

ICH-GCP-Good Clinical Practice

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Introduction

1. Examples of unethical research – why do we need to know GCP?
2. Declaration of Helsinki

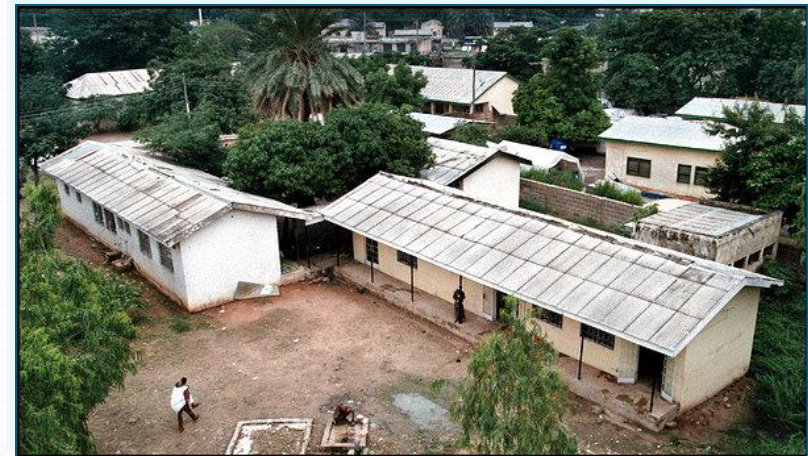
The Pfizer Case

Panel Faults Pfizer in '96 Clinical Trial In Nigeria

Unapproved Drug Tested on Children'

By Joe Stephens, Washington Post Staff Writer (Sunday, May 7, 2006)

A panel of Nigerian medical experts has concluded that Pfizer Inc. **violated international law** during a 1996 epidemic by testing an unapproved drug on children with brain infections at a field hospital.

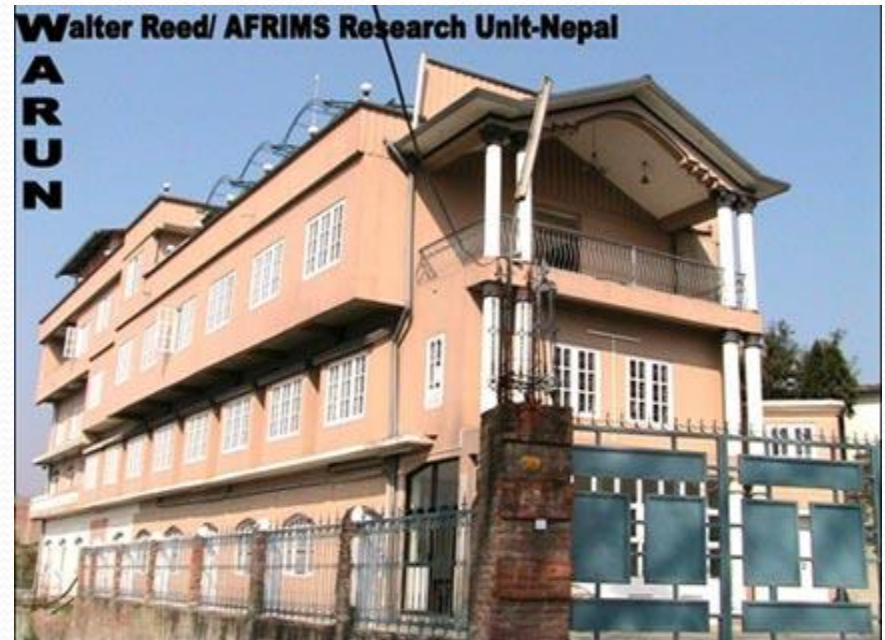


The Infectious Diseases Hospital in Kano, Nigeria, was treating meningitis patients in 1996 when Pfizer administered the experimental drug Trovan to children.

