

# Implementing adaptive study design in clinical trials for psychiatric disorders using band-pass filtering approach

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## Background

- Multicenter randomized clinical trials (RCTs) in depression - relatively inefficient
- Fail to differentiate known effective antidepressant drugs from placebo in ~50% of trials.
- Uncontrolled placebo response is a key reason for failure of these trials

## Objective

- Develop an adaptive approach for conducting RCTs in depression to increase the signal-to noise ratio at study-end using the band-pass filter approach.

## Methods

- Band-pass filtering maximizes signal detection in RCTs by filtering out noise occurring as responses outside low & high cutoff limits of the filter [1]
- This work proposes an adaptive strategy to identify the informative from the uninformative centers based on non-plausible placebo response trajectories generated in a given center in a clinical trial
- A blinded adaptive approach was evaluated to classify each recruitment center on an ongoing basis during patient accrual as informative or non-informative
- Enrollment was discontinued in uninformative centers and increased/continued in informative centers
- Performance and efficiency of this novel adaptive approach is compared with the conventional design
- Impact of level of placebo response as well as level of between and within center variability in placebo responses is evaluated

## Adaptive Patient Allocation Strategy

- Two-arm RCTs were simulated (placebo and active drug) with a balanced treatment allocation per center and per arm
- Evaluation of center performance was conducted on an ongoing basis using the incomplete data once  $\geq 50\%$  of the planned data was available in any center
- A recruitment center was classified as uninformative when the blinded HAMD score derived from the longitudinal non-linear mixed-effect modeling on the partial data indicated an excessively high overall response in that center (median HAMD  $< 11$  at study endpoint in more than 65% of the data/subjects available from that center)
- The recruitment was suspended in the center classified as uninformative but progressed in the informative centers and new centers were opened

## Results

- Clinical trial simulation demonstrated the benefit of the proposed adaptive approach for center evaluation and patient allocation as compared to the traditional study design and study conduct.
- The proposed adaptive approach demonstrated that the expected treatment effect (change of HAMD score in the active vs placebo arm at study endpoint) in placebo-controlled RCTs can be significantly improved when data from informative recruitment centers are considered.
- The benefit of the adaptive approach increased with the increase of the heterogeneity in the response across centers (between center variability) and the level of the placebo response as illustrated in Figure 2.
- The Adaptive approach also saved/required 15 – 35% fewer subjects as compared to the convention study design.

