Principles on Conduct of Clinical Trials
Communication of Clinical Trial Results

PhRMA
RESEARCH ▫ PROGRESS ▫ HOPE

Table of Contents

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 cannot 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 (ICH). 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 (FDA). 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
- Providing Information about Clinical Trials
- Expanded Access to Investigational Drugs
- Commitment to Enhancing Diversity in Clinical Trial Participation

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.

For purposes of these Principles, a "clinical trial" means an interventional trial involving human subjects from Phase 1 and beyond. For example, the term does not include the use of a drug in the normal course of medical practice or non-clinical laboratory studies.

On October 14, 2020, the PhRMA Board approved the addition of Principle 6 and related Q&A in *Commitment to Enhancing Diversity in Clinical Trial Participation*, effective April 14, 2021. The remaining Principles have been in effect since June 1, 2015.

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 high quality clinical research, including trials and observational studies, to test scientific hypotheses rigorously and gather bona fide scientific data 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 ICH. In addition, clinical trial protocols are reviewed by independent IRBs/ECs as well as national health authorities.

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 the 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 protocol 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 healthcare professional associated with the trial.

- Clinical investigators should 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. Payment may be monetary and/or consist of items of modest value based on the factors noted above.

- 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; specifically, resorts are not appropriate venues. While modest meals or receptions may be appropriate during company-sponsored meetings with investigators, companies should not provide recreational or entertainment events in conjunction with these meetings. It is not appropriate to pay honoraria or travel or lodging expenses for those who are not involved in the clinical trial.

d. Potential Conflicts of Interest. A potential 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, career advancement, outside employment, personal considerations or relationships, investments, gifts, payment for services, and board memberships. In the strict sense, some conflict of interest may exist in all research settings. For example, physicians who are specialists 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.

Physicians are subject to an array of professional standards and ethical obligations, including institutional disclosure policies and government regulations regarding disclosure of potential financial conflicts of interest in clinical research during the drug approval process. Companies should recognize and support physicians and researchers in meeting these standards and ethical obligations, including the following requirements for authorship:

- When authors submit a manuscript to a medical journal, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors should state explicitly whether potential conflicts do or do not exist.

- Authors should identify individuals who provide writing or other assistance and disclose the funding source for this assistance. Authors should describe the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the report for publication. If the sponsor had no such involvement, the authors should so state.

4

Providing Information
About Clinical Trials

America's pharmaceutical research companies are committed to the transparency of clinical trials that are sponsored by our member companies. We recognize that there are important public health benefits associated with making appropriate clinical trial information widely available to healthcare practitioners, patients, and others. Such disclosure must maintain protections for individual privacy, intellectual property, and contract rights, as well as conform to legislation and current national practices in patent law.

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. 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. Clinical Trial Registration and Communication of Study Results. Clinical trials may involve already marketed products and/or investigational products. We commit to the timely submission and registration on a public database of summary information about all clinical trials that we conduct involving the use of our marketed or investigational products in patients. We also commit to the timely submission and posting of summary results of all clinical trials conducted in patients involving the use of our products that are approved for marketing, or that are investigational products whose development programs are discontinued, regardless of outcome. In addition, if information from any clinical trial is felt to be of significant medical importance, then we will work with investigators to publish the data.

b. Authorship and Research Contributors.

1. **Authors.** Consistent with standards of the International Committee of Medical Journal Editors and major journal guidelines for authorship, anyone who: (1) provides substantial contributions into the conception or design of a study, or data acquisition, or data analysis and interpretation; and (2) writes or revises the manuscript involving important intellectual content; and (3) has final approval of the version to be published, should receive appropriate recognition as an author when the manuscript is published. Conversely, individuals who do not contribute in this manner do not warrant authorship. Authors should meet conditions 1, 2, and 3.

    - All persons designated as authors should qualify for authorship, and all those who qualify with respect to each of the three criteria should be listed by companies; although journals may restrict the number of authors who may be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

    - When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

    - 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.

2. **Contributors.** Like other research sponsors, 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 or in acknowledgments, depending on their level of contribution.

    - Contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support.

    - Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as "clinical investigators" or "participating investigators," and their function or contribution should be described — for example, "served as scientific advisors," "critically reviewed the study proposal," "collected data," or "provided and cared for study patients."

    - Authors should declare whether or not they had assistance with study design, data collection, data analysis, or manuscript preparation. If such authorship assistance was available, the authors should disclose the identity of the people that provided the assistance and any entity that supported it in the published article. Financial and material support should also be acknowledged.

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 healthcare 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.** We seek to provide investigators with meaningful access to clinical data from the studies in which they participate. 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.

