Randomized Clinical Trials
It is 1950. Dr. L. Craven specializes in treatment of arthritis. Many of his patients receive aspirin and he notes that the incidence of myocardial infarction (heart attack) is lower than expected in these patients.

What type of studies?

1. Case series
2. Case-control
3. Retrospective cohort
4. Prospective cohort
5. Clinical trial
• 1529 patients with a history of myocardial infarction, most of them several years earlier.

• Randomly assigned (double-blind) to aspirin therapy - 324-mg tablet three times daily or placebo treatment.

• Length of follow-up ranged from 10-28 months (average 22 months).
### Coronary Drug Project, 1976

#### CHD Mortality

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>35</td>
<td>723</td>
<td>758</td>
</tr>
<tr>
<td>Placebo</td>
<td>49</td>
<td>722</td>
<td>771</td>
</tr>
</tbody>
</table>

**How would you analyze these data?**
### Coronary Drug Project, 1976

**CHD Mortality**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>35</td>
<td>723</td>
<td>758</td>
<td>4.6%</td>
</tr>
<tr>
<td>Placebo</td>
<td>49</td>
<td>722</td>
<td>771</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

**How would you analyze these data?**

**RR = \( \frac{35}{758} \) = 0.73 (0.48-1.11)\**

\( \frac{49}{771} \)

**p=0.14**

**Interpretation? Conclusions?**
### Coronary Drug Project, 1976

**Definite Non-fatal MI**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td>28</td>
<td>730</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>32</td>
<td>739</td>
</tr>
</tbody>
</table>

**RR** = \( \frac{28}{758} = 0.89 \) (0.54-1.45)

**p** = 0.65
“This difference is suggestive of a beneficial effect for aspirin in the treatment of post-MI men, but not large enough to be conclusive.”
A variety of case-control and cohort type studies with relatively small numbers of subjects suggested that aspirin might reduce coronary “events” by perhaps 20-30%, and it might be beneficial in primary prevention, but none of the observational studies had been conclusive.

The major limitations of all of these observational studies?

1. Small sample size; limited power to detect a modest difference
2. Potential biases: misclassification, selection bias, recall bias
3. Uncontrolled confounding: many other factors influence risk of heart disease
What should be done to determine whether aspirin is effective in *primary* prevention of cardiovascular disease?

How would you do it?
Is it ethical to do this?
Sufficient belief to justify exposing some subjects to new treatment.

Sufficient doubt to justify withholding new treatment from some subjects.

Is the new treatment better? Not sure. Maybe; Maybe not.
Who should we invite to participate?

No known heart disease?
Males? Females?
Young? Old?
Easy to follow up?

Inclusion/exclusion criteria?
Institutional Review Board Approval

Required for all research involving human subjects (not just clinical trials).

“Human Research” means a systematic investigation involving living humans (including research development, testing and evaluation), designed to develop or contribute to generalizable knowledge.
Are you going to use a placebo?

Why or why not?

Is it ethical to use a placebo?
Why Use A Placebo?

- Minimize bias in assessing outcomes
- Makes groups as comparable regarding the perception of treatment.
- Allows “blinding” (not always possible).
Minimizes bias in assessing outcomes

- Single-blind: subjects unaware of treatment group
- Double-blind: subjects *and* investigators unaware

Exposure status is unknown.
### Glucosamine & Chondroitin Trial

<table>
<thead>
<tr>
<th></th>
<th>Pain relief &gt;20%</th>
<th>Minimal Effect</th>
<th>Total # Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucosamine + Chondroitin</td>
<td>211</td>
<td>106</td>
<td>317</td>
</tr>
</tbody>
</table>

\[
\frac{211}{317} = 0.666 = 67/100
\]

<table>
<thead>
<tr>
<th></th>
<th>Pain relief &gt;20%</th>
<th>Minimal Effect</th>
<th>Total # Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>188</td>
<td>125</td>
<td>313</td>
</tr>
<tr>
<td>Anti-inflam. drug</td>
<td>223</td>
<td>95</td>
<td>318</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>203</td>
<td>114</td>
<td>317</td>
</tr>
<tr>
<td>Chondroitin</td>
<td>208</td>
<td>110</td>
<td>318</td>
</tr>
<tr>
<td>Glucosamine + Chondroitin</td>
<td>211</td>
<td>106</td>
<td>317</td>
</tr>
</tbody>
</table>

Glucosamine + Chondroitin: $\frac{211}{317} = 67\%$
Placebo: $\frac{188}{313} = 60\%$

The “placebo effect”

How many should we invite?
Statistical Power

The ability of a study to demonstrate a statistically significant association, if one exists.

