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Methodological challenges of platform trials

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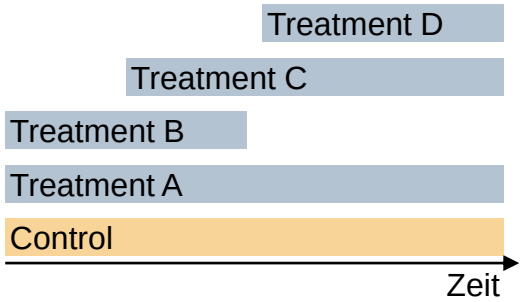
Platform trials - definition

Woodcock, J., & LaVange, L. M. (2017). Master protocols to study multiple therapies, multiple diseases, or both. *New England Journal of Medicine*, *377*(1), 62-70.

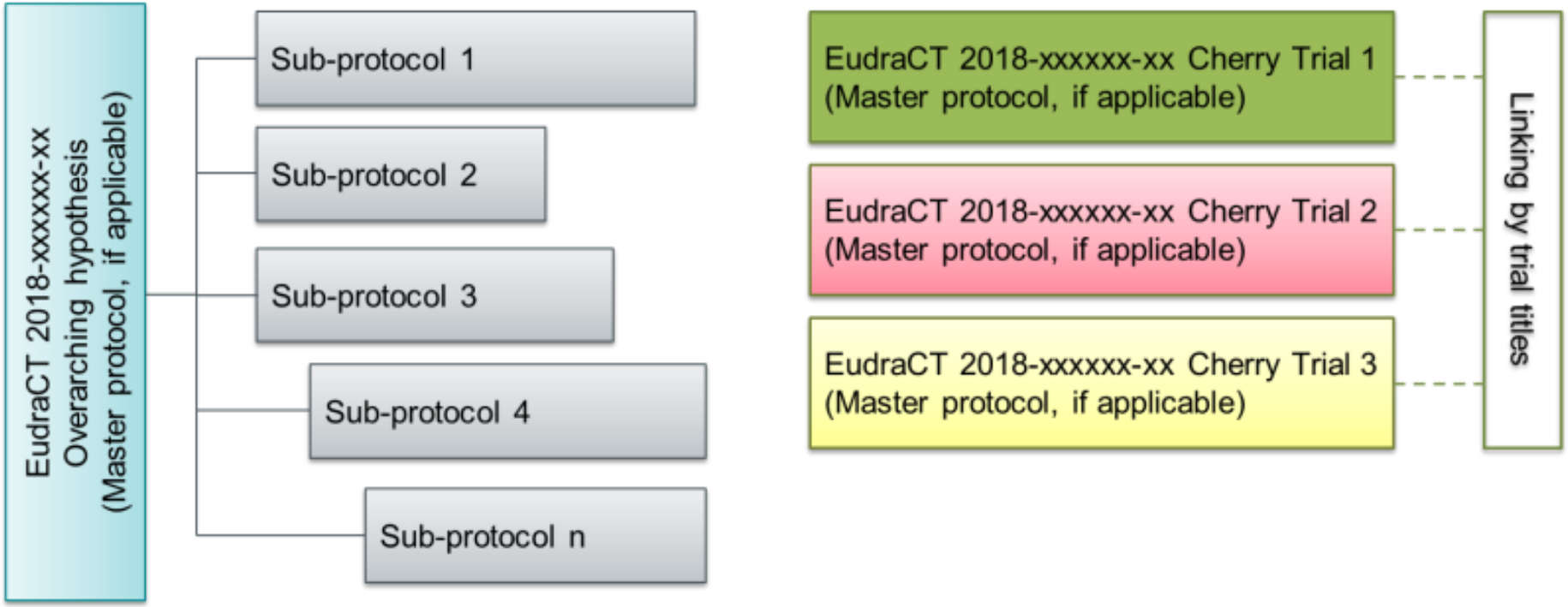
The objective of a platform trial is to study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

→ Key adaptive feature: Treatments can be added to the ongoing trial

- Often combined with other adaptive features e.g. group sequential design
- Often a shared control group is used



