CT 02: 臨床試驗倫理
Ethics in Clinical Trials

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Fundamental Point I

Investigators and sponsors of clinical trials have ethical obligations to trial participants and to science and medicine.

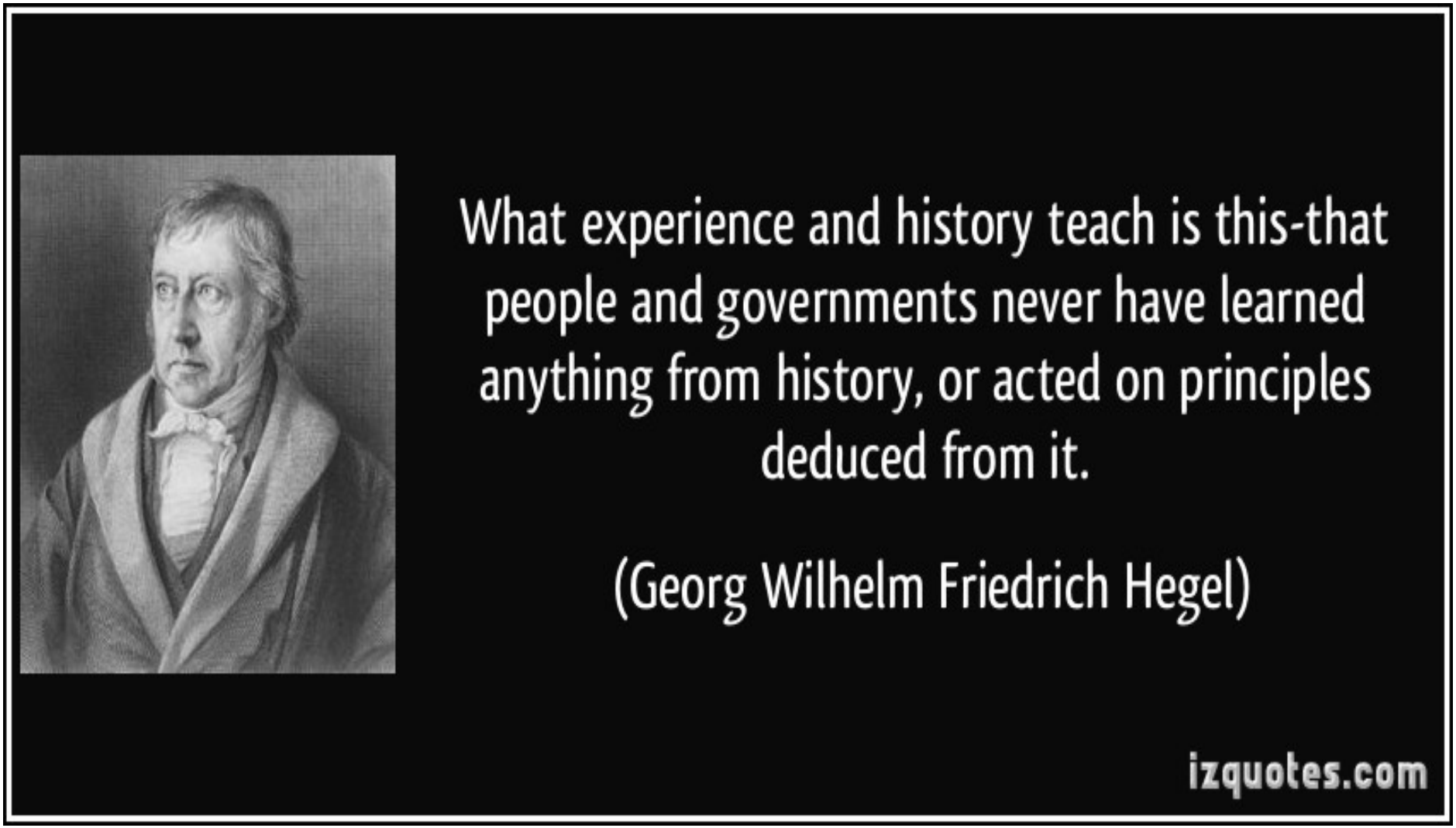


圖 1: Georg W.F. Hegel (1770-1831)

法律, 倫理, 道德

- 道德: 個人或社會對個人行為和觀念的期待價值, 約束個人.
- 倫理: 團體內人與人之間所共同遵守的規範, 人與人之間相互約束.
- 法律: 公民必須遵守共同的最低標準約定, 具約束力與效力,
  這些約定透過一定機制而制定, 且由國家公權力控制與執行.

