

Good clinical Practice (GCP) and Declaration of Helsinki

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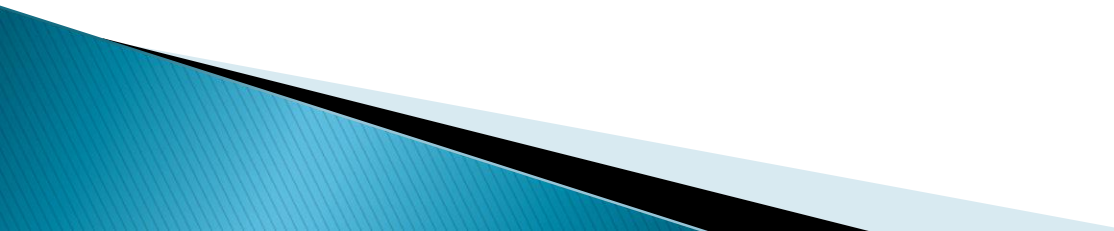


BRIEF INTRODUCTION

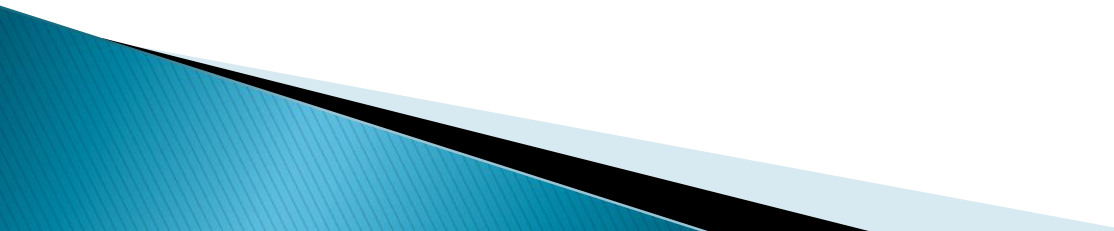
- ▶ *Maximum priority in any clinical trial should go to patient protection and nothing else.*
- ▶ *Patients' rights should be protected and no patient for whatever reasons should be denied these rights.*



INTRODUCTION

- ▶ Ethical questions of clinical research should never be underestimated.
 - ▶ The ethical principles of the Declaration of Helsinki have had a profound influence on GCP and the accepted way that clinical research is undertaken.
 - ▶ Clearly, there is an ethical question as to whether the foreseeable risks and inconveniences to the study subject in participating in the research project are outweighed by the anticipated benefits to that patient.
- 

INTRODUCTION....

- ▶ there are many examples in modern history where the risks to the individual trial subject have outweighed any benefit to either the subject or society.
 - ▶ Society is rightly wary of medical research involving human study subjects.
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HISTORY AND BACKGROUND OF GCP

- ▶ Good Clinical Practice (GCP) is an **international ethical and scientific quality standard** for the **design, conduct, performance, monitoring, auditing, recording, analyses and reporting** of clinical trials.

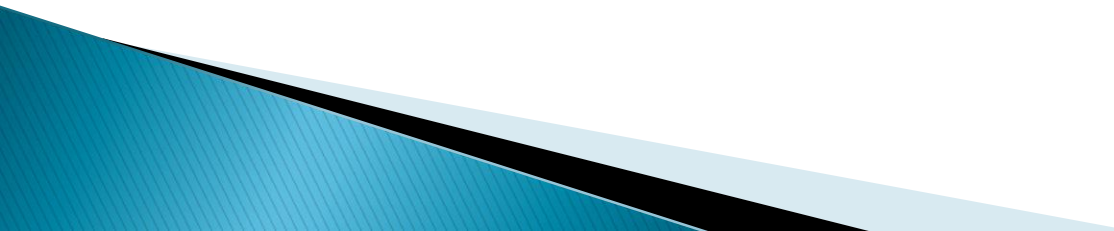
- ▶ GCP provides assurance –

the **data** and reported results are credible and **accurate**, and that the **rights, integrity and confidentiality** of trial subjects are respected and **Protected**.

HISTORY AND BACKGROUND OF GCP

- ▶ GCP aims to ensure that the **studies are scientifically authentic** , and
- ▶ that the clinical properties of the “Investigational Product” (IP) are properly documented.
- ▶ GCP is a key requirement for anyone involved in the conduct of clinical research.

HISTORICAL BACKGROUND

- ▶ It is very important to understand the background of the formation of the ICH–GCP guidelines as this, in itself,
 - ▶ explains the reasons and the need for doing so.
- 

Historical background of GCP

460BC	Oath of Hippocrates
1930's	U.S. Food, Drugs and Cosmetic Act
1947	Nuremberg Code
Dec. 10th 1948	Declaration of Human Rights
1962	Kefauver-Harris Amendment
1964, revised 2000	Declaration of Helsinki
1979	The Belmont Report
1982	International Guidelines for Biomedical Research Involving Human Subjects
1996	ICH-GCP guidelines issued
1997	ICH-GCP guidelines becomes law in some countries

Historical background of GCP

- ▶ The concept of the ‘good physician‘ dates back to the ancient world and it is evidenced by the Hippocratic Oath (460 BC).
- ▶ **1906 – United States** – issued first regulation regarding food & Drugs, came as a result of the fact that just anything could be bought across the counter then.
- ▶ Example - ‘**Grandma’s Secret**’ and ‘**Kopp’s Baby’s Friend**’ which contained **large doses of morphine**, ‘**Dr Bull’s Cough Syrup**’ which contained **morphine and chloroform**.

