History and Principles of ICH GCP

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Why Do Clinical Research?

- Satisfaction of answering important questions which will improve the health of our patients
- Status of researchers
- Skill advancement
- Professional advancement
- Salary and Job Security
History of Clinical Research Practice

• Prior to an actual set of guidelines to follow for good clinical (research) practice, clinical studies were dangerous and could result in serous disease, or possibly death.

• Until comparatively recently, Clinical Research Practice was dependent on the judgement of the clinician and to a lesser extent, their peers.

As far as clinical trials were concerned, this situation was felt to be unacceptable to regulators with responsibility for approval of new drugs from the drug industry. As a result, many national and international organizations provided versions of a guideline for clinical research.
6th century B.C.: Meat and vegetable experiment on young Jewish prisoners in Book of Daniel

~550 B.C. Babylonian Talmud (Niddah (30b)) tells story about Cleopatra, who, to settle an argument between two rabbis about how long it takes for male and female fetuses to develop, had slave girls impregnated and operated on at specified times to examine the development of the fetuses. The investigators reported that boys developed in 40 days and girls took 80 days.
1st Medical Clinical Trial - The “Scurvy Study”

In 1747, Dr. James Lind tested several scurvy treatments on crew members of the British naval ship Salisbury and discovered that lemons and oranges were most effective in treating the dreaded affliction.
James Lind’s trial

The following are the experiments. On the 20th of May 1747, I took twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have

2 got oranges and lemons
2 got cider
2 got vinegar
2 got elixir vitriol
2 got a concoction of spices, garlic, and mustard seeds
2 got sea water

Within six days, the 2 sailors given oranges and lemons became well
• 1832 Physician William Beaumont signs a **contract** with Alexis St. Martin, a long-term research subject with a permanent gastric fistula (hole to his stomach), whereby Mr. Martin **enlists in the Army** for one-year – with no military duties – and receives payment of $150.

• 1833 Physician William Beaumont publishes

  *research ethical guidelines, including **voluntary consent** and *right to withdraw*
Unethical  BUT Famous

• 1845-1849: J. Marion Sims, "the father of gynecology" performed multiple experimental surgeries on enslaved African women without the benefit of anesthesia.

• After suffering unimaginable pain, many lost their lives to infection. One woman was made to endure 34 experimental operations for a prolapsed uterus.

http://www.coax.net/people/lwf/jm_sims.htm
1900: Walter Reed’s Yellow Fever experiments

**Elements present in Yellow Fever Consent Form:**

- **Autonomy (respect for persons):** “gives his consent…for the reasons and under the conditions…”
- **Voluntary Participation:** “being in the enjoyment and exercise of his own free will”
- **Risks:** “In case of the development of yellow fever in him, that he endangers his life to a certain extent.”
- **Benefits:** “He will receive from the said commissioner the greatest care and the most skillful medical service.”
- **Compensation:** “he will receive the sum of $100 in American gold . . .”
- **Study withdrawal conditions:** “The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.”

16/09/56

History & principle of ICH GCP
<table>
<thead>
<tr>
<th>Patterns in Unethical Research</th>
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<tr>
<td>Research subjects are often members of vulnerable groups</td>
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<td>E.g., prisoners, immigrants, educationally or economically disadvantaged, those desperate for healthcare or other services.</td>
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<td>Subjects often have not given consent that is (a) fully voluntary or (b) fully informed.</td>
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<td>Researchers often do not do enough to minimize the risks to subjects.</td>
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1900: Berlin Code of Ethics. Royal Prussian Minister of Religion, Education, and Medical Affairs guaranteed that: "all medical interventions for other than diagnostic, healing, and immunization purposes, regardless of other legal or moral authorization are excluded under all circumstances if

- (1) the human subject is a minor or not competent due to other reasons;
- (2) the human subject has not given his unambiguous consent;
- (3) the consent is not preceded by a proper explanation of the possible negative consequences of the intervention."

http://www.geocities.com/artnscience/00berlincode.pdf

1906 Pure Food and Drug Act prohibits adulteration or misbranding of drugs, with the burden of proof on the FDA.
The Tuskegee Syphilis Study

• 1972 Peter J. Buxton, a law student and former public health worker, *exposes* the Tuskegee Study of Untreated Syphilis in the Negro Male to Jean Heller, an Associated Press reporter, who publishes an expose’. Thousands of physicians had been aware of the study previously. The study is terminated the following year. *(The study began in 1932. Penicillin was accepted for treatment of syphilis in 1943 and became widely available in 1951; it was withheld from the subjects. Between 1932 and 1974, 13 papers about the study were published in medical journals.)*
The Tuskegee Syphilis Study

• 1997 On behalf of the American people, President Bill Clinton apologizes to surviving Tuskegee experimental subjects

• 2004 Ernest Hendon, the last survivor of the Study dies.

