An Introduction to Clinical Trials:
Design Issues

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Type of Studies

- Non-experimental (Observational)
  - Case report
  - Case series
  - Cross-sectional (survey)
  - Case-control
  - Prospective, observational (cohort)
- Experimental
  - Randomized, clinical trial (RCT)

Study designs

- Observational studies:
  - Observe both exposures and outcomes
- Experimental studies (clinical trials)
  - Assign exposures
  - Observe outcomes

Advantages of Clinical Trials

- Often provides the strongest evidence in support of cause-effect relationships
- Basis for clinical and public health policy
- Minimize/eliminate bias and confounding
Randomized Clinical Trial

- Target Population
- Study Population
  - RANDOMIZED
  - Standard Treatment
    - Disease
  - New Treatment
    - Disease

Comparison of Study Designs

<table>
<thead>
<tr>
<th>Type of Study Design</th>
<th>Dimension</th>
<th>Cross-Sectional</th>
<th>Case-Control</th>
<th>Cohort</th>
<th>RCT</th>
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<tbody>
<tr>
<td></td>
<td>Estimate Prevalence</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
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<tr>
<td></td>
<td>Estimate Incidence</td>
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<td>B</td>
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<td>Prove Causality</td>
<td>A</td>
<td>B+</td>
<td>B+</td>
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<td>Generalizability</td>
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<td>B+</td>
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<td>Feasability</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>C</td>
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</table>

Core Elements of a Clinical Trial

- Research Question
- Hypotheses
- Core Design
- Study Participants
- Recruitment
- Allocation
- Masking (Blinding)
- Treatment Groups

Data
- Analytical Issues
- Interpretation of Results

The Research Question

- Critical in the design of a trial
- Types of questions:
  - Assessing efficacy of an intervention
  - Assessing the effectiveness of an intervention
Types of Hypotheses

• Comparative Trial (a.k.a. Superiority Trial)
  – Objective: to demonstrate that a new therapy (n) is superior to standard therapy (s) in terms of incident outcome (I)
    \[ H_0: I_n = I_s \]
    \[ H_a: I_n < I_s \] (one tailed) or \[ H_a: I_n \neq I_s \] (two tailed) at some minimally detectable $\Delta$ judged to have clinical significance

• Equivalence (non-inferiority trial)
  – Objective: to demonstrate that a new therapy (n) is no worse than standard therapy (s) in terms of incident outcome (I)
    \[ H_0: I_n > I_s \]
    \[ H_a: I_n = I_s \] at some $\Delta$, the maximum tolerable difference considered to be clinically acceptable

Basic Types of Design

- Parallel
  \[ A \rightarrow B \]
- Cross-Over
  \[ A \rightarrow A \]
  \[ B \rightarrow B \]

Parallel Study Design (PREMIER)

- Randomization
- ADVICE ONLY
- EST
- EST + DASH

$\dagger$ = Data Visit
Primary Outcomes (6 months)
End of Intervention (18 months)
### Blood Pressure Results (mmHg)

Mean Change from Baseline in Each Diet

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>CARB</th>
<th>PROT</th>
<th>UNSAT</th>
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<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>131.2</td>
<td>-8.2</td>
<td>-9.5</td>
<td>-9.3</td>
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<tr>
<td>HTN Only</td>
<td>146.5</td>
<td>-12.9</td>
<td>-16.1</td>
<td>-15.8</td>
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<td>PreHTN Only</td>
<td>127.5</td>
<td>-7.0</td>
<td>-8.0</td>
<td>-7.7</td>
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<tr>
<td><strong>Diastolic BP</strong></td>
<td>77.0</td>
<td>-4.1</td>
<td>-5.2</td>
<td>-4.8</td>
</tr>
</tbody>
</table>

*Appel et al. 2005*
Effect of Increased Sodium Intake on Systolic Blood Pressure in Two Diets: Results of the DASH-Sodium Trial

- Increase in systolic blood pressure with increased sodium intake in both diets.
- American Diet: +4.6 mmHg, p<.0001
- DASH Diet: +1.7 mmHg, p<.0001
- No other factors considered.

