Specific Populations in Clinical Trials

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Disclosures

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA
- My talk will focus on “specific” populations as defined by FDA

Objectives

- Review the inclusion specific populations in drug development
  - Children
  - Pregnant and lactating individuals
  - Geriatric populations
- Discuss enhancing diversity in clinical trials

Specific Populations

- FDA labeling regulations include requirements for content and format of human prescription drug and biological product labeling under the Physician Labeling Rule (PLR)*
- Includes section 8: Use in Specific Populations
  - Section 8.1: Pregnancy
  - Section 8.2: Lactation
  - Section 8.3: Female and males of reproductive potential
  - Section 8.4: Pediatric use
  - Section 8.5: Geriatric use
- Other definitions of “specific” populations will not be discussed

*21 CFR 201.56(d) and 201.57

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Inclusion of Pediatric Patients in Clinical Trials

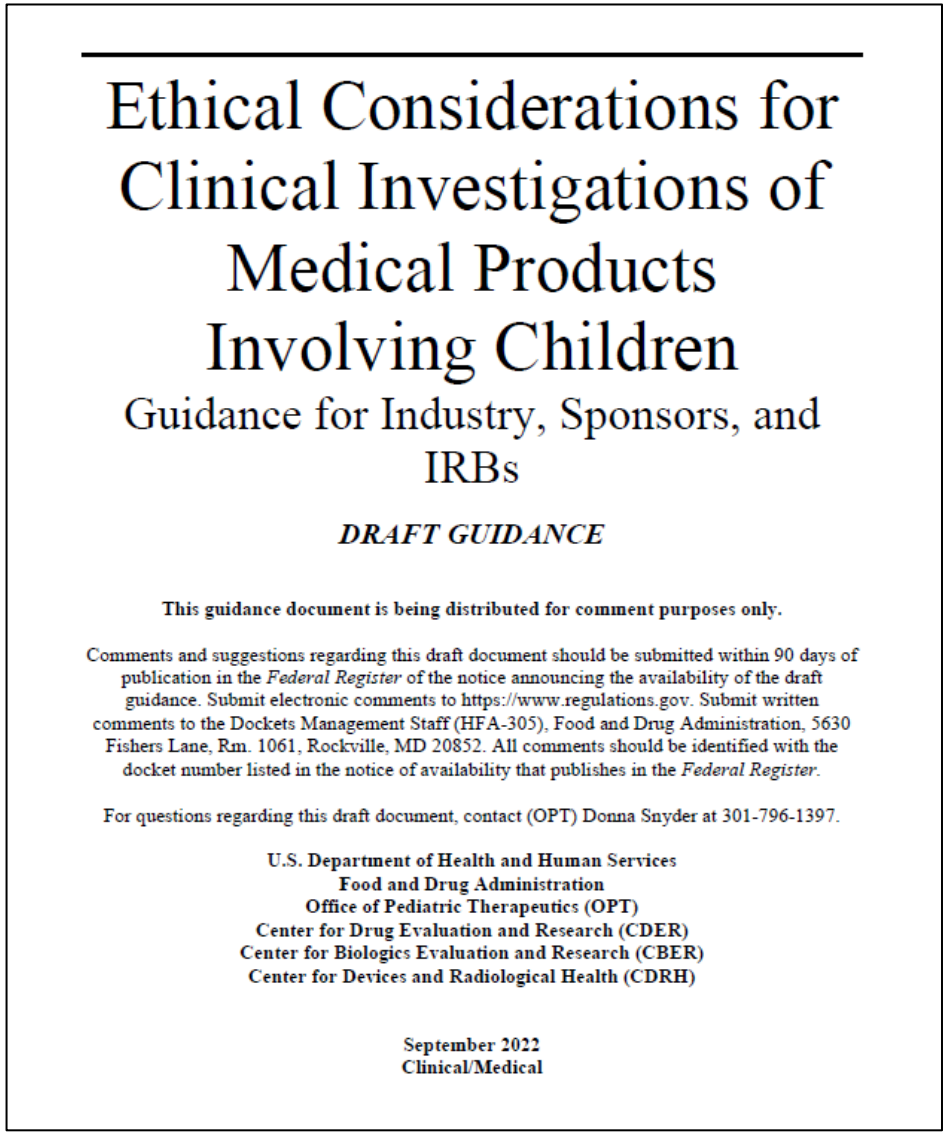
Background

- Pediatric patients should have access to medicines that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