Historical background of GCP

- ▶ In **1938**, the Federal Food, Drug and Cosmetic Act was enacted by the Food and Drug Administration (FDA) and for the
- ▶ **first time, manufacturers were required to test drugs for safety and present the evidence of safety testing to the FDA prior to marketing.**

Historical background of GCP

- unethical and horrific experiments carried out during World War II at Nazi war camps by German physicians, who were subsequently tried and charged at the Nuremberg Military Tribunal.
- As a result, in 1947, the Nuremberg Code was created.
- This code states the need for a scientific basis in research on human subjects
and voluntary consent and protection of participants

Office of Human Subjects Research. The Nuremberg Code [Web Page]. 1949; Available at <http://ohsr.od.nih.gov/guidelines/nuremberg>.

The Doctors Trial (the Medical Case of the Subsequent Nuremberg Proceedings) [Web Page]. Available at http://www.ushmm.org/research/doctors/Nuremberg_Code.htm.

Historical background of GCP

- ▶ The Universal Declaration of Human Rights (December 10th 1948) was also adopted and proclaimed by the United Nations after the atrocities of World War II and it further reiterated the human factor involved in medical experiments.
- ▶ In 1964, the Declaration of Helsinki was developed by the World Medical Association, forming the basis for the ethical principles that underlie the ICH-GCP guidelines we have today.
- ▶ The focus of this declaration is the protection of the rights of human subjects and this is clear in its introduction ::

The Declaration of Helsinki (1964)

- ▶ The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty”.

1962 – Thalidomide tragedy

In 1962 the world was shocked by the severe foetal limb deformities linked to the use of maternal thalidomide.

In fact this drug reaction was only discovered after 10,000 infants were born in over 20 countries worldwide.

Kefauver-Harris Amendment was passed which required the FDA to evaluate all new drugs for safety and efficacy.

Lenz W. Thalidomide and congenital abnormalities. Lancet 1961;i:45.

1962 – Thalidomide tragedy

- Thalidomide was **first introduced in 1956** as a potent and **apparently safe** non-barbiturate **sedative hypnotic** in West Germany.
 - **Animal experiments had shown** that the main difference between thalidomide and other hypnotics was its extremely **low acute toxicity**.
 - Hence, It gained widespread popularity in Europe and Canada.
 - Also, Thalidomide **could be purchased without a prescription**.
- Later, it also became popular in the treatment of **pregnancy-related morning sickness**.

1962 – Thalidomide tragedy

- ▶ In the **United States**, the FDA (Food and Drug Administration) **did not approve thalidomide for clinical use** because of reports of tingling hands and feet in people who used this drug over long periods of time.
- ▶ In **1961** Mc Bride and Lenz, two physicians working independently of each other, realized **a link between the consumption of this drug** and the birth of children with missing digits, arms and legs and deformities of internal organs (**phocomelia**).
- ▶ Worldwide 8000–10000 children in total were born with malformations of the body related to the use of thalidomide. When the severe teratogenic potential was realized, thalidomide was **immediately withdrawn from the markets in Europe and Canada**.

Lenz W. A short history of thalidomide embryopathy. *Teratology* 1988;38:203-15.

1979 – Belmont report

Another *important milestone* in the formation of the ICH-GCP guidelines was *The Belmont Report* - issued in *April 1979* by the National Commission for Protection of Human Subjects of Biomedical and Behavioural Research.

THE BELMONT REPORT (1979) – PRINCIPLES

1. *Respect for Persons*: This principle acknowledges the dignity and freedom of every person.

It requires obtaining informed consent from research subjects (or their legally authorised representatives)

2. *Beneficence*: This principle requires that researchers maximise benefits and minimise harms associated with research.

Research related risks must be reasonable in light of the expected benefits.

3. *Justice*: This principle requires equitable selection and recruitment and fair treatment of research subjects.

‘International Guidelines for Biomedical Research Involving Human Subjects’

- ▶ 1982 - WHO and the Council for International Organizations of Medical Sciences (CIOMS) issued this document.
- ▶ To help developing countries apply the principles of the Declaration of Helsinki and the Nuremberg Code .
- ▶ Worldwide, many organisations and committees issued various documents and guidelines on the same issue as the decision was taken to consolidate all these guidelines into one universal guideline to be used globally.

Finally, the need for GCP –

- ▶ In an effort to overcome international GCP inconsistencies throughout the countries, the International Conference for Harmonisation Of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued the ICH Guidelines: Topic E6 Guideline for GCP.
- ▶ This guideline was approved on 17 July 1996 and implemented for clinical trials from 17 January 1997.
- ▶ The participants of these guidelines were representatives of authorities and pharmaceutical companies.