Organizational Structure



Clinical Trials Facilitation and Coordination Group (CTFG): Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

Examples from our department

RAPID: Platform trial assessing treatment options for **post-COVID syndrom**

- started in Q3 2024 **with one experimental treatment** (Vidofludimus calcium) vs. Placebo **(REVIVE)**
- Second subprotocol **(ELAPSE)** added after termination of first subprotocol

SLEIPNIR: A randomized, Phase 2a, double-blinded, **multi-arm platform trial** to investigate safety, CNS **penetration and target engagement** of tentative disease-modifying therapies compared with placebo in male and female participants with **Parkinson's disease**

- will be initiated with three treatment arms and a shared control

Advantages over conventional trial designs

- **Efficiency**
  - Reduced sample size due to shared control
  - Time and cost savings through integration of new treatments into existing infrastructure
- **Flexibility**
  - Add new treatments or stop treatments early (adaptive design)
  - Other adaptive design elements, e.g., sample size reestimation, adaptive enrichment
- **Patient-centered**
  - Biomarker stratification
  - Response-adaptive Randomization

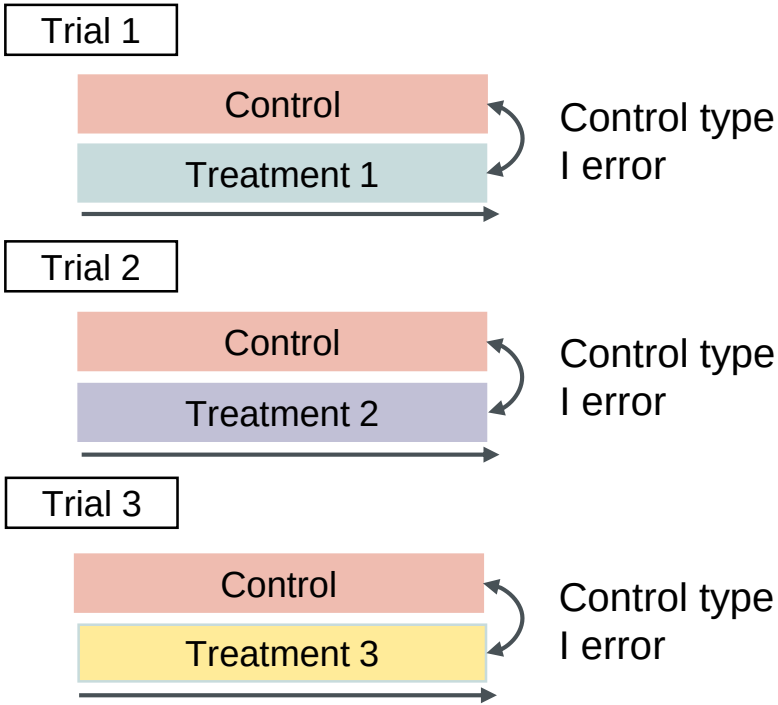
BUT: Numerous methodological and operational challenges

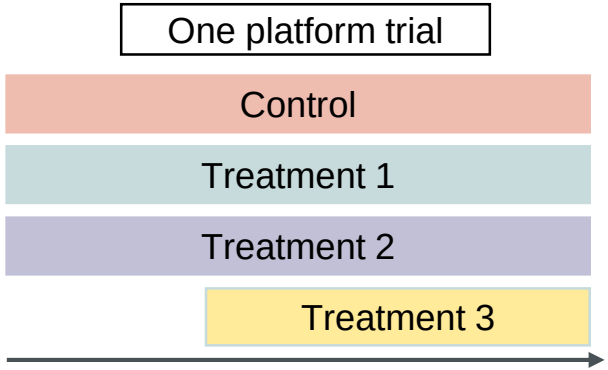
Type 1 error rate control in platform trials

Three possible causes of type I error rate inflation:

