



# Ethical Considerations in Clinical Trials

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22<sup>nd</sup> December, 2007

59<sup>th</sup> Indian Pharmaceutical Congress

Varanasi, India

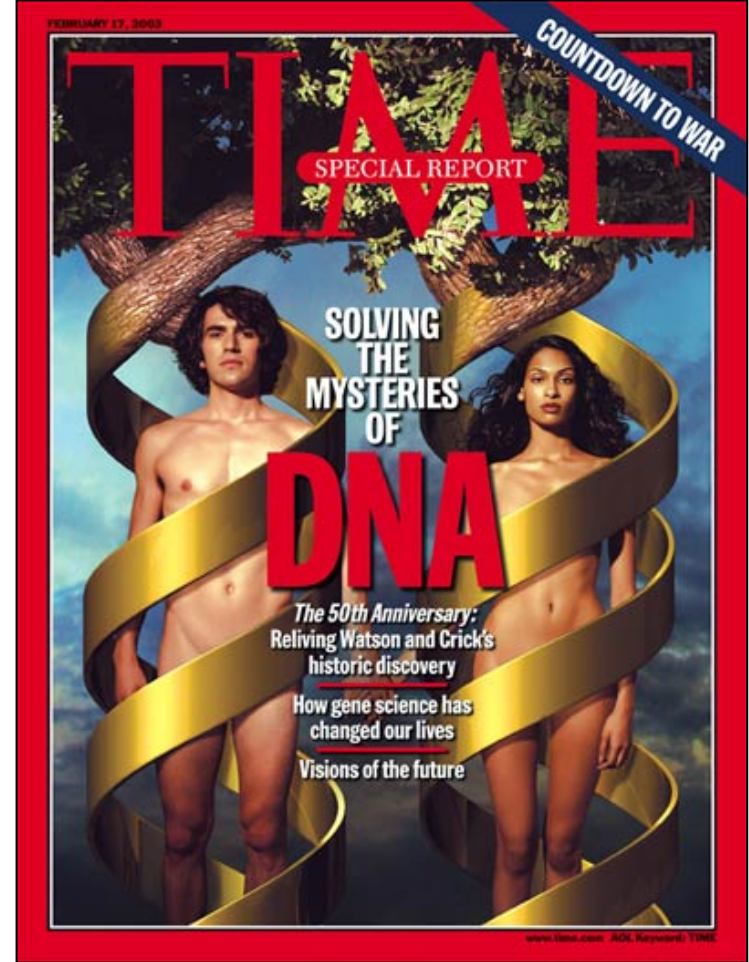
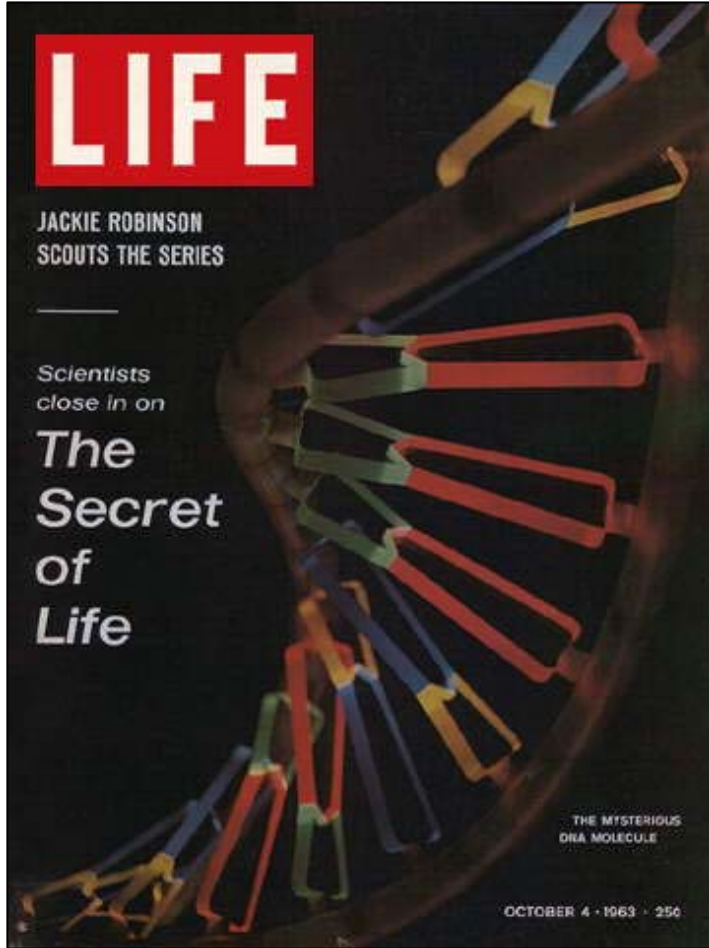
*Ethics is not a natural science, it's a creation of human mind!*

