The Impact of Allocation Bias in Rare Disease Clinical Trials with Multiple Endpoints

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December 12, 2024

Background

- **Challenges in Rare Disease Trials:**
  - Drugs and treatments often lack approval or rely on low levels of evidence.
  - Defining a **single primary endpoint** is difficult due to:
    - Heterogeneous clinical presentations.
    - Multiple phenotypes.
    - Individualized patient experiences with the disease.
    - Limited understanding of the disease's natural history.

- **Advantages of Using Multiple Endpoints:**
  - Capture diverse aspects of the disease.
  - Provide comprehensive information from the trial.
  - Offer a holistic view of treatment effects.
  - Address patient-specific needs, such as patient-centered outcome measures (PCOMs).

Types of Multiple Endpoints

- **Multiple Primary Endpoints:** Each endpoint is evaluated independently, and demonstrating a treatment effect for at least one endpoint indicates efficacy.
- **Co-primary Endpoints:** Requires treatment effects to be demonstrated for all primary endpoints to conclude overall efficacy.
- **Multi-component Endpoints:** Combines multiple outcomes within a subject into a single score or rating that can be either weighted or unweighted, i.e. PCOMs.
- **Composite Endpoints:** Merges several endpoints into a single variable, such as the time-to-first occurrence of a set of events.

Objectives and Research Questions

Key Objective

Enhance the design and analysis strategies of rare disease clinical trials with multi-component endpoints to improve robustness and validity by mitigating allocation bias.

Research Questions

How we can account for allocation bias during the planning and analysis phase of a clinical trial?

Allocation Bias in Rare Disease Trials

- **What is Allocation Bias?**

  Allocation bias is caused by weaknesses in the allocation process of treatment assignment. For example, a lack of concealment or blinding can make the next treatment predictable, allowing the enrollment of certain patients to be denied and more favorable patients to be allocated to preferred treatments.

- **Regulatory Guidelines:**
  - EMA (ICH E9) highlights the importance of addressing bias when interpreting treatment effects and comparisons.

- **Key Requirement:** Addressing allocation bias during the planning, implementation, and evaluation phases ensures trial validity.

Randomization Procedures

CR	Allocation accomplished by a fair coin toss
EBC(p)	Patients are assigned with a probability equal to a biased coin toss that favors the group with less frequent allocations with probability $p \geq 0.5$
BSD(b)	Allocation with CR until a maximum tolerated imbalance b, then deterministic assignment to the group with fewer patients
CHEN(p,b)	Patients are assigned with EBC(p) until a maximum imbalance b, then deterministic allocation to the group with fewer assignments
MP(b)	Assignments by a randomization list which is uniformly selected from the subset of randomization lists generated by CR that keeps the maximum tolerated imbalance b
RAR	The method randomly assigns half of patients to the treatment or control group.
PBR(k)	Patients are allocated in blocks of length k. Within these blocks, the allocation is according to RAR

(Rosenberger,2002)

Allocation Bias Policy

The biasing policy quantifies allocation bias effects in clinical trials with multi-component endpoints.

Key Assumptions

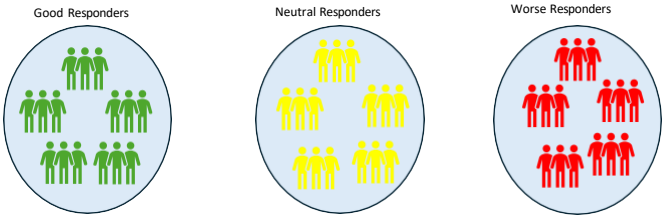
- Researcher knows previous, but not future treatment assignments.
- Researcher favors the experimental group.
- Better responders have higher expected scores in each endpoint component.
- Classification of responders as good, neutral, or worse responders.
- Researcher follows the Blackwell and Hodges convergence strategy (1957), and assigns the next patient to the group with fewer prior allocations.

