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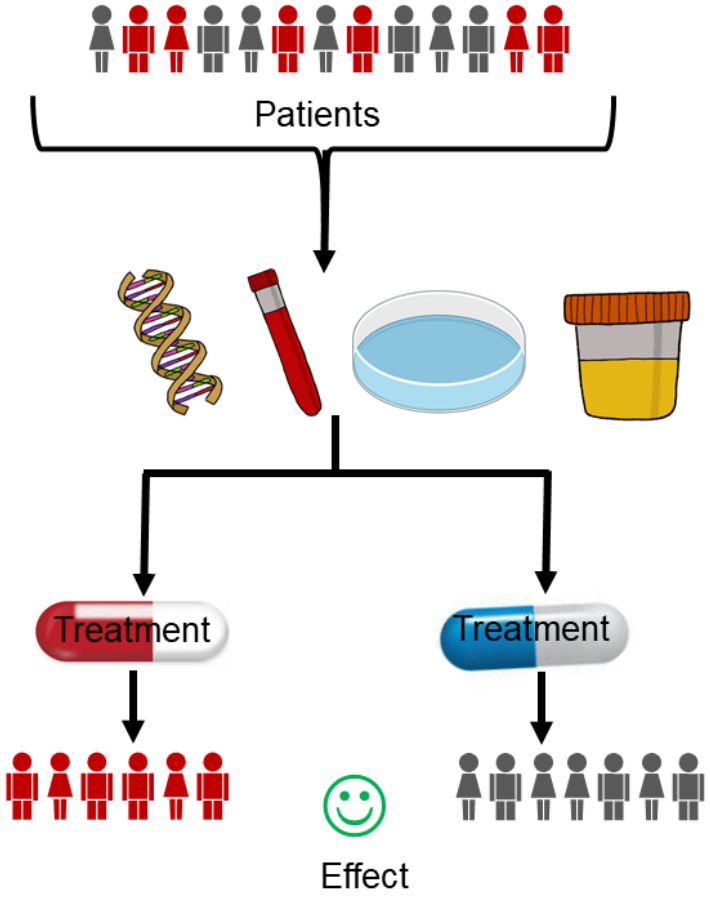
Estimands in personalized medicine

Cynthia Huber
Department of Medical Statistics
University Medical Center Göttingen

Personalized medicine



- Right drug for the right patient at the right time
- Choice of treatment
  - Accounting for disease and patient characteristics
  - Greatest benefit and least safety concerns (compared to alternatives)
- Stratification of patient population which may **differ in the efficacy** (or safety) of a specific treatment