**Issues:**

- How many will have expected end points? Restrict study to persons at higher risk?

- Duration of Follow-up: Is there sufficient time to accumulate end points?

- Acute vs. long-term effects of treatment.

- Do you need multiple study sites?
Informed Consent

Obtain informed consent prior to randomization.

Informed about:
- Treatments
- Potential outcomes; risks/benefits
- Randomization (i.e., treatment is not their choice)
- What is required of them
Randomization

Method of assignment such that each individual has an equal chance of receiving each possible treatment.

**Equal chance:**
- Coin toss
- Random numbers (table or computer)

Other methods have potential problems
- Subject self-selects
- Day of week, order of visit, etc.

Benefits/Strengths:
- Unpredictability
- Leads to comparability
  - Balance of known & unknown confounders
  - Minimizes selection bias
Large, carefully done randomized clinical trials are particularly useful for assessing moderate or small effects which may be clinically important.

1. Random assignment of a sufficiently large number of subjects provides exquisite control over both known and unsuspected confounding factors.

2. A large sample size increases the ability to identify modest, but significant differences.
Active Intervention Group

Reference Population

Experimental Population
(potential participants)

Participants
(willing and eligible)

Allocation

Active Intervention Group
- Compliers
- Non-compliers

Comparison Group
- Compliers
- Non-compliers
What about maintaining compliance (adherence to the protocol) and follow up?

Does compliance matter?
• Following assigned protocol for the duration of the study is crucial to demonstrating a true effect.

• Noncompliance makes the groups more alike & reduces the ability to detect a difference (bias towards null).

Non-compliance Tends to Bias Toward the “Null” (i.e., minimizes any difference)
Truth:
RR = 20/40 = 0.5

Outcome +  
Exp 20 80 100
Not 40 60 100

RR = 30/40 = 0.75

Outcome +  
Exp 10 20 40 100
Not 40 60 100

Non-compliant Exposed:

Outcome +  
Exp 20 80 100
Not 40 60 100

RR = 30/30 = 1.00

Outcome +  
Exp 10 20 40 100
Not 20 30 40 100

Non-compliant Placebos:
RR = 20/30 = 0.67

Outcome +  
Exp 20 30 40
Not 10 20 30

Ratio 2:3

Both Non-compliant

Outcome +  
Exp 10 20 30 40
Not 10 20 30 40

Ratio 1:4

50 in exp. group fail to comply & are not exp. (2:3)

50 in non-exp. grp. fail to comply & are exp. (1:4)
Tips for Maintaining Compliance & Follow-up

- Begin with a motivated, knowledgeable group.
- Identify subjects who are unlikely / unable to comply.
- Make the protocol as simple as possible.
- Be clear about what is involved.
- If possible, mask the treatment so all groups comply.
- Maintain frequent contact with subjects without interfering with treatment.
- Provide incentives (free check-ups, transportation, etc.)
- Conduct a “run-in” or “lead-in” period before the real trial.
Assessing Compliance

Assess compliance, if possible.

- Self-report
- Pill counts
- Biological measures (blood, urine)
A scientifically & financially independent group with expertise in various disciplines charged with safeguarding participants.

Reviews progress of trial & data on outcome
- Interim results
- Adverse events

They can recommend modification or termination of all/part of trial if:
- Treatment results so good cannot withhold from others.
- Treatment side effects/outcome so bad cannot continue.
The Physicians' Health Study

- Randomized, double-blind, placebo controlled trial.

- Primary prevention of CVD & cancer in 22,071 U.S. male physicians, aged 40-84 at baseline.

