



**U.S. FOOD & DRUG
ADMINISTRATION**

PUBLIC WORKSHOP:
**EVALUATING INCLUSION
AND EXCLUSION CRITERIA
IN CLINICAL TRIALS**

WORKSHOP REPORT

The National Press Club • Washington, DC • April 16, 2018

Executive Summary

During drug development, inclusion of broad patient populations in clinical trials helps provide evidence that the investigational medical products will be safe and effective in the full range of patients likely to use the product if the product is approved. Eligibility criteria determine who can participate in clinical trials and, at times, this results in the enrollment of study populations that may not represent the broader patient populations that use approved products.

Over the past few decades, there have been policy initiatives to increase the inclusion of particular subgroups in clinical trials, including women and older adults, and to ensure that all eligibility criteria are scientifically justified. This includes initiatives by the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) that emphasize the importance of inclusive eligibility criteria. Despite these efforts, challenges and barriers that limit participation in clinical trials remain.

Section 610 of the Food and Drug Administration Reauthorization Act (FDARA) of 2017 required FDA to convene a public meeting to discuss clinical trial eligibility criteria to inform a guidance on this subject.¹ Pursuant to that mandate, and under a cooperative agreement with the Duke-Robert J. Margolis, MD, Center for Health Policy, FDA held a public workshop on April 16, 2018, entitled “Evaluating Inclusion and Exclusion Criteria in Clinical Trials.”²

This workshop provided an opportunity for representatives from academia, industry, health care delivery, government, and patient advocacy groups to discuss a variety of topics related to eligibility criteria in clinical trials. The workshop addressed the underrepresentation of various populations in clinical trials, how eligibility criteria affect patient access to investigational drugs and enrollment in clinical trials, alternative clinical trial designs that may increase the enrollment of diverse populations, and whether FDA’s Expanded Access Program could provide an opportunity to facilitate access to investigational products. Discussion at the public workshop will inform FDA guidance on these issues.

Section 610 of FDARA also requires that FDA publish a report within 90 days of the workshop summarizing the topics discussed. This report summarizes the major points explored with stakeholders during the workshop and fulfills FDA’s mandate under FDARA. This report is intended only as a summary of the workshop and does not provide guidance or reflect FDA’s current thinking on this subject.

The Role of Inclusion and Exclusion Criteria in Clinical Research

Eligibility criteria are a critical component of clinical trials, as they define the patient population under investigation. These criteria are often tailored to allow assessments of the effectiveness of a treatment in a well-defined population. Inclusion criteria specify the characteristics required for study entry, such as stage of disease or specific pathophysiological characteristics. They typically identify a population in which it is expected that the effect of the drug can be shown. An obvious example is identifying patients with a specific mutation that is targeted by the treatment,

1 Public Law 115-52, FDARA, <https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pdf>.

2 Federal Register, Evaluating Inclusion and Exclusion Criteria in Clinical Trials; Public Meeting (Docket number: FDA-2018-N-0129), <https://www.federalregister.gov/documents/2018/01/30/2018-01643/evaluating-inclusion-and-exclusion-criteria-in-clinical-trials-public-meeting>.

where the drug is likely to be effective only in those patients with the disease who have the mutation. More broadly, it is usual to not only include patients who have the disease to be treated, but those who also have a threshold severity of disease and do not have certain other conditions, or who are not using medications that could mask the effect. Exclusion criteria specify characteristics that disqualify patients from participation and often include factors such as comorbidities or concomitant treatment or factors that could mask the effect of the intervention. However, if these criteria exclude a subgroup that will eventually receive the drug once approved (e.g., people with comorbidities), relevant effects of the drug on that subgroup will not be detected. Broader inclusion criteria and less-restrictive exclusion criteria will lead to a study that provides more information about the product's effects in the population most likely to use the product if it is approved.

