

Evaluating Effectiveness of Medical Interventions in Infectious Diseases

John H. Powers, MD FACP FIDSA

Assistant Clinical Professor of Medicine

George Washington University School of Medicine

University of Maryland School of Medicine

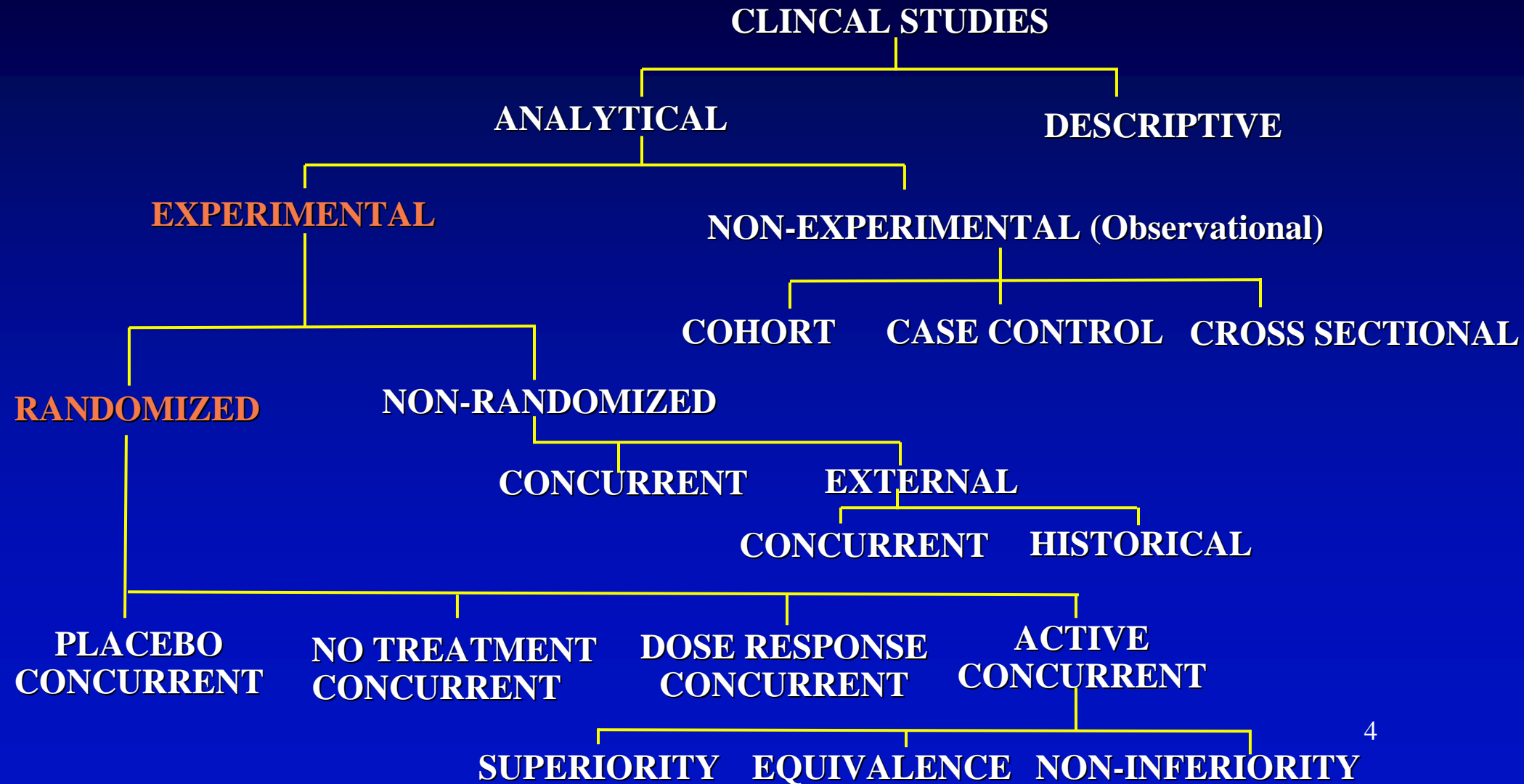
Introduction

- **Evaluating medical interventions requires evidence from clinical research**
- **Overall assessment based on evaluation of benefits compared to harms**
 - “First do no harm”
 - **Risks and benefits depend on clinical situation**
 - **Population – varying treatment benefit/adverse events**
 - **Disease – self-resolving vs. life-threatening**
- **Basic principles regarding evaluation of effectiveness**

