Use of External Control Arms in Rare Disease: Are We Moving Towards an International Gold Standard and How Can We Facilitate Progress?

A European Regulatory Perspective

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Disclaimer

The presenter does not have any conflict of interest

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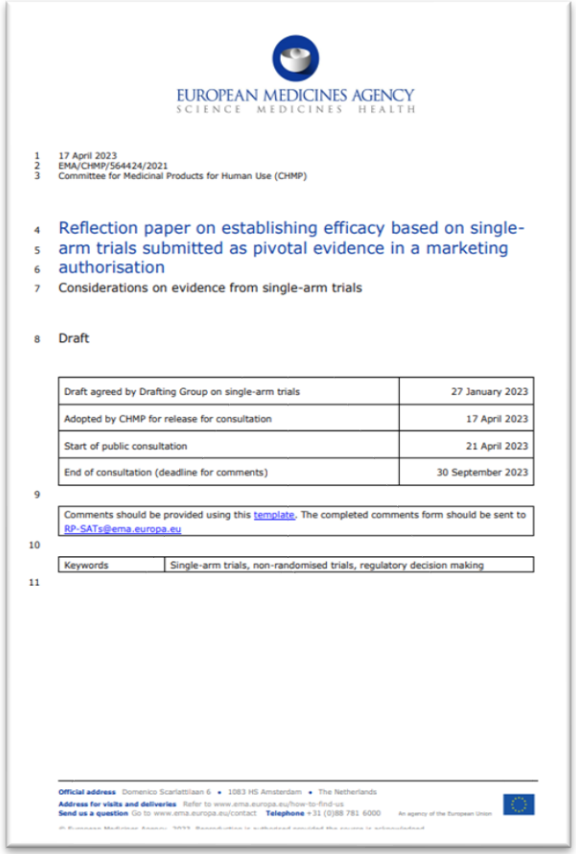
Motivation for a reflection paper on single-arm trials

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

➢ Need to (1) communicate challenges with SATs, and (2) improve the design, conduct, analysis, interpretation and assessment of results from SATs

➢ Relevance of public discussion



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2023
EMA/CHMP/564424/2021
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation
Considerations on evidence from single-arm trials

Draft

Draft agreed by Drafting Group on single-arm trials	27 January 2023
Adopted by CHMP for release for consultation	17 April 2023
Start of public consultation	21 April 2023
End of consultation (deadline for comments)	30 September 2023

Comments should be provided using this template. The completed comments form should be sent to RP-SATs@ema.europa.eu

Keywords	Single-arm trials, non-randomised trials, regulatory decision making

Reflection paper on Single Arm Trials

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

Cox, D. R. (1958). *Planning of experiments.* Wiley

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)
- Considerations on feasibility of RCTs
- Safety
- Detailed guidance on external controls

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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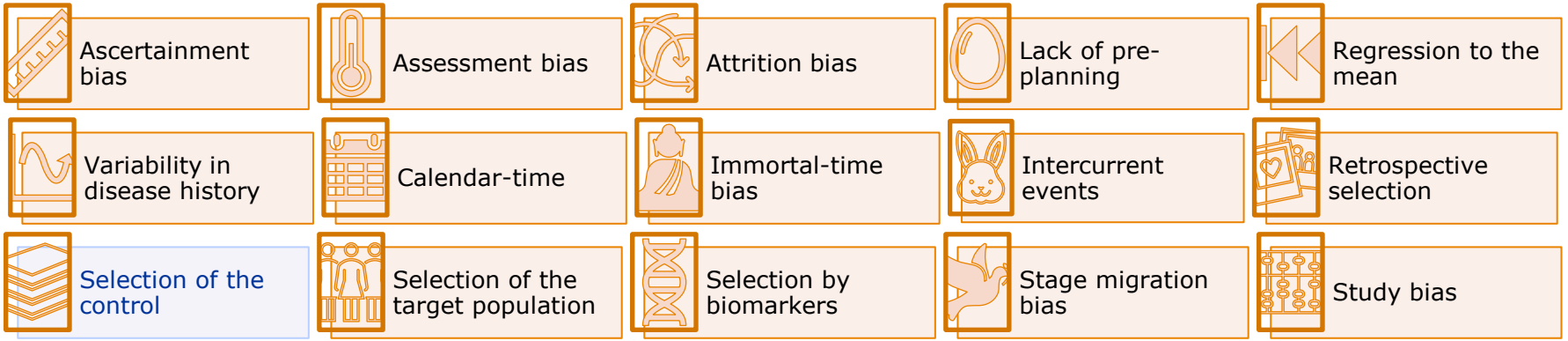
Role of external information

