Today

• Course format, Goals, and Overview
• Types of trials
Course Format

• Lectures
  – Posted on course page after lectures so that you can review material as needed
  – Lecture notes will include suggested and ‘for additional information’ references
  – References to readings on course page when available electronically – these link through library

• Classroom discussion is encouraged
• Homework assignments (2-3)
• Quiz
• Project
Office Hours

• Graham A. Colditz, MD, DrPH
• Esther Liu, PhD

following each class or by appointment (use email)
Course Goals

• To give an introduction to the concepts, principles, and methods used in clinical trials

• Non-mathematical focus

• Heavy reliance on examples from recent medical literature – we will work to make these relevant to your areas of focus

Goal: to inform about “hows” and “whys” of clinical trials, but also to provide a framework for how to think about unanticipated issues that arise in the design, conduct, analysis, and reporting of clinical trials.

Course builds on past teaching at HSPH by Rich Gelber and Steve Lagakos with current help from Jim Ware, ongoing experience with RCTs including input from Bernard Rosner and Esther Liu.
Competencies

1. Ability to design RCT
2. Skills and experience to conduct analysis of RCT
3. Master core reporting strategies
4. Draw inference from data to inform clinical and public health practice
Topics

- Overview – the role of RCTs in evaluating medical and public health interventions
- Phase III trials; Efficacy vs. Effusiveness (Population definitions)
- Ethical considerations: Consent & IRB
- Bias and Error: Randomization
- Study Protocol: Sample size & stopping rules
- Defining and enrolling patients: Baseline data collection
- Adherence to intervention
- Data quality
- Follow-up, data monitoring, interim analysis, & SAEs
- Analysis – main hypothesis, secondary and subgroup analysis
- Per protocol analysis
- Data safety and monitoring
- Managing multi-center trials: RCTs for prevention
- Reporting CONSORT & EXTENDED consort: Applying results of RCTs to clinical practice
- Protocol presentations/Mock IRB session
Homeworks

• 1. Human subjects
• 2. Schema
• 3a. Baseline data forms
• 3b. Follow-up surveillance; endpoint data collection; analysis plan

– All posted to blackboard web site for course
Student Project: Create a Protocol

Protocol (group of size 1-3):
- Develop a protocol for a trial (in your area of interest or suggested by me)
- Work on components of protocol during course
- Submit at end of course

....more in final project handout
One Definition of Clinical Trial

• An *experiment* is a series of observations made under conditions controlled by the investigator.

• A *clinical trial* is an experiment involving a medical *intervention* made to *human subjects* to evaluate a pharmacologic treatment, devise, or procedure aimed to prevent, diagnose, or treat a medical condition.

• Sensitivities around words “experiment” and “subject”
When did we move to use randomized trials?
Other Definitions of a Clinical Trial

...a scientific research activity in human subjects undertaken to determine prospectively the effect and value of preventive, diagnostic, and therapeutic agents, devices, regimens, and procedures.

Hopwood MD, Mabry JC, Sibley WL: Rand Corporation 1980

...any form of planned experiment which involves patients and is designed to elucidate the most appropriate treatment of future patients.

...a scientific experiment that generates clinical data for the purpose of evaluating one or more therapies on a patient population. Implicit in the trial is the fact that the clinical investigator has control of the process by which a treatment is assigned to be a patient.

ELEMENTS OF A CLINICAL TRIAL

Objectives
Patient Population
Treatment (Intervention) Options
Design
Conduct
Endpoints
Analysis
Reporting

M19-550 Randomized Controlled Trials
List a hierarchy of study designs

• If you are to evaluate a medical or public health intervention – list out in increasing order of scientific rigor from a single case study on, the ways (or designs) you could use to do this

• Describe a benefit of each design
Types of Clinical Investigation

Case Reports: detailed description of 1/few patients

Case Series: similar to above, but with more patients

Database Analyses: typically, on existing databases

Observational Studies (No treatment interventions imposed)
   Cross-Sectional Studies: Observe each patient at 1 time point
   Case-Control Studies: Subjects selected by disease status and compared with controls for possible causes.
   Cohort Studies: Subjects observed over time. Cohort studies can focus on treatment as a determinant of course of disease

Controlled Clinical Trials: The treatment assignment is by design. Endpoints and analyses planned in advance
Examples of Observational Studies

• Cross-Sectional Study: Examine a group of teenage school children for nutritional status and academic performance to assess associations.

