OPPI CODE

ON

CONDUCT OF CLINICAL TRIALS
MESSAGE

Clinical trials are the core of research-based pharmaceutical industry. No new drug can come into the market without clinical trials.

Global clinical trials are relatively new to India. No wonder there are several misconceptions on the subject. The companies conducting research need to proactively publicize their commitment to protecting the rights, safety and well being of trial participants.

I hope this booklet will help reassure the public about the high ethical standards that OPPI member companies profess and practice while conducting clinical research.

Ranjit Shahani
President, OPPI
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Mumbai
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FOREWORD

The Pharmaceutical Industry has gone through a metamorphosis over a period of time in its battle against disease and improvement in quality of life. The industry is still evolving. Despite path breaking discoveries in every field of Life Sciences, there is still a need for development of newer medicines and newer ways of addressing ailments to meet the unmet medical needs and to further improve the treatment outcomes for the patients.

The development of new therapies to treat disease and improve quality of life is a long and complex process. A critical part of that process is the conduct of clinical trials. Clinical trials may involve already marketed product(s) and/or investigational products. A clinical trial is defined in the International Conference on Harmonization Guideline for Good Clinical Practice [ICH-GCP E6 (R1)] as any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. Clinical trials (Phase 1 to Phase 4) involve both potential benefits and risks to the participants and are conducted with the primary aim of bringing to patients new medicines with a favorable benefit–risk ratio. Clinical trials are conducted to answer specific questions and some aspects of the therapeutic profile (benefits and risks) of the product(s) tested may not be fully known without study in humans. In sponsoring and conducting clinical trials, OPPI members place great importance on respecting and protecting the safety of research participants.

OPPI members remain committed to sponsoring clinical trials that fully comply with all legal and regulatory requirements in India. The local Regulatory requirements are laid down in the Drugs & Cosmetics Act 1940 and the Rules made there under. The Principles for the conduct of clinical trials are set forth in internationally accepted guidelines, such as the World Medical Association Declaration of Helsinki (Ethical
Principles for Medical Research involving Human Subjects, 59th WMA General Assembly, Seoul, October 2008) and the Guideline for Good Clinical Practice of ICH-GCP E6 (R1). OPPI members conduct clinical trials, strictly adhering to these guidelines. By providing inputs and constructive feedback, OPPI members have made significant contributions when similar reference guidelines were being formulated in India such as the Indian Good Clinical Practice (GCP) Guidelines of the Central Drugs Standards Control Organisation (CDSCO) and the Ethical Guidelines for Biomedical Research on Human Subjects issued by the Indian Council of Medical Research (ICMR, 2006).

OPPI developed the voluntary Code for its members in line with the “Principles on Conduct of Clinical Trials” drafted by PhRMA which became effective in October 2009. The code is now getting amended to include observational studies within its scope (effective May 2010).

All OPPI Member Companies are committed to follow the principles laid down in this document, in conformance to all applicable International and Indian regulations, guidelines and ethical principles.

Dr. Girish Telang                     Tapan Ray
   Chairman                          Director General
OPPI Medical Committee              OPPI
Scope:

For the purpose of this Code, a “clinical trial” means any pharmaceutical industry including biotech industry sponsored interventional Phase 1 to 4 trials involving human subjects. This code will also be applicable for post marketing drug / non drug interventional or observational studies as well.

Investigator initiated studies, registries and any other organized data collection system like market research or health economic studies are outside the scope of this Code unless collected as part of clinical trial

Many different entities and individuals contribute to the safe and appropriate conduct of clinical trials viz. sponsor companies; regulatory agencies; site staff and investigators, hospitals and other institutions where these trials are conducted; and institutional review boards and ethics committees (IRBs/ECs).

OPPI sets forth the following Code as guidance for members to ensure that safety and well-being of research participants are fully protected.

The key issues addressed here are:

1. Protecting Research Participants
2. Conduct of Clinical Trials
3. Ensuring Objectivity in Research
4. Disclosure of Clinical Trial and its Results.

