Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

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European regulators' view on platform trials

Lessons recently learned

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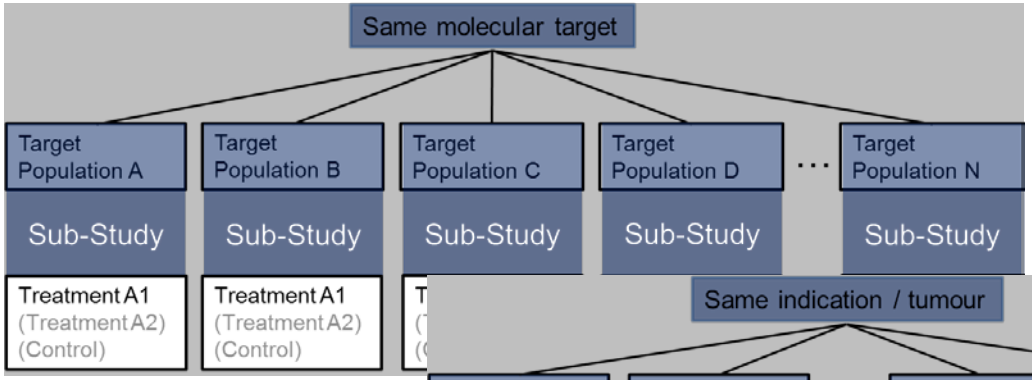
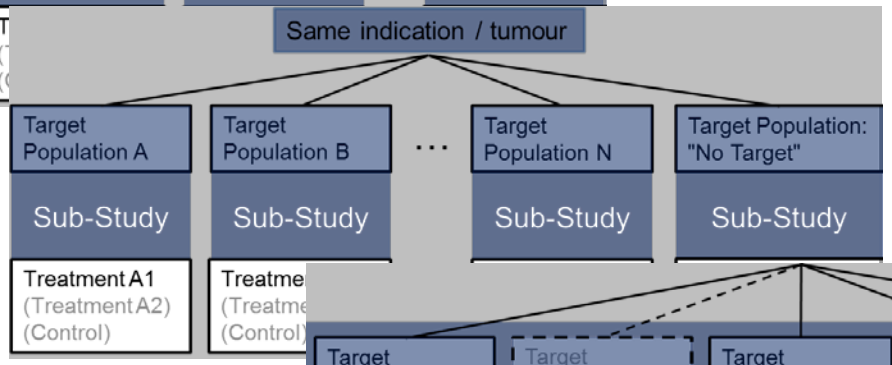
The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

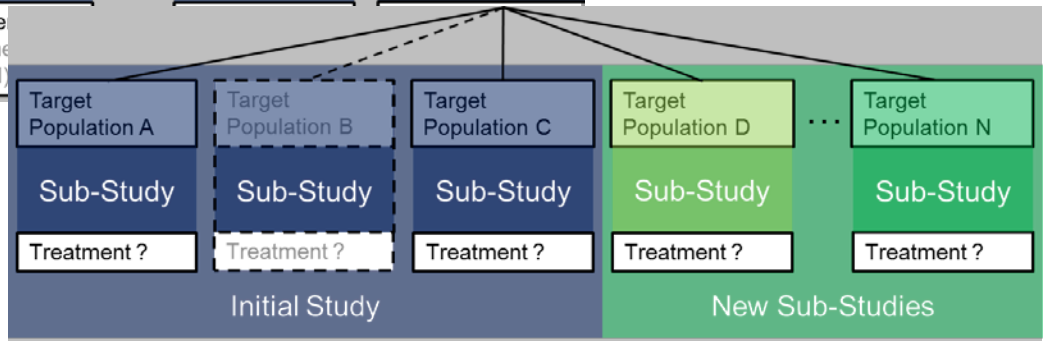
Overview on general designs in master protocols



Basket trial
(same target, same treatment different indications)



Umbrella trial
(different targets, different trmts, same indication)



Platform trial
(adaptive version of any of the above trials)

- Often trials do not fit exactly in any of the above schemes.
- Use design and analysis considerations to judge trial rather than names.

