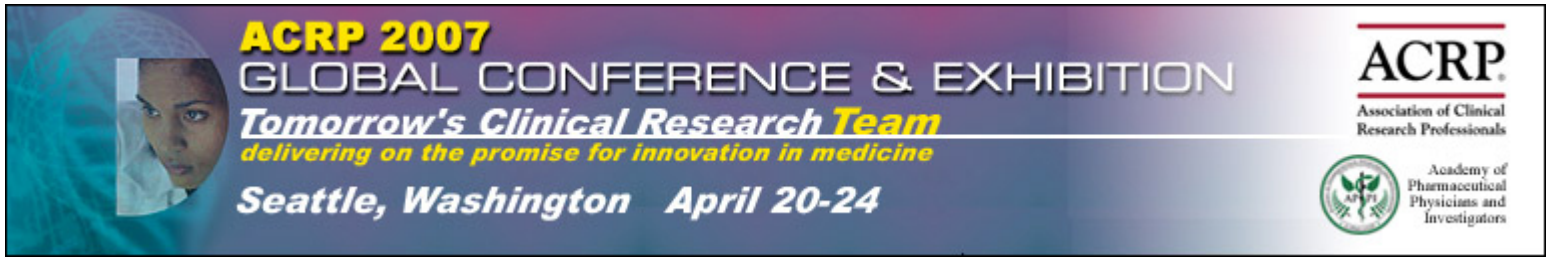
FDA管轄的研究案和國際法規協合會
FDA-Regulate Research and International Conference on Harmonisation (ICH)

高雄醫學大學附設中和紀念醫院
外科部　癌症中心 侯　明　鋒　教授

95年5月30日(星期二)下午2點;地點:啟川大樓六樓 第二講堂,
聯合人體試驗委員會(JIRB) 「各種研究中之受試者保護」研討會**PM2:50~PM3:10**



ACRP

Association of Clinical Research Professionals

Min-Feng Hou, MD, CCTI

Certification Number: ICH-I-0905-002

Has on September 17, 2005 demonstrated a high level of competence by successfully completing an examination documenting professional and educational achievement and has fulfilled the prescribed standards of performance and conduct required to earn the designation Certified Clinical Trial Investigator (CCTI™) as determined by the Exam Committee of the Association of Clinical Research Professionals. The CCTI™ designation is further evidence that this certified professional subscribes to the promotion and advancement of the highest ethical standards and practices in the clinical research profession. Designee is subject to recertification at two (2) year intervals.

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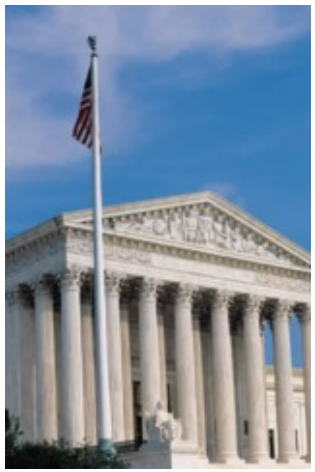
9 September 2006

FDA-Regulate Research and ICH

- I. INTRODUCTION (FDA ICH)
- II. LEGAL STATUS
- III. DIFFERENCES BETWEEN ICH GUIDELINES AND U.S. REGULATIONS
- IV. CONCLUSION



History of Clinical Research

18th Century

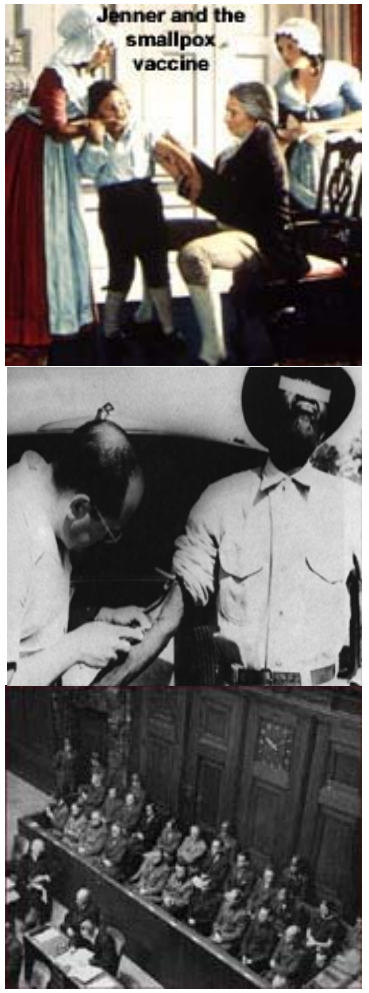
- **Edward Jenner – vaccine experiment for small pox**