These principles reinforce our commitment to the safety of research participants and they provide guidance to address issues that bear on this commitment in the context of clinical trials that enroll research participants and are designed, conducted or sponsored (partially or fully) by member companies.
1. Protecting Research Participants

OPPI members conduct clinical trials in a manner that recognizes the importance of protecting the rights, safety and well-being of research participants. Our interactions with research participants, as well as with clinical investigators and other persons/entities involved in clinical trials, recognize this fundamental principle and reinforce the precautions established to protect research participants.
2. Conduct of Studies

OPPI members have always been committed, and remain committed, to sponsoring / conducting clinical trials or observational studies that fully comply with all legal and regulatory requirements. OPPI supports medical research for the purpose of answering scientific questions that are important and relevant.

OPPI members should conduct clinical trials or observational studies in accordance with applicable laws and regulations, as well as locally recognized GCP (in accordance with schedule Y and Indian GCP), wherever in the world clinical trials are undertaken. When conducting multinational, multi-site trials, in both the industrialized and developing world, OPPI members follow standards based on the ICH-GCP guidelines, in addition to the country laws/regulations. This section has been subdivided into two parts; one for conduct of interventional phase I – IV trials and the other for conduct of drug / non drug interventional or observational studies.

2.1 Conduct of Interventional studies (Phase I – IV)

a. **Clinical Trial Design**: OPPI members will sponsor the conduct of clinical trials based on scientifically designed protocols, which balance potential risk to the research participant with the possible benefits to the participant and to society. Scientific, ethical and clinical judgments must guide and support the design of the clinical trial, particularly those aspects directly affecting the research participants such as inclusion/exclusion criteria, endpoints, and choice of control, including active and/or placebo comparator.

b. **Selection of Investigators**: OPPI members will ensure careful selection of investigators based on qualifications, training, research or clinical expertise in relevant fields, the potential to recruit research participants and ability to conduct clinical trials in accordance with good clinical practices and applicable requirements.

c. **Training of Investigators**: OPPI members will ensure that investigators and their staff are trained on the clinical trial protocol, pharmaceutical product, and procedural issues associated with the conduct of the particular clinical trial.
d. **Institutional Review Board (IRB) / Ethics Committee (EC) Review**: OPPI members will ensure that, prior to commencement, each clinical trial is reviewed by an IRB/EC that has independent decision-making authority and has the responsibility and authority to protect research participants.

- The IRB/EC has the right to disapprove, require changes or approve the clinical trial before any participants are enrolled at the institution or investigative site for which it has responsibility.
- The IRB/EC is provided relevant information from prior studies, the clinical trial protocol and any materials developed to inform potential participants about the proposed research.

e. **Informed Consent**: OPPI members mandate that clinical investigators obtain and document informed consent, freely given without coercion, from all potential research participants. Consent forms should have all essential elements per ICH GCP and schedule Y.

- Potential research participants are to be adequately informed about potential benefits and risks, alternative procedures or treatments as well as nature and duration of the clinical trial, and should be provided the opportunity to ask questions about the study and receive answers from a qualified health care professional associated with the trial.
- In those cases where research participants - for reasons such as age, illness, or injury - are incapable of giving their consent, the informed consent of a legally acceptable representative (LAR) is required. If the LAR is unable to read, an impartial witness should be present throughout the informed consent process as per ICH-GCP guidelines.
Because participation in a clinical trial is voluntary, all research participants have the right to withdraw from continued participation in the clinical trial, at any time, without penalty or loss of benefits to which they are otherwise entitled.

f. **Clinical Trial Monitoring** : OPPI members will ensure adequate oversight by making certain that all clinical trials are monitored using appropriately trained and qualified individuals. OPPI members will have procedures for these individuals to report on the progress of the trial including possible scientific misconduct, and significant deviations or persistent non-compliance to GCP, protocol and all applicable regulations.

- OPPI members will ensure that monitoring staff verify compliance with GCP, including (but not limited to) adherence to the clinical trial protocol, enrollment of appropriate research participants and the accuracy and complete reporting of clinical trial data.

