Investigational Drug

台北醫學大學・市立萬芳醫院

藥劑部　黎燕縈 藥師

Investigational product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with marketing authorization when used or assembled (formulation or package) in a way different from the approved form, or when used for an unapproved indication, or when used to gain (long term safety, efficacy) information about an approved.

Drug Development & Clinical Study

The Drug Development and Approval Process

What is R & D ?

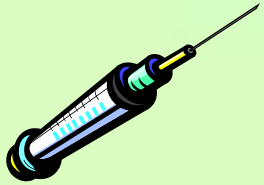
- **Early research and preclinical testing**
- **IND (Investigational New Drug) application filed with FDA**
- **Clinical trials (phases 1, 2, and 3)**
- **NDA (New Drug Application) filed with FDA**
  - About 1 in 5 drugs that enter clinical trials are approved by U.S. FDA
- **FDA validates claim and approves drug**

Adapted from NCI

Research & Development (R & D)

- Steps of Product Development

What is a Clinical Trial



- **Clinical trials are research studies in which people help doctors find ways to improve health and disease care. Each study tries to answer scientific questions and to find better ways to prevent, diagnose, or treat disease.**
- **A clinical trial is one of the final stages of a long and careful research process. Studies are done with patients to find out whether promising approaches to disease prevention, diagnosis, and treatment are safe and effective.**

Phase I Studies (First Time in Humans)

- **Includes the initial introduction of an investigational new drug into humans**
- **Usually conducted in healthy volunteer subjects**
- **Purpose is to evaluate its safety and identify side effects**

~15-30 people

Phase II Studies (Proof of concept)

- Controlled clinical studies conducted to obtain some preliminary data
- Conducted in a relatively small number of patients
- Determine its effectiveness and to further evaluate its safety
  - Administration of several doses to determine minimum effective dose and maximum tolerated dose
  - Provide estimate of variability of the product and the disease state
  - Provide information to determine the design of the phase III studies

~50-100 people

Phase III Studies (Pivotal safety/efficacy)

- They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in phase II
- Intended to gather the additional information about effectiveness and safety
- Confirm its effectiveness, monitor side effects, compare it with standard or equivalent treatments ('gold standard' treatment)
- Usually include several hundred to several thousand people. Regulatory authorities(FDA) generally require 2 well controlled phase III studies for each proposed indication

~Several Hundreds of people

Phase IV Study (post-marketing clinical trial)

- **Studies initiated after a drug's marketing approval.**
- **Post-marketing surveillance studies.**
- **Special studies in patient groups that may not have been included in the previous trials (e.g. children, persons using concomitant medications, etc.)**
- **Pharmacoeconomic (or cost-effectiveness) studies.**

Hundreds to thousands of people

MedWatch The FDA Safety Information and Adverse Event Reporting Program

Tarceva (erlotinib)

Audience: Oncological, dermatological and ophthalmological healthcare professionals

OSI, Genentech and FDA notified healthcare professionals of new safety information added to the WARNINGS AND PRECAUTIONS sections of the prescribing information for Tarceva. Gastrointestinal perforation (including fatalities), bullous, blistering and exfoliative skin conditions including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, in some cases fatal, and ocular disorders, including corneal perforation or ulceration have been reported during use of Tarceva. The new safety information comes from routine pharmacovigilance activities of clinical study and postmarketing reports. Tarceva monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. In combination with gemcitabine, Tarceva is also indicated for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer.

Read the complete MedWatch 2009 Safety summary, including a link to the OSI Dear Healthcare Professional Letter, at:

http://www.fda.gov/medwatch/safety/2009/safety09.htm#Tarceva

You are encouraged to report all serious adverse events and product quality problems to FDA MedWatch at www.fda.gov/medwatch/report.htm

http://www.fda.gov/medwatch/index.html

pump. If this failure occurs, the pump may not respond with a vibration or acoustic confirmation signal to a button press and the display will remain unchanged. Users may contact ACCU-CHEK Spirit hotline noted in the Press Release for a replacement pump or for any other questions regarding this potential defect.

[April 30, 2009 - Press Release - FDA]

Return to Top | MedWatch Home | MedWatch Safety Info | Online MedWatch Report | Contact MedWatch

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Botox and Botox Cosmetic (Botulinum toxin Type A) and Myobloc (Botulinum toxin Type B)

Audience: Cosmetic surgeons, neurologists, consumers

[Posted 04/30/2009] FDA notified healthcare professionals that after an ongoing safety review initiated in February 2008, the manufacturers of licensed botulinum toxin products will be required by FDA to strengthen warnings in product labeling and add a boxed warning regarding the risk of adverse events when the effects of the toxin spread beyond the site where it was injected.

FDA will also require that manufacturers develop and implement a Risk Evaluation and Mitigation Strategy [REMS], including a communication plan to provide more information regarding the risk for distant spread of botulinum toxin effects after local injection, as well as information to explain that botulinum toxin products cannot be interchanged. The REMS would also include a Medication Guide that explains the risks to patients, their families, and caregivers. FDA is requiring the manufacturers to submit safety data after multiple administrations of the product in a specified number of children and adults with spasticity to assess the signal of serious risk regarding distant spread of toxin effects.