Factorial Design

- Type of trial in which individuals are randomized to two or more therapies (example: Physician’s Health Study: tested aspirin (ASA) and β-carotene).

AASK Research Questions

- Among African-Americans with early evidence of hypertension-related kidney disease:
  - Does aggressive blood pressure control to a target blood pressure below current recommendations retard the progression of kidney disease?
  - Do specific classes of anti-hypertensive medications retard the progression of kidney disease?
**Design of AASK**

- Randomized, active controlled trial with a 2 x 3 factorial design
- Participants: 1,094 African-Americans with hypertension-related renal insufficiency
- Planned follow-up of 2.5 to 5 years

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**Treatment Assignments**

(2:2:1 ratio of drug assignment)

3 X 2 Factorial Design

<table>
<thead>
<tr>
<th>Mean Arterial Pressure (MAP)</th>
<th>Metoprolol*</th>
<th>Ramipril</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP &lt;92</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>MAP 102-107</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

N 441 436 217

MAP = Mean Arterial Pressure; * = referent group

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**Mean Arterial Pressure During Follow-up**

- Lower BP Goal (Achieved: 128/78)
- Usual BP Goal (Achieved: 141/85)

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**Composite Clinical Outcome**

Declining GFR Event, ESRD or Death

- Lower BP (Achieved: 128/78)
- Usual BP (Achieved: 141/85)

Low vs. Usual: RR=2%, (p=0.85)

RR=Risk Reduction, adjusted for baseline covariates
Main Clinical Composite Outcome
Declining GFR Event, ESRD, or Death

Metoprolol vs. Amlodipine: RR = 20%, p = 0.17
Ramipril vs. Amlodipine: RR = 38%, p = 0.004

Ramipril vs. Metoprolol: RR = 22%, p = 0.042

Study Participants
- Target Population -> Healthy Elderly
- Accessible Population -> Retired Teachers
- Study Sample -> Volunteer Teachers who respond to mass mailing
Study Participants

• Ideal ‘Accessible’ Population
  – high risk for disease
  – candidates for treatment
  – representative of target population
  – feasibility considerations
    • recruitment
    • follow-up
    • high quality data

Enrollment Criteria

• Inclusion Criteria
  – characteristics of accessible population

• Exclusion Criteria
  – considerations related to:
    • adherence to therapy
    • follow-up
    • safety
    • ethics

Common Recruitment Strategies

• General mailings
  – Licensed drivers
  – Voters
  – Employee paychecks

• Targeted mailings
  – HMO enrollees
  – AARP members

• Mass media
  – Radio
  – TV ads
  – Newspapers
  – Posters/flyers

• Screenings
  – Worksite
  – Community

• Physician Referral

• Medical Record Review

• Internet / WWW
  – Clinical trial registries
  – Banner ads
  – Social networks

Comments on Recruitment

• Recruitment begins with design
• Response rate is always lower than expected
• Required resources are more than expected
• Dedicated personnel are necessary
More Comments on Recruitment

• Recruitment period is often longer than expected
• Implement several strategies to identify best source
• Prepare back-up strategies
• Monitor recruitment
  – Early
  – Often
  – Locally

Recruitment “Funnel”
(Example: VITAL Pilot Study)

4,774 Mailed Invitations
  ↓ 43%
2,034 Questionnaires Returned
  ↓ 38%
765 Interested After Initial Mailing
  ↓ 41%
323 Randomizable after Second Mailing (7% cumulative)
  ↓ 297 Randomized

Allocation

• Random
  – stratified
  – blocked
• Non-Random
  – haphazard
  – systematic

Why randomize?

