PhRMA

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 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 repecting 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.

4

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.

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.

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