

# ADAPTIVE CLINICAL TRIALS INCORPORATING TREATMENT SELECTION AND EVALUATION: METHODOLOGY AND APPLICATIONS IN MULTIPLE SCLEROSIS

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Multiple Sclerosis Society

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# Outline

1. MS background
2. Seamless adaptive design in MS
3. Simulation study
  - Example trial design
  - Comparison to conventional trial
4. Conclusions
5. References

# 1. MS background

**Multiple Sclerosis (MS)** is a condition of the central nervous system (the brain and spinal cord), which controls the body's actions and activities, such as movement and balance.

**Types of MS:** 4 types of MS (BMS, RRMS, SPMS and PPMS)

## **Outcomes:**

- *Disability (long-term):* EDSS score, MSFC score and MSIS-29 score
- *MRI scan (short-term):* T2-lesion vol., “black holes” vol., Cordon Atrophy, T1/T2, number of enhanced lesions, etc.

# 1. MS background

## Traditional route:

- Phase I (safety of the drug) --2 years
- Phase II (with substitute outcome, which takes less time to see if there is an effect)-- 1-2 years
- Phase III (to see an effect in a clinically relevant aspect) --- 2-3 years

*>=10 years to get a drug licensed and available to patients*

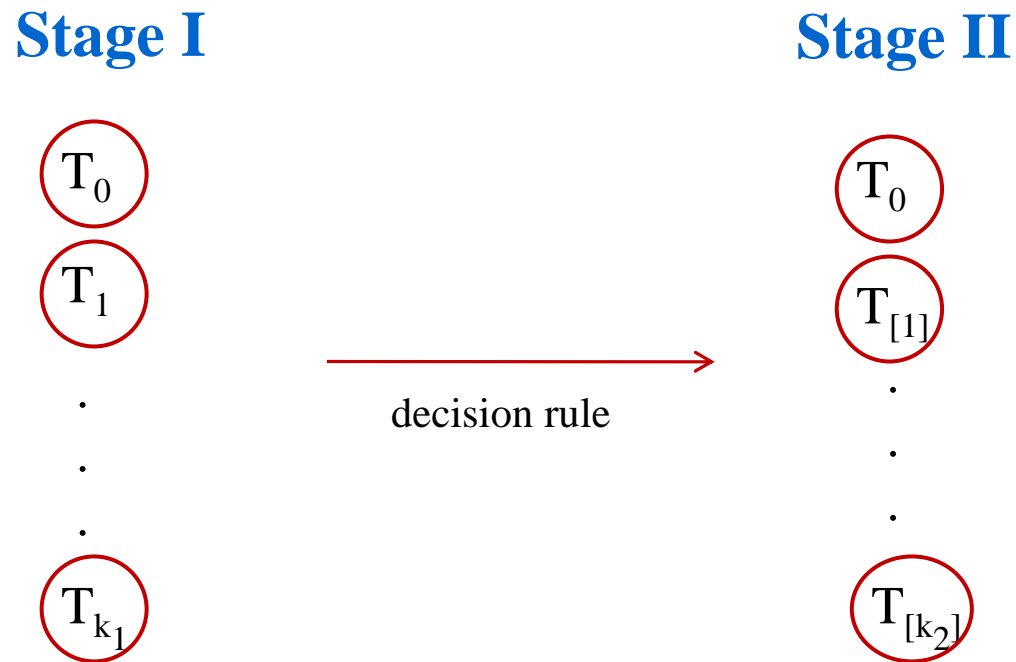
## Treatment:

At present there are no drugs which successfully slow or stop disease progression in MS although there are a number of candidates available simultaneously.

