

PARMA

Principles on Conduct of
CLINICAL TRIALS

and Communication of
CLINICAL TRIAL RESULTS

Preamble

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents research-based pharmaceutical and biotechnology companies. Our members discover, develop, manufacture and market new medicines and vaccines to enable patients to live longer and healthier lives.

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 clinical research, the study of a pharmaceutical product in humans (research participants). Clinical research involves both potential benefits and risks to the participants and to society at large. Investigational clinical research is 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 research, PhRMA members place great importance on respecting and protecting the safety of research participants.

Principles for the conduct of clinical research are set forth in internationally recognized documents, such as the Declaration of Helsinki and the Guideline for Good Clinical Practice of the International Conference on Harmonization. The principles of these and similar reference standards are translated into legal

requirements through laws and regulations enforced by national authorities such as the U.S. Food and Drug Administration. PhRMA members have always been committed, and remain committed, to sponsoring clinical research that fully complies with all legal and regulatory requirements.

Many different entities and individuals contribute to the safe and appropriate conduct of clinical research, including not only sponsoring companies but also regulatory agencies; investigative site staff and medical professionals who serve as clinical investigators; hospitals and other institutions where research is conducted; and institutional review boards and ethics committees (IRBs/ECs).

PhRMA adopts these voluntary principles to clarify our members' relationships with other individuals and entities involved in the clinical research process and to set forth the principles we follow.

The key issues addressed here are:

- ▶ Protecting Research Participants
- ▶ Conduct of Clinical Trials
- ▶ Ensuring Objectivity in Research
- ▶ Disclosure of Clinical Trial 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 and sponsored by member companies.

1

Commitment to Protecting
Research Participants

We conduct clinical research in a manner that recognizes the importance of protecting the safety of and respecting research participants. Our interactions with research participants, as well as with clinical investigators and the other persons and entities involved in clinical research, recognize this fundamental principle and reinforce the precautions established to protect research participants.

2

Conduct of Clinical Trials

We conduct clinical trials in accordance with applicable laws and regulations, as well as locally recognized good clinical practice, wherever in the world clinical trials are undertaken. When conducting multinational, multi-site trials, in both the industrialized and developing world, we follow standards based on the Guideline for Good Clinical Practice of the International Conference on Harmonization.

a. Clinical Trial Design. Sponsors conduct clinical trials based on scientifically designed protocols, which balance potential risk to the research participant with the possible benefit 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. Investigators are selected 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 legal requirements.

c. Training of Investigators. 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. IRB/EC Review. 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. We require that clinical investigators obtain and document informed consent, freely given without coercion, from all potential research participants.

- ▶ Potential research participants are to be adequately informed about potential benefits and risks, alternative procedures or treatments, nature and duration of the clinical trial, and provided the opportunity to ask questions about the study and receive answers from a qualified health care professional.
- ▶ Clinical investigators are encouraged to disclose to potential research participants during the informed consent process that the investigator and/or the institution is receiving payment for the conduct of the clinical 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 is required.
- ▶ 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. Trials are monitored using appropriately trained and qualified individuals. The sponsor will have procedures for these individuals to report on the progress of the trial including possible scientific misconduct.

- ▶ These individuals verify compliance with good clinical practices, 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), and reported to regulatory authorities in accordance with applicable law.

h. Privacy and Confidentiality of Medical

Information. Sponsors respect the privacy rights of research participants and safeguard the confidentiality of their medical information in accordance with all applicable laws and regulations.

i. Quality Assurance.

Procedures are followed to ensure that trials are conducted in accordance with good clinical practices and that data are generated, documented and reported accurately and in compliance with all applicable requirements.

j. Clinical Trials Conducted in the Developing

World. When conducting clinical trials in the developing world, sponsors collaborate with investigators and seek to collaborate with other relevant parties such as local health authorities and host governments to address issues associated with the conduct of the proposed study and its follow-up.

3

Ensuring Objectivity in Research

We 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. Our contracts and interactions with them will not interfere with this independence.

a. Independent Review and Safety Monitoring.

In certain studies, generally large, randomized, 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 bias into the study. In such cases, monitoring of interim study results and of new information from external sources by a DSMB may be appropriate to protect the welfare of the research participants. If a DSMB is established, its members should have varied expertise, including relevant fields of medicine, statistics, and bioethics. Sponsors help establish, and also respect, the independence of DSMBs.

