EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Reflection paper on establishing efficacy based on single-arm trials

Presentation of draft for public consultation

EFSPI Workshop 13/14 September 2023

Presented by Kit Roes

Motivation for a reflection paper on single-arm trials

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- Relevant proportion of marketing authorisation dossiers with pivotal data from single-arm trials (SATs)
- Across different therapeutic areas, including for rare diseases
- Recurring challenges for regulatory assessment across dossiers
- No dedicated regulatory guidance

- ➢ Need to (i) communicate challenges with SATs, and (ii) improve the design, conduct, analysis, interpretation and assessment of results from SATs.
- ➢ Relevance of public discussion

Mandate for a reflection paper on single-arm trials

EMA's **Committee for Medicinal Products for Human Use (CHMP)** work plans 2021 to 2023

"To produce a reflection paper on single-arm trials that are submitted as pivotal evidence in marketing authorisation dossiers across therapeutic areas and publish it for public consultation."

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15 December 2022
EMA/911829/2022
Human Medicines Division

Committee for Medicinal Products for Human Use (CHMP): Work Plan 2023
Adopted by the Committee on 15 December 2022

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Reflection paper also in work plans from

- EMA's **Committee for Advanced Therapies (CAT)**
- EMA's **Methodology Working Party (MWP)**
- EMA's **Oncology Working Party (ONCWP)**

Single Arm Trial as well-defined experiment on its own to establish efficacy

Methodological conditions to establish a treatment effect and causally attribute it to drug treatment.

Methodological considerations and limitations to estimate treatment effects in population(s) of interest.

Reflection paper on Single Arm Trials

In scope

- Methodological considerations across all therapeutic areas
- SATs which are submitted as pivotal evidence
- Efficacy
- Issues specific to SATs: design, conduct and assessment

Not in scope

- Therapeutic area specific guidance (possibly future Annexes)
- Safety
- Detailed guidance on external controls
- Considerations on feasibility of RCTs

Deficiencies

- No concurrent control
- No randomisation
- No blinding: Patients, investigators, assessors
- No ‘unconditional’ enrolment

Consequences

- No causal interpretation of observed outcomes as treatment effect
- Bias
- Assumptions & external information necessary
- **RCT remains standard**

Additional consideration

- Innovations (decentralized trials, novel endpoints) more challenging to implement (bias, confounding and absence of external information).

Section 3: Define and clarify challenging key concepts in SATs (e.g. treatment effect, internal validity)

Section 4: Translate concepts into practice, by key considerations

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Section 3: Define and clarify challenging key concepts in SATs (e.g. treatment effect, internal validity)

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Outcome

- Individual outcome, measurement of endpoint
- Statistical summary measures combine individual outcomes, e.g. '%patients with outcome' (≠'%responders')

Estimands

- Equally important, more difficult to apply, e.g. intercurrent events

Treatment effect of interest

- ICH E9: effect attributed to a treatment, comparison of treatments
- SAT: comparison of summary measure to the population not treated (**counterfactual**)

Isolation of treatment effect in SATs

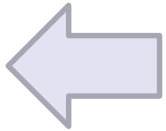
- Observed individual outcome on EP can never occur without active treatment **in any** patient.

Strong requirement

- Knowledge of clinical context
- Qualitative reasoning that leaves no doubt on causality
- Only exceptionally possible, usually residual uncertainty

Treatment effect estimate

- Contrast to 'no effect' (e.g. 0%) as assumed counterfactual
- Estimate impacted by patient selection



- Individual outcomes must not be subject to
  - Bias, variability, measurements errors, flaws in study conduct
  - In general, cannot be verified

Internal validity

- Systematic difference between
  - Treatment effect estimate from SAT.
  - Treatment effect estimate that would have resulted in matching RCT.

➢ SAT specific issue due to lack of internal comparator.

External validity

- Systematic difference between
  - Treatment effect from SAT.
  - True treatment effect in target population.

➢ Also issue in RCTs

- Due to predictive variables (differences in treatment effect)…but…
- amplified in SATs as also due to prognostic variables (differences in outcome).

Quantification of uncertainty (precision)

- **Confidence intervals for the treatment effect** with known coverage probabilities should be obtained.
  - But this is difficult as the counter-factual is not observed.
  - Threshold based approached may underestimate variability.

Section 4: Translate concepts into practice, by key consideration

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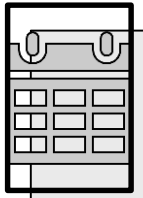
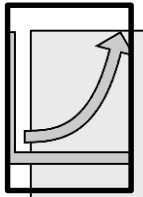
Choice of endpoints

Isolation of treatment effect primary for interpretation. Challenge if not clinically most relevant.