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 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.

e. Research Participant Communication. Clinical studies are collaborations between research participants, investigators, and research sponsors. Investigators are encouraged to communicate a summary of the trial results, as appropriate, to their research participants after conclusion of the trial. As research sponsors, we will support investigators in this regard.

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.

5

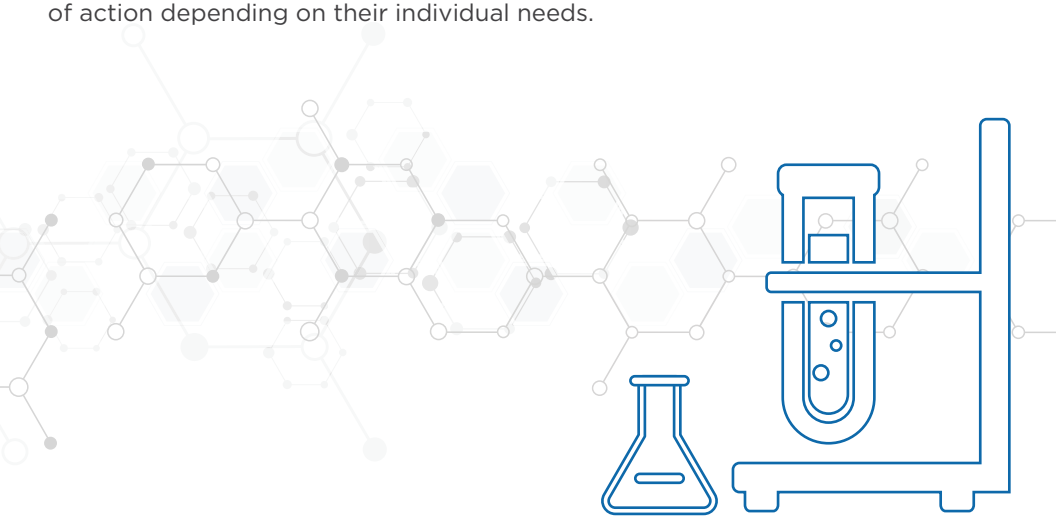
Expanded Access
To Investigational Drugs

Patients facing serious, life-threatening diseases live with the hope that tomorrow will bring a new medicine to extend and improve their lives. Approval of new medicines by regulatory authorities remains the best way to ensure that new safe and effective treatments are broadly available to patients. Biopharmaceutical companies are committed to helping healthcare practitioners and patients understand and navigate the clinical trial process and potential treatment options.

Clinical trials are the primary route by which patients participate in the drug development process, receive access to unapproved investigational drugs, and contribute to the collection of safety and efficacy data necessary for review and regulatory approval by national health authorities. Thus, to the extent possible, patients should be encouraged to participate in clinical trials, which ultimately will result in access to new, safe and effective approved medicines for the greatest number of patients.

For patients with a serious or life-threatening disease who are ineligible or unable to participate in a clinical trial, use of an unapproved investigational drug via an expanded access program may be an option. Expanded access, including treatment use in individual patients, is the use of an unapproved investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition, when there are no other comparable or satisfactory alternative treatment options.

Patients should consult their healthcare provider for determining the best course of action depending on their individual needs.



Considerations for Participation in Expanded Access Programs.
Biopharmaceutical companies following these principles consider providing patients with access to an unapproved investigational drug outside of a clinical trial using guidelines that generally include the following:

- **The patient has a serious or life-threatening illness.** In order for expanded access to be appropriate, the patient should have a serious or life-threatening disease or condition and should have exhausted all available therapeutic options typically used to treat the disease, or is no longer able to tolerate these treatments.

- **The investigational drug should be under active clinical development.** The investigational drug should be under active clinical development for a biopharmaceutical company to support expanded access to an unapproved investigational drug. Once regulatory approval has been secured, or clinical development of an unapproved investigational drug is discontinued for any reason, expanded access programs are generally not appropriate. That said, for approved medicines, biopharmaceutical companies may be able to provide help through separate mechanisms for the uninsured and underinsured.

- **The patient is ineligible for, or otherwise unable to participate in, clinical trials.** A patient seeking expanded access to an unapproved investigational drug generally should not be eligible for participation in a clinical trial. Geographic limitations alone would generally not be considered a barrier to participation in clinical trials.

- **The potential benefit to the patient should outweigh potential risks.** The potential benefit to the patient seeking expanded access should generally outweigh the combined potential risks of the investigational drug and the outcome of the disease itself. To support the use of the investigational drug in medical treatment of the patient, generally, there should be sufficiently robust preliminary safety and efficacy data, including dosing information, to determine that the preliminary benefit-risk balance is positive for the specific indication for which the request is made.