• Case-Control Study: Select 100 women recently diagnosed with breast cancer in your hospital; select 100 ‘control’ women matched for age, race, and educational status. Survey both groups to ascertain information on use of oral contraceptives (OC) earlier in their lives. Are there higher rates of OC use in group with breast cancer?

• Cohort Study: Identify 500 homosexual men aged 18-30. Ascertain rates and types of sexual activity and HIV status every 6 months for 5 years. How does the risk of becoming infected with HIV depend on the specific type of sexual behavior?

• => Observational studies often aim to identify causes or predictors of disease or some other clinical or public health outcome.
Example of Clinical Trial

• Recruit 200 women recently diagnosed with breast cancer, in which standard treatment is radiation therapy.
• Randomly assign 100 to receive standard treatment and 100 to receive radiation therapy + Tamoxifen.
• Follow women for recurrence of breast cancer.
• Does the addition of Tamoxifen delay or prevent recurrence?
• => therapeutic intervention. Asks a question about treatment (or prevention of) a disease/condition.
Scope of Clinical Trials

**Prevention**
- Vaccines
- Pharmaceuticals
- Behavior modification
- Diet, exercise
- Weight loss
- Devices/screening tests/surgical approaches

**Treatment**
- Vaccines
- Pharmaceuticals
- Devices (stents, pacemakers)
- Surgery transplants (cells, organs) and methods
- Weight loss
Clinical Trials Possess Important Properties of the Scientific Method

- Objective and Reproducible Measurement
- Externalizing of Plans and Procedures
- Control of Extraneous Factors
- Submission of work for External Review and Replication or Disproof
Principles of Design of Randomized Clinical Trial are Easily Stated

• Specify a well-defined population of patients
• Enroll every eligible patient
• Randomly assign study treatment regimens to enroll patients
• Complete the treatment of every patient according to the protocol
Principles Easily Stated (continued)

• Retain every patient in follow-up and complete every scheduled follow-up visit and examination
• Include every randomized patient in the analysis
• Use pre-specified analyses to draw conclusions about study hypotheses
## CTs are Not Idealized Experiments

<table>
<thead>
<tr>
<th>Idealized Experiment</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental units are identical</td>
<td></td>
</tr>
<tr>
<td>Treatment exactly reproducible from occasion to occasion</td>
<td></td>
</tr>
<tr>
<td>Experimental units are controlled by investigator</td>
<td></td>
</tr>
<tr>
<td>Measurement error the only source of variability other than effects of treatments</td>
<td></td>
</tr>
<tr>
<td>Measurement error small</td>
<td></td>
</tr>
<tr>
<td>Experimental units are human subjects; free to refuse participation</td>
<td></td>
</tr>
<tr>
<td>Treatments not exactly reproducible</td>
<td></td>
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<tr>
<td>Patients may withdraw</td>
<td></td>
</tr>
<tr>
<td>Not all factors affecting outcomes are controlled, or even known</td>
<td></td>
</tr>
<tr>
<td>Measurement errors and patient heterogeneity often large relative to treatment effects</td>
<td></td>
</tr>
</tbody>
</table>
Experiments Answer a Scientific Question by Isolating the Intervention and the outcome from Extraneous Influences

• Goals
  – Eliminate systematic error (Bias)
  – Minimize random error (Precision)
  – Ensure the generalizability of study results (translation to practice)

• Study Design is the methodology for achieving these goals
How Are These Goals Achieved

• Specify patient population and method of sampling in a generalizable way
• Pre-specify study hypotheses using clear criteria and endpoints
• Standardize diagnostic, staging, assessment, and follow-up procedures
• Describe the treatment protocol
How are These Goals Achieved (cont)?