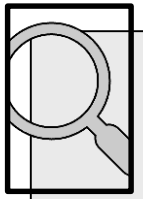
Time to event generally difficult



Continuous also difficult due to variability, measurement error, regression to the mean

Acceptability of endpoint(s) is a therapeutic are specific discussion.

Choice of endpoints



Find the right balance between clinical relevance and ability to isolate treatment effect

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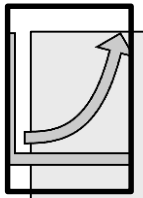


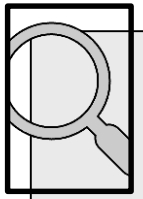
Continuous also difficult due to variability, measurement error, regression to the mean

Events occur in absence or presence of treatment, e.g. time-to-death.

Course of disease and prognostic factors impact TTE.

Starting point of risk: 'time 0' unknown, ≠ start of trial/ treatment.

Choice of endpoints



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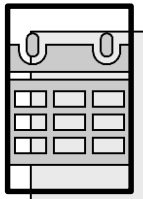

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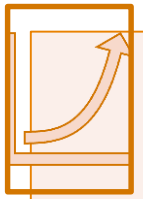


Continuous also difficult due to variability, measurement error, regression to the mean.

Regression towards the mean occurs whenever we select an extreme group based on one variable and then measure […] the same variable at a different point in time) for that group. (Bland and Altman, 1994).

Target and trial population

- Trial population determines plausibility of assumptions about hypothetical control.
- Prognostic variables may compromise generalisability from trial to target population.
- Not possible to disentangle prognostic from predictive effects based on results from single-arm trials.

Even more important to have detailed account of screening & selection.

Role of external information

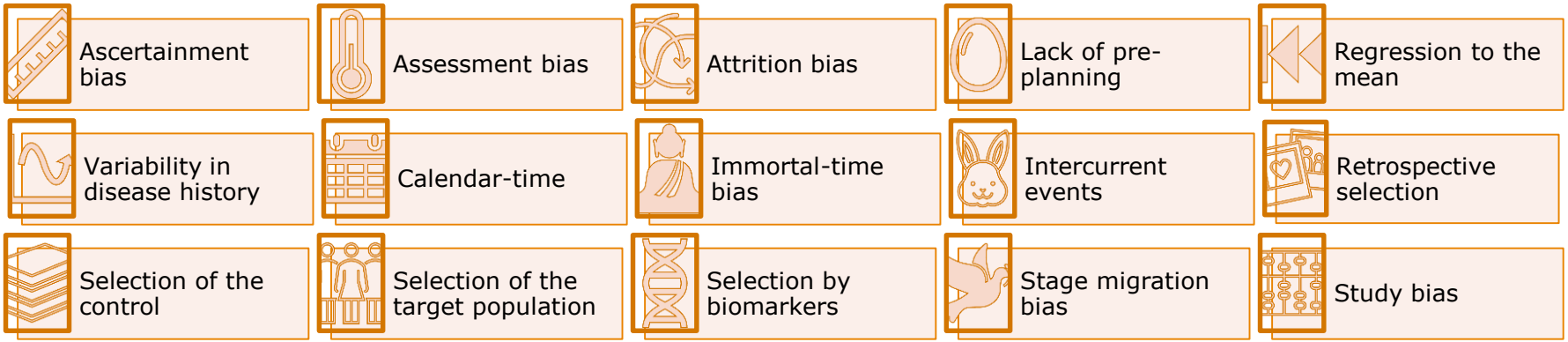
- Either (i) general knowledge about natural course of disease or (ii) external clinical data
- Presented as information, not 'evidence'
- Critical for interpretation of SAT
- Seek Scientific Advice on choice and use of external information

Statistical principles

Standards as for confirmatory setting.

- Pre-specification even more critical.
  - incl. trial success criterion.
  - adherence to study protocol and statistical model (unplanned changes critical).
- Usually full analysis set
  - Unless it overestimates clinical benefit.
- Additional analyses (impact of prognostic factors) to translate to target population.
- Choice of a threshold and including its uncertainty.
- Quantifying uncertainty of estimates from single-arm trials via confidence intervals.
- Important to address multiplicity.

Sources of bias and potential remedies



Any questions?

For further information e-mail RP-SATs@ema.europa.eu

Thank you to **Marcia Rueckbeil** for help in preparing the presentation