Evaluating a Response Adaptive Trial using Simulations

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Background

- New treatments require thorough research and testing to ensure it's safety, efficiency and the ability of the treatment to work.
- The testing on humans are referred to as **Clinical Trials**.

Background

- The usual approach is called **Randomised Control Trials (RCTs)**.
- RCTs assign each patient with equal probability to each treatment.
- RCTs are effective in identifying significant difference between treatments.
- However, they do not allow us to maximise the number of patients successfully treated since the probability is fixed.

Introduction

- This is an example of the **Multi-Armed Bandit problem** in the context of clinical trials.
  - Suppose there are L treatments, one of those treatments are allocated to each patient in order to maximise the number of patients treated within the trial (earning).
  - There is a need to balance the **learning** (identifying the best treatment) and the **earning** (treating as many patients as possible).

Response Adaptive Design

- A proposed design is called the **Response Adaptive Design (RAD)**.
- RADs use the information of previous patients to vary the treatment allocation favouring the treatment with the best predicted outcome.
- An issue with the RAD is that it expects the same outcome of a patient should they be given the same treatment. However **covariates** such as weight, age and blood type of the patients alter the outcome of the treatment.

Response Adaptive Design

Suppose we have N patients in the trial.

Method

1. Assign the first n patients to the treatments and record the outcomes.
2. For patient $n+1$, based on their covariate, use the $\mathbf{K}^{th}$ **Nearest Neighbour** regression method to determine the predicted outcome for each treatment.
3. For the best predicted outcome, we assign that treatment a high probability.
4. Randomly select a treatment with the new probabilities for patient $n+1$ and record the outcome.
5. Repeat steps **2-4** for the remaining patients.

Simulations

- We used a data set of 100 patients.
- 100 simulations were conducted for varying scenarios, all with 2 treatments, for both the RCT and RAD method.
- Throughout the scenarios, for the RAD method, we used 3 nearest neighbours and the first 10 patients were used in the initial step.
- We will be comparing the two designs and investigating the ability of each design to detect a difference in the treatments as well as the number of patients successfully treated.

Power and Proportion

1. **Power** - We consider the hypotheses:

   $\mathbf{H}_0$: $\theta_1 = \theta_2$. (There is no difference in treatments).
   $\mathbf{H}_1$: $\theta_1 \neq \theta_2$. (There is a difference in the treatment).

   Where θ_1 and θ_2 are the outcomes of the two treatments. The power is the probability of **detecting a difference in treatment when there is one**.

2. **Proportion** - The number of patients on the best treatment is used as a measure of the number of patients successfully treating in the trial.

Scenario 1

Both treatments give the same outcome.