When designing clinical trials, there is tension between balancing the desire to minimize heterogeneity (“noise”), which can mask a finding of the effect, and the desire to generate data that are generalizable to a broader patient population that is likely to be treated. Narrow eligibility criteria can result in (1) a homogenous sample of subjects, limiting the variability in a study population, and (2) controlling for confounding factors, maximizing the probability of detecting a treatment effect if one exists. On the other hand, narrow eligibility criteria can diminish the understanding of the risk-benefit of the study treatment relevant to the patient population likely to take the drug if the drug is approved. Sponsors must balance the need to generate evidence of effectiveness to support a regulatory decision while obtaining evidence in the population most likely to utilize the treatment.

Balancing these scientific considerations and designing clinical trials that both generate substantial evidence of effectiveness for regulatory approval and inform the safe and effective use of medical products in patient populations that will be exposed to them after approval will continue to be a challenge for stakeholders across the full spectrum of drug development, regulation, and use.

Ethical and Scientific Considerations that Can Lead to Exclusion

Whether the benefits of enrolling in a study outweigh the potential risks is also a primary consideration for determining eligibility criteria. Older adults and patients with organ dysfunction or multiple chronic conditions may be excluded from clinical trials because of concerns about potential adverse impacts arising from comorbidities and concomitant medications. Ethical considerations may lead to the exclusion of children, adolescents, and pregnant and lactating women in clinical trials. On the other hand, exclusion of such patients provides no information about a drug's benefits and risks in such patients, but they may use the drug if it is approved. Therefore, it is important to consider on a case-by-case basis whether such exclusions are truly necessary.

Organ Dysfunction

Patients with organ dysfunction are frequently excluded from clinical trials.³ For example, in a non-random sample of 38 individual drug trials submitted to FDA, more than 60 percent applied exclusions based on liver aspartate aminotransferase (AST) or alanine aminotransferase (ALT) cut-off levels, 58 percent based on kidney function measured by either creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR rate), and 37 percent based on serum creatinine cut-off values.⁴ FDA did not evaluate whether these renal and liver exclusions were appropriate. Patients

3 H.G. Van Spall, A. Toren, A. Kiss, and R.A. Fowler, “Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals,” *JAMA*, 2007; 297(11): 1233–1240, <https://www.ncbi.nlm.nih.gov/pubmed/17374817>.

4 Review of Eligibility Criteria From a Sample of Approved Drugs and Biologics, Kaveeta Vasisht, Food and Drug Administration, April 16, 2018, <https://healthpolicy.duke.edu/events/evaluating-inclusion-and-exclusion-criteria-clinical-trials>.

with kidney or liver disease may, even after dose adjustment, have effectiveness or safety effects different from patients without that condition, but those patients will not be assessed if they are not included. Exclusion from clinical trials leaves an evidence gap regarding the potential benefits and risks in these populations.

Multiple Chronic Conditions

Chronic conditions other than the one being studied in the trial can lead to different effectiveness or safety responses to the test drug, which can lead to patients taking additional medications that can interact with an investigational product or could lead to morbidities (e.g., functional limitations, breathing problems, infections) that could complicate the assessment of safety and effectiveness of the interventional product. Excluding such patients reduces the risk of adverse events caused by underlying conditions and concomitant drugs and reduces the difficulty in deciding whether an adverse event should be attributed to the pre-existing condition or to the test drug. At the same time, it eliminates the possibility of determining whether the test drug has an adverse or beneficial effect in those populations.

Excluding patients with such chronic conditions can significantly affect whether the trial population reflects those who will ultimately take the drug if the drug is approved. Based on 2014 self-reported survey data, 60 percent of American adults had at least one chronic condition, and of those patients, 42 percent had multiple chronic conditions.⁵ Excluding these patients limits the ability of a trial to generate data that are relevant to the actual users of the drug and limits the ability to describe how investigational therapies affect the pathophysiology of common chronic conditions and interact with other therapies.

