ST520: Statistical Principles of Clinical Trials

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Syllabus

Information

- **Time: 1:30pm-2:45pm**
- **Days: Tuesday and Thursday**
- **Location: 2106 SAS Hall**
- **Instructor: Shu Yang**
- 4266 SAS Hall
- (919) 515-1935
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- **Office hours for Instructor:** Thursdays 3:00-4:00pm, also by appointment

- **Teaching Assistant: Rui Zhu**
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- **Office hours for TA:** 10 am –12 on Wednesday, 1101 SAS Hall

Reference Textbooks

- **Fundamentals of Clinical Trials**
- By Friedman, L.M., Furberg, C.D. and DeMets, D.L.
- **Group Sequential Methods with Applications to Clinical Trials**
- By Jennison, C. and Turnbull B.W.

Note

- These texts are useful in describing principles of clinical trials from an applied perspective. The intended audience is clinicians and others interested in learning what clinical trials are.
- The course will be based primarily on lecture notes that will be available at Moodle: http://wolfware.ncsu.edu.
- Your assignment grades will be posted at Moodle as well. While care is taken to enter the grades, it is your responsibility to alert the instructional team immediately if a mistake has been made during grade entry.

Prerequisties/Co-rerequisites

ST501, ST701 or equivalent.

Grades

- 25% Homework (approximately every two weeks)
- 30% Closed book midterm (1.5–2 hours during class TBA)
- 40% Closed book final (Thursday December 12, 1:00–4:00 pm)
- 5% Class activities and instructor discretion

Course Outline

- Introduction to Epidemiology and Clinical Trials
- The different phases of clinical trials research
- Phase I dosing trials, Clinical pharmacology
- Phase II clinical trials (screening and feasibility)
  - review of confidence intervals
  - Gehan's two-stage design
  - Simon's two-stage sequential design
  - Discussion of surrogate markers
- Phase III clinical trials – fundamentals
  - What is the question? primary, secondary
  - study population
    - whom to target
    - likelihood of seeing event
    - identifying compliant population
    - generalizability
    - control group

Course Outline

- Randomization
  - Role of randomization to control bias
  - competing designs (historical and literature controls)
  - types; simple, blocked, permuted block
  - stratification; pros and cons, how many strata?
  - dynamic balancing
  - response adaptive designs
- Blinding
  - reasons, single blind, double blind
  - use of placebo controlled trials
- Implementation
  - Administrative Issues
  - Institutional review boards (IRB's)
  - Ethical Issues
  - Protocol Documents/Forms
  - Quality Control-data management

Course Outline

Statistical Methods

- Endpoints
  - Continuous
    - t-test for two-sample comparison
    - ANOVA- F-tests for K-sample comparisons
    - Linear regression to adjust for covariates
  - Categorical
    - proportions test for two-sample comparisons
    - Chi-square test for K-sample comparisons
    - arc-sin square root transformation to stabilize variance
  - Time to event
    - staggered entry and censoring
    - Life-table methods and Kaplan-Meier estimator
    - Logrank tests for two and K-sample comparisons
  - For all endpoints
    - power and sample size considerations
    - multiple comparisons
  - Equivalency and Non-superiority trials

Course Outline

- Monitoring Clinical Trials
  - group-sequential designs
  - Data safety monitoring boards
- Intention to treat analysis
  - compliance
  - drop-outs
  - missing data
  - causal inference

Introduction - 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**
- **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.

Epidemiology

Definition (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).

Example

- 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

Definition (Clinical trials)

The evaluation of intervention (treatment or exposure or regime) on disease in a controlled experimental setting.

Example

- 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)

Brief Introduction to Epidemiology

Cross-sectional study

Definition (Cross-sectional study)

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. The prevalence can be 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.

Cross-sectional study

- Consider the exposure (E) and disease (D) are binary (yes/no), 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.

- The counts $(n_{11}, n_{12}, n_{21}, n_{22})$ are random variables

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

Cross-sectional study

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

- prevalence of disease $P[D]$ (estimated by $\frac{n_{+1}}{n_{++}}$)
- probability of exposure $P[E]$ (estimated by $\frac{n_{1+}}{n_{++}}$)
- 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 $\frac{n_{21}}{n_{2+}}$)
- ...

Cross-sectional study

Definition (Relative risk)

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

Properties:

- $\psi > 1 \Rightarrow$ positive association
- $\psi = 1 \Rightarrow$ no association
- $\psi < 1 \Rightarrow$ negative association
- Estimator of ψ from a cross-sectional study:

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

Cross-sectional study

Definition (Odds ratio)

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

Properties:

- $\psi > 1 \iff \theta > 1$
- $\psi = 1 \iff \theta = 1$
- $\psi < 1 \iff \theta < 1$
- Estimator of θ from a cross-sectional study:

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

Cross-sectional study

- Variance of $\log(\widehat{\theta})$:

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

- A $(1-\alpha)$ confidence interval (CI) for $\log(\theta)$:

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

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

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

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

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

Cross-sectional study

- When $\alpha = 0.05$, $z_{0.05/2} = 1.96$
- If the disease under study is a rare one, then

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

In this case, we have

$$\theta \approx \psi.$$

Prospective studies

Prospective studies

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.

