Study Design for Chemoprevention

Cancer Epidemiology, Prevention and Control Workshop
Shanghai, March 12, 2008
Clinical Trial Results
Summaries of Newsworthy Clinical Trial Results
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Cervical Cancer Trial Results
1. *Vaccine Against Cervical Cancer Virus is Effective for More than Four Years*  
(Posted: 04/19/2006) - An experimental vaccine that protects against two types of a virus that can cause cervical cancer remained highly effective for up to 4.5 years and caused very few adverse effects, according to the April 15, 2006, issue of the Lancet.

2. *Cervical Cancer Prevention in Low-Resource Areas*  
(Posted: 11/22/2005) - Innovative approaches to screening and treatment for cervical cancer can increase the number of women who obtain preventive treatment, according to clinical trials conducted in the United States and South Africa. The results appear in the Nov. 2, 2005, issue of the Journal of the American Medical Association.

3. *Cisplatin Plus Topotecan Gives Patients with Advanced Cervical Cancer More Time*  
(Posted: 08/17/2005) - Women with advanced cervical cancer who were treated with a combination of cisplatin (Platinol®) and topotecan (Hyramin®) lived a few months longer, and went longer without their disease progressing, than patients who received cisplatin alone. The additional toxicity did not significantly affect their quality of life compared to the cisplatin-only patients, according to two reports published in the July 20, 2005, issue of the Journal of Clinical Oncology.

4. *Vaccines May Help Reduce Risk of Cervical Cancer*
I. INTRODUCTION

Experimental studies are conducted to assess the effect of a treatment using a drug, or intervention using a preventive agent, etc.

- Treatment
- Prevention
- Early detection/screening
- Diagnostic
- Quality of life/supportive care
A. Defined:

- A study design in which the investigator actively controls who is exposed and who is not. Subjects are randomly assigned to various treatment groups and followed to observe outcomes.
Figure III-1. The anatomy of the epidemiologic study.
Comparison of Two Study Designs

I. Observational Study

- Intervention: 1,300
- No Intervention: 700

Deaths:
- Intervention: 80
- No Intervention: 50

Total Deaths: 180

Mortality: $\frac{180}{1,000} = 18\%$

II. Experimental Study

- Intervention: 1,300
- No Intervention: 700

Deaths:
- Intervention: 65
- No Intervention: 65

Total Deaths: 240

Mortality: $\frac{240}{1,000} = 24\%$

Figure 6–3. Observational vs. experimental studies. I, If the study is not randomized, the proportions of patients with arrhythmia in the two groups may differ. II, If the study is randomized, the proportions of patients with arrhythmia in the two groups are more likely to be similar.
Figure 38
Steps in the selection of participants in a controlled intervention study.
(Adapted from Hutchison [178].)
Stratified Randomization

- Stratify by Sex:
  - 600 Males
  - 400 Females

- Stratify by Age:
  - 360 Young Males
  - 240 Old Males
  - 300 Young Females
  - 100 Old Females

Randomize Each Subgroup:
- New Treatment: \(180 + 120 + 150 + 50 = 500\)
- Current Treatment: \(180 + 120 + 150 + 50 = 500\)
B. Experimental studies compared to cohort studies

1. Similarities between cohort and experimental studies. Both:
   a. Subjects must be free of the outcome at the start of the study.
   b. People are grouped into “exposed”/ “not exposed” categories.
   c. Groups are followed for a period of time to determine outcome.
   d. Yield incidence data so allow the calculation of risk and related measures.
   e. Susceptible to lost-to-follow-up bias.
B. Experimental studies compared to cohort studies

2. Differences between cohort and experimental studies:
   a. Experimental studies involve active manipulation of exposure (treatment/alternative treatment), whereas in cohort studies, the investigator must merely observe the effect of exposure.
   b. Random allocation (or randomization) is an essential part of a good experimental study. Not possible in a cohort.
   c. Ethical issues often a major issue in experimental epidemiological studies.
   d. Compliance with study protocol is an important concern in experimental studies.
C. Random allocation/ randomization

1. Defined:
   A procedure for assigning patients to experimental treatment and other treatment groups so that chance alone is responsible for the group assignment...each subject has an equal chance of being in any of the treatment groups.