From FDA guidance to industry *E11(R1)- Clinical Investigation of Medicinal Products in the Pediatric Population,* 2018

Special Considerations for Pediatric Product Development

- Ethical considerations
  - Children should only be enrolled in a clinical trial if the scientific and/or public health objectives cannot be met through enrolling subjects who can provide informed consent personally (i.e., adults)
  - Absent a prospect of direct therapeutic benefit, the risks to which a child would be exposed in a clinical trial must be “low”
  - Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care
- Feasibility considerations
  - The prevalence and/or incidence of a condition is generally much lower compared to adult populations



Ethical Considerations for Clinical Investigations of Medical Products Involving Children

Guidance for Industry, Sponsors, and IRBs

DRAFT GUIDANCE

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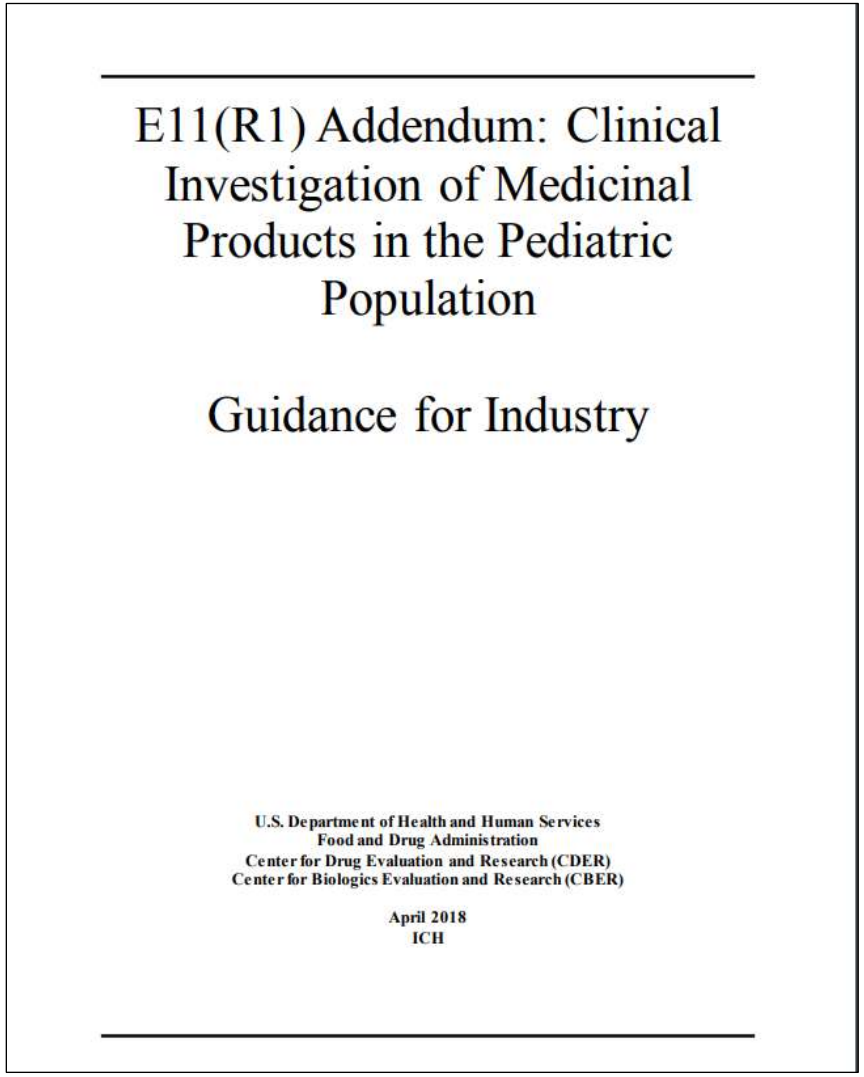
For questions regarding this draft document, contact (OPT) Donna Snyder at 301-796-1397.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Pediatric Therapeutics (OPT)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

September 2022
Clinical/Medical

ICH E11(R1) Addendum (2018)

- Describes use of pediatric extrapolation to improve efficiency and feasibility of pediatric product development
- Describes age-related safety and risk consideration for enrollment
  - Strategies such as staggered enrollment based on age should be justified
- Describes other areas unique to pediatric product development
  - Formulations
  - Safety, including long-term safety