• Utilize statistical design to minimize bias and variability
  –Randomization, stratification, blinding, choice of design

• Establish a sample size sufficient to achieve study goals
R A Fisher – Randomization, 1926

• “One way of making sure that a valid estimate of error will be obtained is to arrange the plots deliberately at random, so that no distinction can creep in between pairs of plots treated alike and pairs treated differently; in such a case an estimate of error, derived in the usual way from the variation of sets of plots treated alike, may be applied to test the significance of observed differences between averages of plots treated differently.”
Fisher...

• Design of experiments... 1951
• “The purpose of randomization... is to guarantee the validity of the test of significance, this test being based on an estimate of error made possible by replication”
A. Bradford Hill

• Not focused on exactness in statistical analysis...
• 1. ensures neither personal idiosyncrasies (our likes or dislikes consciously or unwittingly applied) nor our lack of balanced judgment has entered into the construction of the different treatment groups- the allocation has been outside our control and the groups are therefore unbiased...
  • NEJM 1952; 247:113-9
Hill AB, cont...

2. “It removes the danger, inherent in an allocation based on personal judgments, that believing we may be biased in our judgments we endeavor to allow for that bias, to exclude it, and that in doing so we may overcompensate and by thus ‘leaning over backward’ introduce a lack of balance from the other direction”

3. “And having used random allocation, the sternest critic is unable to say when we eventually dash into print that quite probably the groups were differently biased through our predilections or through our stupidity.”
British streptomycin trial

• Hill writes that in his text, Principles of Medical Statistics, 1937, “he deliberately left out the word randomization and random sampling numbers” at that time because he was trying to persuade doctors to come into controlled trials, ... better to get doctors to walk before I get them to run”

• Limited drug supply after WWII meant it would not be immoral to make a trial – it would be immoral not to make a trial since the opportunity would never rise again (streptomycin would be synthesized, there would soon be plenty, and so on)
  • Hill AB, Controlled Clinical Trials 1990; 11:77-79
Clinical Trials are Part of a Family of Research Methods

- Studies of disease mechanisms
- Controlled studies of disease or health care management (most clinical trials)
- Descriptive studies of clinical populations
- Studies of technology or diagnostic procedures
- Observational studies of health care delivery
Clinical Trials Need Not Involve Randomization

- Uncontrolled trials
- Historical controls
- Concurrent nonrandomized controls
- Randomized controls

- Each design has its role in clinical investigation. These designs represent a hierarchy in terms of degree of control.
Reports from Clinical Trials providing estimates of efficacy of BCG vaccine against TB (Colditz et al, JAMA 1994)