19th Century

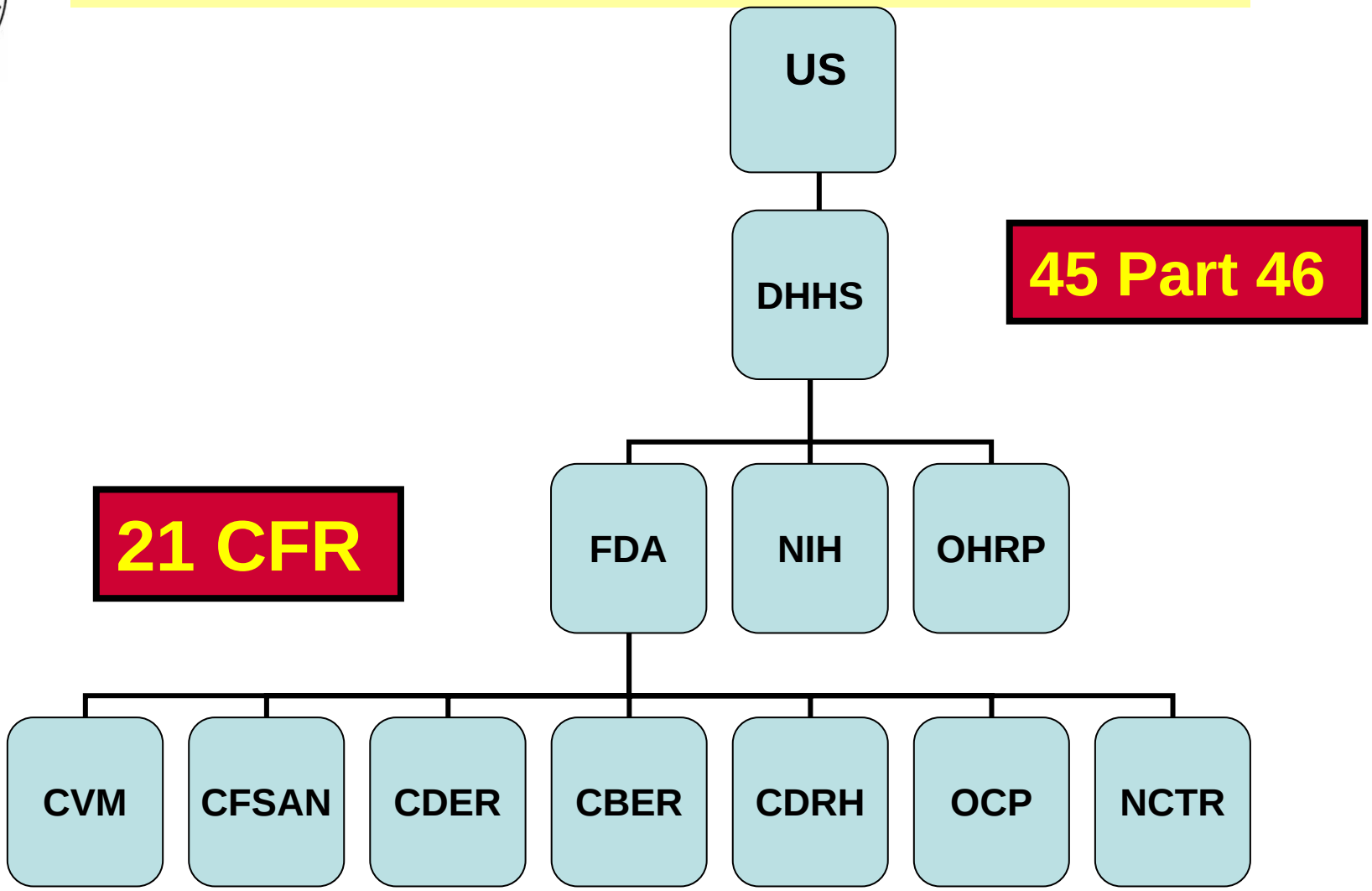
- **US Pharmacopoeia established 1820**

20th Century

- **US FDA formed 1906**
- **First randomized clinical trial 1923**
- **Tuskeegee Syphilis experiments 1930s ~ 1972**
- **1947 – Nuremberg Code of Ethics**
- **1964 – Declaration of Helsinki**
- **1966 – IRBs established in US**
- **1967 – FDA adds Informed Consent requirements**
- **1976 -- US FDA Medical Device Amendments**
- **1979 – Belmont Report**
- **1990 – International Conference on Harmonization (ICH)**
- **2001 – EU Directives**



US Regulatory Structure



DHHS: Department of Health and Human Services
OHRP: Office for Human Research Protection
CFR: Code Federal Regulation

US Regulatory Structure

- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Center for Drug Evaluation and Research (CDER)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Veterinary Medicine (CVM)
- National Center for Toxicological Research (NCTR)
- Office of the Commissioner (OC)
- Office of Regulatory Affairs (ORA)

US CFR Parts Applicable to Clinical Studies

Title 21, Chapter 1- FDA, Department of Health and Human Services:

- Part 11 – Electronic records; electronic signatures
- Part 50 – Protection of Human Subjects 5/80
- Part 54 - Financial Disclosure by Clinical Investigators 2/99
- Part 56 - Institutional Review Boards 1/81

- Part 312 – Investigational New Drug Application 3/87
- Part 314 – New Drug Application
- Part 812 – Investigational Device Expemptions 1/80
- Part 814 - Premarket Approval of Medical Devices

Title 45, Part 46- Protection of Human Subjects

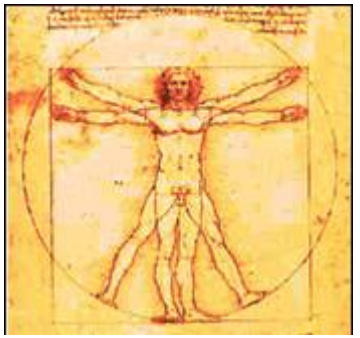
Guidance Documents

- **Describe "how to" accomplish specific FDA requirements described in the CFR or other GCPs**
- **Not mandatory, but are enforceable**

If different methods are used you must have data to demonstrate that you achieve equivalent results

- **Guidance documents address specific products or needs**

e.g.ICH Guidances – E6 (GCPs)



US Federal Human Subject Protection Regulations

- HHS Regulations – Research funded or conducted by any HHS agency
  - Administered by OHRP (Office for Human Research Protection)
  - Authority = funding or conducting of the study
  - 45 CFR, Part 46 (Protection of Human Subjects)

- FDA Regulations - Clinical investigation of products regulated by FDA
  - Oversight by FDA
  - Authority = FDA regulation of the test article

US DHHS Regulations

45 CFR, Part 46 – Subparts

- A: basic requirements, Incorporate Common Rule standards and are equivalent to FDA requirements
- B: regulations for research involving pregnant women, fetuses, and IN Vitro fertilizations
- C: regulations for research involving prisoners
- D: regulations for research involving children