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Current position on master protocols

from a statistical and regulatory perspective

Acceptability might depend on design issues, such as

- 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)

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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[1)], 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

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

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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?**

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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)

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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

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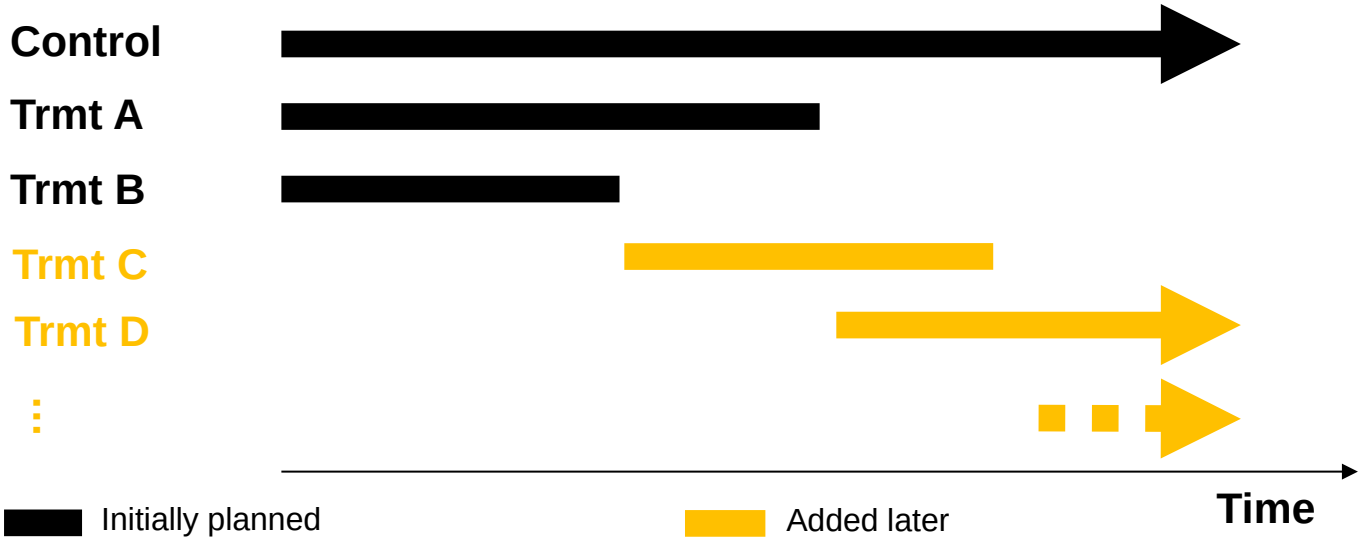
Shared control arm
(especially in umbrella trials)

- 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!