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Population BCG</th>
<th>Population No BCG</th>
<th>Cases of TB BCG</th>
<th>Cases of TB No BCG</th>
<th>RR</th>
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<tbody>
<tr>
<td>Aronson, 1948†</td>
<td>123</td>
<td>139</td>
<td>4</td>
<td>11</td>
<td>0.41</td>
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<tr>
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<td>306</td>
<td>303</td>
<td>6</td>
<td>29</td>
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<td>Rosenthal et al, 1960‡</td>
<td>231</td>
<td>220</td>
<td>3</td>
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<td>Hart and Sutherland, 1977</td>
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<td>Frimodt-Moller et al, 1973</td>
<td>5069</td>
<td>5808</td>
<td>33</td>
<td>47</td>
<td>0.80</td>
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<td>Stein and Aronson, 1953</td>
<td>1541</td>
<td>1451</td>
<td>180</td>
<td>372</td>
<td>0.46</td>
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<tr>
<td>Vandiviere et al, 1973</td>
<td>2545</td>
<td>629</td>
<td>8</td>
<td>10</td>
<td>0.20</td>
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<tr>
<td>Madras, 1980§</td>
<td>88,391</td>
<td>88,391</td>
<td>505</td>
<td>499</td>
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<td>Coetzee and Berjak, 1968∥</td>
<td>7499</td>
<td>7277</td>
<td>29</td>
<td>45</td>
<td>0.63</td>
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<tr>
<td>Rosenthal et al, 1961∥</td>
<td>1716</td>
<td>1665</td>
<td>17</td>
<td>65</td>
<td>0.25</td>
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<tr>
<td>Comstock et al, 1974</td>
<td>50,634</td>
<td>27,338</td>
<td>186</td>
<td>141</td>
<td>0.71</td>
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<tr>
<td>Comstock and Webster, 1969#</td>
<td>2498</td>
<td>2341</td>
<td>5</td>
<td>3</td>
<td>1.56</td>
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<tr>
<td>Comstock et al, 1976#</td>
<td>16,913</td>
<td>17,854</td>
<td>27</td>
<td>29</td>
<td>0.98</td>
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<tr>
<td>Aronson et al, 1958**</td>
<td>1541</td>
<td>1451</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Levine and Sackett, 1948† †</td>
<td>566</td>
<td>528</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Overall RR (95% confidence interval)</td>
<td>0.49 (0.34-0.70)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Stein and Aronson, 1953

- 1935 to 1938 recruited AlAN 1 mo to 20 yrs
- No reaction to PPD
- Allocated single BCG vaccine or normal saline (placebo); by systematic alternation after stratification by school, age, and sex
- Participants blinded to status
- Follow-up included chest X-ray and tuberculin testing annually
  - Am Rev Tuberc 1953; 68:695-712
Choosing Among These Options

• Some persuasive studies have been uncontrolled
  – Clear history, usually of inevitable poor outcome
  – Treatments that are dramatically effective
    (example on next slide)

• Historically-controlled studies also have a role
  – Potential for bias due to secular trends
Discontinuation of Secondary Prophylaxis against Pneumocystis carinii Pneumonia (PCP) in Patients with HIV infection (Furrer et al, NEJM, 1999;340:1301)

• **Background:**
  – HIV patients with low CD4 counts (<200) at risk to develop PCP
  – Once CD4 counts fall below 200, typically given with a prophylactic drug (e.g., TMP/SMX) drug to prevent PCP
  – If patient receives an effective anti-HIV drug regimen (HAART) that raises CD4 count above 200, is PCP prophylaxis still needed?

• **Methods:** Analyzed episodes of PCP in 262 HIV-infected patients who discontinued PCP prophylaxis treated with at least three anti-HIV drugs (HAART) after their CD4 counts were raised above 200.

• **Results:** Median follow-up of 11.3 months, no cases of PCP occurred (prophylaxis was resumed in 9 patients). Estimated PCP incidence = 0 per 100 patient-years (99% CI: 0 to 1.9 per 100 patient-years)
How Could a Randomized Trial Have Been Done Here?

- Once a patient’s CD4 count had been raised above 200 cells, randomly assign them to:
  - Stop prophylaxis for PCP, versus
  - Continue prophylaxis for PCP
- Outcome: compare groups with respect to rates of developing PCP
- Would this have been scientifically stronger?
  - Yes
  - In practice: since no events in group that stopped prophylaxis, the uncontrolled study was pretty convincing; perhaps not so if there had been a few cases of PCP
  - A randomized trial later completed (De Quiros et al, NEJM 2001;344:149)
Read the paper by Banting and Best

- What was standard care?
- How could a randomized trial have been done here? Or could it?
Hill AB, 1952...

• Preferable it is done by the construction of an order of allocation, unknown in advance to the clinician, and based upon random sampling numbers – a modern substitute for tossing up, and one that is a trifle less embarrassing in the ward or office

• Proceeds to talk through blocking so groups don’t run too wildly different, constraining with sub-groups
  • NEJM 1952; 247:113-9
When in the Course of Treatment Development
Should Randomized Trials be done?