<http://www.washingtonpost.com/wp-dyn/content/article/2006/05/06/AR2006050601338.html>

Walter Reed: WARUN

- In Feb 2000, due to outbreaks of HepE, WARUN wanted to test a candidate Hep E vaccine on 8.000 Nepalese volunteers.
 - Protests as the majority of population was illiterate and highly vulnerable.
 - Decision taken to test the vaccine on 2.000 soldiers of the Royal Nepalese Army (also form a vulnerable group as poor and subject to coercion by their superiors). <http://www.ipsnews.net/2006/02/nepal-guinea-pigs-in-hepatitis-e-vaccine-trials/>
- In March 2006, request to GSK for the vaccine to be available for free to the Royal Nepalese Army and the study community and offered to the Nepali Ministry of Health at not-for profit prices. The response from GSK is not known.



Family Health International

FHI Cancels Nigerian Arm of Clinical Trial Testing Tenofovir (active ingredient of oral antiretroviral drug Viread™) **for HIV Prevention** - *Financial Times* 15 March, 2005.

The Bill & Melinda Gates Foundation awarded a \$6.5 million grant to FHI to conduct a randomized, placebo-controlled clinical trial of Viread including 2,000 HIV-negative volunteers at sites in Nigeria, Cambodia, Ghana, Cameroon and Malawi.

Family Health International **cancelled the Nigerian arm** of the ongoing clinical trial testing Viread **because of a failure of local researchers to reach "necessary scientific standards,"**

Novartis Vaccines and Diagnostics

EMA Press release 16 June, 2008



- NVD withdrawn the application for marketing authorization for Aflunov (pre-pandemic flu vaccine) submitted to the EMA on 6 November 2006.
- The request by EMA for additional clinical data could not be met within the timeframe permitted by the centralized procedure.
- Additional data were requested following a GCP inspection showing that the clinical trial had not been conducted in compliance with GCP, thus data integrity was compromised and results were not deemed reliable to support Aflunov licensure in EU.

Introduction

1. Examples of unethical research – why do we need to know GCP?
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Declaration of Helsinki - The Cornerstone of Health Research Ethics [1]

Adopted by the 18th World Medical Association General Assembly (Helsinki - June 1964) and since its creation, has been amended 7 times:

- 1) 29th WMA (Tokyo - Oct 1975)
- 2) 35th WMA (Venice - Oct 1983)
- 3) 41st WMA (Hong Kong - Sep 1989)
- 4) 48th WMA (South Africa - Oct 1996)
- 5) 52nd WMA (Edinburgh - Oct 2000)
- 6) 59th WMA (Seoul – 2008)
- 7) 64th WMA (Fortaleza, Brazil, October 2013)

Declaration of Helsinki - The Cornerstone of Health Research Ethics [2]

- The Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.
- It is the duty of the physician to promote and safeguard the health of patients.
- The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
- While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects

(Intro, Paragraph 2&4&8)

Impact of Declaration of Helsinki

- Though the declaration is not a legally binding instrument under international law, its influence on medical ethics and national regulations on biomedical research should be considered:
 - WHO guidelines for GCP
 - ICH-E6 (GCP)
 - Chinese Clinical Trial Administration Norms
 - Indian Council of Medical Research
 - Israel incorporated the DoH as such in the legislation
 - Uganda 1997 guidelines for the conduct of clinical research
 - South African guidelines on Ethical for Medical Research
 - EMEA Guidelines on Clinical Research
 - USA debate on DoH vs. ICH-GCP

Transparency toward Research Participants

“Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

Declaration of Helsinki 2013, paragraph 25



Public Transparency

“Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.” (Paragraph 35)

Use of Control Arms

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
 - Where no **proven intervention** exists, the use of placebo, or no intervention, **is acceptable**;
 - Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or **no intervention is necessary** to determine the efficacy or safety of an intervention
 - and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention **will not be subject to additional risks of serious or irreversible harm** as a result of **not receiving the best proven intervention**. (Paragraph 33)

Access to Post-study Interventions

- “In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process. (Paragraph 34)
- “ The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.(Paragraph 22)

Question 1:

The Declaration of Helsinki should be followed by medical doctor performing research:

True, MD are the only responsible for patient's health

False, although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

Question 2:

It is the duty of physicians who participate in medical research to protect:

life, health, dignity, family members, integrity, right to self-determination, personal properties, privacy, and confidentiality of personal information of research subjects.