Basic Principles

- **Goal is to measure clinically meaningful benefit for patients (not just affect organisms) based on testing hypotheses**
- **Compare outcomes in group who receive intervention compared to outcomes in group not receiving intervention**
- **Requires comparison with control group**
- **Try to minimize various forms of error that can alter results from the true state in nature**

Clinical Studies



Adequate and Well-Controlled Trials

1. **Clear statement of objectives**
2. **Study design permits valid quantitative comparison with a control**
3. **Select patients with disease (treatment) or at risk of disease (prevention)**
4. **Baseline comparability (randomization)**
5. **Minimize bias (blinding, etc.)**
6. **Appropriate methods of assessment of outcomes**
7. **Appropriate methods of analysis**

- **21 CFR 314.126**

Adequate and Well-Controlled Trials

1. **Clear statement of objectives**
2. **Study design permits valid quantitative comparison with a control**
3. **Select patients with disease (treatment) or at risk of disease (prevention)**
4. **Baseline comparability (randomization)**
5. **Minimize bias (blinding, etc.)**
6. **Appropriate methods of assessment of outcomes**
7. **Appropriate methods of analysis**

- **21 CFR 314.126**

1. Clear Objective of Study

- **Treatment vs prevention vs diagnosis**
 - Disease vs infection vs at risk of disease/infection
 - Effects on enrollment and outcome criteria
- **Superiority vs similarity of intervention to control**
 - Different issues with design of “similarity” trials
 - Similarity trials more prone to various forms of error even if randomized and double-blinded
- **Management vs explanatory**
 - Explaining the effectiveness of an intervention –should come first
 - Exploring effect as part of a multi-dimensional management strategy

Adequate and Well-Controlled

1. **Clear statement of objectives**
 2. **Study design permits valid quantitative comparison with a control**
 3. **Select patients with disease (treatment) or at risk of disease (prevention)**
 4. **Baseline comparability (randomization)**
 5. **Minimize bias (blinding, etc.)**
 6. **Appropriate methods of assessment of outcomes**
 7. **Appropriate methods of analysis**
- **21 CFR 314.126**

Quantitative Comparison with Control

- **Types of Controls**
 - Different types of interventions (none, placebo, active)
 - Timing of control relative to intervention (concurrent or historical)
- **No treatment concurrent control**
- **Placebo concurrent control**
- **Dose-response concurrent control**
- **Active concurrent control**
- **External (historical) control**

Quantitative Comparison with Control

- **Trials can be either superiority or “similarity” trials**
 - No treatment, placebo and dose-response usually superiority
 - Active and historical control can be superiority or similarity
- **“Similarity” trials of two varieties**
 - Equivalence – both no better and no worse by some amount
 - Non-inferiority – no worse by some amount
- **Non-inferiority trials:**
 - Based on clinicians desire for comparative data
 - Do not show two interventions are equal or “as good as” each other
 - rule out degree of *inferiority* of experimental compared to control intervention
 - Powers JH Stats Med 2008; 27(3):343-52

Quantitative Comparison with Control

- **Non-inferiority trials more prone to various forms of bias & incorrect conclusions (false-positive)**
- **No “negative” control – reliance on historical data for effect of control drug introduces same biases as in historically controlled trials**
- **Protections from bias in superiority trials result in false-positive conclusions in NI trial**
 - **Not enrolling subjects with disease makes interventions appear more similar**
 - **Blinding less effective protection from bias since investigators aware all subjects receiving active intervention**
- **Poor conduct of trial (increases in missing data, loss to follow-up, non-adherence) can increase chances of false-positive result in NI trials**

Quantitative Comparison with Control

Criteria for Valid Non-inferiority Trial

1. **Quantitative** assessment of magnitude of benefit of control over placebo

- reliable and reproducible based on trials that are themselves adequate and well controlled (data based, not judgment)
- examination variability of results from prior trials (confidence intervals not just point estimates)

NOTE: Prior approval or accepted use does not address *reproducibility* , *reliability* or *quantification* of benefit

2. Maintenance of the effect of the control from trial to trial

- Similar definition of disease, endpoints, timing of endpoints
- Changes in medical practice, adjunctive therapies, antimicrobial resistance

3. Preservation of part of benefit of control drug by selection of margin of loss of effect that is *less than* the benefit of control over placebo

Adequate and Well-Controlled Trials

1. **Clear statement of objectives**
2. **Study design permits valid quantitative comparison with a control**
3. **Select patients with disease (treatment) or at risk of disease (prevention)**
4. **Baseline comparability (randomization)**
5. **Minimize bias (blinding, etc.)**
6. **Appropriate methods of assessment of outcomes**
7. **Appropriate methods of analysis**

