臨床試驗

課程介紹，歷史，計畫書簡介

2015-2-25

Teachers:
簡國龍老師 klchien@ntu.edu.tw
劉仁沛老師 jpliu@ntu.edu.tw

Outline

- **臨床試驗 (Clinical Trial)，2 學分 846 M0340**
- 授課老師：簡國龍 (klchien@ntu.edu.tw) & 劉仁沛 (jpliu@ntu.edu.tw)
- 上課時間：每週三上午 10:20Am-12:10Pm (Room 212);
- Schedule:Every Wednesday, 10:20Am-12:10pm

- 上課對象：醫護從業人員，公衛、流行病學、預防醫學、統計背景研究生
- Students: Health-professionals background, public health-related, or statistics-major graduate students

修習完成本課程可得到 GCP 認證人體試驗相關訓練共 28 小時

課程目的：

- 以臨床試驗研究設計及實際進行時處理的問題作一通盤性的介紹，使學生能對臨床試驗的方法及運用有一整體的認識。
- 介紹臨床試驗的研究方法，以系統性說明臨床試驗過程需注意的內容，使學習者能熟練臨床試驗的步驟，並且能夠評估臨床試驗報告及設計執行臨床試驗。
- 課程內容：介紹臨床試驗的歷史演變，研究設計、資料分析以及執行臨床試驗過程中各種步驟， GCP 及 ICH 的概念，以及相關臨床試驗之實例介紹等。
- 學生將以團隊方式，完成一個簡要計畫書及其相關受試者同意書與個案報告表的期末報告。
- 授課方式：以演講及文獻回顧討論方式，並邀請專家學者作深入演講。

Course description:

- This course is described for students interested in the scientific, and practical aspects of clinical trials. Topics include types of clinical research, study design, treatment allocation, randomization, sample size requirement, statistical methods for analysis of clinical trial data, good clinical practice, ICH, adverse events, clinical trial activity and documents patient consent and ethical concerns, and monitoring and interpretation of the results. Students will complete homework assignments, explore key ideas, criticize a protocol and recently published medical literature, and design a clinical trial investigation in their own field of interest. The final project for the course, including protocol, informed consent, IRB document and case report form, will be the most achievement for results of clinical trial practice.

課程安排：

週別	日期	Title	老師	Homework due date
1	2/25	課程介紹，歷史，計畫書簡介	簡國龍	
2	3/4	研究設計 (一): 病人族群、臨床試驗之設計	簡國龍	
3	3/11	研究設計 (二): 隨機分派、癌症早期臨床試驗之設計、標靶試驗	劉仁沛	
4	3/18	統計分析 (一): 指標種類與選擇	簡國龍	
5	3/25	統計分析 (二): 無母數、 CMH 檢定、存活分析、非劣性及對等性檢定、多重比較	劉仁沛	
6	4/1	溫書假		
7	4/8	藥品優良臨床試驗規範 (GCP & ICH)/ 評估臨床試驗品質 -CONSORT statement	簡國龍	HW-1 due date
8	4/15	統計分析 (三): 樣本大小、效力計算及期中分析與資料安全監督委員會	劉仁沛	
9	4/22	不良反應及不良事件	簡國龍	
10	4/29	期中報告 - 文獻閱讀與批評	簡國龍 / 劉仁沛	
11	5/6	臨床試驗執行 (一): 計畫書寫作及 SPIRIT Check List, 文件、人體試驗委員會、受試者同意書、個案報告表	劉仁沛	HW-2 due date
12	5/13	統計分析 (四): 交叉設計之分析及對等性檢定	劉仁沛	
13	5/20	統計分析 (五): 檢驗試劑與標靶試驗設計與分析	劉仁沛	Protocol-1 due date
14	5/27	臨床試驗執行 (二): 監測 , 稽核及查核	劉仁沛	
16	6/3	Student Presentation on Protocol	簡國龍 / 劉仁沛	
15	6/10	Special talk: Professor 楊志新 , Experience on Phase III Trial of Afatinib for Lung Cancer	簡國龍 / 劉仁沛	
17	6/17	Student Presentation on Protocol	簡國龍 / 劉仁沛	Protocol-2 due date

