Federal Institute for Vaccines and Biomedicines

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Innovative Study Designs in Oncology
from a regulatory point of view

Dr. Benjamin Hofner
Section Biostatistics

Disclaimer

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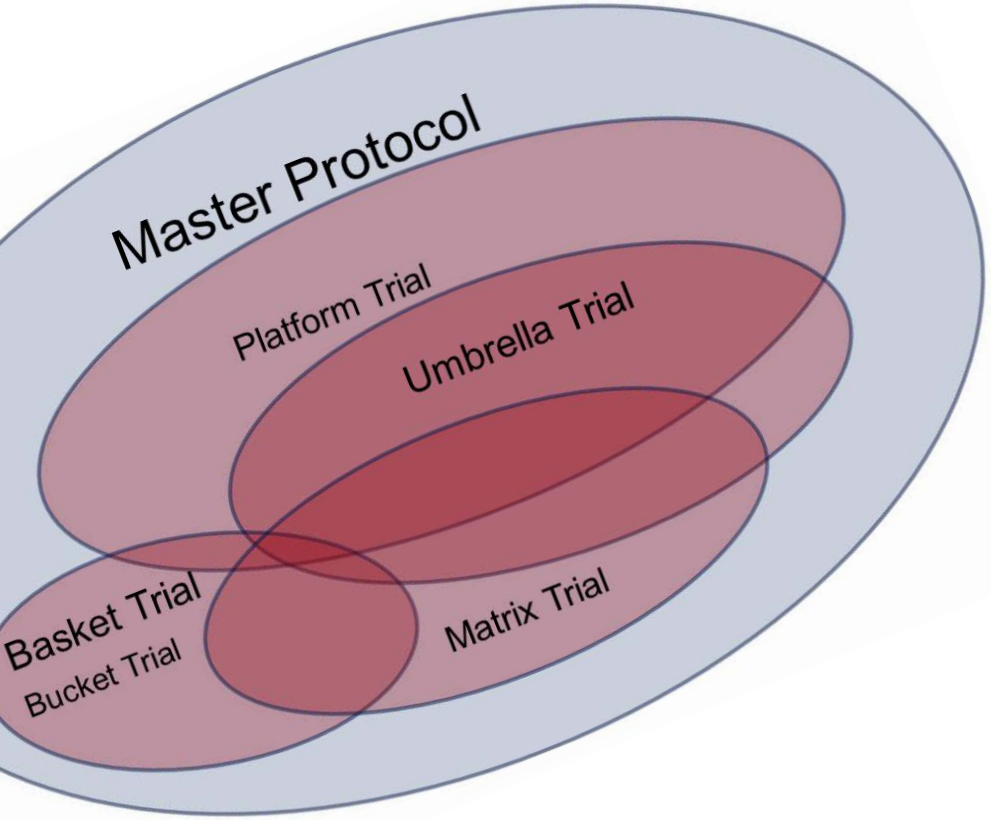
Novel trial designs