醫學倫理

- 醫學倫理規範乃醫療專業人員依其專業知識與技術, 為病人提供醫療服務, 憑其職業自覺所應遵循的心理約束及道德規範.

Ethical Guiding Principles

- Respect for autonomy of each individual (自主原則)

  Self-determination
- Beneficence (行善原則)

  Maximize possible benefits
- Nonmaleficence (不傷害原則)

  Do no harm, Minimize possible harm
- Truth-telling (告知實情原則)
- Justice (公平正義原則)

  Equitable distribution
- Promising-keeping (誠信原則, 遵守義務原則)
- Privacy (保密原則)

目錄

Development of Ethical Guidelines

- 1803: Percival's Medical Ethics
- 1900: The Directive on Human Experimentation
- 1946: Nuremburg "Doctor's Trial" + Nuremberg Code
- 1948: UN Universal Declaration of Human Rights
- 1964: Declaration of Helsinki*
- 1979: Belmont Report
- 1981: DHHS Regulations
- 1982: International Ethical Guidelines for Biomedical Research Involving Human Subjects*

*revised several times

World War II: 日本細菌戰試驗 731 部隊

- 訓練新進軍醫進行戰俘活體解剖, 最後殺死他們, 其主要目的似不在磨練醫師的技術與經驗, 而在使其麻木.
- 蓄意感染疾病: 如瘟疫, 霍亂, 流行性出血熱, 肺結核, 傷寒, 破傷風, 炭疽病, 馬鼻疽病, 斑疹傷寒及痢疾, 目的在尋找疾病的病原體, 評估其傳染能力, 挑選更具傳染能力的品種, 探查細菌武器效果.
- 試驗非標準化的療法: 戰俘接受非標準化, 未經證實, 非正規療法的過程中死去. 例如令戰俘手腳凍瘡, 再浸泡攝氏五十度之熱水.
- 瞭解人體的耐受程度: 吸入瓦斯毒氣, 降低氣壓, 靜脈注射空氣, 製造失血, 禁絕食物, 飲水, 試驗人體能承受之電流或電壓, 以人體試驗新武器.

WWII: Nazi War Crimes I

- 二次大戰時德國以真人做試驗:
  - 低氧試驗: 200 人, 40% 死亡
  - 低溫試驗: 300 人, 30% 死亡
  - 化學戰劑試驗: 25% 死亡

WWII: Nazi War Crimes II

- (A) High-Altitude Experiments
- (B) Freezing Experiments
- (C) Malaria Experiments
- (D) Lost (Mustard) Gas Experiments
- (E) Sulfanilamide Experiments
- (F) Bone, Muscle, and Nerve Regeneration and Bone Transplantation
- (G) Sea-Water Experiments
- (H) Epidemic Jaundice Experiments
- (I) Sterilization Experiments
- (J) Spotted Fever (Fleckfieber) Experiments
- (K) Experiments with Poison
- (L) Incendiary Bomb Experiments

圖 2: 納粹人體實驗: 低溫實驗

圖 3: Nuremberg Physicians' Trial

- All 23 German Scientists pleaded “not guilty”.
  - Their experiments differed little from previous American or German ones.
  - Furthermore, they showed that no international law or informal statement differentiated between legal and illegal human experimentation.
- 5 acquitted.
- 11 prison sentences.
- 7 sentenced to death by hanging sentences.

圖 4: Sentences Carried Out following Doctors' Trial in Nuremberg (1947)

The Nuremberg Code (1947)

- Voluntary participation
  - legal capacity to give consent
  - free of force, fraud, deceit, duress
  - free to withdraw at any time
- Fruitful results for society
  - unprocurable by other means
  - conducted by qualified persons
- Avoid unnecessary risk to subjects
  - risk not greater than importance of RQ

US: Willowbrook State School, Staten Island, New York, 1950s

- 1950-1972, Willowbrook State School, Staten Island, New York.
- 紐約大學 Saul Krugman 向精神殘疾兒童的父母保證,
  如果簽訂一張聲稱“接種疫苗”的程序知情同意書,
  學校就會招收兒童.
- 實際上, 程序中包括通過讓他們進食肝炎患者糞便中的提取物,
  故意把孩子染上病毒性肝炎.