2. Purpose of randomization:
   To (attempt to) assure comparability of the study groups with respect to factors which may be related to outcome.
C. Random allocation/
randomization

3. IMPORTANT: Randomization is done after informed consent is obtained!!!
C. Random allocation/ randomization

4. **Do Not** Confuse Random Allocation with Random Selection!!!

Random *selection* of subjects:

A procedure for *selecting* subjects so that each has the same chance of being included in the study. When we can’t afford to use all possible subjects in the source population.

**Purpose:**

To assure representativeness of subjects (of source pop.)

**When used?**

In any type of study design where a sample of the population is being selected.
Figure 4–3. Schematic of a cohort study and a nested case-control study within the cohort showing how the control group is sampled from the source population.
C. Random allocation/ randomization

5. Randomization does not guarantee similarity of groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Level</th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean value</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Race</td>
<td>% black</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Body weight</td>
<td>% over ideal</td>
<td>64</td>
<td>42</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>% users</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Exercise</td>
<td>% daily</td>
<td>46</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 7–11. Baseline characteristics in a randomized clinical trial of the prevention of osteoporosis.
D. Uses of experimental study design:

1. Evaluate benefits of an intervention:
   - Therapeutic
   - Preventive

2. Confirm etiologic relationship
II. TWO MAJOR TYPES OF EXPERIMENTAL STUDIES: Clinical and community trials
A. Randomized clinical trial (RCT):

1. **Defined (phase III):**
   
   An experimental study where the effectiveness of the intervention is being tested on individuals.

   **Phase I trials**
   - How does the agent affect the human body?
   - What dosage is safe?

   **Phase II trials**
   - Does the agent or intervention have an effect on the disease?

   **Phase III trials**
   - Is the new agent or intervention (or new use of a treatment) better than the standard?
   - Participants have an equal chance to be assigned to one of two or more groups
A. Randomized clinical trial (RCT):

2. Clinical trials are conducted for the treatment/prevention of both infectious diseases and chronic diseases:
   a. Infectious diseases: field trials (often refers to vaccine trials)
   b. Chronic diseases: e.g. Women’s Health Initiative (WHI):
B.4. Recruit study Population:

Figure 7-13. Schema of the Hypertension Detection and Follow-up Program (HDFP).
Table 7-9. Mortality From All Causes During the Hypertension Detection and Follow-up Program

<table>
<thead>
<tr>
<th>Diastolic Blood Pressure at Entry (mm Hg)</th>
<th>Stepped Care (SC)</th>
<th>Referred Care (RC)</th>
<th>5-yr Death Rate</th>
<th>% Mortality Reduction in SC Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-104</td>
<td>3,903</td>
<td>3,922</td>
<td>5.9</td>
<td>7.4</td>
</tr>
<tr>
<td>105-114</td>
<td>1,048</td>
<td>1,004</td>
<td>6.7</td>
<td>7.7</td>
</tr>
<tr>
<td>≥115</td>
<td>534</td>
<td>529</td>
<td>9.0</td>
<td>9.7</td>
</tr>
<tr>
<td>Total</td>
<td>5,485</td>
<td>5,455</td>
<td>6.4</td>
<td>7.7</td>
</tr>
</tbody>
</table>

From: Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of the estrogen plus progestin in healthy postmenopausal women. Principal results from the Women’s Health Initiative Randomized Controlled Trial. JAMA. 2002;288:321-33
B. Community trial

