Discussion of

Adaptive increase in sample size when interim results are promising: A practical guide with examples

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(Statistics in Medicine 2011)

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http://people.bath.ac.uk/mascj

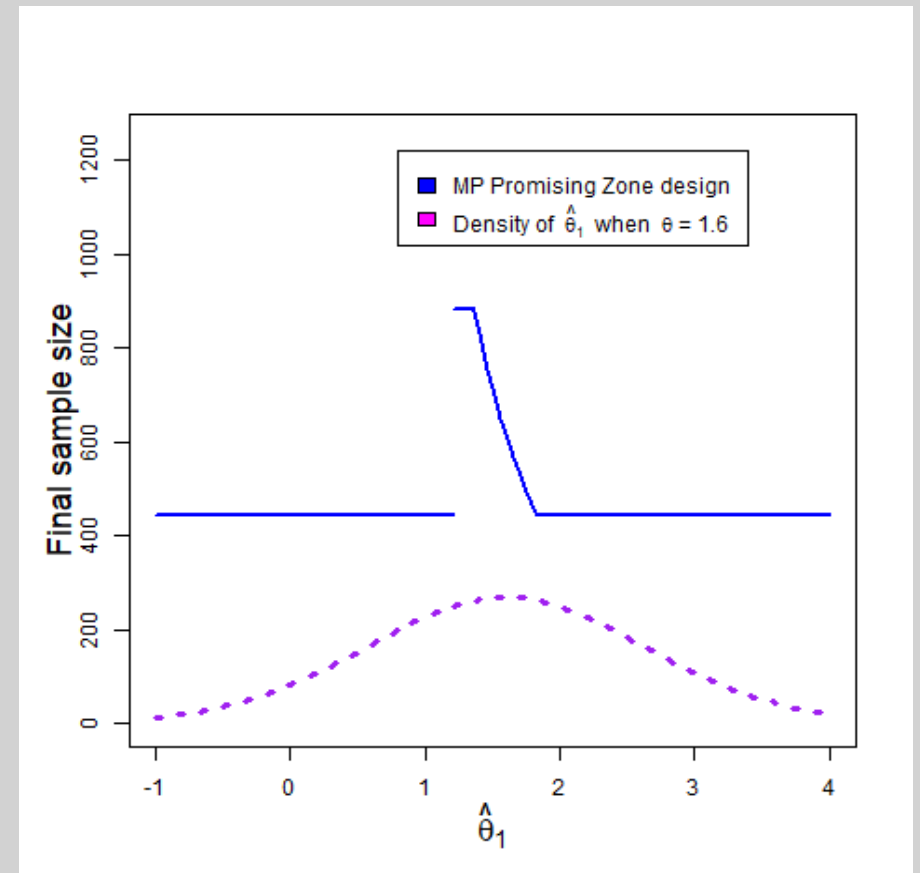# The Sample Size Re-estimation (SSR) approach

Start with an initial specification of

- Type I error rate α

- Power $1-\beta$ when treatment effect $= \delta_0$

Hence, define a fixed sample or group sequential design.

But, at an interim analysis, re-visit the power requirement and, if appropriate, change the study design.

An SSR rule
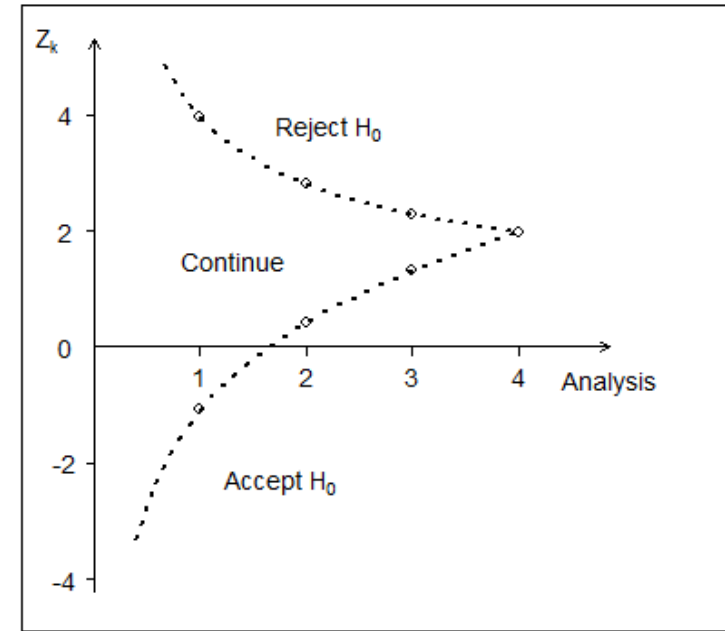
Group Sequential Tests (GSTs)

Fix

- Type I error rate α

- Power $1-\beta$ when treatment effect $= \delta$

- Set maximum sample size

- Set number of interim analyses

Hence, define

A stopping boundary or
An error spending rule.