- ▶ Clinical investigators participating in a clinical trial of a pharmaceutical product should not serve on a DSMB

that is monitoring that trial. It is also not appropriate for such an investigator to serve on DSMBs monitoring other trials with the same product if knowledge accessed through the DSMB membership may influence his or her objectivity.

- ▶ A voting member of a DSMB should not have significant financial interests or other conflicts of interest that would preclude objective determinations. Employees of the sponsor may not serve as members of the DSMB, but may otherwise assist the DSMB in its evaluation of clinical trial data.

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 independent IRB/EC.
- ▶ Payments should be based on research participants' time and/or reimbursement for reasonable expenses incurred

during their participation in a clinical trial, such as parking, travel, and lodging expenses.

- ▶ The nature and amount of compensation or any other benefit should be consistent with the principle of voluntary informed consent.

c. Payment to Clinical Investigators. Payment to clinical investigators or their institutions should be reasonable and based on work performed by the investigator and the investigator's staff, not on any other considerations.

- ▶ A written contract or budgetary 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 tied 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 their time and offered reimbursement for reasonable travel, lodging, and meal expenses. The venue and circumstances should be appropriate for the purpose of the meeting.



Public Disclosure of
Clinical Trial Results

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

a. Communication of Study Results. Clinical trials may involve already marketed products and/or investigational products. We commit to timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing, regardless of outcome. Communication includes publication of a paper in a peer-reviewed medical journal, abstract submission with a poster or oral presentation at a scientific meeting, or making results public by some other means.

- ▶ Some studies that sponsors conduct are of an exploratory nature (early-phase or post-marketing). These are often highly proprietary to the sponsoring company,

and due to their limited statistical power, serve primarily to generate hypotheses for possible future trials. Sponsors do not commit to publish the results of every exploratory study performed, or to make the designs of clinical trial protocols available publicly at inception, as in a clinical trials registry. If the information from an exploratory study is felt to be of significant medical importance, sponsors should work with the investigators to submit the data for publication.

- ▶ 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.

b. Authorship. Consistent with the International Committee of Medical Journal Editors and major journal guidelines for authorship, anyone who provides substantial contributions into the conception or design of a study, or data acquisition, or data analysis and interpretation; and writing or revising of the manuscript; and has final approval of the version to be published should receive appropriate recognition as an author or contributor when the manuscript is published. Conversely, individuals who do not contribute in this manner do not warrant authorship.

- ▶ 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—either as a named author, a contributor, or in acknowledgments 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.

c. 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 health care professionals or patients and therefore may not be supported by sponsors. Such reports should not precede and should always reference the primary presentation or paper of the entire study.

d. Investigator Access to Data and Review of Results. As owners of the study database, sponsors have discretion to determine who will have access to the database. Generally, study databases are only made available to regulato-

ry authorities. Individual investigators in multi-site clinical trials will have their own research participants' data, and will be provided the randomization code after conclusion of the trial. 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.

e. Research Participant Communication. Investigators are encouraged to communicate a summary of the trial results, as appropriate, to their research participants after conclusion of the trial.

f. Sponsor Review. Sponsors have the right to review any manuscripts, presentations, or abstracts that originate from our studies or that utilize our data before they are submitted for publication or other means of communication. Sponsors 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 a short time to protect intellectual property). Where

differences of opinion or interpretation of data exist, the parties should try to resolve them through appropriate scientific debate.

g. 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.

This document is effective from October 1, 2002.

Appendix

Under these principles, may a clinical investigator who owns stock in Company A be employed to conduct a clinical trial sponsored by Company A?

Yes. Ownership of stock in the sponsoring company does not disqualify the investigator from participating in clinical research for the company. However, sponsors may not compensate investigators with stock or stock options for work performed on individual clinical trials. Under the laws and regulations of some countries, stock ownership by investigators may need to be disclosed to regulatory authorities.

A physician has discovered a potential product. The physician licenses the compound to Company B for a royalty payment for any future sales. Can the physician be a clinical investigator of that compound for Company B?

No. Direct ownership interests in a product (such as patent rights or rights to royalty payments) present an inherent conflict of interest, which could introduce bias into the conduct of the clinical trial.

Companies that acquire rights to products which have arrangements that are in conflict with the above should take reasonable steps to modify the relationship.