Reasons for GCP

- ▶ Increased Ethical Awareness
- ▶ Improved Trial Methods
- ▶ Clinical Trial Concept Better Understood
- ▶ Public/Political Concern over Safety Aspects
- ▶ Frauds and Accidents during Trials
- ▶ Growing Research and Development Costs
- ▶ Mutual Recognition of Data

The Declaration of Helsinki



Declaration of Helsinki



- set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA).
- widely regarded as the cornerstone document on human research ethics.
- Its role was described by a Brazilian forum in 2000 in these words "Even though the Declaration of Helsinki is the responsibility of the World Medical Association, the document should be considered the property of all humanity“.

World Medical Association (2013). "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects". JAMA 310 (20): 2191–2194.

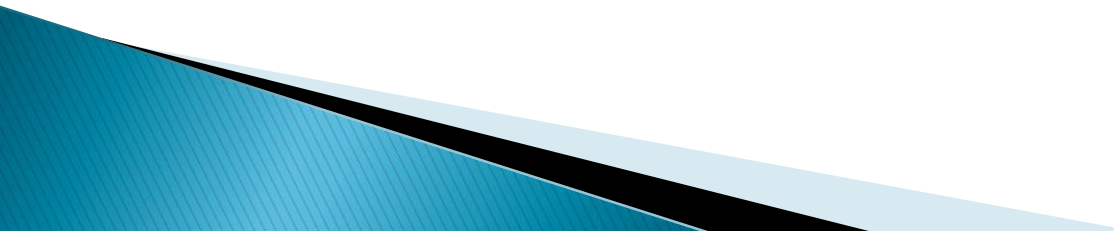
Snežana, Bošnjak (2001). "The declaration of Helsinki: The cornerstone of research ethics". Journal of Oncology 9 (3): 179–84

Declaration of Helsinki

- ▶ The Declaration was **originally adopted on June 1964 in Helsinki, Finland**, and has since **undergone seven revisions** (the most recent at the General Assembly in October 2013)
- ▶ Grown considerably in length from 11 paragraphs in 1964 to 37 in the 2013 version.
- ▶ It is an important document in the history of research ethics as it is the first significant effort of the medical community to regulate research itself.
- ▶ Prior to the 1947 Nuremberg Code there was no generally accepted code of conduct governing the ethical aspects of human research, although some countries, notably Germany and Russia, had national policies
- ▶ The Declaration more specifically addressed clinical research, **reflecting changes from the term 'Human Experimentation' used in the Nuremberg Code.**
- ▶ A notable change from the Nuremberg Code was a **relaxation of the conditions of consent**, which was 'absolutely essential' under Nuremberg. Now research was allowed without consent where a proxy consent, such as a legal guardian, was available

Principles of the Declaration

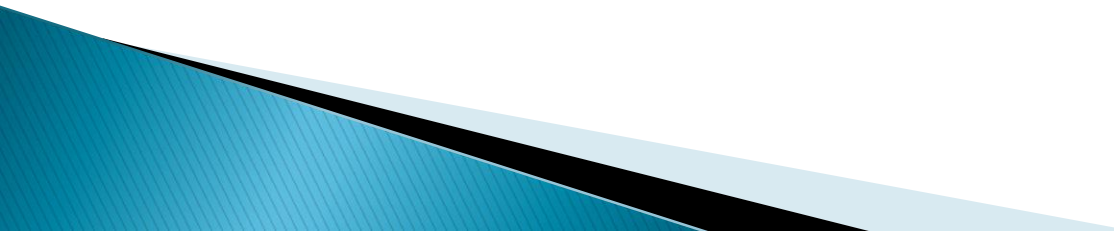
- ▶ The Declaration is morally binding on physicians, and that obligation overrides any national or local laws or regulations, if the Declaration provides for a higher standard of protection of humans than the latter.

 - ▶ The principles include –
 - a. Basic principles
 - b. Operational principles
- 

BASIC PRINCIPLES

- ▶ respect for the individual
- ▶ right to self-determination and the right to make informed decisions regarding participation in research, both initially and during the course of the research.
- ▶ The investigator's duty is solely to the patient or volunteer , and while there is always a need for research, the subject's welfare must always take precedence over the interests of science and society and ethical considerations must always take precedence over laws and regulations.

BASIC PRINCIPLES

- ▶ The recognition of the increased vulnerability of individuals and groups calls for special vigilance .
 - ▶ It is recognised that when the research participant is incompetent, physically or mentally incapable of giving consent, or is a minor , then allowance should be considered for **surrogate consent** by an individual acting in the subjects best interest. In which case their consent should still be obtained if at all possible.
- 

Operational principles

- ▶ Research should be based on a **thorough knowledge of the scientific background** , a **careful assessment of risks and benefits** , have a **reasonable likelihood of benefit to the population studied** and be conducted by **suitably trained investigators** using **approved protocols**, subject to **independent ethical review** and oversight by a properly convened committee .
- ▶ Information regarding the study should be publicly available.
- ▶ **Experimental investigations should always be compared against the best methods**, but under certain circumstances a placebo or no treatment group may be utilised .
- ▶ The interests of the subject after the study is completed should be part of the overall ethical assessment, including assuring their access to the best proven care . Wherever possible unproven methods should be tested in the context of research where there is reasonable belief of possible benefit

Future

- ▶ a final rule was issued on April 28, 2008 replacing the Declaration of Helsinki with Good Clinical Practice effective October 2008.
- ▶ This has raised a **number of concerns regarding the apparent weakening of protections for research subjects** outside the United States.