- Multiple hypotheses
  - Testing multiple treatments in a single trial
  - When is adjustment necessary?
- Repeated testing in (multiple) interim analyses
  - Commonly solved using a group sequential design
- Adaptations to the trial design
  - Type I error rate inflation caused by using the same data for learning and confirming

Multiple Hypotheses

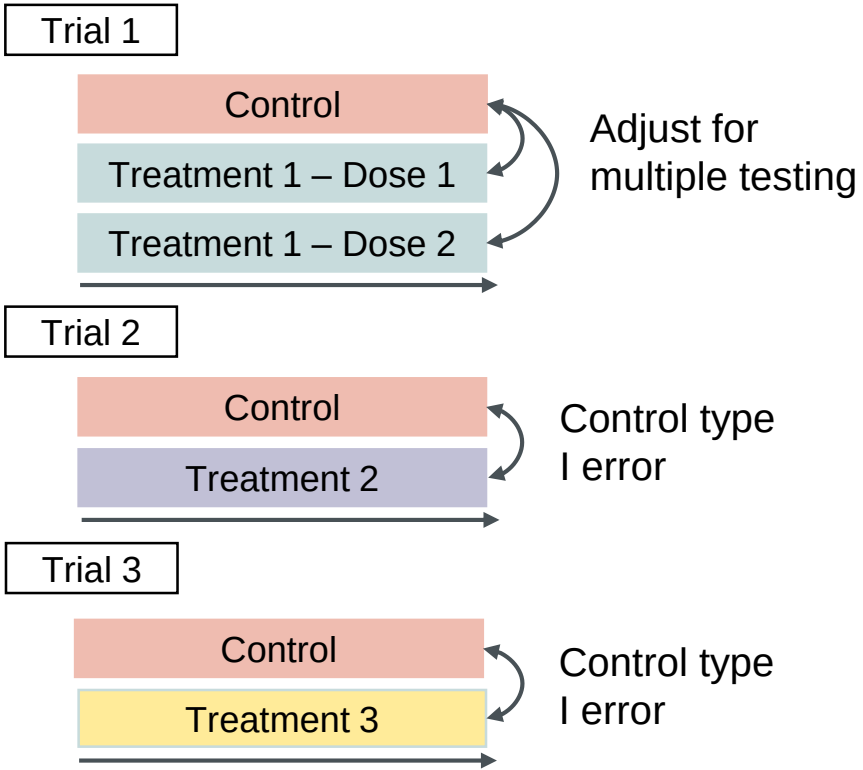


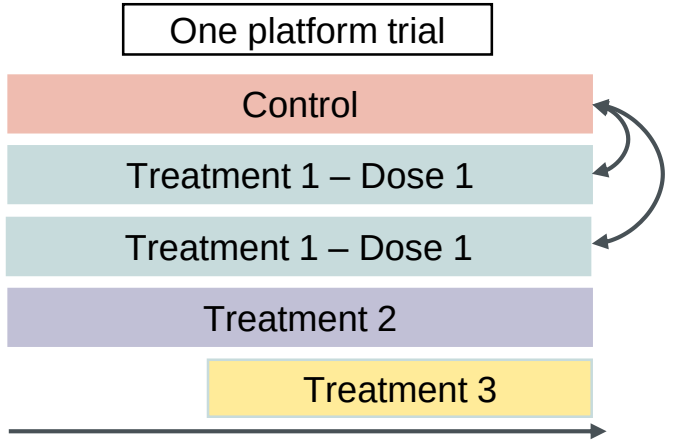


Adjust for multiple testing

Depends on the interrelationship between hypotheses

Multiple Hypotheses

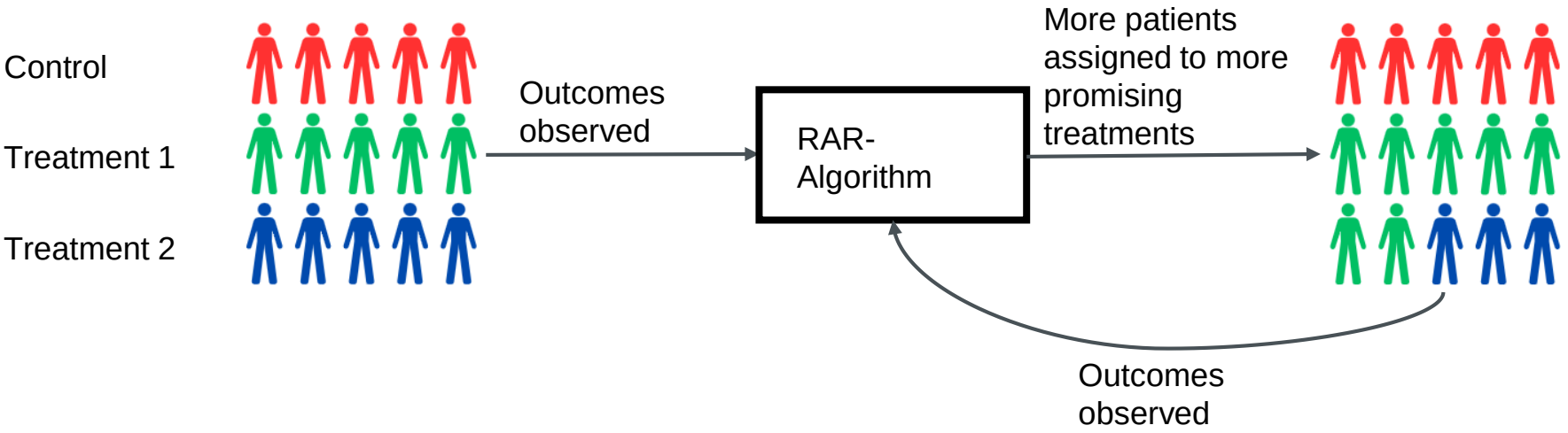




- Adjust for multiple testing between hypotheses that are not “independent”
- Adjusting for multiplity with added treatment arms requires special methods

Response adaptive randomization (RAR)

Definition: Randomization procedure in which the randomization ratio is adjusted regularly during the ongoing study based on the outcomes observed to date.



RAR in RAPID_REVIVE

Initialization phase: Randomization ratio 1:1 until the primary endpoint was observed for 150 patients

RAR-Phase: Randomization ratio proportional to the posterior probability that the respective treatment is the best, given the observed data

Challenges of RAR

- **Acceptance** by regulatory agencies
- **Adjustment in analyses** still an open research topic, e.g. re-randomization test
- **Integration into EDC-System** (secuTrial):
  Data exports at regular intervals → Generation of new randomization lists → Update of randomization lists in secuTrial (not straightforward)
- **Drug Supply:** Expected demand depends not only on expected recruitment, but also on randomization ratio

Randomization and Blinding

Blinding

- Treatments may differ in terms of appearance, dosing regimen, and route of administration
- Publication of results from completed arms may compromise blinding of the ongoing study.

➡ Matched Placebos (data sharing?)