Company C has just completed a controlled clinical trial evaluating the efficacy and safety of an investigational product versus placebo. The trial provides no information other than the relative merits of the investigational product versus placebo. Does Company C have a commitment to communicate the results of this trial?

Perhaps. If the product is ultimately approved for marketing, the results are likely meaningful because they provide information about the safety and efficacy of the marketed product, and should be communicated. The proprietary nature of the trial may be considered when assessing the timing of communication.

If the product never reaches the market and the results are only informative with regard to the specific product being studied, the results are likely not of significant medical importance and need not be communicated.

However, if the results are thought to be of significant medical importance, the sponsor should work with the investigators to communicate the results of the trial.

Company D has completed an exploratory, controlled trial of a product involving a novel and highly proprietary study design. Should Company D communicate the results of this trial?

Perhaps. Exploratory trials rarely provide information of significant medical importance. However, if they do, the sponsor should work with the investigators to communicate the results of the trial.

What are the Guidelines for Good Clinical Practice (GCPs) and in what jurisdictions do they apply?

The GCPs are an international standard for designing, conducting, recording, and reporting clinical research involving human participants. Compliance with GCPs assures that the rights, safety and well-being of human participants are protected and that clinical trial data are credible. The GCPs were developed using best practices from many countries, as well as the World Health Organization (WHO). They were published in 1996 as part of the International Conference on Harmonization (ICH) and are intended to apply in the European Union, Japan, and the United States. However, PhRMA encourages its members to apply the GCPs to studies conducted in all countries, including the developing world. Applying GCPs broadly helps assure that certain minimum ethical standards are consistently applied in countries that may not have rules or laws governing clinical trial conduct.

The Principles state that regardless of outcome, sponsors will communicate “meaningful results of controlled clinical trials” on products that are or will be marketed. What is meant by this and what do sponsors commit to communicate?

PhRMA members commit to communicate the results of all hypothesis-testing clinical trials they conduct, regardless of outcome, for marketed products or investigational products that are approved for marketing. The reference to “meaningful results of controlled clinical trials” is intended to refer to hypothesis-testing trials and to distinguish such trials from those that are merely exploratory in nature. Hypothesis-testing (also known as “confirmatory”) clinical trials are always well-controlled and are intended to provide meaningful results by examining pre-stated questions (i.e., hypotheses) using predefined statistically valid plans for data analysis, thereby allowing firm conclusions to be drawn to support product claims. (ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials. *Stats Med* 1999; 18:1905-42). Hypothesis-testing trials may occur at any

stage of drug development, and include all phase III trials; some earlier-phase trials, and many trials of marketed products.

Examples of results from hypothesis-testing clinical trials that sponsors commit to communicate include:

- ▶ A clinical trial of a marketed product, whether comparing it to placebo (e.g., for a possible new indication), or to a comparator product—regardless of outcome and even if the results would favor the competitor or potentially be adverse to the sponsor’s commercial needs for the marketed product.
- ▶ A clinical trial of an investigational product, regardless of outcome, if the product is ultimately approved for marketing. Although these Principles do not address communication of clinical trials of investigational products that are not subsequently approved for marketing, such trials may provide results that have significant medical importance. In such cases, sponsors are encouraged to work with the study investigators to publish the results.

The Principles state that some studies are exploratory and that sponsors will not commit to publish the results of an exploratory study unless those results are of “significant medical importance.” What is an “exploratory study” and how is it determined if results from such studies are of “significant medical importance?”

Exploratory trials serve to set direction (i.e., to generate hypotheses) for possible future studies (ICH *ibid.*). They provide only preliminary information about a disease, condition or product, and are not intended — or designed — to provide final conclusions on product claims. Moreover, exploratory studies have significant statistical limitations and are almost always proprietary to the sponsor. Even the fact that an exploratory study is being conducted may be highly proprietary because it reflects a company’s choices to pursue certain research strategies, to test various methods of clinical trial design, and/or to utilize certain endpoint measures.

Nevertheless, sponsors recognize that in some cases exploratory trials may provide results that are of significant medical importance, meaning the results would influence a physician’s decisions about

the use of a marketed product or marketed products in the same class. In such cases, sponsors commit to work with the investigators to evaluate the data and to publish the results. The sponsors and investigators should work together to determine the medical importance of exploratory study results and may consult with other experts if needed.

