Challenges when using external control data for regulatory decision making

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The contents of this presentation are my personal opinion. My remarks do not necessarily reflect the official view of AGES, BASG, EMA, or any associated working party or committee.

Introduction

Relevant EMA regulation is taking shape

- Published:
  - RP on establishing efficacy based on Single Arm Trials
  - RP on use of Real-World Data in Non-Interventional-Studies
  - Data Quality Framework
  - RWD Roadmap
- MWP Workplan:
  - Use of RWD in externally control CTs
  - Use of RWD to augment RCTs
  - Reflection paper on Bayesian methods

19 February 2025
EMA/100019/2025
European Medicines Agency
Human Medicines Division/Methodology Working Party

Journey towards a roadmap for regulatory guidance on real-world evidence

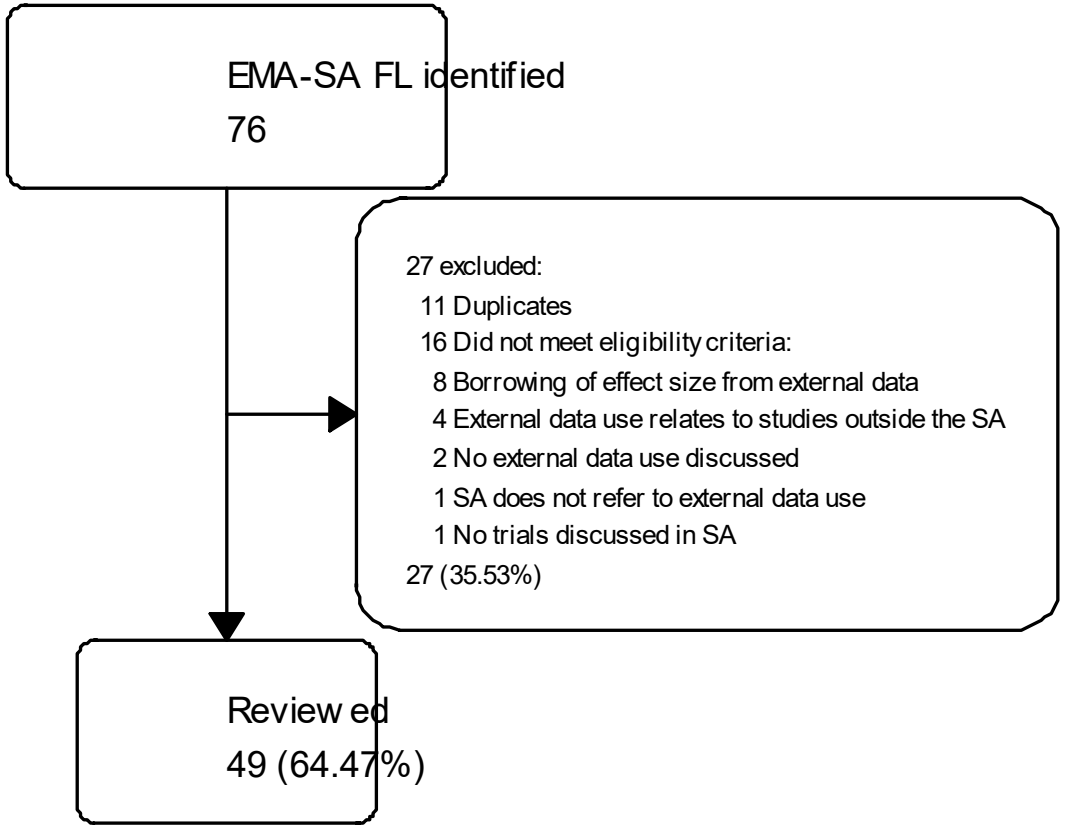
2 December 2024
EMA/324489/2024
Committee for Human Medicine Products / Methodology Working Party
Human Medicines Division

Consolidated 3-year rolling work plan for the Methodology Working Party

A review of EMA scientific advice procedures

Using our in-house database of final letters

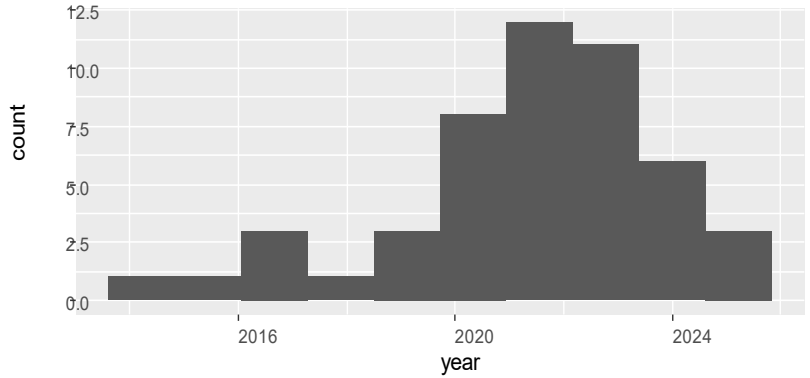
- EMA Scientific Advice was searched for terms
  - “hybrid control”,
  - “external control”,
  - “Bayesian borrowing”
- 49 Advice letters reviewed
  (excl. duplicates, non-relevant matches)
- Limitations:
  search terms, advice only, aggregation of case specific advice

