

Sequential Parallel Comparison Design - Summary

Introduction

The Sequential Parallel Comparison Design (“SPCD”) is a novel clinical trial design which can reduce the detrimental impact of placebo response and thereby allows a trial to (1) have a smaller “ n ”, without loss of power, or (2) achieve higher power if the n of a conventionally designed trial is used. With SPCD, a reduction of “ n ” of 20%-40%, or an increase in power of 10-20 percentage points or more, is achievable.

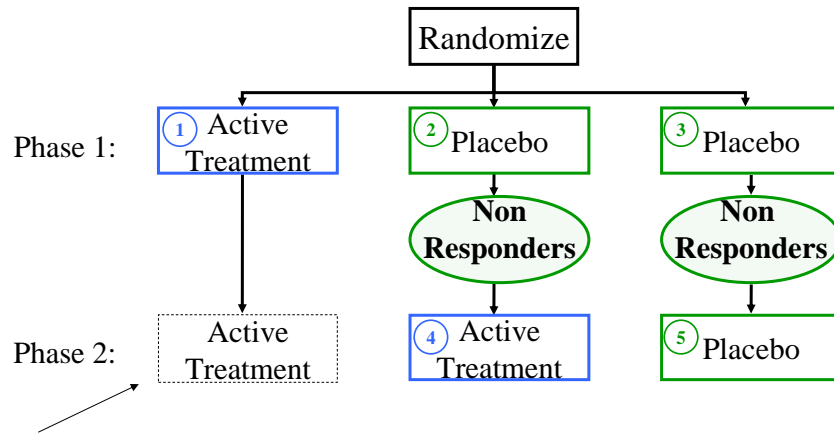
In 2010, Xiaohong Huang of Sanofi-Aventis and Roy Tamura of Eli Lilly wrote their second article about SPCD, in which they said: “Several authors (Fava 2003; Laughren 2007) have argued that in difficult psychiatric diseases such as depression and anxiety, the standard clinical trial design needs substantial improvement. We agree with this assessment and feel that implementation of designs such as the sequential parallel design is essential in the path toward this improvement.” (Huang and Tamura, 2010).

Description of SPCD

An SPCD trial involves two phases of treatment. Only the non-responders to placebo during Phase 1 are included in the efficacy analysis of Phase 2. Other patients, however, enter Phase 2 for blinding purposes and collection of data, but they are not used in the efficacy analysis. Therefore, some data from both phases are utilized for the efficacy analysis, with all patients utilized at least once, and some patients utilized twice.

Phase 1 of an SPCD trial is aimed at: (1) comparing drug and placebo, as in a conventionally designed single phase trial (with the expectation that drug-placebo differences will be of "normal size") and (2) generating a cohort of placebo non-responders. Phase 2 is aimed at comparing drug and placebo, as in a conventionally designed single phase trial design, but utilizing only individuals who were placebo non-responders in Phase 1 (with the expectation that drug-placebo differences will be greater in Phase 2).

Below is a diagram of one typical format of an SPCD trial:



- This group is included in Phase 2 for the purpose of blinding
- **Efficacy analysis pools results of the 5 groups in numbered boxes**

A more detailed diagram is shown in Appendix A

SPCD is a design which can, for example, include the use of an “active comparator” during a trial, or the study of therapy which is adjunctive to a "standard of care" therapy. An SPCD trial does not involve a placebo lead-in period.

Statistical Power of SPCD

The table below illustrates, in two scenarios, the additional statistical power provided by SPCD. The figures in the table are calculated by Anastasia Ivanova, a consultant to RCT who is a biostatistician and member of the faculty at the University of North Carolina. Professor Ivanova utilized a score test which yields results consistent with calculations obtainable by using the linear combination test set forth in the article published in 2003 that first described SPCD (Fava et al, 2003; Erratum, 2004).

The magnitude of the benefit of utilizing SPCD depends upon the response rates to active treatment and placebo. Focusing on Example 1 (below), if a sponsor of a trial is seeking a power of 80%, and believes that in a conventional trial the response rate to active treatment will be 60% and the response rate to placebo will be 50%, then a total sample size, *n*, of 776 is required. If, however, an SPCD trial is conducted with the same intended power of 80%, and the sponsor believes that in Phase 1 the response rate to active treatment and placebo will be the same as in a conventional trial (i.e., 60% and 50%), but that in Phase 2 the response rate to active treatment will be 50% and the response rate to placebo will be 30%, then a total sample size, *n*, of only 396 is required.