- A 2x2 factorial design to test:
  - 325 mg aspirin on alternate days
  - 50 mg beta carotene on alternate days
Exclusion Criteria

- History of:
  - Heart attack
  - Stroke
  - Cancer
  - Current liver or kidney disease
  - Peptic ulcer or gout

- Contraindication to aspirin

- Current use of aspirin or other drugs affecting platelet function

- Current use of a vitamin A or b carotene
261,248 invitation letters sent with questionnaire

112,528 questionnaires returned

59,285 willing to participate

33,223 eligible and enrolled in 18-week run-in phase on active ASA & β-carotene placebo.

22,071 randomized
22,071 U.S. Male Physicians aged 40-84

2x2 Factorial Design

Aspirin 11,037
- β-carotene 5,517
- β-carotene placebo 5,520
- Both

Aspirin Placebo 11,034
- β-carotene 5,519
- β-carotene placebo 5,515
- Neither
Was Randomization Successful?

What are some known risk factors for heart disease?

Were these confounding factors distributed equally?
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Aspirin (n=11,037)</th>
<th>Placebo (n=11,034)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53.2 ± 9.5</td>
<td>53.2 ± 9.5</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>126.1 ± 11.3</td>
<td>126.1 ± 11.1</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78.8 ± 7.4</td>
<td>78.8 ± 7.4</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>13.5</td>
<td>13.6</td>
</tr>
<tr>
<td>History of high cholesterol (%)</td>
<td>17.5</td>
<td>17.3</td>
</tr>
<tr>
<td>Cholesterol level (mg)</td>
<td>212.1 ± 44.2</td>
<td>212.0 ± 45.1</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>History of angina (%)</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Parental MI (%)</td>
<td>13.0</td>
<td>13.1</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n=11,037)</th>
<th>Placebo (n=11,034)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current smoking (%)</strong></td>
<td>11.0</td>
<td>11.1</td>
</tr>
<tr>
<td><strong>Past smoking (%)</strong></td>
<td>39.4</td>
<td>39.1</td>
</tr>
<tr>
<td><strong>Daily alcohol (%)</strong></td>
<td>24.9</td>
<td>25.0</td>
</tr>
<tr>
<td><strong>Exercise &gt;1/week (%)</strong></td>
<td>71.7</td>
<td>71.2</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>24.9 ± 3.1</td>
<td>24.9 ± 3.0</td>
</tr>
<tr>
<td><strong>Multivitamin</strong></td>
<td>19.9</td>
<td>19.9</td>
</tr>
</tbody>
</table>
How can we analyze the data?
Basic analysis is that of a cohort study (i.e. – compare incidence….)

Should we include all subjects in the analysis?
Compliance

After 60.2 months

Aspirin group
85.71% took treatment as intended

Placebo Group
14.23% took aspirin or other platelet-active drugs

Who should we include in our analysis?
Primary analysis: “Intention to treat”

- For the primary analysis all subjects should be included in the groups to which they were randomly assigned, even if they did not complete or even receive the appropriate treatment.
  - Preserves baseline comparability & control of confounding
  - Since compliers and non-compliers may be systematically different it prevents bias.
  - It reflects efficacy in everyday practice.

Secondary analysis: Compliers only.

- Not a randomized comparison.
### Results: Fatal Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>10</td>
<td>11,027</td>
<td>11,037</td>
</tr>
<tr>
<td>Placebo</td>
<td>26</td>
<td>11,008</td>
<td>11,034</td>
</tr>
</tbody>
</table>

You can use “Epi_Tools.xls” to calculate the risk ratio, the p-value, & 95% CI.

You should be able to interpret your findings in words.
### Non-fatal Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>126</td>
<td>10,911</td>
<td>11,037</td>
</tr>
<tr>
<td>Placebo</td>
<td>213</td>
<td>10,821</td>
<td>11,034</td>
</tr>
</tbody>
</table>

You can use “Epi_Tools.xls” to calculate the risk ratio, the p-value, & 95% CI.

