**Randomized Trials**

(experimental; interventional; community trials; health care trials)

- **Disadvantages:**
  - Costs
  - Feasibility
  - Limited exposures (unethical except in therapy issues)
  - Limited outcomes (applicable to common diseases/exposures
  - Validity
    - Placebo Effect
    - Generalizability
    - Differential misclassification of outcome (measurement bias)
    - Differential misclassification of exposure (selection bias)
    - Confounding (unbalanced groups)

**Analysis of Randomized Trials**

(experimental; interventional; community trials; health care trials)

- Outcome continuous: Difference between means
  - T-tests; difference between means
- Outcome dichotomous: (yes/no)
  - Event ratio
  - Incidence rate ratio
  - Survival analysis
- Measures of Association (causal; non-causal; chance; confounding; bias)
  - Correlation coefficients (r)
  - Differences between means
  - Regression coefficients
  - Relative risks
### Proving “Causality”

- **RCT** best study design (only one able to prove causality)
- Temporal relationship (Exposure precedes event)
- Dose-response; consistency; biological plausibility; ? Alternative explanations; Cessation of Exposure; Consistency with other observations; Specificity of association
- Strength of association (not statistical significance!)
  - Large difference between means
  - Correlation coefficients
  - Relative risks (rate ratio, OR, Obs/Exp, SMR, SIR, PMR, PIR, Hazard ratio...)

### Threats to External & Internal Validity

**[external validity = generalizability; internal validity = internal consistency]**

- **External:**
  - Narrow selection criteria
  - Volunteer bias
  - Prevalence (survivor) bias
- **Internal:**
  - non-differential misclassification (too many false negatives & false positives = random measurement error)
  - Differential misclassification (true bias)

### Threats to Validity (RCT)

- Placebo effect
- Generalizability (volunteer bias)
- Differential misclassification of Outcome (measurement bias; experimenter & recall bias) [masking best countermeasure]
- Differential misclassification of Exposure (selection bias; selective dropout)
- Confounding (faulty randomization; selective dropout)
Bias

- Measurement; observational; informational
- Recall or selective recall
- Experimenter
- Regression to mean
- Cross-over (contamination)
- Selection
- Self-selection
- Selective drop-out
- Surveillance (detection; ascertainment)

Observational Study Types

- Cohort (select sample without outcome of interest [exposed/non-exposed] & follow for change [disease onset] or no change
- Case-Control (select cases/non cases then ascertains prior exposure in both)
- Cross-sectional (simultaneous measurement of exposure/outcome; prevalence)
- Ecological (exposure/outcome for geographic areas [populations not individuals]

Cohort Study

(follow-up; longitudinal; prospective; incidence study)
[Defined group followed over time]

- Begin with group(s) without outcome of interest, some exposed some not, follow over time to assess onset or change in disease

<table>
<thead>
<tr>
<th>Disease developed</th>
<th>Disease not developed</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Not exposed</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Incidence Rate = a + b - c + d

(Rate Ratio) RR = IR_{exposed}/IR_{non-exposed} = a/b / c/d

- No randomization or therapy – just observation
- Various Cohort Types:
  - Special exposure cohort (unique/relatively rare exposure
  - General population cohort (exposure common)
  - Prospective
  - Retrospective
  - Ambidirectional
**Analysis of Cohort Study**
(follow-up; longitudinal; prospective; incidence study)
[Defined group followed over time]

- Age-adjusted rate = Exp Events/Stand.population
- Standardized Incident Rate (SIR)
  - SIR = O/EAA
- Standardized Mortality Rate (SMR)
  - SMR = O/EAA; Observed deaths/age-adjust X 100
- Rate Ratio: RR = IRExposed/IRNon-exposed

**Advantages/disadvantages**
Cohort Studies

**Advantages:**
- Time sequence (exposure precedes disease)
- Ethical (exposure not assigned)
- Rare exposure can be studied
- Multiple outcomes can be assessed
- Not dependent on past records
- Exposure-specific IR can be determined
- All outcomes (mild-severe) can be ascertained
- Bias can be minimized in measurement of exposure

**Disadvantages:**
- Cost
- Not appropriate for rare diseases
- Validity (cross-over; differential misclassification of O & E)
- Confounding possible
- Generalizability may be limited

**Case-Control Studies** (case-referent; case-comparison; retrospective studies)

Begin with subjects that have Outcome of interest, identify controls
– then assess previous Exposure in both groups

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were exposed</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Were not exposed</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>Totals</td>
<td>a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>

- Proportion exposed: a/c 
- Rate Ratio (RR): OR = good estimate of RR = ad/bc 
- "matched" OR = b/c
Case-Control Studies (case-referent; case-comparison; retrospective studies)

Advantages:
- Rare diseases can be studied
- Multiple exposures can be simultaneously investigated
- Efficient (fewer subjects)
- Ethical (no safety concerns)
- Good estimate of RR (OR: good estimate of RR)
- Can be "nested" in RCT or Cohort studies

Disadvantages:
- Cannot measure incidence rates
- Validity problems (prevalence bias; temporal relationships [did exposure precede disease?])
- Differential misclassification of Exposure
- Incomplete records
- Confounding
- Generalizability poor if cases not representative of all cases

Cross-sectional Studies (prevalence study)

Advantages and Disadvantages

Advantages:
- Efficient & relatively inexpensive
- Ethical
- Measurement bias minimal
- Generates Hypotheses

Disadvantages:
- Time-sensitive (temporal relationships change)
- Prevalence bias (long duration cases in the population bias the results)
- Differential misclassification of Exposure & Outcome (selection bias)
- Confounding
- Not useful for rare diseases

Ecological Studies (correlational studies)

Select groups (countries, states, regions etc.)
Ascertain Exposure & Outcome on Groups
Usually measure Exposure by continuous variables (average per capita consumption) and incidence rates for Outcomes
E & O linked to groups, not individuals

Advantages:
- Efficient
- Test hypotheses
- Wide range of E & O studies possible

Disadvantages:
- Ecological Fallacy
- Imprecise measurements
- Confounding
- Comparable populations difficult to identify
Descriptive Studies

- Case report
- Case Series (interventional or observational; ≥ 2 subjects)
- Registry Summary
- Survey
  
  **Advantages:** inexpensive; rapid; document complications of therapy
  
  **Disadvantages:** may not be generalizable; exceptions; non-representative samples; surveys often have poor response rate; no hypothesis testing – no comparison group; cannot establish cause-effect relationships