FDA abandons Declaration of Helsinki for international clinical trials. Social Medicine Portal
June 1st 2008

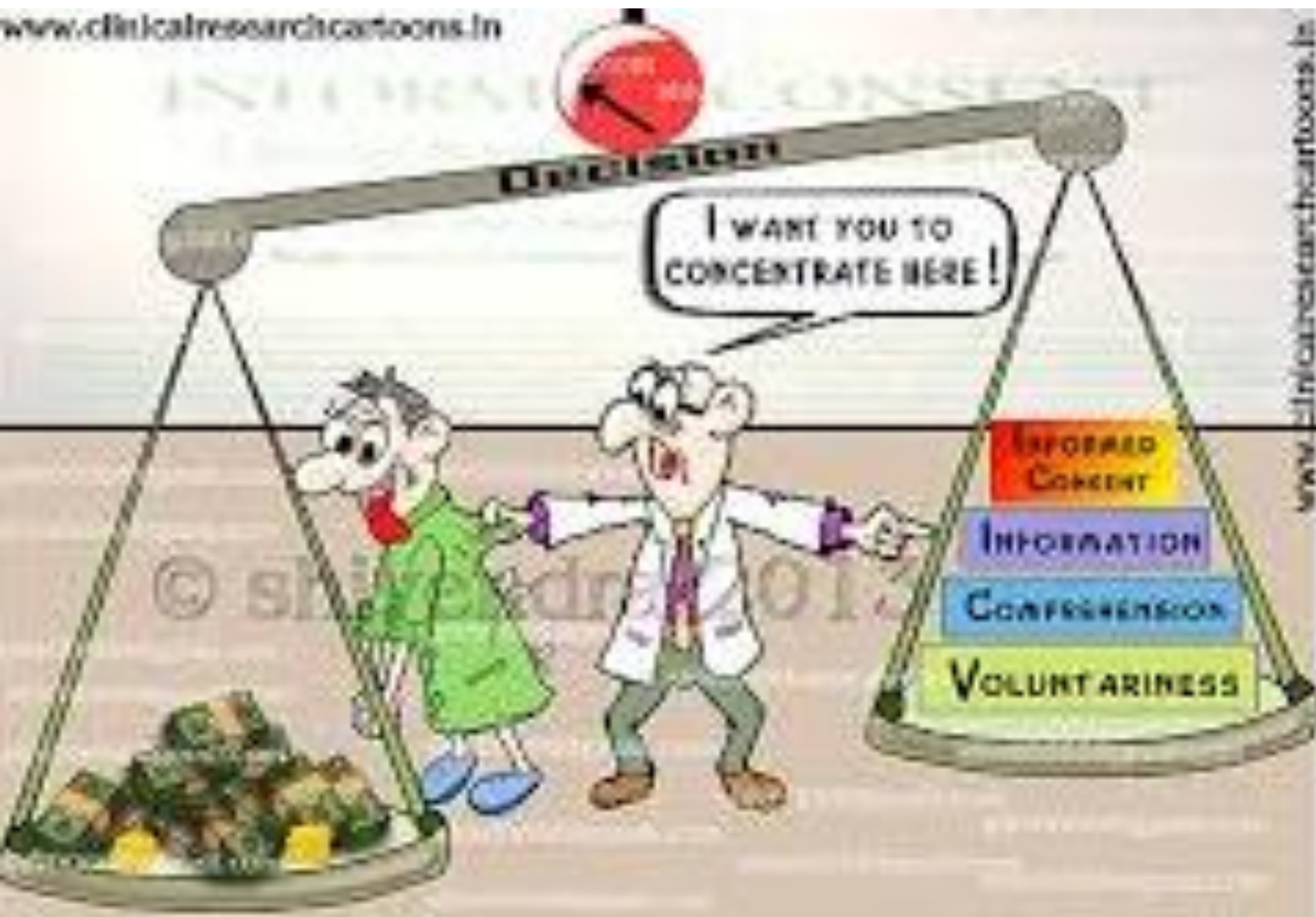
Rennie S. The FDA ditches the Declaration of Helsinki. Global Bioethics Blog May 6 2008.