- **The successful completion of the clinical trial process is necessary to demonstrate that an investigational drug is safe and effective for its proposed indication, which is required to obtain regulatory approval by national health authorities, and to make the new medicine available to the broadest patient population appropriate.** Thus, granting access to

an investigational drug through an expanded access program should not delay, interfere or compromise the completion of clinical trials that are intended to support approval by national regulatory authorities. For example, biopharmaceutical companies should consider the availability of adequate supplies of the investigational drug for ongoing or planned clinical trials and potential impact on the availability of approved medicines.

To determine whether access to an investigational drug is the best possible treatment option for an individual patient, the request for expanded access should generally come from the patient's qualified healthcare provider. Because investigational drugs have not been determined to be safe and effective, regulatory authorities and Institutional Review Boards/ Ethics Committees should generally approve expanded access to an investigational drug before a biopharmaceutical company can provide the investigational drug to a patient.

Enhancing Information about Expanded Access Programs. Biopharmaceutical companies should establish telephone or internet-based information sources to facilitate communication about expanded access programs between a patient's qualified healthcare provider and biopharmaceutical companies.

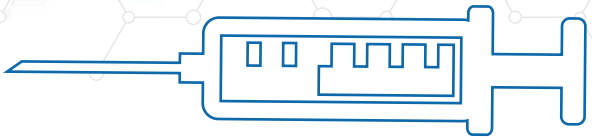
The development of innovative, safe and effective medicines for serious or life-threatening diseases represents an urgent and unique challenge that requires special attention. The biopharmaceutical industry is committed to continuing its work with patients, patient advocacy groups, regulatory authorities, healthcare practitioners, academia and policymakers, to help ensure that there are appropriate and targeted regulatory approaches to accelerate the development and availability of innovative new medicines for patients.

6

Commitment to Enhancing Diversity in Clinical Trial Participation

We recognize that achieving clinical trials that include diverse populations presents an ongoing challenge. Enhancing meaningful representation of diverse participants in clinical trials would help provide information about drug response and measures of safety and efficacy in populations that have been historically under-represented and under-studied, in particular Black and Brown people. Additionally, lack of participation of patients from diverse backgrounds may limit early access to potential therapies through clinical trials, especially in the setting of unmet medical need. Finally, there is a fundamental issue of fairness and justice that must be taken into account. As an ethical matter, clinical development of drugs and biologics should serve the needs of those who are affected by the disease or condition. It is with these core principles in mind that we commit to continuing to work with patients, patient advocacy groups, regulatory authorities, healthcare practitioners, academics, and policymakers to define the systematic and impactful approaches that we will take to enhance the diversity of clinical trial participants and help reduce healthcare disparities.

We aim to conduct clinical research that recognizes the demographics associated with diseases under study and the importance of ensuring that a wide diversity of patients are included in clinical trials. Enhancing diversity in clinical trial populations will lead to studies better reflecting the patient populations most likely to use the product under study if it achieves regulatory approval. When designing and conducting clinical trials, we strive to create a clinical development strategy representative of the intended population. We encourage the inclusion of individuals from a diverse range of backgrounds including, but not limited to race, ethnicity, sex/gender, and age in clinical trials through broad eligibility criteria and novel site placement and recruitment approaches. Recruiting participants from diverse backgrounds is particularly important for clinical trials studying diseases that disproportionately affect specific racial and ethnic populations, such as sickle cell disease, which predominately affects patient populations of African descent. In a trial, it is also important to encourage inclusion of participants who are more likely to be treated for a disease or condition. For example, certain populations may be at higher risk for certain diseases, such as diabetes or heart disease.



a. Building Trust and Acknowledging Past Wrongs. Diverse populations, in particular those from Black and Brown communities, have historically been underrepresented in clinical trial populations.[1] Some patients may not trust medical research due to historical mistreatment of participants, such as those involved in the U.S. Public Health Service Syphilis Study at Tuskegee, 1932-1972.[2] That study's serious mistakes and moral breaches led to major changes in how clinical trials are conducted in order to protect the rights, safety, and well-being of clinical trial participants. Additionally, the exploitation of Henrietta Lacks also led to significant changes in clinical trial practices. Mrs. Lacks was an African American woman whose cancer cells were taken without her knowledge during her cervical cancer treatment at Johns Hopkins Hospital in 1951 and then cultured to create HeLa cells, which have been used by researchers for many medical breakthroughs over the decades since.[3] Today, research participants' rights are protected by law and by ethics committees such as institutional review boards, or IRBs (*see* Chapter 2 of these Principles).