E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population

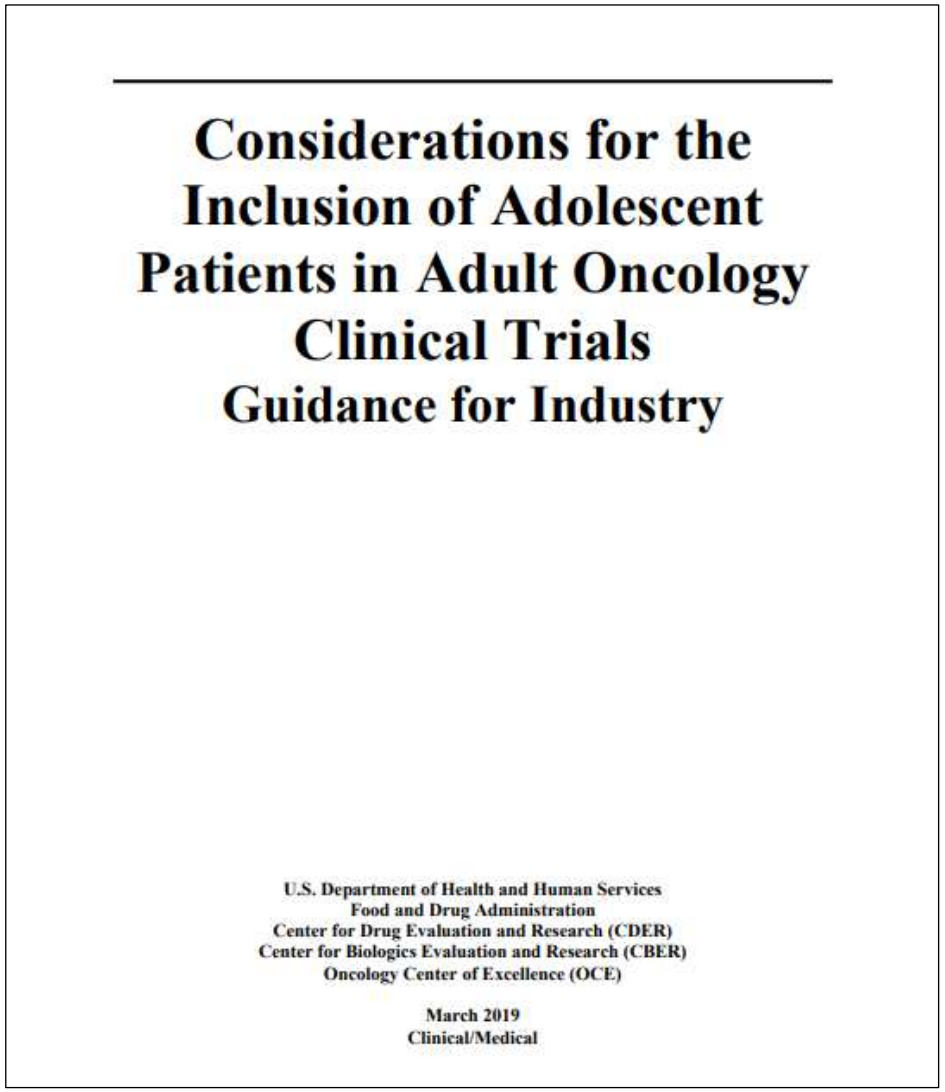
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
ICH

Inclusion of Adolescent Patients in Adult Oncology Trials (2019)

- Adolescent oncology patients, have historically been ineligible for enrollment in adult oncology clinical trials.
  - As a result, adolescent oncology patients may have delayed access to potentially effective therapies.
- Adolescent oncology patients should be eligible for enrollment in adult oncology clinical trials at all stages of drug development when the histology and biologic behavior of the cancer under investigation is the same in, or the molecular target of the drug is relevant to, cancers in both adult and adolescent patients


Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

March 2019
Clinical/Medical

Inclusion of Pregnant Individuals in Clinical Trials

Background

- Pregnant individuals should have access to medicines that have been appropriately evaluated
- Medicines for specific indications approved in adults are also approved in pregnant adults unless specifically contraindicated
  - Pregnant individuals are often automatically excluded from clinical trials
- But. . .
  - Altered physiology in pregnancy may impact dosing and safety of medicines
  - Little to no human data exist to support safety and dosing prior to approval in most cases
  - Prescribers and their pregnant patients are left to make benefit/risk decisions without data