GCP

Patients
rights &
safety

Accurate
credible
Trial data

INFORMED CONSENT

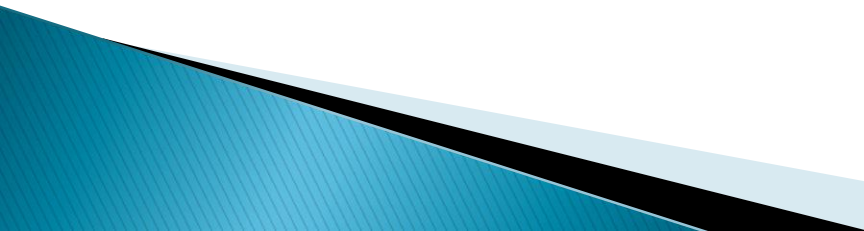


Good Clinical Practice (GCP)

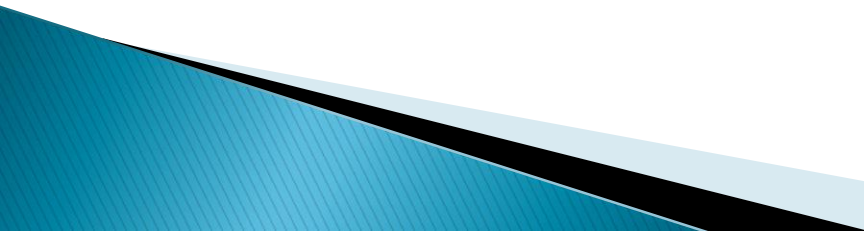
- ▶ The ICH-GCP is a **harmonised standard** that
 - ❑ protects the rights, safety and welfare of human subjects
 - ❑ improves quality of data

- ▶ **Compliance** with this standard **provides public assurance** that the rights, safety and well-being of trial subjects are protected and consistent with the principles of the Declaration of Helsinki, and that the clinical trial data is credible


Core principles of ICH-GCP

1. Clinical trials should be conducted **in accordance with ethical principles** that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
 2. Before a trial is initiated, foreseeable risks and inconveniences **should be weighed against anticipated benefit** for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- 

Core principles of ICH-GCP

3. The rights, safety and well-being of the trial subjects are the most important considerations and **should prevail over interest of science and society.**
 4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
 5. Clinical trials should be scientifically sound, and described in clear, detailed protocol.
 6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/favourable opinion.
- 

Core principles of ICH-GCP


7. The medical care given to, and medical decisions made on behalf of subjects should always be the **responsibility of a qualified physician** or, when appropriate, of a qualified dentist.
 8. Each individual involved in conducting a trial should be qualified by **education, training, and experience** to perform his or her respective task(s).
 9. **Freely given informed consent** should be obtained from every subject prior to clinical trial participation.
 10. All clinical trial information **should be recorded, handled, and stored** in a way that allows its accurate reporting, interpretation and verification.
- 

Core principles of ICH-GCP

11. The **confidentiality of records** that could identify subjects should be protected, **respecting the privacy** and confidentiality rules in accordance with the applicable regulatory requirement(s).

12. Investigational products should be manufactured, handled and stored in accordance with applicable **Good Manufacturing Practice (GMP)**. They should be used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.



I just heard there's a drug in trials that might stop my cancer!!

Great! Are you going to volunteer to participate for the trial?

Of course not...why would I do that?

I wouldn't either. Sure hope they get some results soon...



If we don't know which drugs are safest and most effective for pregnant women and children, why don't they just let us into more clinical trials?