1. Defined:
   An experimental study where the effectiveness of an intervention is tested on a community.

2. Example of a community trial: fluoridation of water.
Fluoridation of Water

Figure 9-3. Net percentage changes in the intervention communities in knowledge and risk factors for persons 25 to 74 years old in the Stanford Five-City Project. Source: Farquhar et al. (1990).
B. Community trial

3. Problems of conducting community trials:
   a. Obtaining an appropriate control group:
      1) Same community before and after intervention
      2) A control community: similar to experimental community with respect to possible confounders.
   b. Other problems:
      1) It is hard to get individual’s informed consent
      2) Intervention not at individuals level
      3) Collaboration of communities
III. STEPS IN CONDUCTING RANDOMIZED CLINICAL TRIALS
Diagram of a design flow:

Figure 8-3. Outline of randomized clinical trial.
B.1. Steps

• 1. Specify Hypothesis
B.2. Steps

- 2. Specify target and source of populations:
B.3 Define endpoints/possible side effects of intervention:

Table 7–1. Types and examples of end points used in clinical trials.

<table>
<thead>
<tr>
<th>Type of End Point</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>Ability to perform usual daily tasks</td>
</tr>
<tr>
<td>Survival</td>
<td>Percentage of patients alive 1 year after entering trial</td>
</tr>
<tr>
<td>Complications</td>
<td>Percentage of patients who develop serious allergic reactions</td>
</tr>
<tr>
<td>Intermediate measures</td>
<td>Percentage of patients who have recurrence of symptoms</td>
</tr>
</tbody>
</table>
B.5. Obtain informed consent from those willing to participate:

1. Informed consent:
   
   An agreement (signed) that the subject understands the benefits and risks of the study.

2. Human Subjects Protection Committees:

   act as watchdogs...review research applications the be sure they comply with issues pertaining to protection of human subjects. To receive research money from NIH (and other agencies), these committees must approve grand proposals. Require that all subjects must read and sign “Informed Consent” form.
Fig. 8-2. Population hierarchy for hypertension detection and follow-up program. (From Hypertension Detection and Follow-up Program Cooperative Group, Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. J.A.M.A. 242:2562, 1979.)
B.6 Randomize to treatment


2. Alternative treatment ("controls"):  
a. The current standard treatment:

b. Placebo:
   1) Defined: An inert substance prepared to look as similar as possible to the experimental treatment.
   2) Placebo effect: Am improvement on health, symptoms, due to fact of being treated...and not due to the treatment!
Randomization
Three advantages of the randomized design:

- Randomization removes the potential of bias in the allocation of subjects to the intervention group or to the control group;

- Randomization tends to produce comparable groups; that is, the measured or unknown prognostic factors and other characteristics of the subjects at the time of randomization will be, on the average, evenly balanced between the intervention and control groups;

- The internal validity of statistical tests of significance is guaranteed.
B.7. Blindness

- **Fundamental Point**: To avoid potential problems of bias during data collection and assessment a clinical trial Ideally we should have a double-blind design. In studies where such a design is impossible, a single-blind approach and other measures to reduce potential bias are favored.

- **Unblinded**: In an unblinded or open trial, both the subject and the investigator know to which intervention the subject has been assigned. The studies involving most surgical procedures, changes in life style (eating habits, exercise, smoking) or learning techniques can be conducted only in this manner. The advantage is that it is usually simpler to carry out and the disadvantage is the possibility of bias.
B.7. Blindness

- **Single-Blind**: Patient does not know which treatment group he/she is in. Only the investigator is aware of which intervention each subject is receiving. The advantage and disadvantage are similar to those of unblinded trials.

