AliraHealth

The Sequential **Parallel Comparison Design** for Reducing Placebo Response

A Two-Stage Adaptive for Enrichment of Placebo Non-Responders

Introduction

In the past several decades, it has been recognised that increasing spending of clinical research does not reflect an increase of the success rate of drug development. Moreover, the pharmaceutical industry has realised that the classical structured clinical trials do not offer enough flexibility to make use of continuously emerging knowledge that is generated as trial progresses.
One of the innovations strongly recommended by the authorities is the use of adaptive designs in clinical trials and the potential use of Bayesian approach in clinical research. Although planning such trials comes at the cost of additional operational complexity, adaptive designs offer the benefit of flexibility to update trial design and objectives as data accrue.
In this white paper, we will explore a two-stage adaptive design called the "**Sequential Parallel Comparison Design**" for enrichment of placebo non-responders.

Background

The placebo response has progressively increased over time in clinical trials for psychiatric disorders. High placebo response reduces the ability of trials to detect the treatment effect, resulting larger rates of failed and negative trials. The sequentially parallel comparison design
(SPCD) invented in 2003 at Massachusetts General Hospital by Dr Fava and Dr Schoenfeld (Fava et al., 2003) is an effective approach for reducing both the high placebo response and the required sample size. Due to the two-stage design, the inference procedure of the SPCD is not straightforward. **The aim of this white paper is to walkthrough the computation of a P value, a confidence interval and an estimate of the overall treatment effect at the termination of the two-stage trial.**