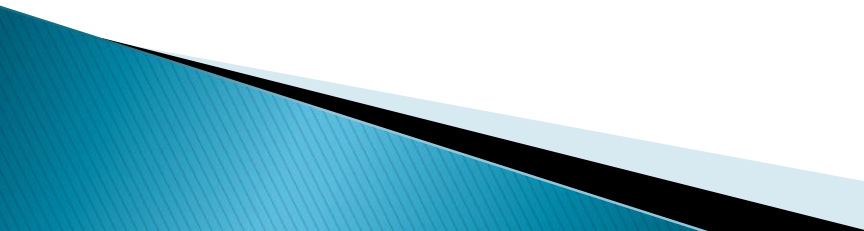
To protect you from untested drugs



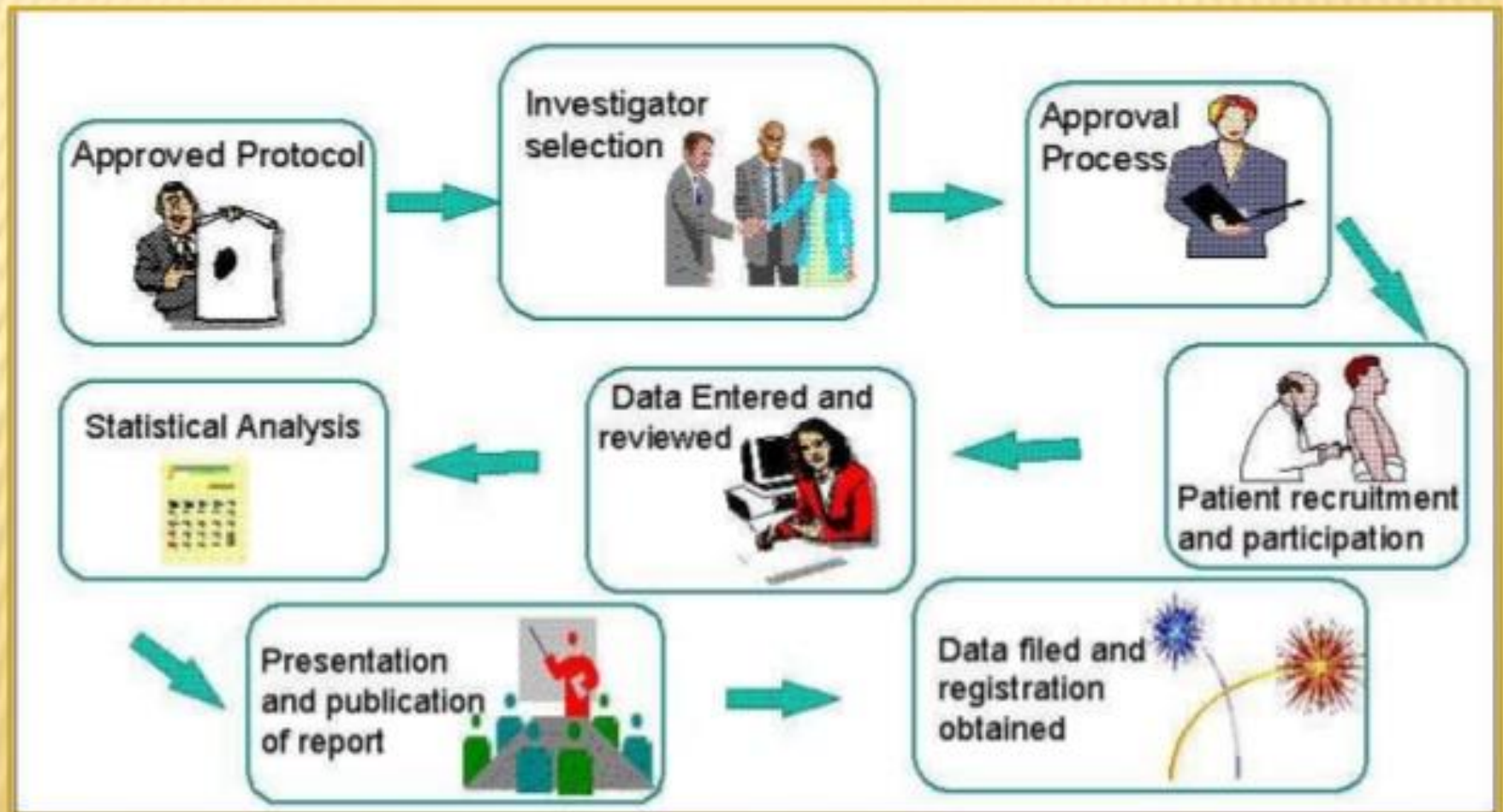
Statistically-funny.blogspot.com

CATCH-22: Clinical Trial Edition

TO SUMMARISE – GCP

- ▶ All clinical trials should be conducted in accordance with ethical principles, sound scientific evidence and clear detailed protocols. The benefits of conducting trials should outweigh the risks. The rights, safety and wellbeing of trial participants are of paramount importance and these should be preserved by obtaining informed consent and maintaining confidentiality.
 - ▶ The care must be given by appropriately qualified personnel with adequate experience. Records should be easily accessible and retrievable for accurate reporting, verification and interpretation.
 - ▶ Investigational products should be manufactured according to Good Manufacturing Practice.
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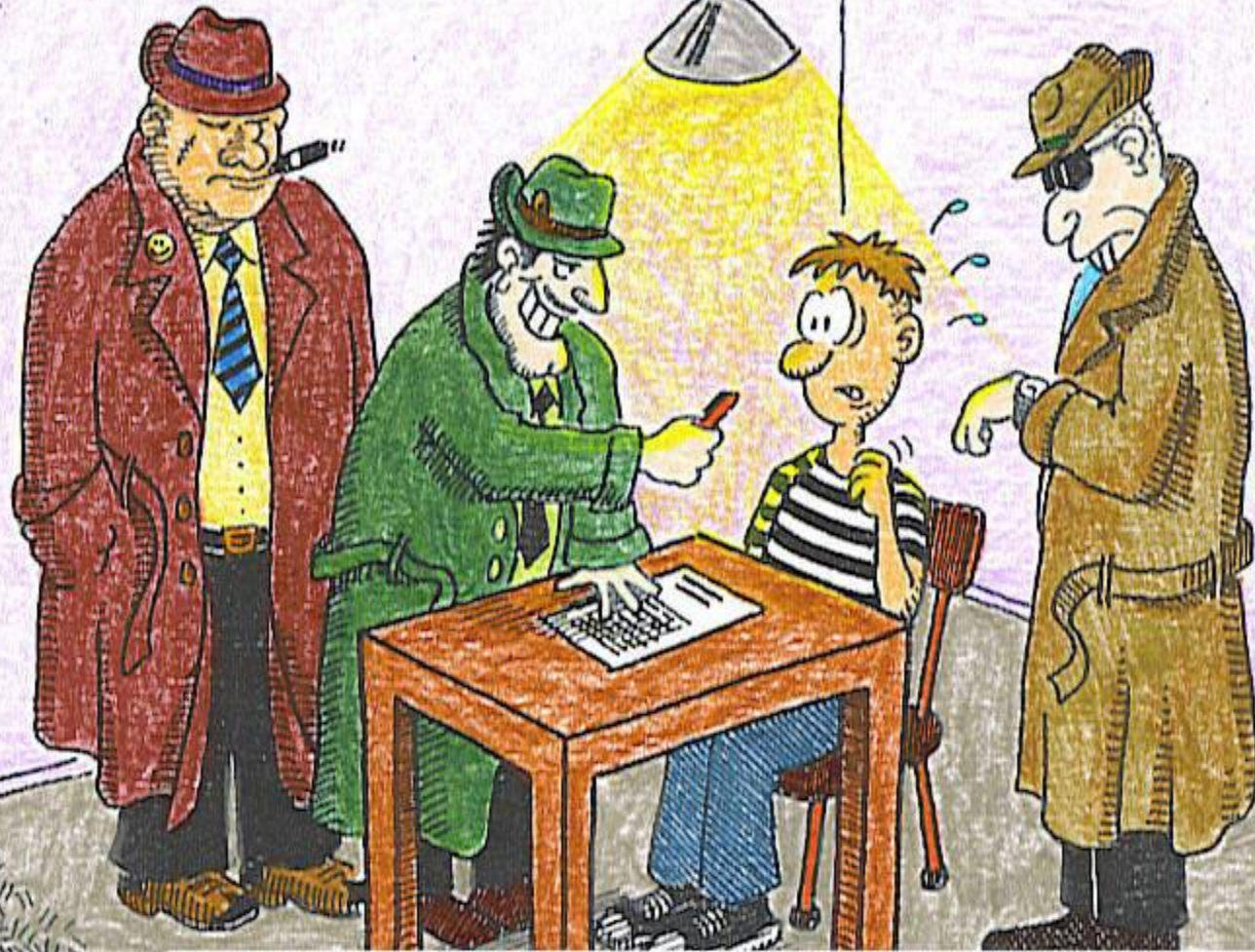
CLINICAL TRIALS IN A NUTSHELL



