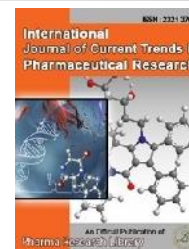




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### REVIEW ARTICLE

## Observations on Guidelines for Post Marketing Surveillance for Pharmaceuticals

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### ABSTRACT

Some issues about healthy volunteer recruitment in first-in-man trials and reimbursement remain unresolved, and they can be summarized as follows: There is a lack of international consensus on the definition of healthy status, based on standard physical, psychological, and laboratory parameters, suitable for the enrolment of candidate subjects in first-in-man trials. There is a need for guidelines about appropriate advertisements addressed to potential participants in first-in-man clinical trials, to set out specific ethical limitations. There is a lack of international and/or local statements about standard criteria for offering fair payments to healthy volunteers enrolled in first-in-man trials. (4) Based on current Italian regulations, there is a need for a national register to monitor the participation of healthy subjects in different early clinical trials at the same or different centers for drug experimentation. (5) In view of a “new era of early phase trials,” the national legislation should offer Italian investigators conducting phase 0 and phase I trials a comprehensive guideline encompassing all principles sanctioned.

**Keywords:** GCP guidelines, WHO, ICH, USFDA

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## 1. 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. 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.

## 2. Clinical trials an overview

The first proper clinical trial was conducted by the physician James Lind. The disease scurvy, now known to be caused by a Vitamin C deficiency, would often have terrible effects on the welfare of the crew of long distance voyages. In 1740, the catastrophic result of Anson's circum navigation attracted much attention in Europe; out of 1900 men, 1400 had died most of them allegedly from having contracted scurvy. John Woodall, an English military surgeon of the British East India Company, had recommended the consumption of citrus fruit (it has an anti-scorbutic effect) from the 17th century, but their use did not become widespread.

**Phases of clinical trials:** Clinical trials involving new drugs are commonly classified into four phases. Clinical trials of drugs may not fit into a single phase. For example, some may blend from phase I to phase II or from phase II to phase III. Therefore, it may be easier to think of early phase studies and late phase studies. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through Phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population. Phase IV are 'post-approval' studies.

A systematic verification of the study, carried out by persons not directly involved, such as:

- (a) Study related activities to determine consistency with the Protocol
- (b) Study data to ensure that there are no contradictions on Source Documents. The audit should also compare data on the Source Documents with the interim or final report. It

should also aim to find out if practices were employed in the development of data that would impair their validity.

(c) Compliance with the adopted Standard Operating Procedures (SOPs).

### Clinical Trial (Clinical Study)

A systematic study of pharmaceutical products on human subjects – (whether patients or non- patient volunteers) – in order to discover or verify the clinical, pharmacological (including pharmacodynamics / pharmacokinetics), and / or adverse effects, with the object of determining their safety and / or efficacy.

### Human/Clinical Pharmacology trials (Phase I)

The objective of phase I of trials is to determine the maximum tolerated dose in humans; pharmacodynamic effect, adverse reactions, if any, with their nature and intensity; and pharmacokinetic behavior of the drug as far as possible. These studies are often carried out in healthy adult volunteers using clinical, physiological and biochemical observations. At least 2 subjects should be used on each dose. Phase I trials are usually carried out by investigators trained in clinical pharmacology and having the necessary facilities to closely observe and monitor the subjects. These may be carried out at one or two centers.

### Exploratory trials (Phase II)

In phase II trials a limited number of patients are studied carefully to determine possible therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centers and carried out by clinicians specialized on the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

### Confirmatory trials (Phase III)

The purpose of these trials is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. These trials may be carried out by clinicians in the concerned therapeutic areas, having facilities appropriate to the protocol. If the drug is already approved/ marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centers primarily to confirm the efficacy and safety of the drug, in Indian patients when used as recommended in the product monograph for the claims made. Data on ADRs observed during clinical use of the drug should be reported along with a report on its efficacy in the prescribed format. The selection of clinicians for such monitoring and supply of drug to them will need approval of the licensing authority under Rule 21 of the Act.

### Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, assessment of therapeutic value, treatment strategies used and safety profile. Phase IV studies should use the same scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to

explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

#### **Clinical Trials in India: Advantages and Challenges:**

- Strong availability of study subjects across major therapeutic segments;
- High level of ICH GCP and US Food and Drug Administration standards compliance (since 2001, the DCGI has implemented conformity to ICH GCP and good laboratory practice guide- lines. Generally, most competent authorities, including the US FDA, will find the standards of Indian clinical trials acceptable);
- High quality of research professionals (India has a strong reputation for graduating students in the medical and scientific fields. The government is involved in curriculum development at major universities and students pursuing these fields of study are given financial incentives to study in India);
- A favorable regulatory environment that allows the conduct of global trials, duty-free imports of drugs intended for use in trials, bioequivalence studies for export of data, etc;
- Cost competitiveness (depending on the number of patients and investigators, and the amount of analytical work completed in India, most sponsors will enjoy a 30-50% cost advantage over a similar trial in Europe or the US6); and
- Increasing prevalence of diseases.
- Approval of clinical trial documents from both the IRB/IEC and the DCGI is mandatory to initiate a study. Some of the major issues that have been recognized as areas in need of improvement are mentioned below.
- Lengthy approval timelines
- Inspections by health authorities
- Manpower crunch and application backlog
- Lack of communication

### **3. Ethical & Safety Considerations**

#### **Ethical Principles**

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current revision of Declaration of Helsinki (see Appendix 1) and should respect three basic principles, namely justice, respect for persons, beneficence (to maximize benefits and to minimize harms and wrongs) and non malaficence (to do no harm) as defined by "Ethical Guidelines for Biomedical Research on Human Subjects" issued by the Indian Council of Medical Research and any other laws and regulations of the country, which ensure a greater protection for subjects.

#### **Clinical trial Requirements in USA**

Clinical trials often involve patients with specific health conditions who then benefit from receiving otherwise unavailable treatments. In early phases, participants are healthy volunteers who receive financial incentives for their inconvenience. During dosing periods, study subjects typically remain on site at the unit for durations of anything

from 1 to 30 nights, occasionally longer, although this is not always required.

Examples of what a clinical trial may be designed to do:

- Assess the safety and effectiveness of a new medication or device on a specific kind of patient (e.g., patients who have been diagnosed with Alzheimer's disease).
- -Assess the safety and effectiveness of a different dose of a medication than is commonly used (e.g., 10 mg dose instead of 5 mg dose).
- The U.S. National Institutes of Health (NIH) organizes trials into five (5) different types:
- Prevention trials: look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.
- Screening trials: test the best way to detect certain diseases or health conditions.
- Diagnostic trials: conducted to find better tests or procedures for diagnosing a particular disease or condition.
- Treatment trials: test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
- Quality of life trials: explore ways to improve comfort and the quality of life for individuals with a chronic illness (a.k.a. Supportive Care trials).

### **4. Phases of clinical research**

Clinical trials involving new drugs are commonly classified into four phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through Phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population.

Phase I: Screening for safety

Phase II: Establishing the testing protocol

Phase III: Final testing

Phase IV: 'Post-approval' studies

Assessment of Volunteer Participation in Clinical Trials

Clinical trials are conducted to collect data regarding the safety and efficacy of new drug and device development.

#### **Volunteering for a Clinical Trial:**

When considering volunteering for a clinical trial, it is important to make an informed decision. Below are answers to frequently asked questions that many potential volunteers have about participating in a study.

#### **Possible benefits for volunteers:**

- Play an active role in their health care.
- Gain access to research treatments before they are widely available.
- Obtain medical care at health care facilities during the trial.
- Help others by contributing to medical research.
- There may be unpleasant, serious, or even life-threatening side effects to experimental treatment.
- The experimental treatment may not be effective.

The protocol may require more time and attention than a non-protocol treatment, including trips to the study site, more treatments, hospital stays, or complex dosage requirements. This guidance is intended to assist applicants and other responsible parties in fulfilling the FDA's existing post marketing safety reporting requirements for human marketed drug and biological products at 21 CFR 310.305, 314.80, 314.98, 600.80, and 600.81 2. Under these regulations, post marketing safety reports must be submitted to the Agency for the following:

- Serious and unexpected adverse experiences from all sources (domestic and foreign)
- Spontaneously reported adverse experiences that occur domestically and that are:
  - Serious and expected
  - Nonserious and unexpected
  - Nonserious and expected

This guidance addresses the following regulations for the following products.