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life, health, dignity, ~~family members~~, integrity, right to self-determination, ~~personal properties~~, privacy, and confidentiality of personal information of research subjects.

Structure of ICH-GCP training

1. History of ICH and background for its development and implementation
2. ICH-GCP structure and principles
3. ICH-GCP Chapter 4 (Investigator)
4. Informed Consent
5. IRB and IEC
6. Final evaluation

International Conference of Harmonization – ICH-

- ❖ ICH is a joint initiative of both **regulators** and **industry** as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.
- ❖ The founder members of ICH which represent the regulatory bodies and the research-based industry in:
 - ❖ European Union (EU, EFPIA)
 - ❖ Japan (MHLW, JPMA)
 - ❖ USA (FDA, PhRMA)
- ❖ Since ICH was initiated, in 1990, there have been observers to act as a link with non-ICH countries and regions. The Observers to ICH are:
 - ❖ The World Health Organization (WHO)
 - ❖ The European Free Trade Area (EFTA), represented by Swissmedic
 - ❖ Canada, represented by Health Canada

The need for ICH

!!IMPORTANT!!!

Evaluation of medicinal products before they are allowed on the market was realized at different times in different regions:

- ❖ In the US a tragic mistake in the formulation of a children's syrup in the 1930s was the trigger for setting up the product authorization system under the Food and Drug Administration.
- ❖ In Japan, government regulations requiring all medicinal products to be registered for sale started in the 1950s.
- ❖ In Europe the trigger was the thalidomide (a new generation of synthetic drug to treat nausea in pregnant women) tragedy of the 1960s,

International Conference of Harmonization – ICH

- When ICH was first established, one of the objectives was to organize an International Conference on Harmonization, and hence the name which was given to the initiative.
- The name of ICH has now, perhaps, become more associated with the process of harmonization, than the actual Conferences, although these have been extremely important for ensuring that the process of harmonization was carried out.
 - ICH 1 Brussels, 1991
 - ICH 2 Orlando, 1993
 - ICH 3 Yokohama (Japan) 1995
 - ICH 4 Brussels, 1997
 - ICH 5 San Diego, 2000
 - ICH 6 Osaka, 2003
 - ICH 7 Vienna, March 29-30, 2007 - cancelled

International Conference of Harmonization – ICH [3]

- The ICH Topics are divided into four major categories:
 - **Safety (S)**
those relating to in vitro and in vivo pre-clinical studies.
Examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing
 - **Quality (Q)**
those relating to chemical and pharmaceutical Quality Assurance. Examples: Q1 Stability Testing, Q3 Impurity Testing
 - **Efficacy (E)**
those relating to clinical studies in human subject. Examples: E4 Dose Response Studies, Carcinogenicity Testing, E6 Good Clinical Practices
 - **Multidisciplinary (M)**
cross-cutting Topics which do not fit only into one of the above categories. Example: M1 Medical Terminology (MedDRA)

MIKE THOMPSON
AN ED DUFFY PRODUCTION



True or False?

ICH has existed since 1800 as result of the discovery of the first antibiotic

False – ICH 1 was held in 1991 (even if harmonization was pioneered by the EU since 1980 as the EC developed a single market for pharmaceuticals)

WHO is a founding member of ICH

False – WHO has been attending ICH as external observer since ICH 1 but it is not a founder member

GCP is part of ICH

True – This is why we use the abbreviation ICH-GCP. GCP are section E6 of ICH.