• 2009 Last widow receiving health benefits dies.

http://www.examiningtuskegee.com/timeline.html
• 1938 Sales of Elixir Sulfanilamide are stopped after a poisonous ingredient kills 107 people, mostly children. Scandal leads to passage of the Food, Drug, and Cosmetic Act.

• 1938 Food, Drug, and Cosmetic Act
The law authorized the FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections.
The Belmont Report (April 18, 1979)

IRB Decision Matrix

**BENEFICENCE**
- Risk/Benefit Analysis
- Experimental Design
- Qualifications of PI

**JUSTICE**
- Subject selection
- Inclusion/exclusion
- Recruitment

**RESPECT FOR PERSONS**
- Informed consent
- Surrogate consent
- Assent
- Protection of subjects (especially vulnerable populations)

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Foundations for the ethical conduct of clinical research

• The Nuremberg Code (1947)
• The Declaration of Helsinki (1964)
• The Belmont Report (1979)
• International Conference on Harmonisation (ICH-GCP)
• International Standards Organization 14155
• Code of Federal Regulations
1962 Kefauver-Harris Drug Amendments to the Food, Drug and Cosmetic Act inspired by the thalidomide tragedy in Europe, require

- pharmaceutical companies to prove drug efficacy,
- firms to submit adverse reaction reports to the FDA,
- drug advertising to include complete Information about risks and benefits,
- informed consent from clinical study subjects.
Public Health Service Policy

- NIH Director and Surgeon General requested that the National Advisory Health Council review human subject protections
- Council recommended prior institutional review for PHS supported research to:
  - Protect the rights and welfare of the subjects
  - Assure appropriate methods of informed consent
  - Determine acceptable balance of risks and benefits

Adopted as Public Health Service policy in 1966

Beginnings of the Institutional Review Board (IRB)

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Prior to ICH - GCPs

• various nations worked in isolation to assure safety, quality and efficacy of pharmaceutical products

• Regulations and guidelines varied from nation to nation with separate clinical trials and standards

• These practices contributed to the
  – high costs of research and development
  – Thus, high cost of consumer healthcare
  – Concern of public expectation of little delay for new: - safe, efficacious Tx
History of ICH

In the 1980s, what is today the European Union began harmonising regulatory requirements. In 1989, Europe, Japan, and the United States began creating plans for harmonisation; ICH is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use was created in April 1990 at a meeting in Brussels.
Why harmonize?

• Avoid duplication in tests to conform to different regulatory guidelines
• More effective utilization of results
• Timely access of patients to safe and effective new drugs
• Promote public health
• Minimize animal testing without compromising safety & effectiveness
Objectives

• More economical use of human, animal and material resources
• Elimination of unnecessary delay in global development
• Make new medicines available while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health
ICH structure

- Joint initiative involving regulators & industry as equal partners
- Founder Members:
  European Commission (EU); European Federation of Pharmaceutical Industries & Associations (EFPIA); Ministry of Health, Labour & Welfare, Japan (MHLW); Japan Pharmaceutical Manufacturers Association (JPMA); US Food and Drug Administration (FDA); Pharmaceutical Research & Manufacturers of America (PhRMA)
- Observers:
  WHO; European Free Trade Area (EFTA), Health Canada; IFPMA
- Administration:
  ICH is administered by the Steering Committee (6 co-sponsors have 2 seats) supported by the ICH Secretariat; The observers nominate non-voting participants to attend ICH Steering Committee meetings
5 Steps in the ICH process

• **Consensus building**
  
  Rapporteur prepares initial draft of a guideline/recommendation for comment with fixed deadline for comment (fax, e-mail). Interim report made to SC meeting, if consensus is reached, sign-off - all members

• **Start of regulatory action**

• **Wide ranging regulatory consultation**
  
  *EU*: published as a draft CPMP guideline; *US*: published as a draft guidance in the Federal Register; *Japan*: translated & issued by MHLW for internal and external consultation. A Regulatory Rapporteur is designated to draw up the final document and sign-off

• **Adoption of a tripartite harmonised text**
  
  Both regulatory and industry parties of SC must be satisfied. Adoption takes place on the signatures from the 3 regulatory parties to ICH, affirming that the Guideline is recommended for adoption by the 3 regulatory bodies

• **Implementation**
“Good clinical practice is a set of internationally recognized **ethical and scientific quality requirements** which must be observed for designing, conducting, recording and reporting clinical trials that **involve the participation of human subjects**. Compliance with this good practice provides assurance that the **rights, safety and well-being of trial subjects** are protected, and that the **results of the clinical trials are credible**.”