書名	作者	出版社	版次	出版年	ISBN
Design and analysis of clinical trials: concepts and methodologies	Chow, SC, Liu, JP	Wiley	3	2013, Oct	978-0-470-88765-3 http://as.wiley.com/WileyCDA/WileyTitle/productCd-0470887656.html
簡體中文翻譯本：Design and analysis of clinical trials: concepts and methodologies	Chow, SC, Liu, JP(周賢忠與劉仁沛)	北京大學醫學出版社	1	2010	978-7-81116-917-1
Fundamentals of clinical trials	Friedman, LM, Furberg, CD, DeMets DL	Springer	4	2010	1441915850
Clinical Trials: A methodologic perspective	Piantadosi, S	Wiley	2	2005	978-0-471-72781-1

Course requirements and Grading:

- 成績計算 homework 30% ，計畫書 40% ，最後口頭報告與批評 30% 成績採用等第制評估。

- 有關最後報告內容除了自己本身的計畫書以外，也需針對另一組計畫書之內容提出批評。

- 計畫書內容需指名特定學生之負責的部分及貢獻，以能對特定同學之成績交待清楚。

修習完成本課程可得到 GCP 認證人體試驗相關訓練共 30 小時

Reference:

- Related Journals:
  - *Contemporary Clinical Trials*
    - http://www.journals.elsevier.com/contemporary-clinical-trials/
  - *JAMA, New Engl J Med, specialist-oriented*
  - *Statistics in Medicine, …,*
- Internet: FDA, DOH, CDE, HTA

Course requirements and Grading:

- Homework assignments, class participants, and the final project. Grades will be based on homework: 30%, protocol: 40% and final presentation and rebuttal to critique: 30%. Letter grades will be given in all

計畫書簡介
Written Protocol for submission

Protocol

- Refer to the Word document

Clinical trial (Introduction)

Clinical trial (Introduction)

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

  (Hopwood MD, Mabry JC, Sibley WL.

Reasons to learn clinical trial methodology

- Interpret literature
- Participate in the clinical trials
- Conduct clinical trials
- Regulatory decision

Scientific knowledge

- The results of clinical trials are regarded as the **gold standard** in terms of **scientific investigations** and **regulatory decisions** *(the definite answer).*

Scientific perspective

- The method of randomized clinical trials is a last resort for the evaluation of medical interventions. It is slow, ponderous, expensive, and often stifling of scientific imagination and creative changes in ongoing protocols. No other method for studying the merits of clinical treatment regimens can

Regulatory perspective

- U.S. Federal Register 1985 Concerning Section 314.126
- The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The FDA considers (these characteristics) in determining whether an investigation is adequate and well-controlled for the purposes of section 505 of the Act. Reports of adequate and well-controlled in investigations provide the primary basis for determining whether there is ‘substantial evidence’ to support the claims of effectiveness for new drug and antibiotics. Therefore the study report should provide sufficient details of study design, conduct and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

Stages of a clinical trial

- Define the objectives (Conceptual hypothesis vs. Operational hypothesis)
- Design the trial– A **written protocol**
- Conduct the trial
  - Patient recruitment, treatment, and outcomes assessment
  - Coordination, Organization, & Monitoring
  - Data management
- Analyze the data: Descriptive statistics, Hypothesis testing, Estimation of effect
- Draw conclusions
  - Publish in scientific journals
  - Submit application to regulatory agencies

臨床試驗的階段

- 確立研究的目的，包括觀念性的假設及操作性的假設
- 臨床試驗的設計 -**A written protocol**
- 臨床試驗的進行
  - 病人收集、治療、成果的評估
  - 配合項目、機構及監測 (monitoring)
  - 資料處理
- 分析資料 - 描述性統計、假設檢定、效果

- 臨床試驗是針對人類為研究對象的科學研究，以前瞻性了解各種預防性，治療性及診斷性的藥材設備、處方或程序的效果及價值。
- 臨床試驗的結果可以當作是一黃金標準，即是在科學研究及藥政管理決策上的黃金標準。