FDA's evaluation of the data continues to support the recommendations made in the 2008 Early Communication.

[April 30, 2009 - Follow-up to the February 8, 2008, Early Communication about an Ongoing Safety Review of Botox and Botox Cosmetic (Botulinum toxin Type A) and Myobloc (Botulinum toxin Type B) - FDA]

Previous MedWatch Alert
[02/08/2008]

Return to Top | MedWatch Home | MedWatch Safety Info | Online MedWatch Report | Contact MedWatch

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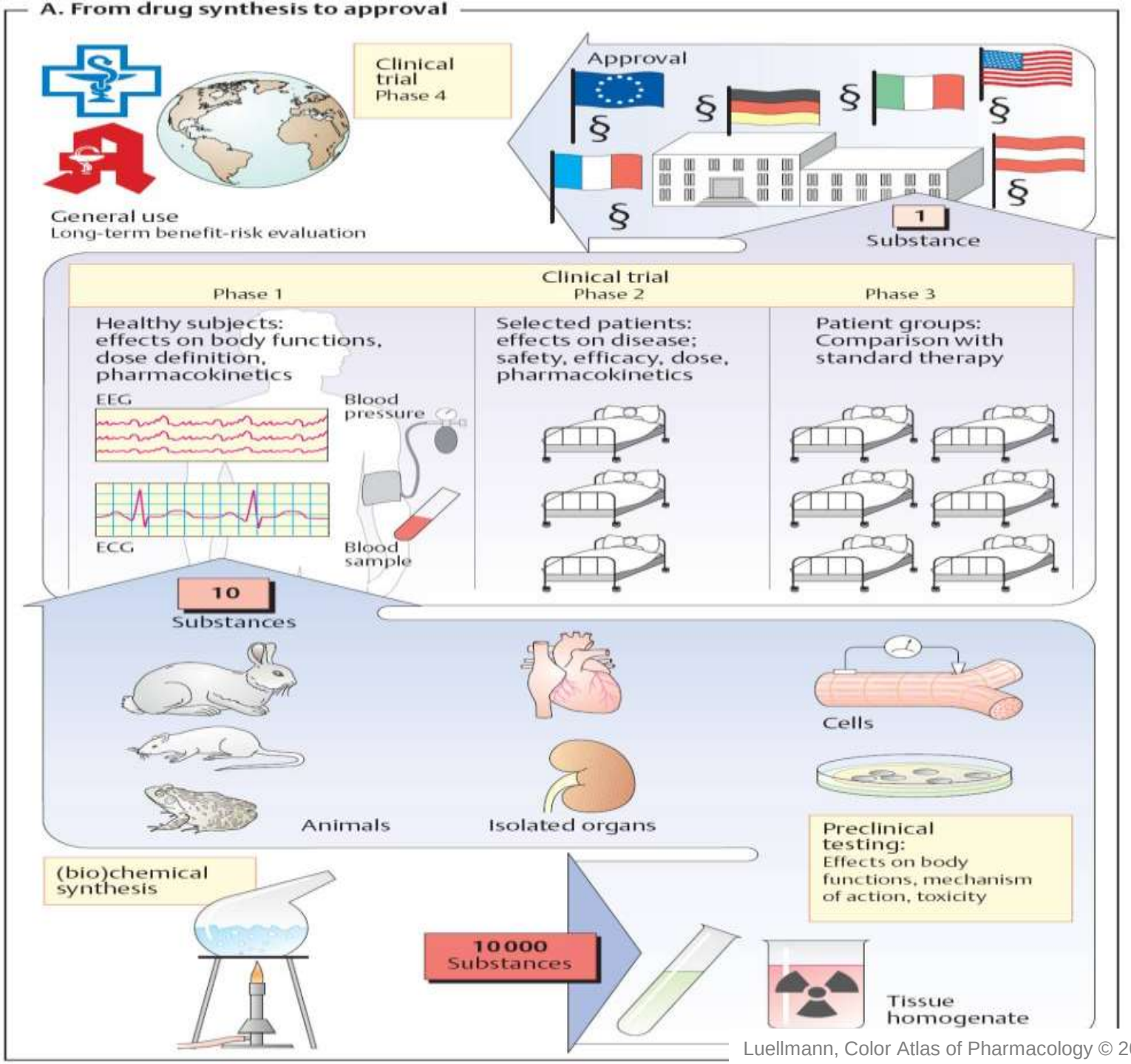


Clinical Trial Design

- **Eligibility criteria: Can range from general (age, sex, type of cancer) to specific (prior treatment, tumor characteristics, blood cell counts, organ function); eligibility criteria also vary with trial phase**
  - **Varies with protocol and phases**
- **Endpoint: Measurable outcome that indicates an intervention's effectiveness**