Regulation	Product
21 CFR 310.305	Prescription drugs marketed for human use without an approved application
21 CFR 314.80	Human drugs with approved NDAs
21 CFR 314.98	Human drugs with approved ANDAs
21 CFR 600.80	Human biological products with approved BLAs
21 CFR 600.81	Human biological products with approved BLAs

**Data Elements to Include in a Post marketing Individual Case Safety Report:**

Before considering any clinical incident for submission to the FDA in an individual case safety report, applicants should, at a minimum, have knowledge of the following four data elements:

- An identifiable patient
- An identifiable reporter
- A suspect drug or biological product
- An adverse experience or fatal outcome suspected to be due to the suspect drug or biological product

The following paragraphs discuss the types of post marketing safety reports that must be submitted to the FDA based on the regulations as listed.

- A. 15-Day Reports of Serious, Unexpected Adverse Experiences.
- B. Periodic Reports
- C. Follow up Reports
- D. Distribution Reports for Biological Products Including Vaccines

According to the regulations, the FDA can require submission of more detailed product distribution information, if needed.

- A. Scientific Literature Reports
- B. Post marketing, Clinical Trials, or Surveillance Studies
- C. Foreign Report
- D. Death Reports
- E. Overdose Reports
- F. Lack of Effect Reports
- G. Information on the Internet
- H. Pediatric Patients
- I. Prescription Drugs Marketed For Human Use without an Approved Application
- J. Another Applicant's Product
- K. Multiple Suspect Products
- L. Suspect Drugs with Multiple NDAs or ANDAs by the Same Applicant
- M. Two or More Marketers of a Product
- N. Unapproved Indications
- O. Product Interactions
- P. Reports from the FDA
- Q. Product Defects
- R. Reporting Ambiguities

**5. Conclusion**

Some issues about healthy volunteer recruitment in first-in-man trials and reimbursement remain unresolved, and they can be summarized as follows: (1) There is a lack of international consensus on the definition of healthy status, based on standard physical, psychological, and laboratory parameters, suitable for the enrolment of candidate subjects in first-in-man trials. (2) There is a need for guidelines about appropriate advertisements addressed to potential participants in first-in-man clinical trials, to set out specific ethical limitations. (3) There is a lack of international and/or local statements about standard criteria for offering fair payments to healthy volunteers enrolled in first-in-man trials. (4) Based on current Italian regulations, there is a need for a national register to monitor the participation of healthy subjects in different early clinical trials at the same or different centres for drug experimentation. (5) In view of a “new era of early phase trials,” the national legislation should offer Italian investigators conducting phase 0 and phase I trials a comprehensive guideline encompassing principles sanctioned.

**6. References**

- [1] Tribulations Second Edition, M edited by Allen Cato, Lynda Sutton, Cato Research Ltd. Durham, North Carolina, Allen Cato III, Cato Research Ltd. San Diego, California 2002 Marcel Dekker, Inc. Marcel Dekker, Inc. New York • Basel
- [2] Clinical Research in Pharmaceutical Development, edited by Barry Bleidt and Michael Montagne c 2002 Marcel Dekker, Inc. Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016
- [3] Drug Products for Clinical Trials: An International Guide to Formulation, Production, Quality Control, edited by Donald C. Monk house and Christopher T. Rhodes Marcel Dekker, Inc. New York.
- [1] US FDA guidelines-www.fda.gov.

- [2] RNCOS, Booming Clinical Trials Market in India, September 2009, [www.rncos.com/ Report/ IM564 .htm](http://www.rncos.com/Report/IM564.htm)
- [3] CDSCO, Good Clinical Practices for Clinical Research in India, Schedule Y (Amended Version – 2005),
- [4] <http://cdsco.nic.in/html/GCP1.html>
- [5] ICMR, Ethical Guidelines for Biomedical Research on Human Participants, 2006.
- [6] [www.icmr.nic.in/ethical\\_guidelines.pdf](http://www.icmr.nic.in/ethical_guidelines.pdf)
- [7] CDSCO, Guidance for Industry, Document No CT/71108, Version 1.1
- [8] <http://cdsco.nic.in/CDSCO-GuidanceForIndustry.pdf>