

# Synthetic control arm in clinical trials for regulatory & HTA/reimbursement decision making

EMA Methodology Working Party

Virtual meeting, June 7th 2024

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# Synthetic control arm in clinical trials

## Why?

- Limits on controlled long-term follow-up
- RCTs can be difficult, e.g. due to
  - exceptional early efficacy + high unmet need
  - unclear/differing standard of care (SoC)
  - withdrawal of current care ethically problematic
  - (ultra) rare disease
- RCT cannot have all arms desired for HTA
- Questions on evidence standards
  - ICH E10 on choice of control groupvs.
  - EMA draft reflection paper on single-arm trials
- New data sources and methodologies

## What?

- External control arm for prospective new trial
  - Tries to emulate control group of target RCT we would ideally conduct
- Data source
  - e.g. RWD, cohort studies, chart review ...
  - Databases often from Europe and/or US
  - individual patient data / aggregate literature data
- Constructed to e.g. match
  - baseline characteristics
  - pre-trial treatment & disease history
- Many possible statistical approaches

# Questions

- How closely external data & trial need to match
  - Countries/regions
  - Time/medical environment
  - Data capture & endpoint assessment
- What is a “good” synthetic control arm?
  - How to assess quality of target RCT emulation?
  - What to look at? How to look? Can external data address this? What if RWD misses information?
  - Does it depend on the type of endpoint?
- How to look at methods & specific situations?
  - What to look at generally vs. case specific?
  - What are general principles?
  - Metrics other than type 1 error control/unbiasedness
  - Additional differences vs. RCTs?
- Uncertainty in inference from different sources
  - Sampling variability within study/data source
  - Between study/data source variability
  - Potential overfitting in matching process
  - Controls not exactly matching trial patients
- Estimands
  - Target trial emulation + estimand ?
  - Additional complications due to data sources
- Implementation issues
  - granularity of data, time zero definition
  - Pre-specification vs. needed deviations
- Approval vs. inclusion in label vs. use for HTA
  - Labeling of comparisons to synthetic controls
  - Longer-term outcomes obtained this way
  - Use for HTA incl. for extra comparators

# References

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