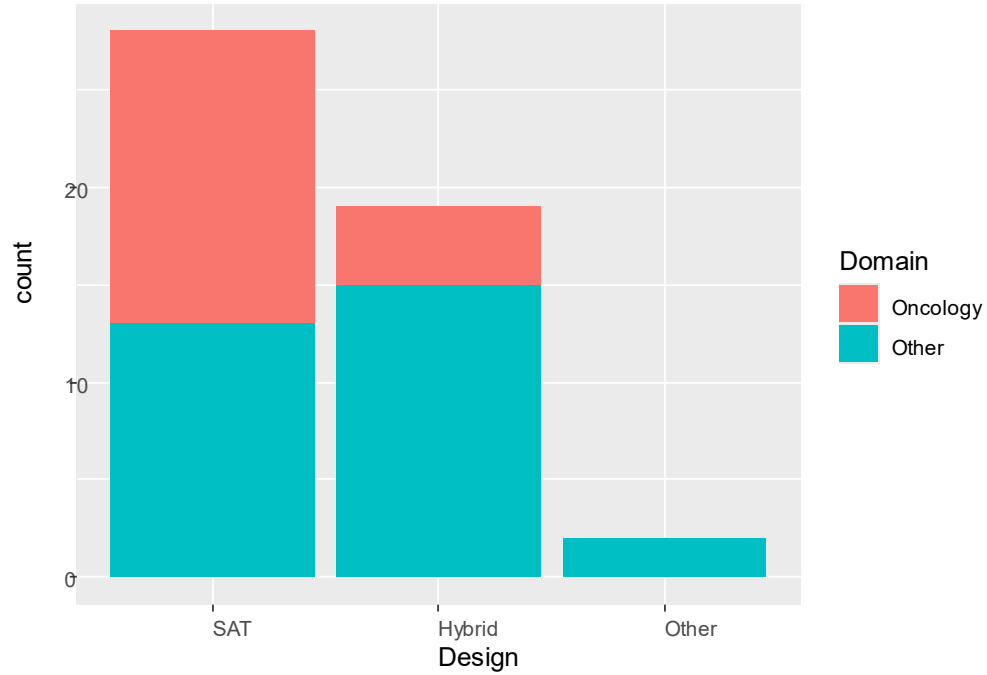


Type of Advice

Time, Domain, Design

- Cover advice between 2013 and 2025
- Most procedures in rare indications
- ~40% Oncology
- Trial Designs:
  - 28 Single Arm Trials
  - 19 Hybrid Trials
  - 2 RCTs: one arm to be compared to ECA