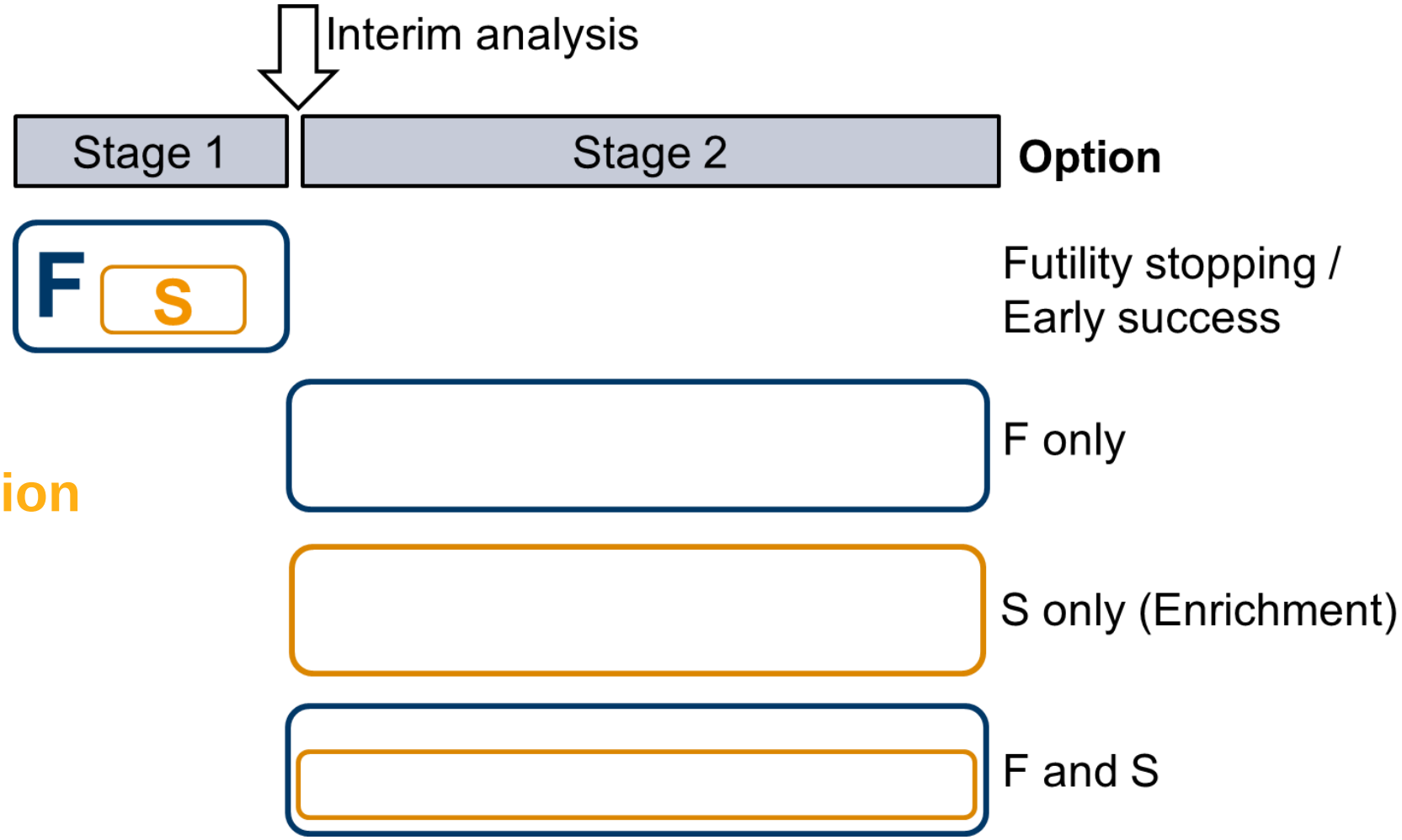
  → Subgroups defined by **predictive** biomarkers

Clinical trial designs for personalized medicine

- Assuming that a treatment works differently in different subgroups of patients
  - Randomized control trials **enrolling all patients not** necessarily **most efficient approach**
  - Enrichment designs (Temple, 2010)
    - → Recruit only patients likely to benefit, e.g. biomarker-positive patients
    - → **Risk of missing out** on subgroups that could benefit from treatment
- Data should be generated in both BM+ and BM- patients from a regulatory and public health perspective
  - Evidence on treatment being beneficial in biomarker-positive (BM+) patients, but uncertainty regarding benefit in biomarker-negative (BM-) patients

→ **Complex innovative trial designs for personalized medicine,** e.g. adaptive designs

Adaptive enrichment design



BM+ sub-population

Full population

Friede et al (2012)

Estimands for adaptations of study population

- **Dual objective** of assessing efficacy in both BM+ patients and full population
  - → Definition of **two separate estimands** in BM+ and in full population (Collignon et al, 2022)
  - → **Estimands differ** in definition of **population**
  - → Other attributes could but do not necessarily have to be the same
- Information regarding **efficacy in BM- needed** for informing the decision of approval and reimbursement in either the full population or the BM+ subgroup only (Collignon et al, 2022)
  - → **Estimand for BM−** may be important
  - → Differs from estimands of full and BM+ population by the ”population” attribute
- **Discontinuation** of the BM- subpopulation at interim
  - → Continuation of trial with a **single estimand**

