

1 Introduction

1.1 Scope and objectives

The focus of this course will be on the statistical methods and principles used to study disease and its prevention or treatment in human populations. There are two broad subject areas in the study of disease; **Epidemiology** and **Clinical Trials**. This course will be devoted almost entirely to statistical methods in Clinical Trials research but we will first give a very brief introduction to Epidemiology in this Section.

EPIDEMIOLOGY: Systematic study of disease etiology (causes and origins of disease) using observational data (i.e. data collected from a population not under a controlled experimental setting).

- Second hand smoking and lung cancer
- Air pollution and respiratory illness
- Diet and Heart disease
- Water contamination and childhood leukemia
- Finding the prevalence and incidence of HIV infection and AIDS

CLINICAL TRIALS: The evaluation of intervention (treatment) on disease in a controlled experimental setting.

- The comparison of AZT versus no treatment on the length of survival in patients with AIDS
- Evaluating the effectiveness of a new anti-fungal medication on Athlete's foot
- Evaluating hormonal therapy on the reduction of breast cancer (Womens Health Initiative)

1.2 Brief Introduction to Epidemiology

Cross-sectional study

In a cross-sectional study the data are obtained from a random sample of the population at one point in time. This gives a snapshot of a population.

Example: Based on a single survey of a specific population or a random sample thereof, we determine the proportion of individuals with heart disease at one point in time. This is referred to as the prevalence of disease. We may also collect demographic and other information which will allow us to break down prevalence broken by age, race, sex, socio-economic status, geographic, etc.

Important public health information can be obtained this way which may be useful in determining how to allocate health care resources. However such data are generally not very useful in determining causation.

In an important special case where the exposure and disease are dichotomous, the data from a cross-sectional study can be represented as

	D	\bar{D}	
E	n_{11}	n_{12}	n_{1+}
\bar{E}	n_{21}	n_{22}	n_{2+}
	n_{+1}	n_{+2}	n_{++}

where E = exposed (to risk factor), \bar{E} = unexposed; D = disease, \bar{D} = no disease.

In this case, all counts except n_{++} , the sample size, are random variables. The counts $(n_{11}, n_{12}, n_{21}, n_{22})$ have the following distribution:

$$(n_{11}, n_{12}, n_{21}, n_{22}) \sim \text{multinomial}(n_{++}, P[DE], P[\bar{D}E], P[D\bar{E}], P[\bar{D}\bar{E}]).$$

With this study, we can obtain estimates of the following parameters of interest

$$\begin{aligned} &\text{prevalence of disease } P[D] \text{ (estimated by } \frac{n_{+1}}{n_{++}}) \\ &\text{probability of exposure } P[E] \text{ (estimated by } \frac{n_{1+}}{n_{++}}) \end{aligned}$$

prevalence of disease among exposed $P[D|E]$ (estimated by $\frac{n_{11}}{n_{1+}}$)
 prevalence of disease among unexposed $P[D|\bar{E}]$ (estimated by $\frac{n_{21}}{n_{2+}}$)
 ...

We can also assess the **association** between the exposure and disease using the data from a cross-sectional study. One such measure is **relative risk**, which is defined as

$$\psi = \frac{P[D|E]}{P[D|\bar{E}]}.$$

It is easy to see that the **relative risk** ψ has the following properties:

- $\psi > 1 \Rightarrow$ positive association; that is, the exposed population has higher disease probability than the unexposed population.
- $\psi = 1 \Rightarrow$ no association; that is, the exposed population has the same disease probability as the unexposed population.
- $\psi < 1 \Rightarrow$ negative association; that is, the exposed population has lower disease probability than the unexposed population.

Of course, we cannot state that the exposure E causes the disease D even if $\psi > 1$, or vice versa. In fact, the exposure E may not even occur before the event D .