# Overview

- Background
- Development and practice of guidelines & principles
- Ethical considerations during various parts of the study
  - a. Planning and conceptualization of the Study
  - b. Conduct of study
  - c. Analysis of study data
  - d. Publication of report
  - e. Trial is completed
- Justice & Conclusion

# Science

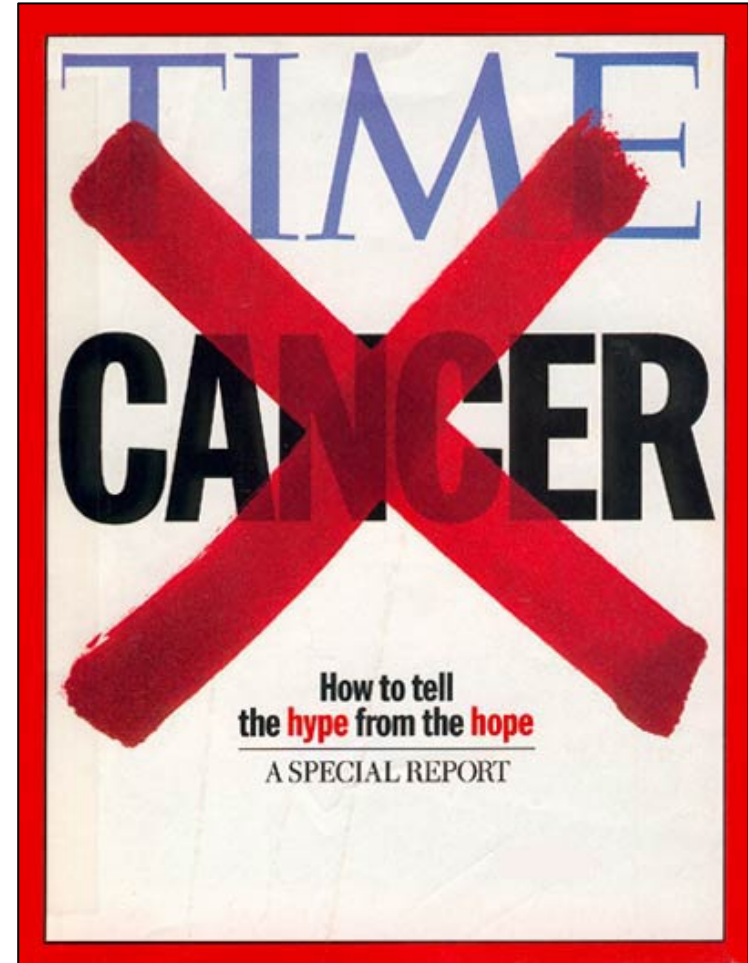
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*How science has changed our lives? Discovery of DNA*

# Medicine

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*When cancer plagued mankind, medicine of hope!*