HHS imposes(強制) requirements additional to those of FDA, for some child studies

DHHS: Department of Health and Human Services

1. INTRODUCTION (A)
What is ICH?

- **International Conference on Harmonization (ICH)國際法規協和會**

ICH由美國，日本和歐盟的製藥廠和法規代表共同組成。此外，觀察員包括加拿大，歐洲自由貿易區和 世界衛生組織。

An attempt to streamline the process for developing and marketing new drugs internationally. 1990

ICH Structure

- **Six parties (total of 17 members)**

  - US Pharmaceutical Research Manufactures Association (PhRMA)
  - European Union (EU)
  - US FDA
  - Japan Ministry of Health and Welfare (MWH)
  - European Federation of Pharmaceutical Industries Association (EFPIA)
  - Japanese Pharmaceutical Manufactures Association (JPMA)

- **Observers (World Health Organization , WHO; European Free Trade Area, Canada)**

- **IFPMA (International Federation of Pharmaceutical Manufacturers Association)**

ICH Areas of Focus

- **Quality**
- **Safety**
- **Efficacy**
  - **E1: Exposure**
  - **E2: Clinical safety**
  - **E3: Safety Reports**
  - **E4: Dose Response**
  - **E5: Ethnic Factors**
  - **E6: Good Clinical Practice (GCP)**
  - **E7: Special Trial Populations**
  - **E8: General Considerations-Trial Design**
  - **E9: Statistical Principles for Clinical Trials**
  - **E10: Choice of Control Group**
  - **E11: Pediatrics**
  - **E12: Therapeutic Categories**
- **Multidisciplinary**

1. INTRODUCTION (B)
What is ICH?

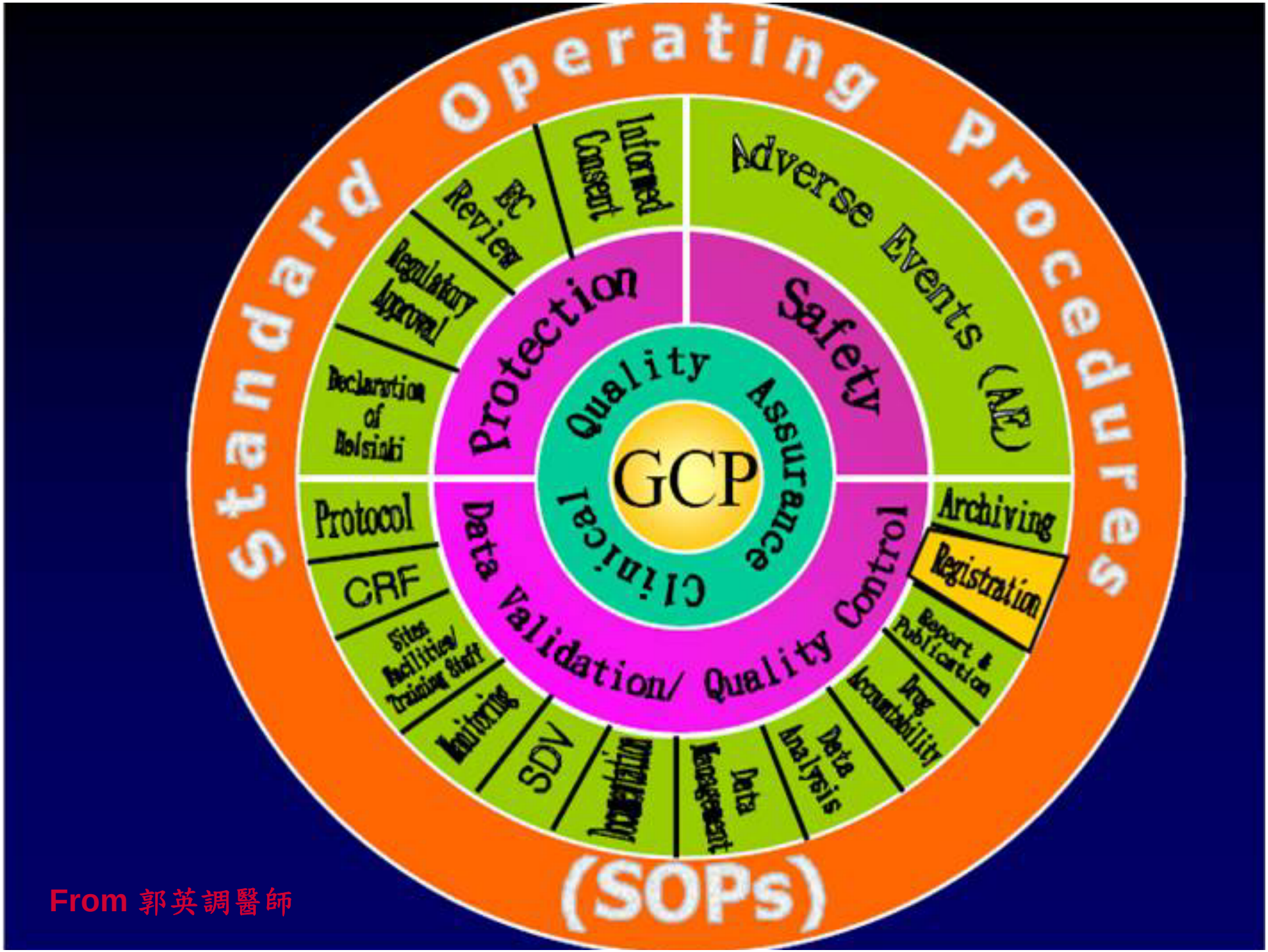
- **Good Clinical Practice (GCP)國際藥品優良臨床試驗規範**

Efficacy 6 guideline

- **(1) Glossary 詞彙**
- **(2) Principles 原則**
- **(3) IRBs 人體試驗委員會**
- **(4) Investigator 計畫主持人**
- **(5) Sponsor 試驗委託者**
- **(6) Protocol and amendments 計畫書和修正案**
- **(7) Investigator's Brochure 主持人手冊**
- **(8) Essential documents 必要文件**

The initial basis for drafting the E6 guidelines was the U.S. FDA regulations for the protection of human subjects (21 CFR 50 and 56).