- 科學研究方面：隨機分配、效果的評估、推論的強度
- 管理法規方面：
  - 排除疾病本身自然史的變化
  - 安慰劑效應、偏差的觀察
- 研究設計、試驗進行步驟、分析資料

Design and conduct of clinical trials

1. Define the objectives
2. Protocol development
   - Background
   - Patients, treatment, & Outcomes
   - Required data
   - Statistical considerations
     - sample size calculation
     - analytical procedures
   - References
   - Regulatory considerations
3. Institutional approval
4. Design of data forms
5. Patient recruitment
6. Evaluate outcomes
7. Monitoring/ Audit
8. Data entry and management
9. Data analysis
10. Report preparation

Personnel

Principal investigator (P.I.) and sponsor P.I., Clinical Research Associates (CRA) & Statistician

Institutional Review Board (IRB) or Human Subject Committee P.I. & CRAs

Clinicians (P.I. & other)

P.I. & Clinicians

Monitors

Data manages

Statistician

P.I. & statistician

History and Ethics

History:

- The first clinical trial?
  - The Book of Daniel in the bible (1:15)
- Assize of Bread
  - 1202 English food law: prohibit the adulteration of bread with ingredients such as ground peas or beans
- Regulations for foods and medicines safety and quality
- American regulation history in shaping

Clinical Trial: history

中國古代		神農嘗百草
About 500 B.C.		Book of Daniel (bible /Old Testament)
1747	Lind	Untreated control group (Vit. C and Scurvy)
1798	Jenner	Smallpox inoculation
1799	Haygarth	Sham procedure (Perkin's Tractor vs. wooden rod)
1834	Luis	(1)exact observation of patient outcomes (2) knowledge of the natural history of untreated controls (3) precise definition of disease (4)careful observation of deviations from intended treatment
1863	Gull	Use of placebo treatment
1923	Fisher	Random allocation in experiment
1931	U.K. MRC	Medical Research Council special committee on clinical trials
1931	Amberson	Random allocation of treatment to patients
1946	Nuremberg Code for Human Experimentation	
1948	MRC	Streptomycin trials
1950	MRC	Placebo control an double-blind assessment
1964	World Medical Assembly Declaration of Helsinki	
1966	U.S.	Institutional Review Board
1947	Chalmers	Separation of monitoring and administration
1975	World Medical Assembly revision of Declaration of Helsinki	
1985	U.S. FDA	Adequate and **Well-Controlled** studies

USA history (1)

- 1848, Drug Importation Act
  - Stop the entry of adulterated drugs from overseas
- 1901, Biological Control Act of 1902
  - A horse named Jim: antitoxin for diphtheria
  - Antitoxin and vaccine development
- 1906, original Food and Drugs Act
  - Prohibit interstate commerce in misbranded

USA history (2)

- 1931, FDA (Food and Drug Administration)
- 1932, initiated the Tuskegee Study of Untreated Syphilis in the Negro Male
  - 399 poor blacks late syphilis & 201 men without the disease as controls
  - Was told treated for “bad blood” and not told of the purpose
  - 1950s, PCN not offered to the men with

USA history (3)

- 1937, 107 died after drinking the “Elixir of sulfanilamide”, mislabeled
- 1938, Food, Drug, and Cosmetic Act
  - Expand the role of FDA in safety of new drugs and control of cosmetics and devices
- 1940-45, Nazi medical personnel
  - In concentration camps, Auschwitz and Dachau, sterilization, eutnanasia, exposure to temperature extremes, bacteria and

USA history (4)

- 1947, Nuremberg Code
  - 10 standards were drafted for biomedical experiments
  - Prototype for further codes in ethical manner
- 1962, thalidomide
  - 9/3879 American women gave birth to phocomelia
  - Both efficacy and safety before marketing

USA history (5)

- 1964, Declaration of Helsinki
  - The World Medical Association
  - Guidelines for the ethical treatment of human subjects
- 1972, regulation of biologics, such as serums, vaccines, and blood products, were transferred from NIH to the FDA
- 1974, National Research Act