  -- primary endpoint

  -- secondary endpoint

Adapted from NCI

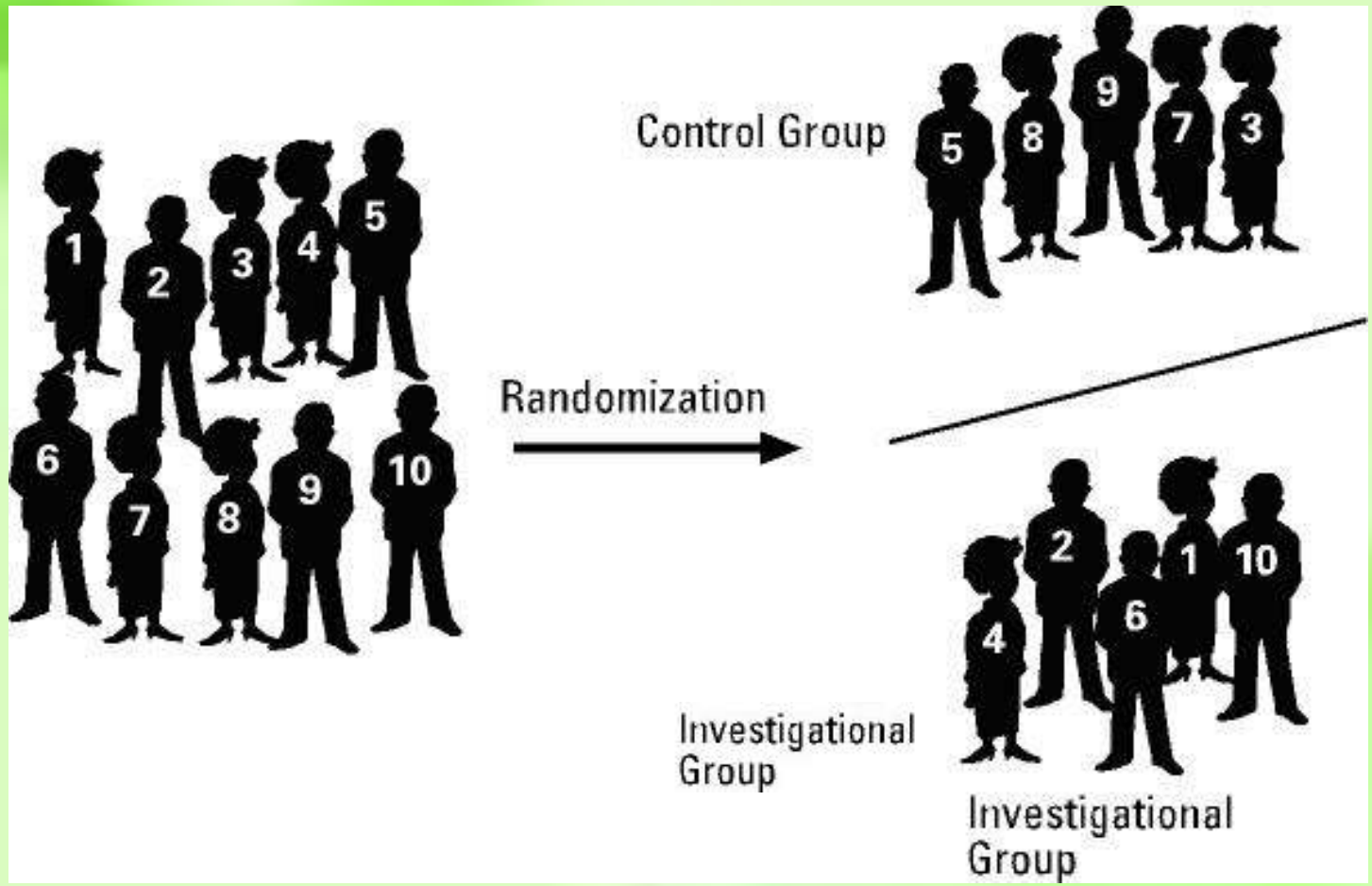
Clinical Trial Design

- **Randomization:**

  A method used to prevent bias in research; a computer or a table of random numbers generates treatment assignments, and participants have an equal chance to be assigned to one of two or more groups (e.g., the control group or the investigational group)