US: Sloan-Kettering Institute (1952)

- 1952, Sloan-Kettering Institute
- US NIH 贊助的實驗
- Southam 向 Ohio State 監獄的犯人注射活癌症細胞, 半數是黑人.
- 在 Sloan-Kettering, 300 名健康女性被注射活癌症細胞.
- 醫生說, 受試者當時知道可能會導致癌症.

Jewish Chronic Disease Hospital Cancer Experiments (1962)

- 1962, Jewish Chronic Disease Hospital.
- U.S.P.H.S. and American Cancer Society 提供研究經費.
- Southam 給 22 名年長病人注射活的癌症細胞.
- 未告知受試者注射活的癌症細胞.
  - 因為受試者對癌症無知且恐懼.
  - 避免引起受試者不安與焦慮.
- 起初醫院的管理層試圖掩蓋這項實驗.
- 最終 NY medical licensing board 給 Southam 判了一年緩刑.
- 兩年後, American Cancer Society 選舉 Southam 為副會長.

1964: Declaration of Helsinki

- 赫爾辛基宣言.
- 世界醫學會於紐倫堡大審之後,
  體認到有必要制定一範圍更廣更清楚的規範.
- 於 1964 年召開 世界醫學大會 (WMA General Assembly)
  制定了 赫爾辛基宣言.
- 副標題: "醫師參與涉人體試驗之生物醫學研究的行為指導建議"
  (Recommendations Guiding Physicians In
  Biomedical Research Involving Human Subjects).
- 此宣言至今已歷幾次修改, 其中以 2000 年所作修改範圍最大.
- Seventh revision (2013).

1966: IRB

- U.S. Surgeon General
  - Mandated peer review by a committee.
  - Required informed consent of research subjects.
- The Office for Protection from Research Risks (OPRR) was established in National Institutes of Health.
- Institutional Review Boards (IRB) were required.

Henry K. Beeche (1904-1976) 美國麻醉醫師

- Ethics and Clinical Research, NEJM, 1966.
- 在醫療試驗中的不道德行為.
- 許多醫學研究對受試者造成的嚴重傷害,
  包括死亡, 以及不必要的傷殘.
- 這些研究居然赤裸裸地刊登在著名的學刊上!
- 相信未被刊登和受到隱瞞的傷害更以倍數遠超乎這些數字.

Tuskegee Syphilis Study (1932-72) I

- 1932-1972, 美國公共衛生署 (USPHS) 經費支助.
- Macom County, AL.
- 600 poor, illiterate, black men.
- 339 黑人 w/ 梅毒, 201 黑人 w/o 梅毒 .
- 1932 年, arsenic 與 mercury 治療梅毒已有 22 年.
- 339 梅毒的貧困男性黑人被告知在接受治療.
- Never Treated!!

Tuskegee Syphilis Study (1932-72) II

Tuskegee Syphilis Study (1932-72) III

Tuskegee Syphilis Study (1932-72) IV

- 1947: penicillin 成為治療梅毒的標準療法.
- 研究人員想看到梅毒在人體上的影響, 並未給予治療.
- 28 人死於梅毒, 100 人死於併發症,
  40 位妻子被傳染, 19 孩子有先天性梅毒.

Tuskegee Syphilis Study (1932-72) V

The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men.

Tuskegee Syphilis Study (1932-72) VI

- 1972, Heller, New York Times 媒體舉發.
- 1973 停止.
- 1997 美國總統 Clinton 公開道歉.

Tuskegee Syphilis Study (1932-72) VII

Tuskegee Syphilis Study (1932-72) VIII

"The United States government did something that was wrong–deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens... clearly racist."

President Bill Clinton apologizes to study survivors, May 16, 1997.