• The concept of equipoise: there still must be adequate uncertainty about benefit/risk

• Previous trials may not be definitive with respect to benefit and/or risk

• Previous trials may have been in different population; applicability of previous results to a new population might be unclear
Clinical Trials

Phase I
  • Clinical pharmacology, dose tolerance

Phase II
  • Toxicity

Phase III
Phase I Studies

• Initial clinical investigation for safety and dose-response
• Very small-scale investigations, often as few as 10 to 25 patients
• Requires close monitoring of each patient and efficacy of different doses – often has a focus on pharmacology and toxicity
• Frequently designed to allow exploration of the safety and efficacy of different doses – often has a focus on pharmacology and toxicity
• Usually not randomized
• Defines maximally tolerated dose
Clinical Trials

Phase I
Phase II
• Efficacy – preliminary
Phase III
Phase II Studies

• Initial clinical investigation for treatment effect, or biologic activity with continued looking at toxicity
• Relatively small-scale investigations of effectiveness and safety of a drug
• Frequently employ surrogate or intermediate endpoints
• Usually involves no more than 100 to 200 patients, sometimes much less
• Often randomized
Clinical Trials

Phase I
Phase II
Phase III • Efficacy- definitive
Phase III (Pivotal Studies)

• Full-scale evaluation of treatment efficacy and safety

• Usually a multicenter, randomized trial

• Compares new therapy against the current standard as control

• Typically involves a substantial number of patients

• Used as basis for regulatory approval of a new drug or device, or for a new indication for marketed product
Phase IV Studies

Post-marketing surveillance
  • Observational studies involving case reports, cohort studies, case-controls studies
  • Assess drug safety under the conditions of use in general practice, as opposed to the conditions under which they were tested in Phase III trials

Post-marketing clinical trials
  • Uncontrolled clinical trials designed to gain more experience with efficacy and safety...and promote use of the drug or device
  • Controlled clinical trials designed to obtain regulatory approval for a new indication (Phase IIIB)
Numerous variations and complexities in Practice

- Phase I/II studies
- Phase II/III studies
- Phase IIb study with potential extension
- Studies of combination therapies with different knowledge of effects
  - Treatment X + Y + Z, where
    - Drug X in Phase I
    - Drug Y Has Completed Phase II
    - Drug Z Has Completed Phase III
Examples from Lung Cancer Research

- **Phase I**
  - After animal (pre-clinical) studies, high and low dose methotrexate administered (alternatively) to 8 patients with advanced inoperable lung cancer to determine dose and side effects.

- **Phase II**
  - High dose methotrexate given to 28 patients with advanced inoperable lung cancer. One patient (4%) responded with partial regression. Three patients developed severe or life-threatening complications (acute shortness of breath, renal failure and bone marrow suppression).
Examples from Lung Cancer Research (cont)

• **Phase III** (Historically Controlled)
  - After Surgery, with or without chemotherapy, BCG was administered to 455 patients with lung cancer. Overall survival was significantly improved over historical controls, both in the entire group ($p < 0.001$), and in subgroups defined by stage and cell type.
Examples from Lung Cancer Research (cont)

• Phase III (RCT)
  – Patients with resected stage I non-small cell lung cancer were entered into a randomized trial. Surgery alone (plus placebo) was the standard therapy. The possible benefit of BCG injected into the pleural space was being investigated.
  
  – Randomized

  After an average follow-up of 452 patients for 1.2 years, there was no significant benefit for BCG in disease-free interval or overall survival. In fact, BCG group did slightly worse. (Cancer 1986;58:2411-6)
Phase III Studies-Randomized Trials of Treatment ‘Z’: many possible designs

- Direct tests (usually when no known treatment for this)
  - Z versus placebo (P)
- Active control ‘W’ (standard treatment for this disease)
  - Z versus W
- Fairly direct tests of value of adding Z to a standard therapy ‘Y’
  - Y + Z versus Y + P
- Amount, Timing of ‘Z’
  - Low dose versus high dose of Z
  - Z initially versus Z delayed
  - Z intermittently versus Z continuously
Basic Phase III Designs
(P=placebo, E=experimental, Std- standard)