Federal efforts to include patients with multiple chronic conditions in clinical research are ongoing. A U.S. Department of Health and Human Services (HHS) initiative in this area has focused on improving the lives of those with multiple chronic conditions, including reducing knowledge gaps in research about effective care and interventions for those living with chronic conditions.⁶ As part of that effort, FDA updated its internal policies to examine more closely which patients are represented in clinical trials, including patients with multiple chronic conditions.⁷

Older Adults

Older adults are often not well represented in clinical trials designed to investigate products targeted for the adult population. In one NIH analysis of clinical trials for diseases that are highly prevalent among older adults, about 27 percent excluded subjects based on age, with arbitrary upper age limits.⁸ Older adults may also be excluded even when age restrictions are absent, because they often suffer from multiple chronic conditions and are more likely to take multiple prescription medications, both of which are often exclusion criteria. In addition, physical disabilities may limit their ability to travel to clinical sites.

Including older adults in clinical trials is especially important because older adults often make up a majority of the patient population for certain conditions, and information obtained in clinical trials is used to support Medicare coverage decisions. Coverage determinations are made based on whether there is enough evidence to conclude that

5 C. Buttorff, T. Ruder, and M. Bauman, *Multiple Chronic Conditions in the United States*, Rand Corporation, 2017, <https://www.rand.org/pubs/tools/TL221.html>.

6 Health and Human Services, Office of the Assistant Secretary for Health, *HHS Initiative on Multiple Chronic Conditions*, <https://www.hhs.gov/ash/about-ash/multiple-chronic-conditions/addressing-multiple-chronic-conditions/index.html#framework>.

7 *Good Review Practice: Clinical Review of Investigational New Drug Applications*, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM377108.pdf>.

8 *Inclusion Across the Lifespan*, Marie Bernard, National Institute on Aging, National Institute of Health, April 16, 2018, <https://healthpolicy.duke.edu/events/evaluating-inclusion-and-exclusion-criteria-clinical-trials>.

a drug improves clinically meaningful health outcomes for the Medicare population. Without the inclusion of adults over age 65 in clinical trials, it can be challenging to determine the strength and generalizability of the evidence for the Medicare population. Since the early 1980s, FDA has developed guidance (finalized in 1989) on including the elderly (patients over age 65) in clinical trials;⁹ and an ICH-E7 guidance¹⁰ also urges this with a recent amendment to encourage inclusion of patients over age 75.

There have been renewed efforts to include older adults in clinical trials. The 21st Century Cures Act requires NIH to examine barriers to including older adults in clinical trials and identify ways to design age-inclusive trials. Beginning in 2019, applications for research must describe plans for including individuals across the lifespan, with scientific justifications for both the age range specified in the context of the study and any exclusions. NIH must also collect data on clinical trial participants by age.¹¹ Under FDA regulations, new drug applications must include effectiveness and safety data presented by gender, age, and racial subgroups and, when appropriate, other subgroups of the population of patients treated, such as patients with renal failure or patients with different levels of severity of the disease (21 CFR 314.50(d)(5)(v)).

Children, Infants, and Adolescents

Changes to U.S. drug laws to strengthen regulatory oversight for these subgroups have often been in reaction to tragic cases of harm from drugs and biologics. For example, (1) the Biologics Control Act was passed in 1902 following the deaths of 22 children from contaminated diphtheria antitoxin and smallpox vaccine; (2) the Federal Food, Drug and Cosmetic Act of 1938 legislation followed the deaths of over 107 persons, many of whom were children, caused by a preparation of the antibiotic sulfanilamide that was formulated in diethylene glycol (antifreeze), and (3) the passage of the Kefauver-Harris Drug Amendments of 1962, which created a requirement that drugs be shown effective prior to their marketing, followed the thalidomide tragedy that led to thousands of birth defects in Europe. Legislation was established to define additional safeguards to limit the risk to children in research if there is no prospect of direct benefit (21 CFR 50, subpart D). An unintentional outcome of these additional safeguards is a lack of early drug testing in children, leading to reduced knowledge about the safety and effectiveness of these medications for children, and language in labeling that may discourage pediatric use.