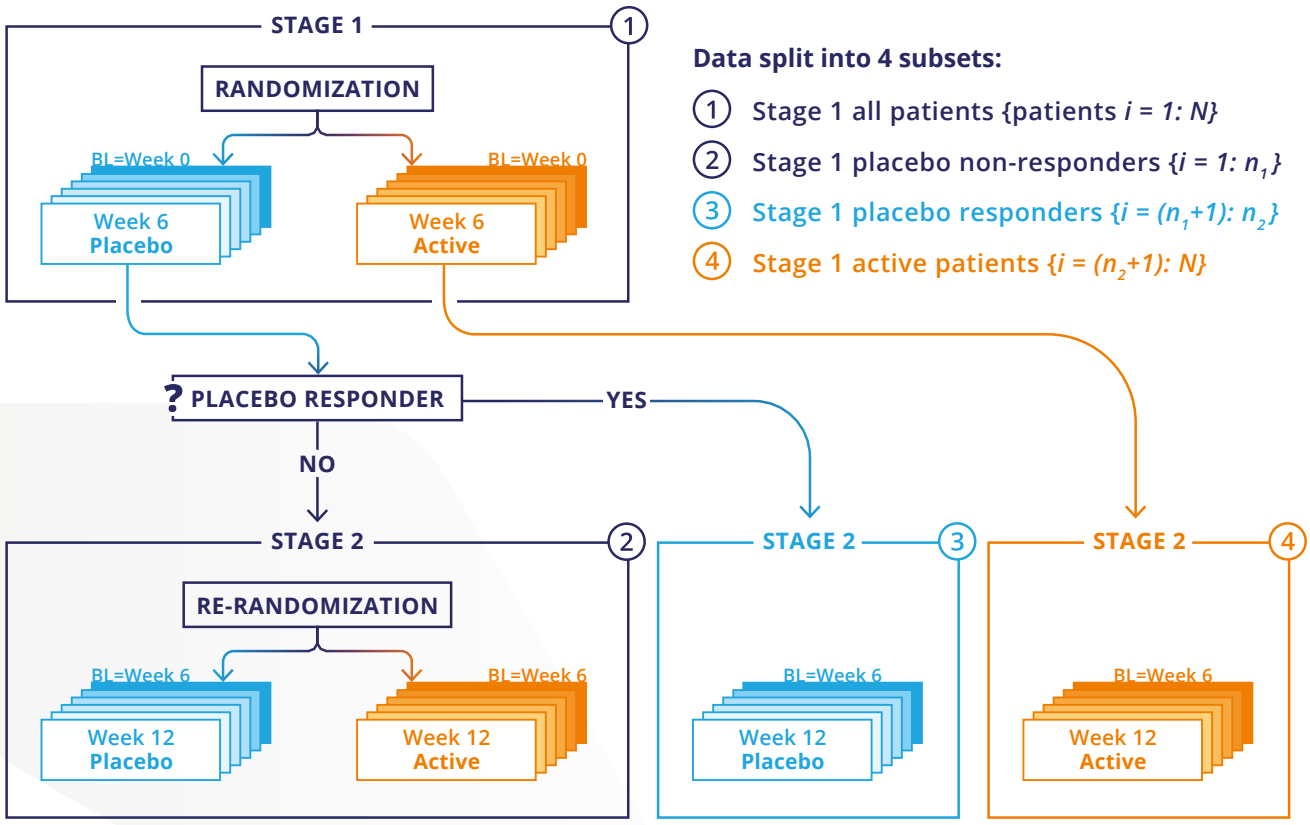
Description of the SPCD

The basic structure of the SPCD contains two consecutive double-blind treatment stages. In the first stage, often more patients are allocated to the placebo arm to ensure enough numbers of placebo non-responders are identified at the end of Stage 1. In the second stage, the placebo non-responders are re-randomized in equal numbers to placebo and active drug arms. Overall, this process results in four data subsets (Figure 1).

The outcome measure can be continuous, binary, time-to-event or other types, as long as placebo responder and non-responder is definable.

Model ①	$CHG_{i1} = \beta_{01} + \beta_{11}BASE1 + \beta_{21}TREAT + e_{i1}$	for patients $i = 1: N$
Model ②	$CHG_{i2} = \beta_{02} + \beta_{12}BASE2 + \beta_{22}TREAT + e_{i2}$	for patients $i = 1: n_1$
Model ③	$CHG_{i3} = \beta_{03} + \beta_{13}BASE2 + e_{i3}$	for patients $i = (n_1+1): n_2$
Model ④	$CHG_{i4} = \beta_{04} + \beta_{14}BASE2 + e_{i4}$	for patients $i = (n_2+1): N$

To demonstrate how the SPCD is analysed, consider an SPCD with two 6-week stages and a change from baseline to 6 weeks continuous outcome with predictors: treatment (active, placebo) and baseline covariate. A separate (analysis of covariance) model is specified for each data subset, where *TREAT* is the treatment indicator, *BASE1* as baseline value at start of Stage 1 (Week 0), and *BASE2* as baseline value at start of Stage 2 (Week 6).