Since we got good estimates of $P[D|E]$ and $P[D|\bar{E}]$

$$\hat{P}[D|E] = \frac{n_{11}}{n_{1+}}, \quad \hat{P}[D|\bar{E}] = \frac{n_{21}}{n_{2+}},$$

the relative risk ψ can be estimated by

$$\hat{\psi} = \frac{\hat{P}[D|E]}{\hat{P}[D|\bar{E}]} = \frac{n_{11}/n_{1+}}{n_{21}/n_{2+}}.$$

Another measure that describes the association between the exposure and the disease is the **odds ratio**, which is defined as

$$\theta = \frac{P[D|E]/(1 - P[D|E])}{P[D|\bar{E}]/(1 - P[D|\bar{E}])}.$$

Note that $P[D|E]/(1 - P[D|E])$ is called the **odds** of $P[D|E]$. It is obvious that

- $\psi > 1 \iff \theta > 1$
- $\psi = 1 \iff \theta = 1$
- $\psi < 1 \iff \theta < 1$

Given data from a cross-sectional study, the **odds ratio** θ can be estimated by

$$\hat{\theta} = \frac{\hat{P}[D|E]/(1 - \hat{P}[D|E])}{\hat{P}[D|\bar{E}]/(1 - \hat{P}[D|\bar{E}])} = \frac{n_{11}/n_{1+}/(1 - n_{11}/n_{1+})}{n_{21}/n_{2+}/(1 - n_{21}/n_{2+})} = \frac{n_{11}/n_{12}}{n_{21}/n_{22}} = \frac{n_{11}n_{22}}{n_{12}n_{21}}.$$

It can be shown that the variance of $\log(\hat{\theta})$ has a very nice form given by

$$\widehat{\text{var}}(\log(\hat{\theta})) = \frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}.$$

The point estimate $\hat{\theta}$ and the above variance estimate can be used to make inference on θ . Of course, the total sample size n_{++} as well as each cell count have to be large for this variance formula to be reasonably good.

A $(1 - \alpha)$ confidence interval (CI) for $\log(\theta)$ (log odds ratio) is

$$\log(\hat{\theta}) \pm z_{\alpha/2} [\widehat{\text{Var}}(\log(\hat{\theta}))]^{1/2}.$$

Exponentiating the two limits of the above interval will give us a CI for θ with the same confidence level $(1 - \alpha)$.

Alternatively, the variance of $\hat{\theta}$ can be estimated (by the delta method)

$$\widehat{\text{Var}}(\hat{\theta}) = \hat{\theta}^2 \left[\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}} \right],$$

and a $(1 - \alpha)$ CI for θ is obtained as

$$\hat{\theta} \pm z_{\alpha/2} [\widehat{\text{Var}}(\hat{\theta})]^{1/2}.$$

For example, if we want a 95% confidence interval for $\log(\theta)$ or θ , we will use $z_{0.05/2} = 1.96$ in the above formulas.

From the definition of the odds-ratio, we see that if the disease under study is a rare one, then

$$P[D|E] \approx 0, \quad P[D|\bar{E}] \approx 0.$$

In this case, we have

$$\theta \approx \psi.$$

This approximation is very useful. Since the relative risk ψ has a much better interpretation (and hence it is easier to communicate with biomedical researchers using this measure), in studies where we cannot estimate the relative risk ψ but we can estimate the odds-ratio θ (see **retrospective studies** later), if the disease under studied is a rare one, we can approximately estimate the relative risk by the odds-ratio estimate.

Longitudinal studies

In a longitudinal study, subjects are followed over time and single or multiple measurements of the variables of interest are obtained. Longitudinal epidemiological studies generally fall into two categories; **prospective** i.e. moving forward in time or **retrospective** going backward in time. We will focus on the case where a single measurement is taken.

Prospective study: In a prospective study, a cohort of individuals are identified who are free of a particular disease under study and data are collected on certain risk factors; i.e. smoking status, drinking status, exposure to contaminants, age, sex, race, etc. These individuals are then followed over some specified period of time to determine whether they get disease or not. The relationships between the probability of getting disease during a certain time period (called **incidence** of the disease) and the risk factors are then examined.