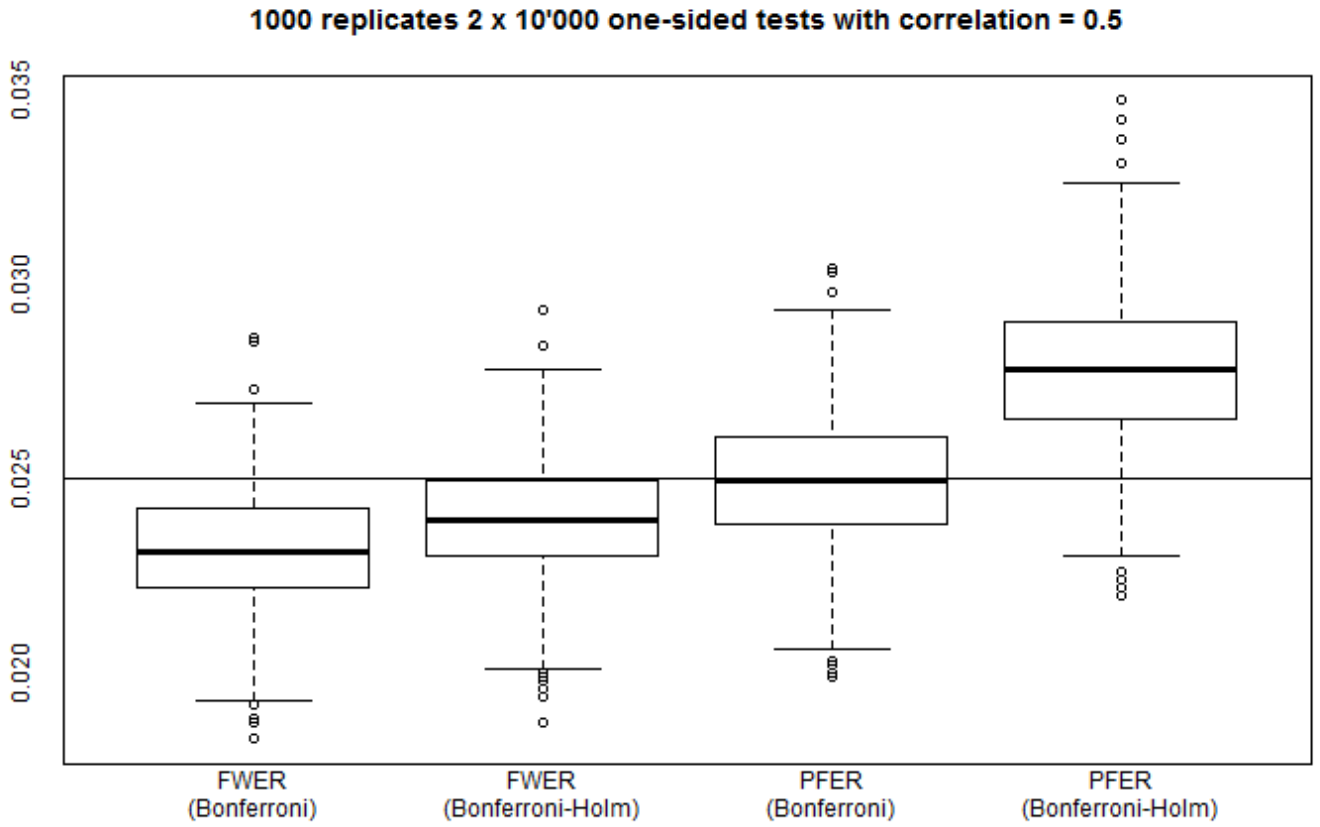
Shared control arm
(especially in umbrella trials)

- 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
  - 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.

Shared control arm
(especially in umbrella trials)



Further challenges

not related to statistics… but very relevant to regulators!

- Complexity of study (negatively) impacts, e.g.,
  - patient information and informed consent
  - logistics
  - legal aspects
- Conduct of study
  - DMC are important (irrespective of study phase)
  - Changes in ongoing study need to be approved by NCAs
  - Initiation of next phase (e.g. in seamless designs) needs to be approved by NCAs (via substantial amendment)
  - Whole study will be stopped if issues in one arm arise
- Risk of never ending studies
  - End of study must be pre-specified within the protocol

General recommendations

- Provide sound scientific (and operational) rationale for master protocol
- Identify possible issues
- Pre-specify solutions within protocol

✓ Pre-specify and discuss T1E control
  - Given study goals and study phase

✓ Pre-specify and discuss measures to prevent bias
  - Operational and statistical methods to reduce or prevent bias
  - Bias might be less of an issue if signal is large and consistent over multiple endpoints and sub-studies (matter of assessment)

✓ Pre-specify possible adaptions of the study design
  - Describe decision criteria and following changes
  - Describe impact on study integrity and validity
  - Pre-specify a plan to check impact of changes

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.

Acknowledgments
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