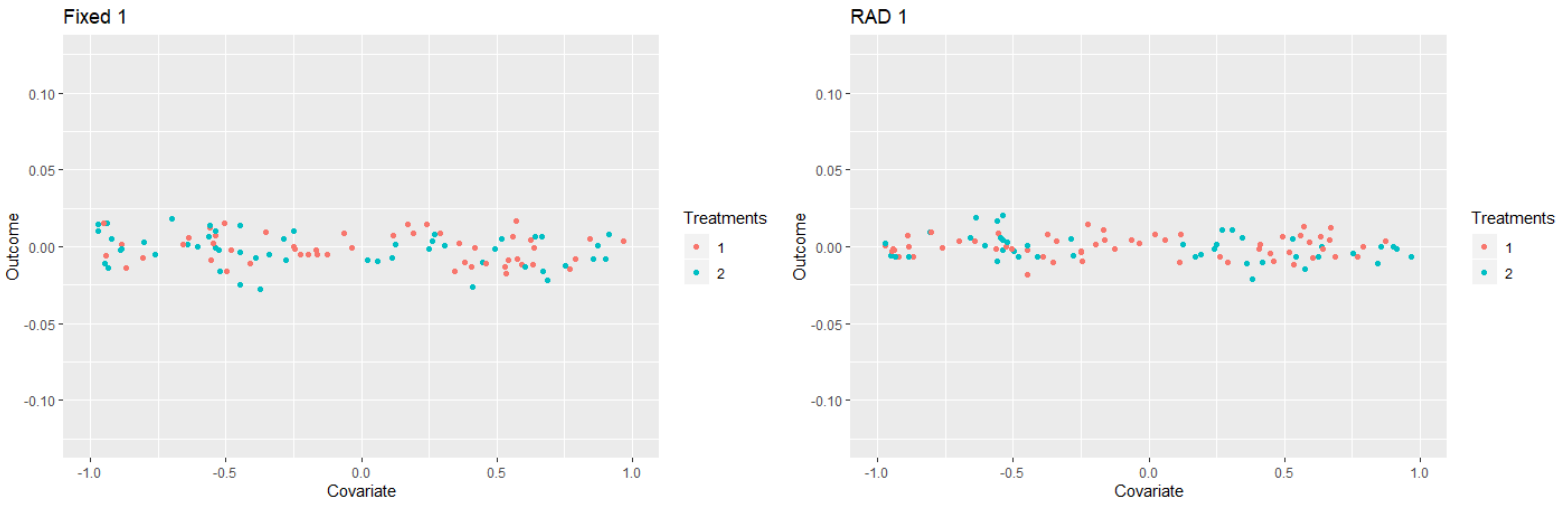

Figure: Left figure is RCT, right figure is RAD.

- **Type I error** is the probability of incorrectly identifying a difference in the treatments when there is no difference.

Scenario 2

Suppose the scenario is that the covariate is the **body weight centered around the mean** and the outcome being a **success or failure in treating chicken pox**. This is an example of a **binary outcome**.

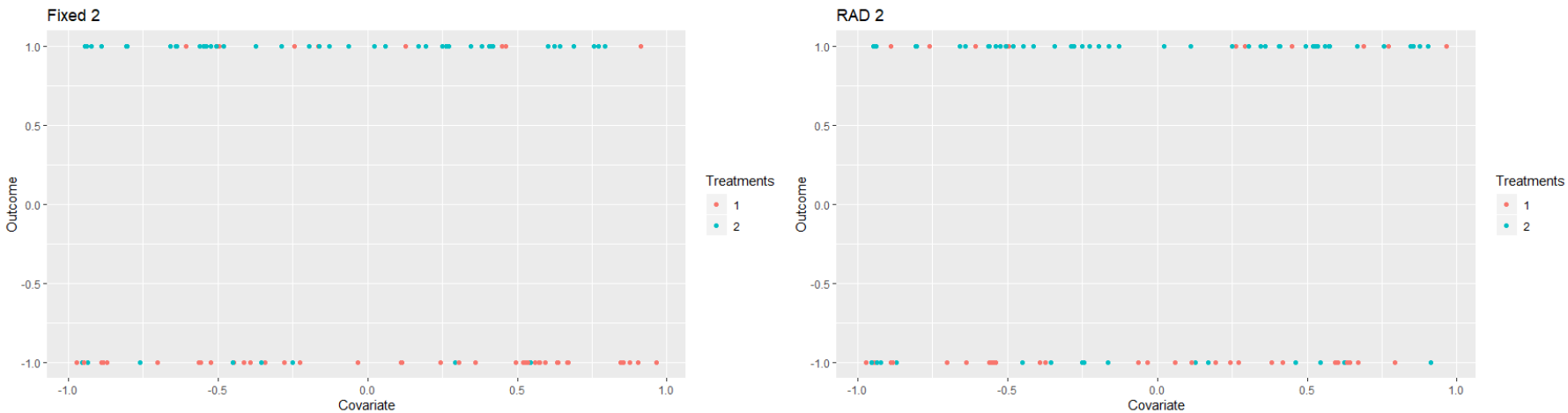

Figure: Left figure is RCT, right figure is RAD.

Scenario 3

Suppose the scenario is that the covariate is the **body weight centered around the mean** and the outcome being a **decrease in the blood cholesterol levels**. This is an example of a **continuous outcome**.