The topics

• Safety (S)
  – Dealing with in vitro & in vivo pre clinical testing

• Quality (Q)
  – Chemical & Pharmaceutical QA
  – Stability, Specifications, Analytical

• Efficacy (E)
  – Clinical studies in humans

• Multidisciplinary (M)
  – Terminology
  – Electronic standards
  – Common Technical Documents
Efficacy Guidelines

- Clinical Safety E1-E2F
- Clinical Study Reports E3
- Dose Response Studies E4
- Ethnic Factors E5
- **Good Clinical Practice** E6
- Clinical Trials E7-E11
- Guidelines for Clinical Evaluation by Therapeutic Category E12
- Clinical Evaluation E14
- Pharmacogenomics E15-E16
- Joint Safety / Efficacy Topic M3
Recent bad history

http://www.aatchb.org/epi/docs/ResearchEthics/T1P-History.PPT

• *Haida Gwai anthropologic research, 1970s?*
• *PhD student -> worked as a schoolteacher*
• *Documented effects of alcohol*
  – incest, murder, etc.
  – instances not widely or legally known in the community
• *Book published 1990s, names “hidden”*
  – to outsiders -- but not to community members!
• *Author almost physically assaulted in next visit*
SUPPORT trial, which sought to determine whether oxygen saturation targets at the higher end of the then-standard range led to better or worse outcomes in premature infants on ventilators than targets at the lower end.

*It was financed by the National Institutes of Health.*

- The consent forms were written by researchers at the University of California, San Diego, a spokesman for the University of Alabama at Birmingham said, and were approved by the review boards of all 23 Institutions in the study.
- The risk the consent form did mention was far less significant: abrasion of the infants’ skin by an oxygen monitoring device. It also said there was a possible benefit to participating — a decreased need for eye surgery depending on the group the infant was assigned to.
- The consent form should have explained that “there is significant evidence from past research indicating that the oxygen provided to an infant can have an important effect on many outcomes including whether the infant becomes blind, develops a serious brain injury or even possibly whether the infant dies.”
Current status of the research ethics committees in Thailand.

Lack of persons knowledgeable in human research ethics 49.3%
Members cannot attend the meeting regularly 33.3%
Lack of resources for operation 27.5%
Lack of recognition of RECs 21.7%
Lack of support from higher administrators 18.8%
Problems with independent status 7.2%
Other problems 2.9%
แนวทางกฎระเบียบจริยธรรมวิจัยของประเทศไทย ได้แก่

• พ.ศ.2541 จรรยาบรรณนักวิจัย
• พ.ศ.2541 คำประกาศสิทธิผู้ป่วย
• พ.ศ.2544/49 ข้อบังคับแพทยสภา
• พ.ศ.2544 ระเบียบกรมการแพทย์ ว่าด้วยเกณฑ์การพิจารณาจริยธรรมการวิจัยในมนุษย์
• พ.ศ.2550 พ.ร.บ. สุขภาพแห่งชาติ 2550
• พ.ศ.2551 พ.ร.บ.สุขภาพจิต 2551
พระราชบัญญัติสุขภาพแห่งชาติ พ.ศ. 2550

มาตรา 7
• ข้อมูลด้านสุขภาพของบุคคลเป็นความลับส่วนบุคคล ผู้ใดจะนำไปเปิดเผยในประการที่
 น่าจะทำให้บุคคลนั้นเสียหายไม่ได้ เว้นแต่การเปิดเผยนั้นเป็นไปตามความประสงค์ของ
 บุคคลนั้นโดยตรง หรือมีกฎหมายเฉพาะบัญญัติให้ต้องเปิดเผย แต่ไม่ว่ากรณีใด ๆ ผู้ใดจะ
 อาศัยอำนาจหรืออิทธิพลตามกฎหมายว่าด้วยข้อมูลข่าวสารของราชการ หรือกฎหมายอื่น เพื่อ
 ขอเอกสารเกี่ยวกับข้อมูลด้านสุขภาพของบุคคลที่ไม่ใช่ของตนเองไม่ได้

