# 1. Introduction

## 1.1. Randomized Controlled Trials

In drug development, randomized clinical trials have become the gold standard approach for evaluating the efficacy of new experimental treatments in the last decades. In the traditional setting, one drug for treating a single disease is investigated in each trial and patients receiving this drug are compared to patients in the control arm, which can be either the current standard of care or placebo. The differences in outcomes between these two groups are then assessed in the final analysis at the end of the trial in order to determine whether the new treatment is effective or not. An example of such standard RCT is illustrated in Fig. 1.1.

In order to guarantee the theoretical comparability of the two treatment groups, patients are allocated randomly, i.e. *randomized*, to the groups, to ensure that the assigned treatment is independent of the baseline characteristics. This classical randomized controlled clinical trials (RCTs), have been considered the most reliable form of scientific evidence for evaluating drug efficacy, since the randomization reduces spurious causality and bias.

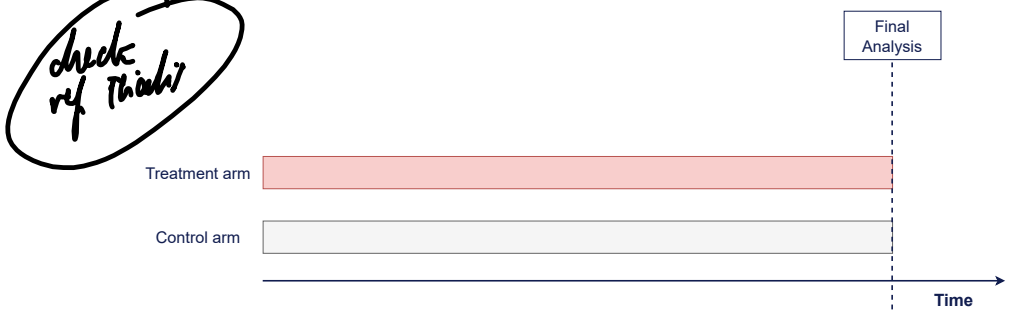


Figure 1.1.: Example scheme of a classical randomized controlled trial.

However, traditional RCTs also come with many disadvantages. In particular, their conduct may take a lot of time, usually several years, and is very expensive. Moreover, trials to test drugs for the same disease are often conducted simultaneously by different companies, while each company needs to set up its own trial with a separate control group. This lack of sharing of resources also leads to increased required sample sizes to detect the difference between the groups, since more patients need to be allocated to a control arm.

In recent years, there have been efforts to address these drawbacks by introducing adaptive platform trials, which allow for more flexibility in the trial design.
**PENDING:** Write more about adaptive clinical trials in general.

check into wiener and Jenn.

## 1.2. Platform Trials

Platform trials are multi-arm multi-stage clinical trials that aim at evaluating the efficacy of multiple treatments for a single disease simultaneously. The number of experimental treatment arms is not known in advance and the treatments are also allowed to enter and leave the ongoing trial. Moreover, interim analyses can be conducted before the final analysis, which allows for earlier stopping due to either efficacy or futility. This setting enables faster evaluation of drugs that are being developed during the ongoing trial, as they can be directly included to the shared platform. The control group is shared across all treatment arms and thus less patients are required to be randomized into this arm as compared to separate RCTs. The control may also change in the course of the trial, if an effective treatment arm becomes the new standard of care. Fig. 1.2 illustrates a platform trial with 4 experimental treatment arms and a shared control arm.

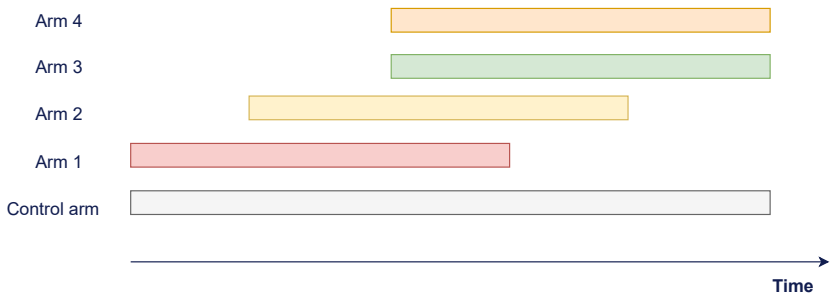


Figure 1.2.: Example scheme of a platform trial with 4 experimental treatment arms and a shared control group.