The complex landscape

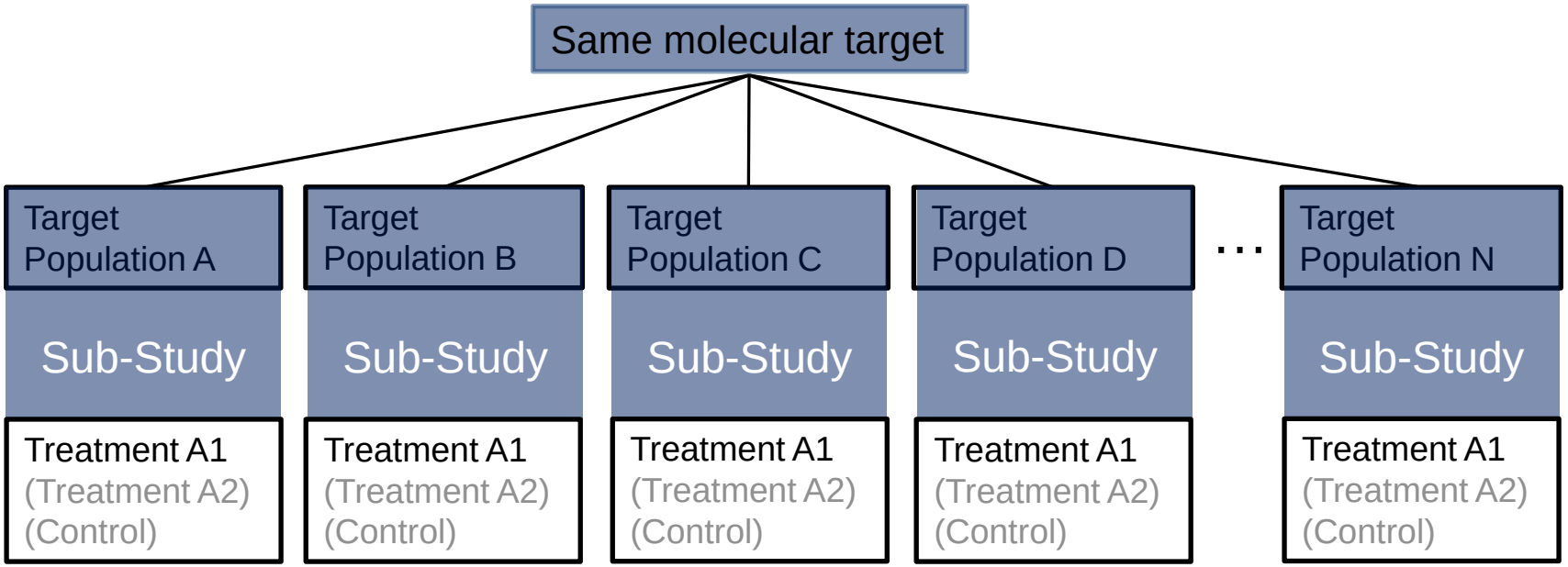


- No unique definition exists
- Different authors and sponsors use different definitions
- **Example**: NCI Match Study
  - Allocate patients based on tumour profiles
  - Enrol patients with different tumour entities
- Renfro & Sargent (Ann. Oncol., 2017): **Basket Trial**
- Woodcock & LaVange (NEJM, 2017): **Umbrella Trial**
- Names not so important to assess / judge trial
  - Design and analysis considerations count

Central aspects of master protocols

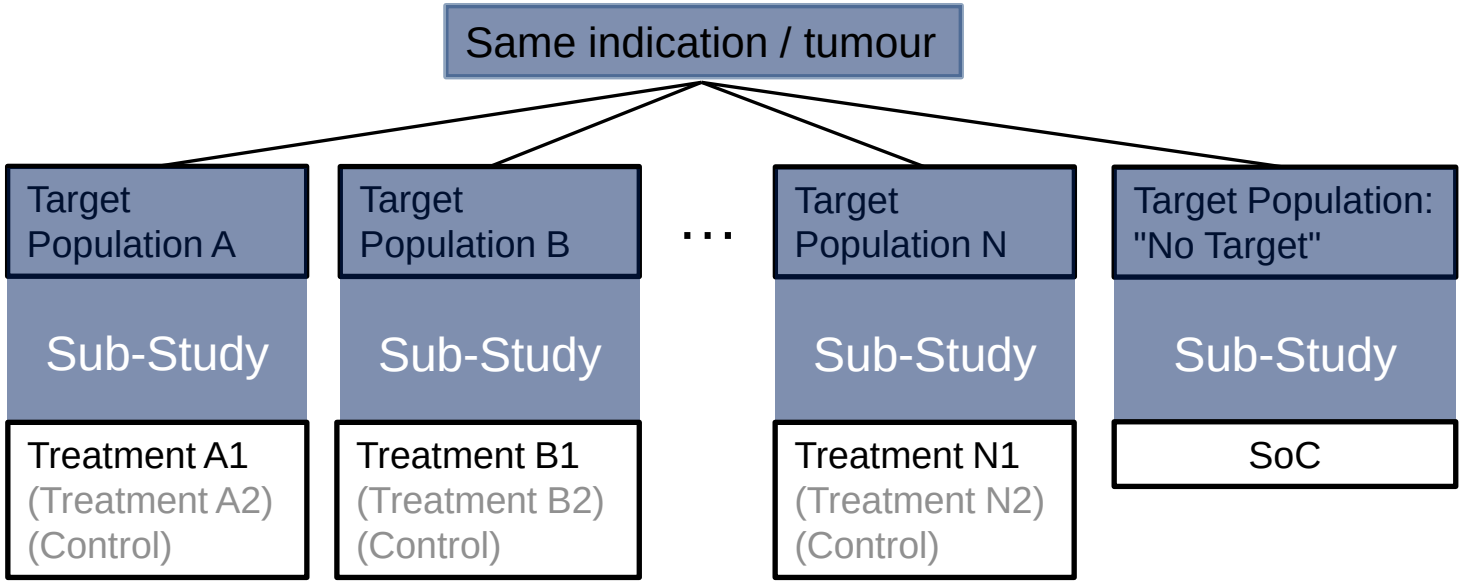
- Multiple **target populations** based e.g. on
  - Biomarkers
  - Indications
  - Tumour histologies
- Target population(s) define **sub-studies**
- Sub-studies can have **one or more arms**
  - Controlled or uncontrolled sub-studies