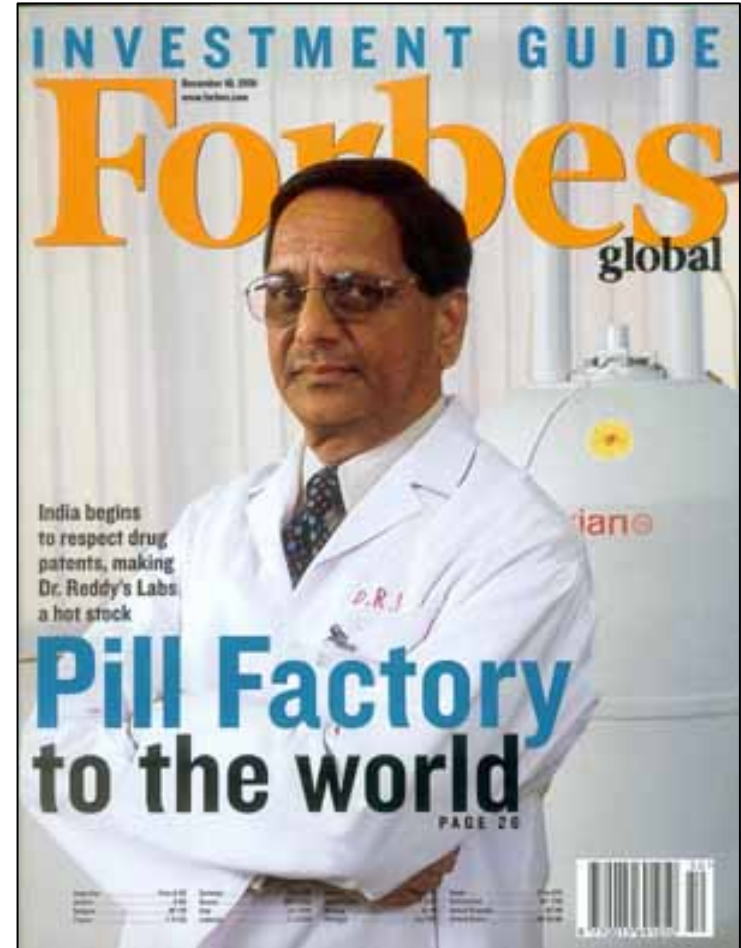
# Health Research



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*Its not immutable! Being open to the influence of time, place and situation; MAY BENEFIT OR CAUSE HARM*

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*No man cared less for the profits of the profession, or more for the honour of it!*

# The Demands of Society

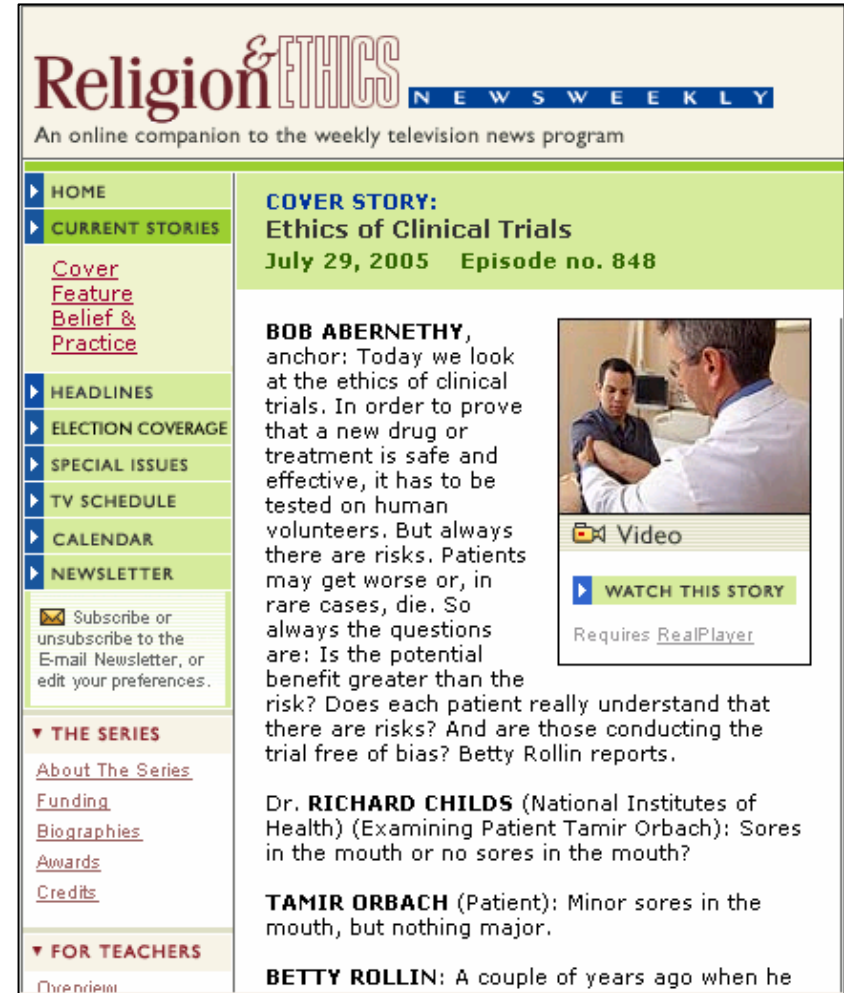
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*Are we meeting expectations with the advances in medicine?*