You should be able to interpret your findings in words.
Follow-up After 60.2 Months

Morbidity follow-up 99.7%
Vital status only 0.3%
Mortality follow-up 100.0%
<table>
<thead>
<tr>
<th></th>
<th>Aspirin Group</th>
<th>Placebo Group</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Stroke</td>
<td>119</td>
<td>98</td>
<td>1.22</td>
<td>(0.93-1.60)</td>
</tr>
<tr>
<td>Total CV Deaths</td>
<td>81</td>
<td>83</td>
<td>0.96</td>
<td>(0.60-1.54)</td>
</tr>
</tbody>
</table>

More follow-up needed, but . . .
On December 18, 1987, the Data & Safety Monitoring Board recommended early termination of the aspirin component of the trial.
<table>
<thead>
<tr>
<th></th>
<th>Aspirin (/10,000)</th>
<th>Placebo (/10,000)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>125.9</td>
<td>216.6</td>
<td>0.58</td>
</tr>
</tbody>
</table>

What should we recommend?
<table>
<thead>
<tr>
<th>Condition</th>
<th>Aspirin (/10,000)</th>
<th>Placebo (/10,000)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>125.9</td>
<td>216.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Stroke</td>
<td>107.8</td>
<td>88.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Ischemic</td>
<td>82.4</td>
<td>74.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>20.8</td>
<td>10.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Upper GI ulcer with hemorrhage</td>
<td>153.1</td>
<td>125.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2699.1</td>
<td>2037.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Transfusion need</td>
<td>43.5</td>
<td>25.4</td>
<td>1.7</td>
</tr>
</tbody>
</table>

What should we recommend?
<table>
<thead>
<tr>
<th>Condition</th>
<th>Aspirin (/10,000)</th>
<th>Placebo (/10,000)</th>
<th>RR</th>
<th>RD (/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td>125.9</td>
<td>216.6</td>
<td>0.58</td>
<td>-91</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>107.8</td>
<td>88.8</td>
<td>1.2</td>
<td>19</td>
</tr>
<tr>
<td>Ischemic</td>
<td>82.4</td>
<td>74.3</td>
<td>1.1</td>
<td>8</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>20.8</td>
<td>10.9</td>
<td>1.9</td>
<td>10</td>
</tr>
<tr>
<td>Upper GI ulcer</td>
<td>153.1</td>
<td>125.1</td>
<td>1.2</td>
<td>28</td>
</tr>
<tr>
<td>with hemorrhage</td>
<td>34.4</td>
<td>19.9</td>
<td>1.7</td>
<td>15</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>2699.1</td>
<td>2037.3</td>
<td>1.3</td>
<td>690</td>
</tr>
<tr>
<td>Transfusion need</td>
<td>43.5</td>
<td>25.4</td>
<td>1.7</td>
<td>18</td>
</tr>
</tbody>
</table>
Results Of The Physicians' Health Study

- Clear benefit of aspirin on risk of myocardial infarction in male physicians.

- Unable to evaluate aspirin's effect on stroke or total cardiovascular mortality, due to early termination of the trial.

- In primary prevention, aspirin should be prescribed on an individual basis by the health care provider as an adjunct to, not an alternative to, the management of other risk factors.
Sample size:

- Only 1 out of 10 physicians over 40 years were women in 1982.
- By age 60 women have only 1/3 the # of cardiovascular events as men.
At the time, they were unable to say whether aspirin was effective in women or if the effect of aspirin was different in women.
And...

The effect of aspirin did turn out to be different in men & women.

Low-dose aspirin reduced strokes in healthy women, but had no effect on heart attacks unless the women were >65 years old.


**METHODS:** We randomly assigned 39,876 initially healthy women 45 years of age or older to receive 100 mg of aspirin on alternate days or placebo and then monitored them for 10 years for a first major cardiovascular event (i.e., nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes).

**RESULTS:** During follow-up, 477 major cardiovascular events were confirmed in the aspirin group, as compared with 522 in the placebo group, for a nonsignificant reduction in risk with aspirin of 9 percent (relative risk, 0.91; 95 percent confidence interval, 0.80 to 1.03; P=0.13). With regard to individual end points, there was a 17 percent reduction in the risk of stroke in the aspirin group, as compared with the placebo group (relative risk, 0.83; 95 percent confidence interval, 0.69 to 0.99; P=0.04), owing to a 24 percent reduction in the risk of ischemic stroke (relative risk, 0.76; 95 percent confidence interval, 0.63 to 0.93; P=0.009) and a nonsignificant increase in the risk of hemorrhagic stroke (relative risk, 1.24; 95 percent confidence interval, 0.82 to 1.87; P=0.31).

