European regulators’ view on platform trials

Lessons recently learned

Disclaimer

The following slides represent our personal views and do not necessarily reflect the views of the Paul-Ehrlich-Institut, EMA or any other European agency.
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.
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)
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

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1) National agencies (NCAs) are directly responsible for the authorisation of clinical trials; Approval of marketing authorization applications usually centralised via EMA
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
  - More information, e.g., in Howard et al. 2018\(^2\)

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1) V: Number of false positives
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.
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