• Two critical reasons:
  – to eliminate selection **BIAS**
  – to reduce/avoid **CONFOUNDING** from known and, more importantly, unknown confounders
Masking (Blinding)

- **Single Blind**
  - Observers (persons who collect outcome variable) do not know treatment assignment
- **Double Blind**
  - Study participants AND observers do not know treatment assignments
- **Triple Blind**
  - Data interpreters, study participants, and observers do not know treatment assignments

<table>
<thead>
<tr>
<th></th>
<th>Single Masked</th>
<th>Double Masked</th>
<th>Triple Masked</th>
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<tbody>
<tr>
<td>Outcome Assessor(s)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Participant</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Data Interpreter</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Selection of Groups

- **Active Treatment Group**
- **Comparison Group**
  - Placebo (no active therapy)
  - Usual care (referral back to personal MD)
  - Active control group (provision of standard therapy)

Problems with selecting active treatment group

- **Many Candidate treatments**
  - observation studies, animal models, or theoretically based
- **Strong evidence rarely exists to guide selection of intervention**
- **Dose/intensity are uncertain**
Comparison Group

- Placebo – used in setting of:
  - No standard therapy OR
  - Standard therapy but risk of not providing it is minimal
- Usual care OR active control – common

Problems with standard of care approach

- Efficacy of ‘Usual care’ often not tested
- Variations in standard of care are common:
  - across providers
  - between experts and providers
  - secular trends occur

Data

- Baseline data
  - Determine eligibility
  - Describe study participants
  - Define subgroups
  - Address confounding
- Measures of Adherence
- Outcome Variables

Outcome Variables

- Principal outcome
  - most important variable after randomization code
  - specified in hypothesis
  - determinant of sample size
- Secondary Outcomes
  - relevant to research question
Desirable Features of Outcome Variable

- clinically relevant
- easy to measure
- little measurement error
  - random error – leads to imprecision
  - systematic error – leads to bias
- masked (blinded) ascertainment

Surrogate Outcomes

- Definition: a laboratory measurement or physical sign used as a substitute for a clinically meaningful outcome
- Types: physiologic variable, clinical risk factor, or sub-clinical disease

Advantages of Surrogate Outcomes

- Surrogate outcomes typically increase statistical power compared to clinical outcomes
  - Surrogate outcomes
    - often continuous
    - measured repeatedly
  - Clinical outcomes
    - often categorical
    - surveillance till outcome occurs

Advantages of Surrogate Outcomes (continued)

- Enhanced power means
  - shorter duration of follow-up and/or reduced sample size
  - less cost
- Less contamination by competing comorbidities if the study duration is short
- Useful in studies of mechanisms
Surrogate and clinical outcomes: a continuum

Surrogate and clinical outcomes: an example

Relationship between Surrogate and Clinical Outcomes

Relationship between Change in Surrogate Outcome and Change in Clinical Outcomes
## Clinical and Surrogate Outcomes: Cardiovascular

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Surrogate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>Ultrasound measurement of intimal medial thickness of the carotid artery Blood pressure</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Quantitative coronary angiography Electron beam computerized tomography</td>
</tr>
<tr>
<td>Sudden death</td>
<td>Ventricular arrhythmia</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Ejection fraction</td>
</tr>
</tbody>
</table>

### Weaknesses

- Measurement of surrogate outcomes can involve complex, technical procedures
  - procedures sometimes new (therefore, longitudinal data is scant)
  - procedures become obsolete
  - many technical and analytic issues, often unapparent
Disadvantages of Surrogate Outcomes (continued)

- Missing values are commonplace
- Missing values result from loss to follow-up and poor quality of data
- Potential for bias
  - missing values occur in the sickest people, sometimes because of the clinical outcome of interest
  - informative censoring, that is, loss of follow-up data potentially related to treatment assignment

Models for success and failure of surrogate outcomes*

Model for failure: the surrogate is not in the causal pathway of the disease process

Intervention → Surrogate Outcome → Clinical Outcome

Model for failure: the intervention affects only the pathway mediated through the surrogate

Intervention → Surrogate Outcome → Clinical Outcome

Model for failure: the surrogate is not in the causal pathway of the disease process