USA history (6)

- 1976, Medical Device Amendments
  - Exemption from pre-market notification, approval to encourage the discovery and development of useful medical devices
- 1979, Belmont Report
  - Three basic ethical principles and guidelines
    - Respect for persons, decisions and protection
    - Beneficence, obligation to do no harm,

USA history (7)

- 1980-81, Title 21 of the Code of Federal Regulations (21 CFR)
  - Part 50: protection of human subjects
  - Part 56: IRBs
  - Part 312: Investigational New Drug applications, responsibility of investigators, control of drugs, record keeping and retentions, and assurance of IRB reviews

USA history (8)

- 1983, Orphan Drug Act
  - Unprofitable drugs needed for treating rare diseases
- 1988, Food and Drug Administration Act
  - An agency of the Department of Health and Human Service
- 1990, Safe Medical Devices Act
  - Report promptly any incident that reasonably suggest that a medical device

USA history (9)

- 1990, International Conference on Harmonization for Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
  - Europe, Japan and US
  - Standardization to reduce or eliminate duplication of testing in various countries

USA history (10)

- 1991, FDA regulations to accelerate the review of drugs for life-threatening diseases
- 1995, FDA declared cigarettes to be “drug delivery devices” and proposed restrictions on marketing and sales to reduce smoking by young
- 1997, Food and Drug Administration

USA history (11)

- 2000, Gene therapy trial
  - 1999 death of an 18-year-old died from multiple organ failure by infusion of genetically altered cold viruses into diseased liver
  - Ensure patient protection and fully informed consent
  - Monkeys had died from the therapy, and several previous participants had suffered serious toxic reactions

USA history (12)

- Adverse drug effects
  - Ceristatin withdrawal
  - Cox-2 inhibitor withdrawal
- Clinical trial registration
  - Anti-depressant clinical trial
  - Website: clinicaltrials.org.

Principles of Ethics

- Respects for persons / autonomy
- Beneficence and Non-maleficence
- Justice (Distributive justice)

Ethical norms in clinical trials

- Good research design
- Competent investigators
- Potential benefits justify potential risks
- Equitable selection of subjects
- Informed consent
- Compensation for research-induced injury
- Special populations

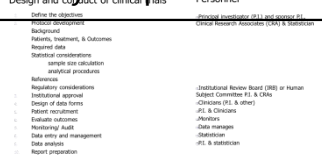
Practical considerations in clinical trial

- Clinical equipoise: genuine UNCERTAINTY within the clinical community
  - About which study treatment would be more beneficial for a patient
- Potential benefits vs. possible risks
- Human rights and Confidentiality
- Adequate and competent review

References

- http://www.fda.gov/opacom/backgrounders/miles.html
  - FDA Backgrounder: Milestones in U.S. Food and Drug Law History
- Websites
- Academic journals

版權聲明

頁碼	作品	版權圖示	來源 / 作者
1~43			本作品轉載自 Microsoft Office 2010 PowerPoint 設計主題範本 -Pixel ，依據 Microsoft 服務合約及著作權法第 46 、 52 、 65 條合理使用。
14	A clinical trial is a scientific research… devices, regimens, and procedures.		The role of general clinical research centers in clinical trials: A characterization with recommendations/Marsha D. Hopwood, John C. Mabry, William L. Sibiley http://www.rand.org/content/dam/rand/pubs/reports/2008/R2669.pdf 瀏覽日期： 2015/03/02 ，本作品依據著作權法第 46 、 52 、 65 條合理使用。
18	The purpose of conducting…adequate and well-controlled study are present		U.S. Federal Register 1985 Concerning Section 314.126 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.126 本作品屬公共領域之著作。
23			《 Design and analysis of clinical trials: concepts and methodologies 》， 作者 :Chow, SC, Liu, JP 。本作品依據著作權法第 46 、 52 、 65 條合理使用。
27~38	USA history (1) 1848, Drug Importation Act …USA history (12)		Milestones in U.S. Food and Drug Law History / U.S. FDA http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm 瀏覽日期 : 2015/2/26 ，本作品屬公共領域之著作。