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ICH Efficacy (E) Guidelines

E 1-E 2 Clinical safety

E 3 Clinical study reports

E 4 Dose response studies

E 5 Ethnic factors

E 6 GCP (R1)

E 7 Special populations

E 8 General considerations of clinical trial

E 9 Statistical principles of clinical trial

E 10 Choice of control group

E 11 Studies in Pediatric Population

E 12 Evaluation of Antihypertensive drugs

E14 Studies to delay cardiac repolarization

Go to www.ich.org for the ICH web site and all guidelines

ICH Guidelines Efficacy E6 Guideline: GCP

- The objective of ICH GCP Guideline is to provide a unified standard for the EU, Japan and the US to facilitate the mutual acceptance of clinical data by the regulatory authorities in these areas.
- The guideline was developed with consideration of the good clinical practices of the EU, Japan, and the US, as well as those of Australia, Canada, the Nordic European countries and the WHO.
- WHO and National guidelines have aligned and refer to ICH-GCP for clinical research
- This guideline **should be followed** when generating clinical trial data that are intended to be submitted to regulatory authorities

Question:

What is the difference between a guideline and a regulation?

Guidance



Regulation



ICH Guidelines Efficacy E6 Guideline: GCP

- ✓ The tripartite harmonized ICH guideline E6 was finalized in May 1996 and implemented:
 - ✓ EU: July 96 (issued as CPMP/ICH/135/95/Step5 and CPMP/768/97) and implementing guidance texts (EU, 2001-2003)
 - ✓ Ministry of Health, Labour and Welfare (MHLW – Japan): March 97 (PAB Notification No.430, MHLW Ordinance No.28)
 - ✓ FDA: Published in the Federal Register (May 1997)
 - ✓ Development of Regional & National GCP Guidances (PAHO, India, China, Indonesia, Thailand, Malaysia, Singapore, South Africa)
 - ✓ WHO: Guidelines for good clinical practice (GCP) for trials on Pharmaceutical products. Annex 3 of The Use of Essential Drugs Sixth report of the WHO Expert Committee. Geneva. WHO, 1995: 97–137 and Handbook for GCP, Guidance for implementation 2002.

ICH-GCP Guidelines



The need for GCP

In general studies in the past had:

- ✓ No ethics approval
- ✓ No written informed consent
- ✓ Poor study design
- ✓ No real monitoring
- ✓ Unacceptable data collection
- ✓ Poor data recording
- ✓ Unsatisfactory statistical analyses
- ✓ Fraud and negligence
- ✓ Inadequate AE and SAE/SUSAR reporting systems
- ✓ Inadequate data retention period

Frequently Reported Violations

- Record keeping errors / Incomplete or incorrect source data
- Incomplete accountability of study medication
- Failure to follow the protocol / Protocol violations
- Informed consent problems and/or No Informed consent
- Enrollment of ineligible subjects
- Violation of protocol affecting safety / Problems with the reporting of (S) AEs
- Extensive data corrections and questionable changes
- Failure to communicate with IRB / Problems with approval
- Inadequate oversight of study personnel
 - *Division of tasks within the investigational team was not evident*
 - *Inappropriate delegation of authority*
 - *Poor oversight of satellite sites*

Inappropriate delegation to co-investigators

- Investigator – individual who actually conducts an investigation (i.e., *under whose immediate direction* the Vaccine - or drug - is administered or dispensed to subjects).
- How many miles away ????