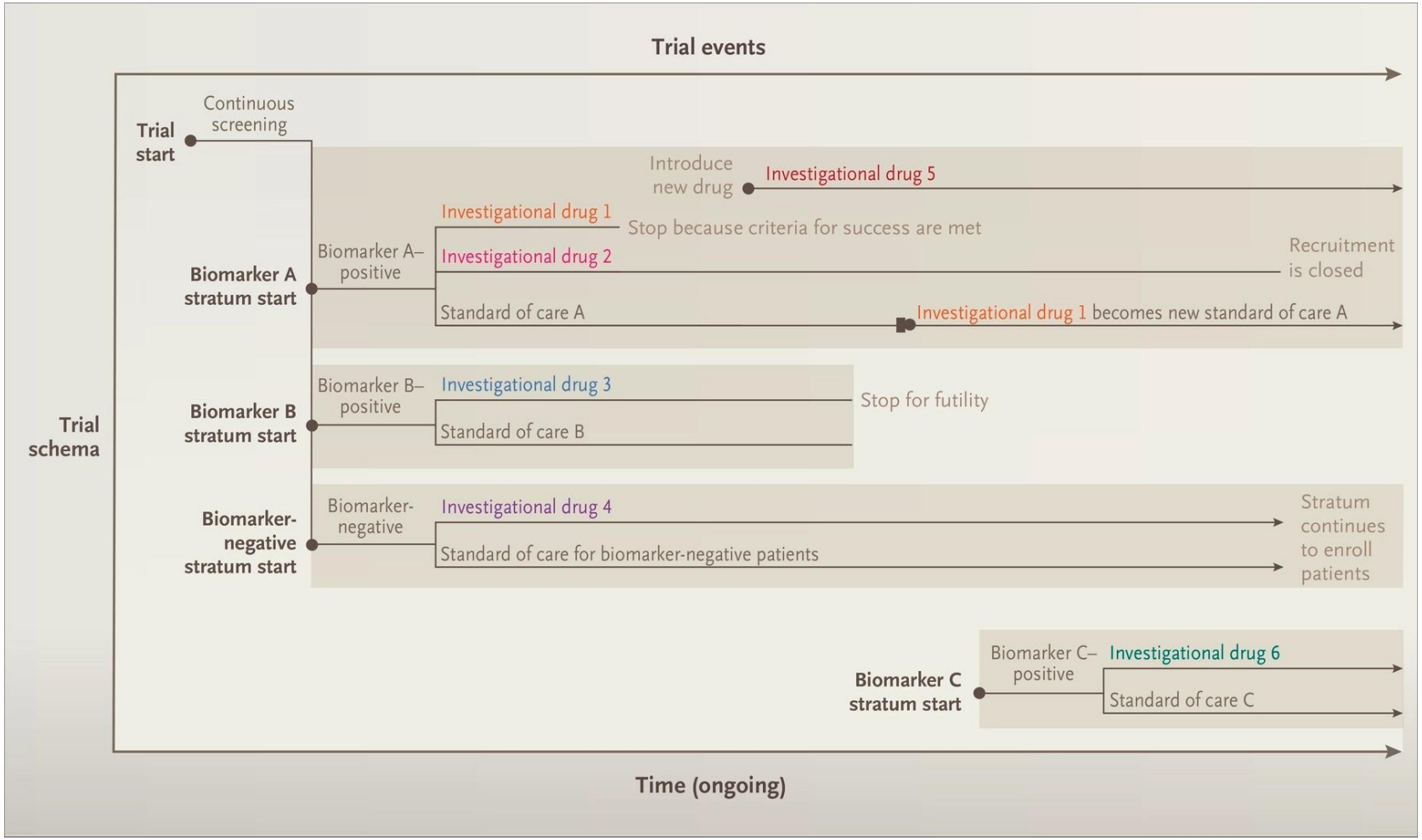
Other attributes of estimands framework

- Sometimes the **primary endpoint only available after long-term follow-up**
  - → Subgroup selection needs to be based **on early outcome data** (Friede et al ,2011; Kunz et al, 2012)
    - → E.g. PFS and OS in oncology (Jenkins et al, 2011)
  - → Different summary effect measure might be needed
  - → **Estimands** at interim analysis and final analysis **might differ** in **"variable"** and **"population-level summary"** attributes
- Meaning of **intercurrent events** might be different at interim and final analysis
  - E.g. Treatment discontinuation less likely at early interim analysis
- Some **intercurrent events** might only occur in one of the subgroups, i.e. BM+ or BM-
  - E.g. Different safety and/or efficacy profile in subgroups leading to treatment discontinuation due to adverse events/ lack of efficacy in just one of the subgroups

Other adaptations

- **Optimal cut-off** could be adaptively chosen in a trial
  - Biomarkers often measured on a continuous scale
  - Cut-off selection needed for defining BM+ and BM- subgroups
  - Pre-specification of a continuum of subgroups
    - → **Continuum of** pre-specified **estimands** (Collignon et al, 2022)
    - → Only one of these estimands will be chosen
- **Data-driven subgroup selection** at interim analysis, e.g. Johnston (2021)
  - Pre-specification of subgroup identification method
  - No pre-specification of subgroups, i.e. biomarkers and corresponding cut-offs
  - “Population” attribute cannot be described initially