Enhancing diversity in clinical trial populations may also help reduce health care disparities through increasing access to clinical trials. Education of healthcare providers and community outreach to build trust and increase clinical trial awareness can directly help address recruitment, enrollment, and retention of a diverse clinical trial population, while also expand access to investigational treatments for underserved populations.

Biopharmaceutical companies following these principles are committed to:

1. **Enhancing Education About the Role of Clinical Trials Throughout the Medical Community and Enhancing Diversity Among Clinical Investigators.** The lack of participation by historically understudied populations may result from a lack of clinical trial awareness at hospitals and clinics that treat diverse populations. To address this gap, we commit to conduct outreach to the medical community in communities that have been underserved and support trial sites with comprehensive education on medical product development. We will do so in a manner that is culturally competent and developed in partnership with the communities we are seeking to serve. Creating greater awareness of clinical trials allows investigators and clinical trial staff, including those with diverse racial and ethnic backgrounds and those serving underrepresented communities, to be included in an expanded clinical investigator pool. We will seek to further encourage the recruitment and retention of clinical trial personnel with diverse backgrounds, including racial and ethnic backgrounds. A pool of diverse investigators can serve as a trusted and knowledgeable source of information for underrepresented diverse populations.

2. **Increasing Clinical Trial Awareness and Diversity by Improving Individual Health Literacy and Community Outreach.** Educational efforts are a key component of reaching underrepresented populations. Our educational efforts are aimed at increasing access and reducing barriers for underrepresented and diverse populations to participate in clinical trials. When conducting clinical trials, we are committed to using approaches to address all health literacy backgrounds and different levels of clinical trial awareness. Improving health literacy and clinical trial awareness should also extend to the individual needs of a diverse population with a given disease, potential comorbid conditions, and continued experience with a disease or condition(s).[4] Improving participants' understanding of clinical trials could help enhance the trial experience for participants with an aim to both recruitment and retention of diverse populations. We commit to conduct community outreach such as partnering with health and community advocacy groups that are working with the communities we aim to reach to increase clinical trial awareness and potential opportunities for participation.

b. Considerations for Inclusive and Diverse Clinical Trials and Reducing Barriers to Clinical Trials Access. The clinical trial process is complex and lengthy, and without volunteer participation the development of new medicines would not be possible. Enhancing diversity in clinical trials depends on identifying and reducing barriers to clinical trial access and participation throughout the medical product development lifecycle. To this end, we work with patients, healthcare providers, and investigators to understand and identify methods to address these barriers and enhance access to clinical trials for diverse patient populations. We also follow applicable laws and regulations and seek to implement guidelines and practices to enhance the diversity of clinical trial populations.[5]

To help enhance broader clinical trial participation by diverse and underserved or underrepresented populations, biopharmaceutical companies following these principles should employ strategies and encourage use of practices meant to reduce the barriers to participation in company-sponsored clinical trials, as follows:

1. **Adopting Enrollment and Retention Practices that Enhance Inclusiveness and Make Trial Participation Less Burdensome for Participants.** We commit to prospectively plan and design medical product development programs that promote inclusion of diverse populations in clinical trials and aim to understand the needs of those who are affected by the disease or condition being investigated. Such proactive science-driven strategies may include identifying sites where diverse patients with a particular disease or condition

may be located, identifying healthcare providers that treat underserved or underrepresented populations, and collaborating with investigators to address the goals of enrolling a diverse population in a clinical trial. When designing a trial, sponsors should consider recruitment challenges and enrollment barriers that may occur as a result of factors such as planned visit schedules, location, financial implications, and how these factors might be addressed.[6] For example, flexible scheduling and utilizing digital technologies (e.g., mobile tools and wearable technologies to gather data from participants, decentralized or virtual trials) may help to encourage greater participation from diverse patient populations who do not have easy access to a clinical research site.

2. **Taking into Account the Needs of Diverse Populations in Clinical Trial Design.** When designing clinical studies, sponsors and investigators should consider the incidence, prevalence, and severity of the condition or disease in various populations, as well as other prognostic factors that might influence the response to any intervention or outcome variable.