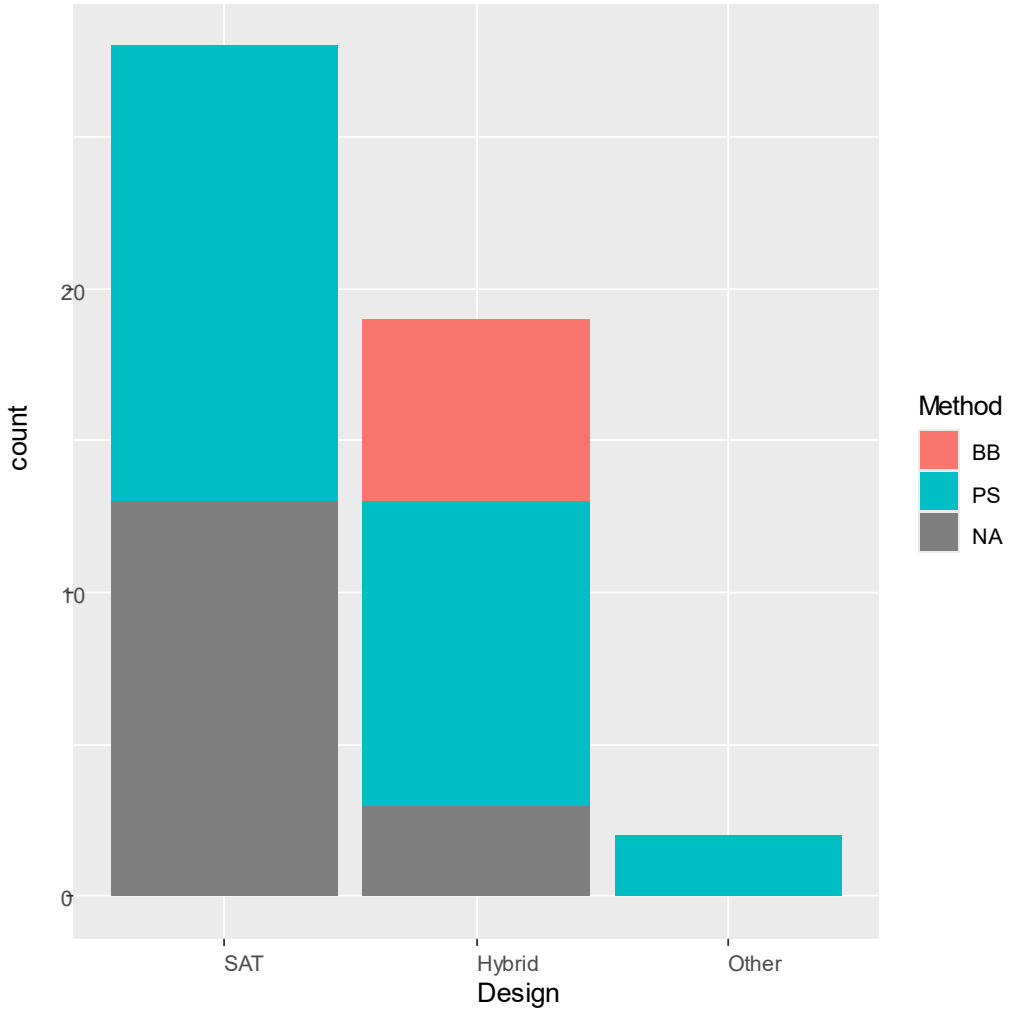




Methods

Mostly matching, usually few details

- Method:
  - 28 Propensity score
  - 6 Bayesian borrowing
  - 16 not specified
- No clear regulatory preference for any approach identifiable (though personally I feel more comfortable with PS)
- Comments focus on principles (plausibility of assumptions, bias, confounding, Type I error) not methodological detail



Common positions

Approximate order of frequency

- Conclusion supported by external control cannot replace self-standing RCT
- RCT recommended in majority of advices
- External control maybe useful to contextualize results – however, supportive only
- External control maybe useful to support additional conclusions
  - long-term outcomes, bridging between administration routes, comparative effectiveness
  - but not if pivotal to determine B/R, or in support of SmPC claims
- RCT with augmented control preferred over SAT with external control
- External control from comparable RCT preferred over RWD
- Sometimes self-standing conclusion based on SAT is preferred over ECA comparison

Common concerns

No particular order

- Comparability between external and internal control
  - Comprehensive identification of confounding factors
  - Ability to correct for all potential biases/maintain Type I error control
- Limited external data
- Data quality and completeness (esp. confounding factors)
- Balance between potential bias and potential savings in trial size
- Pre-specification:
  - Post-hoc selection of design (ECA proposed after RCT/SAT concluded)
  - Post-hoc selection of controls (ECA selected with known results)
- Sharing controls across developments raises multiplicity concerns

Resulting challenges

- Trust: retrospective elements may influence design choice
- Believe: unverifiable assumptions that underpin approaches
- Success much less clear-cut as $p < 0.025$, much more outcome dependent
- Complexity of approaches (Bayesian models, causal inference)
  - Requires specialized expertise and experience from developers and regulators
- Interdisciplinary assessment – not a question that statisticians can answer alone
  - Knowledge of data landscape
  - Clinicians critical to evaluate assumptions
  - Understanding of approach needs to extend beyond statisticians

Some recommendations

- Justification
  - Evaluate savings vs. bias/Type I error inflation
  - Evaluate alternative options (adaptive designs, platform trials, surrogate endpoints, …)
- Pre-specification
  - Address potential retrospective elements
  - Be transparent in assumptions and justify their plausibility
  - Sensitivity analyses to address potential deviations from assumptions
- Interpretation
  - Explain how methodological approach relates to clinical context
- Seek regulatory interaction early on

Some conclusions

- RCTs remain the cornerstone of regulatory decision making
- Replacing internal controls with external controls may reduce evidentiary standards
- Comparisons to external data may be irrelevant (or misleading) due to bias
- External control data can augment evidence from a trial
- Complexity of approaches require additional resources
  - Methodology Working Party and European Specialized Expert Community strive to connect expertise in the system across NCAs and across disciplines
  - Scientific collaborations can contribute to broader understanding of approach

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