If there is only one exposure variable which is binary, the data from a prospective study may be summarized as

	D	\bar{D}	
E	n_{11}	n_{12}	n_{1+}
\bar{E}	n_{21}	n_{22}	n_{2+}

Since the cohorts are identified by the researcher, n_{1+} and n_{2+} are fixed sample sizes for each group. In this case, only n_{11} and n_{21} are random variables, and these random variables have the

following distributions:

$$n_{11} \sim \text{Bin}(n_{1+}, P[D|E]), \quad n_{21} \sim \text{Bin}(n_{2+}, P[D|\bar{E}]).$$

From these distributions, $P[D|E]$ and $P[D|\bar{E}]$ can be readily estimated by

$$\hat{P}[D|E] = \frac{n_{11}}{n_{1+}}, \quad \hat{P}[D|\bar{E}] = \frac{n_{21}}{n_{2+}}.$$

The relative risk ψ and the odds-ratio θ defined previously can be estimated in exactly the same way (have the same formula). So does the variance estimate of the odds-ratio estimate.

One problem of a prospective study is that some subjects may drop out from the study before developing the disease under study. In this case, the disease probability has to be estimated differently. This is illustrated by the following example.

Example: 40,000 British doctors were followed for 10 years. The following data were collected:

Table 1.1: *Death Rate from Lung Cancer per 1000 person years.*

# cigarettes smoked per day	death rate
0	.07
1-14	.57
15-24	1.39
35+	2.27

For presentation purpose, the estimated rates are multiplied by 1000.

Remark: If we denote by T the time to death due to lung cancer, the death rate at time t is defined by

$$\lambda(t) = \lim_{h \rightarrow 0} \frac{P[t \leq T < t+h | T \geq t]}{h}.$$

Assume the death rate $\lambda(t)$ is a constant λ , then it can be estimated by

$$\hat{\lambda} = \frac{\text{total number of deaths from lunge cancer}}{\text{total person years of exposure (smoking) during the 10 year period}}.$$

In this case, if we are interested in the event

$$D = \text{die from lung cancer within next one year} \mid \text{still alive now},$$

or statistically,

$$D = [t \leq T < t + 1 | T \geq t],$$

then

$$P[D] = P[t \leq T \leq t + 1 | T \geq t] = 1 - e^{-\lambda} \approx \lambda, \quad \text{if } \lambda \text{ is very small.}$$

Roughly speaking, assuming the death rate remains constant over the 10 year period for each group of doctors, we can take the rate above divided by 1000 to approximate the probability of death from lung cancer in one year. For example, the estimated probability of dying from lung cancer in one year for British doctors smoking between 15-24 cigarettes per day at the beginning of the study is $\hat{P}[D] = 1.39/1000 = 0.00139$. Similarly, the estimated probability of dying from lung cancer in one year for the heaviest smokers is $\hat{P}[D] = 2.27/1000 = 0.00227$.

From the table above we note that the relative risk of death from lung cancer between heavy smokers and non-smokers (in the same time window) is $2.27/0.07 = 32.43$. That is, heavy smokers are estimated to have 32 times the risk of dying from lung cancer as compared to non-smokers.

Certainly the value 32 is subject to statistical variability and moreover we must be concerned whether these results imply causality.

We can also estimate the odds-ratio of dying from lung cancer in one year between heavy smokers and non-smokers:

$$\hat{\theta} = \frac{.00227/(1 - .00227)}{.00007/(1 - .00007)} = 32.50.$$

This estimate is essentially the same as the estimate of the relative risk 32.43.

Retrospective study: Case-Control

A very popular design in many epidemiological studies is the case-control design. In such a study individuals with disease (called **cases**) and individuals without disease (called **controls**) are identified. Using records or questionnaires the investigators go back in time and ascertain exposure status and risk factors from their past. Such data are used to estimate relative risk as we will demonstrate.