Adapted from NCI

Randomization



Adapted from NCI

Clinical Trial Design

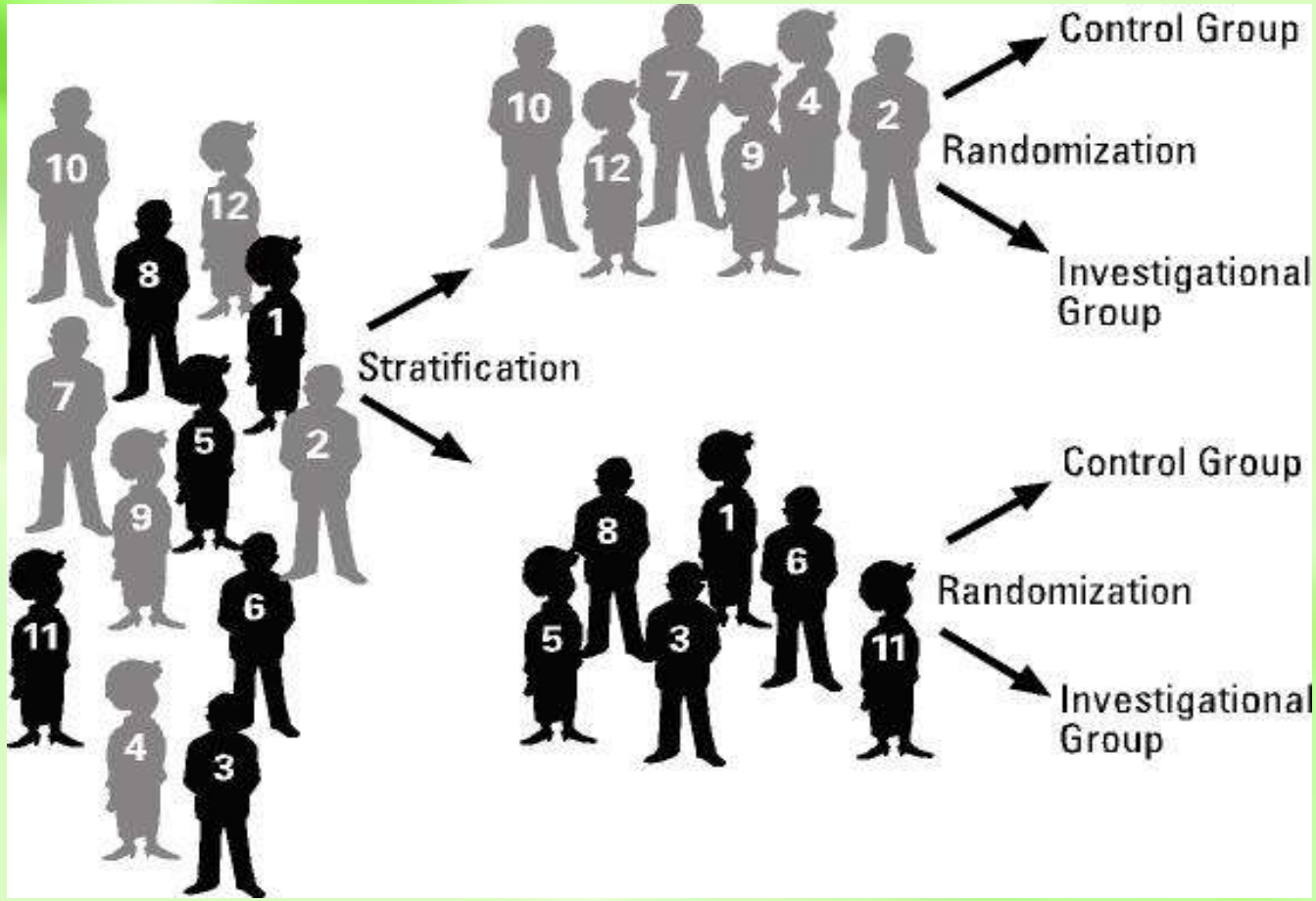
- **Stratification:**

  Categorizing subjects into subgroups by specific characteristics

  – **Enables researchers to look into separate subgroups to see whether differences exist**

Adapted from NCI

Stratification



Adapted from NCI

Protecting Participants Before a Trial

- Scientific review by sponsoring organization
- Institutional review board (IRB) approval
- Informed consent

Adapted from NCI

Protecting Participants During a Clinical Trial

- Institutional review boards (IRBs)
- Data and safety monitoring boards (DSMBs)
  - An independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing
  - Minimize risks
  - Ensure integrity of data
  - Can stop study if necessary

Adapted from NCI

Important issues of investigational products

- Developing tracking systems
- Storage, accountability and transport
- Compliance and non-compliance
- Randomization, codes and code breaks