Basket trial



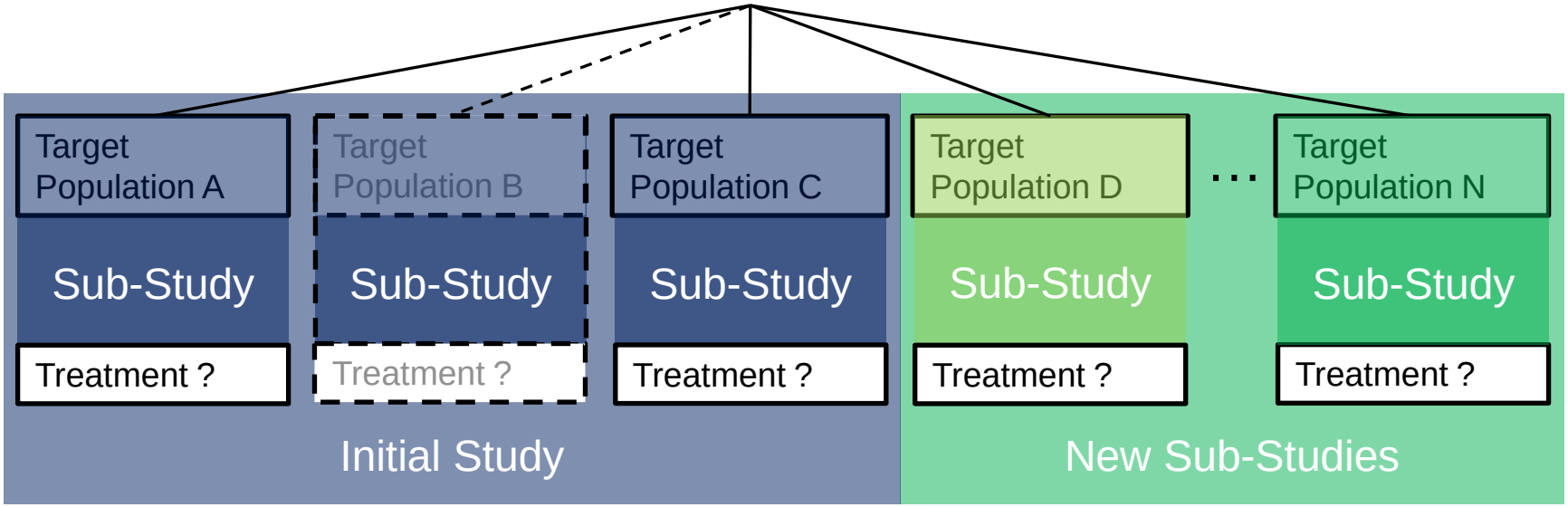
Identical treatment(s) for all sub-studies
→ basket trial

Umbrella trial



Different treatment(s) for sub-studies
→ umbrella trial

Platform trial



Adaptive trial with sub-studies or arms within sub-studies opening/closing, either of basket or umbrella-type
→ platform trial