   We should use a patient-centered approach that takes into account patient input and experiences that may be incorporated into medical product development (e.g., clinical trial design, the identification of patient reported outcomes, development of endpoints, barriers to clinical trial participation). Incorporating the patient perspective and taking into account the specific disease burden on patients' and caregivers' daily lives and activities (e.g., time commitment, time away from work, travel, caregiver responsibilities, status of the disease) helps improve clinical trial designs, clinical trial access and participation, and recruitment, enrollment, and retention of diverse populations. Biopharmaceutical companies and other stakeholders established and follow a number of existing recommendations on addressing these issues.[7]

   Study design, target enrollment population, endpoint selection, and recruitment and retention plans should be scientifically-driven and responsive to the patient perspective. Such patient-centric approaches help improve the availability and quality of data that is representative of the population(s) most likely to use the drug. Understanding how certain demographic subgroups respond to therapies and incorporating these data into labeling may help patients, healthcare providers, caregivers, and other stakeholders make informed treatment decisions. Therefore, we should design appropriately inclusive study protocols that address the circumstantial needs of patients by more closely involving patients, patient advocates, and caregivers from Black and Brown and other underrepresented groups in the trial design process.

3. **Broadening Eligibility Criteria to Increase Diversity in Enrollment When Scientifically and Clinically Appropriate.** Broadening eligibility criteria for a clinical trial, when scientifically and clinically appropriate, maximizes the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice, without jeopardizing patient safety.[8] We commit to adopt practices for determining eligibility criteria that will help the clinical trial population to reflect the diversity of the patients who will be using the drug if approved. We use information on the populations at risk for a particular disease, data from earlier trials, the therapy's mechanism of action, any available post-approval data, and/or real-world evidence to enhance understanding of the heterogeneity of treatment effect, or lack thereof, for selected subgroups.[9] This information should allow medical product development programs to broaden the inclusion and exclusion criteria and improve enrollment of diverse populations in clinical trials.

c. **Using Real-World Data to Enhance Information on Diverse Populations Beyond Product Approval.** We continue to gather a comprehensive understanding of how a treatment or preventative measure works in certain diverse populations after a medical product is approved. During the post-approval phase, collecting clinical real-world data/real world evidence may be an important method of supplementing trial data, in compliance with all applicable local laws and regulations, serving as an effective and efficient means to enhancing understanding of drug effects in diverse patient populations.

d. **Enhancing Information About Diversity and Inclusion in Clinical Trial Participation.** Biopharmaceutical companies that voluntarily adopt these principles should establish or maintain policies or practices addressing the points outlined in this Chapter. These policies or practices should be specifically focused on enhancing the diversity of clinical trial populations and promoting enrollment practices that lead to clinical trials better reflecting all populations who are likely to use the medical product once it is approved. Such policies or statement(s)/ information about such practices should be available on the individual company's public website. A company could also post materials describing its efforts to increase participation of underrepresented populations in clinical trials, broaden eligibility criteria when scientifically and clinically appropriate, and develop patient-centric medical development programs per these principles. Any such company efforts should aim to directly address challenges associated with, and enhance enrollment of, underrepresented populations in company-sponsored clinical trials.

Chapter 6 Citations

1. U.S. Food and Drug Administration, 2015-2016 Drug Trials Snapshots Summary Report, **https://www.fda.gov/media/103160/download**.
2. See Centers for Disease Control and Prevention (CDC), U.S. Public Health Service Syphilis Study at Tuskegee, **https://www.cdc.gov/tuskegee/index.html**.
3. The Legacy of Henrietta Lacks, **https://www.hopkinsmedicine.org/henriettalacks/**.
4. The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (The MRCT Center): Health Literacy in Clinical Research, **https://mrctcenter.org/health-literacy/**.
5. See, e.g., FDA, Draft Guidance for Industry, Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs (June 2019), **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.**
6. See, e.g., TransCelerate materials developed to support patient-centric design and execution of clinical trials: **https://transceleratebiopharmainc.com/initiatives/patient-experience/.**
7. See TransCelerate, Clinical Trial Diversification Solutions, **https://transceleratebiopharmainc.com/assets/clinical-trial-diversification-4/**; The MRCT Center, Diverse Representation and Inclusion in Clinical Research Principles, **https://mrctcenter.org/wp-content/uploads/2019/12/2019-11-24-Diversity-Principles.pdf**; The MRCT Center, Diversity, Inclusion, and Equity in Clinical Trials, **https://mrctcenter.org/diversity-in-clinical-trials/.**
8. FDA, Draft Guidance for Industry, Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs (June 2019), **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial**.
9. Id.

Q&A

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 in patients 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 could help inform patient care and therefore should be communicated in a timely manner after marketing approval is obtained. If the company is still developing the product, disclosing the results prematurely could cause the company to jeopardize important intellectual property. If, however, a company discontinues the development of a drug product, under these Principles, the company should post a summary of clinical trial results conducted in patients.

Importantly, under these Principles if the clinical trial results are thought to be of significant medical importance, the sponsor should work with investigators to communicate the results of the trial through posting or publication.

Principle 4 states that companies commit to providing registration and results information about clinical trials conducted "in patients." What is meant by this?

