Single-arm clinical trials: data, statistics and ethics

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Disclosures: none

Disclaimer: 35+ years working, exclusively in oncology

- Adults
- Pediatrics

Single-arm Trials (SAT)

Definition:
A clinical study design where all participants receive the same experimental treatment, with no concurrent control or comparison group.

Commonly used clinical trial design in all four phases of clinical research:

- Phase I: dose finding and PharmacoKinetic properties
- Phase II: safety and early signs of efficacy
- Phase III: assessing clinical value and guiding regulatory decision-making
- Phase IV: post-marketing studies to monitor long-term effectiveness and safety

Establishing efficacy

When:

- Disease is common
- Anticipated efficacy of the experimental therapy is limited
- Significant heterogeneity accross patient cohorts
- Suboptimal biomarkers and
- Effective treatment options are available

Randomized Controlled Trials indispensable

When:

- Disease is rare
- High unmet need – life-threatening conditions
- Strong biological rationale
- No effective treatment exists
- Ethical reasons

Single-Arm Trials

Methodological challenges of SATs versus RCTs

Key strenghts of an RCT:

- Concurrent random allocation of interventions
- Controlled standards and frequencies of outcome assessment
- Established statistical tools and methods
- Allowing for blinding

establish a fair and **unbiased** comparison

most reliable method for establishing a **cause-and-effect** relationship between an intervention and an outcome.

SATs

- All participants receive the same treatment
- (Need for) external comparison

more susceptible to **bias and confounding**

lower level of evidence for establishing efficacy of a new intervention

Building External Control in Single-Arm Trials: external data sources

Method	Description	Advantages	Disadvantages
Historical Controls	Previously collected data from similar populations	Often readily available, properly documented	Different population, methods of diagnoses, risk of bias
Real World Data	Use of patient files, insurance , registers	Large populations, actual data	Variance in data quality, granularity, confounding
Published Data	Studies, Case series	Peer reviewed	Difficult to assess similarities, lacks details
Synthetic control groups	Statistically modeled control groups from external data	Flexible reproducable	Complex modeling, depending on data quality

Statistical methods when *Ind Patient Data available*

Propensity score-based methods

a. Propensity Score Matching

- Patients are matched to trial patients based on similar covariates

b. Propensity Score Weighting (IPTW, SMRW)

- Regression model is fitted using IPD from the single-arm trial and then projected to match

Covariate adjustments

a. Multivariable Regression Adjustment

- Fit a model (e.g. cox, logistic or linear) accounting for covariate differences

b. Bayesian Dynamic Borrowing

- allows to "borrow strength" from external data or prior knowledge using Bayesian statistics.

Statistical methods when *only aggregated data* available

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Matching-Adjusted Indirect Comparison (MAIC)

- Reweights trial patients so their weighted baseline characteristics match published data