Prospective studies

- Data from a prospective study can be summarized as

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

  where n_{1+} and n_{2+} are fixed sample sizes for each group.
- Only n_{11} and n_{21} are random variables:

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

- The relative risk ψ and the odds-ratio θ can be estimated in exactly the same way.

Prospective studies

Example

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

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

# cigarettes smoked per day	death rate
0	.07
1-14	.57
15-24	1.39
25+	2.27

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

Prospective studies

- One problem of a prospective study is drop out before the event is observed.
- Define $T =$ the time to death due to lung cancer; the death rate at time t is defined by

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

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

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

- The probability of dying from lung cancer in one year:

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

Prospective studies

- $\widehat{P}[D]$ for non-smoking British doctors:

$$\widehat{P}[D] = 1.39/1000 = 0.00139$$

- $\widehat{P}[D]$ for the heaviest smoker:

$$\widehat{P}[D] = 2.27/1000 = 0.00227$$

- Relative risk of dying from lung cancer in one year between heavy smokers and non-smokers:

$$\widehat{\psi} = 2.27/0.07 = 32.43$$

- Odds ratio of dying from lung cancer in one year between heavy smokers and non-smokers:

$$\widehat{\theta} = \frac{.00227/(1-.00227)}{.0007/(.0007)} = 32.50$$

Retrospective study: Case-Control

Cases and controls

In case-control studies, 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.

Retrospective study: Case-Control

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.

Retrospective study: Case-Control

- Data from a case control study can be summarized as

	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.
- The counts n_{11} and n_{12} are random variables:

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

Retrospective study: Case-Control

- We hope to estimate the relative risk ψ in a case-control study

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

  But we can only estimate $P[E|D]$ and $P[E|\bar{D}]$.
- What if we treat the case-control study as a prospective or cross-sectional study and use the incorrect formulas to estimate ψ?

$$\widehat{P}[D|E] = \frac{n_{11}}{n_{1+}} = \frac{n_{11}}{n_{11} + n_{12}} \text{ (\textbf{incorrect!})}$$
$$\widehat{P}[D|\bar{E}] = \frac{n_{21}}{n_{2+}} = \frac{n_{21}}{n_{21} + n_{22}} \text{ (\textbf{incorrect!})}$$

- We can make $\widehat{P}[D|E]$ and $\widehat{P}[D|\bar{E}]$ go to one! (**Not sensible!**)

Retrospective study: Case-Control

- In our example, if incorrect formulas were used

$$\widehat{P}[D|E] == \frac{1289}{1289+921} = 0.583 \text{ (**incorrect!**)}$$

$$\widehat{P}[D|\bar{E}] = \frac{68}{68+436} = 0.135 \text{ (**incorrect!**)}$$

$$\widehat{\psi} = \frac{\widehat{P}[D|E]}{\widehat{P}[D|\bar{E}]} = \frac{0.583}{0.135} = 4.31 \text{ (**incorrect!**).}$$

Retrospective study: Case-Control

- Let us try to estimate the odds ratio:

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

- right hand side = odds ratio of being exposed between cases and controls and can be estimated

Retrospective study: Case-Control

- From the distributions:

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

- $\Longrightarrow$

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

- θ can be estimated by

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

- The same formula!
- Variances of $\log(\widehat{\theta})$ and $\widehat{\theta}$ have the same formula too; inference is similar.

Retrospective study: Case-Control

- Lung cancer example:

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

- If we can view lung cancer as a rare event, then

$$\widehat{\psi} \approx \widehat{\theta} = 8.97.$$

- Smokers are 9 times as likely as non-smokers to develop lung cancer.
- The incorrect estimate of the relative risk 4.32 is too low.

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 is more efficient:

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

- Cons
  - Bias in getting exposure information! This can be a severe drawback.

Brief Introduction and History of Clinical Trials

Definition of Clinical Trials

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

Definition (Clinical trials)

- 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.

- In clinical trials, the control group is the group of people who are on best current standard therapy or on no active intervention.

Definition of Clinical Trials

- The treatment may be prophylactic, diagnostic or therapeutic agents, devices, regimens, procedures, etc.
- At baseline, the control group must be sufficiently similar in relevant respects to the intervention group so that differences in outcome may reasonably be attributed to the action of the intervention.
- The experimental subjects are humans not animals, so ethics factor is very important and we must obtain informed consent from participants.

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.

Early History

1753 James Lind (British doctor, Father of Nautical Medicine)

"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..."

Early History

1835 Louis

Lays a clear foundation for the use of the *numerical method* in assessing therapies.

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.

Early History

Table: *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%

- 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.
- Incidence rate is low (1 per 2,000)
- Randomized component: 0.8 million children were randomized in a double-blind placebo-controlled trial.
- Result: Incidence of polio in treated group is less than half of that in the control group.
- Non-randomized component: Second graders were offered vaccine and first and third graders were formed control group.
- Result: similar.
- However, 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).
- Question: were treated children (second graders) and the control (first and third graders) similar?

Government sponsored studies

NIH (National Institutes of Health)

- NHLBI- (National Heart Lung and Blood Institute) funds individual and often very large studies in heart disease.
- NIAID- (National Institute of Allergic and Infectious Diseases) Much of their funding now goes to clinical trials research for patients with HIV and AIDS.
- NIDDK- (National Institute of Diabetes and Digestive and Kidney Diseases). Funds large scale clinical trials in diabetes research.

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.