The most important clinical trials are those that test a medicine on subjects who actually require medical care: patients. The results of trials such as these are integral to drug development, because they provide medical evidence regarding the safety and effectiveness of medicines in the population intended to use the medicine. These are the clinical trials for which companies commit to providing information. Therefore, companies commit to providing registry and results information to applicable clinical trials involving patients. By contrast, some very early exploratory clinical trials (i.e., most Phase 1 studies) typically involve limited testing in a small set of healthy adults, and therefore do not generally provide robust information regarding safety or effectiveness. Because these studies typically involve healthy adults, a clinical trial registry would not be useful for patients seeking to enter such trials. In addition, due to their small size, and because such studies would not provide safety or effectiveness data in actual patients, results information would be limited. Of course, the FDA and other national health authorities receive detailed and timely reports of significant safety information regarding clinical trials for drugs seeking approval.

Principle 4 states that submission of registration information for clinical trials conducted in patients should be "timely." What does "timely" mean?

Companies typically submit applicable clinical trials to a government clinical trial database (e.g., www.clinicaltrials.gov operated by the U.S. National Library of Medicine) within 21 days of the enrollment of the first patient. This is an appropriate standard under these Principles.

Where will clinical trials be registered and results posted?

Companies commit to registering clinical trials and posting results on a publicly available website, including www.clinicaltrials.gov.

Principle 4 states that submission and posting of clinical trial results should be "timely." What does "timely" mean?

Generally for approved products, companies submit applicable clinical trial results to a government database by the latter of 12 months after the trial ends or within 30 days after approval of the drug. This is an appropriate standard under these Principles. For unapproved products whose development program has been discontinued, companies commit to posting results within one year of such discontinuation.

Principle 4 states that companies should submit and post results of clinical trials conducted in patients involving the use of investigational products whose development programs are discontinued. What does "discontinued" mean?

Under these Principles, a development program is discontinued when the company is no longer studying the applicable molecule, does not expect to resume development, and has no plans for the molecule on its own or through collaboration or out-licensing.

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

Perhaps. Exploratory trials conducted in healthy adults rarely provide information of significant medical importance. However, if such a trial did provide significant medical information, sponsors should work with the investigators to communicate the results of the trial.

When a company registers a clinical trial, what information must be provided?

Governments and health organizations have settled on standard data elements for clinical trial registries. For example, the Food and Drug Administration Amendments Act of 2007 (FDAAA) established a standard listing of data elements that should be posted for applicable clinical trials. The FDAAA data elements, which are substantially similar to a list developed by the World Health Organization (WHO), includes the following information:

- *Descriptive information*, including: a brief title, a brief summary, the primary purpose, the study design, the study phase, study type, the primary disease or condition being studied or the focus of the study, the intervention name and intervention type, the study start date, the expected completion date, the target number of subjects, and outcomes, including primary and secondary outcome measures;
- *Recruitment information*, including: eligibility criteria, gender, age limits, whether the trial accepts healthy volunteers, overall recruitment status, and individual site status;
- *Location and contact information*, including: the name of the sponsor, the responsible party by official title, and the facility name and facility contact information; and
- *Administrative data*, including: the unique protocol identification number and other protocol identification numbers, if any.

For clinical trials subject to the FDAAA, companies should list the data elements required by the statute. In addition, companies should consider providing the FDAAA data elements for all other clinical trials covered in these Principles, except if providing such information could jeopardize the intellectual property protection with respect to the product. During the course of a clinical trial, a significant amount of information may be collected, including routine laboratory values and radiological images (e.g., x-ray and magnetic resonance images). Consistent with the FDAAA, the collection of such information would not be registered unless the value is being used in the evaluation of a primary or secondary clinical outcome according to the clinical trial protocol. Clinical trials required to be posted under FDAAA must be posted on www.clinicaltrials.gov. Trials not covered by the FDAAA requirements could be posted on a publicly available web site such as www.clinicaltrials.gov.

When a company provides results of a clinical trial, what information must be provided?

At a minimum, companies commit to providing basic information about the study design, study population, primary and secondary outcomes, as well as serious or frequent adverse events. Of course, companies may choose to provide additional information either voluntarily or subject to governmental requirements.

What is the ICH Guideline for Good Clinical Practice (GCPs) and in which jurisdictions does it apply?

The ICH Guideline for Good Clinical Practice (GCPs) is 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 WHO. They were published in 1996 as part of the 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.

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 or disclose results from clinical trials of drugs. 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 or disclosed 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 tables, figures, and 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.

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.

May companies perform clinical trials or observational studies just to provide healthcare professionals with experience using a medicine?