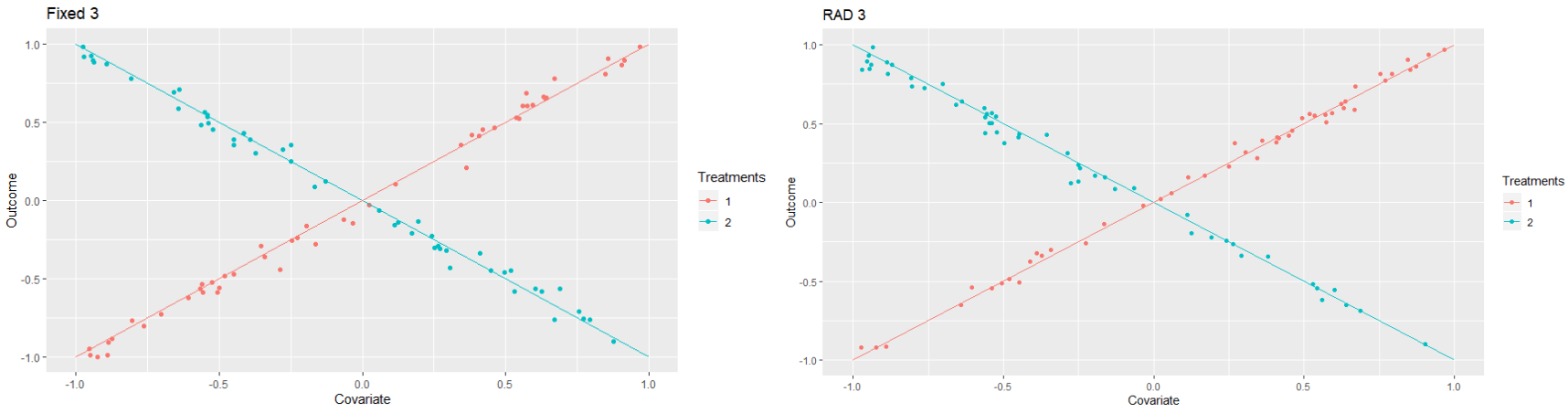

Figure: Left figure is RCT, right figure is RAD.

Scenario 4

Suppose the scenario is that the covariate is the **body weight centered around the mean** and the outcome being a **decrease in the blood cholesterol levels**. This is an example of a **continuous outcome**.

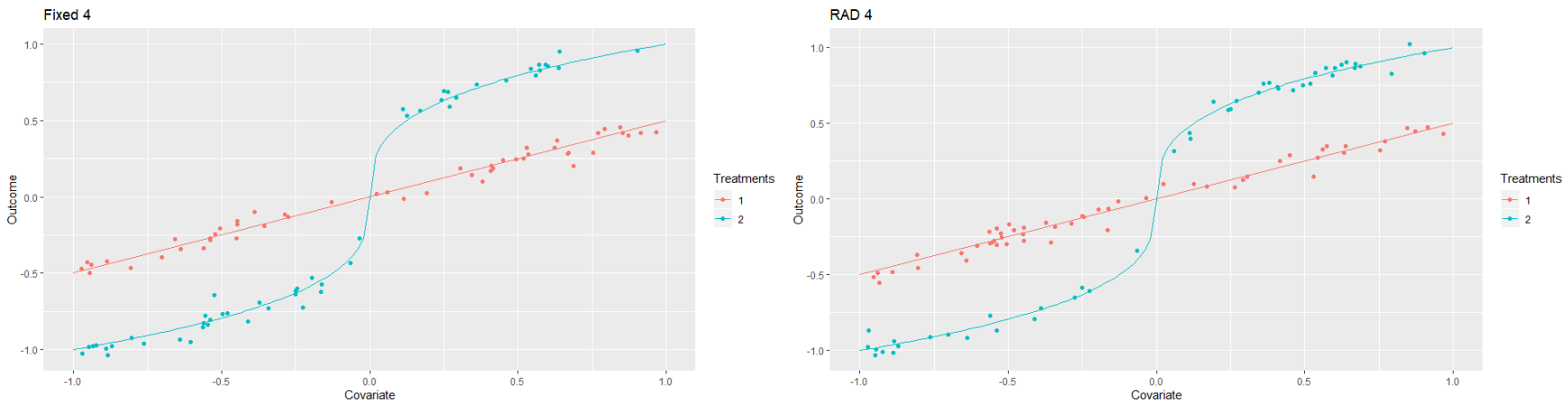

Figure: Left figure is RCT, right figure is RAD.

Scenario 5

Suppose the scenario is that the covariate is the **body weight centered around the mean** and the outcome being either an **increase, decrease or no change in the red blood cell count**. This is an example of a **categorical outcome**.