Presented as information, not 'evidence'

- Role of relevant external (extra-study) information in the form of (1) general knowledge about the natural course of the disease or (2) external clinical data
- Use of external information in the analysis or interpretation of a SAT to be pre-specified in the study protocol
- Strongly recommended to seek scientific advice on the use and the choice of external information before the study protocol of the SAT is finalised

In exceptional cases, the assessment of efficacy is envisaged to be informed by a direct comparison against external clinical data (i.e. an external control). Guidance on the choice of and comparison with external data is beyond the scope of this reflection paper

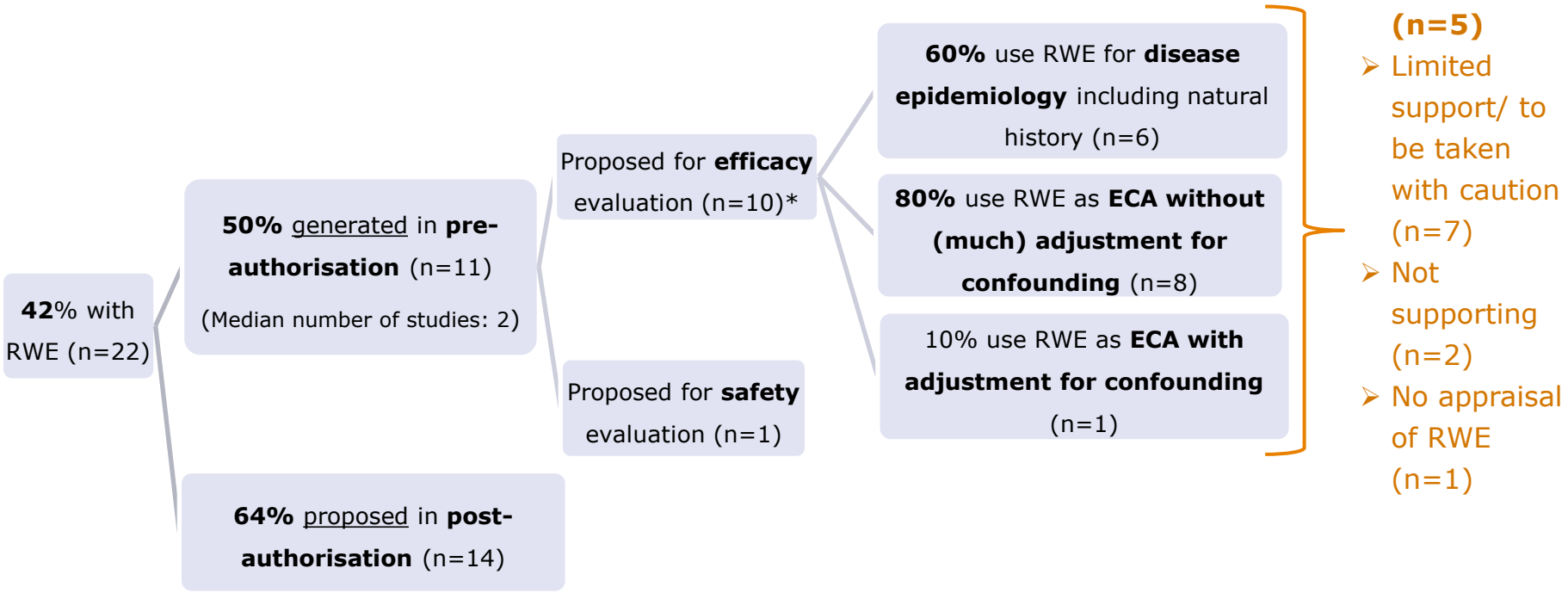
Sources of bias and potential remedies



Selection bias in relation to the hypothetical control group	Patients enrolled in a SAT may systematically differ from the hypothetical control group in ways that impact their prognosis.	Precisely pre-specify inclusion and exclusion criteria such that the enrolled trial population matches well the external information that assumptions are based on.

Initial Marketing Authorisation Applications

N=221 applications (2020-2023); Review of a random sample n=52 applications



* 50% for Orphan Drugs

Business pipeline meetings

What kind of questions related to RWD/RWE stakeholders are asking us?

6 questions related to external controls
(out of 11 RWD/RWE topics)
over the last 3 years

Conclusion

- Current draft Reflection Paper focus on the stand-alone interpretation of the results from a single-arm trial — *while external controls can further contextualise the results, the single-arm trial should also be interpretable on its own*
- Public consultation ended on Sep. 30 — *comments under review*
- Potential topic for further guidance development?

Any questions?

Further information

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