- **Double-Blind**: Neither the subjects nor the investigators responsible for following the subjects know which intervention the subject has been assigned. Such designs are usually restricted to trials of drug efficacy. The advantage is that the risk of bias is reduced. The disadvantage is that certain responsibilities, which in open or single-blind studies could be accomplished by the investigators, must be taken over by others in order to maintain the blindness.
B.7. Blindness

• **Triple-Blind**: Neither the subjects, nor the investigators, nor the committee monitoring response variables is told the identity of the groups. The theoretical **advantage** is to allow the monitoring committee to evaluate the response variable results more objectively. The **disadvantage** is that in a trial where the monitoring committee has an ethical responsibility to ensure subject safety, such a design may be counterproductive.
Table 7-4. Summary of various types of blinding to assignment of treatment in clinical trials.

<table>
<thead>
<tr>
<th>Blinding</th>
<th>Patient</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Single</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Double</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
b. Purpose of blinding:
   To prevent biases in assessing outcome, which may be influenced by knowledge of treatment group.

c. Blinding is most important when

d. Blinding is less important when

e. Not always possible to blind subjects and/or investigators
B.8 Follow-up study groups for outcomes
B.9. Analyze results:
Use “Intention to treat” analyses

1. Defined:

Data are analyzed so that subjects remain in groups as originally assigned...even if subjects do not comply or change treatments on their own. This means that, even if the day after a subject was assigned to the control group, he starts the experimental treatment on his own...the outcome for that patient is analyzed as if he were still in the control group! ...In short: “Once randomized, always analyzed.”
B.9. Analyze results:

Use “Intention to treat” analyses

2. Why we must use intention to treat analyses:
   a. The results reflect what happens in the real world when the treatment is offered.
   b. The trial concerns whether the offering of a new treatment is more effective.
   c. Non-compliers are often different with respect to outcome, so likely to be less bias in keeping them in original groups than analyzing data in other ways.
   d. Though final results must reflect intention-to-treat analysis, investigators should look at compliers and non-compliers and their possible effect on the results.
B.10. Establish procedures for terminating the trial and informing subjects of results.

To Protect the welfare of subjects, data must be monitored regularly and analyzed for any obvious benefits or clear risks to subjects. If either occurs, the trial must be stopped and appropriate action taken (if there is a benefit, then controls must be offered new treatment. If a risk, experimentals must be taken of exper. treatment.
B.10. Establish procedures for terminating the trial and informing subjects of results.

Caveat: Small, transient differences between the groups may be observed early in the trial. So there must be a balance between a long-enough follow-up to see whether true benefits occur vs. depriving the controls of a better treatment.
IV. SOME MEASURES OF EFFECT IN EXPERIMENTAL STUDIES
A. Risk ratio:

\[
\frac{I_C}{I_T}
\]
B. Risk difference:

$I_C - I_T$
C. Efficacy:

\[ \frac{I_c - I_t}{I_c} \times 100 \]
D. Example:

849 working adults between the ages of 18-64 took part in a double-blind, placebo-controlled, randomized trial of the effect of influenza vaccination on three outcomes: upper respiratory illness (URI), absenteeism from work due to URI, and visits to doctors for URI. Baseline characteristics were compared to assure comparability of the two groups. The subjects were followed from Dec. 1, 1994, to March 31, 1995. (Nichol, K.L. et al. N Engl J Med 1995; 333: 889-93.)
D. Examples

- a. The following tables show the baseline characteristics of the two groups: does the randomization appear to have been successful, that is, do the two groups appear to be similar for those variables?
Baseline Assessment

**Fundamental Point:** Relevant baseline data should be measured in all study subjects before the start of the study.

- Baseline data include risk factors, prognostic factors, demographic and socioeconomic factors, and medical history. Baseline assessment can be used to assess comparability of the study groups. Although the randomization on the average produces balance between comparison groups, **it does not guarantee balance** in any specific trial. If baseline factors are not balanced, statistical adjustment methods such as stratified analysis and multivariate analysis can be used.
Baseline Assessment