Are there ever times when it would not be appropriate to publish results from a hypothesis-testing clinical trial?

There are some situations where publication of results from a hypothesis-testing clinical trial would not be appropriate, and which have nothing to do with whether the study is “positive” or “negative” with regard to the performance of the sponsor’s product. Examples are provided below.

- 1.** Studies occur in which the data are found to be invalid. There is an implicit assumption that the data collected in a clinical trial will be “valid,” but sometimes this turns out not to be the case. For example, there might be an erroneous laboratory assay or equipment malfunction, or disruption of study sample shipment rendering test data using these samples unreliable. Publication of results based on invalid data is inappropriate as it could adversely affect physician and patient decisions (invalid results could appear positive for the product or intervention, for example). However, sponsors want to be clear that valid results which do not support the hypothesis being tested, or which are contrary to the sponsor’s preferred outcome, should be pub-

lished, because they are meaningful. In other words, negative results do not mean invalid results.

- 2.** A study may not answer the question(s) for which it was designed. For instance, a study may be ended prematurely and the amount of data gathered is insufficient to draw conclusions (e.g., when preclinical data become available after a trial has been initiated and the sponsor must terminate the trial well before its planned conclusion). This is an example of a “failed” clinical trial. Frequently these types of studies are not accepted for publication by medical journal editors, but the sponsor should review the data with the study investigators to determine whether they warrant submission for publication or are otherwise meaningful.

The Principles refer to “communication” of trial results, either by publication in a peer-reviewed journal, presentation at a medical meeting, or making results public by some other means. Why don’t the Principles just say that sponsors commit to publish all clinical trial results in peer-reviewed medical journals?

While publication of study results in a peer-reviewed medical journal (such as the *New England Journal of Medicine*, *JAMA* or *Lancet*) is the preferred method of communication, this is not always possible. These journals are independent and, with the assistance of recognized experts in the relevant fields (peer reviewers), make their own determination about what to publish, and when. Some medical journals accept less than 10% of the manuscripts submitted to them. Manuscripts may be rejected for a variety of reasons, including lack of interest, lack of novelty, or inconclusive results.

Consequently, the Principles provide some alternatives for the communication of clinical trial results. For instance, clinical trial data can be made public through presentation of the results at a professional scientific meeting, which involves oral presentations

or educational posters displayed for meeting attendees to review. Such presentations sometimes reach a larger and more diverse audience than publication in a journal with limited readership and can provide an opportunity for discussion. Abstracts summarizing the data to be presented are first submitted for approval of the meeting organizers and may be peer-reviewed.

Another possible method for communicating clinical trial data (not explicitly mentioned in the Principles) is through on-line posting on the Internet. The format could be similar to a poster displayed at a scientific meeting. The sponsoring company, however, would need to comply with all applicable regulatory requirements when posting such information on a web-site and, in some cases, might be prevented from posting such information by the regulatory authorities (i.e., sponsors are subject to substantial penalties for promoting an off-label use of its product).

Depending on the circumstances, one of these methods (or others not described above) may be more appropriate than the other alternatives for publication of the study results. Companies are urged to use the best and most widely distributed means at the appropriate time.

The Principles discuss the importance of “timely” communication of clinical trial results. Why don’t sponsors commit to publish all of their results in a peer-reviewed journal as soon as a clinical trial is complete? What is “timely”?

Many factors affect the timing of publication. After a trial ends, sponsors and investigators need time to fully collect, review and analyze the complete data set and then prepare and revise the manuscript. This often takes many weeks or even months depending on the complexity of the clinical trial data, consistency of results and other factors.

Once articles are submitted, journal editors vary substantially in the time they take to review and (once accepted) publish a manuscript. It is not uncommon for a paper to be published more than a year after original submission to a journal. For these reasons, the Principles specify publication in a timely manner, rather than within a specific timeframe, recognizing that circumstances differ between studies (and journals) and that timing is not always within the control of the study sponsor.

How does the relationship between the company and the investigator affect the publication of clinical trial results?

The roles and responsibilities for publishing clinical trial results can be significantly affected by the relationship between the pharmaceutical company and the investigator. As a general matter, if the company acts as the sponsor of a clinical trial, it should work with the investigator to publish meaningful results from controlled trials of drugs that are or will be marketed. If the investigator acts as the trial sponsor, either with or without the knowledge or assistance of the company, it is the investigator's sole responsibility to ensure that the results are published since the company did not sponsor the study (and might not even be aware of it).