# Ethics of clinical trials

- E = Empowering the subject for the consent
- T = Transparent processes to follow
- H = Humane thinking in the clinical trial
- I = Internationally accepted data by following ethics
- C = Consult the guidance regularly
- A = Authenticity of trial objectives
- L = Legal representation



The screenshot shows the website for "Religion & Ethics News Weekly". The main headline is "COVER STORY: Ethics of Clinical Trials" dated July 29, 2005, Episode no. 848. The article text discusses the ethics of clinical trials, mentioning anchor Bob Abernethy and Dr. Richard Childs. It also includes a video player for "WATCH THIS STORY" which requires RealPlayer. A sidebar on the left contains navigation links like HOME, CURRENT STORIES, HEADLINES, and a newsletter subscription form.

*How can our society promote clinical research?*

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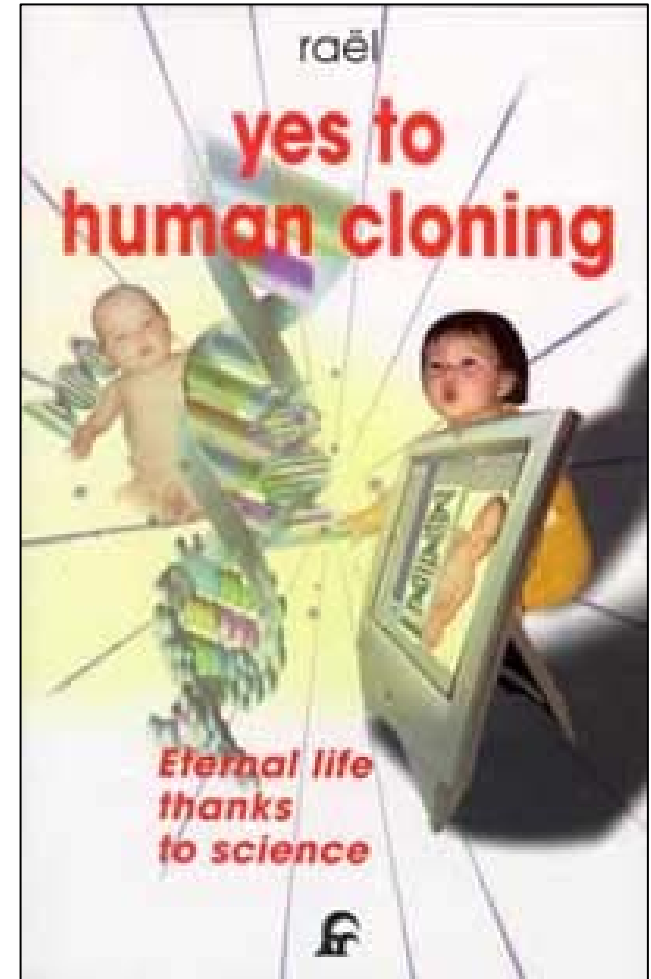
What should we expect from a  
Good Clinical Practice  
framework  
for clinical trials?

vis-à-vis India?  
vis-à-vis the United States & Europe?  
globally?