Allocation Bias Policy

Biased Recruitement Process: The researcher assigns the next patient to the group with fewer prior allocations:

- **Experimental Group (E):** A good responder with increased expected response is recruited.
- **Control Group (C):** A worse responder with decreased expected response is selected.
- **Balanced Allocation:** A neutral responders are assigned.

Allocation Bias Policy



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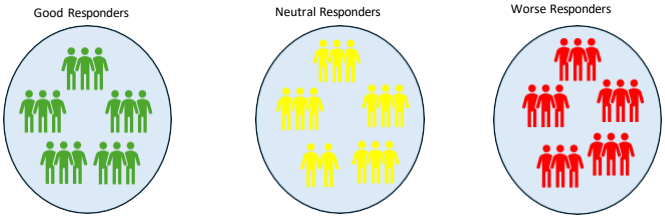

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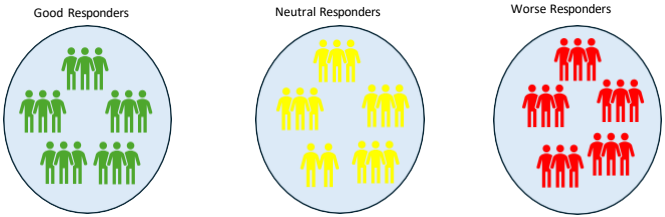

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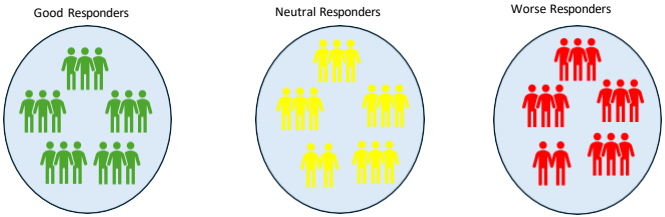
Allocation Bias Policy



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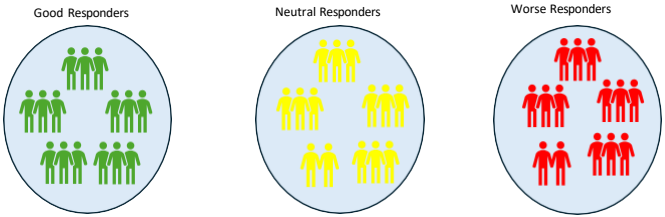

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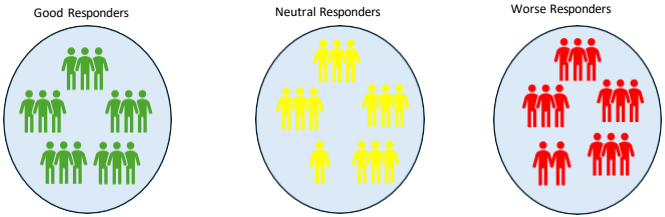

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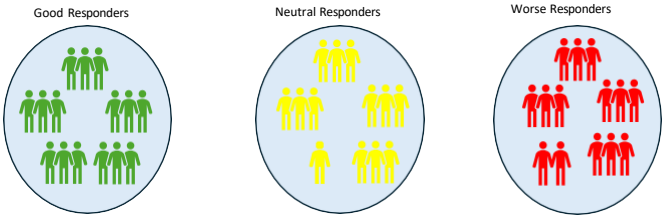

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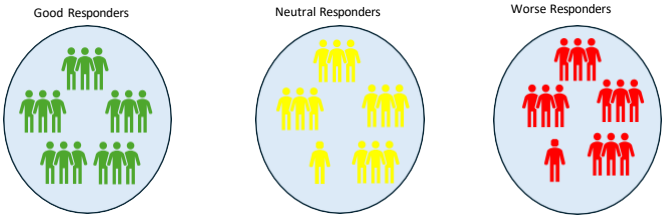

