Clinical Study Design Tree

Comparison Basis?

Implicit Control Group
- Case Series
- Case Report

Explicit Control Group

Major Strength
Fatal weakness

Timing of Control Group?

Concurrent

Major Strength

Observational

Randomized Factor Assignment?
- Yes
- No

Hill-Evans Postulates

Unique

Used reference (gold) standard comparison?
- Yes
- No

Diagnostic Test Evaluation
[2 parallel studies]

Study "Direction"?

Retrospective from Outcome
- Case-Control Study

Prospective from Exposure
- Cohort Study
(incidence study)

Experimental
(Fisher's Principles)

- Randomized Blinded Controlled Trial (RBCT)
- Randomized Cross-Over Trial
- Experimentally induced Disease

- Exception: Self-controlled (N of 1) chronic condition trial

Historical

Cohort Study

Case-Control Study

Retrospective from Outcome

Prospective from Exposure

Retrospective from Outcome

Prospective from Exposure

None

- Cross-Sectional Study (prevalence study)
- Ecological Study [Aggregate data]
Study Weak Points and Their Correction

**Study Design**

- **Systematic Bias**
  - Using objective, prospective, primary data
  - Blinding of trained observer doing exams, running tests, reading films.
  - Increasing objectivity of measurements, incorporating assay standards, validating reliability of subjective scales
  - Reducing batch and time effects by blocking over time and batch and randomizing within batch
  - Randomizing processing sequence at best or maintaining process symmetry at least (sample holding times, storage conditions, reagent batches, observer learning)

- **Measurement Bias**
  - Using random assignment / allocation
  - Using a concurrent control group
  - Restriction or matching of enrollees on known confounders
  - Analytic control of known confounders
  - Minimizing differential losses to follow-up

- **Confounding Bias**
  - Increasing study size (4 fold increase halves imprecision)
  - Using a statistical data type with higher information content
  - Reducing measuring imprecision by more personnel training, controlling environmental conditions, using more precise equipment
  - Replicating then averaging an imprecise measurement or test on each sample
  - Blocking, stratifying, pairing, or pre-post design may reduce
  - Repeated measures design to remove between subject variation
  - Reducing subject heterogeneity (inbred lines)
  - Increase initial study size (~20%) to compensate for potential losses

**Reduced by:**

- Establishing prior eligibility criteria (inclusion, exclusion)
- Selecting from similar populations
- Blinding of selector
- Using random selection from a population
- Increasing study size (4 fold increase halves imprecision)
- Using a statistical data type with higher information content
- Reducing measuring imprecision by more personnel training, controlling environmental conditions, using more precise equipment
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