Table 1. Base-Line Characteristics of the Study Subjects.*

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>PLACEBO GROUP (N = 425)</th>
<th>VACCINE GROUP (N = 424)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>39.9</td>
<td>39.2</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>66.4</td>
<td>60.2</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–12 yr</td>
<td>5.2</td>
<td>5.0</td>
</tr>
<tr>
<td>High-school graduates</td>
<td>15.5</td>
<td>14.9</td>
</tr>
<tr>
<td>College</td>
<td>40.7</td>
<td>44.8</td>
</tr>
<tr>
<td>Other</td>
<td>38.6</td>
<td>35.3</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>63.7</td>
<td>65.7</td>
</tr>
<tr>
<td>Divorced</td>
<td>11.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Single</td>
<td>21.5</td>
<td>22.2</td>
</tr>
<tr>
<td>Other</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Annual income (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$20,000</td>
<td>16.4</td>
<td>17.2</td>
</tr>
<tr>
<td>$20,000–$39,000</td>
<td>49.3</td>
<td>44.3</td>
</tr>
<tr>
<td>$&gt;39,000</td>
<td>34.3</td>
<td>38.5</td>
</tr>
<tr>
<td>Mean no. of persons in household</td>
<td>3.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Child in day care (% of subjects)</td>
<td>18.5</td>
<td>19.7</td>
</tr>
<tr>
<td>Child in school (% of subjects)</td>
<td>45.8</td>
<td>44.9</td>
</tr>
<tr>
<td>Health status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>54.2</td>
<td>55.5</td>
</tr>
<tr>
<td>Good</td>
<td>44.1</td>
<td>43.4</td>
</tr>
<tr>
<td>Fair</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Cigarette-smoking status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>13.4</td>
<td>13.1</td>
</tr>
<tr>
<td>Former smoker</td>
<td>32.3</td>
<td>28.7</td>
</tr>
<tr>
<td>Never smoked</td>
<td>54.2</td>
<td>38.2</td>
</tr>
<tr>
<td>Household exposure to cigarette smoke (%)</td>
<td>19.1</td>
<td>17.0</td>
</tr>
<tr>
<td>Sick leave during previous 6 mo (%)</td>
<td>40.9</td>
<td>33.6</td>
</tr>
<tr>
<td>No prior influenza vaccination (%)</td>
<td>76.6</td>
<td>74.0</td>
</tr>
</tbody>
</table>

*Because of rounding, percentages do not always total 100.
D. Examples

- b. One concern in any experimental study, even if subjects are blinded, is whether subjects can tell whether they are in the treatment or control group. One way to determine is to ask the subject which group they think they are in. In the above study, 60% of the placebo and 54% of the vaccine recipients correctly identified their group (slightly better than chance along).
D. Examples

- c. Another way to look at this is to see if the two groups differ in reporting side effects. Table 2 shows the side effects reported by each of the groups. Does it look as if any of the side effects might give away a subject’s status?
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo Group</th>
<th>Vaccine Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>6.1</td>
<td>6.2</td>
<td>0.96</td>
</tr>
<tr>
<td>Tiredness</td>
<td>19.4</td>
<td>18.9</td>
<td>0.93</td>
</tr>
<tr>
<td>Feeling “under the weather”</td>
<td>17.5</td>
<td>16.0</td>
<td>0.63</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>5.7</td>
<td>6.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Headaches</td>
<td>14.4</td>
<td>10.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Arm soreness</td>
<td>24.1</td>
<td>63.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*The data represent the proportions of subjects who reported having the symptom during the seven days after the study injection.*
D. Example:

d. Table 3 summarizes the data regarding the three outcomes, using rates per 100 subjects. For “Episodes of UPI”, calculate the three measures of effect:

- Risk ratio:
- Risk difference
- Efficacy (or “Vaccine Effectiveness”)
Table 3. Health-Related Benefits Associated with Vaccination.*