Fluoride → ↑ Bone Density → Osteoporosis

Model for failure: the intervention affects only the pathway mediated through the surrogate

Protein Restriction → ↓ Proteinuria → Kidney Failure
Model for failure: The intervention has several mechanisms of action

Example: Dihydropyridine calcium channel blockers

The Cardiac Arrhythmia Suppression Trial (CAST\*): Background

- Ventricular arrhythmias are a risk factor for sudden death after MI
- Four fold higher risk of cardiac mortality among persons with frequent premature ventricular contractions (PVCs)
- In the CAST pilot study, the antiarrhythmic drugs (encainide, flecainide) suppressed PVCs


CAST Research Question

Does suppression of ventricular ectopy after a MI reduce the incidence of sudden death?
CAST Design

- Design: randomized trials of
  - encainide vs placebo
  - flecainide vs placebo
- Participants (n=1498)
  - recent MI (6 days to 2 years ago)
  - ventricular ectopy (6 or more PVCs /hr)
  - at least 80% suppression of PVCs by active drug during open label titration period prior to randomization

CAST results: number of deaths and cardiac arrests by group

- Active treatment: 63 events / 755
- Placebo: 26 events / 743
  \[ p = 0.0001 \]

- same pattern of results for
  - death from arrhythmia
  - death from any cardiac cause
  - death from any cause

Lessons from CAST

- Active treatments can be harmful (one of several recent trials in which placebo was superior to active treatment)
- Reliance on surrogate outcomes can be misleading
- The scientific community should encourage researchers and sponsors to conduct studies with 'hard' clinical outcomes
Examples from the Field

- Surrogates that go in the right direction (easy to explain – fit your hypothesis)
- Surrogates that go in unexpected directions (create a greater need for hand-waving and can still be made to fit your hypothesis)
- Surrogates that behave badly

Model for potential success: Surrogate outcome in the casual pathway

Diet Change

↑ oxidative stress → ↓ oxidative stress → ASCVD

Time

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**Figure 2b**

**Dietary Patterns**
- Dietary Antioxidants
  - Vitamin C
  - Vitamin E
  - Beta-carotene

**LDL Cholesterol**
- Oxidized LDL

**Free Radical Activity**
- Oxidative stress Markers

**Inflammatory Markers**

**Fatty Streak Formation**

**Atherosclerosis**

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**Figure 1.** Oxidation of plasma components (left axis scale, 0–

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**Figure 2b**
Nurses Health Study

- Design: Prospective Cohort Study
- Participants: 121,700 female nurses free of diagnosed cardiovascular disease
- Exposure: Dietary questionnaire at baseline
- Assessment: Vitamin E and Multivitamin Use
- Follow-up: 8 years
- End Points: 1) Major Coronary Disease, 2) Non-fatal MI, 3) Deaths Due to Coronary Disease


Summary of Biological Evidence

- Antioxidants are necessary
- Oxidized lipids are associated with CVD
- Oxidation of lipids is reduced by antioxidant supplementation
- Does supplementation lower risk of CVD?
  - Observational studies
  - trials

Clinical Trials – Clinical Outcomes

- Cardiovascular Events
  - Fatal and Non-fatal MI
  - Stroke
  - Peripheral artery disease

- Mortality

Do Vitamin E supplements reduce risk?

- Observational studies are confounded – vitamin E takers exercise more, have a lower BMI, eat healthier diets and smoke less often than non-vitamin users
- Observational studies are hypothesis generating
- Surrogate markers are only indirectly related to clinical events
- Benefits can only be assessed in randomized controlled clinical trials

FIGURE 1. Mean changes (and 95% CIs) in urinary 8-iso-prostaglandin F_2alpha (PGF_2alpha) in the placebo group, −150.0 (−275.4, −24.6) in the vitamin E group, −141.3 (−230.6, −52.1) in the vitamin C group, and −112.5 (−234.8, 9.8) in the vitamin C + E group. There was no synergistic interactive effect of vitamins C and E (P = 0.12).
ATBC Study