What does GCP mean?  
*to me?*

# Ethical Issues in Biomedical Research

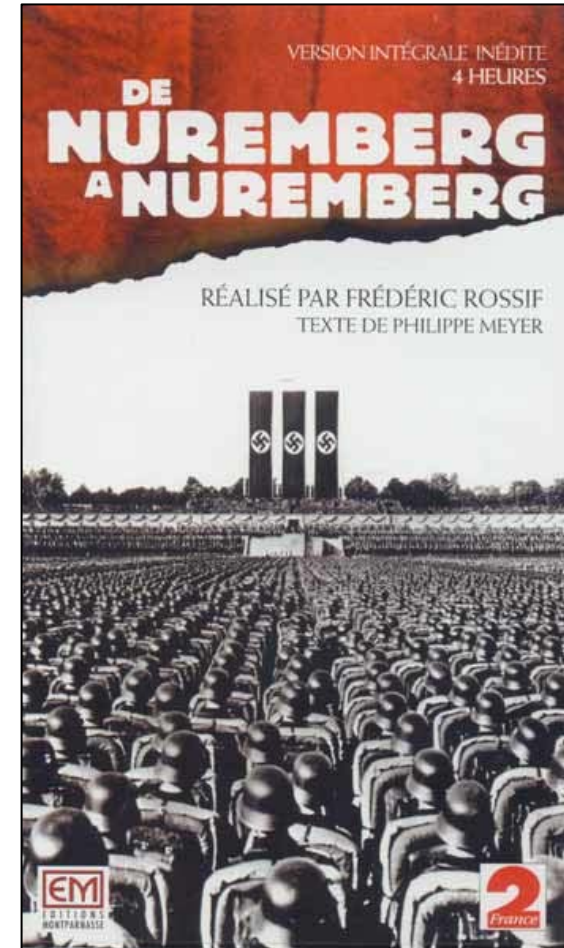
- The use of control arms (placebo)
- 'Standard of care'
- Informed consent process
- Community consultation
- Individual and community access to research
- The role & responsibility of ethics committees (ECs)
- Compensation for trial injury
- Counselling
- Patient/Participant Confidentiality and Privacy
- Locating phase I, II, and III trials



*Falsification, Alteration of data, plagiarism, favouritism*

# Ethical Issues in Biomedical Research (cont.)

- Medical treatment during the course of research
- Product availability
- Sponsorship
- Liability & Insurance
- Tissues
- Stem Cell Research
- Gene Transfer
- Data Protection
- Monitoring (DSMBs)
- Data Ownership
- Proprietary Information/Knowledge
- Botanical/Traditional Medicines



*Respect for human dignity includes beneficence / non-maleficence, utility, justice*

# M.H. Pappworth in 1967

“No physician is justified in placing science or the public welfare first and his obligation to the individual, who is his patient or subject, second. No doctor, however great his capacity or original his ideas, has the right to choose martyrs for science or for the general good.”

- ‘ My proposal is that researchers and reviewers should be expected to contemplate and sign a statement that says: “I would not hesitate to submit myself, or members of my own family, or anybody for whom I have any respect or affection, if in circumstances identical to those of the intended subjects”’.



# Codes of Ethics, Guidelines & Regulations

- 1000 BC : *Caraka Samhita* to 1-2 AD
- 1947 : Nuremberg Code
- 1956 : Code of Medical Ethics, MCI
- 1964 : Helsinki Declaration
- 1979 : Belmont Report (USA)
- 1980 : Policy Statement on Ethical Considerations involved in research on Human Subjects
- 1982/1992 : Proposed International Guidelines (WHO/CIOMS)
- 1986 : EPA Act for r-DNA products
- 1997 : Guidelines for Exchange of Human Biological Material for Biomedical Research Purposes
- 2000 : Delhi Medical Council Regulations
- 2000 : Revised ICMR Ethical guidelines
- 2001 : Indian GCP Guidelines
- 2004 : ART Guidelines

*What is the minimum that I can do?*



# EU Directive 2001/20/EC

Good clinical practice is a set of internationally recognised 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.