*There is a need for testing them in a single study*

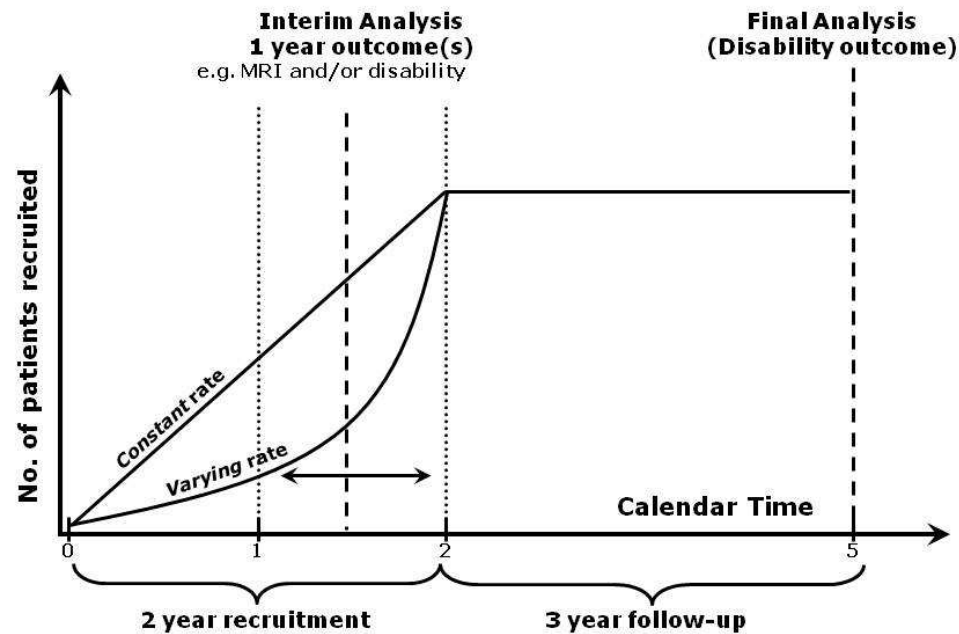
## 2. Seamless adaptive design in MS

*Focus on methodology for comparison of a number of distinct experimental treatments with a common control in a single study with two distinct stages (Bretz et al.; 2006)*



$T_0$ : control treatment ;  $T_1, \dots, T_{k_1}$ : experimental treatments;  
 $T_{[1]}, \dots, T_{[k_2]}$ : selected experimental treatments

## 2. Seamless Adaptive design in MS



### *Short-term outcomes (MRI endpoints):*

- Change on T2 lesion load, black holes load, brain atrophy at 1 year from baseline

### *Long-term outcomes (Disability endpoint):*

- Change in EDSS at 3 years from baseline, Time to half-point change in EDSS score

## 2. Seamless Adaptive design in MS

### Treatment selection:

- **Combination test (Bauer and Kieser, 1999)** combines stagewise p-values and applies the closed testing principle (*Marcus et al, 1976*) to control the overall test size across multiple hypothesis

*Closed testing principle:*

- Elementary null hypothesis:  $H_i: T_i = T_0$  ( $i=1, \dots, k$ )
- Intersection Hypotheses:  $H_I = \cap_{i \in I} H_i$  ( $I \subseteq \{1, \dots, k\}$ )
- **Reject  $H_i$  if all  $H_I$  are rejected at level  $\alpha$  with  $i \in I$**
- Procedure controls familywise type I error rate (FWER) in the strong sense

## 2. Seamless Adaptive design in MS

*Combination function:*

- Stagewise p-values (*Dunnett, 1955*):

$$p_i = \int_{-\infty}^{+\infty} [\Phi(\sqrt{2}Z_{\max,i} + x)]^{k_i} \phi(x) dx; i = 1, 2$$

$Z_j$  (standardized test statistic);  $Z_{\max,i} = \max_{j \in \{1, \dots, k_i\}} Z_j$

- Weighted inverse normal method (*Lehmacher and Wassmer, 1999*):

$$C(p_1, p_2) = 1 - \Phi(w_1 \Phi^{-1}(1-p_1) + w_2 \Phi^{-1}(1-p_2)); 0 < w_i < 1$$