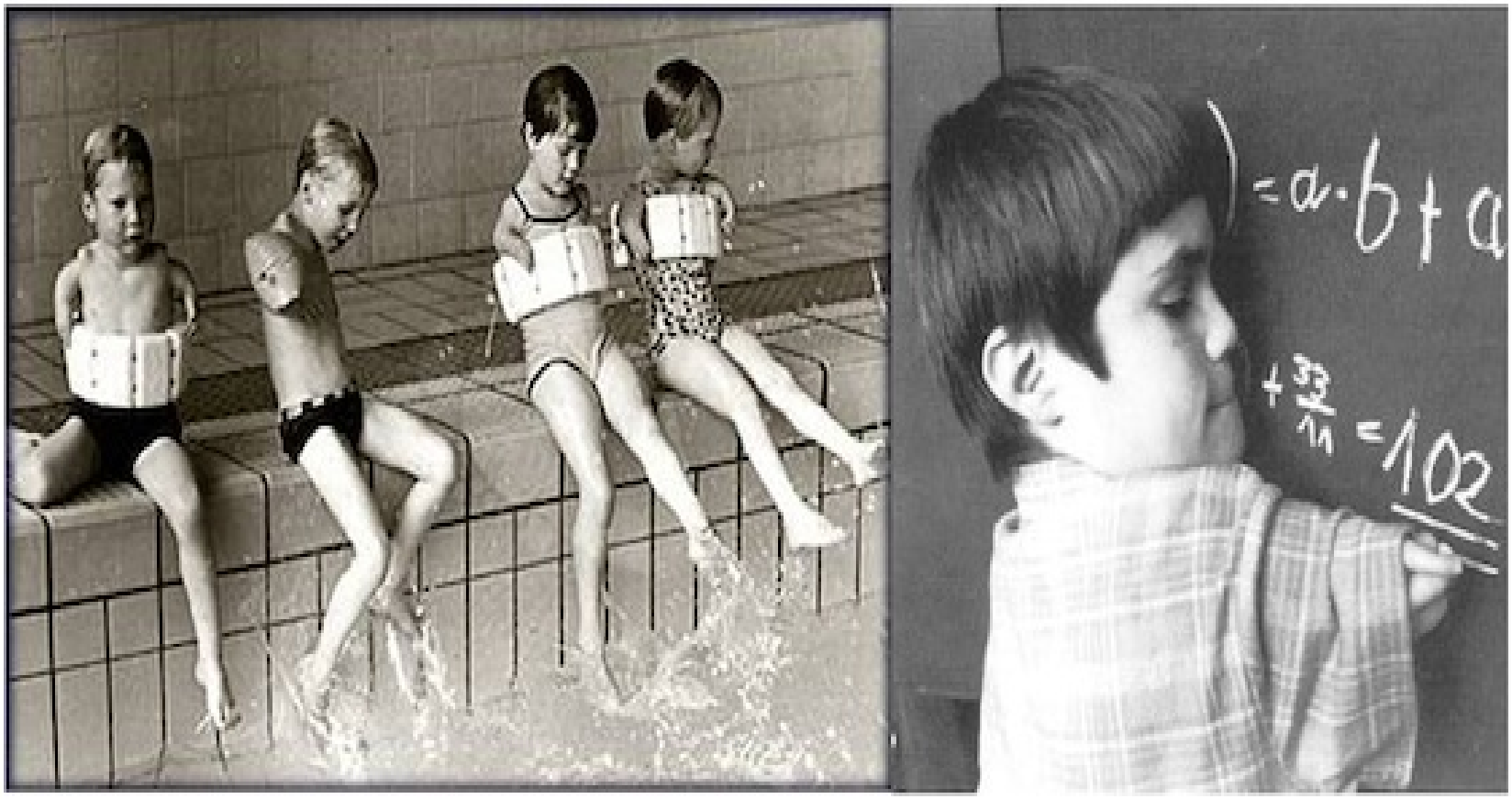
1979: Belmont Report

- Tuskegee Outcome
- 修改法令: 定出研究之倫理及法律上的基本要求 (IRB 同意函).
- 定出倫理原則.

The Thalidomide Tragedy, Early 1960s I

- 沙利竇邁 (thalidomide) 悲劇, 是 20 世紀最著名的藥害事件.
- 西德 Chemie Grunentha) 研發生產.
- 1957 在德國上市, 1958 在英國也獲准上市.
- 常用來舒緩產婦的孕吐症狀.
- 對動物胎兒發育不會造成嚴重的不良影響.
- 一直未經過 FDA 審查核准.
- 對人類造成海豹狀的畸形新生兒.
- 1961 揭露後, 估計約有 1 萬名嬰兒受害, 其中約一半存活.

The Thalidomide Tragedy, Early 1960s II



The Thalidomide Tragedy, Early 1960s III

- 真相揭發時引起媒體很大的轟動.
- 悲劇導致歐美修訂新藥上市許可的試驗流程與安全標準.
- 對於藥物管制規則的建立有很大的影響.