(continued)
As compared with placebo, aspirin had no significant effect on the risk of fatal or nonfatal myocardial infarction (relative risk, 1.02; 95 percent confidence interval, 0.84 to 1.25; P=0.83) or death from cardiovascular causes (relative risk, 0.95; 95 percent confidence interval, 0.74 to 1.22; P=0.68). Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group (relative risk, 1.40; 95 percent confidence interval, 1.07 to 1.83; P=0.02). Subgroup analyses showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction among women 65 years of age or older.

**CONCLUSIONS:**
In this large, primary-prevention trial among women, aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes, leading to a nonsignificant finding with respect to the primary end point.
Double cheeseburger, large fries, jumbo coffee... oh, and an aspirin – gotta take care of the old ticker, ya know.
“Take an aspirin every day, but before you swallow it, take it for a five-mile walk.”
Community Trials

Entire communities can be assigned to a treatment or intervention.

Does fluoridation of water prevent dental caries? (1944 - The Newburgh-Kingston Caries Trial)

School children have the highest attack rates for influenza, and many observers believe that student proximity in classrooms promotes the spread of the influenza virus. Infected children then infect family members. Studies in Michigan and Japan suggested that influenza immunization programs in children reduced mortality and morbidity in adults, because school-to-home transmission was reduced. The study cited above tested this by conducting a childhood immunization program in two communities (Temple and Belton) and measuring subsequent rates of influenza in adults. About 20-25% of eligible children were vaccinated. The adult rates of influenza in the test communities were compared to adult rates of influenza in three communities that did not have childhood immunization programs (Waco, Bryan, and College Station).
The Karachi Hand Washing Trial
“Every year, more than 3.5 million children aged less than 5 years die from diarrhea and acute lower respiratory-tract infection. These deaths are concentrated in low-income communities in developing countries. Several studies have shown that regular hand washing with soap reduces the incidence of diarrhea in children younger than 5 years in communities with a high incidence of diarrhea, although we are unaware of any reports of the effect of hand washing on acute respiratory-tract infections in settings where pneumonia is a leading cause of death.

In developed countries, the promotion of hand washing has reduced respiratory-tract infections in several settings....”
“We undertook the Karachi Soap Health Study… to measure the broad health benefits brought about by improvement of handwashing and bathing with soap in settings where communicable diseases are leading causes of childhood morbidity and mortality.”

Background:
More than 3.5 million children aged less than 5 years die from diarrhoea and acute lower respiratory-tract infection every year. We undertook a randomised controlled trial to assess the effect of handwashing promotion with soap on the incidence of acute respiratory infection, impetigo, and diarrhoea.
Methods:
In adjoining squatter settlements in Karachi, Pakistan, we randomly assigned 25 neighbourhoods to handwashing promotion; 11 neighbourhoods (306 households) were randomised as controls. In neighbourhoods with handwashing promotion, 300 households each were assigned to antibacterial soap containing 1.2% triclocarban and to plain soap. Fieldworkers visited households weekly for 1 year to encourage handwashing by residents in soap households and to record symptoms in all households. Primary study outcomes were diarrhoea, impetigo, and acute respiratory-tract infections (ie, the number of new episodes of illness per person-weeks at risk). Pneumonia was defined according to the WHO clinical case definition. Analysis was by intention to treat.
Findings:
Children younger than 5 years in households that received plain soap and handwashing promotion had a 50% lower incidence of pneumonia than controls (95% CI (-65% to -34%). Also compared with controls, children younger than 15 years in households with plain soap had a 53% lower incidence of diarrhoea (-65% to -41%) and a 34% lower incidence of impetigo (-52% to -16%). Incidence of disease did not differ significantly between households given plain soap compared with those given antibacterial soap.

Interpretation:
Handwashing with soap prevents the two clinical syndromes that cause the largest number of childhood deaths globally-namely, diarrhoea and acute lower respiratory infections. Handwashing with daily bathing also prevents impetigo.