Current situation in CTA

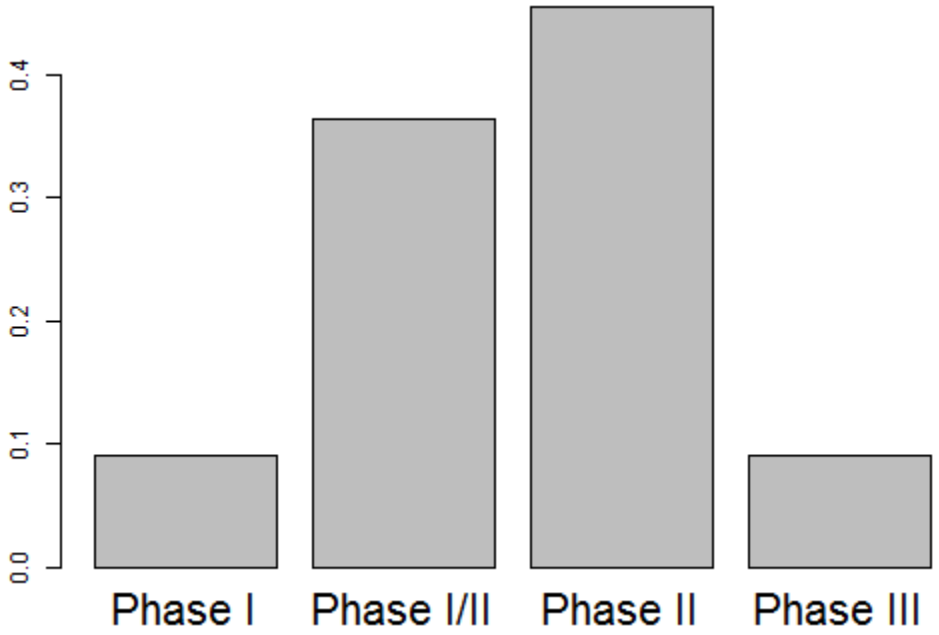
Current situation at PEI

- Approximately 2 master protocols per months are submitted to PEI for CTA[1)]
  - 22 in 11 months (= since we started counting prospectively)
  - Per month we receive approx. 40 to 50 CTAs in total
  - ➢ Approx. 5% are master protocols

[1)]National agencies (NCAs) are directly responsible for the authorisation of clinical trials; Approval of marketing authorization applications usually centralised via EMA

Current situation at PEI

Trial phase

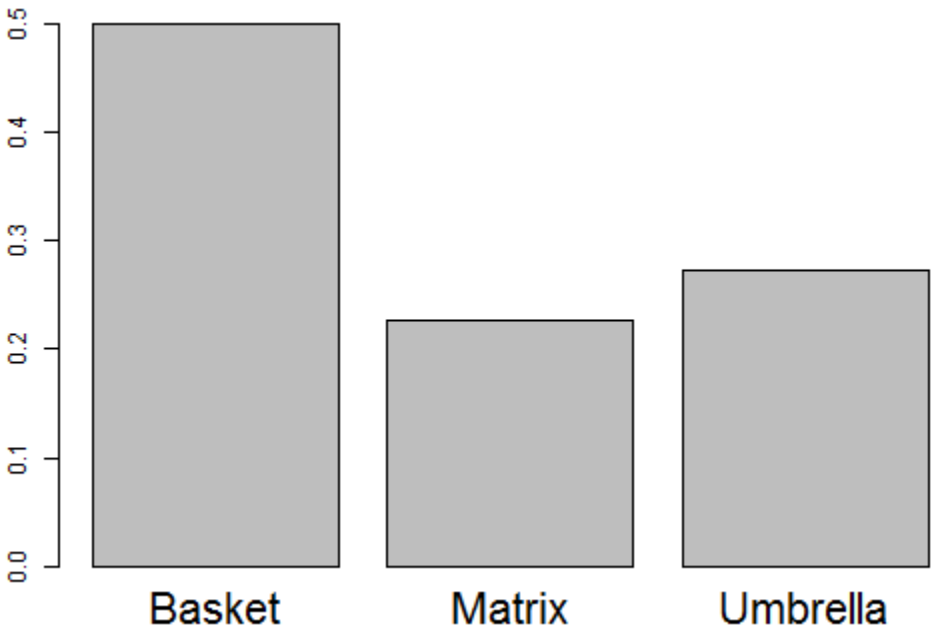


- Mostly early phase trials
- Note that the fraction of pivotal trials might be higher than 10%