- Figure 1: SPCD with two 6-week stages -

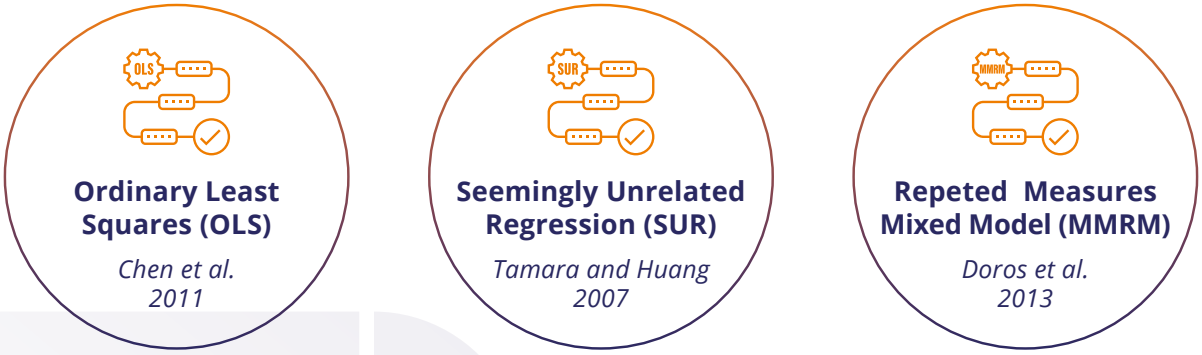
Overall Treatment Effect

The overall treatment effect is estimated using only inference (model parameters) from the Stage 1 and Stage 1 placebo non-responders.
The overall treatment effect is the weighted average of the estimated treatment effects in Stage 1 all patients and Stage 1 placebo non-responders: $w\hat{\beta}_{21} + (1\text{-}w)\hat{\beta}_{22}$, where w is a prespecified weight ($0 \le w \le 1$) and $\hat{\beta}_{21}$, $\hat{\beta}_{22}$ are model parameters representing stage-specific treatment effects.

Since the $1{:}\ n_1$ patients contributing data to the estimation in ① also contribute data to the estimation in ②, the errors (e_{i1}, e_{i2}) corresponding to data from the same patients would be correlated. The variance of the overall treatment effect depends on how the correlation between Stage 1 and Stage 2 measurements from the same patients are modelled.

Analysis Methods

Three methods have been proposed for analysis of SPCD trials:



The OLS method assumes the error terms are independent (correlation $\rho=0$). The SUR method estimates the correlation between the same patients appearing in both stages as $\hat{\rho}$.

$$\textbf{OLS: } \begin{pmatrix} e_{i1} \\ e_{i2} \end{pmatrix} \sim N\begin{pmatrix} \sigma_1^2 & 0 \\ & \sigma_2^2 \end{pmatrix}; \qquad \textbf{SUR: } \begin{pmatrix} e_{i1} \\ e_{i2} \end{pmatrix} \sim N\begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ & \sigma_2^2 \end{pmatrix}$$

MMRM can account for more complex study designs, such as using all the repeated measurements collected within each stage, have a range of correlation structures to choose from and incorporate random effects. In the presence of MAR missingness in the outcome data, Chen (2011) demonstrated MMRM had larger power and accurate estimation of the treatment effect compared to OLS and SUR with single or multiple imputation.

Doros et al. (2013) proposed an MMRM including data of all 4 subsets, where the data models of Stage 1 placebo responders ③ and Stage 1 active patients ④ contribute to estimation of the common variance-covariance parameters (σ_1^2, σ_2^2, σ_{12}), but whose main effects remain separately modelled and are not used for inference of the overall treatment effect.

$$\textbf{MMRM:} \quad \begin{pmatrix} e_{i1} \\ e_{i2} \end{pmatrix} \sim N \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ & \sigma_2^2 \end{pmatrix}; i = 1{:}n_1$$

$$\begin{pmatrix} e_{i1} \\ e_{i3} \end{pmatrix} \sim N \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ & \sigma_2^2 \end{pmatrix}; i = (n_1{+}1){:}n_2$$

$$\begin{pmatrix} e_{i1} \\ e_{i4} \end{pmatrix} \sim N \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ & \sigma_2^2 \end{pmatrix}; i = (n_2{+}1){:}N$$

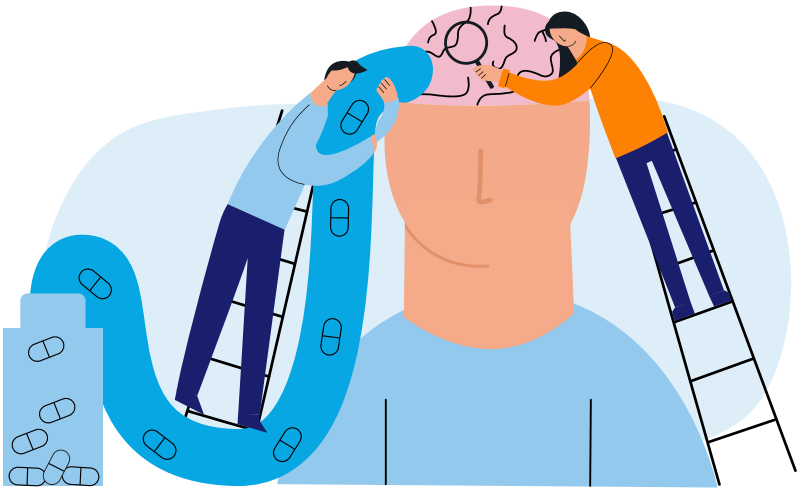
Variance of the Overall Treatment Effect