- **21 CFR 314.126**

3. Selecting Research Subjects

- **Depends on goal of study**
 - **Treatment – subjects with defined disease**
 - “Empirical” therapy acts “as if” subjects have disease (how valid is this conclusion?)
 - **Prevention – subjects at risk of disease**
- **Difference between clinical practice (who clinicians would choose to treat) and clinical research (exposing subject to experiment)**
- **Description affects generalizability of results**
- **Incorrect selection of subjects can result in false-positive conclusions of effectiveness in NI trials**

Adequate and Well-Controlled Trials

1. **Clear statement of objectives**
2. **Study design permits valid quantitative comparison with a control**
3. **Select patients with disease (treatment) or at risk of disease (prevention)**
4. **Baseline comparability (randomization)**
5. **Minimize bias (blinding, etc.)**
6. **Appropriate methods of assessment of outcomes**
7. **Appropriate methods of analysis**

- **21 CFR 314.126**

4. Baseline Comparability

- **“Fair comparisons” between intervention and control group is basis for all comparisons**
 - Random error – sampling bias
 - Systematic error – selection bias
- **Randomization most accurate way of distributing baseline variables between groups**
 - Non-systematic method of allocation
 - Requires allocation concealment (blinding of randomization code) to prevent selection bias
 - Account for unmeasured as well as measured variables
 - Historical (external) controlled trials are not randomize