Stopping boundary for a GST

Sample Size Re-estimation (SSR) vs Group Sequential Tests (GSTs)

SSR Methods – "Start small and ask for more"

Start a trial with an initial target sample size.

Examine interim data: if appropriate, increase the sample size.

Use a combination test, say, to protect the type I error rate.

GSTs

Plan the trial with a maximum sample size and early stopping rule.

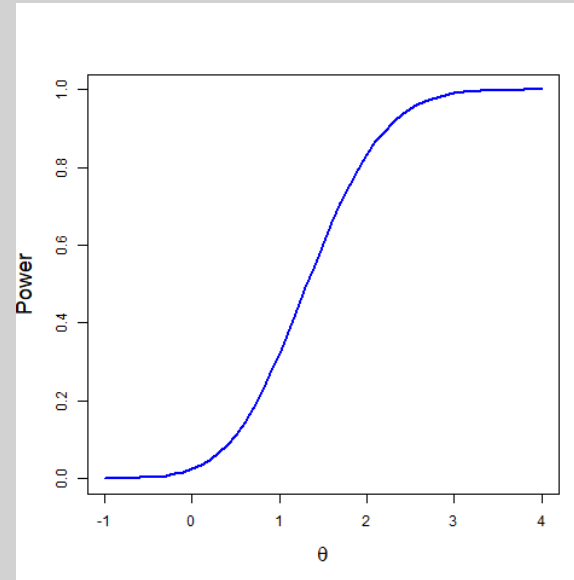In both cases, the data determine the number of subjects observed.

Comparing GST and SSR designs

In both types of design, the final sample size is determined by the observed data.
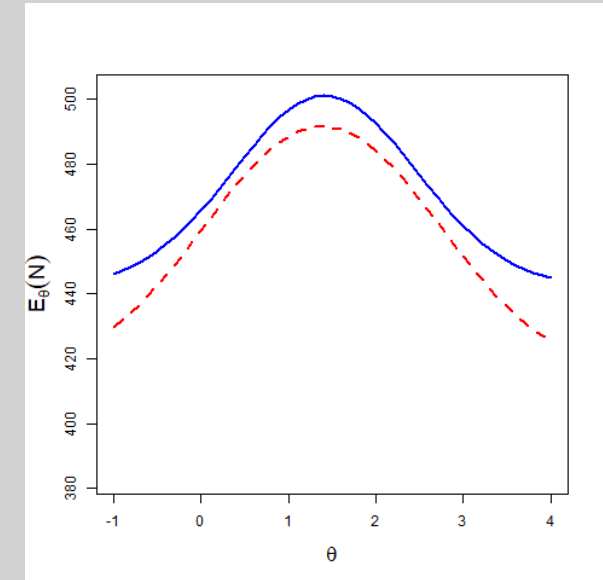
Once a design is fully specified, we can compute its:

- Power as a function of treatment effect Θ

- E(Sample size) as a function of Θ

Power curves

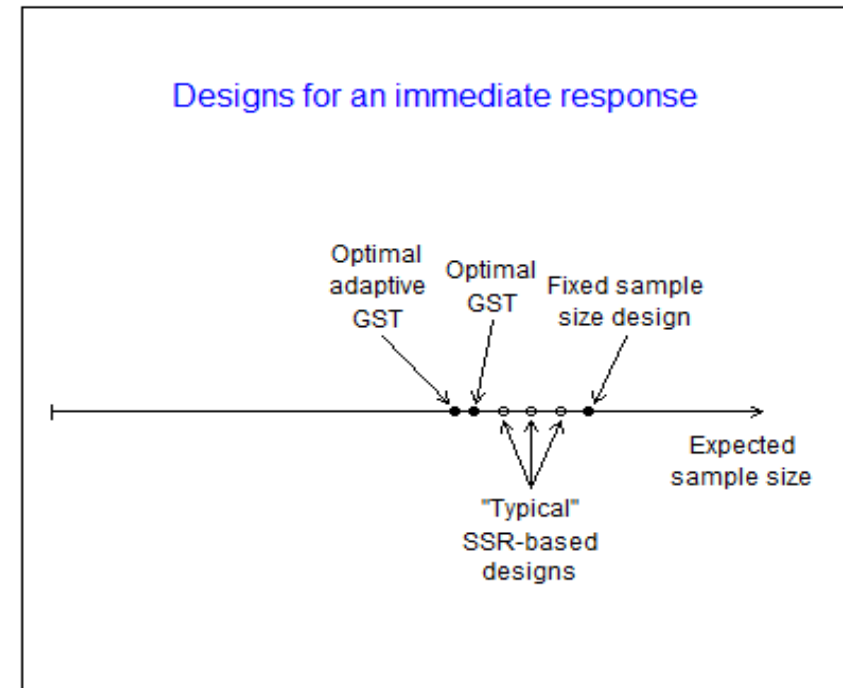**Expected sample size functions**

The two designs have almost identical power curves.