- If a sponsor learns that a clinical investigator is significantly deficient in any area, it will either work with the investigator to obtain compliance or discontinue the investigator’s participation in the study, and notify the relevant authorities as required.

g. **Ongoing Safety Monitoring** : All safety issues are tracked and monitored in order to understand the safety profile of the product under study. Significant new safety information will be shared promptly with the clinical investigators and any Data and Safety Monitoring Board or Committee (DSMB), if formed prior to or during the conduct of the trial, and reported to regulatory authorities in accordance with applicable law.
h. **Privacy and Confidentiality of Medical Information**: OPPI members respect the privacy rights of research participants and safeguard the confidentiality of their data and related medical information in accordance with applicable laws and regulations.

i. **Quality Assurance**: Procedures are followed to ensure that trials are conducted in accordance with GCP and that data are generated, documented and reported accurately and in compliance with all applicable requirements.
2.2 Conduct of post marketing observational studies

Observational study is defined as non-interventional research that involves the collection of scientifically valuable information for the purpose of answering an important research question. The term “non-interventional” means that the healthcare provider’s decisions regarding the proper treatment and care of the patient are made in the course of normal clinical practice.

OPPI members will observe the following code for the purpose of conducting such studies:

a. The study should be designed to answer scientific and medical questions(s). The design of an observational study (including the type of data points collected and number of patients enrolled) should be driven by the data needed to answer relevant scientific and medical question(s) or if required by regulators.

b. The conduct of an observational study should not be combined with any promotional activity (e.g., sampling programs or distribution of promotional materials).

c. The sample size and the population studied should be defined to address the research question and the objectives of the study. The sample size of the population needs to reflect the statistical requirements in order to meet the study objectives.

d. The protocol or observational study plan should be designed such that the treatment decision for a patient in an observational study should be made by the investigator independently from the study prior to enrolling the patient, and should not be influenced by the observational study design.

e. Observational studies represent non-interventional research, and therefore these studies should not involve randomization of patients to particular comparator arms or therapies.

f. Free drug samples should not be provided to patients participating in observational studies as this may potentially influence the treatment decision of the investigators.

g. In an observational study that includes comparator arms, which require enrollment patterns of patients (e.g., enrollment of 2:1 ratio or stratification of patients based on disease severity), scientific justification should be provided in the protocol and the cohort sizes should not impact or be influenced by normal prescribing patterns.

h. These studies should be planned and managed by the medical department of the organization. There should be no involvement of sales or marketing personnel in activities such as selection of investigators, encouraging enrollment or in scientific study related discussions on these...
studies except for providing the list of potential sites/Investigators and the logistical help if needed such as facilitating getting the necessary documents OR their role should be clarified.

i. All observational studies should be approved by the institutional ethics committee. They may be notified to the regulatory authorities depending on the objective of the study.
3. Ensuring Objectivity in Research

OPPI Members respect the independence of the individuals and entities involved in the clinical research process so that they can exercise their judgment for the purpose of protecting research participants and to ensure an objective and balanced interpretation of trial results. OPPI members’ contracts and interactions with them will not interfere with this independence.

a. Independent review and safety monitoring: In certain studies, especially large, multi-site studies that evaluate interventions intended to prolong life or reduce risk of a major adverse health outcome, the patients, investigators and the sponsor may each be blinded to the treatment each participant receives to avoid the introduction of any bias into the study.

In such studies, safety monitoring of interim study results and of new information from external sources by a Data and Safety Board or Committee (DSMB) may be appropriate to protect the welfare of the participants. If such a committee is formed, the clinical investigators participating in a clinical trial of a pharmaceutical product and the employees of the sponsor company should not serve as members of such a committee.

b. Payment to Research Participants: Research participants provide a valuable service to society. They take time out of their daily lives and sometimes incur expenses associated with their participation in clinical trials. When payments are made to research participants:

- Any proposed payment should be reviewed and approved by an overseeing Ethics committee
- Payments should be based on research participants’ time and/or reimbursement for reasonable expenses incurred during their participation in a clinical trial, such as travel and lodging expenses.
The nature and amount of compensation or any other benefit should be consistent with the principle of volunteer consent and applicable regulations and guidelines.

c. **Payment to Investigators / Sites (Hospital / Institution):** Payment to Investigators or Sites (Hospital / Institution) should be reasonable and based on work performed by the investigator and the investigator’s staff, not on any other considerations.