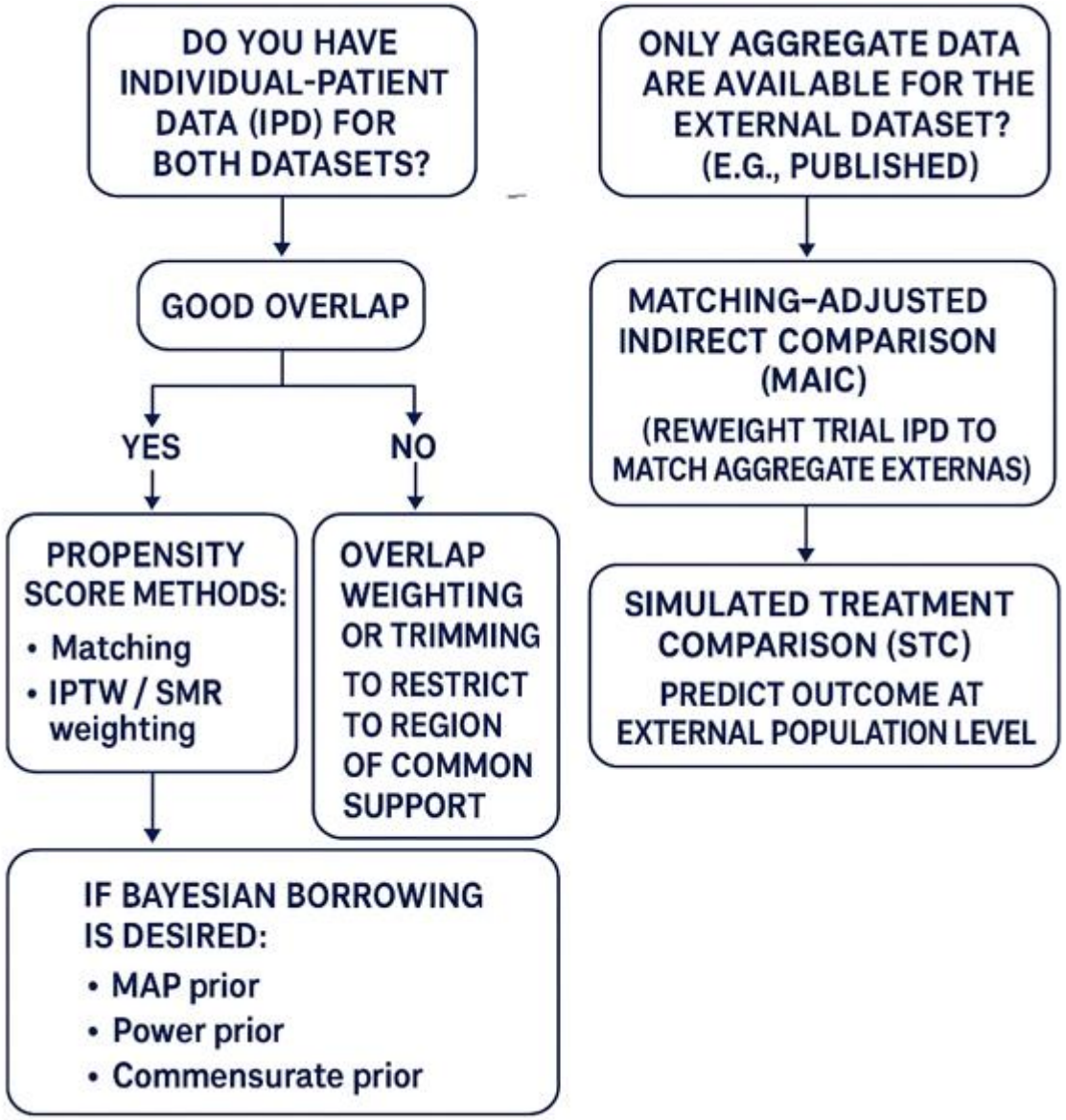
Simulated Treatment Comparison (STC)

- All patients are retained but given weights

Machine-Learning Causal Methods

- G-computation
- Inverse Probability of Treatment / Censoring Weights
- Targeted Maximum Likelihood Estimation (TMLE)

Flowchart for matching external data to a SAT



Ethical considerations

Advantages (compared with RCTs):

- Equity in treatment (equal opportunities and risks)
- Feasibility in rare diseases
- Feasibility in Life-Threatening Conditions
- Feasibility when suspected (proven) highly effective

expected benefit must outweigh the risks

Ethical (and methodological) Considerations (2)

Considerations	Measures
Intensive safety monitoring	independent, stopping rules
Proper Informed Consent	no control group, treatment effect less certain
Fair Participant Selection	clearly predefined in-/exclusion criteria
Scientific Validity and Bias Minimization	robust design, external controls, blinded outcome assessment where possible, transparent pre-specification of endpoints and analysis
Appropriate Endpoint Selection	objective, clinically meaningful
Transparency and Data Sharing	public registration, disclosing results
Regulatory and Post-Approval Responsibilities	confirmatory trials and data, timelines, post-marketing availability

Key Takeways for running Single-Arm Trials

1

Ethics & Balance

Single arm trials are ethically justified when RCTs are infeasible, but require transparency about limitations and commitment to confirmatory evidence.

2

Statistical Rigor

Design, performance, analysis and reporting should follow similar Good Clincial Practice.

3

Data & Controls

Multiple analytic approaches and sensitivity analysis are essential to assess robustness of findings

Collaboration between statisticians, ethicists, physicians, and patients is essential


Thanks!