Due to their higher flexibility, platform trials pose many operational and statistical challenges. In particular, their planing is much more complex and requires computer simulations, since the progress of the trial (i.e. how many experimental arms will be evaluated and the times of their adding and dropping) is unknown in advance.
**PENDING:** Discuss statistical challenges in platform trials:

- Multiplicity - multiple treatment groups, endpoints, subgroups ...
- Adaptation rules - number and timing of interim analyses, stopping rules, timing of adding treatments, randomization rules ...

also here → it's enough to give an short discussion / explanation about these issues.

- Estimands
- Shared control group
- ~~TBD~~

1.3

### ~~1.2.1.~~ Concurrent and Non-concurrent Controls

One of the statistical issues that arises concerns the use of the shared control in the trial analysis. For treatment arms that enter the ongoing trial later on, the control group is divided into two separate groups - the concurrent controls (CC), which includes patients that were randomized to the control arm at the same time as the given treatment arm was active in the trial, and the non-concurrent controls (NCC), which denotes patients randomized to the control group before the evaluated treatment arm entered the platform. Fig. 1.3 shows a platform trial with 2 experimental arms, where the 2nd arm joined the trial later. NCC data for this arm are highlighted.

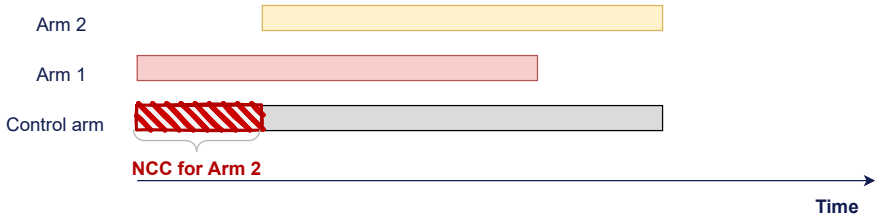


Figure 1.3.: Non-concurrent control data for arm 2.

The question is if and how to incorporate the NCC data to the analysis of the given treatment arm and there is still no consensus regarding this issue. Including NCC data to the analysis may, on one hand, improve the statistical power of the treatment-control comparison, as the underlying sample size increases. However, bias might be introduced to the analysis, if time trends are present in the trial. Such time trends might be caused for instance by changes in the standard of care, patient population or by seasonal effects. Therefore, appropriate methodology that takes into account possible temporal changes is required in order to analyze such trials properly.

## ~~1.3. State of the Art (or maybe a different title)~~

**PENDING:** Discuss differences between NCC and historical controls and review methods proposed for borrowing historical data:

- naive approaches - pooled and separate analysis
- test-then-pool, dynamic pooling, MAP, propensity score methods
- model-based approaches - covariate adjustment

I think this part can be short (let's say 1,2 paragraphs), just a high level explanation of the diff approaches.

## 1.4. Thesis Contribution

This thesis focuses on ~~the issue of~~ using non-concurrent controls for individual treatment-control comparisons in platform trials with continuous endpoints in the presence of time trends. We will review the current methods presented in the literature so far and discuss their assumptions and limitations. ~~Moreover~~, we propose novel frequentist model-based methods for incorporating NCC data into the analysis, evaluate ~~their~~ performance in a simulation study and assess the conditions under which these approaches lead to valid statistical inference. The considered methods and simulations are implemented in an R package, ~~which~~ enables users to simulate platform trials with a flexible number of treatment arms and a common control group and assess the efficacy of individual treatments, while utilizing NCC data.

i) extension; ii) new modeling.
In Ch 3, we
In Ch 2, we first ....
#
second,
the
of the proposed models
presented in ch 4.
the package, called NCC,

# we finish the master thesis summarizing the work and discussing further steps.

Well done! Version 1!
keep going