The Thalidomide Tragedy, Early 1960s IV

- The German drug company Grunenthal broke its fifty year silence.
- 2012: Thalidomide Manufacturer Finally Apologizes.
- Survivors Say It's Not Enough!

Jesse Gelsinger & U Penn (1999) I

- Jesse Gelsinger was the first person publicly identified as having died in a clinical trial for gene therapy.
- Ornithine transcarbamylase deficiency.
- X-linked genetic disease of the liver.
- Inability to metabolize ammonia.
- A clinical trial run by the University of Pennsylvania.
- Gelsinger was injected with an adenoviral vector carrying a corrected gene.
- Suffered a massive immune response triggered by the viral vector.
- He died at 18 years old.

Jesse Gelsinger & U Penn (1999) II

- Violate the exclusion criteria.
- Two patients also had experienced serious side effects from the gene therapy.
- Failure to disclose the deaths of monkeys given a similar treatment.

Ellen Roche & Johns Hopkins University (2001) I

- Ellen Roche was a lab technician at the JH Asthma Center.
- “Mechanisms of Deep Inspiration-Induced Airway Relaxation.” conducted by Permutt & Togias, funded by US NIH.
- She volunteered to participate in the experiment.
- Compensation for her participation: $365.
- She received ”Methacholine” challenges.
- ”Methacholine is a drug” induced a mild asthma attack.
- Roche had lost 1/3 of her lung capacity after inhalation.
- She died at 24 years old.

Ellen Roche & Johns Hopkins University (2001) II

- Hexamethonium was obtained from a chemical company labeled “for laboratory use only”.
- Hexamethonium is a “medication” approval by the FDA in the 1950’s to treat hypertension.
- Hexamethonium had been withdrawn in 1972.
- It cited the drug’s “substantial potential toxicity”.

Ellen Roche & Johns Hopkins University (2001) III

- IRB searched PubMed and did not show potential toxicity.
- Unfortunately, PubMed covers medical research, not FDA rulings.
- Investigation found literature on the dangers of hexamethonium in Google and Yahoo.
- Medical librarians found relevant information on MedLib listserv.
- The informed consent made the drug sound like routinely in use.
- The informed consent completely ignoring known pulmonary side effects.

法新葯臨床試大悲劇 (2016, Jan/Feb)

- 法國藥物實驗室 Biotrial 為葡萄牙藥物公司 Bial 而做的臨床試驗.
- 試驗一個化學口服藥物: 鎮痛和解除焦慮療效.
- 參與臨床試驗的共有 90 名志願者. 他們服用的劑量不盡相同.
- 目前試驗還在第一階段.
- 造成 6 名健康志願者住院觀察.
- 1 人腦死, 3 人腦部受不可逆之傷害, 1 人神經出狀況.

Requirements for an Ethical Clinical Trial

- Value: social or scientific value
- Scientific validity: use methods produces reliable results
- Fair selection of participants: avoids preferential access
- Favorable benefit/risk balance: min benefits outweigh max risks
- Independent review: review is not directly affiliated
- Informed consent: respects participant autonomy
- Respect for enrolled participants: porotect participants' rights

目錄

台灣相關指引

- 醫療法
- 藥品優良臨床試驗規範 (含報告)
- 新醫療技術人體試驗申請與審查作業程序 (含新醫療技術合併新醫療器材)
- 醫療機構人體試驗委員會組織及作業基準
- 人體研究倫理政策指引
- ...

2002: 藥品優良臨床試驗規範 I

- 第六三條: 臨床試驗之執行應符合赫爾辛基宣言的倫理原則, 並與藥品優良臨床試驗規範及相關法規要求一致.
- 第六四條: 在試驗開始前, 應權衡對個別之受試者和整體社會所造成可預期的危險, 不便與預期利益. 只有在預期利益超過風險時, 才應開始並持續此試驗.
- 第六五條: 受試者之權利, 安全與福祉是最重要之考量, 且應勝於科學及社會之利益.
- 第七一條: 受試者參與試驗前, 應獲得其自願給予之受試者同意書.
- 第七三條: 應保護可辨認受試者身分之紀錄的機密性, 符合相關法規對隱私及機密之規定.

目錄

Planning and Design I

- Ethics Training
  - All clinical trial investigators should have training in research ethics.

