

## **Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials**

The National Press Club • Washington, DC

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### **Discussion Guide**

During the clinical development of medical products, sponsors establish patient eligibility criteria that determine who may or may not be enrolled in a clinical trial. Inclusive eligibility criteria specify characteristics required for study entry, such as a certain stage of disease or a positive diagnostic screening result. Exclusive eligibility criteria specify characteristics that disqualify individuals from study entry, for example comorbidities that would increase the risk of participation. At the beginning of a development program, when little is known about the safety and efficacy of a product, more restrictive inclusion/exclusion criteria may be warranted. As the product moves through the development process and the trials are designed to demonstrate evidence of efficacy in the target population, it is expected that a more diverse population will be eligible for enrollment. In general, inclusion and exclusion criteria can help define a target population that is representative of the broader population that may benefit from an approved investigational therapy.

While no single clinical study can be expected to accommodate all patients, restricting patient eligibility can limit the generalizability of the study findings. Studies that lack sufficient heterogeneity among participants may be difficult to generalize to the broader population that will make use of an approved medical product. However, eligibility criteria is not the only factor determining who ultimately participates in clinical trials. Knowledge about clinical trials, access to health care systems that facilitate trial referral, physical and financial challenges that may limit participation, regulatory frameworks, and other socioeconomic circumstances can all affect which patients are willing and able to participate in clinical studies.

Limited participant diversity during clinical trials may mean patients and providers in certain demographic or care settings may not have information on the outcomes or risks associated with particular populations. Payers may struggle to ascertain whether an approved medical product is reasonable or necessary for their covered population. Deriving clinical trial data from very specific patient subpopulations may complicate the development of relevant clinical practice guidelines. On the other hand, for targeted therapies it may be necessary to limit the study population based on a biomarker or other clinical indicator that is predictive of potential benefit. For these reasons, striking a balance between enrolling relevant populations that are likely to respond to the treatment under study in pivotal trials and achieving sufficiently generalizable data for downstream use will be key.

Striking this balance and ensuring that inclusion and exclusion criteria are allowing for sufficient diversity in study populations will require stakeholders to work together on potential innovative solutions. The U.S. Food & Drug Administration (FDA) is committed to engaging stakeholders with expertise throughout the clinical development process to discuss strategies to improve the judicious use of inclusion and exclusion criteria and the enrollment of diverse populations in clinical trials.<sup>1</sup> Promising approaches may involve alternative and innovative trial designs and pre-specified statistical analyses for specific patient subpopulations. These and other measures aim to increase clinical trial participation among patient subpopulations including children, adolescents, older adults, pregnant and lactating women, demographic minorities, and patients with multiple chronic conditions or organ dysfunction.

In light of these ongoing issues, this workshop, convened by the Duke-Margolis Center for Health Policy under a cooperative agreement with FDA, will bring together stakeholders to discuss a variety of topics related to inclusion and exclusion criteria in clinical trials. Discussion will encompass underrepresentation in clinical trials, how eligibility criteria impact patient access to investigational drugs and enrollment in clinical trials, and alternative clinical trial designs that may increase enrollment of diverse populations and the potential use of expanded access to facilitate access to investigational products. It is important to note that inclusion in clinical trials is an important, complex, and multifaceted issue. This workshop will synthesize additional stakeholder input and help define future activities on this topic.

### **Session I: Historical Application of Inclusion and Exclusion Criteria and Recent Federal Activities**

This session will offer federal agency perspectives on eligibility criteria in clinical trials. Over the last several years, FDA has been working to provide further commentary and guidance on patient eligibility and recruitment issues, as well as data collection for specific populations enrolled in trials.<sup>2,3,4,5,6,7</sup> During this session, the agency will provide an overview of recent internal research on subjects related to the application of inclusion and exclusions criteria, as well as a reflection on the agency's past and current efforts on this front. Leadership from the Centers for Medicare and Medicaid Services will discuss the importance of eligibility criteria in how payers make coverage decisions. Staff from the National Institutes of Health (NIH) will provide a summary and key takeaways of the June 2017 NIH Workshop, "Inclusion Across the Lifespan".<sup>8,9</sup> This workshop focused on the barriers and opportunities for participation of children and older adults in clinical research studies. NIH will also present on deliberations from the taskforce on Research Specific to Pregnant Women and Lactating Women (PRGLAC).<sup>10</sup> Part of this group's charge is to address the ethical issues surrounding the inclusion of pregnant and lactating women in clinical research.

### **Session II: What Leads to Underrepresentation?**

Certain eligibility criteria in clinical trials can exclude patient subgroups, resulting in the enrollment of study populations that may not be fully representative of the broader patient population. Encouraging greater diversity in clinical trials whenever appropriate may address some of these issues, but there are ongoing challenges to ensure that a wide range of patient populations are represented. In this session, discussion will center on factors that impact the inclusion and enrollment of underrepresented populations. These may entail ethical considerations as well as barriers to enrollment, including geographical, socioeconomic, and physical impairments. The first part of this session will focus on the challenges affecting inclusion of children, infants, and adolescents, while the second part will focus on older patients and patients with multiple chronic conditions.