➢ see e.g. Keytruda in MSI-high/dMMR patients which was approved based on pooled trial results (“basket type”) from uncontrolled Phase II data by FDA

Current situation at PEI

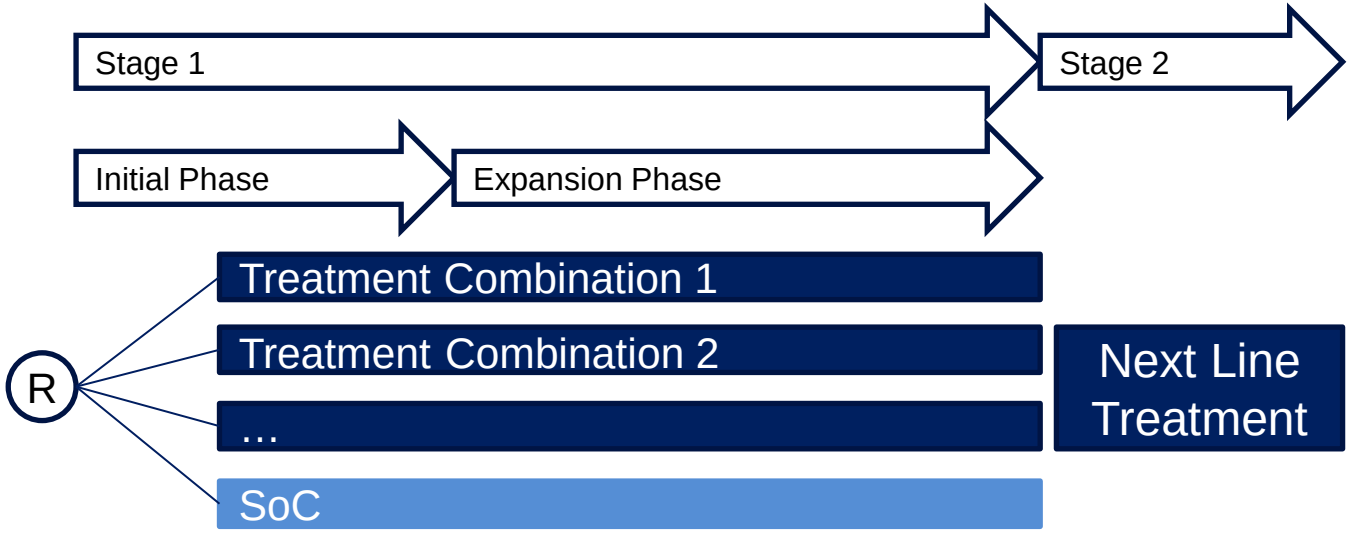
Type of trial



- Matrix trial = multiple indications, multiple treatments
- Some of the trials plan for modifications / new sub-studies / new study arms

Example 1

Randomized umbrella trial



- Progression in Stage 1 > New treatment in Stage 2
- DMC/DSMB is implemented to oversee the safety of the study
- Global in-/exclusion criteria + specific exclusion criteria exist for all study arms (but SoC), i.e.,
  - At randomization an arm will be removed from the list of potential arms for that patient if exclusion criteria for a specific arm are met