We reject the null hypothesis if  $C(p_1, p_2) \leq \alpha$

## 2. Seamless Adaptive design in MS

### Methodology:

#### *Begin:*

- k treatments and 1 control (placebo) with equal sample size

#### *Interim Analysis:*

- Treatment comparison using one decision rule (fixed, variable and futility) based on a short-term outcome.
- Trial can stop for futility or continue with one or more treatments are selected into stage 2

#### *Final Analysis:*

- Analysis of disability endpoint (long-term outcome).
- Combining data from the two stages and controlling the FWER

### 3. Simulation Study

**Purpose:** *To investigate a range of potential options for the trial design including when to carry out the interim analysis ( $n_1$ ); sample sizes per arm at stage 2 ( $n_2$ ); measure(s) to decide go/no go at interim analysis*

**Methods:** *Simulation of virtual trials based on realistic assumptions about the distributions of the endpoints, effect sizes, correlations. etc., obtained from available data, clinical sources and literature review*

### 3. Simulation Study

#### Evaluation of designs options:

(Benda et.al., 2009)

- *Choice of design options*

Sample size, timing of interim analysis, decision rule for dropping arms

- *Range of assumptions*

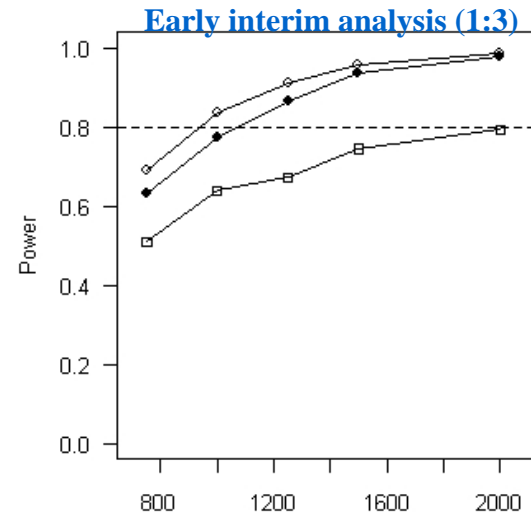
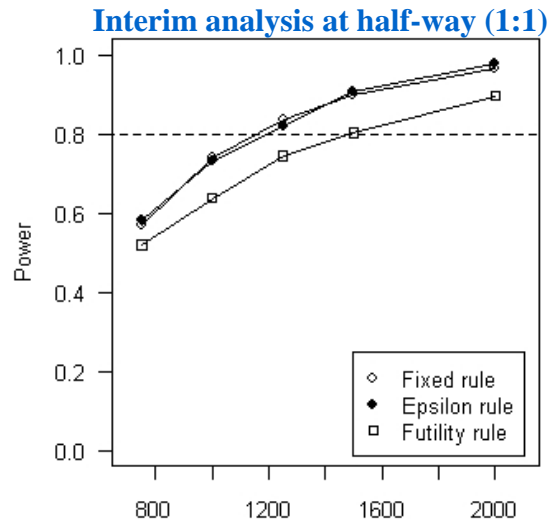
Treatment effect on primary outcome treatment effect on short-term outcome

- *Simulate to estimate*

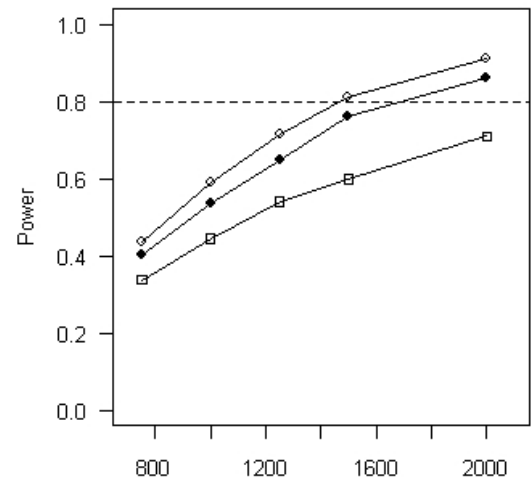
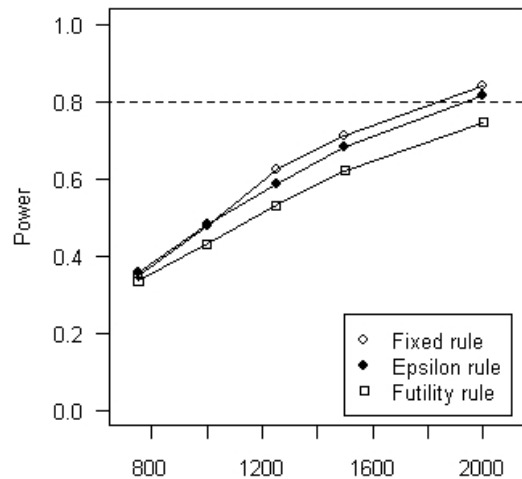
Power to reject at least one false  $H_0$  selection probabilities