Planning and Design II

- Does the Question Require a Clinical Trial?
  - Cardial Arrthymia Supression (CAST): new drugs had more harms
  - quinidine (similar and older): design to prove harmful?
  - Marketing: non-inferiority, bioequivalence
  - Early Phase: same healthy volunteers to get more payment
  - SUPPORT: Surfactant, Positive Pressure, and Oxygenation Randomized Trial
  - premature infants: informed consent
  - less retinopathy with lower oxygen target
  - but unexpectedly higher mortality

Planning and Design III

- Randomization
  - ISIS-2 (International Study of Infarct Survival)
    - "Proof beyond reasonable doubt"
    - Streptokinase reduced mortality
      for patients 0-4 h after onset of pain
    - Information was shared with investigators
    - Randomized subjects to placebo?
  - Cluster trial: REDUCE MRSA Trial
    - Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA trial
    - Randomized cluster not subject: informed consent?
  - ESPRIT trial
    - Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin trial
    - Placebo or proven IIb/IIIa receptor inhibitor?

Planning and Design IV

- Control Group
  - SYMPLICT HTN-3: renal denervation
  - Placebo or Sham Control?

Planning and Design V

- Protection from Conflicts of Interest
- Informed Consent

Conflict of Interest (COI) 利益衝突

ACI occurs when “a professional judgement concerning a primary interest... tends to be unduly influenced by a secondary interest ...”

- Or better: “risk being unduly influenced...”

Conflict of Interest 利益衝突

Professional judgement unduly influenced by interests:

- Primary interest:
  - patients' health benefit
- secondary interest:
  - promotion
  - reputation
  - financial interests

    ownership, stock, gifts, consulting fees, travel, entertainment, research support
- Personal interest
- Institutional interest

Informed Consent 受試者同意書

- Purpose of trial
- Why asked to participate
- Visits, procedures, time and costs
- Discomforts or risks
- Benefits to subject and society
- Alternatives
- Confidentiality
- Return or withdraw
- Injury statement
- Contact for questions, problems
- Consent statement
- Signatures

Informed Consent 受試者同意書 I

藥品優良臨床試驗準則, 第一三八條:
提供給受試者之受試者同意書和任何其他書面資料應詮釋以下內容:

- (一) 臨床試驗為一種研究.
- (二) 試驗的目的.
- (三) 試驗治療及每個治療之隨機分配的機率.
- (四) 治療之程序, 包含所有侵入性行為.
- (五) 受試者的責任.
- (六) 臨床試驗中尚在試驗的部分.
- (七) 對受試者或對胚胎、嬰兒或哺乳中幼兒的可預期的危險或不便處.
- (八) 可合理預期的臨床利益. 如無預期的臨床利益, 應告知受試者.
- (九) 其它治療方式或療程, 及其可能的重要好處及風險.
- (十) 試驗相關損害發生時, 受試者可得到的補償及/或治療.

Informed Consent 受試者同意書 II

- (十一) 如有預期可獲得的酬勞, 需告知參與臨床試驗的受試者.
- (十二) 如有預期支付的費用, 需告知參與臨床試驗的受試者.
- (十三) 受試者為自願性參與試驗,
  可不同意參與試驗或隨時退出試驗, 而不受到處罰或損及其應得之利益.
- (十四) 經由簽署受試者同意書, 受試者即同意其原始醫療紀錄可直接受監測者,
  稽核者, 人體試驗委員會/獨立倫理委員會及衛生主管機關檢閱,
  以確保臨床試驗過程和/或數據符合相關法律及法規要求,
  且不違反受試者身分之機密性.
- (十五) 辨認受試者身分之紀錄應保密, 且在相關法律及法規要求下將不公開.
  如果發表試驗結果, 受試者的身分仍將保密.

Informed Consent 受試者同意書 III

- (十六) 如果新資訊可能影響受試者繼續參與臨床試驗的意願, 受試者或其法定代理人會被即時告知.
- (十七) 進一步獲知有關試驗之資訊和受試者權利的聯絡人, 及與試驗相關之傷害發生時的聯絡人.
- (十八) 受試者終止參與試驗之可預期的情況及理由.
- (十九) 受試者預計參與臨床試驗的時間.
- (二十) 大約的受試者人數.