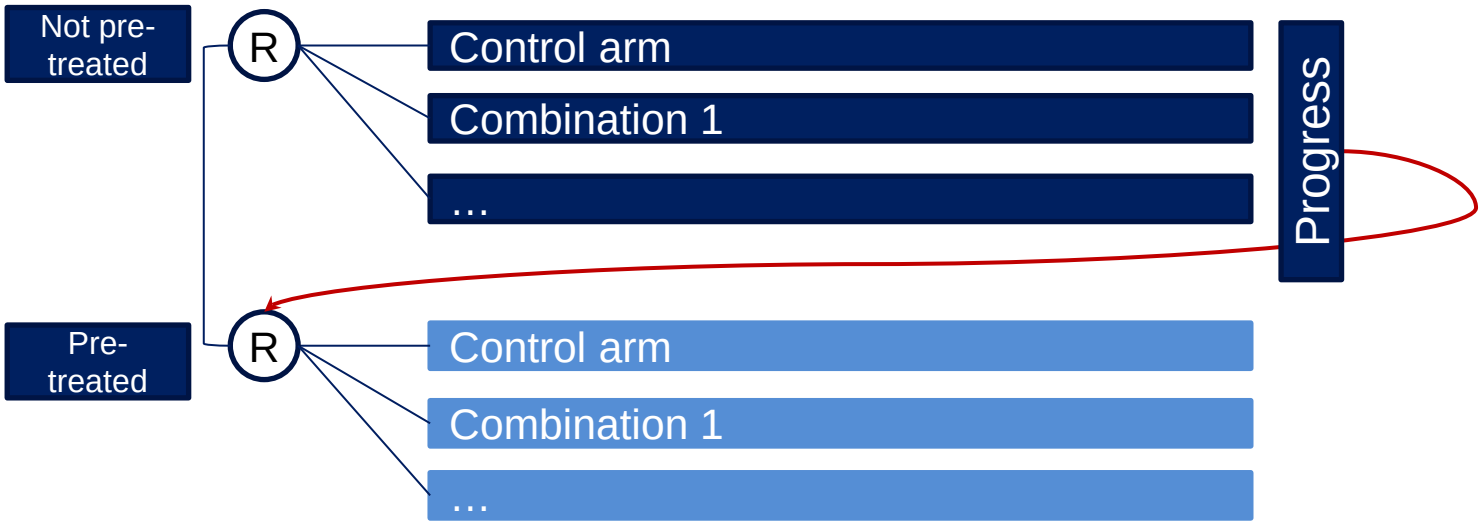
Statistical methods

- Bayesian two-stage approach:
  - Posterior probabilities will be used to guide further enrollment based on the interim analysis of clinical activity in the experimental arm compared with the control arm.
  - If the interim analysis suggests that the activity in an experimental arm is higher than that in the control arm, there may be enrollment of additional patients in the experimental arm.
- Primary analysis:
  - ORR and difference in ORR to control arm together with 90% CIs
- Arms can be opened and closed at the discretion of the sponsor
- Dynamic randomization
  - to account for fluctuation in the number of treatment arms that are open for enrolment during the study
  - to account for promising efficacy in specific arms
  - randomized to the control arm can be capped at any given time

Example 2

“Real” master protocol

- The Sponsor proposes a Phase II study for oncologic indications
- Currently, one indication under investigation
- Two cohorts depending on pre-treatment with targeted therapies
- Sub-studies might have different in-/exclusion criteria



- Sub-studies are submitted as separate protocols

Statistical methods

- Overarching statistical analysis plan and study design defined within master protocol
- Primary analysis:
  - Based on Simon's 2-stage design for ORR
  - Futility / efficacy boundaries depend on cohort (but not on treatment)
  - ORR with 95% CIs per sub-study
- Additionally, median DOR, PFS and OS rates at various landmarks will be obtained with 95% CIs
- All analysis will be conducted independently
- Relative benefits will be additionally assessed for decision making

Example 3

Phase III basket trial

- The Sponsor proposes a Phase III study for an oncologic indication. The IMP is a monoclonal antibody targeted to PD-L1.
- Two independent cohorts are planned based on eligibility of backbone therapy

Statistical methods

- Randomization is done per cohort using the same strata.
- Analyses are (almost) identical for both cohorts but are conducted strictly separate with separate (but equal) objectives and hypotheses.
- Importantly, the Sponsor plans to use a separate significance level of $\alpha = 0.05$ (two-sided) for each of the cohorts.

➢ The Sponsor does not call this study a basket trial but all statistical and design elements equal a basket trial.

  ➢ Hence, one can conclude that this is a basket trial.

✓ It would be acceptable to conduct separate studies for each of the cohorts *or,* as done here, to use separate T1E control.

Summary of examples

- A wide variety of trial designs and analysis approaches exists under the label of master protocols
- “Master protocol”-like designs exist longer than the advent of corresponding terms and research (but were of course not called that way)
- Especially in orphan indications, the phase of study does not necessarily translate into its purpose
  - Phase I or II can be pivotal!
- **Cave:** Master protocols are the exception, not the norm

Current statistical-regulatory position

Current position

from a statistical-regulatory perspective

Acceptability might depend on

- Phase of study (exploratory *vs* confirmatory)
- Rationale for master protocol (combined study *vs* a series of studies)
- Study design (dependent *vs* independent sub-studies)
- Planned analyses (pooled analysis *vs* separate analyses)
- Rationale for analyses (common indication *vs* separate indications)
- Adaptive design (adaptive *vs* fixed design; pre-specified *vs* ad-hoc; type of adaptions)

Note:

In this talk I will not cover the reasons for conducting such trials as this will be done in other talks.