<table>
<thead>
<tr>
<th>Study Outcome</th>
<th>Rate per 100 Subjects</th>
<th>Difference</th>
<th>Vaccine Effectiveness Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Group</td>
<td>Vaccine Group</td>
<td></td>
</tr>
<tr>
<td>Episodes of upper respiratory illness</td>
<td>140</td>
<td>105</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Clinical Outcomes by Randomization Assignment*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Patients (Annualized %)</th>
<th>Hazard Ratio</th>
<th>Nominal 95% CI</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, mean (SD), mo</td>
<td>Estrogen + Progestin (n = 8506)</td>
<td>Placebo (n = 8102)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>62.2 (16.1)</td>
<td>61.2 (15.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CHD death</td>
<td>164 (0.37)</td>
<td>122 (0.30)</td>
<td>1.29</td>
<td>1.02-1.63</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>33 (0.07)</td>
<td>26 (0.06)</td>
<td>1.18</td>
<td>0.70-1.97</td>
</tr>
<tr>
<td>CABG/PTCA</td>
<td>183 (0.42)</td>
<td>171 (0.41)</td>
<td>1.04</td>
<td>0.84-1.28</td>
</tr>
<tr>
<td>Stroke</td>
<td>127 (0.29)</td>
<td>85 (0.21)</td>
<td>1.41</td>
<td>1.07-1.85</td>
</tr>
<tr>
<td>Fatal</td>
<td>16 (0.04)</td>
<td>13 (0.03)</td>
<td>1.20</td>
<td>0.58-2.50</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>94 (0.21)</td>
<td>59 (0.14)</td>
<td>1.50</td>
<td>1.08-2.08</td>
</tr>
<tr>
<td>Venous thromboembolic disease</td>
<td>151 (0.34)</td>
<td>67 (0.16)</td>
<td>2.11</td>
<td>1.58-2.82</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>115 (0.26)</td>
<td>52 (0.13)</td>
<td>2.07</td>
<td>1.49-2.87</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>70 (0.16)</td>
<td>31 (0.08)</td>
<td>2.13</td>
<td>1.39-3.25</td>
</tr>
<tr>
<td>Total cardiovascular disease</td>
<td>694 (1.57)</td>
<td>546 (1.32)</td>
<td>1.22</td>
<td>1.09-1.56</td>
</tr>
</tbody>
</table>

| Cancer                                 |                                |              |                |                |
| Invasive breast                        | 166 (0.38)                     | 124 (0.30) | 1.26           | 1.00-1.59      | 0.83-1.92      |
| Endometrial                            | 22 (0.05)                      | 25 (0.06)  | 0.83           | 0.47-1.47      | 0.29-2.32      |
| Colorectal                             | 45 (0.10)                      | 67 (0.16)  | 0.63           | 0.43-0.92      | 0.32-1.24      |
| Total                                  | 502 (1.14)                     | 458 (1.11) | 1.03           | 0.90-1.17      | 0.86-1.22      |

| Fractures                              |                                |              |                |                |
| Hip                                    | 44 (0.10)                      | 62 (0.15)  | 0.66           | 0.45-0.98      | 0.33-1.33      |
| Vertebral                              | 41 (0.09)                      | 60 (0.15)  | 0.66           | 0.44-0.98      | 0.32-1.34      |
| Other osteoporotic‡                    | 579 (1.31)                     | 701 (1.70) | 0.77           | 0.69-0.86      | 0.63-0.94      |
| Total                                  | 650 (1.47)                     | 788 (1.91) | 0.76           | 0.69-0.85      | 0.63-0.92      |

| Death                                  |                                |              |                |                |
| Due to other causes                    | 165 (0.37)                     | 166 (0.40) | 0.92           | 0.74-1.14      | 0.62-1.35      |
| Total                                  | 231 (0.52)                     | 218 (0.53) | 0.98           | 0.82-1.18      | 0.70-1.37      |

| Global index§                          | 751 (1.70)                     | 623 (1.51) | 1.15           | 1.03-1.29      | 0.95-1.39      |