Informed Consent: Special Population

- Children
- Fetus
- Mentally disabled persons
- Institutionalized persons
- Prisoners
- Unconscious or severely ill persons

Alternatives to Informed Consent

- Waiver of consent
  - life threatening situation
  - consent not possible
- Permission from parent or guardian
- Deferred informed consent
  - enter study without consent
  - later consent or participation terminated
- Prospective consent

Active Compression-Decompression for CPR, Schwab et al., 1994 I

- Randomized, controlled trial
- 860 persons with cardiac arrest
- ACD CPR or standard CPR
- Outcome = Discharged Alive

Active Compression-Decompression for CPR, Schwab et al., 1994 II

Active Compression-Decompression for CPR, Schwab et al., 1994 III

- No informed consent
- Trial halted by FDA

Prevention of AIDS in Africa

- Standard care for HIV + pregnant women in US
  - zidovudine orally before delivery
  - IV during labor, then orally for newborns
  - RR = 0.33 for infection in newborn
- Pregnant HIV + African women
  - randomized to oral AZT or placebo
  - most funded by US agencies
- Ethics: No Standard care in African women?

IRB

- Institutional Review Boards (IRB)
- 人體試驗委員會
- 獨立倫理委員會
- 醫療機構人體試驗委員會組織及作業準

IRB

Clinical research reviewed by IRB: Minimal Requirement!!

- All researches should be reviewed if investigators are not sure.
- Assure that risks are ethically acceptable.
- Minimized and reasonable in relation to expected benefits.
- Subject selection is equitable,
  and informed consent will be obtained from each subject.

赫爾辛基宣言第 13 點 (2000.10):

所有以人為對象之研究計畫都必須經過倫理審查委員會的審查及批准.

藥品優良臨床試驗規範

- 第七六條:

  人體試驗委員會/獨立倫理委員會應確保

  受試者的權利, 安全以及福祉受到保護.

  對可能包括易受傷害的受試者之試驗應特別留意.
- 建議人體試驗委員會/獨立倫理委員會組成人員應包含:
  - (一) 至少五位成員
  - (二) 至少一位專業為非科學背景人士
  - (三) 至少一位醫療機構/試驗機構外人士

Institutional Review Boards

- At least 5 members

  Not all male, female or one professional
- At least one concerns nonscientific issue

  Lawyer, clergyman, ethicist.
- One member not affiliated with institution where research to be conducted.

IRB: Exempted Review I

- Recoding data from subjects >= 18 y/o
- Noninvasive procedures routinely in practice
- Moderate exercise by healthy volunteer
- Actual patient clinical records have been collected or will be collected
- Minimal risk

IRB: Exempted Review II

- Surveys
- Interviews
- educational tests, unlinked biomaterials from public sources
- Studies of existing records