Nuremberg Code (1947)
紐倫堡宣言

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

Nuremberg Code (1947)
紐倫堡宣言

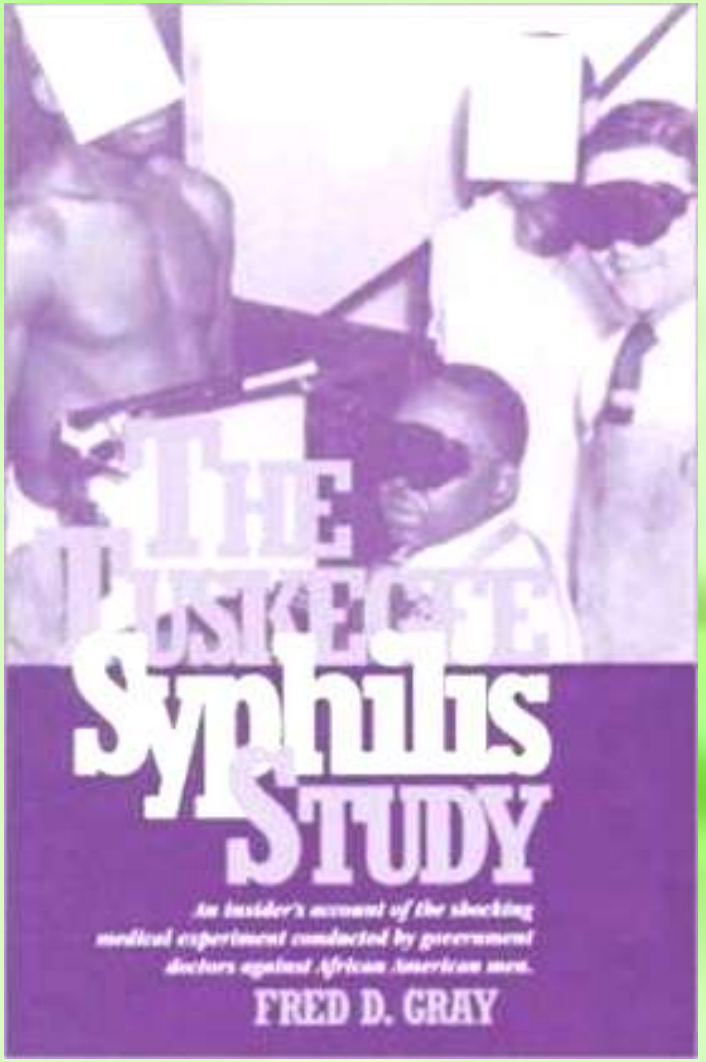
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.
8. The experiment should be conducted only by scientifically qualified persons.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Declaration of Helsinki (1964)
赫爾辛基宣言

- 2000年中文版
  - 甲.引言
  - 乙.醫學研究之基本原則
  - 丙.兼顧醫療照護的醫學研究之附加原則
- 主要精神
  - 自主
  - 有益
- No legal force

2000 中文版
赫爾辛基

Tuskegee Trial (1932-1972)



Tuskegee Trial (1932-1972)

- In 1932, The America Government conducted a study
- 399 young healthy black males who were part of an U.S. Public Health Service experiment of black men in the late stages of syphilis
- The most part were illiterate, and they were never told of what disease they were suffering from
- Doctors had no intention of curing them of syphilis at all
- By the end of the study in 1972, only 74 of the test subjects were alive. 28 of the original 399 men had died of syphilis, 100 were dead of related complications, 40 of their wives had been infected, and 19 of their children had been born with congenital syphilis.

Tuskegee Trial (1932-1972)

- In 1966, a venereal disease investigator named Peter Buxtun learned of the study and sent a letter to his department director expressing his moral concerns regarding the experiment.
- The US Center for Disease Control (CDC) responded by asserting that the study must continue until all of the patients had died, allowing the researchers the opportunity to autopsy all of the patients.
- This conclusion was supported by the National Medical Association and the American Medical Association.

Tuskegee Trial (1932-1972)

- On 25 July 1972, an article appeared in the *Washington Star* newspaper condemning the Tuskegee study and its practices. The story appeared on the front page of the New York Times the following day.
- The National Association for the Advancement of Colored People (NAACP) won a $9 million settlement on behalf of the victims, and the sum was divided among the survivors
- On 16 May 1997, President Clinton apologized to the surviving Tuskegee patients on behalf of the nation

The Tuskegee Syphilis Experiment

Belmont Report (1978)

- 前美國衛生教育福利部 (Department of Health and Human Services的前身)
- 發表的報告Ethical Principles and Guidelines for the Protection of Human Subjects of Research
- 3 principles
  - Respect for persons 對人的尊重
  - Beneficence 行善
  - Justice 公平正義
- 人體試驗委員會(IRB)必須參考的規範
  - 1981 Federal Regulation：建議IRB法規

NIH (National Institutes of Health) & Clinical Research

- **http://clinicalresearch.nih.gov/**
- **http://clinicaltrials.gov/**

Good Clinical Practice (GCP)

(ICH I.24)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

What is ICH GCP?

- ICH (國際醫藥法規協和會)
  - International Conference on Harmonization
- **1990's initiative involving regulatory authorities of Europe, Japan and USA and experts from the pharmaceutical industry**
- **Consideration taken of current GCP practices of EU, Japan, USA, Australia, Canada, Nordic Countries and WHO**

ICH/GCP Steering Committee

- US Food & Drug Administration
- European Commission
- Japanese Ministry of Health & Welfare
- The expert working groups are concentrating on
  - Quality
  - Safety
  - Efficacy

ICH/GCP

The guideline was developed with consideration of GCP practices in:

- European Union
- United States
- Australia
- The Nordic Countries
- World Health Organization
- Japan
- Canada

目的

- 保障受試者之權利與安全
  - 受試者同意書
  - 人體試驗委員會
  - 不良反應通報
- 確保試驗資料之可信度與正確性
  - 試驗計畫書之遵守
  - 正確而完整的文件記錄
  - 試驗藥品管理
  - 試驗監測
  - 檔案建立