Simulation based on asymptotically normal test statistics. We conducted 10,000 simulations under each 28,800 different scenarios

### 3. Simulation Study (example trial design)



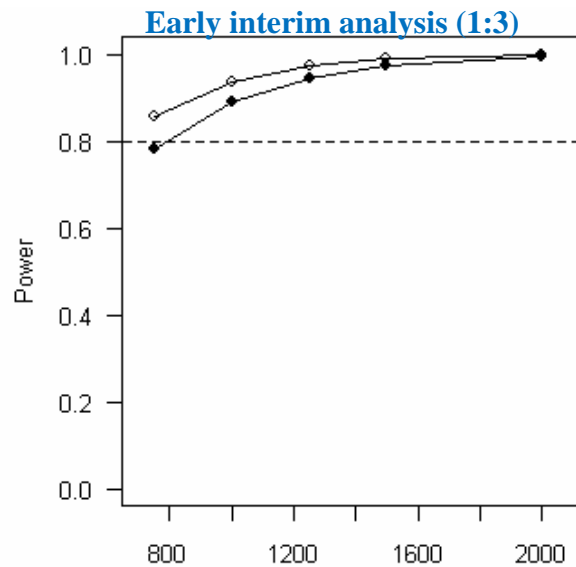
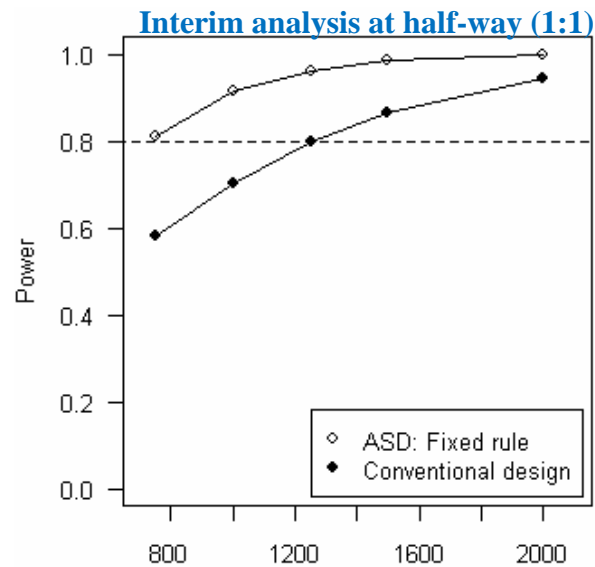
$\Delta = 0.25$



$\Delta = 0.20$

### 3. Simulation study (Comparison to conventional designs)

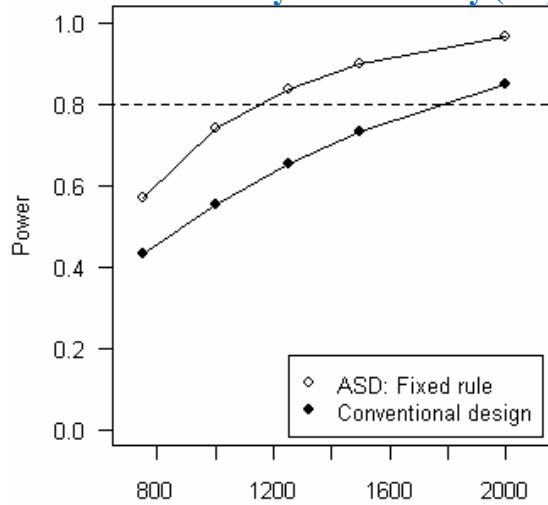
Suppose we have control and 2, 4 and 6 treatments, a treatment effect of  $\Delta=0.25$  and one decision rule for seamless adaptive design.