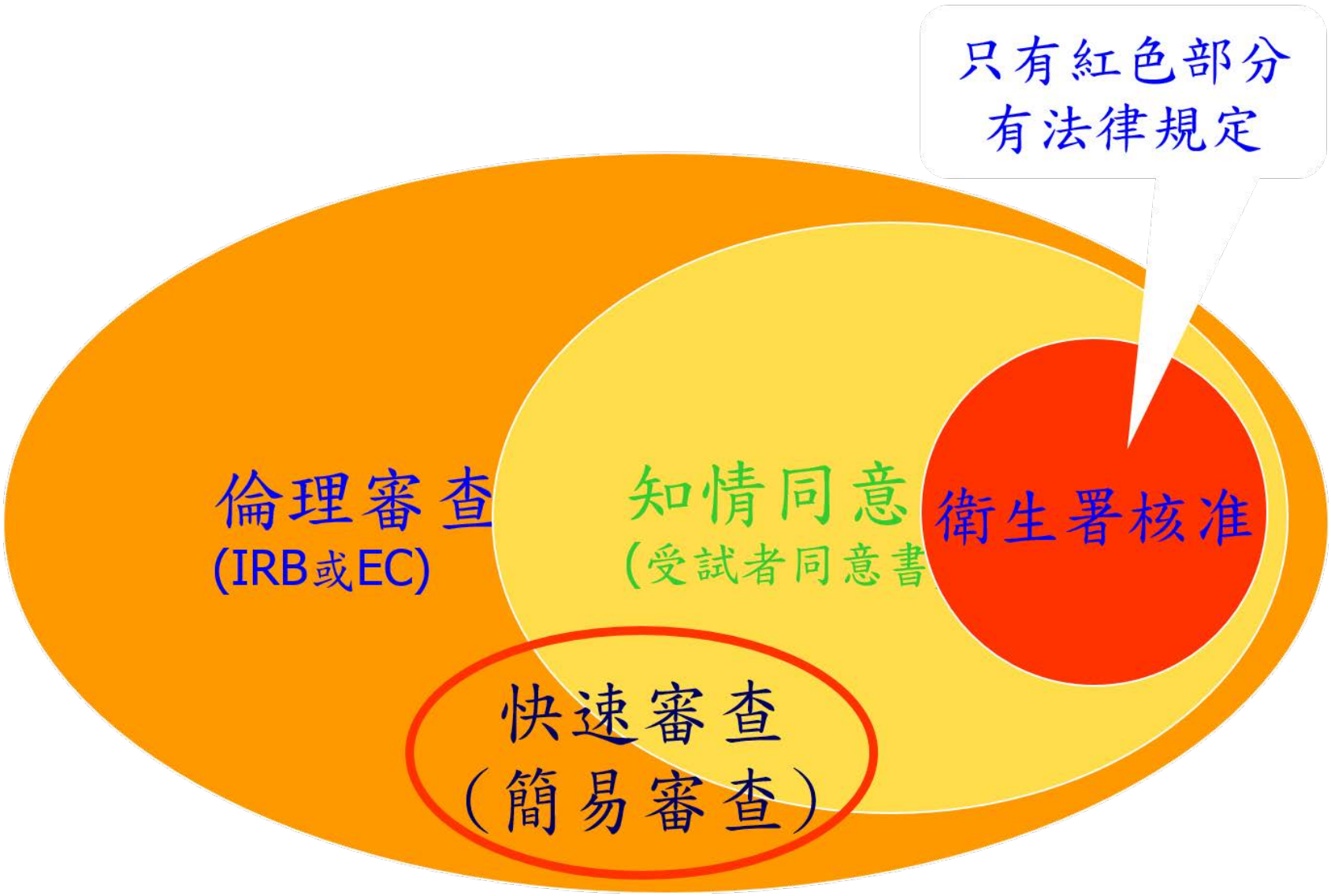
  provided that the data are collected in such a way

  that subjects cannot be identified.

IRB: Exempted Review III

- Except:
  - Sensitive issues such as
    drug abuse, sexual behavior or criminal activities.
  - Actual patient clinical records are used,
    IRB approrval is required.

IRB: Exempted Review IV



Conduct I

- Trials in Low- and Middle-Income Countries
  - Tamoxifen Trial:
  - Adjuvant oophorectomy and tamoxifen for breast cancer in Vietnamese and Chinese.
  - State-of-the-art treatment by US standards was not available and not likely to be available.
  - Generalization to US?
  - Obligation after trial?

Conduct II

- Recruitment
  - Pay finder's fees?
  - Pay to investigators?
  - Pay to study participants?

Conduct III

- Safety and Efficacy Monitoring
  - Alpha-Tocopherol Beta Carotene Cancer Prevention Study: harm
  - Inform to participants in the ongoing trials?

    A) Carotene and Retinol Efficacy Trial (CARET)

    B) Age-Related Eye Disease Study (AREDS)

Conduct IV

- Early Termination for Other Than Scientific or Safety Reasons
- CONVINCE:

  Controlled Onset Verapamil Investigation of Cardiovascular End Points Trial

Conduct V

- Privacy and Confidentiality
  - Genetic information?
  - Health Insurance discrimination?

Conduct VI

- Data Falsification
  - Bone morphogenetic protein-2 in fractures due to combat injuries (JBJS-B, 2009)
  - Lumpectomy and radiation therapy for breast cancer (NEJM, 1995)

Reporting I

- Publication Bias, Suppression, and Delays
  - Turner (NEJM 2008)
    - 74 trials
    - 37/38 favorable results published
    - 22/36 non-favorable results: not published
  - Heres et al. (Am J Psychiatry 2006):
    - 2nd-generation antipsychotic agents
    - 90% of published favorable results: industry sponsor's drug
  - (PRAISE-2)
    The Second Prospective Randomized Amlodipine Survival Evaluation 2 trial
    - Published resluts: 13 years after the trial was completed

Reporting II

- Conflicts of Interest and Publication
  - Many multi-investigator studies
  - 台大: 校長 楊泮池 & 毒理所 郭明良 & 口腔生物科學研究所 張正琪
    ...

Thanks!