E ecutive Summar

During drug development, inclusion of broad patient populations in clinical trials helps provide evidence that the investigational medical products will be safe and e f ective 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 scienti fcally justi fed. 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 e f orts, 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 a f ect 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 ful fls FDA's mandate under FDARA. This report is intended only as a summary of the workshop and does not provide guidance or re f ect FDA's current thinking on this subject.

The Role of Inclusion and E clusion Criteria in Clinical Research

Eligibility criteria are a critical component of clinical trials, as they de f ne the patient population under investigation. These criteria are often tailored to allow assessments of the e f ectiveness of a treatment in a well-de f ned population. Inclusion criteria specify the characteristics required for study entry, such as stage of disease or speci f c pathophysiological characteristics. They typically identify a population in which it is expected that the e f ect of the drug can be shown. An obvious example is identifying patients with a speci f c 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.

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

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 guidance[10] 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

Investigators may consider enrolling adolescents in adult trials when there is adequate information to support a prospect of direct benef t 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 e f orts 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, scienti fc justi fcation 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 identi fes pregnant women as a vulnerable population.[14] The protections a f orded in subpart B to pregnant women are in place not because pregnant women are vulnerable to coercion or undue in f uence 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 a f ecting &o u A ˛ φ includ ll tau

Challenges and Barriers to Eligibilit and Enrollment Outside of Inclusion and E clusion Criteria

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 o f ering 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] ъ h ɣ ъ M ⌙ "

Strategies to Support Better Development of Eligibilit 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 Transparenc 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 frst 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 b ᵐ w̄ ƿ M thrg я ˢ stud ō re Ǐ r Ơ ȳ ʊ ˢ h ˢ

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.

Utili ing Data From E panded 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, investigat g м l ragnest ‘ ‘ Я ‘ ces si

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