Background

	藥品優良臨床試驗規範（GCP)-初版	藥品優良臨床試驗規範（GCP）	藥品優良臨床試驗準則
施行日期	July 1, 1997	Jan 1, 2003	Jan 6, 2005
依據	WHO, EU, JP GCP	參考國際醫藥法規協和會(ICH)E6修訂	
法規性質	行政規範	行政規範	法規命令 (依藥事法第42條第2項)
章節	10章73條	8章232條	8章123條
對象	查驗登記用之藥品臨床試驗—應遵守 學術研究用之藥品臨床試驗—建議參考		

內容

藥品優良臨床試驗規範（GCP）

- 名詞解釋
- 基本方針
- 人體試驗委員會
- 試驗主持人
- 試驗委託者
- 臨床試驗計畫書
- 試驗主持人手冊
- 試驗執行之必要文件

藥品優良臨床試驗準則

- 總則
- 受試者保護
- 人體試驗委員會
- 試驗主持人
- 試驗委託者
- 臨床試驗之申請與審查
- 試驗進行應遵行事項
- 附則

人體試驗委員會
(IRB, institutional review board)

- 委員至少五人，其中至少一位為非科學背景者，且至少一位為非試驗機構成員
- 人體試驗委員會之組成及運作，應符合主管機關公告之規定
- 最大目的在保護受試者
- 整個研究過程均要追踪和審查，以確保受試者的福祉與安全

受試者同意書

藥品優良臨床試驗準則

- 第五條　同意權之行使
  - 受試者為無行為能力人者，由法定代理人代為之
  - 受試者為限制行為能力者，應得法定代理人之同意
  - 受試者雖非無行為能力或限制行為能力者，但因無意識或精神錯亂無法自行為之時，由有同意權之人為之
  - 有同意權人為配偶及同居之親屬

受試者同意書

藥品優良臨床試驗準則

- 第二十一條　見證人

受試者、法定代理人或有同意權之人皆無法閱讀時，應由見證人在場參與所有有關受試者同意書之討論。

見證人應閱讀受試者同意書及提供受試者之任何其他書面資料，以見證主持人或其指定之人員已經確切地將其內容向受試者法定代理人或有同意權之人解釋，並確定其了解同意書之內容。

- 受試者、法定代理人或有同意權之人，仍應於同意書親筆簽名並載明日期
- 見證人確定受試者、法定代理人或有同意權之人之同意完全出於自由意願後，應於受試者同意書簽名並載明日期
- 試驗相關人員不得為見證人

Retain documents

- Seven years for identification record by the investigator
- Ten years for patient original records by the institution

Investigational Drug Management

- **Drug Accountability(試驗藥物流向管理)**
  - **Record of Delivery and Returning of Investigational Drug**
  - **Record of Drug Used by Trial Subjects**
- **Investigational Drug**
- **Storage**

Serious Adverse Event (SAE)

- **Any untoward medical occurrence that results in (at any dose)**
  - **Death**
  - **Life threatening**
  - **Inpatient hospitalization or prolongation existing hospitalization**
  - **Persistent or significant disability / incapacity**
  - **Congenital anomaly / birth defect**
  - **Requires medical intervention to prevent permanent impairment or damage**

Reporting of SAE

- Any SAE must be reported immediately to the trial sponsor
- Death or life threatening:
  - The investigator or sponsor should report to IRB and DOH in writing within 7 calendar days.
- For other SAE:

  The investigator or sponsor should report any other SAE to IRB and DOH in writing within 15 calendar days.

Inspection

Inspection conducted by DOH

- Definition:

  The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

GCP Implementation

- ***Common Discrepancies at Inspections***
  - **Eligibility of inclusion/exclusion criteria**
  - **CRF signed and dated**
  - **Incompleteness of medical record**
  - **Incompleteness of CRF**
  - **Lack of source documents**
  - **Lack of lab data**
  - **Incompleteness of AE/SAE record**
  - **Incompleteness of concomitant medicine record**
  - **Incompleteness of investigational drug shipment**
  - **Discrepancies of CT record between investigators and radiologists**

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TAIPEI 台北市立萬芳醫院

- 接收及清點研究用藥品
- 儲存研究用藥品
- 研究用藥品的給予
- 研究用藥品的餘藥回收及銷毀

藥師職責

接收及清點研究用藥品

- 一旦接收研究用藥品，清點接收的藥量，並確認包裝上的藥品資訊是否與內容物符合，包括：
  - 數量
  - 批號
  - 每一瓶/容器中的量(若容易確認的話)
- 若清點之後有發現不一致，馬上通知試驗委託者。
- 若試驗委託者有提供到研究用藥品簽收單，要有適當的簽署並回覆給試驗委託者/CRO。
- 要保留一份相關法規要求文件的影印本。

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儲存研究用藥品

- 儲存研究用藥品在安全且設有門禁的地方(藥櫃必須上鎖)，依據試驗計劃書中或試驗委託者所提供的相關文件中詳細的規定儲存藥品。確認研究用藥品有儲存在適當溫度，並定期記錄溫度、溼度。維持儲存區域的溫度。