Important considerations

- Master protocols cannot be used to **lower regulatory standards**
  - Strength of pivotal evidence needs to be the same as with “regular” trials in the same indication

- Master protocols cannot be used to **reduce contact with regulators**
  - Initiation of new sub-trials must be submitted to NCAs, either as new protocol linked to the master protocol or as substantial amendment
  - Seamless designs cannot be approved as a whole; Sponsors must provide a substantial amendment after first phase to update B/R

Type 1 error control
in basket / umbrella trials

- Depends on study phase
  - Exploratory vs confirmatory
  - Yet, always sensible in order to minimize false positive results (and risk in further development)

- Possibly no impact on T1E if sub-studies are independent
  - ➢ Using separate T1E per sub-study might be acceptable
  - Separate hypotheses?
  - Clear separation of target populations?
  - *Rationale and regulatory acceptance* to evaluate B/R separately for each sub-study?

- Possible approaches for dependent sub-studies
  - Confirmatory analysis in pooled data followed by exploratory analyses in sub-studies (to assess consistency)
    > Subgroup GL (EMA/CHMP/539146/2013)
  - Common T1E control also for sub-trials, e.g. in an hierarchical fashion
    > Multiplicity GL (EMA/CHMP/44762/2017)

- ➢ **What about platform trials / adaptive designs?**

Type 1 error control
in platform trials / adaptive designs

- Platform trials are usually **more challenging** than fixed design basket / umbrella trial

- T1E might **not** be affected if sub-studies are independent and new treatment introduced via a new sub-study
  - T1E control per sub-study
  - ➢ New sub-study same as new external study

- T1E if sub-studies are modified?
  - Adaption needs to be pre-planned and
  - Measures to control T1E must be pre-specified!

- T1E if sub-studies are dependent?
  - Common hypothesis
  - Common control arm
  - ➢ Adaptions and measures to control T1E must be **pre-specified**!

Bias

in platform trials / adaptive designs

- Bias might occur (in both cases, independent and dependent sub-studies)
  - Selection bias (overestimating therapy effect due to selection of sub-studies)
  - Operational bias (change of patient population and conduct of study)
  - ➢ How to avoid, minimize or correct for this?
  - ➢ Measures must be **pre-specified**!

- ➢ For dependent sub-studies see also GL on adaptive trials (CHMP/EWP/2459/02)

Pooling and transfer of evidence
(especially in basket trials)

- Clinical rationale for pooling
  - is strongly required, at least if primary endpoint is based on pooled population
- Grounds for pooling might be challenged
  - Same prognosis?
  - Same effect size / homogenous effect in all sub-studies?
  - Same SOC / treatment possible in control arm?
  - Same effect with control?
- In general, pooling can be envisaged as supportive / exploratory analysis but might be difficult to justify as primary analysis.
- Same considerations apply for transfer of evidence (“borrowing”)