E6根據美國食品藥物管理局的受試者保護規定（21 CFR 50和56）做為草案基礎。

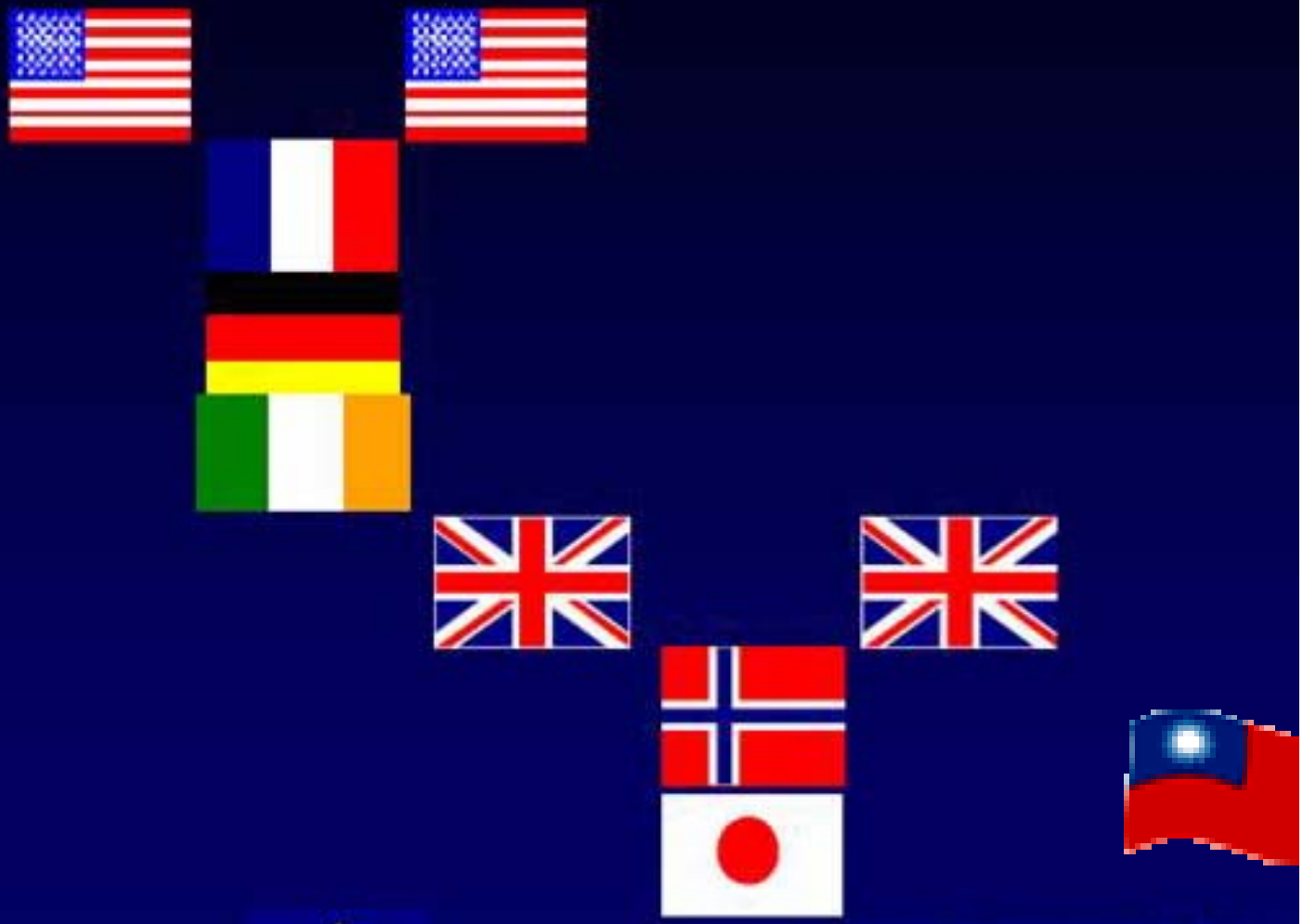

Standard Operating Procedures
(SOPs)
GCP
Quality Assurance
Clinical Data Validation/ Quality Control
Safety
Protection
Adverse Events (AE)
Informed Consent
EC Review
Regulatory Approval
Declaration of Helsinki
Protocol
CRF
Sites Facilities/ Training Staff
Monitoring
SDV
Documentation
Data Management
Data Analysis
Drug Accountability
Report & Publication
Registration
Archiving

From 郭英調醫師

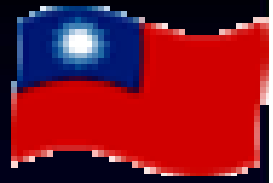
各國GCP公佈時間

77 87 88 89 90 91

- USA
- France
- Germany
- Ireland
- UK
- Nordic
- Japan
- Europe



From 郭英調醫師



國內GCP公佈時間

- 藥品優良臨床試驗規範

八十五年十月十五日修正公布

- 藥品優良臨床試驗準則

九十年九月公布草案 九十一年九月公布

藥品優良臨床試驗準則 **2005 Jan 6公佈**

From 郭英調醫師

II. LEGAL STATUS (A)

- **Law - several countries**
- **Guidance (Federal Register, Vol. 62, No. 90, May 9, 1997, pages 25691-25709).**
- ***Therefore, compliance is voluntary, but as with any published FDA guideline compliance is considered part of good clinical practice.***

自願的

遵循法規為藥品優良臨床試驗規範的一部份

II. LEGAL STATUS (B)

一. 遵循ICH 規範的好處是食品藥物管理局和其他國家類似的政府機構將考慮這些依ICH 規範執行的研究案符合這些國家藥品核准過程的要求。(試驗委託者)