*CI indicates confidence interval; NA, not applicable; CHD, coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; and PTCA, percutaneous transluminal coronary angioplasty.
†CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 8 silent MIs. Total cardiovascular disease is limited to events during hospitalization except venous thromboembolic disease reported after January 1, 2000.
‡Other osteoporotic fractures include all fractures other than chest/axilla, skull/face, fingers, toes, and cervical vertebrae, as well as hip and vertebral fractures reported separately.
§The global index represents the first event for each participant from among the following types: CHD, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Major potential biases in experimental studies:

- Lost-to-follow-up
- Compliance/adherence to study’s protocol, e.g., WHI:
Reasons for non-compliance:

1. Misunderstanding of instructions.
2. Inconvenience of participation.
4. Cost of participation.
5. Forgetfulness.
6. Disappointment with results.
Ways to improve compliance:

1. Select motivated persons.
2. Pretest ability and willingness of participants to comply.
3. Provide simple and lucid instructions to subjects.
4. Offer incentives to comply (e.g., no charge for therapeutic intervention and associated examinations).
5. Provide positive reinforcements to subjects for adherence to treatment regimen.
6. Maintain frequent contract with participants and remind them about importance of adherence to the regimen.
7. Measure adherence through pill counts or sampling of biologic specimens.
8. Limit duration of intervention.
Sample Size:

**Fundamental Point:** Clinical trials should have sufficient statistical power to detect differences between groups considered to be of clinical interest. Therefore, calculation of sample size with provision for adequate levels of significance and power is an essential part of planning.

Clinical trials tend to be small. Even if there is a real difference in two treatments, the difference may not be statistically significant because of the small numbers. That is, the study did not have the power to detect (statistically) a real difference.
Sample size

- False positive (alpha-level, or Type I error). The alpha-level used and accepted traditionally are 0.01 or 0.05. The smaller the level of alpha, the larger the sample size.

- False negative (beta-level, or Type II error). (1-beta) is called the power of the study. Investigator like to have a power of around 0.90 or 0.95 when planning a study, which means that there have a 90% or 95% chance of finding a statistically significant difference between study and control groups.

- The difference between study and control groups (delta). Two factors need to be considered here: one is what difference is clinically important, and the another is what is the difference reported by previous studies.
V. The Validity of Results of Epidemiologic Studies
A. Internal Validity

1. Defined:

*The truth or accuracy of results from a study with respect to its defined source population*
2. Factors affecting internal validity:

- **Information bias:** *distortion of true effects due to systematic errors in collection of data on exposure OR outcome*

- **Selection bias:** *distortion of true effects due to error in selection of subjects*

- **Confounding:** *distortion of true effects from other risk factors or exposures extraneous to the study*
3. Algorithm for assessing flaws in an experimental study:

Are study and control groups of similar inherent risk at the beginning of the experiment?

- yes
  - After loss to follow-up exclusions, are they still similar?
    - yes
      - Was outcome assessed equally for the two groups?
        - yes
          - Could this difference be due to chance?
            - yes
              - Derive confidence intervals
            - no
              - No internal validity problem
        - no
          - Confounding from biased loss to follow-up - assess direction of bias
    - no
      - Confounding - assess direction and/or of bias

- no
B. External Validity

1. Defined:

- Applicability of study results to other populations (ie, to specified target or reference population)

- Generalizability
2. Factors affecting external validity:

a. Does the study have internal validity?

*external validity is not possible without internal (ie, a study must be internally valid first before it can also be externally valid)*

a. Is the study group representative of the target population?

*if the study group is non-representative, then the study is not externally valid*
3. Algorithm for assessing external validity:

Is experimental population representative of the reference population?

- YES
  - No external validity problem
  - You CAN extrapolate

- NO
  - Would reference population have same response to treatment as experimental population?
    - YES
      - No external validity problem
      - You CAN extrapolate
    - NO
      - External validity problem
      - You CANNOT extrapolate