  - 對管制藥品要遵循特定法規要求。

  - 確認試驗隨機編號。

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研究用藥品的給予

- 確認每個排定的時間點時研究用藥品均有給予，而且研究用藥品流通管理表也要完整填妥。
- 須建檔的文件包括：
- 給予的研究用藥品數量(及批號、保存期限，若可行)
- 給予的每個研究用藥品名稱
- 受試者編號
- 受試者代號
- 研究用藥品給予的日期(及時間，若可行)
- 研究用藥品餘藥回收的日期及時間。
- 研究用藥品餘藥回收的數量
- 研究用藥品經受試者使用之後，若可以的話必須回收所有用過的藥瓶/單位包裝給試驗藥師。若任何的藥瓶有遺漏，必須記錄其理由。
- 若受試者使用的藥量跟預期的餘藥數量不符時，必須記錄理由。
- 若有試驗計畫差異狀況，必須進行稽核監測，給予文件記錄。
- 確認研究用藥品有在保存期間內給予。
- 若因為必要而必須緊急破壞研究用藥品的盲性試驗，必須記錄詳細情形。

臨床試驗門住診發藥流程

受試者經確認符合試驗條件後，進入試驗。

↓

研究護士撥打IVRs系統，或其他計劃書所載之方式，取得組別及研究用產品之編號。請主持醫師將受試者的組別及研究用產品編號，手寫至試驗專用處方箋及病歷、個案報告書上。

↓

研究護士取得專用處方箋後，聯絡試驗藥師，由試驗藥師將受試者的研究用產品組別及編號記錄在Dispensing / Return Log上。若有其他與服藥順從性相關之內容，可視需要由試驗主持人或研究護士填寫。