## Adaptive & Conventional Approaches

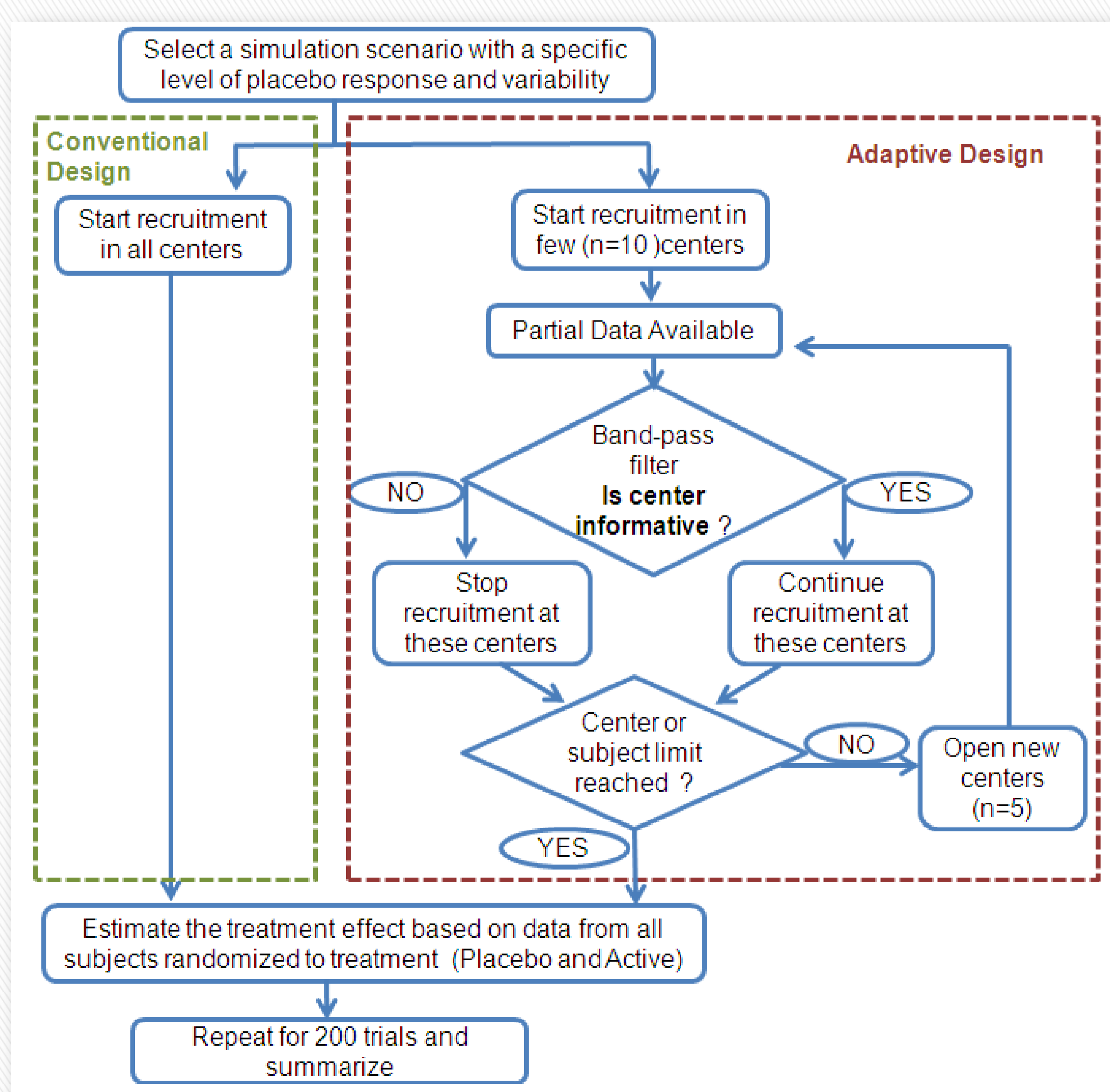


Figure 1. Simulation setup for the conventional and Adaptive study design

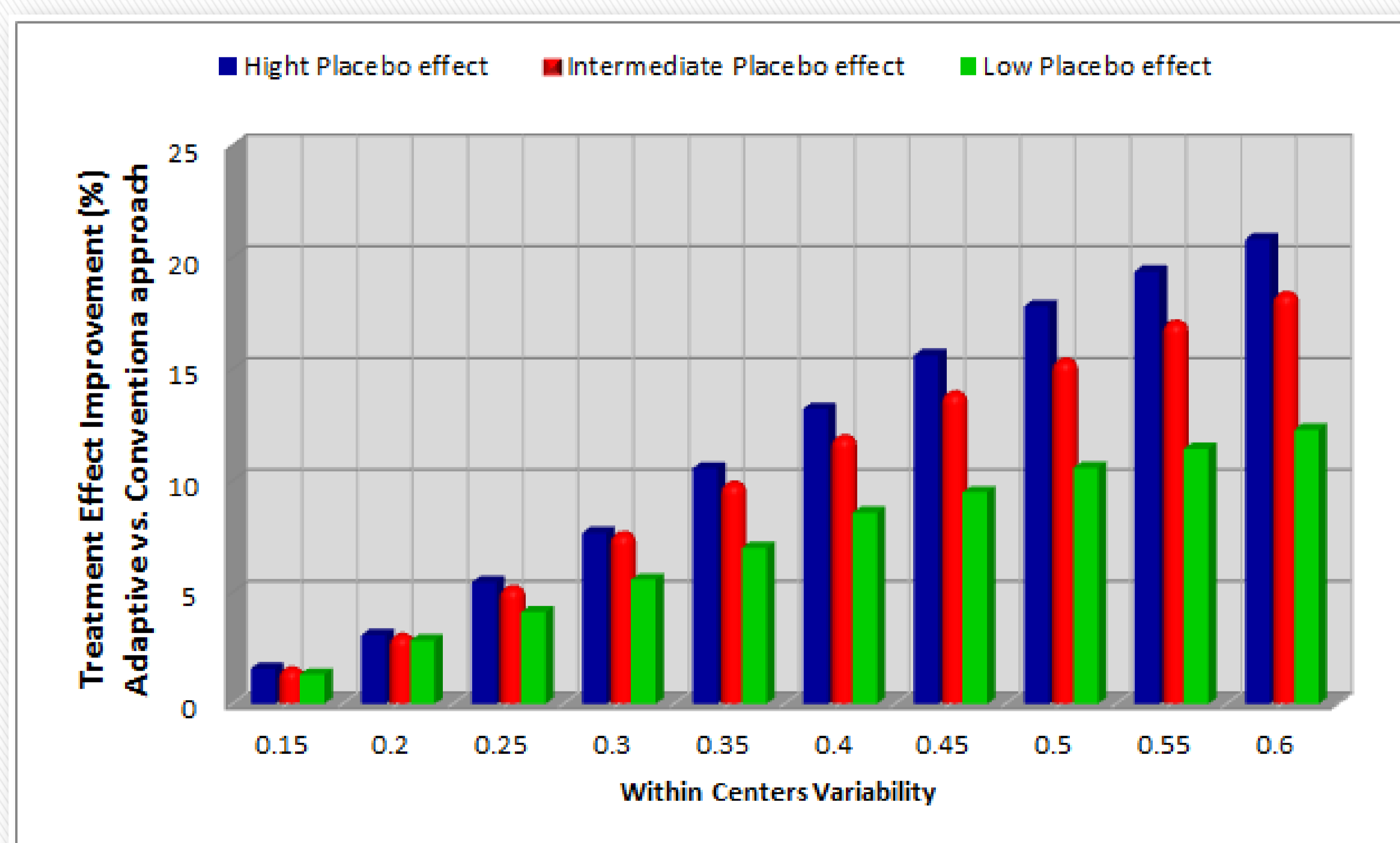


Figure 2. Expected treatment effect improvement with proposed adaptive strategy for center assessment and patient allocation

**Conclusions:** With this novel adaptive approach, the overall placebo response rate can be reduced and the signal-to-noise ratio substantially increased. Overall, such adaptive approach could markedly facilitate the process of clinical development of new compounds for the treatment of psychiatric disorders.

**References:** [1] Merlo-Pich E., Alexander R.C., Fava M., and Gomeni R. A new population enrichment strategy to improve efficiency of placebo-controlled clinical trial in depression. *Clin. Pharmacol. Ther.*, 2010 Nov;88(5):634-42.