As shown in table, for any particular n used in a trial, SPCD can offer significantly greater power than a conventionally designed trial.

SPCD Statistical Power - Examples

Example 1			Response Rate		
			Active Treatment	Placebo	Difference
Phase 1			60%	50%	10%
Phase 2			50%	30%	20%
			2X		
Total <i>n</i>			Power		
Power	Conventional Parallel Design	SPCD	Total <i>n</i>	Conventional Parallel Design	SPCD
70 %	610	312	400	52 %	81 %
80 %	776	396	500	61 %	88 %
90 %	1038	531	600	69 %	93 %

Example 2			Response Rate		
			Active Treatment	Placebo	Difference
Phase 1			50%	30%	20%
Phase 2			30%	10%	20%
			1X		
Total <i>n</i>			Power		
Power	Conventional Parallel Design	SPCD	Total <i>n</i>	Conventional Parallel Design	SPCD
70 %	148	91	100	53 %	75 %
80 %	186	115	150	71 %	90 %
90 %	248	153	200	82 %	96 %

In the tables above, sample sizes and power for the parallel design and SPCD are computed based on the asymptotic formulae for corresponding two-sided score tests with one degree of freedom, and with a type I error rate of 0.05. The parallel design is assumed to have active treatment and placebo groups of equal size. SPCD is assumed, in phase 1, to have an active treatment group and two placebo groups, with patients allocated according to a 3:2:2 ratio.

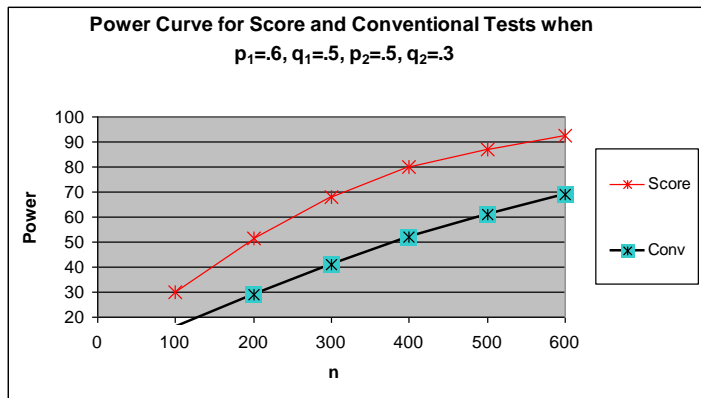
Analysis by Biostatisticians at Sanofi-Aventis and Eli Lilly

Xiaohong Huang of Sanofi-Aventis and Roy Tamura of Eli Lilly have presented the graphs below which show illustrative cases in which the power of SPCD is substantially higher than the power derived from a conventional trial design.

Power Curves – Case 1

“Score” = SPCD “Conv” = Conventional Design

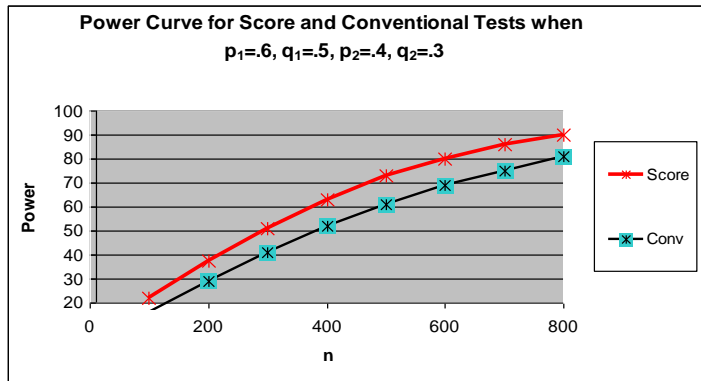
	Assumed	
	<u>Response Rate</u>	
	<u>Drug</u>	<u>Placebo</u>
Conventional Single Phase Design <u>or</u> SPCD Phase 1	60%	50%
SPCD Phase 2	50%	30%



Power Curves – Case 2

“Score” = SPCD “Conv” = Conventional Design

	Assumed	
	Drug	Placebo
Conventional Single Phase Design	60%	50%
SPCD Phase 1	60%	50%
SPCD Phase 2	40%	30%