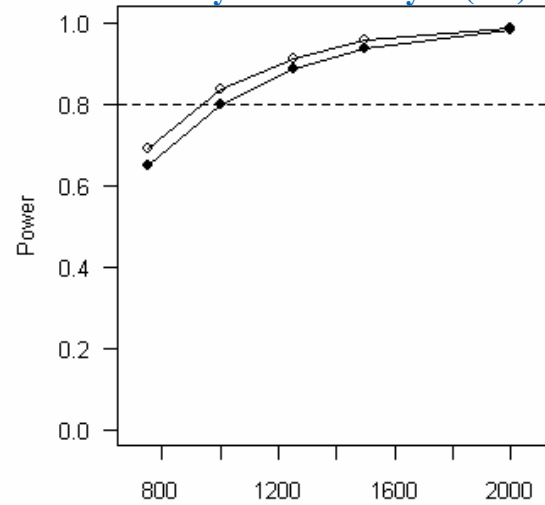
**2 treatments**

*based on 10,000 simulations*

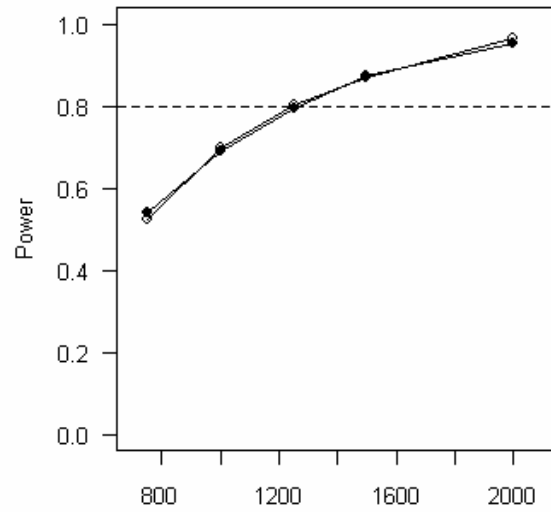
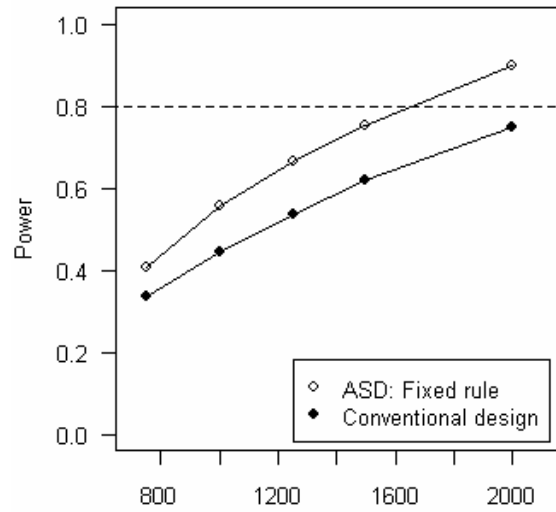
Interim analysis at half-way (1:1)



Early interim analysis (1:3)



**4 treatments**



**6 treatments**

## 4. Conclusions

- Adaptive seamless design (ASD) approach has proved to be effective in other clinical research areas, but this is the first occasion that this approach has been suggested, developed and shown to work for progressive MS.
- The ASD approach used here, that combines the “traditional” phase II and phase III stages of a clinical development programme into a single trial, is more efficient than the traditional approach. It provides a sample size saving

## 5. References

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