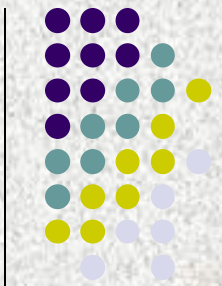
Clinical Trials

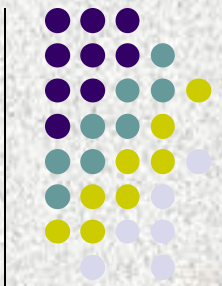
Susan G. Fisher, Ph.D.
Dept. of Clinical Sciences

When to Do a RCT



- Exposure of interest is modifiable and individuals are willing to relinquish control
- Legitimate uncertainty exists about outcomes
- Outcome is reasonably common or detrimental

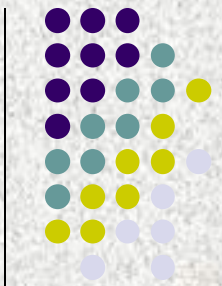
Experimental Studies



Phase I Clinical Trials

- May be first administration of a drug to humans;
- Designed to :
  - Establish a safe dose and schedule of administration
  - Identify side effects and toxicity
  - Investigate basic clinical pharmacology of drug
  - Demonstrate evidence of activity
- Incorporates a dose escalation scheme to identify maximum tolerated dose.

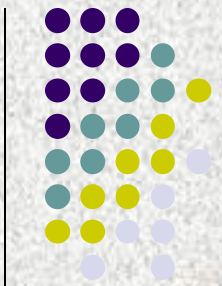
Experimental Studies *(continued)*



Phase II Trials

- Designed to test the feasibility and efficacy of a new agent/procedure
- Tests a fixed dose to estimate treatment efficacy
- Usually does not include a concurrent control group