二. 試驗委託者會要求計畫主持人必須符合ICH 要求。

三. ICH的某些要求並未包括在食品藥物管理局或者健康與人員服務部(HHS)的法規。因此，計畫主持人需要知道ICH和食品藥物管理局規範的差別，以便於試驗委託者要求遵循ICH 規範時能完全符合。

III. DIFFERENCES BETWEEN ICH GUIDELINES AND U.S. REGULATIONS

ICH E6 規範與食品藥物管理局法規大致相符

人體試驗委員會 **IRBs**
計畫主持人 **investigators**
受試者同意書 **informed consent**

但有些部份，ICH 規範的要求超越食品藥物管理局或健康與人員服務部(HHS)（共同規定)的要求。

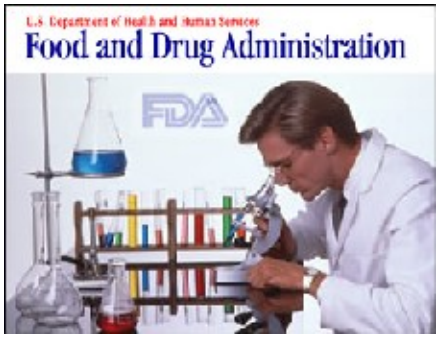
ICH E6 規範,食品藥物管理局法規21 CFR 50或56。

FDA Review Introduction

FDA Review

- **Drugs, biologics, and medical devices for safety and effectiveness before granting approval for marketing**

- **IND (Investigational New Drug application) or an IDE (Investigational Device Exemption).**



A. Drugs and Biologics

1. IND Investigational New Drug

- **Data from prior animal or human testing.**
- **Methods of manufacturing.**
- **Plans for testing and reporting significant toxicities.**
- **A well-developed clinical research plan that minimizes risks to the subjects**

A sponsor can be a drug company, a cooperative group, or even an individual physician

(21CFR 312)

2.Investigational Use of a Marketed Drug

Marketed drug does not require an IND if the following conditions are met

- **The data will not be used to support a new indication, new labeling, or change in advertising.**
- **The research does not involve a route of administration/dosage level or subject population that significantly increases the risks of the drug product.**
- **The research is conducted in compliance with IRB review and informed consent requirements.**
- **The research is conducted in compliance with requirements for promotion and sale.**

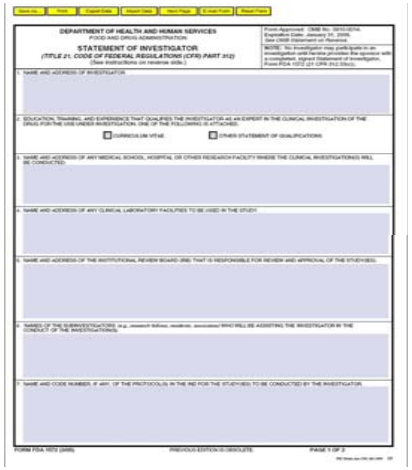
(21CFR312.2(b))

3. FDA Form 1572

Investigators participating in drug and biologic studies subject to the IND regulations MUST sign Form 1572.

- **Form 1572 outlines the commitments that must be made by the investigator(s) regarding the conduct of the study.**
- **Form 1572 must list co-investigators who will be administering the drug or separate forms need to be submitted for these individuals.**
- **Form 1572 must list the IRB of record for that study site.**

(21CFR312.53)



4. "Off Label" Use of Drugs, Devices, and Biologics

- **If physicians use products for an indication not listed in the approved labeling, they have the responsibility to be well informed and to base the proposed use on scientific rationale and medical evidence.**

- **Use of a marketed product in this manner when the intent is *practice of medicine* does not require the submission of an IND or IDE. However, an individual institution may under its authority require oversight for this practice such as review by a Medical Practice or Pharmaceutics and Therapeutics Committee.**

(21CFR312.2(d))

B. Devices

1.Definition of a Medical Device

- **Any health care product that does not achieve its primary intended purpose by a chemical interaction or by being metabolized.**

- **Medical devices include surgical lasers, sutures, pacemakers, and diagnostic aids such as reagents and test kits for *in vitro* diagnosis.**

2. The Medical Device Amendments of 1976

- **The Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990 provide the regulatory framework for medical device development, testing, approval, and marketing.**

- **Manufacturers who wish to market a new medical device may need to submit a pre-market notification to the FDA. Some medical devices are exempt from the pre-market approval process. If the device is not exempt, FDA determines whether the device is substantially equivalent *(21CFR807.81(a)(1))* to similar devices marketed before the 1976 amendment. These devices are often referred to as 510K devices *(21CFR807.92).***

- **If the new device is not substantially equivalent, the company may need to demonstrate safety and efficacy in a pre-market approval application, which could include clinical trials.**

3.Investigational Device Exemption (IDE)

免除審查

- To evaluate safety and effectiveness. The IDE regulations specify how to conduct these clinical trials *(21CFR812.2).*

- "significant risk" or "non-significant risk" devices.

- The sponsor often first makes this classification, but the IRB must agree with the determination. The risk determination should be based on the proposed use of the device and not on the device alone.

4.Significant Risk (SR) Devices

- Implanted into a human
- Supporting or sustaining human life
- Is of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise prevents impairment of human health; or otherwise presents serious risk to health, safety, and welfare of a subject.

IDE application to the FDA
The trial cannot begin until FDA grants an IDE and the IRB grants approval
IRB review

(21CFR812.20).

(21CFR812.3(5)(m))

5.Non-Significant Risk (NSR) Devices

- A non-significant risk device, by default, does not meet the criteria of significant risk. It is considered to have an approved IDE application (i.e., no application is filed with the FDA), and is studied without FDA oversight if the sponsor complies with certain FDA requirements such as monitoring, record-keeping, and properly labeling the investigational device.

- The IRB must agree that the study meets the criteria for non-significant risk. The clinical trial of a non-significant risk device requires IRB approval, informed consent, and proper study monitoring and it must meet all other regulatory compliance requirements.

