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# Patented Clinical Trial Designs

8<sup>th</sup> EFSPi Statistics Leaders Meeting

Ludwigshafen, 04-Jul-2017



Background

The SPCD

Questions and Discussion

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## Background

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In 2003 at Massachusetts General Hospital, a new clinical trial design was invented – the Sequential Parallel Comparison Design (SPCD).

Psychotherapy  
and Psychosomatics

### Special Article

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Psychother Psychosom 2003;72:115–127  
DOI: 10.1159/000069738

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## **The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach**

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<https://www.ncbi.nlm.nih.gov/pubmed/12707478>

## Background

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### Sequential Parallel Comparison Design (SPCD)

- Reducing both the placebo response rate and the sample size
- Particularly interesting for indication with high placebo response rates, like psychiatric disorders

On September 3, 2014, PPD acquired an exclusive license

- Trimentum™

The SPCD was used in more than 30 trials and by several companies

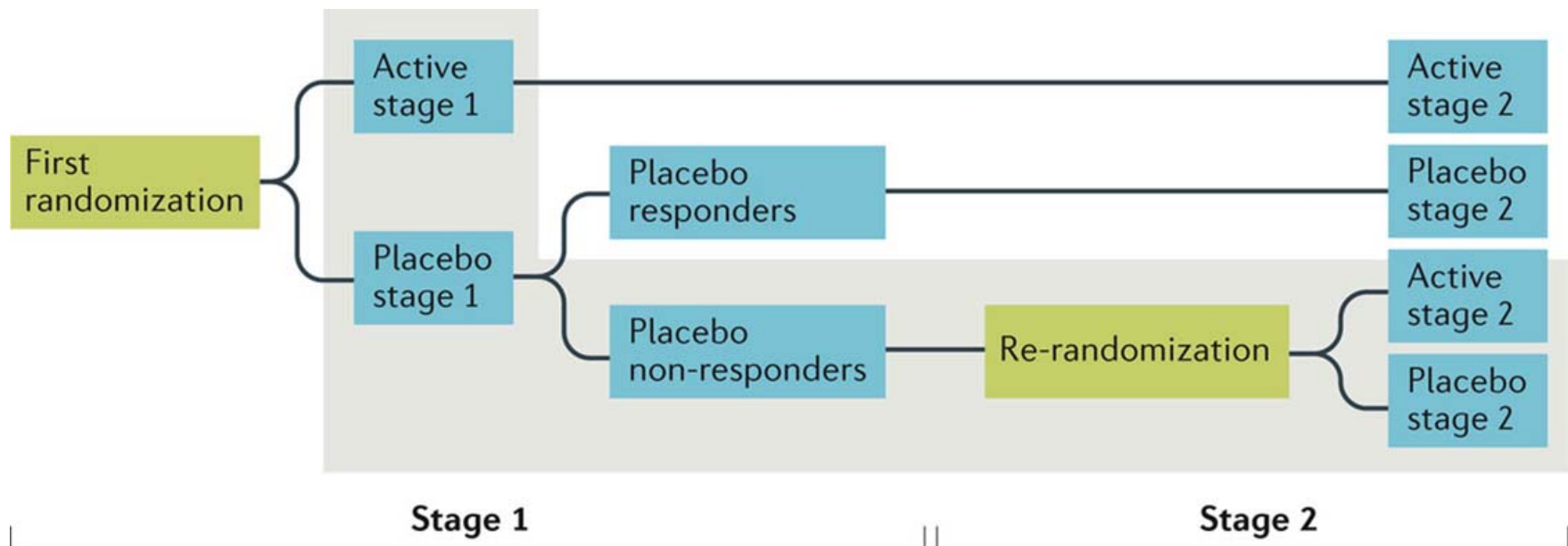
- Alkermes – ALKS 5461, depression
- Janssen Pharmaceuticals – esketamine, depression  
→ FDA approval 2016
- Avanir Pharmaceuticals – AVP 923, Alzheimer disease

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# SPCD – The Sequential Parallel Comparison Design



## Basic SPCD design.

Nature Reviews | Drug Discovery

Sequential parallel comparison design (SPCD) involves a two-stage design.

In the first stage of the trial, the majority of patients are randomized to placebo.

In the second stage of the trial, placebo non-responders are re-randomized to active or placebo treatment.

Data from the patient groups in the grey box are pooled for the final analysis.

**From:** Asher Mullard: Paring down the placebo response.

Nature Reviews Drug Discovery **15**, 807–808 (2016) doi:10.1038/nrd.2016.255

[http://www.nature.com/nrd/journal/v15/n12/full/nrd.2016.255.html?WT.feed\\_name=subjects\\_clinical-trials](http://www.nature.com/nrd/journal/v15/n12/full/nrd.2016.255.html?WT.feed_name=subjects_clinical-trials)

# SPCD – The Sequential Parallel Comparison Design

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## Stage 1

- Patients are randomized to drug/ placebo-drug/ placebo-placebo.
- Allocation ratio is  $1-2\alpha/ \alpha/ \alpha$ , e.g., 2/ 3/ 3, with  $\alpha=0.375$

## Stage 2

- Stage 1 responders → exit double-blind treatment
- Stage 1 non-responders → receive their randomized treatment

## Analysis

- Stage 1 response rates ( $p_1$  and  $q_1$ )
- Stage 2 response rates in placebo non-responders ( $p_2$  and  $q_2$ )
- Estimate/ test a pooled weighted difference  $w(p_1-q_1)+(1-w)(p_2-q_2)$

**Choice of  $\alpha$  and  $w$  → maximize power**



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## Questions and Discussion

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1. Are there any other patented clinical trial designs known?
2. How can patented clinical trial designs affect
  - commercial clinical research,
  - academic clinical research,
  - the freedom of science?
3. What is the potential for further patented clinical trial designs?
4. Is there a need/ does it make sense to take action and which?
5. Is there any other aspect to patented clinical trial designs?

**Five breakout groups**

**Discussion (20 min)**

**Presentation of results to the group (20 min)**

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