The Principles state that investigators “will be able to review relevant statistical tables, figures, and reports” with regard to the entire study. Please define “relevant” in this context.

For purposes of investigator access to data, relevance refers to data from the trial and is determined by the study design and pre-stated research objectives. Simply stated, investigators will be given access to any data (tables, figures, reports) they need from the study that are related to the hypothesis being tested or explored or which are needed in order to understand the results of the study.

The Principles state that sponsors will make a “summary” of the study results available to the study’s investigators. Why is disclosure limited to a summary, and what will the summary include?

Most investigators are not interested in reviewing extensive raw data displays from a clinical study in which they participated. A summary of the study results is often sufficient to inform them of the results of the study. The intention of these Principles is that sponsors will provide all investigators with a full summary of the study results regardless of whether the investigator is an author or otherwise contributes to the publication on the study. This summary could be the primary manuscript submitted for publication, a slide presentation, or a synopsis of the sponsor’s Clinical Study Report (CSR).

Investigators who participated in the conduct of a multi-site clinical trial and are interested in more extensive data displays will be able to review the data for the entire study at the sponsor’s facility or other mutually agreeable location in response to a reasonable scientific inquiry. Investigators who are authors of study-related manuscripts will be given all study data needed to support the publication.

Is it appropriate to include extra participants in a clinical trial in order to allow more investigators to gain experience with the product being studied?

No. Clinical trials must be designed with the scientifically necessary number of participants to achieve the intended outcome; too few or too many participants are both signs of poor study design.

The Principles state that research participants may be compensated for their time and reasonable expenses incurred during their participation in a clinical trial. Can such payment be made contingent upon completion of the clinical trial?

No. While the entire payment should not be contingent upon completion of the study, payment of a small portion as an incentive for completion of the study is acceptable, provided that such incentive is not excessive. All proposed payments to research participants (amount and method) must be reviewed and approved by an independent IRB/EC prior to the commencement of a clinical trial.

How do companies ensure the quality and integrity of clinical trial data they sponsor?

PhRMA member companies work hard to assure the quality and integrity of their clinical research. One of the most important safeguards is compliance with the Guidelines for Good Clinical Practice (GCPs) developed by the International Conference on Harmonization (ICH). We select investigators and others who are trained in GCPs for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials, which provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected. The Principles commit PhRMA member companies that sponsor clinical trials to adhere to the GCPs.

Furthermore, PhRMA members spend considerable resources monitoring clinical investigators to assure compliance with GCPs and the study protocol, as well as protection of participant safety, and accurate collection and reporting of data. Sponsors also often have separate review groups conduct audits of investigator sites

and of the study data to verify that the sponsor's routine monitoring procedures ensure data integrity. Sponsors work closely with regulatory agencies and with IRBs/ECs to provide for independent audits of investigators and of the sponsor's own clinical trial practices. The U.S. Food and Drug Administration (FDA) conducts more than 500 inspections of clinical investigators annually, including foreign sites.

What safety information do sponsors report to regulatory authorities about their trials? Can sponsors choose what safety information they report?

Sponsors cannot choose what safety information they report. Instead, they are required by local laws to report comprehensive safety information to regulatory authorities (and clinical investigators) throughout the clinical trial process and even after a drug product is approved and marketed. For example, sponsors typically are subject to the following safety reporting requirements:

- ▶ During the clinical trial, sponsors are obligated to record and evaluate all safety information they receive from investigators or from any other source. If a sponsor receives adverse event information that suggests a potential significant safety concern for the sponsored trial, the sponsor must notify all investigators in the trial and the health authorities in an expedited fashion. For example, in the U.S. and some other countries, sponsors must report unexpected serious adverse events within 15 days, and life-threatening adverse events within 7 days.

- ▶ Sponsors must maintain and distribute to clinical investigators and to IRBs/ECs an Investigator's Brochure that summarizes all relevant safety information about the investigational product, including a description of possible risks and side effects. The Investigator's Brochure must be updated periodically to keep investigators informed of new safety risks discovered during the study.
- ▶ In most countries, sponsors must report to the regulatory authorities the final results of the study, including all safety information, to the regulatory authorities. In some countries (including the U.S.), reports summarizing all safety information for the product are required to be submitted by the sponsor on an annual basis.
- ▶ Upon approval of a medicinal product, the holder of a marketing authorization must continue to monitor the safety of the approved product, report significant safety concerns in an expedited fashion, and regularly summarize and communicate all relevant safety information to the regulatory authorities. If important new safety information is discovered after approval, holders of marketing authorizations must update the product information (e.g., product labeling, patient information leaflet).