Example: A sample of 1357 male patients with lung cancer (cases) and a sample of 1357 males without lung cancer (controls) were surveyed about their past smoking history. This resulted in

the following:

smoke	cases	controls
yes	1,289	921
no	68	436

We would like to estimate the relative risk ψ or the odds-ratio θ of getting lung cancer between smokers and non-smokers.

Before tackling this problem, let us look at a general problem. The above data can be represented by the following 2×2 table:

	D	\bar{D}
E	n_{11}	n_{12}
\bar{E}	n_{21}	n_{22}
	n_{+1}	n_{+2}

By the study design, the margins n_{+1} and n_{+2} are fixed numbers, and the counts n_{11} and n_{12} are random variables having the following distributions:

$$n_{11} \sim \text{Bin}(n_{+1}, P[E|D]), \quad n_{12} \sim \text{Bin}(n_{+2}, P[E|\bar{D}]).$$

By definition, the relative risk ψ is

$$\psi = \frac{P[D|E]}{P[D|\bar{E}]}.$$

We can estimate ψ if we can estimate these probabilities $P[D|E]$ and $P[D|\bar{E}]$. However, we cannot use the same formulas we used before for cross-sectional or prospective study to estimate them.

What is the consequence of using the same formulas we used before? The formulas would lead to the following incorrect estimates:

$$\begin{aligned} \hat{P}[D|E] &= \frac{n_{11}}{n_{1+}} = \frac{n_{11}}{n_{11} + n_{12}} \quad (\mathbf{incorrect!}) \\ \hat{P}[D|\bar{E}] &= \frac{n_{21}}{n_{2+}} = \frac{n_{21}}{n_{21} + n_{22}} \quad (\mathbf{incorrect!}) \end{aligned}$$

Since we choose n_{+1} and n_{+2} , we can fix n_{+2} at some number (say, 50), and let n_{+1} grow (sample more cases). As long as $P[E|D] > 0$, n_{11} will also grow. Then $\hat{P}[D|E] \rightarrow 1$. Similarly $\hat{P}[D|\bar{E}] \rightarrow 1$. Obviously, these are NOT sensible estimates.

For example, if we used the above formulas for our example, we would get:

$$\begin{aligned}\hat{P}[D|E] &= \frac{1289}{1289 + 921} = 0.583 \text{ (incorrect!)} \\ \hat{P}[D|\bar{E}] &= \frac{68}{68 + 436} = 0.135 \text{ (incorrect!)} \\ \hat{\psi} &= \frac{\hat{P}[D|E]}{\hat{P}[D|\bar{E}]} = \frac{0.583}{0.135} = 4.32 \text{ (incorrect!).}\end{aligned}$$

This incorrect estimate of the relative risk will be contrasted with the estimate from the correct method.

We introduced the odds-ratio before to assess the association between the exposure (E) and the disease (D) as follows:

$$\theta = \frac{P[D|E]/(1 - P[D|E])}{P[D|\bar{E}]/(1 - P[D|\bar{E}])}$$

and we stated that if the disease under study is a rare one, then

$$\theta \approx \psi.$$

Since we cannot directly estimate the relative risk ψ from a retrospective (case-control) study due to its design feature, let us try to estimate the odds-ratio θ .

For this purpose, we would like to establish the following equivalence:

$$\begin{aligned}\theta &= \frac{P[D|E]/(1 - P[D|E])}{P[D|\bar{E}]/(1 - P[D|\bar{E}])} \\ &= \frac{P[D|E]/P[\bar{D}|E]}{P[D|\bar{E}]/P[\bar{D}|\bar{E}]} \\ &= \frac{P[D|E]/P[D|\bar{E}]}{P[\bar{D}|E]/P[\bar{D}|\bar{E}]}.\end{aligned}$$