มาตรา 9
• กรณีที่ผู้ประกอบวิชาชีพด้านสาธารณสุขประสงค์จะใช้ผู้รับบริการเป็นส่วนหนึ่งของ
 การทำทดลองในงานวิจัย ผู้ประกอบวิชาชีพด้านสาธารณสุขต้องแจ้งให้ผู้รับบริการทราบ
 ล่วงหน้า และต้องได้รับความยินยอมเป็นหนังสือจากผู้รับบริการก่อน จึงจะดำเนินการได้
 ความยินยอมดังกล่าว ผู้รับบริการจะเพิกถอนเสียเมื่อใดก็ได้

มาตรา 49
• ผู้ใดฝ่าฝืนมาตรา 7 หรือมาตรา 9 ต้องระวางโทษ จำคุกไม่เกินหกเดือน หรือปรับไม่
 เกินหนึ่งหมื่นบาท หรือทั้งจำทั้งปรับ ตามความผิดตามมาตราที่ 7 หรือมาตราที่ 9 นี้เป็นความผิดอันยอมความได้
การวิจัยใดๆ ที่กระท่ำต่อผู้ป่วยจะกระท่ำได้ต่อเมื่อได้รับความยินยอมเป็นหนังสือจากผู้ป่วย และต้องผ่านความเห็นชอบของคณะกรรมการที่ดำเนินการเกี่ยวกับจริยธรรมการวิจัยในคนของหน่วยงานที่เกี่ยวข้อง

(ผู้ป่วยใน พ.ร.บ.สุขภาพจิต 2551 หมายความว่า บุคคลที่มีความผิดปกติทางจิตส่งเสริมการได้รับการบ่มบังคับ)

หลักเกณฑ์จริยธรรมการวิจัยในคน

1. จำเป็นต้องทดลองในคน
2. วัตถุประสงค์ชัดเจน มีประโยชน์เป็นไปได้
3. มีหลักฐานความปลอดภัย
4. Design + Methodology ดี
5. ผู้วิจัยมีความรู้ ความสามารถ ประสบการณ์ดีพอ
6. อาสาสมัครน้อยที่สุด ที่แปลผลทางสถิติได้
7. Risk assessment Risk managment
8. เป็นไปตามลำดับ ไม่ข้ามขั้นตอน
9. Informed consent process
10. ตอบแทนขาดแย่อาหารมีการยอม เหมาะสม
11. GCP
12. Monitor DSMB
13. หยุดโครงการเมื่อมีเหตุผลสมควร
What are the 13 principles of ICH-GCP? [1/5]

• Ethics:
  1. Ethical conduct of clinical trials
  2. Benefits justify risks
  3. Rights, safety, and well-being of subjects prevail
What are the 13 principles of ICH-GCP? [2/5]

- **Protocol and science:**
  4. Nonclinical and clinical information supports the trial
  5. Compliance with a scientifically sound, detailed protocol
What are the 13 principles of ICH-GCP? [3/5]

- Responsibilities:
  6. IRB/IEC approval prior to initiation
  7. Medical care/decisions by qualified physician
  8. Each individual is qualified (education, training, experience) to perform his/her tasks
What are the 13 principles of ICH-GCP? [4/5]

• Informed Consent:
  9. Freely given from every subject prior to participation

• Data quality and integrity:
  10. Accurate reporting, interpretation, and verification
  11. Protects confidentiality of records
What are the 13 principles of ICH-GCP? [5/5]

• Investigational Products
  12. Conform to GMP’s and used per protocol

• Quality Control/Quality Assurance
  13. Systems with procedures to ensure quality of every aspect of the trial
Problems with ICH-GCP

http://ichgcp.net/practical-implementation-of-gcp.htm

• The guidelines have been developed based on an informal consensus restricted to US, EU and Japan, neglecting the developing economies like India and China. The guideline, established in 1996, has never been revised or updated.

• There is no scientific basis for the development of such guidelines, since it was proposed without references to any scientific data.

• Medical professionals and academia researchers were not involved in the development of the guidelines. It is purely bureaucratic in nature.

• Excessive importance on monitoring, auditing and detection of fraud has led to unnecessary paperwork. Though the intention is right, the method is invalidated.
Problems with ICH-GCP

http://ichgcp.net/practical-implementation-of-gcp.htm

• Practical implementation of GCP principles still differs considerably from country to country
• Generally the ICH GCP guidelines are used by the non ICH countries to form their own GCP, which are more detailed, user friendly and address country specific issues.
• ICH GCP is not mandatory, it is only a guideline. Hence global implementation of this has become difficult. If it was law then all countries would have to ensure its implementation and compliance
• The guideline diverts scarce funds towards unnecessary compliance activity, making even the smallest of trials expensive