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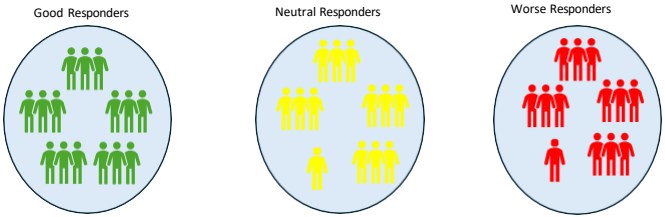

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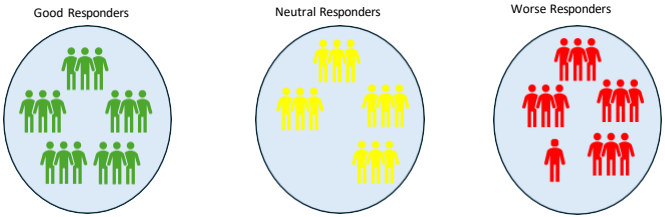

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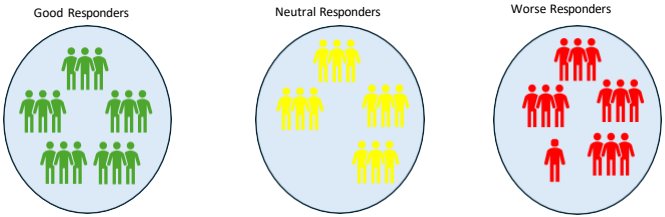

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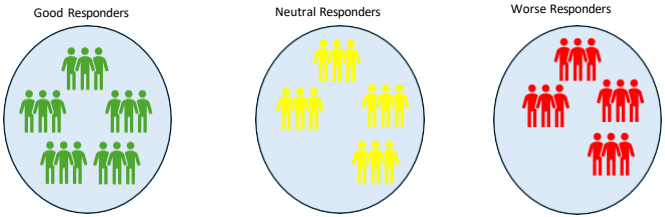

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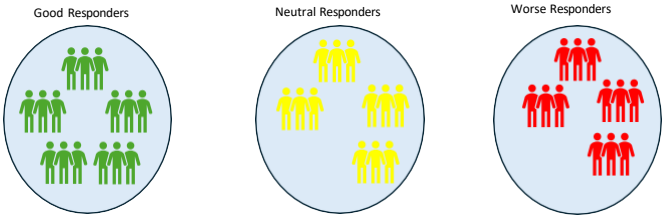

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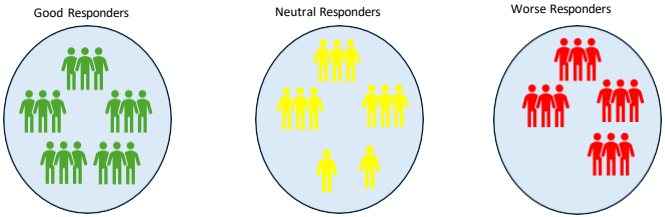

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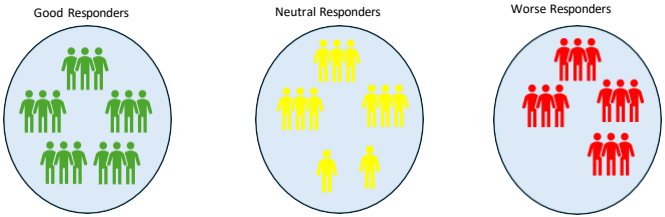

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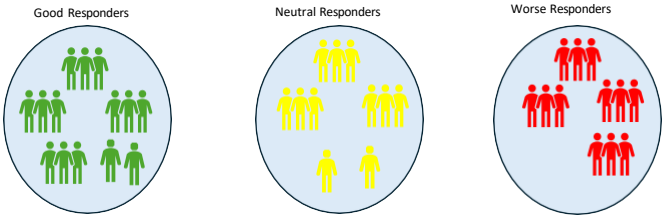