Huang and Tamura, “Statistics in Biopharmaceutical Research”, 2010

SPCD Utilization

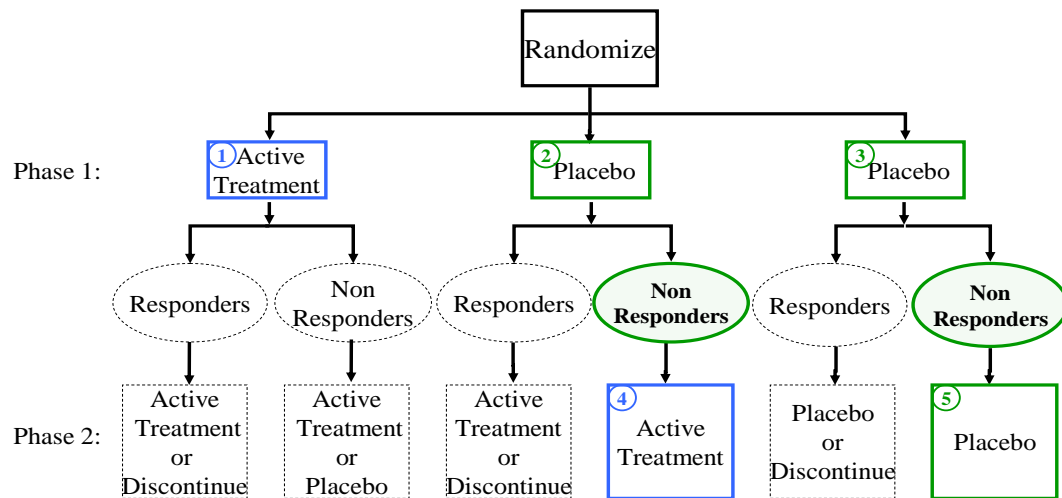
Six companies have decided to sponsor SPCD trials. Three of these sponsors are large pharmaceutical companies. Many other companies are considering the use of SPCD, including several additional large pharmaceutical companies. Bristol-Myers Squibb sponsored the first SPCD trial (“ADAPT-A”), completed in 2009 (NCT 00683852 at clinicaltrials.gov). Two other SPCD trials are currently enrolling, and should be completed this year (NCT 00555997 and NCT 00955955). Three other SPCD trials are planned.

The results of the ADAPT-A trial demonstrate the benefits of SPCD: In the second phase there was a marked reduction in placebo response, and a large increase in drug-placebo difference. A poster describing the ADAPT-A results is available.

Licenses Available for Corporate, Charitable and Governmental Sponsors of Trials

In January 2010, a patent relating to SPCD was issued to Massachusetts General Hospital (“MGH”). A second patent is pending. The intellectual property of MGH related to SPCD is licensed to RCT Logic, LLC (“RCT”). The mission of RCT is to significantly accelerate the pace, and reduce the cost, of developing new medical therapies by providing novel, highly efficient designs for conducting clinical trials. RCT licenses in, and also develops on its own, patented clinical trial designs, actively enhances these designs, and then offers such designs for use in trials sponsored by both industry and non-profit entities. For sponsors who choose to take a license, RCT charges a license fee, which is significantly discounted for non-profit users of SPCD. Please contact Matt Bowman at 914-722-1628 or Matt.Bowman@RCTLogic.com.

Appendix A



- Efficacy analysis pools results of the 5 groups in numbered boxes

Appendix B

• Selected SPCD Literature:

- (1) “The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach”
Fava M et al; Psychother Psychosom. 2003 May-June;72:115-27
- (2) “The Sequential Parallel Comparison Model: A Revolution in the Design of Clinical Trials”
Grandi; Psychother Psychosom. 2003;72:113-114
- (3) “An examination of the efficiency of the sequential parallel design in psychiatric clinical trials”
Tamura R and Huang X; Clinical Trials. 2007;4:309-317
- (4) “Comparison of Test Statistics for the Sequential Parallel Design”
Huang X and Tamura R; Statistics in Biopharmaceutical Research. 2010, Vol.2, No. 1

• SPCD Software

- (1) <http://biostatistics.mgh.harvard.edu/biostatistics/node/57>
 - This software is available to analyze power and sample size for SPCD trials (not applicable for trials with very small sample sizes)
- (2) Software is available through RCT Logic, LLC which analyzes power and sample size for SPCD trials in comparison to trials with a conventional parallel design