Federal efforts have sought to address these issues by incentivizing the inclusion of children, infants, and adolescents in clinical trials. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) have significantly increased the inclusion of children in research, but often only after approval of the drug based on data from adult populations.¹² Investigators should consider children when designing adult trials (e.g., evaluating exposure-response, incorporating endpoints that are applicable to all ages) to support extrapolation of efficacy from adults to adolescents and/or younger children when appropriate.

9 *Guideline for the Study of Drugs Likely To Be Used in the Elderly*, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072048.pdf>.

10 *ICH-E7 Studies in Support of Special Populations: Geriatrics*, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073131.pdf>.

11 National Institute of Health, Office of Extramural Research, Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects (notice number: NOT-OD-18-116), <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>.

12 Food and Drug Administration, Drugs, Development & Approval Process, Development Resources, Pediatric Product Development, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm607982.htm>.

Investigators may consider enrolling adolescents in adult trials when there is adequate information to support a prospect of direct benefit to adolescent patients to justify the risk. As investigators work to increase the inclusion of pediatric populations in clinical research, special characteristics related to pediatric populations may impact efforts to boost their enrollment. Obtaining consent requires the engagement of adult guardians. Assent from the older pediatric patients may also be needed. Not all investigators have familiarity working with these subgroups, and there may be additional opportunities to expand research in pediatric patients. The 21st Century Cures Act requires that NIH examine barriers to include children and older adults in clinical research. Beginning in 2019, children must be included in all NIH-sponsored clinical research; and if they are excluded, scientific justification is required.¹³

Pregnant and Lactating Women

Exclusion of pregnant or lactating women in clinical trials is complex and multifactorial. Uncertainty regarding the risk of adverse events in pregnant or lactating women and their fetuses or newborns has historically led to their exclusion from research. There are concerns on the part of sponsors and researchers regarding potential liability from adverse outcomes. In addition, HHS regulations (45 CFR part 46, subpart B) outline additional protections for pregnant women and include language that identifies pregnant women as a vulnerable population.¹⁴ The protections afforded in subpart B to pregnant women are in place not because pregnant women are vulnerable to coercion or undue influence or are incapable of protecting their own interests, but rather because of the potential for injury to the fetus. There are, however, good reasons to seek data in the pregnant population. Physiologic changes resulting from pregnancy, for example, can alter the pharmacokinetics and pharmacodynamics of an investigational therapy, potentially affecting its safety and efficacy. Failure to include these patients results in knowledge gaps regarding the safe and effective use of medicines during pregnancy and lactation. Increasing the enrollment of pregnant and lactating women in clinical trials is therefore an important public health issue that raises specific ethical concerns.

To address these concerns, the 21st Century Cures Act required that a Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) be formed.¹⁵ This group will ultimately produce a report that includes (1) a plan to identify and address gaps in knowledge and research regarding safe and effective drugs for pregnant and lactating women, (2) ethical issues surrounding their inclusion in clinical research, and (3) recommendations to improve the development of safe and effective therapies for these populations. FDA has also recently issued draft guidance on the scientific and ethical considerations for inclusion of pregnant women in clinical trials.¹⁶ These efforts are important steps toward enhancing the inclusion of pregnant and lactating women in clinical research, while recognizing the complexity associated with these populations.

13 National Institute of Health, Office of Extramural Research, Revision: NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects (notice number: NOT-OD-18-116), <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>.

14 Code of Federal Regulations, 45 CFR 46, <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html>.

15 National Institutes of Health, National Institute of Child Health and Human Development, About NICHD, Advisory Groups, Task Force on Research Specific to Pregnant Women and Lactating Women, <https://www.nichd.nih.gov/About/Advisory/PRGLAC>.

16 *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials*, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM603873.pdf>.

Challenges and Barriers to Eligibility and Enrollment Outside of Inclusion and Exclusion Criteria

Beyond eligibility criteria, workshop participants discussed several challenges and barriers that may prevent patients from enrolling in clinical trials.

