Treatment Selection with the Sequential Parallel Comparison Design

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Placebo response

• “The fact that an increasing number of medications are unable to beat sugar pills has thrown the industry into crisis… Some products that have been on the market for decades, like Prozac, are faltering in more recent follow-up tests. It's not that the old meds are getting weaker… It's as if the placebo effect is somehow getting stronger” (Silberman, 2009).

Yellow pills
make the most effective antidepressants, like little doses of pharmaceutical sunshine.

Red pills
can give you a more stimulating kick

More is better
Placebos taken four times a day deliver greater relief than those taken twice daily.
Increased placebo response over time

Data from 86 major depressive disorder trials submitted to FDA during 1986 to 2008 (Khin et al., 2011)
Diminished treatment effect over time

+ US trials
- Non US trials
The Sequential Parallel Comparison Design (SPCD) for trials with high placebo response

SPCD (Fava, et al. 2003)
- After parallel first stage, re-study the patients who do not respond to placebo
- Efficacy analysis includes data from both stages
The Sequential Parallel Comparison Design (SPCD) for trials with high placebo response

\[ H_0: p_1 = q_1 \cap p_2 = q_2 \]
SPCD: Hypothesis testing

• Parallel single stage trial
  \[ H_0: p_1 = q_1 \]

• Placebo lead-in
  \[ H_0: p_2 = q_2 \]

• SPCD
  \[ H_0: p_1 = q_1 \cap p_2 = q_2 \]
  \[ H_1: p_1 > q_1 \text{ OR } p_2 > q_2 \]
Dose-finding with SPCD

3:1:1

RANDOMIZE

PLACEBO

No Response

RANDOMIZE

PLACEBO

LOW DOSE

4 week trt

HIGH DOSE

4 week trt

LOW DOSE

HIGH DOSE
Advantages of the SPCD for dose-finding

Advantages

• We are able to estimate drug and placebo response in both overall population and placebo non-responders to aid the planning of future studies

• Increase in power for any given sample size
  – From potentially larger effect size in placebo non-responders
  – From reuse of patients
Disadvantages of the SPCD for dose-finding

Disadvantages

• **Longer trial duration for individual subjects** compared to the parallel design
Two-stage, adaptive design
assign to doses proportional to the posterior probability of that dose being the best
(Ivanova, Xiao, Tymofyeyev, 2012)

- Performs better than a single stage and “pick the best” two-stage design
- Performs comparably to fully sequential designs
Combining SPCD with 2-stage dose-finding

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LOW DOSE

PLACEBO

HIGH DOSE

RANDOMIZE

\( q_1 \)

\( \delta p_1 \)

\( p_1 \)

No Response

RANDOMIZE

\( q_2 \)

\( \delta p_2 \)

\( p_2 \)

PLACEBO

LOW DOSE

HIGH DOSE
Testing for SPCD treatment effect of selected dose against placebo

Hypothesis about the high dose
\[ H_0: p_1 = q_1 \cap p_2 = q_2 \]

Hypothesis about the low dose
\[ H_0: \delta p_1 = q_1 \cap \delta p_2 = q_2 \]

Overall hypothesis
\[ H_0: p_1 = q_1 \cap p_2 = q_2 \cap \delta p_1 = q_1 \cap \delta p_2 = q_2 \]
Testing for SPCD treatment effect of selected dose against placebo

How to account for

- Multiplicity of treatments and the selection processes in stage 1?
- Multiple stages?
Hochberg and weighted Z statistics

• Stage 1:
  o **Hochberg’s method** (1988) to obtain adjusted p-value for
    High dose vs. placebo
  o Compute $Z_1$ from adjusted p-value

• Stage 2:
  o Similarly Hochberg, then compute $Z_2$ from adjusted p-value

• After both stages use weighted Z statistics (Liu et al., 2012)

  $$Z = \sqrt{w} Z_1 + \sqrt{1-w} Z_2,$$

  recommended weight $w = 0.6$
Sample size calculations for dose finding with SPCD

- No closed form for sample size for Hochberg

- Instead, consider testing
  - Stage 1: **High dose + Low dose** vs. placebo
  - Stage 2: **High dose + Low dose** vs. placebo

- Hypothesis
  \[ H_0: (0.5 p_1 + 0.5 \delta p_2) = q_2 \cap (\pi p_1 + (1 - \pi) \delta p_2) = q_2, \]

  where \( \pi \) is the proportion assigned to the high dose in stage 2
Sample size calculations for dose finding with SPCD

- To test
  \[ H_0: \ (0.5 \ p_1 + 0.5 \ \delta p_2) = q_2 \ \cap \ (\pi \ p_1 + (1 - \pi) \ \delta p_2) = q_2, \]

  - can use sample size formula from Liu et al. (2012)

  - or score test formula (Ivanova et al., 2012) at
    http://www.rctlogic.com/

- Approximates required sample size with Hochberg well when
  \[ 0.75 \leq \delta \leq 0.5, \]
  otherwise Hochberg needs less sample size
Sample size calculations
for dose finding with SPCD: example

- True parameters are
  \[ p_1 = 0.4, \quad q_1 = 0.2, \quad p_2 = 0.2, \quad q_2 = 0.1, \quad \delta = 0.75 \]
  retention rate \( s = 0.9 \)
  allocation 3:1:1 (that is, allocation prop to placebo = 0.6)
  \( w = 0.6 \)
  one-sided 0.05 test
  power of 80%

\[ \pi = ?, \text{ depends on sample size and true parameters} \]
Sample size calculations for dose finding with SPCD: example

- Step 1. With the initial value $\pi = 0.75$, the score test formula yields the total sample size of $n = 189$.

- Step 2. The total sample size of $n = 189$ yields 37 patients allocated to each of the two doses in stage 1.

37 patients per dose and response rates 0.4 and $0.75 \times 0.4 = 0.3$, yield $\pi = 0.81$

- Step 1 (repeated). $\pi = 0.81$ yields the total sample size of $n = 185$
Example: Alkermes SPCD Dose-Finding Study
Phase 2 Study of ALKS 5461 in Depression

• ALKS 5461, a novel opioid modulator, in patients with major depressive disorder and inadequate response to standard therapies

• Primary Endpoint
  - Hamilton Depression Rating Scale (HAM-D17)

• Secondary Endpoints
  - Montgomery-Åsberg Depression Rating Scale (MADRS)
  - Clinical Global Impression (CGI-S)

• ALKS 5461 was significantly better than placebo based on the primary and both secondary endpoints
SPCD Dose-Finding Study of ALKS 5461 in Depression

\[ n = 142 \]
\[ 2:1:1 \]

RANDOMIZE

PLACEBO

LOW DOSE

HIGH DOSE

4 week trt

RANDOMIZE

PLACEBO

LOW DOSE

HIGH DOSE

4 week trt

No Response
References


Fava M (2013). Results from Phase 2 clinical study of ALKS 5461 in major depressive disorder. 53rd Annual NCDEU Meeting, Hollywood, FL.


Silberman, S. Placebos are getting more effective. Drugmakers are desperate to know why. (2009). Wired Magazine http://www.wired.com/wired/issue/17-09

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