Randomized Trials versus Observational Studies: Advantages and Disadvantages

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Study Designs for Clinical Research

Weakest evidence

Strongest evidence

- Single case report (anecdote)
- Consecutive case series
- Retrospective case-control or cohort study
- Prospective cohort with historical controls
- Prospective cohort with contemporary controls
- Single randomized clinical trial
- Multiple large, randomized clinical trials

What do RCTs do well?

- Provide for a controlled clinical experiment in which to assess for treatment effect
- By definition, true randomization eliminates differences between groups due to bias except for the randomized exposure– any observed difference is necessarily by chance.
- Validated statistical methods allow direct comparisons between groups to quantify differences between a *specified* control and the treatment group
- Control group is contemporaneous

Potential RCT Flaws

- Poor design
  - “Straw man” controls
  - Treatment effect assumptions (underpowered)
  - Non-inferiority trials with inappropriate delta or control
  - Lack of uniform endpoint definitions
  - Over-reliance on subgroup analyses
- Poor execution
  - Protocol deviations
  - Crossovers/Withdrawals
  - Absence of blinding
  - Bias in endpoint assessment or adjudication

Limitations of RCTs

- Timing of Evaluation
  - **Too early in development**
    - **Inadequate data for selection of controls or estimate of treatment effect**
    - **Instability of the study treatment**
  - **Too late**
    - **Study treatment or potential control accepted as standard of care**

Limitations of RCTs

- Costs (including time factor)
  - **Compromise in design or overly optimistic assumptions**
    - **Unreasonable treatment effects or event rates**
    - **Inappropriate composite endpoints**
  - **Increase Type 2 error (limit ability to detect small but possibly clinically significant differences)**
- Duration
  - **Time from design to enrollment to results may outlast the viability of the question (evolution of standard of care)**

Limitations of RCTs

- Generalizability
  - **Homogeneous population**
    - **Reduced variability (noise)**
    - **May not apply to large segments of population**
  - **Other factors**
    - **Volunteer bias**
    - **Lower risk patients**
    - **Operator effect (procedural trials)**
  - **Overreliance on subgroups**

Role of Observational Studies
What do they do well?

- Assess historical and current therapies across a broad range of patients (use of stents, rate of emergency CABG)
- Assess overall outcomes over time (decline in MI mortality, impact of time of MI presentation)
- Evaluate population-based trends (risk factor frequencies, MI types)
- Determine population risk predictors (Framingham study)

Role of Observational Studies in Comparing Treatment Effects

Can observational studies overcome RCT limitations?

- Less costly
- Usually no enrollment and follow-up delay
- Generally less selected population (increased generalizability)
- May include population with treatments that are not easily randomized (generalizability)
- Large population (increased statistical power; address low frequency outcomes)

Role of Observational Studies in Comparing Treatment Effects

Limitations

- Adequacy and quality of data collection
  - Includes lack of systematic time-based endpoint assessment
- Measured confounding – variables associated with treatment and outcome
  - **Multivariable adjustment**
  - **Propensity matching**
    - **best method of correcting for measured differences**
    - **limited by quantity and quality of data collected**
    - **May lose generalizability and power**

Role of Observational Studies in Comparing Treatment Effects

Limitations

- Unmeasured confounding – unmeasured or unknown variables associated with treatment and outcome
  - **Confounding by Indication**
    - **BMS vs DES observational studies**
    - **Distal protection in SVG PCI**
  - **Non-Contemporaneous Control**
    - **Unable to control for changes in adjunctive therapy**
    - **Unable to control for changes in delivery of study treatment**

Role of Observational Studies in Comparing Treatment Effects

Interpretation of Findings

- Valid as documentation of current practice.
- Generally not valid for establishing practice standards or changing practice
  - Example: BMS vs DES
    - Based on current practice, *including physician selection of device*, DES associated with lower mortality than BMS
    - Not valid to conclude that DES should be preferred in all cases
- Well designed observational study may be informative when randomized comparison not feasible

RCTs and Observational Studies Synergy of Strengths

- Observational studies may improve efficiency of subsequent RCTs
  - Identify expected event rates and estimate treatment effects (sample size)
  - Identify appropriate endpoints to be tested
  - Identify subgroups likely (or not likely) to benefit
- Observational studies may be used to expand generalizability of RCTs
  - Post market safety studies to assess low frequency events

Maximizing Usefulness of Observational Data

- Collection of adequate baseline data so can adjust for differences between groups
- Provide for systematic follow-up to assess outcomes of interest
- Provide for assessment of meaningful clinical endpoints
- Assess adjunctive therapies that may impact outcomes and be different between groups

Conclusions

Quality more important than study type

- Well designed RCTs and OBS can be used to assess outcome of study therapy and frequently arrive at similar conclusions
- Poorly designed RCTS can result in misleading conclusions and inference for practice guidelines, usually due to compromises in sample size or lack of generalizability.
- While OBS are mostly useful to document current practice and guide or extend RCTs, well designed studies can be used for some comparative effectiveness questions not easily addressed in RCT setting.