Platform trial



Woodcook and LaVange (2017)

Estimands in platform trials

- Adding a new treatment arm to a platform trial
  - → Adding another objective (comparing the new treatment vs. control)
  - → Adding another estimand
- Prespecification of estimand not necessarily at start of platform trial
  - → But before adding the new treatment arm (Collignon et al, 2022)
- Interim analyses in platform trials for dropping ineffective treatment arms
  - → Trial continuation with remaining estimands

Modification of treatment

- New evidence during a running trial can lead to a **modification of the control arm**
  - → E.g. Approval of a **new treatment replacing** the original **standard of care**
  - → **Two stages in the trial**: One with control treatment 1 and one with control treatment 2
- Comparable situation in platform trials when new treatment is added as data accrue
- Patients recruited to control prior to the addition of the new treatment/ prior to new control treatment are **nonconcurrent**
  - Discussion on whether or not including nonconcurrent patients for estimation in literature, e.g. Lee and Wason (2020), Lee et al (2021)
  - If main interest is comparison of treatments with a control regardless of any changes to the standard of care throughout the trial
    - → Treatment attribute of estimands would remain aspecific: state-of-the-art control therapy
    - → No update to estimands needed

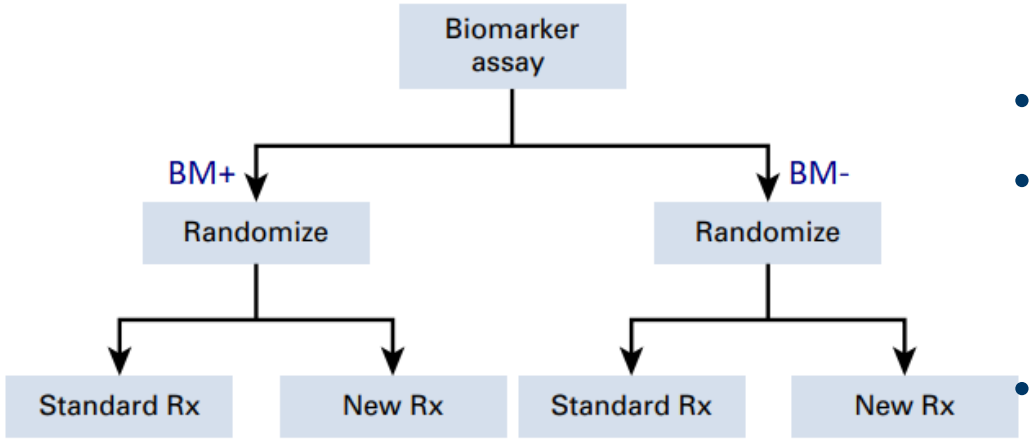
Estimation

- Selection of a subgroup at the interim analysis (Kimani et al, 2015)
  - Estimates are expected to be biased
  - Adjustment of confidence intervals and hypothesis test needed to control the error probabilities for the selected estimand
- For platform trials adding treatments during the trial
  - Proposals of borrowing information from nonconcurrent controls
  - Less bias by borrowing information within a trial than from external trials (Burger et al, 2021)

    → Many standardized aspects of trial less likely to cause bias
  - Adjustment of time trends needed when nonconcurrent controls are used

    → Otherwise, risk of bias (Lee and Wason, 2020; Dodd et al, 2021)

Collapsibility



Biomarker-stratified design

- Common practice for estimating **efficacy in full population**: Combining the strata and comparing the drug to the control in a meta-analytic approach (Okwuokenye, 2019)
- Estimates should be collapsible over subgroups
- Estimate of full population is collapsible if it is a weighted average of estimates in the subgroups, i.e. BM+ and BM-
- Odds ratios (OR) and hazard ratios (HR) are non-collapsible (Didelez et al, 2021)
- OR and HR can make a prognostic biomarker appear predictive even in RCTs (Liu et al 2022)

Discussion

- Recent review on estimands and complex innovative designs including master protocols, adaptive designs by Collignon el al (2022)
  - Estimand framework is applicable to complex innovative designs which are also used for personalized medicine
- All five attributes could be affected using adaptive designs and master protocols for personalized medicine purposes
- Development of new adaptive designs using data-driven subgroup identification
  - Lack of experience in practice of such designs
  - Lack of experience on the applicability of the estimand framework

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