Test of Timing

Test of Combination Tx

Test of Switching

M19-550 Randomized Controlled Trials
Factorial Designs

• Randomize to each level of several factors
• For example: 2x2 factorial (2 factors, each at 2 levels)
  – Placebo
  – Treatment A
  – Treatment B
  – Treatment A + Treatment B
• Example: Physician’s Health Study:
  • ‘A’=aspirin, ‘B’=betacarotene
• Attempts to assess the value of each factor
Neonatal Network Study of Early Dexamethasone Tx in ELBW Infants
(Stark et al, NEJM, 2001;344:95)

• Population: Infants with extremely low birth weight (ELBW)

• In a two-by-two factorial design, tested both dexamethasone treatment (vs. placebo) and a strategy of minimal ventilatory support (permissive hypercapnia vs. routine ventilatory support).

• Infants were randomly assigned to one of four groups according to the study medication (dexamethasone or placebo) and type of ventilatory support
ISIS-4
(Lancet, 1995;345:669)

• ISIS-4: a large, simple trial. Enrolled 58,050 acute MI patients at centers around the world and randomly assigned treatment in a 2x2x2 factorial design (Lancet, 1995;669-85):
  – 1 Month Oral Mononitrate vs Placebo
  – 1 Month Oral Captopril vs Placebo
  – 24 Hour IV Magnesium Sulfate vs. Open Control
Linxian nutrition prevention trial

- 2 x 4 factorial design
- Retinol plus zinc
- Riboflavin and niacin
- Vitamin C and molybdenum
- Beta-carotene, vitamin E and selenium
- 16 combinations evaluated – see table 1
  - Taylor et al Cancer Research 1994;54:2029s-31s
Factorial Designs: Advantages and Limitations

• Factorial designs can be very efficient. They allow simultaneous tests of two hypotheses in the same population (efficacy of aspirin, efficacy of betacarotene).

• Key limitation is assumption of no interaction. If the difference in efficacy of regimen A relative to control differs according to the presence or absence of B, the factorial design can produce misleading results in pooled analysis and low power in separate analyses (by levels of B) of efficacy of A (e.g., for Physician’s Health Study, see Stampfer et al, Stat Med. 1985;4:111).
Factorial Designs: Advantages and Limitations (cont)

• These are all variants of the parallel groups design. In the parallel groups design, each patient is assigned to one treatment regimen and the experience of groups assigned to different groups is compared.

• An important, though less frequently used design is the *crossover* design
Crossover Design

This is the 2-group, 2-period crossover design. Critical issues in all cross-over designs: carry-over effects & patient ‘drop outs’. Not commonly used in Phase III trials.
Fiber and Lipids
Swain et al NEJM 1990;322:147-52

• Isocaloric supplements high-fiber oat bran (87g/day) and low fiber refined wheat
• 20 healthy subjects, 23 to 49
• 6 week double-blind crossover trial
### Table 2. Intake of Nutrients and Body Weight during the High-Fiber and Low-Fiber Study Periods.*

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Base Line</th>
<th>High Fiber</th>
<th>Low Fiber</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>2065±598</td>
<td>2429±675</td>
<td>2315±616</td>
<td>0.18</td>
</tr>
<tr>
<td>Dietary fiber (g)</td>
<td>23.3±10.1</td>
<td>38.9±8.5</td>
<td>18.4±10.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fat (% of kcal)</td>
<td>30.6±6.0</td>
<td>35.4±3.5</td>
<td>30.0±4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Saturated fat (% of kcal)</td>
<td>11.6±2.9</td>
<td>9.8±2.2</td>
<td>8.9±2.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Monounsaturated fat (% of kcal)</td>
<td>10.9±2.7</td>
<td>11.4±2.1</td>
<td>9.5±1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Polyunsaturated fat (% of kcal)</td>
<td>6.1±2.0</td>
<td>11.1±2.3</td>
<td>8.9±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mg)</td>
<td>274±111</td>
<td>184±99</td>
<td>182±82</td>
<td>0.9</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>1290±444</td>
<td>980±315</td>
<td>1177±284</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>—</td>
<td>287±101</td>
<td>303±117</td>
<td>0.4</td>
</tr>
<tr>
<td>Potassium (mg)</td>
<td>—</td>
<td>3516±1042</td>
<td>3287±1137</td>
<td>0.2</td>
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<tr>
<td>Body weight (kg)</td>
<td>61.5±9.7</td>
<td>61.8±9.5</td>
<td>61.7±9.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ± SD.