Sponsor should ensure that the PI has the study under control

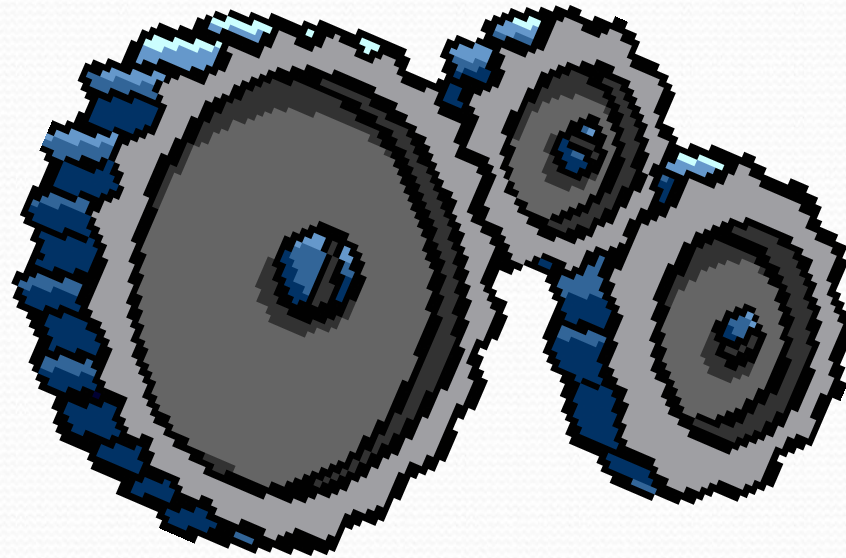
Definition of GCP

"an international **quality** standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that **provides assurance** that the data and related results are **credible** and **accurate**, and that the rights, integrity, and confidentiality of **trial subjects** are protected"

Who does GCP concern ?

- Sponsor (i.e. pharmaceutical companies, academic units)
- Investigators and all members of the study team
- Study monitor
- Contract Research Organisation (CRO)
- Ethics Committee/Institutional Review Board/NRAs

Monitor/CRO



Sponsor

Investigator

GCP Table of Contents

Introduction

1. Glossary
2. The Principles of ICH GCP
3. Institutional Review Board / Independent Ethics Committee (IRB/IEC)
4. Investigator (*Including Investigator's Responsibilities*)
5. Sponsor (*Including Monitor and Monitoring*)
6. Clinical Trial Protocol and Protocol Amendment
7. Investigator's Brochure
8. Essential Documents for the Conduct of a Clinical Trial

1st principle of ICH-GCP



Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the appropriate regulatory requirements.

Most Relevant principles of ICH-GCP

- ❖ Clinical study should be conducted in compliance with the protocol
- ❖ Each individual involved in trial should be qualified by education, training and experience to perform his/her tasks
- ❖ Informed consent should be obtained before participation in trial
- ❖ Information should be recorded, handled and stored to allow accurate reporting, interpretation and verification
- ❖ Records that could identify participants should be protected to respect privacy and confidentiality
- ❖ Systems to assure the quality of every aspect of the trial shall be implemented

True or False?

The benefits of participation into a clinical trial should exceed the risks and inconveniences

False – The risks and inconveniences should be weighted against the benefits

Rights, safety and well being of subjects are of secondary importance if compared to the final results of the clinical study

False – Rights, safety and well being of subjects are the most important consideration

IRB approval should be obtained within 60 days of starting the trial

False – A trial should be conducted in compliance with the protocol that has received prior IRB/IEC approval

Clinical trials should be scientifically sounding

True – As described in a clear and detailed study protocol

Subjects medical care decision can be taken by any member of the study team as long as the principal investigator will sign off later on

False – The medical care given, and medical decision made, should always be responsibility of a qualified physician.

Members of the study team can be selected among any employee of the study site institution, training can be provided at later stage.

False – Each individual involved in conducting a clinical trial must be qualified based on education , training and experience to conduct his/her tasks

Subject Informed Consent is not necessary if community leaders already gave their approval for the study to be conducted in the area.