The variance of the overall treatment effect based on the OLS method is simply the variance of the sum two independent random variables:method is simply the variance of the sum two independent random variables:

$$w^2 Var(\hat{\beta}_{21}) + (1\text{-}w)^2 Var(\hat{\beta}_{22})$$

Whereas, for the MMRM and SUR methods, the expression would be for the sum of two correlated random variables:

$$w^2 Var(\hat{\beta}_{21}) + 2w(1\text{-}w) Cov(\hat{\beta}_{21}, \hat{\beta}_{22}) + (1\text{-}w)^2 Var(\hat{\beta}_{22})$$



where $Var(\beta_{21})$, $Var(\beta_{22})$, $Var(\beta_{21}, \beta_{22})$ are the model estimated variances and covariance of stage-specific treatment effects.
Asymptotic confidence intervals for the overall treatment effect can be constructed using these variance estimates.

Hypothesis Testing

The null and alternative hypothesis structure of the overall treatment effect is stated in terms of the stage-wise treatment effects without declaring the prespecified weight w. The null is an intersection ('and') and the alternative is a union ('or'):

$$\textbf{H0: } \{\beta_{21}=0 \text{ and } \beta_{22}=0\} \quad \text{vs} \quad \textbf{H1: } \{\beta_{21}\neq 0 \text{ or } \beta_{22}\neq 0\}$$

To establish efficacy of the active drug, the combination test statistic Z is used: $Z=\sqrt{v}Z_1+\sqrt{1-v}Z_2$

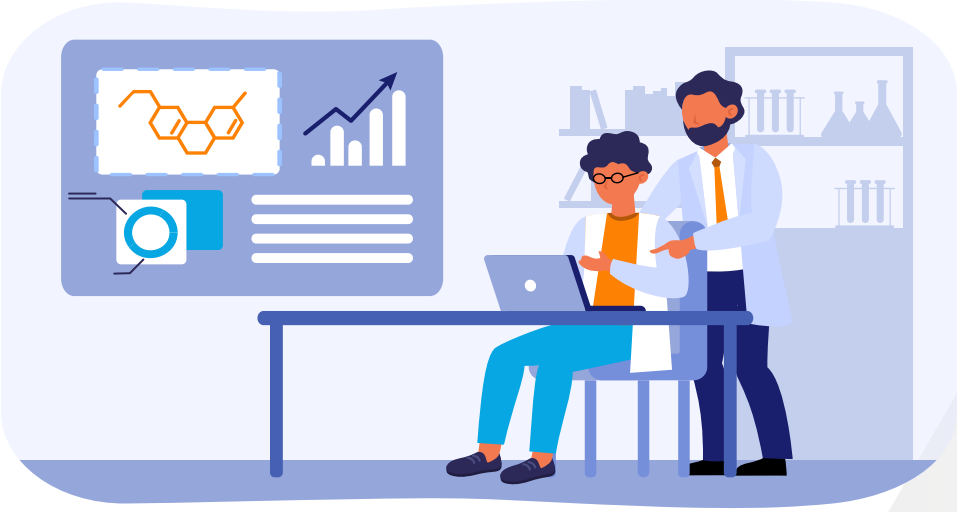
where v is a prespecified weight ($0\leq v\leq 1$) and Z_1, Z_2 are asymptotically normal test statistics in the individual data models ① and ② :

$$Z_1=\frac{\hat{\beta}_{21}}{\sqrt{var(\beta_{21})}} \qquad Z_2=\frac{\hat{\beta}_{22}}{\sqrt{var(\beta_{22})}}$$