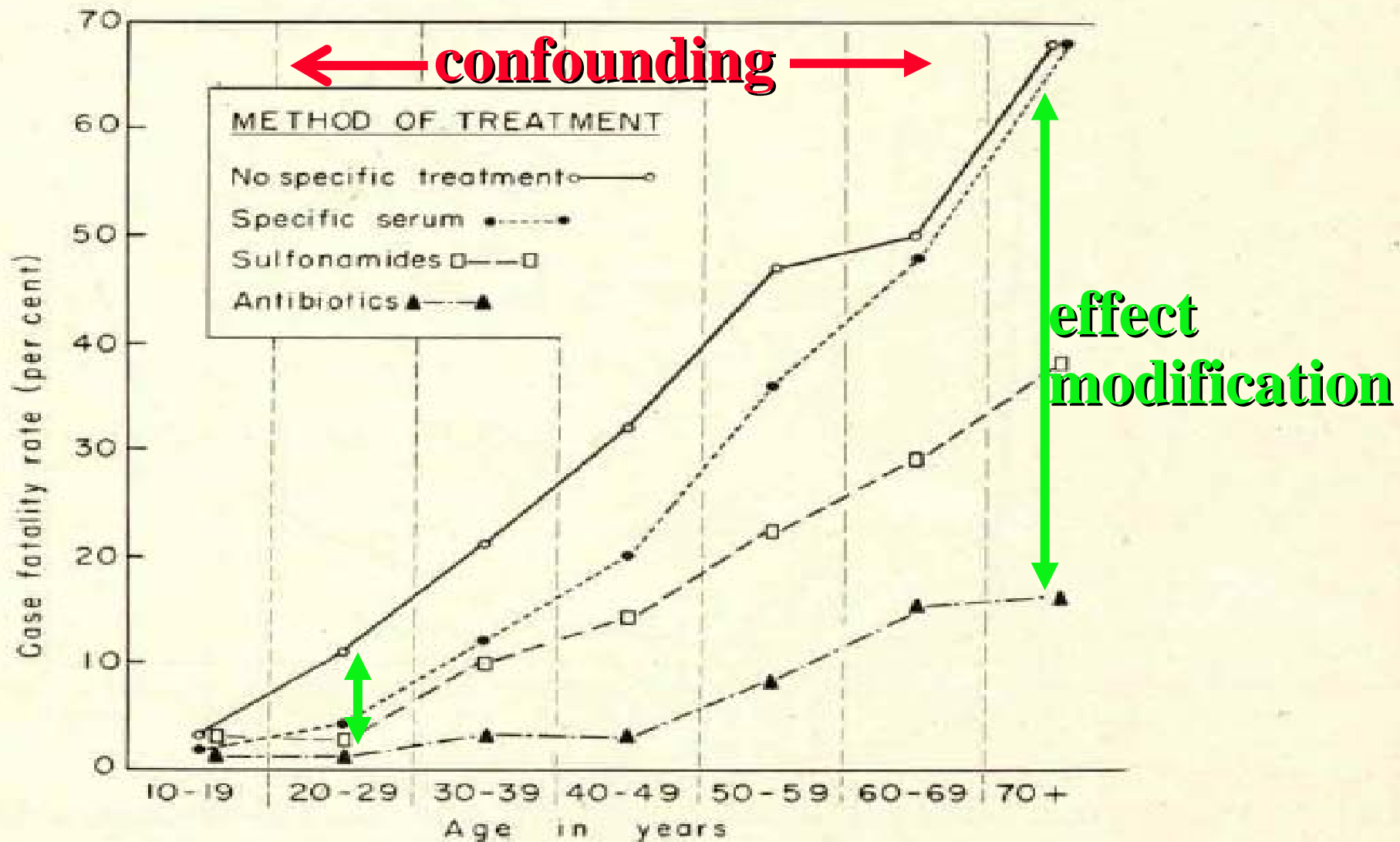
Adequate and Well-Controlled Trials

1. **Clear statement of objectives**
2. **Study design permits valid quantitative comparison with a control**
3. **Select patients with disease (treatment) or at risk of disease (prevention)**
4. **Baseline comparability (randomization)**
5. **Minimize bias (blinding, etc.)**
6. **Appropriate methods of assessment of outcomes**
7. **Appropriate methods of analysis**

- **21 CFR 314.126**

5. Minimizing Bias

- **Bias** = systematic error that results in deviation of results from “true” results (measurement is incorrect)
- **Confounding** = systematic error in which measurement is correct but assessment of causality flawed (due to factor other than intervention)
 - Associated with exposure (intervention and control)
 - Associated with outcome
 - Confounding can occur in NI trials even if equal between groups e.g. concomitant antimicrobials
 - *Independent* of treatment
- **Effect modification** = size of treatment effect varies depending on baseline factors e.g. age, seriousness of disease and baseline risk of death
 - *Dependent* on treatment



1.—Case fatality rates in patients with pneumococccic pneumonia in relation to age.

5. Minimizing Bias

- Randomization **accounts for *selection bias* at baseline (start of trial) – does not account for biases DURING trial**
- Operational biases – investigators treat one group of subjects or subjects within a group differently = **standardize protocol**
- Ascertainment/observer bias – **knowledge of treatment assignment biases outcomes**
- Measurement bias – **error associated with methods used to measure (technical or “judgment”)**
 - Sackett D J Chronic Dis 1979;32:51-63.

Adequate and Well-Controlled Trials

1. **Clear statement of objectives**
2. **Study design permits valid quantitative comparison with a control**
3. **Select patients with disease (treatment) or at risk of disease (prevention)**
4. **Baseline comparability (randomization)**
5. **Minimize bias (blinding, etc.)**
6. **Appropriate methods of assessment of outcomes**
7. **Appropriate methods of analysis**

