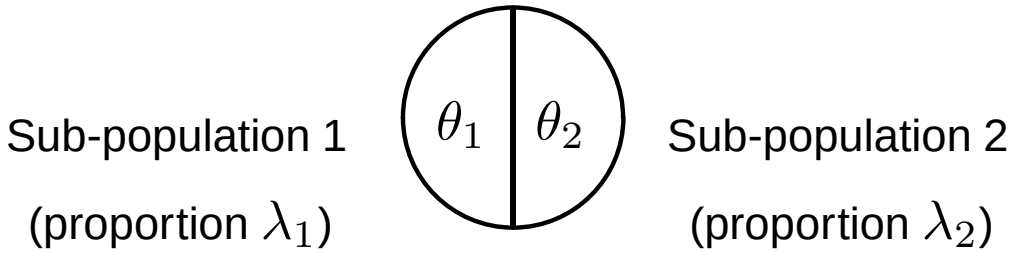
Proof of strong control of family-wise error rate

Let $\tilde{I}$ denote the set of indices of all true hypotheses H_i.

For a family-wise error to be committed, we must reject $H_{\tilde{I}}$.

Since $H_{\tilde{I}}$ is true, $Pr\{\text{Reject } H_{\tilde{I}}\} = \alpha$ and, thus, the probability of a family-wise error is no greater than α.

Enrichment: Example



First, consider a design testing for a whole population effect, $\theta = \lambda_1\theta_1 + \lambda_2\theta_2$.

The design has two analyses and one-sided type I error probability 0.025.

Sample size is set to achieve power 0.9 at $\theta = 20$.

Data in each stage are summarised by a Z-value:

	Stage 1	*Stage 2*	*Overall*
H_0	$Z_{1,0}$	$Z_{2,0}$	$Z_0 = \frac{1}{\sqrt{2}}Z_{1,0} + \frac{1}{\sqrt{2}}Z_{2,0}$

Enrichment: Example

Two stage design, testing for a whole population effect, θ.

	Stage 1	*Stage 2*	*Overall*
H_0	$Z_{1,0}$	$Z_{2,0}$	$Z_0 = \frac{1}{\sqrt{2}} Z_{1,0} + \frac{1}{\sqrt{2}} Z_{2,0}$

Decision rules:

If $Z_{1,0} < 0$ — Stop at Stage 1, Accept H_0

If $Z_{1,0} \geq 0$ — Continue to Stage 2, then

- If $Z_0 < 1.95$ — Accept H_0
- If $Z_0 \geq 1.95$ — Reject H_0

Enrichment: Example

Assume equal sub-population proportions, so $\lambda_1 = \lambda_2 = 0.5$.

Properties of design for the whole population effect, θ:

θ_1	θ_2	θ	*Power for* H_0
20	20	20	0.90
10	10	10	0.37
20	0	10	0.37
0	20	10	0.37

Is it feasible to identify at Stage 1 that θ is low, but it would be worthwhile to switch resources to test a sub-population?

Enrichment: A closed testing procedure

We wish to be able to consider three null hypotheses:

		On rejection, conclude:
H_0:	$\theta \leq 0$	Treatment is effective in the whole population
H_1:	$\theta_1 \leq 0$	Treatment is effective in sub-population 1
H_2:	$\theta_2 \leq 0$	Treatment is effective in sub-population 2

To apply a *closed testing procedure*, we need tests of intersection hypotheses:

H_{01}:	$\theta \leq 0$ and $\theta_1 \leq 0$
H_{02}:	$\theta \leq 0$ and $\theta_2 \leq 0$
$H_{12} = H_{012}$:	$\theta_1 \leq 0$ and $\theta_2 \leq 0$

(Since $\theta = \lambda_1\theta_1 + \lambda_2\theta_2$, it is clear that H_{012} is identical to H_{12}.)

Enrichment: An adaptive design

At Stage 1, if $\hat{\theta} < 0$, stop to accept H_0: $\theta \leq 0$.