Pregnancy and Lactation Labeling Rule (PLLR)

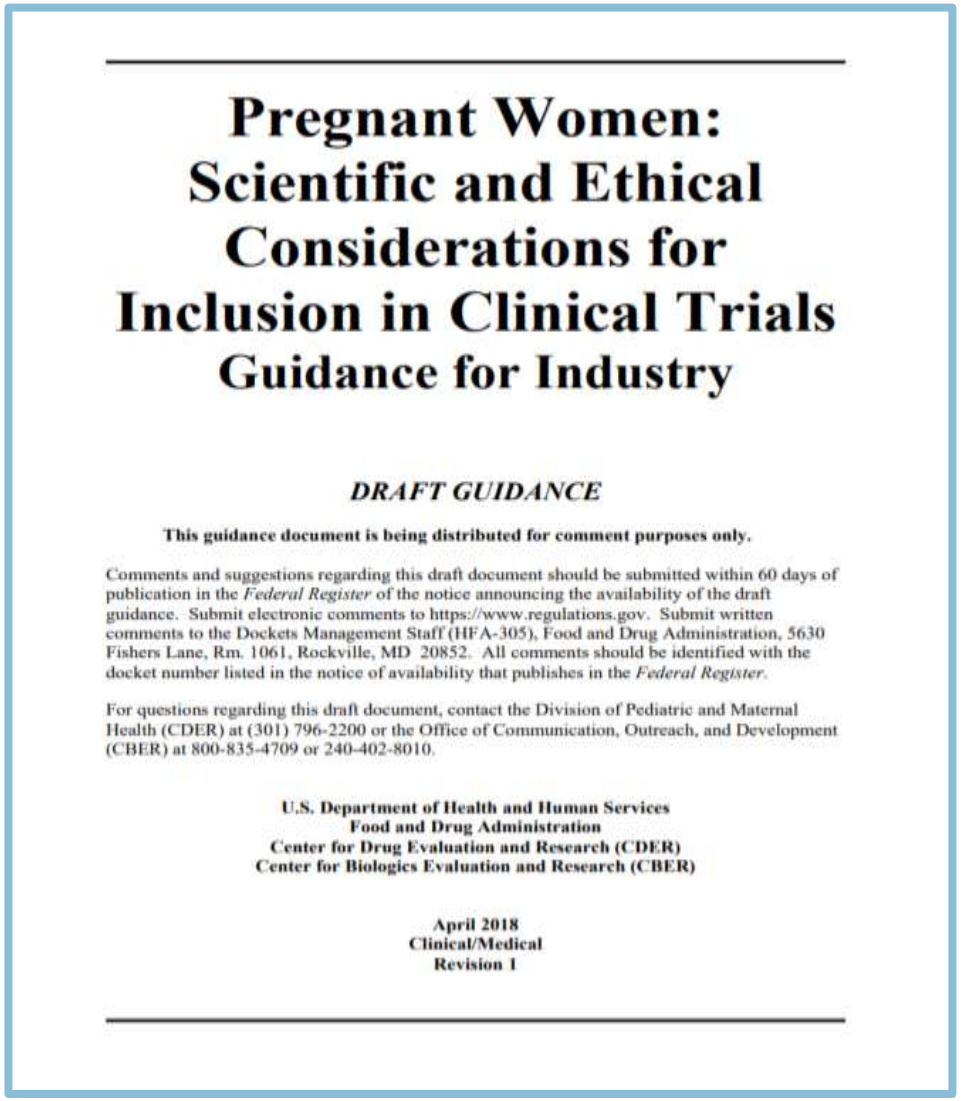
- ALL prescription drugs are required to remove pregnancy letter categories
- Revise content and format of Sections 8.1, 8.2, and 8.3
- Intended to improve communication of risk information

Lessons from PLLR Implementation

- New format provide excellent framework to discuss data and provide risks statements when data are sufficient
- The data in many cases are absent
- When some data are available the quality and quantity of data are often limited
- Data to support definitive risk statements are usually lacking

Inclusion of Pregnant Patients in Clinical Trials (2018)