Geographical

Geographic distance from the trial site may preclude enrollment by those who would like to participate in a trial. Clinical trial sites are often concentrated near academic medical centers. Traveling to these trial sites on a regular basis may be difficult for many patients, and it may be necessary to revisit standard clinical trial infrastructure to see if there are opportunities to broaden site availability. Distributed trial networks, which could allow patients to participate in clinical research via multiple types of care settings, may provide one pathway to increasing enrollment and trial size by eliminating the geographic factor.

Financial

Clinical trial participation can impose considerable financial burdens on patients. It can be difficult for patients to take time off from work, for example, particularly when trials require a substantial time commitment for treatment or travel. Furthermore, there may be expenses for attendant care or transportation. Some of these burdens may be minimized through home-based and telehealth-focused efforts or by reducing the number of in-person patient visits required in a study. Participants noted that other thoughtful approaches to lowering potential patient costs associated with trial participation should be considered by sponsors. FDA recently updated its guidance on payment and reimbursement of research participants to clarify that reimbursement for travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging do not raise issues of undue influence and are generally considered acceptable practice.¹⁷

Transportation

Transportation considerations alone can impact decisions to enroll in clinical trials even when geographic or financial barriers are not present. Potential enrollees may not have good transportation options to access clinical trial sites. Older adults may no longer drive or may not have suitable public transit options, and children and adolescents need a parent or caregiver to provide transportation. Although many sites now offer to provide transportation, the ability to get to clinical trial sites should be considered.

¹⁷ Food and Drug Administration, Regulatory Information, Payment and Reimbursement to Research Subjects- Information Sheet, <https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm>.

Caregivers

Another major barrier to enrollment in a clinical trial is a lack of available caregivers, particularly for older adults. Caregivers can be important partners for providing transportation to clinical trial sites, ensuring that patients adhere to the clinical trial protocol, and offering support throughout the process — all factors in helping certain patients participate in trials who otherwise may not be able to. Participants noted that investigators should do more to engage with caregivers to understand the factors that may broaden patient enrollment in clinical trials.

Consent Issues

Obtaining consent or assent from children for clinical trials is particularly challenging for certain populations, such as adolescents, older patients who are cognitively impaired, and those with mental illness. It may be difficult for these patients to understand what is required as part of a clinical trial or to understand the potential benefits and risks of participation. Furthermore, the administrative burden and costs of enrolling these patients may dissuade researchers from trying to include them.

Historical Mistrust

Unfortunately, there have been well-documented cases of participant abuse in clinical research, including (1) questionable human radiation experiments conducted by the U.S. government,¹⁸ (2) forced sterilization and birth control studies on women of color,¹⁹ and (3) ethically questionable experiments conducted without informed consent.²⁰ The Tuskegee Syphilis Study in particular is an enduring and salient example of such abuse and is often cited as contributing to significant suspicion of clinical research among African Americans.²¹

Overcoming this historical mistrust of clinical research within particular subgroups of the American public is therefore an important priority for enabling evidence generation within these communities, especially for diseases that may disproportionately affect them. It will require careful attention to communication processes for clinical trial recruitment and participation. Community engagement and outreach to connect communities with the potential benefits of participating in clinical research may represent strategies to overcome this mistrust.²²

Health Care Fatigue

Health care fatigue also prevents certain populations from enrolling in clinical trials. This is particularly relevant in populations with multiple chronic conditions and in patients who have a substantial pill burden. These populations are already frequently engaging with the health care system and may not want the additional inconvenience of enrolling in a clinical trial.

18 Roadmap to the Project. DOE Openness: Human Radiation Experiment, <https://ehss.energy.gov/ohre/roadmap/index.html>. Published December 13, 2012.

19 Philip R. Reilly, "Eugenics and Involuntary Sterilization: 1907–2015," *Annu Rev Genomics Hum Genet*, 2015; 16(1):351–368, <https://www.annualreviews.org/doi/10.1146/annurev-genom-090314-024930>.

20 Ruth R. Faden and Tom L. Beauchamp, *A History of Informed Consent*, Oxford University Press, New York, 1986, ISBN 0-19-503686-7.