C. INFORMED CONSENT

1. Informed Consent Waiver 免除

Elements of informed consent are found in the regulations at *21 CFR 50.25*

The FDA *21 CFR 50.23* and *21 CFR 50.24* provide exceptions to the requirement for informed consent under certain circumstances:

A. Emergency research (21 CFR 50.24)
B. Life-threatening conditions

FDA regulations *(21 CFR 50.23)* permit *exception*

1. **The investigator, with the concurrence of another physician, believes the situation for the human subject is life-threatening and necessitates the use of a test article (i.e., an investigational drug, device, or biologic).**
2. **The subject and/or legally authorized representative is unable to communicate consent. The FDA indicates that a Legally Authorized Representative is "*An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.*"**
3. **There is insufficient time to obtain consent.**
4. **No alternative exists that will provide an equal or better chance of saving the subject's life**

2. Is Oral Consent Appropriate?

FDA allows waiver (免除)of *written* informed consent

- **When study participation presents minimal risk of harm to the subject**

- **When the research involves no procedures requiring consent outside the context of participation in a research study.**

The IRB may require the investigator to provide the subject with written materials about the research. *(21CFR56.109)*

D. Emergency Use of an Investigational Biologic, Drug, or Device

Regulations exist- *21 CFR 50.23* -for unplanned emergency use (Regulations also exist for "planned" emergency research and can be found at *21 CFR 50.24*

1.The Definition of Emergency Use

The use of an investigational drug or device with a human subject in a life-threatening situation or in which no standard acceptable treatment is available and there is not sufficient time to obtain IRB approval.

Life-threatening means that the likelihood of death is high unless an intervention interrupts the process. It also applies to a condition that is immediately and severely debilitating and that causes irreversible morbidity such as blindness or paralysis. (21CFR56.102(d))

2.IND/IDE Requirements for Emergency Use

- If an individual patient does not meet the criteria for an existing protocol or an approved protocol does not exist, the usual procedure is for the physician to contact the manufacturer and determine if the drug can be made available for an "emergency use" under the company's IND.

- If there is no IND, the FDA may authorize the manufacturer to allow the drug to be used in advance of an IND submission or if the company agrees to provide the product, the physician can contact FDA, explain the situation, and obtain an emergency IND to permit shipment of the drug (21CFR312.36).

- If there is no IDE, the physician may use the device and notify FDA of its use after the fact. The physician should obtain an independent assessment from another physician and informed consent, however, before emergency use of the device occurs.

a. IRB Review Requirements for Emergency Use

- In an emergency use situation the FDA permits an exemption from prior review and approval by an IRB (21CFR56.104c). For emergency use of devices, concurrence of the IRB chair is required before the use takes place. However, individual institutions may have a variety of policies to handle this situation. For example, the investigator may be required to **notify the IRB office** when an emergency use is being considered. Contact your local IRB office for further information.

- DHHS regulations do not prohibit an investigator from using any investigational or approved drug or device in an emergency situation for the clinical care of a patient. However, the information collected from the patient in whom the drug or device has been used should not be considered **research data**. **IRB review and approval is required in all circumstances** if the investigator wishes to use the data for research purposes.

b. Informed Consent Requirements for Emergency Use

In accordance with FDA regulations *(21CFR50.23(a))*, investigators are required to obtain informed consent from the subject or legally authorized representative unless both the investigator and uninvolved physician certify in writing that:

- **The life threatening condition necessitates the use of the test article (i.e., an investigational drug, device, or biologic).**
- **There is an inability to communicate with or obtain informed consent.**
- **There is no time to obtain consent from a legal representative.**
- **There are no alternatives to provide equal or greater benefit**

c. After an Investigational Drug or Device has been used in an Emergency

- **Subsequent use of the investigational product at the institution should have prospective IRB review and approval. If the IRB was not notified before the investigational drug or device was used in an emergency situation, the IRB should be notified per institutional policy or within 5 working days *(21CFR50.23(c)).* The FDA and sponsor should be notified as necessary.**

E. RESPONSIBILITIES

1.Sponsor Responsibilities

- Selecting clinical investigators qualified by training and experience.
- Informing and qualifying investigators by obtaining their commitment to supervise the study, follow the protocol, and obtain consent.
- Monitoring the conduct of the study by auditing documentation and conducting site visits.
- Completing regulatory filings related to the IND or IDE, adverse events, amendments or revisions, progress reports, withdrawal of IRB approval, and final reports.
- Controlling the distribution, tracking, and dispensation of the regulated products

2. Investigator Responsibilities (A)

- Ensuring IRB approval for the study is obtained before any subjects are enrolled.
- Ensuring that informed consent is obtained in accordance with FDA regulations.
- Ensuring that the investigation is conducted according to the investigational plan and applicable regulations.
- Administering the drug or using the device only in subjects under the investigator's supervision or under the supervision of a recognized sub-investigator.
- Maintaining adequate records of the dispensation of the drug or device.
- Returning unused materials at the end of trial.