- **21 CFR 314.126**

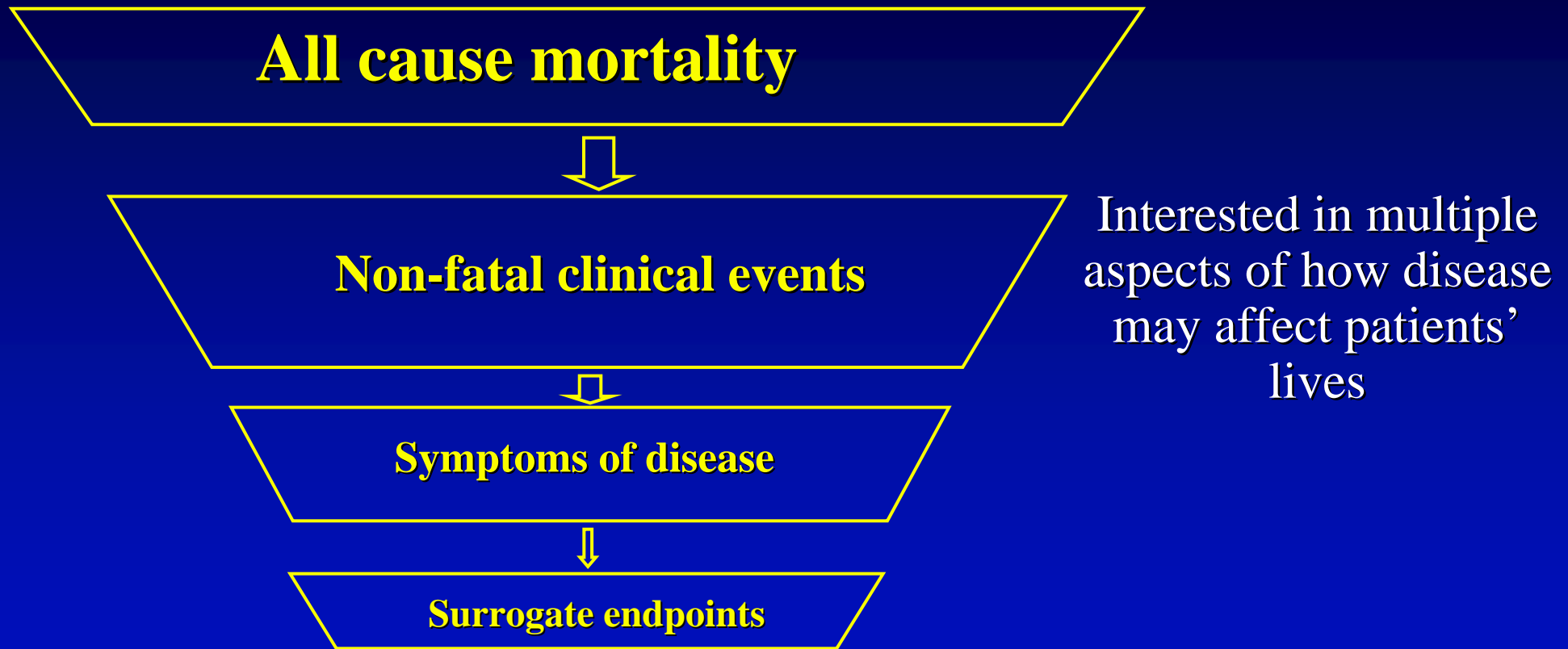
6. Assessing Outcomes

- **Want to measure a difference that makes a difference to patients**
 - **WHAT to measure**
 - **HOW to measure it**
 - **WHEN to measure it**
 - **HOW MUCH of a difference is clinically significant**
- **Look at outcomes from patients perspective, not the intervention's perspective**
 - **Measure clinically meaningful events even if intervention is not capable of affecting them**
 - **Misleading claim to base “cure” of disease on variables that were not measured**

6. Assessing Outcomes

- **Clinical endpoint** = *direct* measure of how a patient feels, functions or survives (“feels” means symptoms not emotions)
 - mortality
 - symptoms of disease
 - 21 CFR 314.500
- **Surrogate endpoint** = biomarkers that measure laboratory measurement or physical signs used as a substitute for clinical endpoint; surrogate endpoint by itself does not confer *direct* clinical benefit to the patient
 - Scales which combine biomarkers into a single measure are still biomarkers

Multiple Endpoints



Lubsen J et al. Stat Med 2003;21:2159-70.

Adequate and Well-Controlled Trials

1. **Clear statement of objectives**
2. **Study design permits valid quantitative comparison with a control**
3. **Select patients with disease (treatment) or at risk of disease (prevention)**
4. **Baseline comparability (randomization)**
5. **Minimize bias (blinding, etc.)**
6. **Appropriate methods of assessment of outcomes**
7. **Appropriate methods of analysis**

- **21 CFR 314.126**

7. Analyzing Results

- A whole course unto itself! ...Some common things to look out for
- **VALIDITY** – actually measure what you purport to measure, not based on ability to publish, consensus, “accepted” or “used”
- A p-value does not measure validity of hypothesis, only probability of chance results
- P-value only measures **RANDOM** error, not bias
- Increased sample size makes bias **WORSE** – “the largest trial in disease X” is not necessarily more valid

7. Analysis of Results

- **Precision is different than validity; measure of variability around a given estimate measure**
- **Use of confidence intervals to express precision of estimates and evaluate clinically meaning**
- **Results can be more precisely wrong if affected by bias**
- **Bias is best controlled at design stage of trial**

7. Analysis of Results

- Compare the results to the original hypothesis
- Evaluate all the subjects randomized (intention to treat population), not just an “evaluable” population – a smaller population selected among the whole group can reinsert the selection bias randomization was meant to attempt
- Subgroup analysis and secondary endpoints – issues of multiple comparison and increasing chance of false positive conclusions
- Basic principle is various populations and analyses should confirm overall results, not contradict them

Conclusions

- **Clinical research supplies clinicians with verifiable scientific evidence upon which to base decisions with patients**
- **Seven criteria provide useful method when evaluating clinical trial results**
- **Need to compare benefits (effectiveness) of intervention to potential harms to obtain overall risk-benefit analysis (first do no harm)**
- **Areas for improvement in ID trials are evident**
- **The most impractical trial is the one that provides no useful evidence for patients and clinicians**