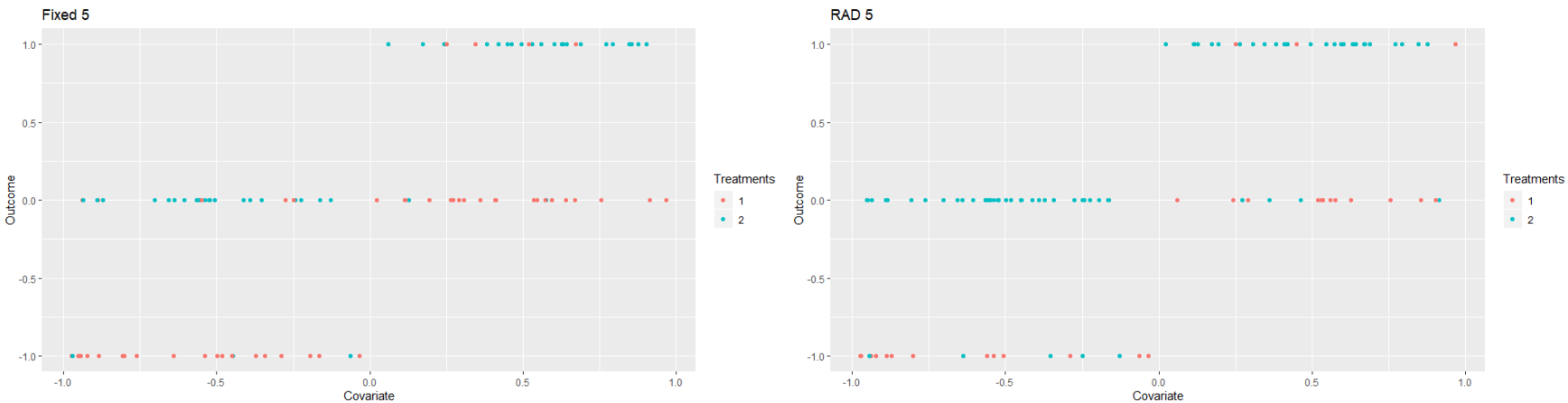

Figure: Left figure is RCT, right figure is RAD.

Scenario 6

Suppose the scenario is that the covariate is the **body weight centered around the mean** and the outcome being either an **increase, decrease or no change in the red blood cell count**. This is an example of a **categorical outcome**.

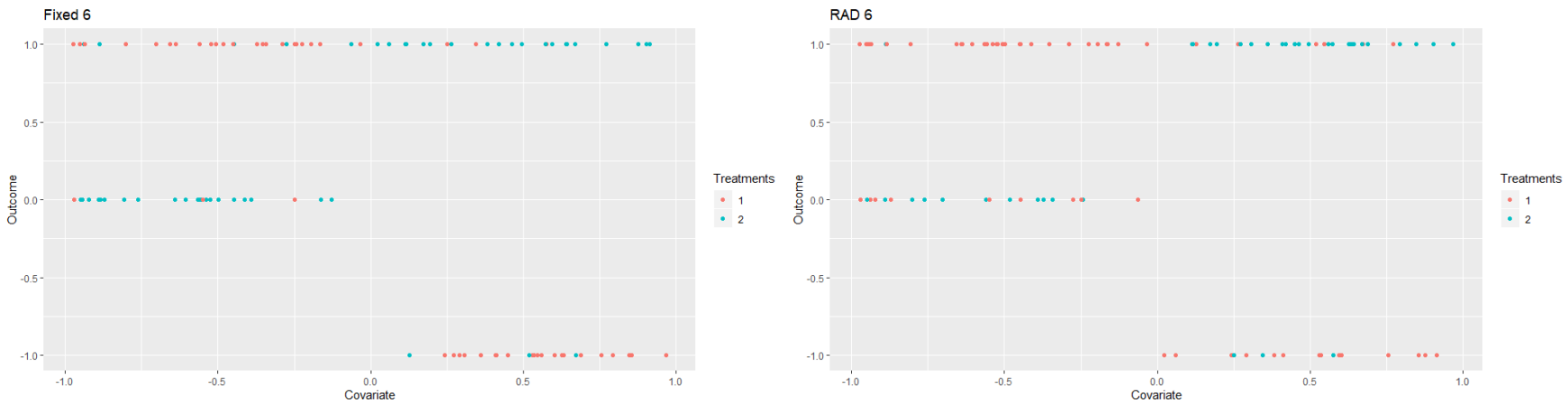

Figure: Left figure is RCT, right figure is RAD.