#### **Inclusion of Children, Infants and Adolescents**

##### *Discussion Questions:*

- What are the considerations for excluding children, infants and adolescents?
- What are barriers to enrollment when there are not specific exclusions?
- What strategies can be used to enhance inclusion and increase enrollment?

## **Inclusion of Older Adults and Patients with Multiple Chronic Conditions**

### *Discussion Questions:*

- What are the considerations for excluding elderly patients and patients with concomitant illness?
- What are barriers to enrollment when there are not specific exclusions?
- What strategies can be used to enhance inclusion and increase enrollment?

## **Session III: Morning Synthesis Discussion**

This session will allow stakeholders the opportunity to reflect on the morning's discussion and revisit any key issues or concerns that were raised. Furthermore, the panel will identify any outstanding questions that must still be addressed as well as outline potential next steps that must take place to move this field forward.

### *Discussion Questions:*

- What are the factors that ensure representative enrollment?
- How can we balance enrichment strategies with providing more generalizable trial results?
- How does the variability in designing and applying inclusion and exclusion criteria effect generalizability of trial results?
- What can we learn from the design of in rare disease trials regarding inclusiveness?
- How can subjects with different degrees of disease severity be appropriately included into clinical trials?

## **Session IV: Inclusion of Patients with Organ Dysfunction in Phase III Trials**

Building on previous discussion, this session will highlight strategies for including patients with organ dysfunction in clinical trials. Patients with organ dysfunction (e.g., renal or hepatic impairment) are often excluded from clinical efficacy trials, creating a knowledge gap in terms of adequate prescribing recommendations for these patients. Generally, for patient subgroups not adequately represented in registration trial(s), dosing recommendations are often derived from stand-alone clinical pharmacology studies. In these studies, the primary objective is to characterize pharmacokinetics (PK) across the range of patients to derive a final dose/regimen that normalizes drug concentrations across the entire clinical subset (i.e., exposure-matching). While the exposure-matching approach leverages foundational clinical pharmacology and physiological principles is efficient and is routinely applied across many therapeutic areas, the approach is not without limitations. Speakers in this session will focus on alternatives to this paradigm that could allow broader enrollment of patients with organ dysfunction into efficacy trials as an example of strategies that could be relevant to other special populations.

### *Discussion Questions:*

- What are the advantages and limitations of the current paradigm of using stand-alone clinical pharmacology studies in lieu of broadening enrollment criteria for efficacy trials?
- How should clinical efficacy trials be designed a priori to account for potential different dosing needs in patients varying degrees of organ function?
- What are pros and cons of the alternative paradigms that broaden enrollment of patients with organ dysfunction in efficacy trials?

## **Session V: Innovative Methods and Designs**

In this session, discussion will focus on innovative trial designs being utilized within specific patient subpopulations, including rare disease populations and underrepresented demographic minorities. These innovative methods and approaches may allow an expanded use of subgroup analysis and support adaptive designs that maximize external validity. Design characteristics are likely to involve increased trial pre-specification and transparency among statisticians, investigators, and regulators, while allowing creativity and flexibility.

### *Discussion Questions:*

- How might the following innovative trial designs and methods that maximize external validity affect study eligibility for appropriate patient populations?
  - Expanded size to allow subgroup analysis
  - Smaller trials in targeted populations
  - Pragmatic trials
  - Adaptive designs
  - Other trial designs and methods (basket based on population)
- Are there use-case examples of how a particular trial design improved external validity?

## **Session VI: Utilizing Data from Expanded Access**

In situations where patients are not able to participate in an ongoing clinical trial because they did not meet the inclusion or exclusion criteria, access to the experimental treatment may be granted through FDA's expanded access program (also referred to as "compassionate use"). While the process for expanded access has been well established and FDA grants the vast majority of patient and provider applications, there are still open questions surrounding how data for regulatory submissions could be effectively generated outside a controlled study environment and how these data could be utilized by the sponsor and FDA. This session will further explore potential approaches for generating and utilizing data from the expanded access program.

### *Discussion Questions:*

- What are the benefits and challenges to utilizing data from the expanded access program?
  - What are the limitations to using the data?
  - What considerations should be taken if the data will be used to support or expand an indication?
- How would expansion of data obtained via expanded access protocols potentially impact enrollment in registration trials?

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<sup>1</sup> <https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pdf>

<sup>2</sup> <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf>

<sup>3</sup> <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126396.pdf>

<sup>4</sup>

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM507278.pdf>

<sup>5</sup> <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm603873.pdf>

<sup>6</sup> [http://www.geriatriconcology.net/article/S1879-4068\(16\)30163-1/pdf](http://www.geriatriconcology.net/article/S1879-4068(16)30163-1/pdf)

<sup>7</sup> <http://www.nejm.org/doi/full/10.1056/NEJMp1615879>

<sup>8</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>

<sup>9</sup>

[https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report%20\\_FINAL\\_508.pdf](https://report.nih.gov/UploadDocs/NIH%20Inclusion%20Across%20the%20Lifespan%20Workshop%20Summary%20Report%20_FINAL_508.pdf)

<sup>10</sup> <https://www.nichd.nih.gov/About/Advisory/PRGLAC>