The red design has lower expected sample size for all Θ.

Comparing GST and SSR designs

CJ and Bruce Turnbull (2003, 2006, 2006) reported comparisons which showed traditional GSTs to have superior performance to a variety of SSR-based designs.

When the most efficient forms of each type of design are compared, the SSR designs have a slight advantage – but they may be challenging to implement.

Efficiency of GSTs and SSR-based designs

Designs for an immediate response

Optimal adaptive GST · Optimal GST · Fixed sample size design · Expected sample size · "Typical" SSR-based designs
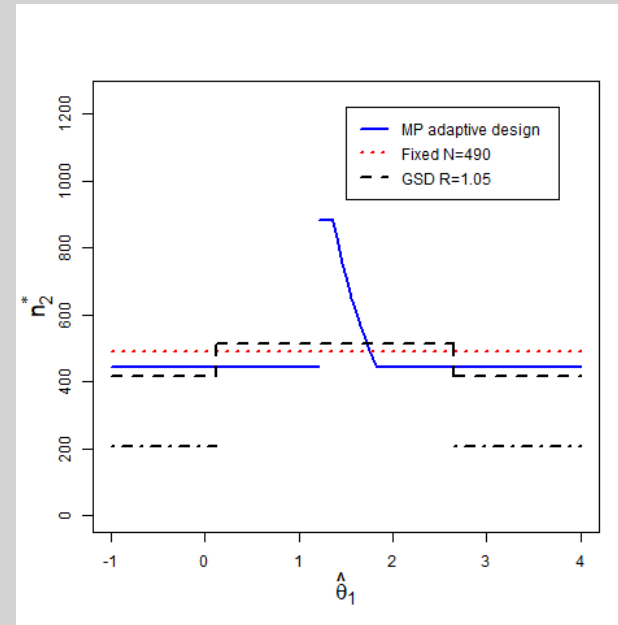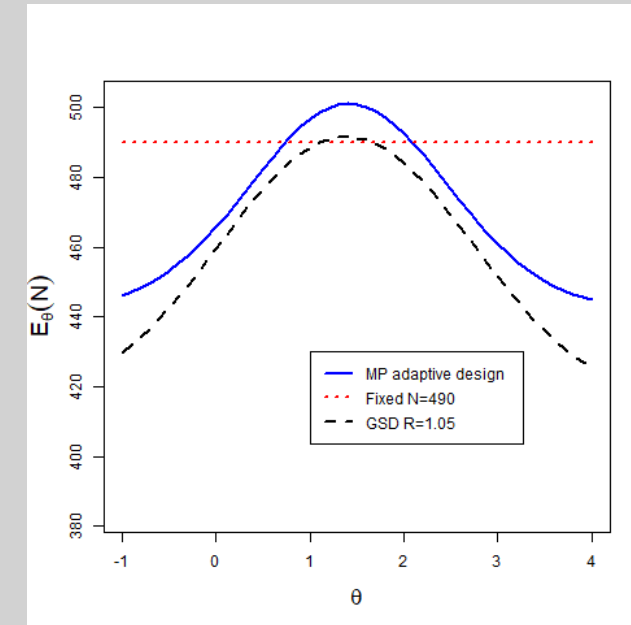
Mehta and Pocock (2011): Example 1

CJ and BWT (2015) assessed the Promising Zone design and found superior performance in

- A 2-stage GST that is charged for but does not use "pipeline" data,

- A fixed sample design.

Sample size rules

Expected sample size functions.

GST vs SSR when there is a delayed response

Lisa Hampson and CJ (2013) defined efficient GSTs for studies with a delayed response (DRGSTs). They reached similar conclusions about the relative efficient of DRGSTs and SSR-based designs.

If the most efficient designs are compared, SSR designs have a slight advantage – but may be challenging to implement.