Proportions

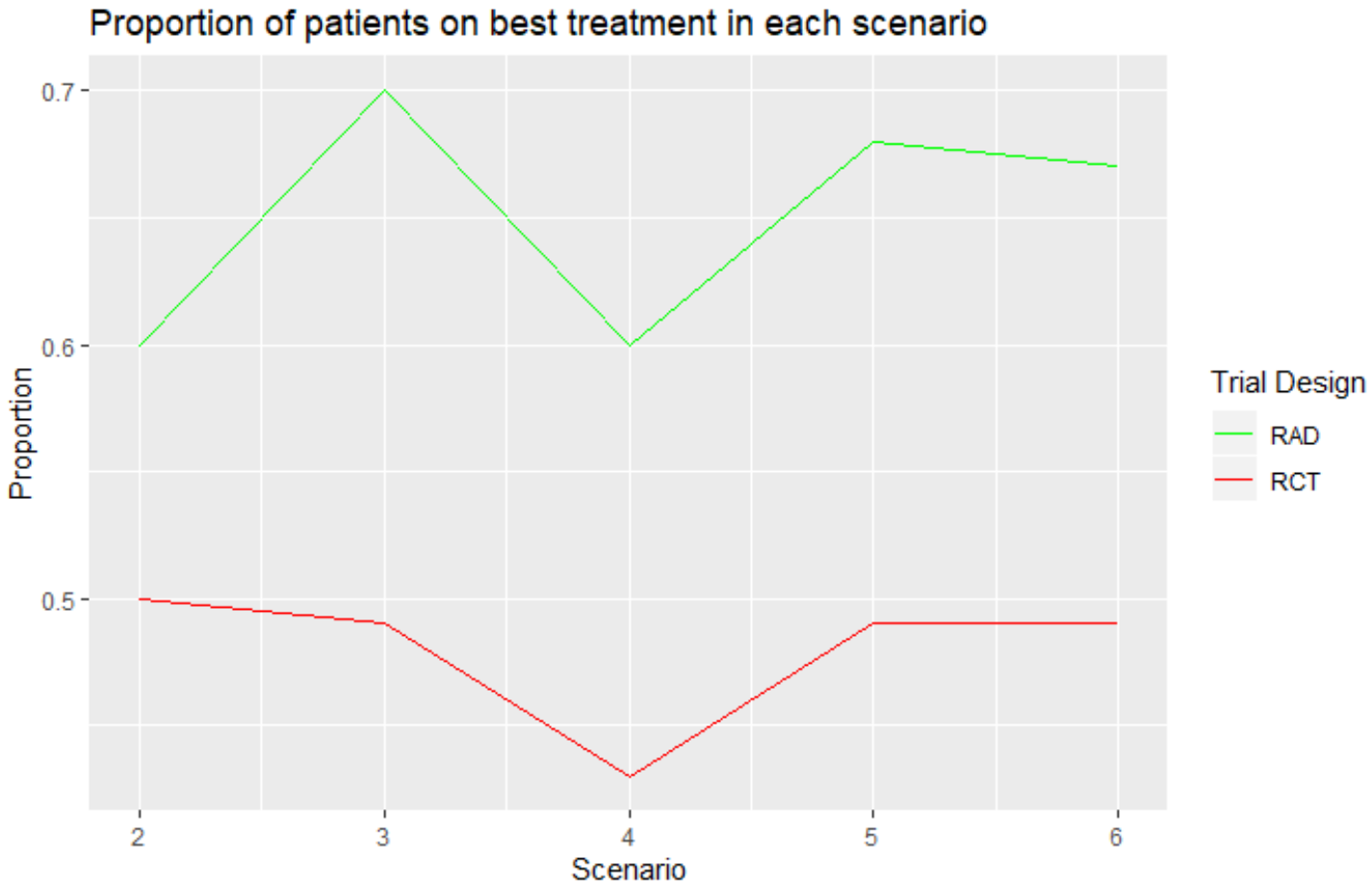

Figure: Comparison of the proportion of patients on their best treatment for both designs, for all the scenarios.