➡ Double-Dummy Design

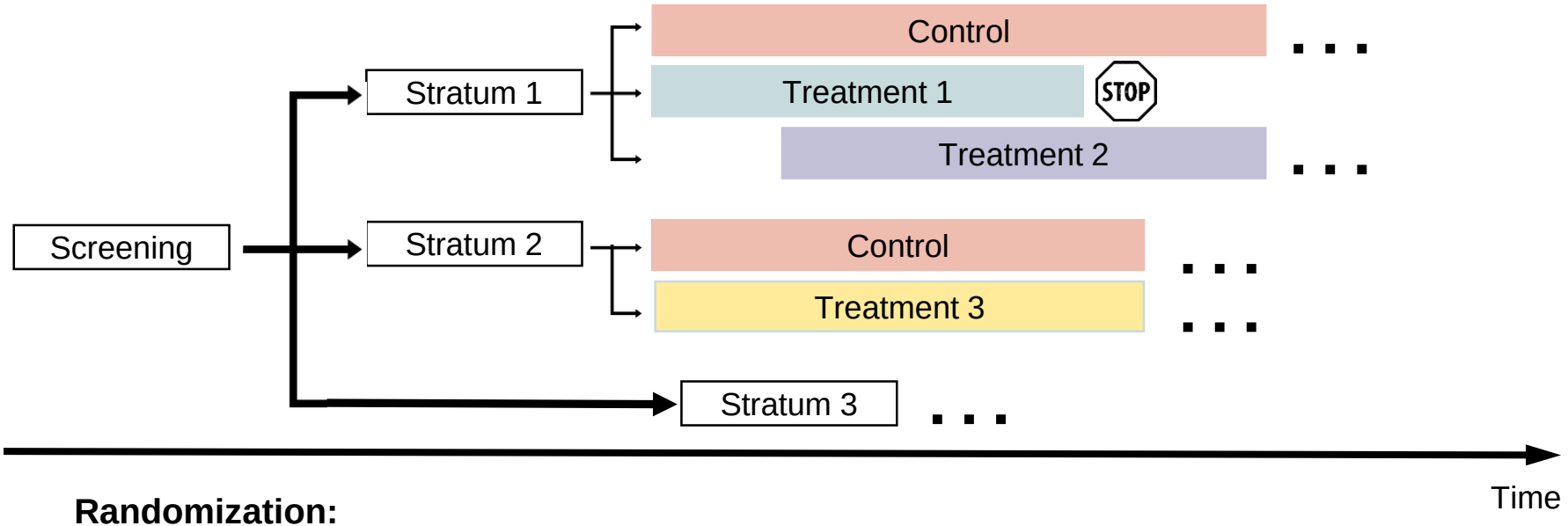
➡ Approximately 2/3 of all platform studies are open-label.

Randomization:

- Biomarker-stratification
- Differing eligibility criteria

➡ Two-stage randomization process

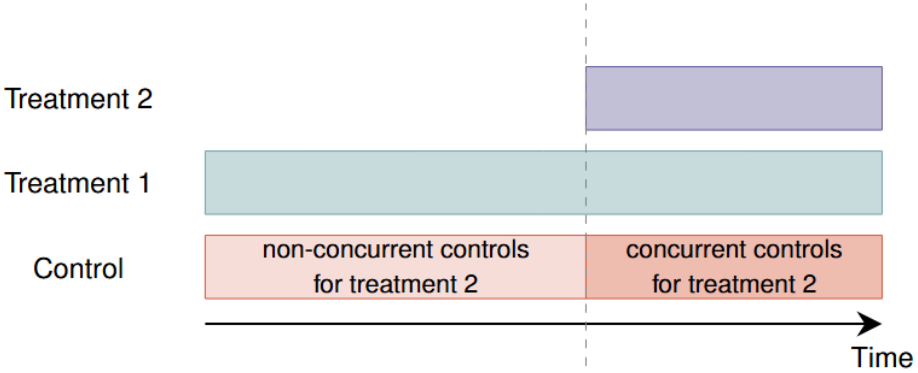
Two-stage randomization process



Randomization:

- Stage 1: Randomize patient between eligible strata
- Stage 2: Randomize between ongoing treatments within the stratum

Non-concurrent controls



The use of non-concurrent controls can:

- ✚ increase power / reduce the total sample size
- ▬ lead to biased treatment effect estimates if time trends are present in the data

Time trends can be caused, for example, by:

- Changes in the control group
- Changes in the baseline characteristics of trial participants
- Seasonal effects
- Mutations

⟶ The longer the duration of the study, the higher the risk of time trends

Non-concurrent controls

Non-concurrent controls can be considered “ideal” historical control data:

- Same inclusion/exclusion criteria
- Same endpoints measured
- Data collected within the same infrastructure

➡ Many potential sources of bias eliminated, but risk of bias due to time trends remains

➡ Established methods for historical controls can also be applied to non-concurrent controls: Bayesian borrowing, propensity score matching, etc.

But: typically only accepted by regulators for rare diseases, pediatric studies, exploratory studies, etc.

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Using simulation to design platform trials