If significant new safety information is identified after participants have signed the informed consent form, will they be advised by the sponsor of the new information?

Yes. Participants will be provided with significant new findings identified during the study, which may affect their willingness to continue participation. Sponsors collect information on new adverse experiences from all investigators participating in the research study and then notify all the other investigators of this new safety information. Investigators then inform their IRB/EC and if the sponsor, investigator, or the IRB/EC believes this new information should be communicated to patients, the consent form will be updated with significant new safety information. Participants are informed of the significant new information by the investigator through the consent process when the informed consent form is updated.

What is an investigator “conflict of interest” and how do clinical trial sponsors handle such conflicts of interest?

A conflict of interest exists, in the research setting, whenever an investigator’s professional judgment could be influenced by a secondary interest, such as a potential financial gain, publication opportunity, career advancement, outside employment, personal considerations or relationships, investments, gifts, payment for services and board memberships. In the strict sense some conflict of interest is inherent in all research settings in that physicians usually receive compensation for their work, often seek publication opportunities, and are recognized professionally for advancing knowledge in their field. Moreover, physicians who are specialized and/or leaders in their field are often extensively engaged by both the private and public sectors to provide their expertise. Further, by the nature of their practices, there are often a limited number of physicians who are best qualified to ensure that a specific trial will be able to reach and enroll the required number of patients.

While physicians face conflicts of interest in all aspects of their work, they are expected to put patient care above all other concerns.

As such, they are subject to an array of professional standards and ethical obligations. Pursuant to these *PhRMA Principles*, sponsors may not use investigators if investigators or their immediate family have a direct ownership interest in the investigational product, and sponsors may not compensate investigators in company stock or stock options. In the U.S., FDA law requires sponsors to collect and disclose information on investigators' financial interests that exceed defined thresholds when the sponsor submits a product for regulatory approval. Investigators must also meet local requirements imposed by their institutions and/or the institutional review board or ethics committee. Most medical journals monitor conflicts of interest by reviewing the financial interests of investigator-authors, require the disclosure of affiliations and financial interests in the articles they publish, and reserve the right to reject publications involving significant conflicts of interest. Finally, potential bias from a conflict of interest is also managed by sponsors using double-blind study designs (e.g., neither the physician nor the patient knows whether the patient is receiving the study drug or the placebo or comparator drug), multiple investigators, contractual provisions in the sponsor-investigator clinical trial agreement,

periodic auditing of investigator sites by third-parties, and other Good Clinical Practice requirements that are commonly used in clinical trials.

How are participants protected when clinical trials are conducted in the developing world?

The Principles affirm that clinical trials in the developing world must be conducted in accordance with ethical principles established by the Guidelines for Good Clinical Practice of the International Conference on Harmonization, in addition to applicable laws and regulations and the requirements of local ethics committees. PhRMA members recognize the challenges inherent in applying the standards of the developed world to trials in developing countries. Informed consent is a cornerstone of ethical clinical research and should be obtained in a manner that is understandable by the research participant, consistent with local requirements, regardless of the location of the clinical trial, and in writing whenever possible. Our members work with local governments, non-governmental organizations (NGOs) associated with the United Nations, and local institutions to ensure the appropriate selection of research participants, appropriate use of placebo comparators, and access to post-trial treatment for research participants.

Are research participants told about all archival or secondary uses of their tissue and health information? Why are the samples stored for so many years, and can they be used for other purposes?

Potential research participants are informed in the informed consent or authorization process, when identifiable tissue, samples, or information collected during a clinical trial will be archived for future uses by the investigator, the investigator's institution, or the sponsor. If research using archival biological materials is to occur, investigators need to inform participants of this possibility. Identified samples will only be used for future research according to the scope and duration defined in the informed consent or for purposes that are permitted by law. The samples may be kept for many years, for example, so that if new relevant research assays are discovered during that time the samples can also be tested with these. If the participant withdraws from a study, the participant may ask that any unused portion of their stored sample be destroyed so long as the sample can be identified.

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