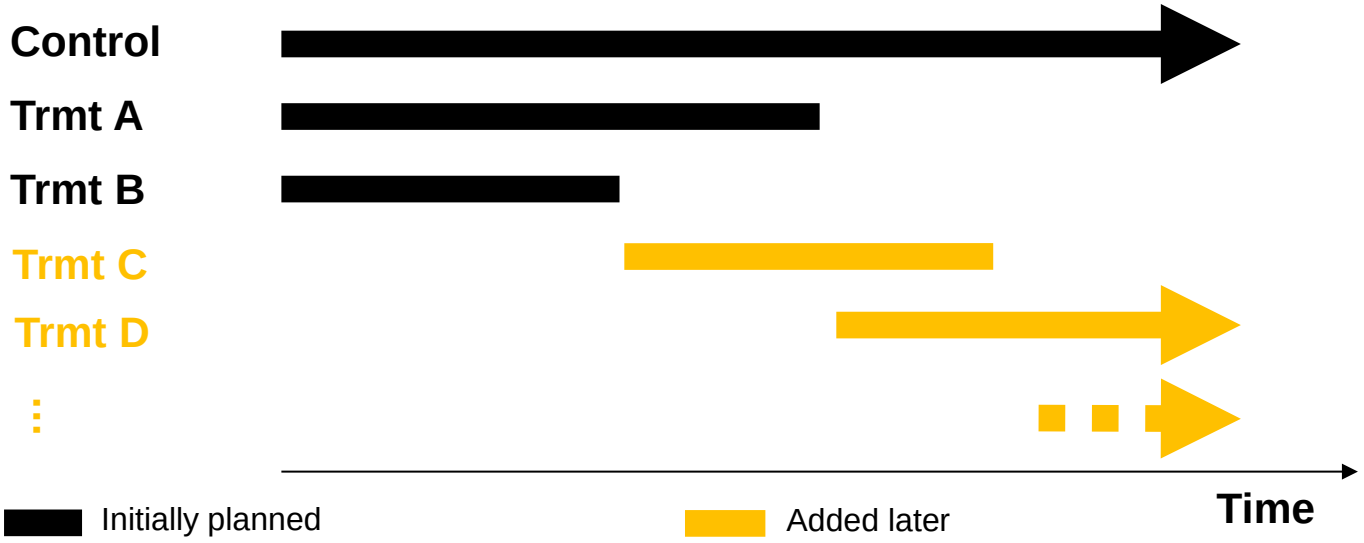
Overlapping target populations
(especially in umbrella trials)

- Regulatory decisions are complicated if target populations overlap

- E.g. in umbrella trials when patients express multiple biomarkers, allocation to sub-studies not uniquely defined
- ➢ If biomarker distribution in sub-study does not reflect population prevalence, bias might occur (see issues with pooling), e.g., due to
  - different prognoses or
  - different treatment effects

Shared control arm
(especially in umbrella trials)

- How can we define a relevant control group?



  - Preferably use separate control arms per sub-study
  - If using a shared control,
    - use *concurrent* controls.
    - use controls which *would have been eligible for the treatment arm*.
  - Pooling controls should be reflected carefully!

Shared control arm
(especially in umbrella trials)

- How can we deal with multiplicity?
  - Separate T1E control not (negatively) affected by shared control arm
  - Common T1E control
    - (Positive) correlation reduces the overall FWER ($= P(V \geq 1)$) [1)]
    - Bonferroni-type adjustments controls the PFER ($= E(V)$) and FWER
    - Sequential methods (hierarchical testing, graphical methods, …) inflate PFER but control FWER

[1)] V: Number of false positives

Shared control arm
(especially in umbrella trials)

- **Problem** (in both cases)
  - Positively correlated decisions → $Var(V)$ is increased[1)]
    - If shared control group is especially bad → V is increased (→ many wrong approvals)
    - If shared control group is especially good → V is decreased (→ many wrong denials)
  - No final regulatory solution!

- More information, e.g., in Howard et al. 2018 [2)]

[1)] V: Number of false positives

[2)] Howard, Brown, Todd, Gregory (2018). *"Recommendations on multiple testing adjustment in multi-arm trials with a shared control group*". Statistical Methods in Medical Research. 27 (5): 1513-1530.

General recommendations

- Provide sound scientific (and/or operational) rationale for master protocol
- Identify possible issues
- Pre-specify solutions within protocol
  - ✓ Pre-specify possible adaptions of the study design
  - ✓ Pre-specify and discuss T1E control
  - ✓ Pre-specify and discuss measures to prevent bias

Take-home messages

- Of note, this is an *ongoing discussion*.
- Sound planning and scientific rationale required
- Master protocols are generally (more) acceptable for *exploratory studies*
  - Possibly acceptable as pivotal study if T1E is adequately controlled
- Pre-specification of possible adaptions helps to maintain study integrity, validity and T1E control
  - Data driven ad-hoc changes are considered problematic
- Consider existing guidelines
  - Adaptive clinical trials (CHMP/EWP/2459/02)
  - Sub groups (EMA/CHMP/539146/2013)
  - Multiplicity (EMA/CHMP/44762/2017)
  - (Specific guidelines and position papers are in preparation)
- Especially for *confirmatory trials* scientific advice is highly recommended.

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(in alphabetic order)

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