21 Vicki S. Freimuth, et al., "African Americans' Views on Research and the Tuskegee Syphilis Study," *Soc Sci Med*, 2001; 52(5):797–808, [http://dx.doi.org/10.1016/S0277-9536\(00\)00178-7](http://dx.doi.org/10.1016/S0277-9536(00)00178-7).

22 Travonia B. Hughes, et al., "African Americans and Clinical Research: Evidence Concerning Barriers and Facilitators to Participation and Recruitment Recommendations," *Gerontologist*, 2017;57(2):348–358, doi: 10.1093/geront/gnv118.

Strategies to Support Better Development of Eligibility Criteria and Increase Enrollment

Although there are several reasons patients can be excluded from clinical trials or are unable to enroll, participants in the public workshop highlighted a number of strategies to support better development of eligibility criteria and to increase enrollment.

Improving Transparency and Increasing Patient Involvement in Clinical Trial Design

Participants called for more transparency in how eligibility criteria are determined. Patients screened for enrollment in a clinical trial may not understand why they were ultimately excluded from participation or how the eligibility criteria were determined. Sponsors and their clinical research associates are encouraged to clearly communicate trial eligibility criteria to potential participants and explain why patients may not be eligible.

Opening better lines of communication with patients about eligibility criteria could include conversations around establishing such criteria in the first place and could lead to developing patient-relevant study endpoints that could further encourage trial participation. For example, diabetic patients may be more interested in preventing hypoglycemia than in reducing their level of hemoglobin A1c, a common study outcome measure for diabetic medications. There is no doubt that hemoglobin A1c will continue to be a critical endpoint in diabetes trials, but more attention to hypoglycemia could be important to potential participants as a relevant outcome. More-frequent and routine patient involvement in trial design could lead to more trials that explicitly address outcomes important to patients and achieve greater patient enrollment.

Understanding why patients choose not to participate in clinical trials is also important. Surveys indicate that patients who say they are willing to participate in clinical research may decide not to enroll when faced with the decision to participate. Understanding the factors that patients consider when deciding not to participate may allow investigators to tailor trial protocols to address common concerns.

Finally, engaging in similar conversations with providers and clinicians who are not typically part of trial conduct may bolster efforts to improve referrals to clinical trials. Clinicians play a critical role in encouraging patients to participate in clinical trials and could serve as important resources for designing trials that patients will be more likely to participate in.

Re-examining Exclusion and Inclusion Practices

There may be longstanding eligibility criteria practices that unnecessarily limit eligibility for certain patient populations. In designing eligibility criteria, sponsors, investigators, and regulators should avoid assumptions and revise criteria lacking clear scientific justification. Exclusions based on age alone are rarely appropriate. For example, heart failure is more prevalent in older adults. In a trial for heart failure, excluding patients over 70 years old would lead to a lack of data for an important component of the heart failure population and would lead to a failure to evaluate appropriate dosages and needed monitoring in a significant portion of the U.S. population.

To design inclusive trials, sponsors can engage expert clinicians to ensure that the needs and priorities of specific populations are addressed. For example, it may be useful for sponsors to engage gerontologists when designing clinical trials that anticipate enrolling primarily older adults.

Several times throughout the workshop, participants also pointed to pervasive copy-and-paste approaches in setting eligibility criteria. Participants cited examples of investigators using eligibility criteria from a prior study without thinking about whether the exclusions are rational for their trial or scientifically justifiable. To reduce carryover effects from poorly-established eligibility criteria in previous trials, sponsors should spend additional time and resources ensuring that eligibility criteria are scientifically justifiable in every individual study.

Increasing the Use of Innovative and Alternative Trial Designs and Methods to Support Inclusion

Pediatric Studies

There is often a lag time after the completion of the adult trial before pediatric trials are undertaken, leaving practitioners with no choice but to utilize data from adults in their decision to treat children. Including pediatric patients in the clinical trial development program will provide data on the safety and efficacy of a drug in a pediatric population. To ensure that adequate safety and efficacy evidence in pediatric populations is available when the treatment is approved, it may be especially important to plan early in the clinical development program how pediatric patients will be included.