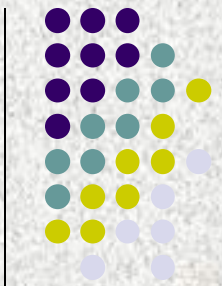
Experimental Studies *(continued)*

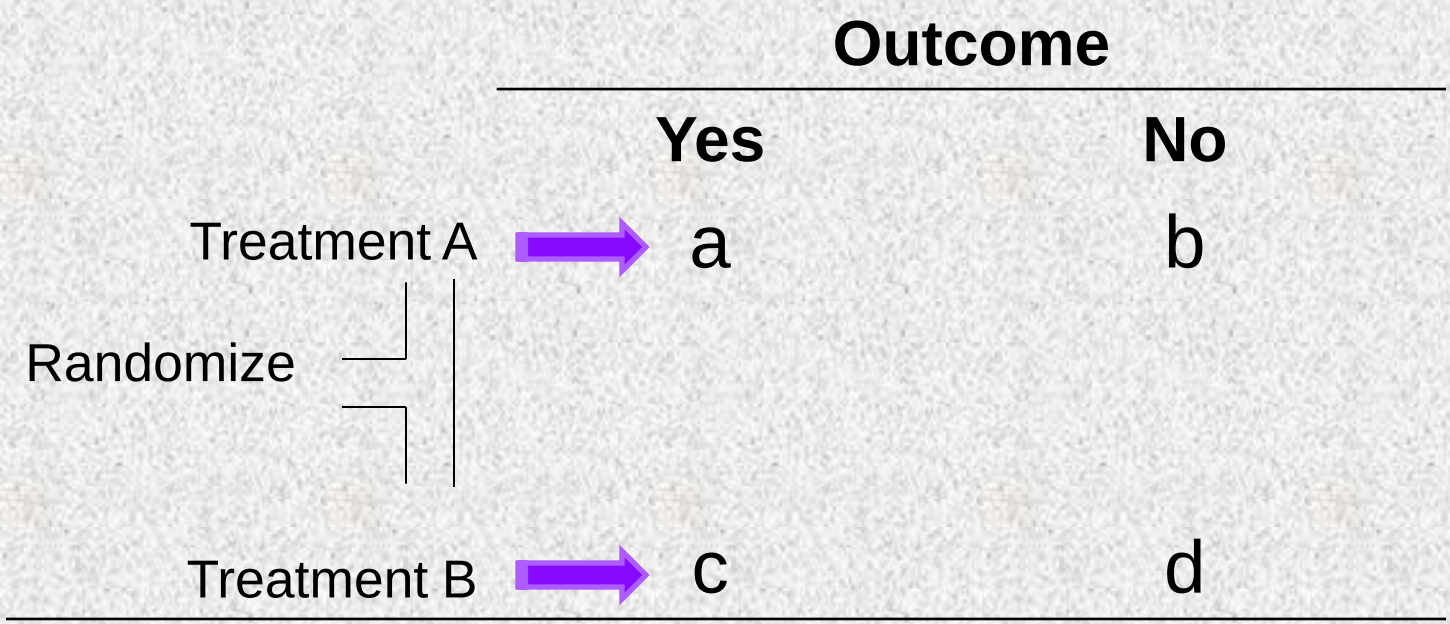


Phase III Randomized Clinical Trials

- Best method for providing evidence related to direct causation/treatment benefit;
- Experiment designed to test a specific hypothesis involving a particular intervention(s);
- Controlled and randomized;
- Assign a group of subjects to one of two or more interventions;
- Follow prospectively to determine outcome of interest

Randomized Clinical Trial

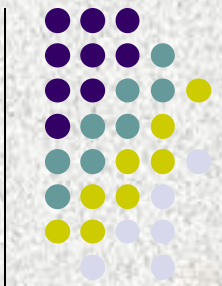




Evidence Often Quantified by:

Kaplan-Meier Survival Analysis

Randomization



- Randomization is the process of assigning subjects to different treatments by using a predetermined, random scheme;
- Eliminates bias in treatment assignments;
- Balances prognostic factors between treatment groups;
- Replaces random sampling as method to guarantee the validity of the statistical test.

Randomization:

….*Do we need to worry?*

- Randomization means that *on average*, the distribution of potential confounders (e.g., age, sex, etc.) will be similar in each treatment group
  - i.e., no association between treatment variable and other variables
  - Thus, no confounding
  - Works for both known and unknown (or unmeasured) risk factors

Randomization:

….*Do we need to worry?*

- However, it is possible that *by chance* (unlucky randomization), the treatment groups will end up different with respect to an important variable
  - e.g., by chance, randomization assigns most of the older patients to one treatment, younger patients to the other
  - Thus, potential confounding of treatment effect with age effect
  - Note: in moderate/large studies this is *very* unlikely

Stratification

- Is a method of dividing subjects into subpopulations (or strata) based on very important prognostic factors before randomization to assure that the groups are balanced.

	Male	Female
Drug A	70 (50%)	30 (50%)
Drug B	70 (50%)	30 (50%)
Total	140	60

Blinding

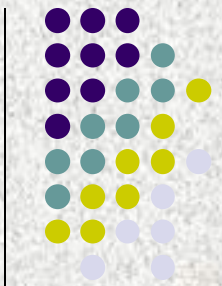
- Process in which the identity of the treatment being received is unknown to certain individuals.
  - Single blind → patient
  - Double blind → patient & physician
  - Triple blind → patient, physician, reviewer

Intention To Treat

- Analytic principle in which all randomized patients are included in the group to which they were originally assigned.

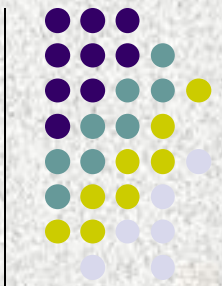
	Standard R_X	New R_X (Received)	New R_X (Intention to Treat)
Improved	60	40	40
Not Improved	40	15	15
Off Study	0	45	45
Success Rate	60%	73%	40%

Intention to Treat *(continued)*



- *Include* all randomized patients
  - Treatment refusals
  - Early deaths
  - Inadequately treated patients
- *Exclude* ineligible randomized patients based on pre-randomization data
- Secondary analyses with “protocol perfect” patients should be reviewed to examine any conflicting results

Number Needed to Treat



- Number that must be treated to change outcome in 1 individual
- NNT = $$\frac{1}{\text{Rate in Untreated Group} - \text{Rate in Treated Group}}$$

Example: RCT demonstrated a 10% rate of death with Drug A among patients with severe allergic reaction compared to a 20% rate of death with standard drug therapy.