No. Clinical trials and observational studies should be performed only to test legitimate scientific hypotheses or to gather bona fide data about a medicine. Consistent with GCP, before a clinical trial is initiated, "foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks." International Conference on Harmonization, ICH E6, Guideline for Good Clinical Practice (2002). We note that it is possible that a regulatory agency may require certain clinical trials or observational studies as part of a risk management program for a medicine.

Such clinical research may measure compliance or the behavior of healthcare professionals. If such a trial is required or reviewed as part of a risk management plan, it would be appropriate under these Principles.

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 for trials 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 GCPs developed by the 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. Under these Principles PhRMA member companies that sponsor clinical trials commit 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 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 seven 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. 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.

How do clinical trial sponsors handle conflicts of interest?

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., the FDA 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 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. Under these PhRMA Principles, when authors submit a manuscript to a medical journal, they are responsible for disclosing all financial and personal relationships that might bias their work. 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 ICH, 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 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 them. If the participant withdraws from a study, the participant may ask that any unused portion of their stored sample be destroyed. Whether the sample can be destroyed will depend on whether it can be identified by the sponsor.

What is meant by diversity in clinical trial participation?

Diversity in clinical trial participation means that the clinical trial patient population should, to the extent possible, reflect the diversity of the intended patient population once the medicine is approved. Sponsors should understand the prevalence of the disease in diverse populations, including people of different races, ethnic groups, sex/genders and ages, and seek to enroll patients that appropriately reflect the disease prevalence for various groups.

Why is enhancing diversity in clinical trial populations important?

It is critical to have diverse, inclusive trials to ensure that trials conducted better reflect the patient population likely to be treated for the disease or condition being studied. For example, certain populations may be at higher risk for certain diseases, such as diabetes or heart disease. Recruiting participants from diverse backgrounds is particularly important for clinical trials involving diseases that disproportionately affect specific racial and ethnic populations, such as sickle cell disease, which predominately affects patient populations of African descent. Ultimately, diverse clinical trials support better informed regulatory review and decision making. The inclusion of information about diverse participants in the product labeling can help better inform medical practice by providing more detailed information about the use of a medical product in the patient populations for which it is intended. This would help improve the ability of patients, caregivers, and healthcare providers to make more informed decisions regarding treatments.

What are the primary considerations for including diverse patient populations in clinical trials?

The research question, current standard of care, and prior knowledge of the disease or condition, including the prevalence of the disease in diverse populations, should be taken into account on a case-by-case basis when designing a clinical trial. Sponsors should also analyze and carefully consider pre-clinical and early clinical data, an assessment of outcomes of similar products, and prior evidence of differences when determining what sub-populations to include in a particular clinical trial. The specific research question, disease or condition under study, and research locale (e.g., research site location) informs consideration of inclusion of specific patient populations. In addition to the proposed intervention (e.g., investigational medicine) itself, these factors will impact how different patient populations are considered in the research process, trial planning and analyses. Sponsors should consider which dimension

of diversity is relevant to the safety or efficacy of a particular intervention as not every dimension may be applicable to every intervention. Sponsors should select sites that have access to the racial/ethnic population who experience the disease and should consider enriching sites and selecting investigators with demonstrated experience and capabilities recruiting such racial and ethnic diverse populations.

When addressing diversity across the medical product development program and in a specific clinical trial, it is also important to note that because less is known about the safety and efficacy of the product at the outset of clinical development, early stage research may differ from later-stage research in terms of the diversity of the clinical trial population.

How does a proactive patient-centric approach to medical product development help enhance clinical trial diversity?

Incorporating the patient perspective and taking into account the specific disease burden on patients' and caregivers' daily lives and activities (e.g., time commitment, time away from work, travel, caregiver responsibilities, cycle and status of the disease) will help improve clinical trial designs, clinical trial access and participation, and recruitment, enrollment, and retention of diverse populations.

A proactive strategy to enhance diversity in clinical trial populations takes into account considerations of race, sex/gender, ethnicity, age, comorbidities, etc., as applicable based on the disease being studied. A patient-centric approach takes into account patient input and experiences that may be incorporated into medical product development (e.g., clinical trial design, the identification of patient reported outcomes, development of study endpoints that are important to patients, how to address barriers to clinical trial participation). A proactive product lifecycle approach focuses on understanding efficacy, safety, clinical characteristics, and the demographic characteristics of the population associated with the disease being studied. Addressing the circumstantial needs and outcomes of greatest importance to patients by more closely involving patients, patient advocates, and caregivers in the trial design process is a pathway to an inclusive, more diverse, and potentially more informative clinical study.

How may barriers to clinical trial access and participation be identified and addressed?