- Design: Randomized, double-blind, placebo-controlled primary prevention trial
- Participants: 29,133 male Finnish smokers, age 50-69
- Intervention: 1) Vitamin E 50 IU/day  
  2) B-carotene 20 mg/day  
  3) Combination  
  4) Placebo
- Follow-up: 5-8 years
- End Points: Incident lung cancer & deaths

ATBC Trial Results

- Beta-carotene group (20 mg/day)  
  - increase in total mortality (9%)  
  - increased incidence of angina (13%)*  
  - increased CVD mortality (11%)*  
  - increased incidence of lung cancer (18%)
- Vitamin E Group (50 mg/day)  
  - reduction in total coronary events (3%)  
  - reduction in incident angina (9%)  
  - reduction in non-fatal MI (11%)

CARET Study

- Design: Randomized, double blind, placebo-controlled primary prevention trial
- Participants: 18,314 smokers, former smokers, and workers exposed to asbestos
- Intervention: 1) B-carotene (30 mg/day) and vitamin A (25,000 IU/day)  
  2) Placebo
- Follow-up: 4 years
- End Points: Incident lung cancer, Cardiovascular Disease
Meta-Analysis: High-Dosage Vitamin E Supplementation May Increase All-Cause Mortality

Background: Surveillance models and epidemiological studies suggest that vitamin E supplementation may prevent cardiovascular disease and cancer. However, several trials of high-dose vitamin E supplementation showed non-statistically significant increases in all-cause mortality.

Purpose: To perform a meta-analysis of the dose-response relationship between vitamin E supplementation and all-cause mortality, using data from randomized controlled trials.

Methods: CHENG et al. published 5 trials. Of these trials, 3 failed vitamin E dosage and 1 failed vitamin E combined with other vitamins or minerals. The dosage of vitamin E ranged from 100 to 4000 IU daily (median, 400 IU).

Data Sources: Published from 1978 through 2004, comprising 54,505 participants. Meta-analysis was not performed due to small and inconsistent results of individual trials.

Results: High-dose vitamin E led to mortality rates in all trials, with increased mortality in trials that used high doses of vitamin E. Near-dose mortality was not increased in low-dose trials.

Conclusions: High-dose vitamin E supplements may increase all-cause mortality and should be avoided.

Failed surrogate marker: example

- Smoking
- β-carotene
- Lung Cancer

Need for reliable surrogate markers
Disadvantages of Surrogate Outcomes (continued)

• The relationship between a surrogate outcome and a clinical outcome has face validity but is often uncertain

• Relationship between change in surrogate and risk of clinical outcomes is rarely known

The Bottom Line

“Trust but verify”
Ronald Reagan

Analytical Issues

• Sample Size (Power Calculations)
• Analytical Approach (a priori)
• Intention-to-treat (vs ‘as treated’)

Analytic Techniques: Crude analyses

• Analysis depends on the type of outcome data
• Basic tests
  – Continuous outcome variable: t-test
    • Examples: Blood pressure, serum cholesterol
  – Dichotomous or categorical data: chi-squared, logistic regression, cox modeling for time to event
    • Example: Incident HIV, MI, cancer, renal failure, death
Epidemiology in a box: The 2x2 table

- The EXPOSURE (E)
  - Example: obesity
- The OUTCOME (D)
  - Example: Hypertension
- Applicable to most study designs

<table>
<thead>
<tr>
<th></th>
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<th>D-</th>
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</thead>
<tbody>
<tr>
<td>E+</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>E-</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

\[ \begin{array}{c|c}
\text{Total} & a+b \\
\hline
a+c & b+d \\
\end{array} \]

Analytic Techniques: Adjusted (Regression) Analyses

- Regression determines association between exposure and outcome
- Procedures depends on outcome variable:
  - Continuous outcome: linear regression
  - Dichotomous outcome: logistic regression
  - Time-to-event: Cox proportional hazards