## Article 1, Scope

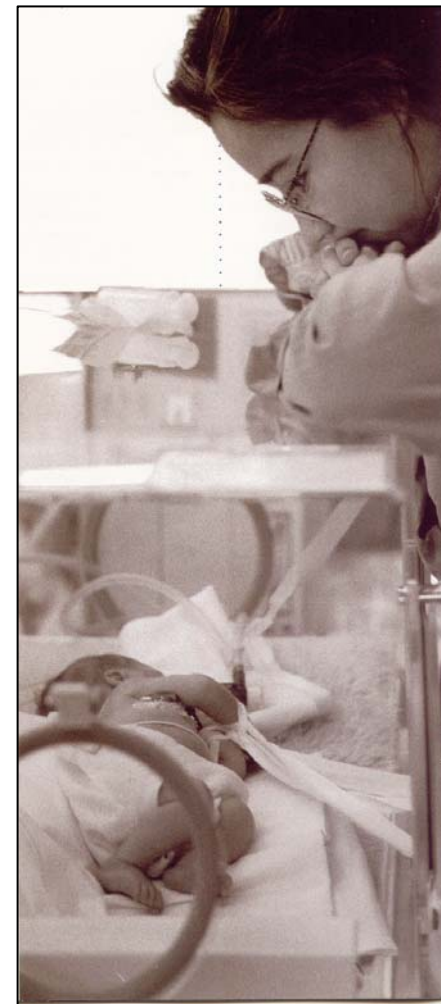
L 121/34	EN	Official Journal of the European Communities	1.5.2001
<b>DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL</b> of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use			
THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,		(3)	Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.
Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,		(4)	In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.
Having regard to the proposal from the Commission (1),		(5)	The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.
Having regard to the opinion of the Economic and Social Committee (2),		(6)	In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries. The harmonisation of technical requirements for the development
Acting in accordance with the procedure laid down in Article 251 of the Treaty (3),			
Whereas:			
(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (4) requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product. Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (5) lays down uniform rules on the compilation of dossiers including their presentation.			
(2) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.			
(3) OJ C 306, 8.10.1997, p. 9 and OJ C 161, 8.6.1999, p. 5.			
(4) OJ C 95, 30.3.1998, p. 1.			
(5) Opinion of the European Parliament of 17 November 1998 (OJ C 379, 7. 12. 1998, p. 27), Council Common Position of 20 July 2000 (OJ C 300, 20.10.2000, p. 32) and Decision of the European Parliament of 12 December 2000. Council Decision of 26 February 2001.			
(6) OJ 22, 9.2.1965, p. 1/65. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).			
(7) OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).			

# Good Clinical Practice

A set of responsibilities

- Shared responsibilities
- Individual responsibilities

”

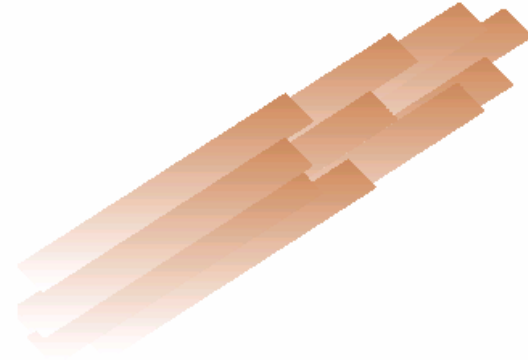


*Makes all parties to a study responsible  
for patient safety and study quality*

# ICH GCP

'The objective of this ICH GCP guidance is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.'