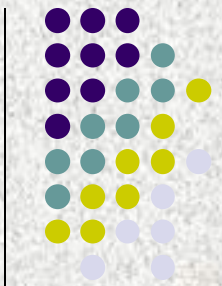
$$\text{NNT} = \frac{1}{0.20 - 0.10}$$

$$= \frac{1}{0.10}$$

$$= 10$$

For every 10 patients with severe allergic reaction treated with Drug A, 1 additional life will be saved.

Number Needed to Treat *(continued)*

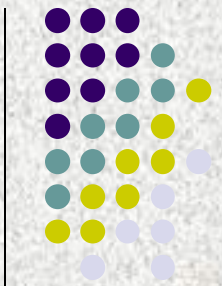


- Example: Lung Cancer: Smokers: 140/100,000
  Non-Smokers: 10/100,000

$$\frac{1}{130/100{,}000} = 769$$

- If 769 individuals quit smoking, 1 additional lung cancer death would be prevented.

Growth & Maturation of RCT



- Many clinical trials take a long time
  - Patient enrollment is spread out over time
  - For some outcomes (e.g., survival time), each patient has to be followed a long time
- Early patients may provide data before late patients have completed treatment, or even been enrolled

Data “Peeking”

- Temptation is to look at early study results
  - Curiosity
  - Trip to a warmer climate
  - Anxious to publish
  - Desire to be famous

Release of Preliminary Results

Operational Impact:

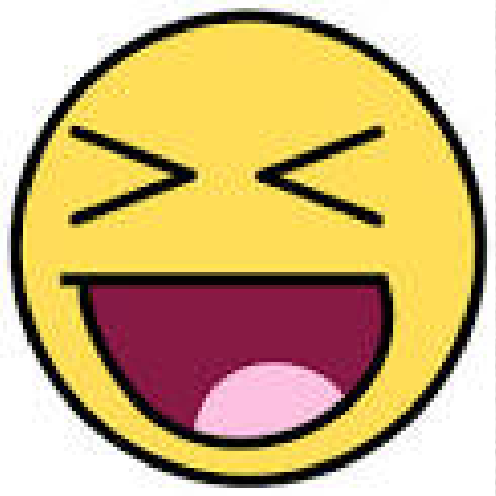
- Decreased maintenance of follow-up schedule
- Decreased adherence to therapy
- Decreased accrual
- Informed consent becomes ethical struggle for physicians
- Objectivity of physician evaluations decreases

Response:

...SLOW DEATH OF STUDY

Release of Preliminary Results *(continued)*

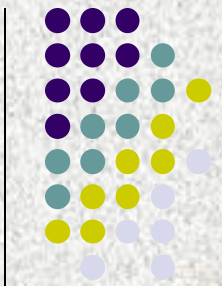
- Result:
  - Treatment benefit never clearly established
  - Long-term complications never examined
  - Potential harm to society if early results are wrong
  - Significant financial loss to funding agency
  - Future trial to replicate findings is not feasible



Interim analyses

- **Planned** analysis of available data prior to study completion is an *interim analysis*
- Plans for interim analyses should be specified in advance, and carried out by a separate group (DSMB)
- An important method to decide whether to continue or abandon the study
- Ethical obligation if one treatment is clearly inferior to another
  - Save time, effort, money if there is clearly no difference in outcome between treatments

Subgroup analyses



- Primary analysis of a trial is usually an overall comparison of treatments among all patients

- Often then ask:
  - Is the difference the same within meaningful subgroups of patients?
  - In statistical terms: is there an *interaction* ?

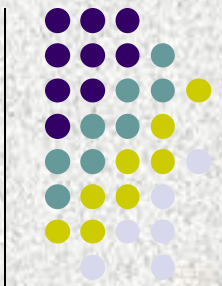
Subgroup analyses *(continued)*

- Reasonable if a limited number of plausible interactions to test are specified in advance
- More problematic: Suppose *no statistically significant overall difference* between treatments is found ("negative study")
- Tempting to examine subgroups of patients to see if there are any for which treatments differ.

  But:

  - Hypotheses often not specified in advance
  - High probability of false positives: type I errors

Critiquing a Clinical Study



- Clinical significance of research question
- Appropriateness of study design
- Representativeness of sample
- Adequate sample size
- Random treatment assignment
- Withdraw bias
- Adequate patient follow-up
- Statistical analysis
- Conclusions
- Clinical interpretation