GCP participants and their responsibilities

- ▶ **Regulatory Authorities** - Review submitted clinical data and conduct inspections
- ▶ **The sponsor** - Company or institution/organization which takes responsibility for initiation, management and financing of clinical trial
- ▶ **The project monitor** - Usually appointed by sponsor
- ▶ **The investigator** - Responsible for conduct of clinical trial at the trial site. Team leader.
- ▶ **The pharmacist at trial location** - Responsible for maintenance, storage and dispensing of investigational products eg. Drugs in clinical trials
- ▶ **Patients** - Human subjects
- ▶ **Ethical review board or Committee** - for protection of subjects
Appointed by Institution or if not available then the Authoritative Health Body in that Country will be responsible

THE CONSENT PROCESS...



Don Payne

Good clinical Practice (GCP) vs Declaration of Helsinki

- ▶ Since 1964, the Declaration of Helsinki has stood as one of the world's most authoritative statements on ethical standards for human research.
- ▶ Drafted by the World Medical Association to provide medical researchers with ethical guidance, the Declaration has undergone major revisions, most recently in October, 2008.
- ▶ For many years the US FDA has required that foreign clinical studies supporting applications for drug licensure comply with the Declaration.
- ▶ on Oct 27, 2008, the FDA formally discontinued its reliance on the Declaration and substituted the International Conference on Harmonization's Guideline for Good Clinical Practice (GCP).

Aschcroft RE. The Declaration of Helsinki. In: Emanuel EJ, Grady C, Crouch RA et al, eds. The Oxford Textbook of Clinical Research Ethics. New York: Oxford University Press, 2007.

World Medical Association. Declaration of Helsinki. October, 2008.
<http://www.wma.net/e/policy/b3.htm> (accessed Oct 25, 2015)

WHY GCP?

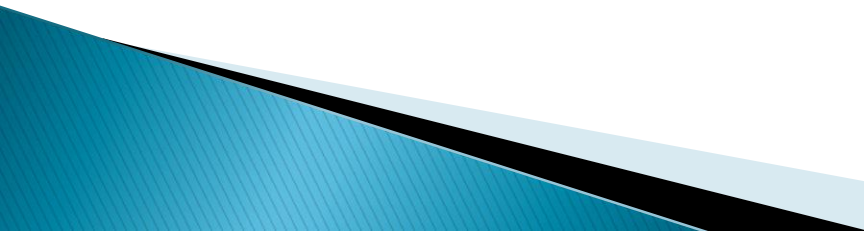
- ▶ rationale behind FDA's action is complex
- ▶ reflects an effort to balance important interests and public-policy goals.
- ▶ Among the **FDA's reasons** are –
 - a) **need to assure quality of foreign data** submitted to the agency
 - b) a wish **to prevent confusion** among researchers when the Declaration of Helsinki under goes revision
 - c) a worry that future modifications could “contain provisions that are inconsistent with US laws and regulations”.

Department of Health and Human Services, Food and Drug Administration. Human subject protection; foreign clinical studies not conducted under an investigational new drug application. Fed Reg April 28, 2008. 22800-16.
<http://www.fda.gov/cber/rules/forclinstud.pdf> (accessed Oct 9, 2015).