Open-Label Safety Studies

Even if the population in the controlled trials is not broadened, it may be possible to gain experience in the broader population through open-label safety studies. Open-label safety studies are uncontrolled studies (meaning there is no control arm and they are unblinded) and are usually conducted after the conclusion of phase 3 studies to obtain additional safety data. This data may be used to supplement data from phase 3 clinical trials, allowing more patients to access investigational drugs after efficacy trials have concluded.

Clinical Pharmacology Approaches

For patient subgroups in which there may be differences in the systemic exposure of the drug, such as those with kidney or liver disease or the elderly, pharmacokinetic data may provide sufficient bridging information to generate dosing information for the purposes of labeling. Using this data assumes that the exposure-response relationship remains unaltered in these patient subgroups. Generally, pharmacokinetic data for these subgroups are not available before phase 3 trials. This lack of data limits the ability to include the patient subgroups in the phase 3 trials and characterize the exposure-response relationship. However, the early availability of pharmacokinetic data has improved significantly over the last several decades, and such information has been useful in expanding the inclusion of certain subgroups in some large phase 3 trials, thus providing the clinical data needed to inform dosing recommendations.

In general, pharmacokinetic modeling and simulation of data from patients with organ dysfunction, from younger or older patients, or from patients with polypharmacy and other factors might allow an expanded inclusion of these subgroups in clinical trials. Expanding phase 3 inclusion criteria could be based on prospective dose-adjustment, which is based on exposure-matching from a pharmacokinetic model. In some cases, exposure-matching may not be sufficient to account for differences between subgroups because of confounding factors or uncertainty in the understanding of exposure-response relationships. In such situations, planning the inclusion of those subgroups (formal or exploratory) is important to generate clinical data and inform dosing recommendations.

Other Possible Clinical Trial Designs

Incorporating a broad study population in a clinical trial enhances the generalizability of the results. Discussions addressed several design options that may enhance the inclusion of a broader population. One option discussed was using a design with a broader patient population, but including only a pre-specified subset of the population in the primary analysis. Other options discussed included studies with adaptive features where the eligibility criteria may be expanded during the course of a clinical trial, based on accumulating data or use of master protocols such as basket and umbrella trials. There are challenges and limitations to any clinical study design, and when considering any design option, discussions with experts and regulators are essential.

Utilizing Data From Expanded Access

Workshop participants discussed expanded access programs as a pathway that can support broader patient access to an experimental drug. Expanded access allows access to an investigational therapy for patients with a serious or immediately life-threatening disease or condition who might not meet eligibility criteria for a clinical trial. FDA grants over 99 percent of sponsor and provider applications for expanded access.²³

There are questions, however, about the extent of data collection that can be obtained through the expanded access process. The goal of expanded access is to treat patients. It is not, as many participants noted, to generate or obtain the kind of evidence collected in a traditional clinical trial. To the extent that expanded access is a viable alternative to broadening eligibility criteria, however, stakeholders suggested exploring opportunities for capturing data, particularly safety data, that can further inform a drug's risk-benefit profile. Such data collection in expanded access programs may require standardized protocols, as well as a significant amount of interaction between regulators and sponsors.

It is critical to consider the need for humanitarian access to an investigational therapy while not undermining the overall clinical trial process. The expanded access program is one route for some patients to receive treatment outside of a clinical trial.

Conclusion

Enhancing inclusion and encouraging greater diversity in clinical trial populations is a priority for regulators, sponsors, investigators, and patient advocates. This workshop represents an important step in ongoing efforts to move towards more inclusionary clinical research. The strategies and recommendations from this workshop will help inform future activities on this topic.

Acknowledgements

FDA's Center for Drug Evaluation and Research thanks the Duke-Robert J. Margolis, MD, Center for Health Policy at Duke University for their support in the planning and execution of the public meeting.

²³ United States Government Accountability Office, GAO Highlights, Investigational New Drugs, FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used, <https://www.gao.gov/assets/690/685727.pdf>. Published July 2017.



U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
www.fda.gov