False – Freely given informed consent should be obtained from every subject prior to participation

Structure of training

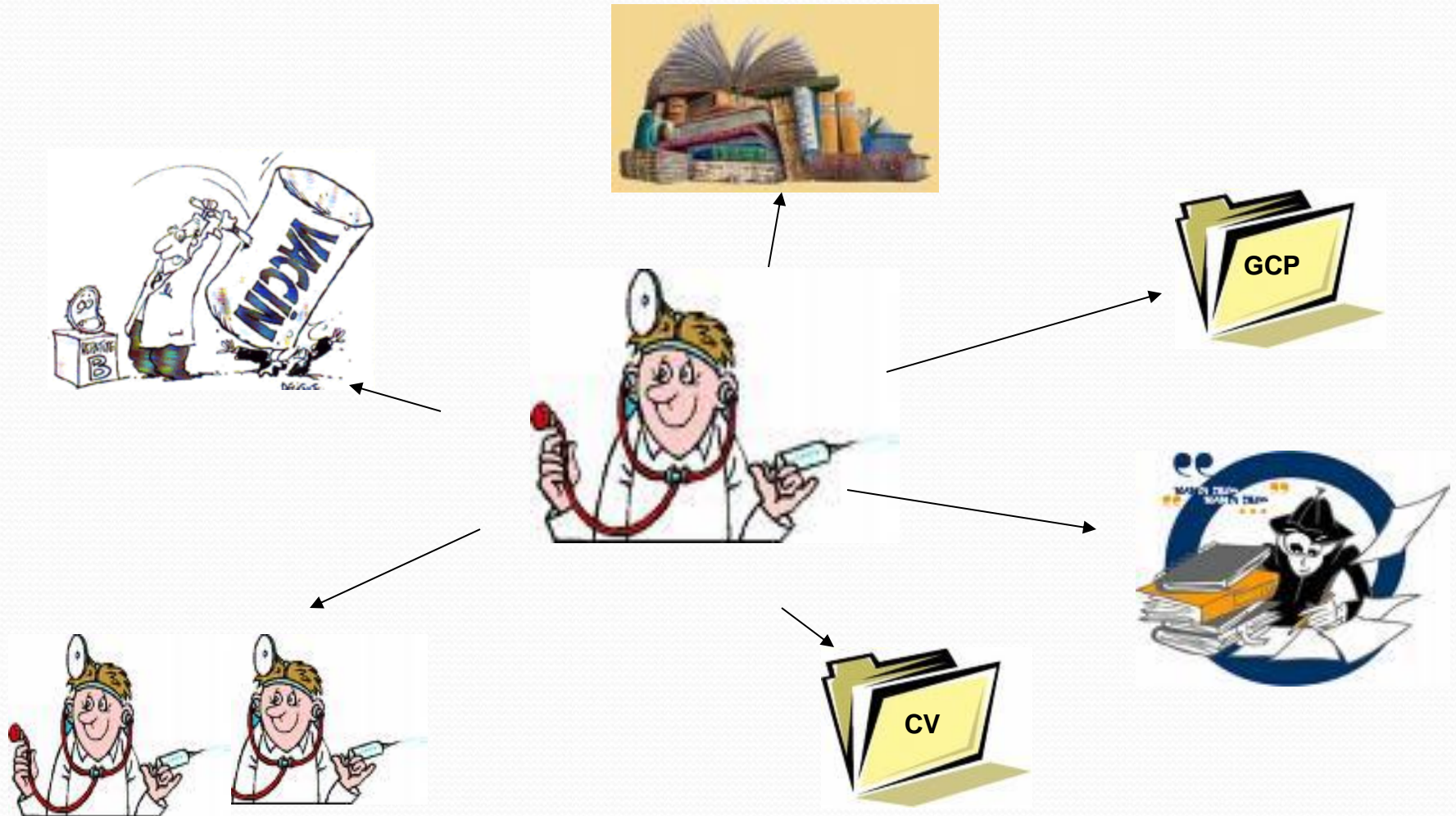
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Who is the Investigator?