FDA's efforts and its criticism

- ▶ The FDA's latest action completes a process begun in 2001 when the agency declined to recognise the 2000 revision.
- ▶ **Certain schools of thought** say that at a time when the volume of overseas trials is increasing, the FDA's new policy is troubling.

The reasons being –

- ▶ First, the Declaration of Helsinki has a **moral authority** that **GCP lacks**.
 - ▶ Second, the Declaration of Helsinki has a **breadth and depth** that **GCP lacks**.
 - ▶ Third, the FDA's departure from the Declaration of Helsinki **could undermine its stated goals of clarity** and regulatory harmonisation.
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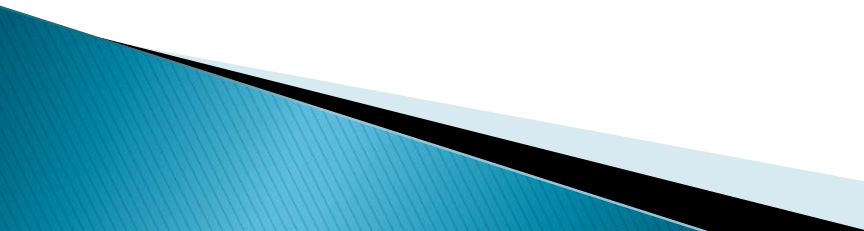
Moral authority that GCP lacks.

- ▶ The Declaration - long been recognised as a leading international ethical standard for research.
- ▶ **World Medical Association includes 85 national medical societies from every part of the globe, the International Conference on Harmonization (ICH) consists of only voting members from the USA, the European Union, and Japan.**
- ▶ authors of GCP acknowledge the authority of the Declaration of Helsinki when they state that **a goal of GCP is “consisten[cy] with the principles that have their origin in the Declaration of Helsinki”**.
- ▶ The FDA regulates the largest drug market in the world and we worry that its replacement of the Declaration of Helsinki with a less morally authoritative document may undermine the international ethical standards for research.

breadth and depth that GCP lacks

- ▶ focus of GCP is regulatory harmonisation, not the articulation of ethical commitments.
- ▶ Careful examination of the two documents reveals several important ethical issues that are addressed in the Declaration about which GCP is silent.

Requirements in latest revision of Declaration of Helsinki but absent in GCP

1. **Investigators to disclose** funding, sponsors, and other potential conflicts of interest to both research ethics committees and study participants
 2. **Study design to be disclosed publicly** (eg, in clinical trial registries)
 3. **Research**, notably that in developing countries, to benefit and **be responsive to health needs of populations** in which it is done.
 4. **Restricted use of placebo controls** in approval process for new drugs and in research done in developing countries
 5. **Post-trial access to treatment**
 6. **Authors to report results accurately**, and publish or make public negative findings.
- 

undermine its stated goals of clarity

- ▶ if many countries continue to use the Declaration, US researchers will encounter the same “confusion” that the FDA is attempting to prevent with its new rule.
- ▶ Similarly, if other countries follow the FDA’s lead and abandon the Declaration of Helsinki, the result could be the balkanisation of ethical standards in international research.

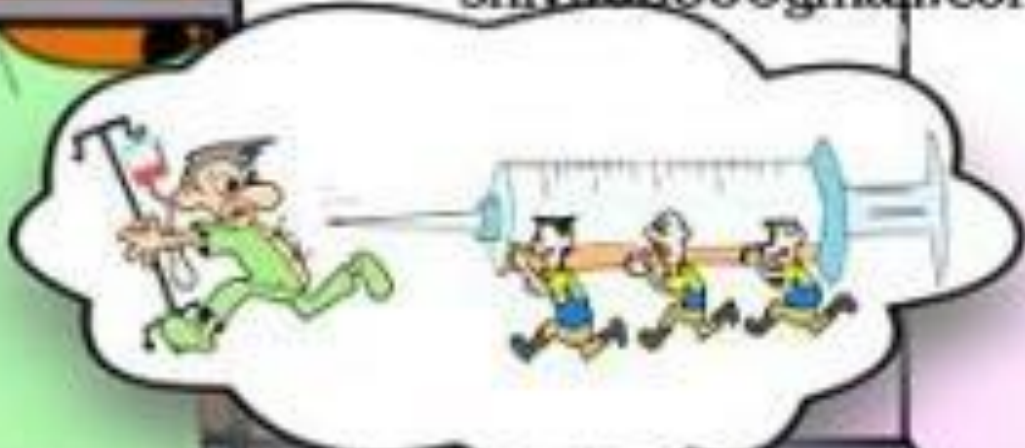
Following the above criticism, few societies and scholars suggest that the FDA should rejoin the international community in requiring that studies be done in accordance with the Declaration of Helsinki.

However,

- ▶ Despite of all the criticism, it is strongly believed globally that GCP will lead to data from clinical trials that are more acceptable –
 - I. for publication, and
 - II. for submission to health authorities to support a new treatment.

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IT'S DIFFERENT FROM
CLINICAL PRACTICE....
...IT WILL BE CONDUCTED
ON A LARGER SCALE...



www.clinicalresearchcartoons.in



Its been a humble effort by me

Thanks for your patience and cooperation

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