If $\hat{\theta} > 0$ and the trial continues:

If $\hat{\theta}_2 < 0$ and $\hat{\theta}_1 > \hat{\theta}_2 + 8$	Restrict to sub-population 1 and test H_1 only, needing to reject H_1, H_{01}, H_{12}, H_{012}.
If $\hat{\theta}_1 < 0$ and $\hat{\theta}_2 > \hat{\theta}_1 + 8$,	Restrict to sub-population 2 and test H_2 only, needing to reject H_2, H_{02}, H_{12}, H_{012}.
Else,	Continue with full population and test H_0, needing to reject H_0, H_{01}, H_{02}, H_{012}.

The same *total* sample size for Stage 2 is retained in all cases, increasing the numbers for the chosen sub-population when enrichment occurs.

Enrichment: An adaptive design

Each null hypothesis, H_i say, is tested in a 2-stage group sequential test.

With Z-statistics Z_1 and Z_2 from Stages 1 and 2, H_i is rejected if

$$Z_1 \geq 0 \quad \text{and} \quad \tfrac{1}{\sqrt{2}} Z_1 + \tfrac{1}{\sqrt{2}} Z_2 \geq 1.95.$$

When continuing with the full population, we use Z-statistics:

	Stage 1	*Stage 2*
H_0	$Z_{1,0}$	$Z_{2,0}$
H_{01}	$Z_{1,0}$	$Z_{2,0}$
H_{02}	$Z_{1,0}$	$Z_{2,0}$
H_{012}	$Z_{1,0}$	$Z_{2,0}$

where $Z_{i,0}$ is based on $\hat{\theta}$ from responses in Stage i.

So, there is no change from the original test of H_0.

Enrichment: An adaptive design

When switching to sub-population 1, we use:

	Stage 1	*Stage 2*
H_1	$Z_{1,1}$	$Z_{2,1}$
H_{01}	$Z_{1,0}$	$Z_{2,1}$
$H_{12} = H_{012}$	$Z_{1,0}$	$Z_{2,1}$

When switching to sub-population 2, we use:

	Stage 1	*Stage 2*
H_2	$Z_{1,2}$	$Z_{2,2}$
H_{02}	$Z_{1,0}$	$Z_{2,2}$
$H_{12} = H_{012}$	$Z_{1,0}$	$Z_{2,2}$

where $Z_{i,j}$ is based on $\hat{\theta}_j$ from responses in Stage i.

The need to reject intersection hypotheses adds to simple tests of H_1 or H_2.

Simulation results: Power of non-adaptive and adaptive designs

				Non-adaptive	***Adaptive***			
	θ_1	θ_2	θ	*Full pop^n*	*Sub-pop 1 only*	*Sub-pop 2 only*	*Full pop^n*	*Total*
1.	30	0	15	**0.68**	0.43	0.00	0.41	**0.85**
2.	20	20	20	**0.90**	0.03	0.03	0.84	**0.90**
3.	20	10	15	**0.68**	0.11	0.01	0.59	**0.71**

Case 1: Testing focuses (correctly) on H_1, but it is still possible to find an effect (wrongly) for the full population.

Case 2: Restricting to a sub-population reduces power for finding an effect in the full population.

Case 3: Adaptation improves power overall, but there is a small probability of restricting to the wrong sub-population.

Enrichment: Example

The rules for sticking or switching to a sub-population can be adjusted, but we cannot eliminate the probability of making an error in these decisions.

This is to be expected since the standard error of interim estimates $\hat{\theta}_1$ and $\hat{\theta}_2$ is 12.3 — much higher than the differences between θ_1 and θ_2 that interest us.

Similar results are found if only one sub-population is specified as a candidate for restricted sampling.

Conclusions:

1. **Switching to a sub-population can improve power. In general, larger sample sizes are needed for accurate sub-population inference.**
2. **This form of *adaptation* goes beyond standard *group sequential designs*.**

Conclusions

- Together, group sequential tests and adaptive designs provide a powerful set of techniques for clinical trial design.
- For early stopping, I would recommend group sequential tests, not adaptive sample size re-estimation (Case Study 1).
- Other applications involving multiple hypotheses need to use adaptive methods (Case Study 2).
- Adaptation can be part of a *pre-planned* and *pre-tested* trial design
  - does it do what is needed?
  - does it do so efficiently?

  "Flexible adaptation" brings risks as well as opportunities.