By Bayes' theorem, we have for any two events A and B

$$P[A|B] = \frac{P[AB]}{P[B]} = \frac{P[B|A]P[A]}{P[B]}.$$

Therefore,

$$\begin{aligned}\frac{P[D|E]}{P[D|\bar{E}]} &= \frac{P[E|D]P[D]/P[E]}{P[\bar{E}|D]P[D]/P[\bar{E}]} = \frac{P[E|D]/P[E]}{P[\bar{E}|D]/P[\bar{E}]} \\ \frac{P[\bar{D}|E]}{P[\bar{D}|\bar{E}]} &= \frac{P[E|\bar{D}]P[\bar{D}]/P[E]}{P[\bar{E}|\bar{D}]P[\bar{D}]/P[\bar{E}]} = \frac{P[E|\bar{D}]/P[E]}{P[\bar{E}|\bar{D}]/P[\bar{E}]},\end{aligned}$$

and

$$\begin{aligned}\theta &= \frac{P[D|E]/P[D|\bar{E}]}{P[\bar{D}|E]/P[\bar{D}|\bar{E}]} \\ &= \frac{P[E|D]/P[\bar{E}|D]}{P[E|\bar{D}]/P[\bar{E}|\bar{D}]} \\ &= \frac{P[E|D]/(1 - P[E|D])}{P[E|\bar{D}]/(1 - P[E|\bar{D}])}.\end{aligned}$$

Notice that the quantity in the right hand side is in fact the odds-ratio of being exposed between cases and controls, and the above identity says that the odds-ratio of getting disease between exposed and un-exposed is the **same** as the odds-ratio of being exposed between cases and controls. This identity is very important since by design we are able to estimate the odds-ratio of being exposed between cases and controls since we are able to estimate $P[E|D]$ and $P[E|\bar{D}]$ from a case-control study:

$$\hat{P}[E|D] = \frac{n_{11}}{n_{+1}}, \quad \hat{P}[E|\bar{D}] = \frac{n_{12}}{n_{+2}}.$$

So θ can be estimated by

$$\hat{\theta} = \frac{\hat{P}[E|D]/(1 - \hat{P}[E|D])}{\hat{P}[E|\bar{D}]/(1 - \hat{P}[E|\bar{D}])} = \frac{n_{11}/n_{+1}/(1 - n_{11}/n_{+1})}{n_{12}/n_{+2}/(1 - n_{12}/n_{+2})} = \frac{n_{11}/n_{21}}{n_{12}/n_{22}} = \frac{n_{11}n_{22}}{n_{12}n_{21}},$$

which has exactly the same form as the estimate from a cross-sectional or prospective study. This means that the odds-ratio estimate is **invariant** to the study design.

Similarly, it can be shown that the variance of $\log(\hat{\theta})$ can be estimated by the same formula we used before

$$\widehat{\text{Var}}(\log(\hat{\theta})) = \frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}.$$

Therefore, inference on θ or $\log(\theta)$ such as constructing a confidence interval will be exactly the same as before.

Going back to the lung cancer example, we got the following estimate of the odds ratio:

$$\hat{\theta} = \frac{1289 \times 436}{921 \times 68} = 8.97.$$

If lung cancer can be viewed as a rare event, we estimate the relative risk of getting lung cancer between smokers and non-smokers to be about nine fold. This estimate is much higher than the incorrect estimate (4.32) we got on page 9.

Pros and Cons of a case-control study

- Pros
 - Can be done more quickly. You don't have to wait for the disease to appear over time.
 - If the disease is rare, a case-control design can give a more precise estimate of relative risk with the same number of patients than a prospective design. This is because the number of cases, which in a prospective study is small, would be over-represented by design in a case control study. This will be illustrated in a homework exercise.
- Cons
 - It may be difficult to get accurate information on the exposure status of cases and controls. The records may not be that good and depending on individuals' memory may not be very reliable. This can be a severe drawback.

1.3 Brief Introduction and History of Clinical Trials

The following are several definitions of a clinical trial that were found in different textbooks and articles.

- A clinical trial is a study in human subjects in which treatment (intervention) is initiated specifically for therapy evaluation.
- A prospective study comparing the effect and value of intervention against a control in human beings.
- A clinical trial is an experiment which involves patients and is designed to elucidate the most appropriate treatment of future patients.
- A clinical trial is an experiment testing medical treatments in human subjects.