†P values were calculated by paired, two-tailed t-tests for the difference between the high-fiber and low-fiber periods.
Table 3. Serum Lipoprotein Cholesterol Levels before and during High-Fiber and Low-Fiber Dietary Supplementation.*

| CHOLESTEROL† | BASE LINE | HIGH FIBER | LOW FIBER | DIFFERENCE
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HIGH FIBER–LOW FIBER‡</td>
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<td></td>
<td></td>
<td>HIGH FIBER–BASE LINE</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LOW FIBER–BASE LINE</td>
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<tr>
<td>Total</td>
<td>4.80±0.80</td>
<td>4.44±0.73§</td>
<td>4.46±0.64§</td>
<td>-0.02 (-0.20, 0.17)</td>
</tr>
<tr>
<td>mmol/liter</td>
<td>186±31</td>
<td>172±28§</td>
<td>172±25§</td>
<td>-1 (-8.7)</td>
</tr>
<tr>
<td>mg/dl</td>
<td>2.96±0.61</td>
<td>2.69±0.63§</td>
<td>2.77±0.59§</td>
<td>-0.08 (-0.22, 0.06)</td>
</tr>
<tr>
<td>LDL</td>
<td>115±23</td>
<td>104±24§</td>
<td>107±23§</td>
<td>-3 (-8.2)</td>
</tr>
<tr>
<td>mmol/liter</td>
<td>1.40±0.43</td>
<td>1.40±0.39</td>
<td>1.32±0.39</td>
<td>0.09 (0.03, 0.14)¶</td>
</tr>
<tr>
<td>mg/dl</td>
<td>54.0±16.7</td>
<td>54.2±15.0</td>
<td>50.9±15.2</td>
<td>3.3 (1.1, 5.5)¶</td>
</tr>
<tr>
<td>HDL</td>
<td>0.44±0.42</td>
<td>0.34±0.27</td>
<td>0.37±0.29</td>
<td>-0.02 (-0.11, 0.06)</td>
</tr>
<tr>
<td>VLDL</td>
<td>17.0±16.3</td>
<td>13.2±10.5</td>
<td>14.2±11.2</td>
<td>-1.0 (-4.2, 2.3)</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ± SD. Values in parentheses are 95 percent confidence limits.
†LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and VLDL very-low-density lipoprotein.
‡P>0.05 for all differences, by analysis of variance.
§P<0.05 for the comparison with base line, by analysis of variance and the Student–Newman–Keuls test.
¶Although the confidence limits do not include zero, neither the overall analysis of variance nor the mean difference after adjustment for multiple comparisons by the Student–Newman–Keuls test is significant.
Examples of How Designs Change as Knowledge is Gained: HIV/AIDS Theory

• Early studies compared single drug, e.g., AZT, to placebo
• Once AZT was demonstrated to be effective, studies compared other therapies to AZT
• Investigations of timing of AZT (based on CD4 count) and value of switching
• More recent studies have established the efficacy of combination therapies (HAART)
• Factorial designs have been used to test two questions at the same time
  – A is an antiretroviral agent
  – B is a prophylactic agent for opportunistic infection
Our Focus in this Course

• Phase III (comparative) randomized trials
  – Design
  – Monitoring
  – Analysis & Reporting

Next time: Superiority versus Noninferiority Designs