## **Guidance for Industry** **E6 Good Clinical Practice:** **Consolidated Guidance**



ICH  
April 1996

# Dimensions of GCP

## General Frameworks

- WHO GCP
- ICH GCP

## Regional/Applied Frameworks

- EU GCP
- US CFR

## National/Applied GCP Guidelines

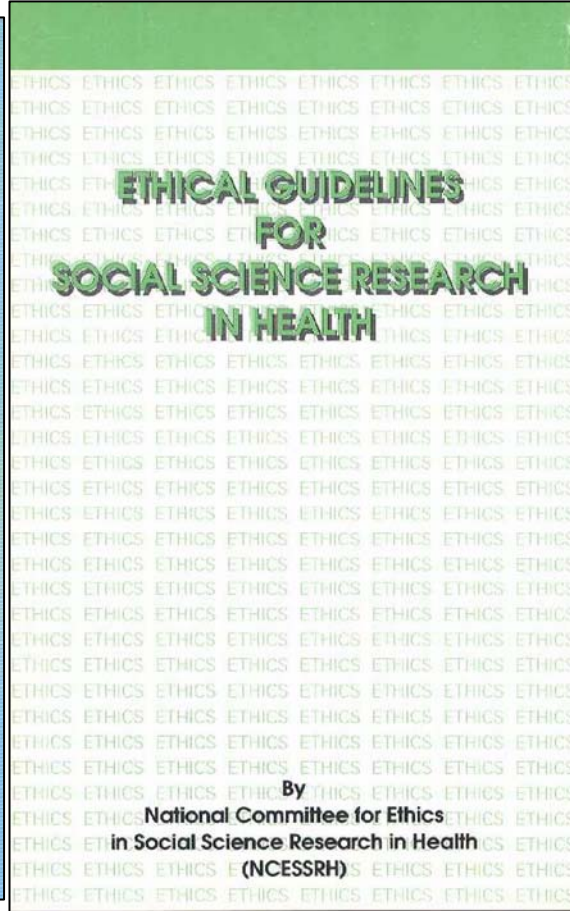
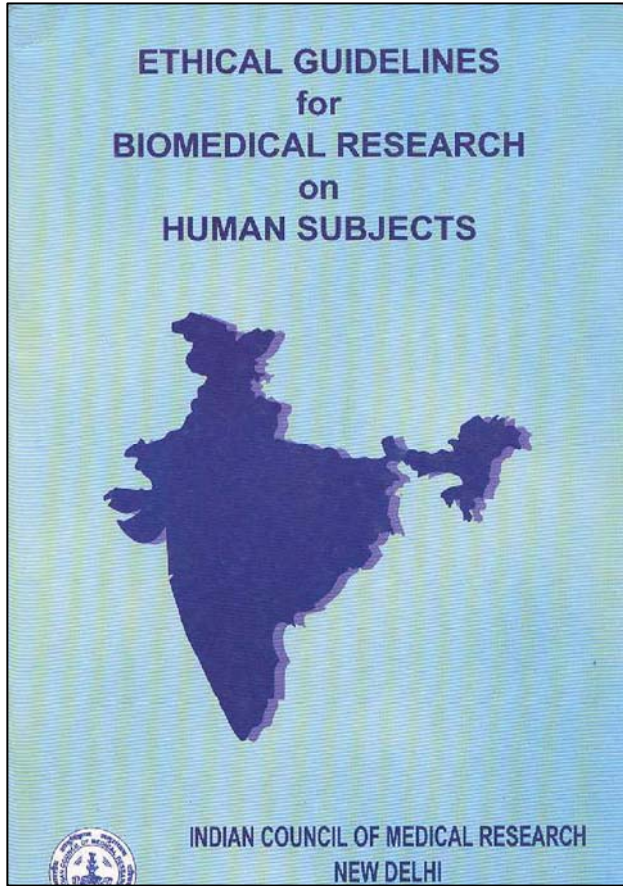
- India, China, Russia, Singapore, Malaysia, Indonesia, South America, South Africa, Turkey



*GCP is universally accepted as the standard for accepting data across borders.*



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## Good Clinical Practice Guidelines

GOOD CLINICAL PRACTICES FOR CLINICAL RESEARCH IN INDIA

**FOREWORD**

Clinical research is the key to the discovery of latest diagnostic methods and to develop modern drugs for treatment of diseases. Good Clinical Practices (GCP) is an ethical and scientific quality standard for designing, conducting and recording trials that involve the participation of human subjects. Compliance with this standard provides assurance to public that the rights, safety and well being of trial subjects are protected, consistent with the principles enshrined in the Declaration of Helsinki and ensures that clinical trial data are credible.

It has been widely recognized that India offers unique opportunities for conducting clinical trials in view of the large patient pool, well-trained and enthusiastic investigators and premiere medical institutes available in the country along with considerable low per patient trial cost, as compared to developed countries.

A need was, however, felt to develop our own Indian Guidelines to ensure uniform quality of clinical research throughout the country and to generate data for registration for new drugs before use in the Indian population. An Expert Committee set up by Central Drugs Standard Control Organisation (CDSCO) in consultation with clinical expert has formulated this GCP guideline for generation of clinical data on drugs.

The Drug Technical Advisory Board (DTAB), the highest technical body under D&C, Act, has endorsed adoption of this GCP guideline for streamlining the clinical studies in India.

I am confident that this guideline will be immensely useful to research institutions, investigators, institutional ethics committees and regulators in providing desired direction. The guideline would also be helpful to companies who may want to locate their clinical programme in the country.

Place: New Delhi  
Dr. S. P. Aganval, Director General of Health Services and Chairman, DTAB

### INTRODUCTION

The history of Good Clinical Practice (GCP) statute traces back to one of the oldest enduring traditions in the history of medicine: The Hippocratic Oath. As the guiding ethical code it is primarily known for its edict to do no harm to the patient. However, the complexities of modern medicine research necessitate a more elaborate set of guidelines that address a Physician's ethical and scientific responsibilities such as obtaining informed consent or disclosing risk while involved in biomedical research.