Interpretation of Results

- Internal Validity
  - conclusions correctly describe what happened in the study
- External Validity (‘generalizability’)
  - the degree to which the conclusions apply to the study population and other populations

Why RCTs Can Be Difficult

- Hard to find and recruit the right people
  - Many don’t want to be “guinea pigs”
- Greater responsibility, documentation
- May take years for outcomes to develop
- People are free to do as they please
  - Some assigned to treatment don’t adhere
  - Some assigned to control seek treatment
  - Some drop out of the trial completely
Adherence (compliance)

• Difficult to measure
• Difficult to promote
• Must be promoted and measured, at least in efficacy or explanatory trials

Why be worried about adherence?

- Active
- Drop-In’s
- Control
- Drop-Out’s

Intention-to-Treat: analysis by randomized group, not by final groupings

Adherence (compliance)

• Measurement
  – self report
  – pill count
  – blood levels of drug
  – biological changes (urine or blood)
• Promotion
  – exclude poor candidates before randomization
  – keep intervention simple
  – respond to evidence of inadequate adherence

How To Handle Participants Who Don’t Adhere to Trial Assignment

• Intention-to-Treat Approach
  – Least optimistic
  – Maintains initial balance from randomization
  – Highlights problems from adverse effects
• On-Treatment Approach
  – Most optimistic
  – Upsets initial balance from randomization
  – Downplays problems from adverse effects

Because of its conservatism, the Intention-to-Treat approach is strongly preferred.
Cardiac Event-Free Survival in 192 Adults with Refractory Angina by Random Assignment and Cross-Over (from Medical Treatment to TMR) Status

TMR = transmyocardial laser revascularization

Clinical Trials: Design and interpretation Considerations
When Trials Are Impossible (or Nearly Impossible)

- Adverse Exposures (e.g. Cigarettes)
- Rare Outcomes (e.g. Reye’s Syndrome)
- Intervention Already in Wide Use

In these circumstances, one must rely on observational studies—i.e. prospective cohort studies and case-control studies. When interventions are already in wide use, “outcomes research” is a good option. In outcomes research, medical interventions (e.g. drugs, surgical procedures) are considered as exposures. Data on these interventions, and on relevant clinical outcomes, are available from medical records and often from large-scale electronic databases.

Statistical vs Clinical Significance

- Statistical significance pertains to whether or not the observed results could occur from chance alone
- Clinical significance pertains to whether or not the observed results have “important” clinical, research or public health relevance.

How To Interpret Negative Results

- Treatment is worthless
- Treatment is worthwhile, BUT study had…
  - Bias against the treatment (e.g. crossing in)
  - Inadequate contrast between groups
    - Suboptimal treatment (e.g. unskilled surgeons)
    - Low adherence (e.g. drug causes GI distress)
    - Controls sought treatment despite assignment
  - Insufficient statistical power
    - Very common cause of negative findings
    - Meta-analysis a potential remedy

Efficacy (Explanatory) Trial vs Effectiveness (Pragmatic) Trial

- Theory
  - Efficacy: What is the effect of the therapy under ideal conditions
  - Effectiveness: What is the effect of therapy under ‘real world’ conditions
- Reality
  - The dichotomy between efficacy and effectiveness is artificial
  - Broad continuum
Typical Implementation Units

- Clinical Centers
  - recruit participants
  - collect data
  - administer intervention/therapy
- Laboratory or Reading Centers
  - perform assays or readings of procedures
- Data Coordinating Center*
  - receive/assemble data
  - coordinate activities
  - perform data analyses

* similar to Contract Research Organization (CRO)

Oversight Units

- Internal
  - Sponsor
  - Data Coordinating Center or Contract Research Organization
- External
  - Institutional Review Board
  - Data and Safety Monitoring Board

Organizational Structure of a Multi-Center Trial
(Weight Loss Maintenance Trial)