- A written contract/agreement should be in place, specifying the nature of the research services to be provided and the basis for payment for those services.
- Payments or compensation of any sort should not be linked to the outcome of clinical trials.
- Clinical investigators or their immediate family should not have a direct ownership interest in the specific pharmaceutical product being studied.
- Clinical investigators and institutions should not be compensated in company stock or stock options for work performed on individual clinical trials.
- When enrollment is particularly challenging, reasonable additional payments may be made to compensate the clinical investigator or institution for time and effort spent on extra recruiting efforts to enroll appropriate research participants.
- When clinical investigators and their staff are required to travel to meetings in conjunction with a clinical trial, they may be compensated for reasonable travel, lodging, and meal expenses. The venue and circumstances should be appropriate for the purpose of the meeting. It is not appropriate to pay honoraria or travel or lodging expenses for those who are not involved in the clinical trial.
- There should be no conflict of interest in the research setting, where the investigator’s judgment could be influenced by a secondary interest like potential financial gain, career advancement, outside employment, personal considerations, investments, gifts, payment of services or board memberships.
4. Disclosure of Clinical Trial and its Results

Availability of information about clinical trials and their results in a timely manner is often critical to communicate important new information to the medical profession, patients and the public. OPPI members design and conduct clinical trials in an ethical and scientifically rigorous manner to determine the benefits, risks and value of pharmaceutical products. As sponsors, OPPI members are responsible for ensuring the quality of data from all research sites for the studies we conduct as well as for the accuracy and integrity of the entire study database, which is owned by the sponsor.

a. Registration of Clinical Trials in the Clinical Trials Registry: OPPI members are committed to timely registration of clinical trials and observational studies in the Clinical Trials Registry - India (CTRI) that has been set up by the ICMR’s National Institute of Medical Statistics (NIMS). In addition, OPPI members remain committed to comply with any other relevant regulatory requirements.

b. Communication of Study Results: OPPI members commit to timely communication of meaningful results of clinical trials and observational studies of marketed products or investigational products, regardless of outcome. Communication includes publication of a paper in preferably a peer-reviewed medical journal, abstract submission with a poster or oral presentation at a scientific meeting or making results public by any other means with genuine intention to bring factual information to public.

In all cases, the study results should be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study.

c. Authorship: Consistent with standards of the International Committee of Medical Journal Editors and major journal guidelines for authorship, appropriate recognition as an author should be based on:

- substantial contributions into the conception or design of the study, or data acquisition, or data analysis and interpretation;
• drafting or revising the manuscript, involving for important intellectual content;
• final approval of the version to be published.

Authors should preferably meet all the above mentioned conditions.

Companies sometimes employ staff to help analyze and interpret data and to produce manuscripts and presentations. Such personnel must act in conjunction with the investigator-author. Their contributions should be recognized appropriately in resulting publications depending on their level of contribution.

All authors, whether from within a sponsoring company or external, will be given the relevant statistical tables, figures and reports needed to support the planned publication.

d. **Related Publications**: For a multi-site clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or patients. Such reports should not precede and should always reference the primary presentation or paper of the entire study.

e. **Investigator Access to Data and Review of Results**: OPPI members may consider to provide investigators with meaningful access to clinical data from the studies in which they participate. Generally, study databases are only made available to regulatory authorities. Individual investigators in multi-site clinical trials will have their own research participants’ data and may be provided the randomization code after conclusion of the trial if it is in line with each company policy and based on the request from the Investigator. Sponsors will make a summary of the study results available to the investigators. In addition, any investigator who participated in the conduct of a multi-site clinical trial will be able to review relevant statistical tables, figures and reports for the entire study at the sponsor’s facilities or other mutually agreeable location.
f. **Research Participant Communication**: Investigators are encouraged to communicate a summary of trial results as appropriate, to their research participants after conclusion of the trial.

g. **Sponsor Review**: Sponsors have the right to review any manuscripts, presentations or abstracts that originate from their studies or that utilize their data before they are submitted for publication or other means of communication. OPPI members commit to respond in a timely manner and not suppress or veto publications or other appropriate means of communication (in rare cases it may be necessary to delay publication and/or communication for some time to protect intellectual property). Where differences of opinion on interpretation of data exist, the parties should try to resolve them through appropriate scientific debate.

h. **Provision of Clinical Trial Protocol for Journal Review**: If requested by a medical journal when reviewing a submitted manuscript for publication, the clinical trial sponsor will provide a synopsis of the clinical trial protocol and/or pre-specified plan for data analysis with the understanding that such documents are confidential and should be returned to the sponsor.
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