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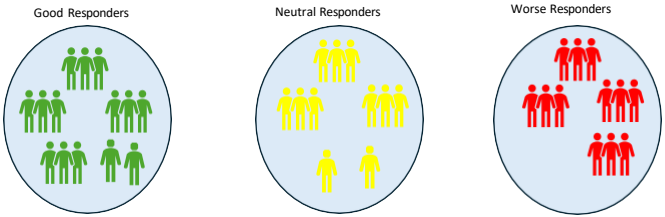

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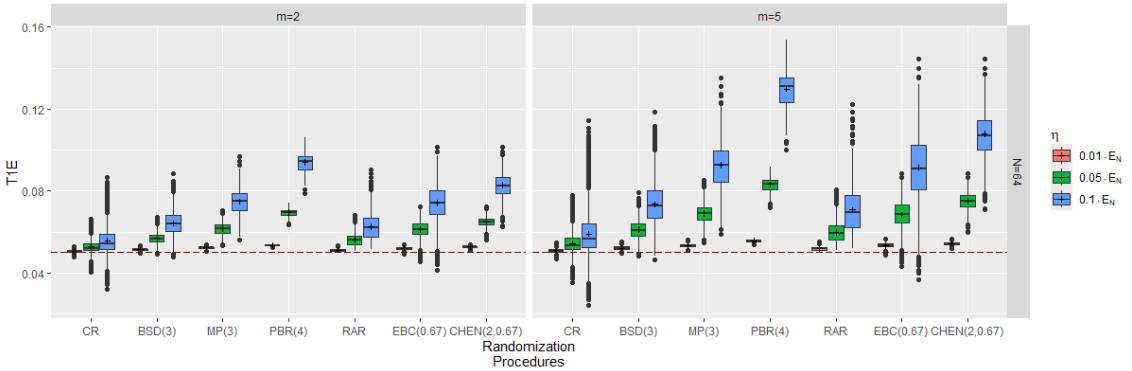
Impact of Allocation Bias Policy

Simulation of **type I errors** (T1Es) of the **scoring test** when ignoring the presence of allocation bias, conditioned on 10 000 randomization lists, under homogeneous allocation bias effects of 1%, 5%, and 10% of the effect size E_N.



Discussion

- **Impact of Allocation Bias:** Allocation bias inflates T1Es, potentially distorting trial results.
- **Role of Randomization Procedure:**
  - The extent of T1E inflation depends on the randomization method used.
  - **Best Performance:** Complete Randomization (CR) and Big Stick Design (BSD(3)).
  - **Worst Performance:** Permuted Block Randomization (PBR(4)).
  - Relaxing the final balance between treatment and control groups reduces bias.
- **Effect of Endpoint Components:** Increasing the number of endpoint components amplifies T1E inflation due to more components may introduce bias.

Conclusion and Perspectives

- The allocation bias policy can be used to optimize clinical trials through:
  - Identifying the best randomization procedure that reduces allocation bias.
  - Validating trial results by performing bias-adjusted tests.

This approach ensures a more accurate assessment of treatment effects and enhances the validity of trial outcomes, particularly in small and complex trials that uses multi-component endpoints, such as PCOMs.

- **Further Research:** Extension to mixed endpoint types, as often in PCOMs, and more general statistical models.

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Biased Patient Responses

$$X_j \sim \mathrm{N}_m(\mu_E t_j + \mu_C(1 - t_j) + \tau_j, \Sigma), \quad j \in \{1, \ldots, N\}$$

- N: Total sample size
- m: The number of endpoint components
- $t_j = 1$ if patient j is allocated to treatment group (E), and $t_j = 0$ if allocated to control group (C)
- $\mu_i \in \mathbb{R}^m$: Expected response vector for treatment $i \in \{E, C\}$
- $\tau_j \in \mathbb{R}^m$: Allocation bias effect for patient j
- Σ: covariance matrix