2.Investigator Responsibilities (B)

- Preparing and maintaining adequate case histories and signed informed consent documents.
- Maintaining correspondence with the IRB and the sponsor to make sure that both have reviewed protocol amendments, recruitment materials, investigator brochures.
- Retaining records in accordance with regulations.
- Providing progress, safety, final and financial disclosure reports.
- Notifying the sponsor if IRB approval is withdrawn.
- Comply with International Conference on Harmonization (ICH) guidelines

3.Inspections and Audits

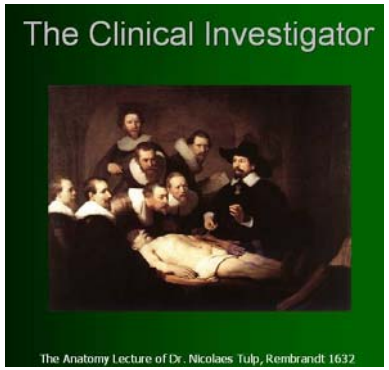
- **The Bioresearch Monitoring Program of the FDA conducts routine, "not for cause," and "for cause" audits of IRBs, clinical investigators, and sponsors. The purpose of this monitoring is to ensure the quality and integrity of data submitted to FDA for regulatory decisions and to protect human subjects.**

- **The FDA may conduct on-site reviews of IRBs, research sites, pharmacies, manufacturing sites, etc. The FDA may also inspect, review, and copy records associated with the research.**

1. Investigator to Obtain IRB Assurance that the IRB is in Compliance with ICH.

ICH 規範其中之一要求“試驗委託者從*計畫主持人/機構*……[a]從人體試驗委員會取得有關組成及運作皆符合藥品優良臨床試驗規範(GCP)及適用的法律及法規的陳述。”(ICH 5.11)。

經常，試驗委託者*直接*向人體試驗委員會取得這樣的陳述，有些則要求計畫主持人向人體試驗委員會取得後再轉交給試驗委託者。



- **One of the requirements of the ICH guideline is that "the sponsor obtain from the investigator/institution . . .[a] statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations." (ICH section 5.11). Oftentimes, sponsors will approach IRBs directly to obtain this statement, but some sponsors will request that the investigator obtain the statement from the IRB and then forward it to the sponsor**

2. Confidentiality of Medical Records
醫學紀錄的機密性

有關經由第三者取得可識別的研究紀錄的可能性，ICH比起食品藥物管理局或者健康與人員服務部(HHS)的要求較為寬鬆。

ICH 4.8.10(n) 說明受試者同意書應指出包括監測員、稽查員、人體試驗委員會和業管單位可為確認臨床試驗的過程或數據資料在相關法規的範圍內以不侵犯受試者隱私的方式取得受試者的原始醫療紀錄。受試者或其法定代理人必須在受試者同意書上簽名以表示同意。

ICH 5.15.2 說明試驗委託者應該確認每位受試者已經以書面同意為了試驗的監測、稽核、人體試驗委員會審查和主管機關查核的原因，必要時需取得原始醫療紀錄。

食品藥物管理局法規(50.25(A)（5)) 說明尋求受試者同意，下列訊息將必須提供給每位受試者：….(5) 如果可辨試受試者的紀錄須維護其機密性，必須告知食品和藥品管理局有可能會查核該紀錄。

2. Confidentiality of Medical Records
醫學紀錄的機密性

ICH 允許較多人參與研究記錄和對較不祕密的醫學記錄提供。

大多數受試者同意書目前允許研究的範圍及試驗委託者的記錄，且大多數計畫主持人和受試者沒有麻煩。

外國研究協調機構參與研究記錄和對受試者，外國的醫學記錄對一些計畫主持人來說是較成問題。

計畫主持人必須決定是否他們想遵循ICH 和同意參與受試者的醫學記錄，必須在應允期間清楚把這訊息透露給受試者。

3. Signature by Person Conducting the Consent Discussion

進行同意的人的簽名 討論

ICH 4.8.8 說明那在之前一受試者參與在方面 審訊，書面明智的應允形式應該被簽字，和親自 以受試者或者透過受試者的合法可接受的代表斷定的年代， 並且由進行明智的應允的人討論

食品藥物管理局規章 *只需要受試者的簽名*和 受試者在同意形式上簽字的*日期*(50.27(A))為了保證服從這要求，計畫主持人應該 包括一個簽名標號" 人處理明智的討論。 " 這方面不應該被貼標籤" 計畫主持人的簽名，" 除非計畫主持人總是獲得的人 同意。.

3. Signature by Person Conducting the Consent Discussion

進行同意的人的簽名 討論

ICH 4.8.8 states that prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

- **The FDA regulations only require the signature of the subject and the date the subject signed the consent form (50.27(a)).**
- **To assure compliance with this requirement, the investigator should include a signature line labeled "person conducting informed consent discussion." This line should not be labeled "Investigator's Signature," unless the investigator is always the person who obtains consent.**

4. Subject Receipt of a Signed and Dated Copy of the Consent Form

受試者收到簽字及寫上日期的同意書副本

ICH 4.8.11 要求受試者或者合法審定的代表（家屬）得到一簽字並且寫上通知的年代同意書。

食品藥物管理局規章允許受試者得到或者一簽字或者未簽字文本。（食品藥物管理局諮詢表" 常見問題，" 1998年9月，第11 頁）.

按照ICH 規範， 計畫主持人應該包括在同意內的一陳述形成那受試者 將收到簽字並且在上寫上日期的同意形式的副本。 人獲得 同意然後必須保證這個步驟被跟隨。

5. Assent of Children and Mentally Disabled Adults孩子和心智殘障大人的同意

ICH 4.8.12 臨床試驗(治療或者 非治療) 經受試者同意或合法代表(例如，未成年人或者有嚴重的智力衰退的病患)同意, 受試者應該被通知 關於對與受試者理解相容的程度的討論 ，如果受試者有能力應親自寫明同意，簽字和日期 的同意書。

HHS 規章和食品藥物管理局規章 ,需要那孩子 同意研究除非有適當原因。 不過食品藥物管理局和 **HHS** 規章並無明確規定喪失能力成年人同意研究參與。

1861 electrotherapy

6. Impartial Witness for Illiterate Subjects

文盲的公平證人

The ICH definition of "impartial witness", found at section 1.26, is, "A person who is independent of the trial, who cannot be unfairly influenced by people involved in the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject."

The FDA addresses the documentation of informed consent for illiterate subjects by allowing the use of a short form consent document and a written summary for oral presentation (50.27(b)(2)).

7. Elements of Consent

同意的要素

A few of the ICH guideline requirements for elements of informed consent go beyond the FDA requirements, and would need to be included by the IRB for studies that are intended to meet ICH requirements.