Efficiency of GSTs and SSR-based designs
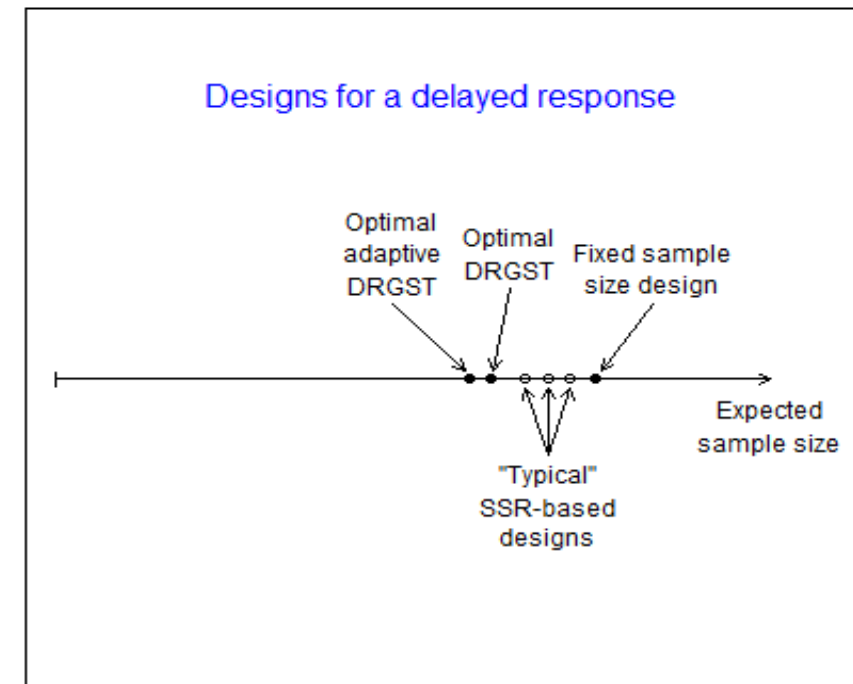
Mehta and Pocock (2011): Example 1

CJ and BWT (2015) recommended modifications to improve performance of the Promising Zone design.

- Use a combination test, not the Chen, DeMets & Lan construction

- Apply a consistent "Rate of exchange" between sample size and conditional power

- Have a lower maximum sample size

Recent developments in Promising Zone designs

Hsiao, Liu and Mehta (2019) published new versions of the Promising Zone design.

They treat JT's design as the "gold standard".

Now the Promising Zone design is efficient
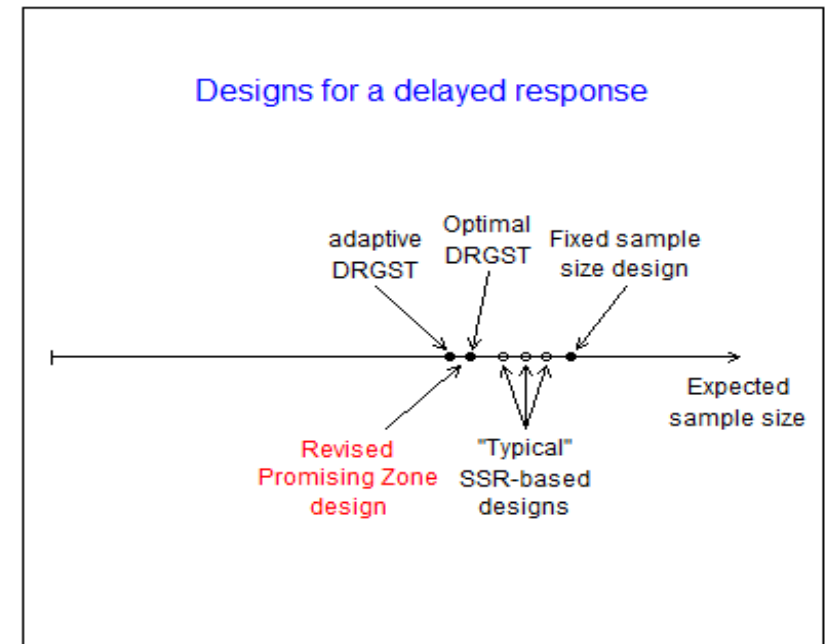
References

Jennison and Turnbull (2003, *Statistics in Medicine*)

"Mid-course sample size modification in clinical trials based on the observed treatment effect."

Jennison and Turnbull (2006, *Biometrika*)

"Adaptive and non-adaptive group sequential tests."

Jennison and Turnbull (2006, *Statistics in Medicine*)

"Efficient group sequential designs when there are several effect sizes under consideration."

Hampson and Jennison (2013, *J. Royal Statistical Society, Series B*)

"Group sequential tests for delayed responses."

Jennison and Turnbull (2015, *Statistics in Medicine*)

"Adaptive sample size modification in clinical trials: Start small then ask for more?"

Hsiao, Liu and Mehta (2019, *Biometrical Journal*)

"Optimal promising zone designs."