Power

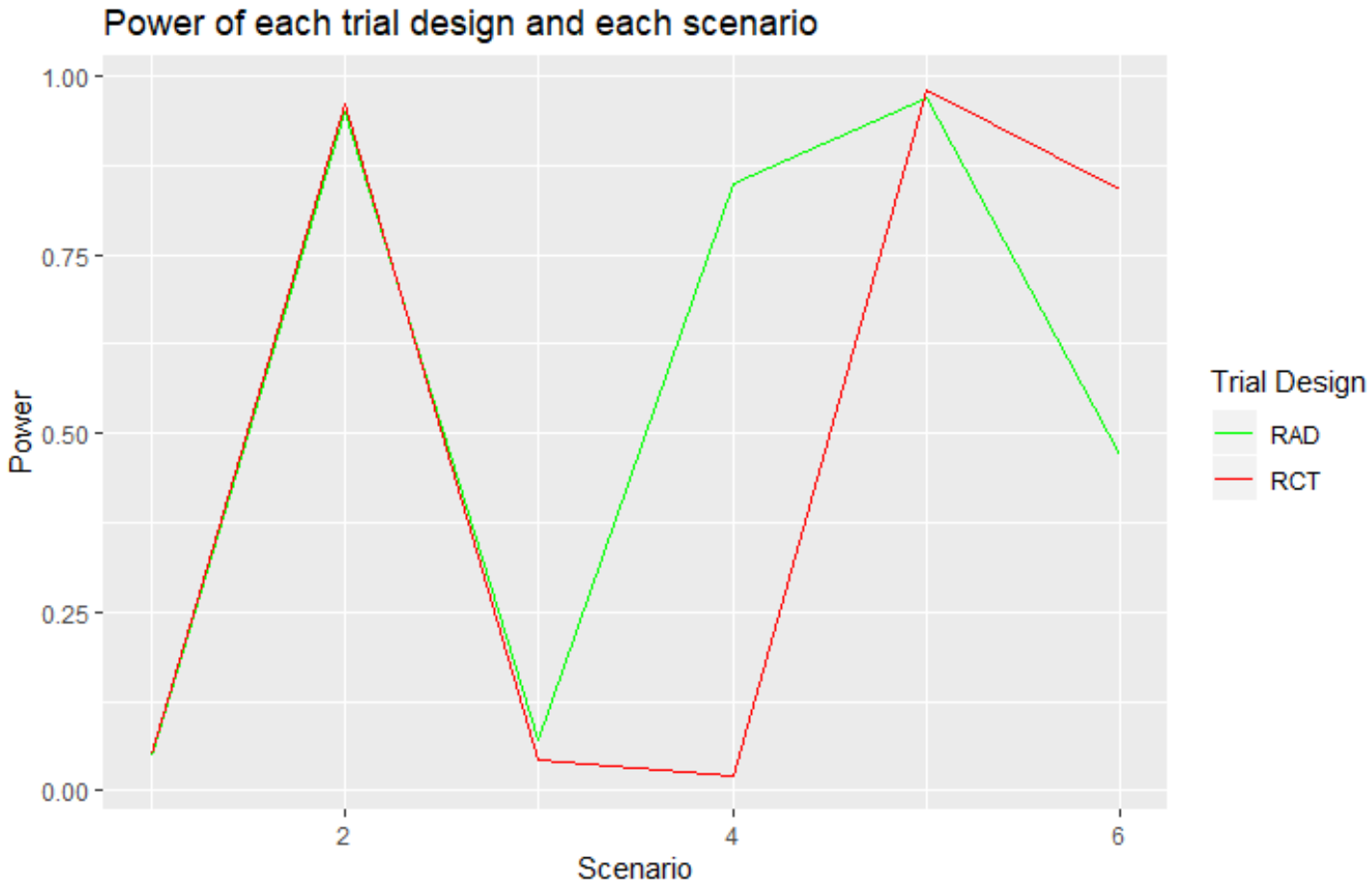

Figure: Comparison of the power of trial for both designs, for all the scenarios.

Key points

- Proportion tends to be higher in the RAD method than the RCT method.
- Power varies with scenarios but RCT method has higher power than RAD method majority of the time.
- Since only 100 simulations were carried out, there may be some simulation error.
- The type of outcome and in particular the scenario may influence the power of the trial for both methods.

Further work

- RAD method assumes outcome of patient is known immediately, which is not the case in real life.
- Try different regression techniques.
- For rare diseases, the proportion of patients in the trial is a higher proportion of the population with that disease. Hence we would want to treat even more patients successfully as possible.

Thank you for listening, any questions?