Historical perspective

Historically, the quantum unit of clinical reasoning has been the case history and the primary focus of clinical inference has been the individual patient. Inference from the individual to the population was informal. The advent of formal experimental methods and statistical reasoning made this process rigorous.

By statistical reasoning or inference we mean the use of results on a limited sample of patients to infer how treatment should be administered in the general population who will require treatment in the future.

Early History

1600 East India Company

In the first voyage of four ships– only one ship was provided with lemon juice. This was the only ship relatively free of scurvy.

Note: This is observational data and a simple example of an epidemiological study.

1753 James Lind

“I took 12 patients in the scurvy aboard the Salisbury at sea. The cases were as similar as I could have them... they lay together in one place... and had one common diet to them all...

To two of them was given a quart of cider a day, to two an elixir of vitriol, to two vinegar, to two oranges and lemons, to two a course of sea water, and to the remaining two the bigness of a nutmeg. The most sudden and visible good effects were perceived from the use of oranges and lemons, one of those who had taken them being at the end of six days fit for duty... and the other appointed nurse to the sick...

Note: This is an example of a controlled clinical trial.

Interestingly, although the trial appeared conclusive, Lind continued to propose “pure dry air” as the first priority with fruit and vegetables as a secondary recommendation. Furthermore, almost 50 years elapsed before the British navy supplied lemon juice to its ships.

Pre-20th century medical experimenters had no appreciation of the scientific method. A common medical treatment before 1800 was blood letting. It was believed that you could get rid of an ailment or infection by sucking the bad blood out of sick patients; usually this was accomplished by applying leeches to the body. There were numerous anecdotal accounts of the effectiveness of such treatment for a myriad of diseases. The notion of systematically collecting data to address specific issues was quite foreign.

1794 Rush *Treatment of yellow fever by bleeding*

“I began by drawing a small quantity at a time. The appearance of the blood and its effects upon the system satisfied me of its safety and efficacy. Never before did I experience such sublime joy as I now felt in contemplating the success of my remedies... The reader will not wonder when I add a short extract from my notebook, dated 10th September. “Thank God”, of the one hundred patients, whom I visited, or prescribed for, this day, I have lost none.”

Louis (1834): Lays a clear foundation for the use of the *numerical method* in assessing therapies.

“As to different methods of treatment, if it is possible for us to assure ourselves of the superiority of one or other among them in any disease whatever, having regard to the different circumstances

Table 1.2: *Pneumonia: Effects of Blood Letting*

Days bled after onset	Died	Lived	proportion surviving
1-3	12	12	50%
4-6	12	22	65%
7-9	3	16	84%

of age, sex and temperament, of strength and weakness, it is doubtless to be done by enquiring if under these circumstances a greater number of individuals have been cured by one means than another. Here again it is necessary to count. And it is, in great part at least, because hitherto this method has been not at all, or rarely employed, that the science of therapeutics is still so uncertain; that when the application of the means placed in our hands is useful we do not know the bounds of this utility.”

He goes on to discuss the need for

- The exact observation of patient outcome
- Knowledge of the natural progress of untreated controls
- Precise definition of disease prior to treatment
- Careful observations of deviations from intended treatment

Louis (1835) studied the value of bleeding as a treatment of pneumonia, erysipelas and throat inflammation and found no demonstrable difference in patients bled and not bled. This finding contradicted current clinical practice in France and instigated the eventual decline in bleeding as a standard treatment. Louis had an immense influence on clinical practice in France, Britain and America and can be considered the founding figure who established clinical trials and epidemiology on a scientific footing.

In 1827: 33,000,000 leeches were imported to Paris.

In 1837: 7,000 leeches were imported to Paris.

Modern clinical trials

The first clinical trial with a properly randomized control group was set up to study streptomycin in the treatment of pulmonary tuberculosis, sponsored by the Medical Research Council, 1948. This was a multi-center clinical trial where patients were randomly allocated to streptomycin + bed rest versus bed rest alone.