Alternative Treatments

- ***ICH 4.8.10(i) requires an explanation of "the alternative procedure (s) or course (s) of treatment that may be available to the subject, and their important potential benefits and risks.***
- ***" Most sponsors, investigators and IRBs have not included the benefits and risks of alternative treatments in consent forms, as consent forms are already long and difficult to understand. This is an area where many sponsors and IRBs decide to limit their compliance with ICH.***
- ***However, the investigator should explain the risks and benefits of alternative treatments to subjects when the information is necessary for the subject's full understanding and exercise of autonomy***

7. Elements of Consent

同意的要素

Probability of assignment to each study arm in a study.

- **The FDA regulations (50.25(a)(1)) state that the consent form must include: "A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental."**

- **ICH 4.8.10(c) states in addition that the informed consent should include: "The trial treatment (s) and the probability for random assignment to each treatment."**

- **This difference can be addressed by including a description of each arm of the study in the consent form, and including a statement about the likelihood of receiving each of the study arms.**

7. Elements of Consent (C)

***Description of subject's responsibilities*.**

- **ICH 4.8.10(e) requires an explanation of "The subject's responsibilities." Some investigators include this information as part of the procedures section of the consent form.**

Statement of no benefit

- **ICH 4.8.10(h) requires an explanation of "The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this." Many investigators customarily include this information in the consent form.**

Prorated payment in the consent form

- **ICH 4.8.10(k) states that "anticipated prorated payment, if any, to the subject for participating in the trial" must be included in the consent form.**
- **While not an FDA requirement, prorated payment is addressed in the FDA Information Sheet entitled "Payment to Research Subjects," and it is common practice for IRBs and investigators in the United States to include in consent forms.**

8. Non-therapeutic Trials

・Two ICH sections address non-therapeutic research and the requirements for consent. These issues are not specifically addressed in the FDA regulations.

- **ICH 4.8.13 Except as described in ICH 4.8.14, a non-therapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.**

- **ICH 4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:**
  - **The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.**
  - **The foreseeable risks to the subjects are low.**
  - **The negative impact on the subject's well-being is minimized and low.**
  - **The trial is not prohibited by law.**
  - **The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.**

- **Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed. The ICH requirements for inclusion of subjects in non-therapeutic trials are straightforward. To comply with ICH requirements, investigators should ensure that subjects without capacity are not used for non-therapeutic trials, except as described above.**

9. Investigator Notification to Subject's Primary Physician

ICH section 4.3.3. states that it is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

- **There is no equivalent to this requirement under FDA regulations. Investigators should have a policy in place to address this notification requirement. It can be included in the consent form so that the subject's choice about the notification is documented in the consent form**

10. IRB Responsibilities (A)

Documents the IRB must review.

- **The ICH provides a list of documents that the IRB should review, and IRBs *routinely review* most of the materials listed. Compliance with ICH requires reviewing all the listed materials.**

- **ICH 3.1.2 The IRB/IEC should obtain the following documents (*lists*):**

  - **Trial protocol(s)/ amendment(s).**
  - **Written informed consent form(s) and consent form updates that the investigator proposes for use in the trial.**
  - **Subject recruitment procedures (e.g., advertisements).**
  - **Written information to be provided to subjects.**
  - **Investigator's Brochure (IB).**
  - **Available safety information.**
  - **Information about payments and compensation available to subjects.**
  - **The investigator's current curriculum vitae and/or other documentation evidencing qualifications.**
  - **Any other documents that the IRB/IEC may require to fulfill its responsibilities.**

The FDA regulations do *not* specifically *list* in one place what documents an IRB should review. FDA requires the IRB to review the consent form (56.109(b)), and 56.115(a) requires the IRB to keep "copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents."

10. IRB Responsibilities (B)

Review of Changes in Research

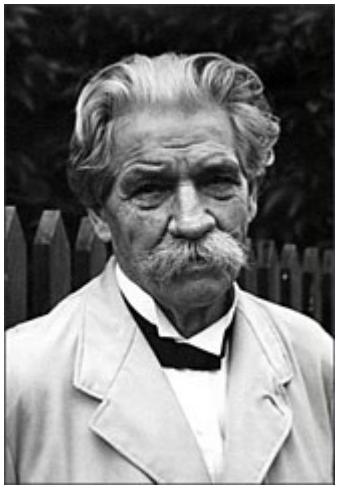
- **ICH 3.3.7 states that "The IRB/IEC should [specify] that no deviations from, or changes of, the protocol should be initiated … without prior IRB/IEC written approval." ICH 4.5.3 adds that "Investigators should document and explain any deviations from the approved protocol."**

- **FDA regulations (56.108(a)(4)) requires review of changes in research. However, review of deviations is not required by FDA, and the ICH 4.5.3 requirement is quite burdensome when applied literally. Investigators should clarify with sponsors and their IRB whether and how this requirement will be satisfied.**

IV. CONCLUSION

- **In the U.S., compliance with the ICH E6 guidelines is voluntary for investigators in that it is not federal regulation.**

- **For research institutions that conduct clinical trials of drugs, however, pharmaceutical sponsors often insist that the ICH requirements be met. Investigators should assess their level of compliance and decide if ICH requirements can be met without compromising subject protections or institutional values.**



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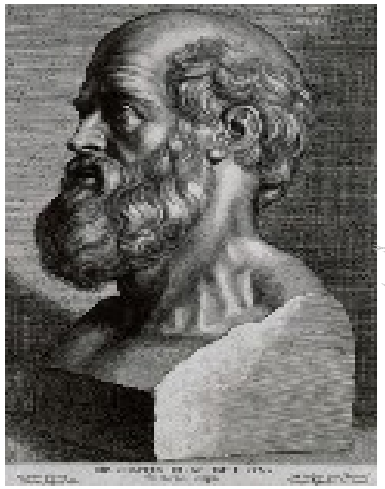

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