A person **responsible** for the conduct of the clinical trial at a trial site

Qualifications and agreements



Adequate resources

Time

Recruitment



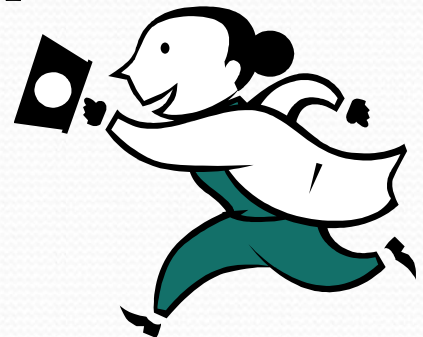
Acknowledgment
Protocol &
duties

Staff & Facilities



Investigator responsibilities [1]

- **Communication with IRB/IEC**
 - Written and dated approval before initiating a trial
- **Compliance with protocol**
 - Protocol signed to confirm the agreement
 - Deviations not implemented without prior approval (sponsor/ethics)
 - Deviations should be documented





Investigator responsibilities [2]

➤ IMP

- Accountability (pharmacist delegation)
- Maintains records of delivery, inventory, use and return
- Stored appropriately
- Used in accordance with protocol
- Explain correct use to subject



➤ Randomisation

- Code to be broken only in accordance with protocol
- Document any premature unblinding



Investigator responsibilities [3]



➤ Records and reports

- Accurate, complete, legible, timely
- Consistent with source documents
- Changes to a CRF should be dated, initialled & explained
- Trial documentation maintained & protected against premature destruction
- Archiving of essential documentation





Investigator responsibilities [4]

- **Progress reports**
 - Annual reports to EC
- **Safety reports**
 - SAEs reported immediately (24hrs) to the Sponsor
- **Study premature termination**
 - Promptly inform trial subjects
- **Final reports**
 - Provide to EC and regulatory authority summary of trial outcome



True or False?

Investigator: “I’m only doing small phase 1 and 2 studies – I’ll never be audited.”

False - Clinical investigators of studies in all phases may be (and are) inspected on all GCP regulations apply

Diaries, questionnaires, photos are not subject to audit/inspection

False – These need to be maintained by investigator

Once a trial is completed, documents should be archived for 2 years at study site.

False – At least 2 years after last approval of a marketing application.

Summary of Investigator's responsibilities

A qualified

Conduct the study as described in the study protocol and implement deviations/modifications after sponsor agreement and EC/IRB approval

Responsible for informed consent, discussion, documentation, and control of medical subjects

through curriculum vitae

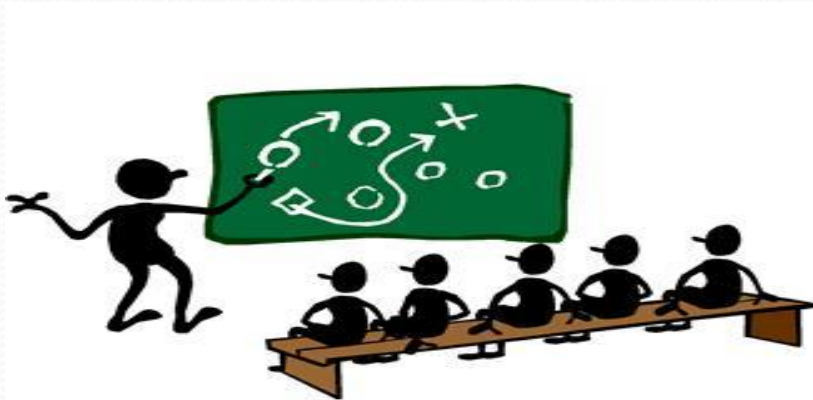
Summary of Investigator's responsibilities

Report all SAE immediately to the sponsor and comply with applicable regulatory requirement for reporting

Investigator

❖ PI

- ❖ is fully accountable for the trial/project
- ❖ able to motivate clinical team towards the goal to achieve the trial/project completed on time, within cost and technical specifications
- ❖ Able to delegate and guide team



Case

- **You are the PI** and within 4 weeks you will participate to the investigator meeting initiating a new clinical trial. You are aware that study team has a negative attitude towards this new project as everyone worked very hard last year and the new study is sponsored by a small company with limited resources...
- What should you do to prepare your team for the investigator meeting?