Good Clinical Practice is a set of guidelines for biomedical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the well being of the study subject. It aims to ensure that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical substances under investigation are properly documented. The guidelines seek to establish two cardinal principles: protection of the rights of human subjects and authenticity of biomedical data generated.

These guidelines have been evolved with consideration of WHO, ICH, USFDA and European GCP guidelines as well as the Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India.

*In letter and spirit to follow GCP; covers prophylactic, treatment, diagnostic and epidemiology*

# Clinical Development

Was there really a need for this CT?



Literature available?  
Scientific advice sought?  
Studies in sub-groups?

Are sample size and statistical power adequate to show an effect?



Were calculations based on

- Potential previous experience
- Validated end points
- Clinically relevant differences

Were patient's chances of receiving an active medicines acceptable?



Treatment ratio balanced towards

- Equal chances
- Sample size
- Severity of disease

What type of patients should have been entered?



- Volunteers or patients
- In/Out patients
- Vulnerable groups

*Relevance of standard of care in design of the study!*

# Planning of Study

- Age:
  - Younger or older populations or dementia patients
- Gender:
  - Women of childbearing potential
- Present clinical status:
  - Unstable / emotional patients
- History of other diseases:
  - anticipated benefits outweigh the risks associated with the trial.
- Wash out period of non-trial medicinal products:
  - duration of wash out with drug and its risks
- Occupation:
  - ambulatory patients involved in heavy machinery work

***Trial involving human not fulfilling simple scientific demand is unethical***

# Conduct of the Study

## Violations

- Minor/Major
- Extent of the violation
- Risks for the patient due to violation in trial

## Compliance

- Checking signed ICF for signature of patient and the investigator
- Invasion of patient privacy
- Compliance to the local and regulatory guidance

## Discontinuation from the Clinical Trial

- Obligation to take care of the patient until recovery or improvement to prior state
- Risk of rechallenging

## Early termination

- Investigator's decision
- Justifiable reasons

*Getting into details*

# Analysis and Reporting of Trial Results

## Power of the study

- Sufficient sample size critical to have power of the study
- Statistical significance vs clinical significance

## Communication of the study

for validity, timeliness and accessibility of new knowledge for patients, physicians and regulatory

## Safety of the study

Withholding data on ADRs highlights the threat of unethical reporting of research results to public safety and physician's trust in research

*Just because it is recorded doesn't mean its done!*

# Publication of trial results

- a. Over interpretation of “significant” findings in small trials
- b. Selective reporting based on p values
- c. Selective reporting of outcomes in the abstracts
- d. Subgroup analysis done without interaction tests
- e. Negative or detrimental studies not published
- f. Putting undue stress on results from subgroup analysis
- g. Inappropriate subgroup analysis
- h. Selective reporting of (1) subgroups, (2) outcomes, (3) time points
- i. Selective reporting of positive results or omission of adverse events data
- j. Failure to report results or long delays in reporting
- k. *Post hoc* analysis not admitted
- l. Giving incomplete information about analysis with no significant results
- m. Analysis conducted by the sponsor of the trial.

***CONSORT guidelines***

# When trial is completed?

- What responsibilities are owed to the research community?
- Encourage access to the benefits from findings
- Train researchers and care providers in the community
- Ensure privacy of participants and researchers

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ISO 9001:2000  
ISO 27001:2005

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# Justice

- **Vulnerability:** In research ethics, the principle of distributive justice forbids research risks and burdens being borne disproportionately by vulnerable groups within society;
- **Benefits:** Privileged in society cannot disproportionately reap research benefits
- **Distribution:** Research may be impossible to achieve in settings where equality, fairness, and the distribution of social good and harm are routinely abrogated
- **Potential Misuse:** Where permission is granted by the very people who are oppressing the potential participants, researchers must be aware of potential misuse of findings.
- **Permission:** there may be instances in which participation would be in the best interests of the minority group, but government officials deny access

# Conclusion

- Research entails risk
- Should we permit high risk research? (e.g. Gelsinger, Roche)
- Respect for persons + Beneficence = Paternalism or Disclosure of Risk
- subject as individual overrides all scientific hypothesis
- Controlled environment to practice environment
- Homogeneity of the data

*Pursuit of knowledge vs fame/fortune*

F. NO. A15169  
F. NO. A15170



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