A meaningful and proactive approach to understanding and addressing barriers to clinical trial access and participation is essential to enhance diversity of clinical trial populations. Improving access to clinical trial participation for patients may include a wide variety of mechanisms, including those described in Chapter 6 of these Principles, to make trial participation less burdensome for patients and may help enhance clinical trial diversity. Working with patients, community health care providers, and clinical trial investigators to understand these barriers and identify methods to address them is key to effective communication, building trust, increasing clinical trial awareness, and enhancing access to clinical trials for diverse patient populations at various stages of a medical product development program.

When designing a trial, sponsors should consider approaches to identify potential barriers to clinical trial access for diverse populations, such as recruitment and retention challenges, including those that may occur as a result of planned visit schedules, location, and financial risks. For example, designing studies that are more location-flexible, including through the use of mobile tools to gather data from patients may be useful in reducing barriers (e.g., time commitment, reducing number of site visits, patient expenses, travel logistics) to clinical trial participation. Likewise, to address barriers relating to lack of trust and/or awareness of clinical trials, sponsors may, for example, undertake educational programs to explain the importance of the clinical trial process and the benefits of enrolling a diverse population. Involving patients and caregivers in the clinical trial design process may help identify potential barriers for participants and propose solutions for reducing burdens of clinical trial participation. To address potential financial barriers in clinical trial participation, sponsors should consider FDA guidance to IRBs and clinical investigators for payment and reimbursement for research subjects.[1]

What is usually included in educational efforts to increase clinical trial awareness and how they can help improve participation of diverse populations?

Educational efforts to enhance clinical trial awareness of a variety of stakeholders (e.g., patients, caregivers, patient advocacy groups, investigators, and clinical trial staff) generally include discussing the personal and societal value of clinical trials, explaining the purpose of clinical trials, and improving understanding of the clinical trial design (e.g., explaining the difference between placebo-controlled trials and clinical trials using standard of care). Also, educational

efforts should include clarifying roles and responsibilities of participating in a clinical trial and describing the rights of participants in trials, the informed consent process and how research participants' rights are protected by law and by ethics committees such as institutional review boards, or IRBs (see Chapter 2 of these Principles). Improving the understanding of clinical trials can help enhance both recruitment and retention of clinical trial participants, including diverse populations. Sponsors' educational efforts should be aimed at increasing access and reducing barriers for underrepresented and diverse populations to participate in clinical trials, as described in Chapter 6 of these principles. Working closely with communities and participants on educational efforts is critical for enhancing clinical trial diversity.

How can broadening clinical trial eligibility criteria help enhance clinical trial diversity?

Using a science-based approach, including evaluating populations at risk for a particular disease, existing data from earlier trials, the drug's mechanism of action, pharmacodynamics, pharmacokinetics, or pharmacogenetics, post-approval data collection, and/or real-world evidence, the broadening of clinical trial eligibility criteria may enhance understanding of whether an investigational medicine's safety and/or efficacy is different in different populations.[2] This information may allow sponsors to broaden the inclusion and exclusion criteria for medical product development programs and improve clinical trial enrollment of diverse populations that may have been excluded with a narrower set of eligibility criteria. Broadening eligibility criteria, when appropriate, may help maximize the utility of trial results and understanding of the therapy's benefits and risks across the patient population likely to use the drug in clinical practice, without jeopardizing patient safety.

Understanding baseline lab values in varying ethnicities can help ensure that the eligibility criteria are reflective of the intended populations. For example, if a trial is conducted in triple negative breast cancer and it is known for Black and Latina women to have high rates of this cancer type, a sponsor should understand the baseline lab values of these patient sub- populations and ensure clinical trial eligibility criteria account for these values to avoid inadvertently excluding some participants.

Why is unconscious bias training important for clinical trials?

Clinical investigators and clinical trial site personnel may be unaware of unconscious bias impacting recruitment decision making when managing trial enrollment. Unconscious bias training is important for those involved in conducting and reviewing clinical trials. The training may improve healthcare disparities through increased understanding and use of inclusive approaches to increase enrollment and retention of diverse populations in clinical trials. Sponsors should consider providing unconscious bias training for clinical investigators and site personnel during investigator engagements, such as investigator meetings.[3]

Q & A Citations:

1 FDA, Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators, Payment and Reimbursement to Research Subjects (Jan. 2018),: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects.

2 FDA, Draft Guidance for Industry, Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs (Jun. 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

3 Unconscious bias training should also be considered for sponsor clinical trial staff, CROs, and IRBs, as appropriate.

Pharmaceutical Research and Manufacturers of America

950 F Street, NW, Suite 300 • Washington, DC 20004 • www.phrma.org