The evaluation of patient x-ray films was made independently by two radiologists and a clinician, each of whom did not know the others evaluations or which treatment the patient was given.

Both patient survival and radiological improvement were significantly better on streptomycin.

The field trial of the Salk Polio Vaccine

In 1954, 1.8 million children participated in the largest trial ever to assess the effectiveness of the Salk vaccine in preventing paralysis or death from poliomyelitis.

Such a large number was needed because the incidence rate of polio was about 1 per 2,000 and evidence of treatment effect was needed as soon as possible so that vaccine could be routinely given if found to be efficacious.

There were two components (randomized and non-randomized) to this trial. For the non-randomized component, one million children in the first through third grades participated. The second graders were offered vaccine whereas first and third graders formed the control group. There was also a randomized component where .8 million children were randomized in a **double-blind placebo-controlled** trial.

The incidence of polio in the randomized vaccinated group was less than half that in the control group and even larger differences were seen in the decline of paralytic polio.

The nonrandomized group supported these results; however non-participation by some who were offered vaccination might have cast doubt on the results. It turned out that the incidence of polio among children (second graders) offered vaccine and not taking it (non-compliers) was different than those in the control group (first and third graders). This may cast doubt whether first and third graders (control group) have the same likelihood for getting polio as second graders. This is

a basic assumption that needs to be satisfied in order to make unbiased treatment comparisons. Luckily, there was a randomized component to the study where the two groups (vaccinated) versus (control) were guaranteed to be similar on average by design.

Note: During the course of the semester there will be a great deal of discussion on the role of randomization and compliance and their effect on making causal statements.

Government sponsored studies

In the 1950's the National Cancer Institute (NCI) organized randomized clinical trials in acute leukemia. The successful organization of this particular clinical trial led to the formation of two collaborative groups; CALGB (Cancer and Leukemia Group B) and ECOG (Eastern Cooperative Oncology Group). More recently SWOG (Southwest Oncology Group) and POG (Pediatrics Oncology Group) have been organized. A Cooperative group is an organization with many participating hospitals throughout the country (sometimes world) that agree to conduct common clinical trials to assess treatments in different disease areas.

Government sponsored clinical trials are now routine. As well as the NCI, these include the following organizations of the National Institutes of Health.

- NHLBI- (National Heart Lung and Blood Institute) funds individual and often very large studies in heart disease. To the best of my knowledge there are no cooperative groups funded by NHLBI.
- NIAID- (National Institute of Allergic and Infectious Diseases) Much of their funding now goes to clinical trials research for patients with HIV and AIDS. The ACTG (AIDS Clinical Trials Group) is a large cooperative group funded by NIAID.
- NIDDK- (National Institute of Diabetes and Digestive and Kidney Diseases). Funds large scale clinical trials in diabetes research. Recently formed the cooperative group TRIALNET (network 18 clinical centers working in cooperation with screening sites throughout the United States, Canada, Finland, United Kingdom, Italy, Germany, Australia, and New Zealand - for type 1 diabetes)

Pharmaceutical Industry

- Before World War II no formal requirements were made for conducting clinical trials before a drug could be freely marketed.
- In 1938, animal research was necessary to document toxicity, otherwise human data could be mostly anecdotal.
- In 1962, it was required that an “adequate and well controlled trial” be conducted.
- In 1969, it became mandatory that evidence from a randomized clinical trial was necessary to get marketing approval from the Food and Drug Administration (FDA).
- More recently there is effort in standardizing the process of drug approval worldwide. This has been through efforts of the International Conference on Harmonization (ICH).
website: <http://www.pharmweb.net/pwmirror/pw9/ifpma/ich1.html>
- There are more clinical trials currently taking place than ever before. The great majority of the clinical trial effort is supported by the Pharmaceutical Industry for the evaluation and marketing of new drug treatments. Because the evaluation of drugs and the conduct, design and analysis of clinical trials depends so heavily on sound Statistical Methodology this has resulted in an explosion of statisticians working for th Pharmaceutical Industry and wonderful career opportunities.