↓

研究護士會與受試者親自至藥局，將處方箋交給試驗藥師。試驗藥局服務時間為週一至週五早上九點至下午五點。逾期恕不受理！

↓

試驗藥師取得專用處方箋後，將核對受試者編號並根據處方籤的研究用產品編號，拿取研究用產品。

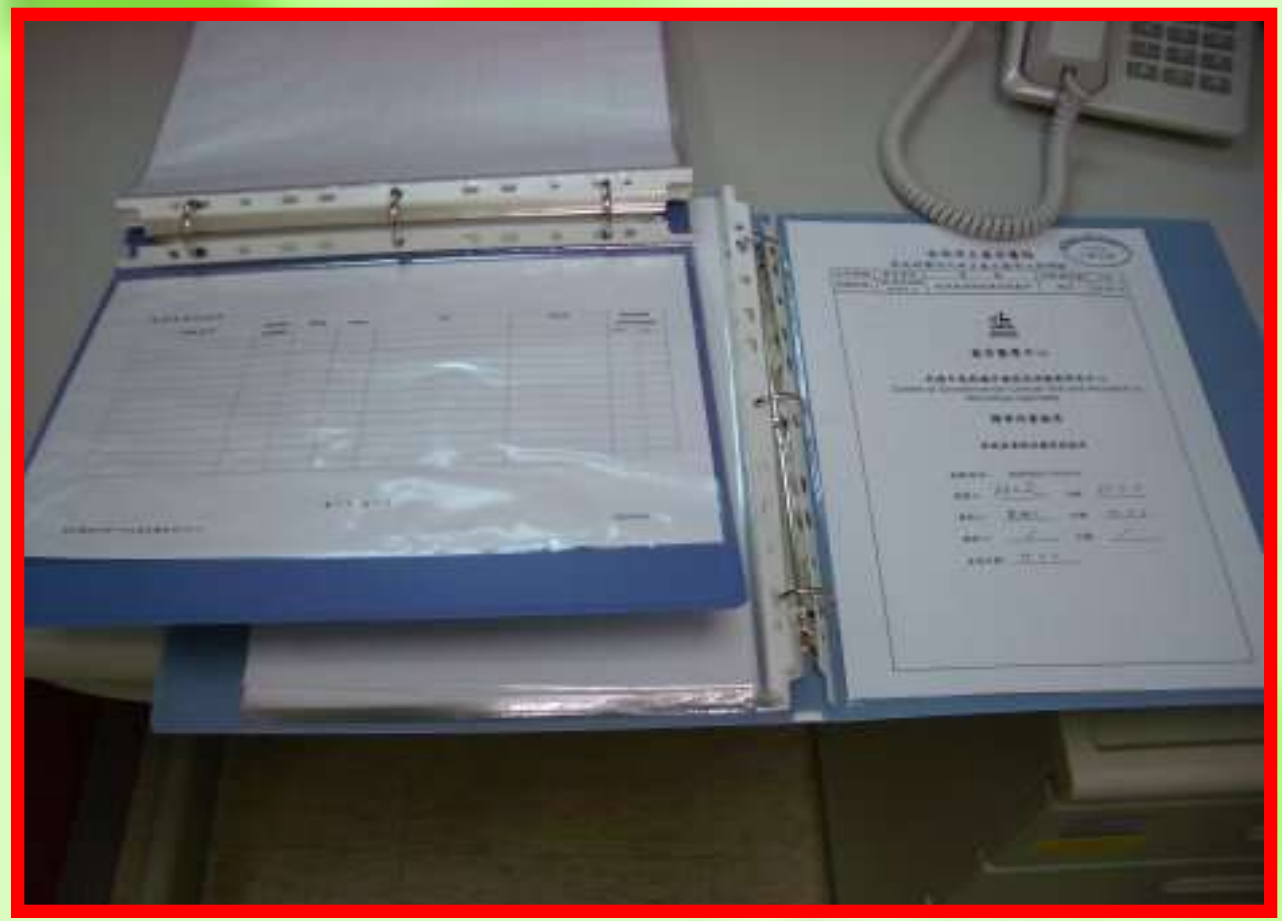
↓

請試驗藥師與研究護士共同核對所拿取的研究用產品之組別及編號，並填寫Dispensing / Return Log。
(提醒：請撕下一張在藥盒上的貼紙標籤，貼於Dispensing / Return Log上之Medication Number空格中)

↓

確認後，由試驗藥師將研究用產品交給研究護士及受試者，並衛教受試者。

藥師職責



⇐ 流向管理表:

patient level

site level

Placebo 製作
(Harborview Medical Center)

Placebo 製作
(Harborview Medical Center)

臨床試驗還藥流程

由研究護士聯絡受試者返診，將剩餘的研究用產品或空瓶攜回。

研究護士與試驗藥師共同清點剩餘之研究用產品數量，並確實填寫試驗藥物流向管理表。

試驗藥師先將受試者所歸還的研究用產品、藥瓶存放於上鎖的櫃子中保管。

試驗期間，試驗委託者會定期派Monitor或Auditor至藥局抽點研究用產品數量，是否符合Dispensing / Return Log的紀錄。

試驗進行中或試驗終止後試驗委託者會定期派員至臨床試驗藥局來清點剩餘之研究用產品，確認無誤後會一併回收。若剩餘之研究用產品要由試驗藥局進行銷毀，必須事先經由試驗委託者授權許可。

研究用藥品管理表

Protocol #: _____

Protocol title: _____

_____

_____

_____

Investigational article received

Bottles ☐ Blister packs ☐ Capsules ☐

Ampules ☐ Patches ☐ Other (describe) ☐

Date of receipt: _____/_____/_____ Received by: _____

Amount: _____ Lot number: _____

Amount: _____ Lot number: _____

Investigational article dispensing record:

Pt.#	Pt. initials	Number dispensed	Number used	Number returned	OK? Y/N	Comments

For investigational article not returned or accounted for, complete the following:

Pt.#	Pt. initials	Reason

Date that all investigational articles was returned to sponsor Date ____/____/____

Signature of person completing this form: _____ Date ____/____/____

台北市立萬芳醫院

卓越神經醫學專科臨床試驗與研究中心

Center of Excellence for Clinical Trial and Research in Neurology Specialty

藥櫃溫濕度紀錄表

Investigator Name: Temperature Limits: _____

Site Number:_____ Temperature Model Number _____

Material stored (medication or blood samples): Study Medications

Date	Time	Temperatures(℃)			Humidity %	Performed By/DATE	Is temperature within limits? (Y/N)	If No, record actions taken (see note below)
		Actual °C	Minimum °C	Maximum °C				

NOTE: Please record amount of time at this temperature, when the temperature came back within limits and actions required if any. Please contact your Study Monitor.

Reviewer Signature:_____ Date:_____

Review Question 1

- 依據赫爾辛基宣言，試驗主持人進行研究時應以誰的利益爲主要考量？

1. 醫院(機構)
2. 人體試驗委員會(IRB)
3. 社會國家
4. 參與試驗的受試者

Review Question 2

- 貝蒙報告 (Belmont Report) 中包括哪三個倫理原則？

1. 尊重個人，行善，公正
2. 尊重隱私，互助，誠信
3. 尊重法規，人道，公正
4. 尊重隱私，誠信，公正

Review Question 3

- 人體試驗委員會 (IRB) 爲什麼該關心調查研究(Survey research) 之回覆比率 (response rate)?

1. 低的回覆比率可以改變研究的風險/利益分析之結果
2. 提高回覆比率是很昂貴的
3. 回覆比率之計算可能會算錯
4. 回覆比率過高會增加受試者之風險

Review Question 4

- 下列有關 phase I 腫瘤藥物試驗之敘述，何者正確？

1. 試驗目的爲安全性研究，對受試者無直接益處
2. 參與這類試驗的後試者中約有10%被治癒
3. 這類試驗主要受試者爲健康人
4. 這類試驗的研究設計是無法更改的

Review Question 5

- 人體試驗委員會 (IRB) 審查試驗發現有設計不良時，應採取下列何種態度？

1. 只要受試者的風險是低的，就可以核准
2. 以試驗所涉的重要性作爲是否核准的主要考量
3. 不核准，核准不良試驗設計的研究是違反紐倫堡宣言
4. 核准，有品質不佳的研究總比沒有研究好

Thank You for Your Attention!!!!