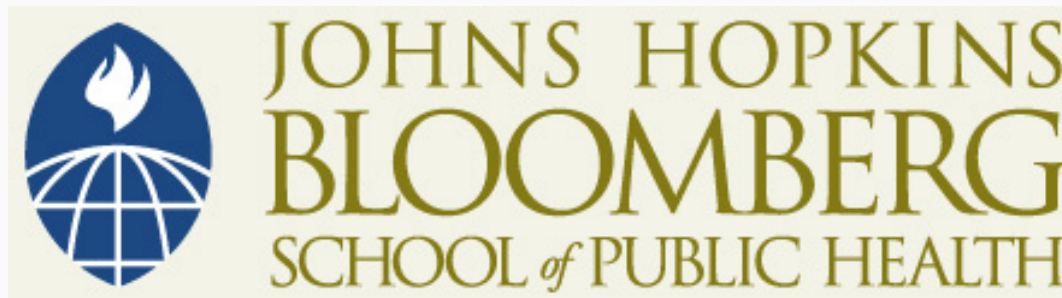


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Comparison/Control Groups

Mary Foulkes, PhD
Johns Hopkins University



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Section A

Control Groups

Adequate and Well-Controlled Studies: 21 CFR 314.26

- Generally, the following types of controls are recognized:
 - i. Placebo concurrent control
 - ii. Dose-comparison concurrent control
 - iii. No treatment concurrent control
 - iv. Active treatment concurrent control
 - v. Historical control

Purpose of the Control Group

- To allow discrimination of the patient outcome from an outcome caused by other factors (such as natural history or observer or patient expectation)
- To avoid bias (any aspect of the design, conduct, and analysis that would make the estimate of the treatment effect deviate from the true effect)

Two Techniques to Control Bias

- Randomization (randomly dividing a single population to avoid systematic differences between study groups with respect to baseline variables that could effect outcome)
- Blinding (helps assure that the study groups are treated in a similar manner during the trial)

- Placebo
- No treatment
- Different doses or regimens of same treatment
- Different active treatments
- Historical (external and non-concurrent)

- Ethical and practical issues
- Impact on study design
- Study objective
- Ability to minimize bias
- Usefulness in particular inference situations
- Advantages and disadvantages

Placebo Concurrent Control

- Usually randomized double blind
- Goal: to show a difference (for efficacy)
- Goal: to show equivalence (for safety)
- Ethical
 - When no effective treatment exists or when add on studies or early escape designs are appropriate
- Needs no assumption of sensitivity to drug effect nor assay sensitivity

No-Treatment Concurrent Control

- Usually randomized
- May be difficult to blind
- Important that study endpoints are objective
- Potential for observer bias needs to be assessed
- Validation of ability to detect drug effect and assay sensitivity is required

Dose-Response Concurrent Control

- Goal: to establish a relationship between dose and efficacy and safety
- Usually randomized and double blind
- May include other control groups (active or placebo)
- Doses may be fixed or gradually raised
- If the therapeutic range is not known, the design may be inefficient

Active Concurrent Control

- Ethical whenever approved drugs are available for the disease under study
- Randomized
- Double blind
- Goal: to show equivalence, non-inferiority, superiority
- Goal: could relate to both efficacy and safety

Historical Controls

- No randomization
- No blinding
- Source of controls external to the present study
- Patients in control group were treated at earlier time
- Patients in control group treated in another setting

Concurrent Controls

- Systematic assignments can bias study and should generally be avoided
- Randomized trials are the “gold standard”

Purpose of a Clinical Trial

- Assessment of efficacy, safety, or benefit:risk
- Goal may be superiority, non-inferiority, or equivalence
- In a regulatory setting:
 - The goal may be to “show that the drug has the effect it purports to have”

Conclusions

- Active control trials are here to stay
- The goal is usually to obtain an indirect test of effectiveness
- Active control trials will become more common in phases II and III
- Active control trials need to be carefully preplanned (setting, choice of control, what the goal is, choice of delta or margin)
- Changing goals (equivalence to non-inferior is not an option)

In the Next Section We'll Look at . . .

- More on control groups
- Placebos, in particular



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Section B

Placebos

Definitions

- Placebo: a form of medical therapy, or an intervention designed to simulate medical therapy, without specificity for the condition being treated
- Placebo effect: the change in the patient's condition that is attributable to the symbolic import of the healing intervention rather than to the intervention's specific pharmacologic or physiologic effects

Rationale for Use of Placebos

- Discriminate outcomes due to intervention (new product) from outcomes due to other factors
- Estimate efficacy
- Interpret adverse events
- Minimize bias, maximize accuracy and reliability

Uncontrolled/Controlled Results

Therapeutic area	Percentage of positive findings	
	Uncontrolled	Controlled
Psychiatric	83%	25%
Antidepressant	57%	29%
Respiratory distress	89%	50%
Rheumatoid arthritis	62%	25%

Types of Controls

- Placebo concurrent controls
- Dose-comparison controls
- No treatment concurrent controls
- Active treatment concurrent controls
- Historical controls

Use of Placebo/No RX Control

- Control for influences other than study agent
 - Concomitant therapy, regression to the mean, placebo effect
- Placebo permits blinding
 - Reduces bias in therapeutic management
 - Reduces bias in outcomes assessment
 - May decrease drop-outs, crossovers, etc.

Placebos in Trials

- Not all trials using placebos are placebo-controlled
 - Double-dummy ($A + P_B$ vs. $P_A + B$)
 - Placebo run-in (P then A vs. P then B)
- Not all placebo-controlled trials involve giving no treatment
 - Add-on ($A + B$ vs. $A + P$)

Ethics of Placebos

- Ethical where no available tx
- Unethical in the context of an available tx to prevent or delay death
- Ethical if no permanent harm in delaying available active tx for the duration of the trial

New Is No More Effective than Old

Drug class	Existing drug(s)	New agents	Advances
Antidepressants	Tricyclics	SSRIs and others	Different, tolerable array of side effects
Antipsychotics	Phenothiazines, buterophenones	Risperidone, olanzapine, quetiapine	Decreased extra-pyramidal effects
Antihistamines	Sedating antihistamines	Non-sedating antihistamines	Lack of sedation
Anti-inflammatory	Non-selective NSAIDS	COX-2 selective NSAIDs	Improved GI tolerance
Anti-hypertensives	Diurectics, reserpine	Low dose diurectics, ACE inhibitors, calcium channel blockers	Elimination of important side effects

In the Next Lecture We'll Look at . . .

- Outcomes and endpoints
 - Hypotheses
 - Binary endpoints vs. continuous endpoints
 - Subjective vs. objective endpoints
 - Primary, co-primary, and composite