If the weight is re-expressed as $v=\frac{w\beta_{21}+(1-w)\beta_{22}}{w^2Var(\beta_{21})+(1-w)^2Var(\beta_{22})}$, a more intuitive formula of the same test statistic resolves as the ratio of the overall treatment effect and its OLS standard error, sometimes referred to as the overall test statistic:

$$Z=\frac{w\hat{\beta}_{21}+(1-w)\hat{\beta}_{22}}{\sqrt{w^2Var(\hat{\beta}_{21})+(1-w)^2Var(\hat{\beta}_{22})}}$$

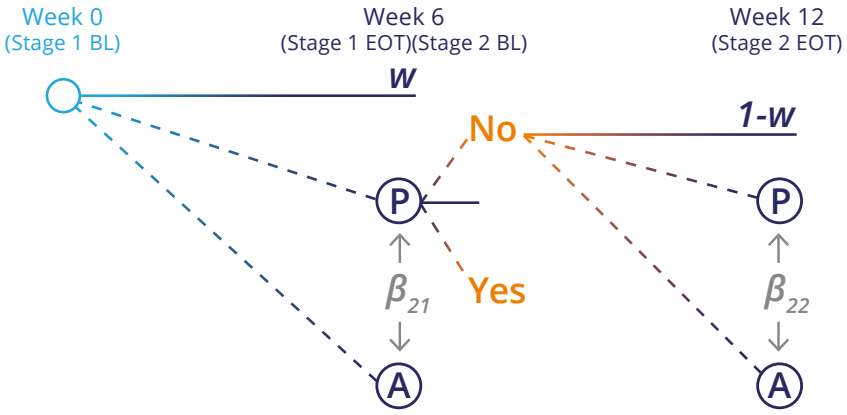
Then the two-sided P value is calculated as: $p=2\times(1-\Phi\{abs(Z)\})$.



For continuous, binary, time to event and count outcomes, the stage-wise test statistics and estimated treatment effects, after standardization, are asymptotically bivariate normal and are uncorrelated under the null hypothesis (Chen et al. 2011, Silverman et al. 2018). Therefore, this SPCD Z statistic based on the OLS variance can be used for hypothesis testing even in the case of continuous outcome comparisons estimates using MMRM or SUR.

Choice of Weight

There is no agreed process for deciding the prespecified value of w (or v). The default choice might be considered the equal weighting of both stages, w=0.5. Or to choose w less than 0.5 since intuitively we expect the treatment effect size at the end of Stage 2 is greater than at end of Stage 1. Or to choose w more than 0.5 since it is intuitive to put more weight on the larger sample size of the Stage 1 data.



- Figure 2: Treatment effect diagram -

Doros (2013) selected w to be inversely proportional to the variance. For 2:1 placebo:active allocation in Stage 1, $w = 4/(4+3p_{NR})$, where p_{NR} is the expected probability of placebo nonresponse. Silverman 2018 selected w based on prior knowledge of treatment effects and their variability in the 2 stages of SPCD, $w = \frac{Var(\beta_{22}) / \beta_{22}}{Var(\beta_{21}) / \beta_{21} + Var(\beta_{22}) / \beta_{22}}$, where β and $Var(\beta)$ are the expected treatment effects and their variances.

Closing Summary

The SPCD is an effective approach that reduces placebo response and thus enhances the signal detected at Stage 2 as well as in the overall treatment effect. The combination test statistic can be used in conjunction with most outcome types and its construction is accessible using the parameters estimates and standard errors from each stage-wise analysis. The validity of this analytical method has been proven to preserve the type 1 error, maintain adequate power and accurately estimate the treatment effect.

In addressing the problem of impaired signal detection due to high placebo response, the SPCD has improved the success rate of clinical trials in psychiatric disorders, and along with it the positive impact on reducing time and cost of R&D.

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