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Informed Consent

- **Process** by which a subject voluntarily confirms willingness to participate in a trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate.
- **The process is documented** by means of a written, signed and dated informed consent form.
- ✓ **The IC should be updated in case:**
 - ✓ Occurrence of new SAE
 - ✓ Increase in incidence of a known risk
 - ✓ Change in protocol
 - ✓ Change in contact details or contact personnel



Informed Consent Process

- The investigator retains overall responsibility
- Consent form documented in source documents
- All Informed consents must be checked by the study monitor at each visit

Informed Consent Form

- To be written and obtained in accordance with
 - ICH-GCP
 - The Declaration of Helsinki
 - All applicable regulatory requirements
- Two sections:
 - Subject Information Sheet
 - Consent Form

Informed Consent Process [1]

GCP requirements are:

1. **DO NOT coerce or unduly influence** a subject to participate or to continue to participate in a trial.
2. **PROVIDE the subject with ample time** and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial.
3. **ANSWER to all questions** to the satisfaction of the subject or the subject's legally acceptable representative.

Informed Consent Process [2]

During the informed consent discussion, do you always provide the following information?

- This is a research
- You will be randomly assigned to XYZ treatment group
- All trial procedures to be followed (including all invasive procedures)
- There are a possible risks
- There is a treatment available in the event of trial-related injury
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time
- That external people (i.e. monitors), will have direct access to the subject's original medical records
- Who should be contacted for further information regarding the trial and/or in the event of trial-related injury
- For how long the study will last
- The approximate number of subjects involved in the trial

Witness for ICF process

- If a subject is **unable to read**, an impartial witness should be present during the entire informed consent discussion
- After the written informed consent form is read and explained to the subject, and after the subject orally consented to participate (and possibly has marked and personally dated the informed consent form), **the witness should sign and personally date the consent form.**
- The witness **does not accept for study participation** on behalf of the subject but ONLY document in written that the subject agreed to participate

For discussion:

How/where is impartial witness identified?

Common ICF errors

- Non IRB approved
- Date or signatures inconsistencies
- No copy to subject
- Obtained after start of study procedures
- Language not suitable for the subject (e.g. too high level)
- Amended version used without IRB/IEC approval
- Fails to state the expected duration of the study
- Is overly optimistic in tone and wording



Exercise

Informed Consent Form Review

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IEC/IRB Responsibilities (ICH-GCP 3)

“An IRB / IEC should safeguard the rights, safety and well-being of all trial subjects”.

Which documents does the IEC/IRB review?

- Protocol & amendments
- Consent & updates
- Recruitment procedures
- Patient instructions (written)
- Investigator brochure
- Safety information
- Payments and compensation available to subjects
- Investigator CV
- Any other documents as deemed necessary

IEC/IRB [1]



IEC/IRB **must confirm** the CTA review in writing and by listing all submitted documents with the respective identifier and version number

IEC/IRB [2]

- ✓ Reasonable number of members (at least 5)
- ✓ Collectively have qualifications to review the study (at least 1 member independent from the institution + 1 member non-scientific)
- ✓ Only independent members should vote
- ✓ A list of members should be available
- ✓ Should operate according to written SOP
- ✓ Meetings planned and announced
- ✓ Document opinion in writing
- ✓ Receive reports on safety
- ✓ Receive reports on deviations
- ✓ Retain relevant records (at least 3 years after study completion)
- ✓ Majority vote required

Yes or No?

Should document be resubmitted to EC for:

1. A modification in the informed consent?

Yes

2. A modification in the study site SOPs?

No

3. A protocol amendment?

Yes



Exercise

IRB Approval Document

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