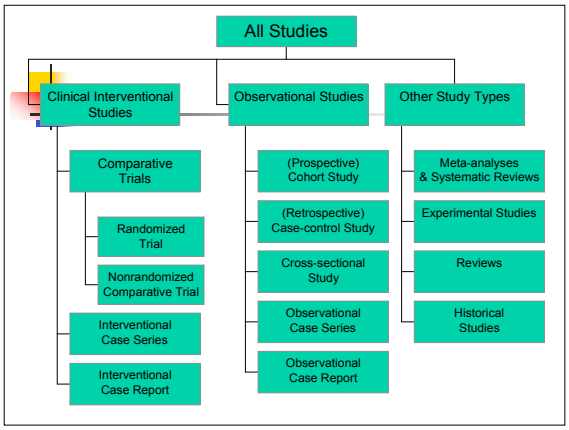

Randomized Trials (experimental; interventional; community trials; health care trials)

- 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
  - Regression 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

	Disease develops	Dis. does not develop	Totals	Incidence Rate
Exposed	a	b	a + b	a/a+b
Not exposed	c	d	c + d	c/c+d

(Rate Ratio) RR = IRexp/IRnon-exp = $\frac{a/a+b}{c/c+d}$

- 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/E_{AA}
- Standardized Mortality Rate (SMR)
  - SMR = O/E_{AA} ; Observed deaths/age-adjust X 100
- Rate Ratio: RR = $IR_{Exposed}/IR_{Non\text{-}exposed}$

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

	Cases	Controls
Were exposed	a	b
Were not exposed	c	d
Totals	a+c	b+d
Proportion exposed	a/a+c	b/b+d
Rate Raio (RR)	a/a+b / c/c+d	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