- When to include pregnant women in clinical trials
- Follows HHS framework of human subject protection regulations
- Considerations for postmarket vs. premarket setting
- Women who become pregnant during a trial



Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials
Guidance for Industry

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For questions regarding this draft document, contact the Division of Pediatric and Maternal Health (CDER) at (301) 796-2200 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

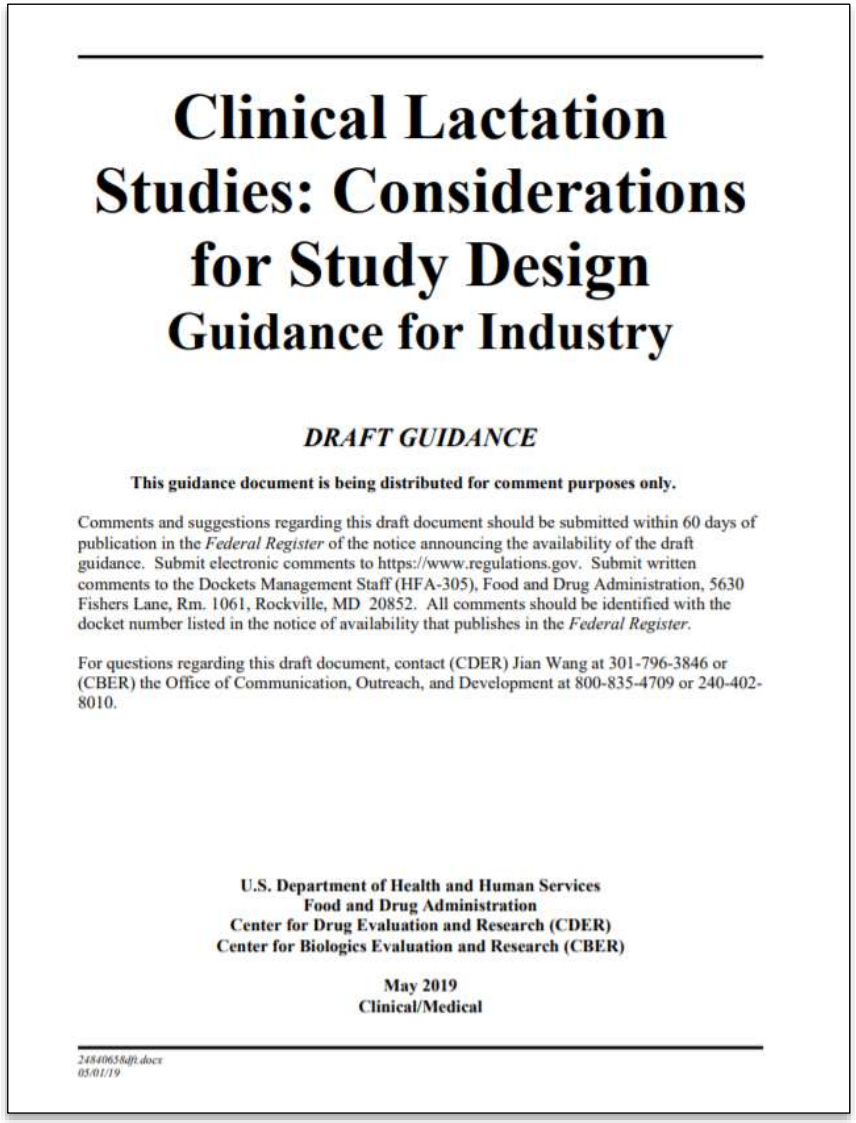
April 2018
Clinical/Medical
Revision 1

Lactation

- Medications are used in lactating individuals often with little to no human data about the safety of drug in the breastfed infant
- Collection of data transfer of drug into human milk and into the breastfed infant can provide important information on the safety of the drug when used during lactation
  - Such data are generally not available pre-approval

Clinical Lactation Studies (2019)

- Describes scenarios when a lactation study would be appropriate
- Discusses ethical considerations for participation in lactation studies
- Describes study design considerations
  - Milk-only study
  - Milk and maternal plasma study
  - Mother-infant pair study
- Milk sampling and Pharmacokinetic Analysis Methods



Clinical Lactation Studies: Considerations for Study Design

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Clinical/Medical

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Inclusion of Geriatric Patients in Clinical Trials

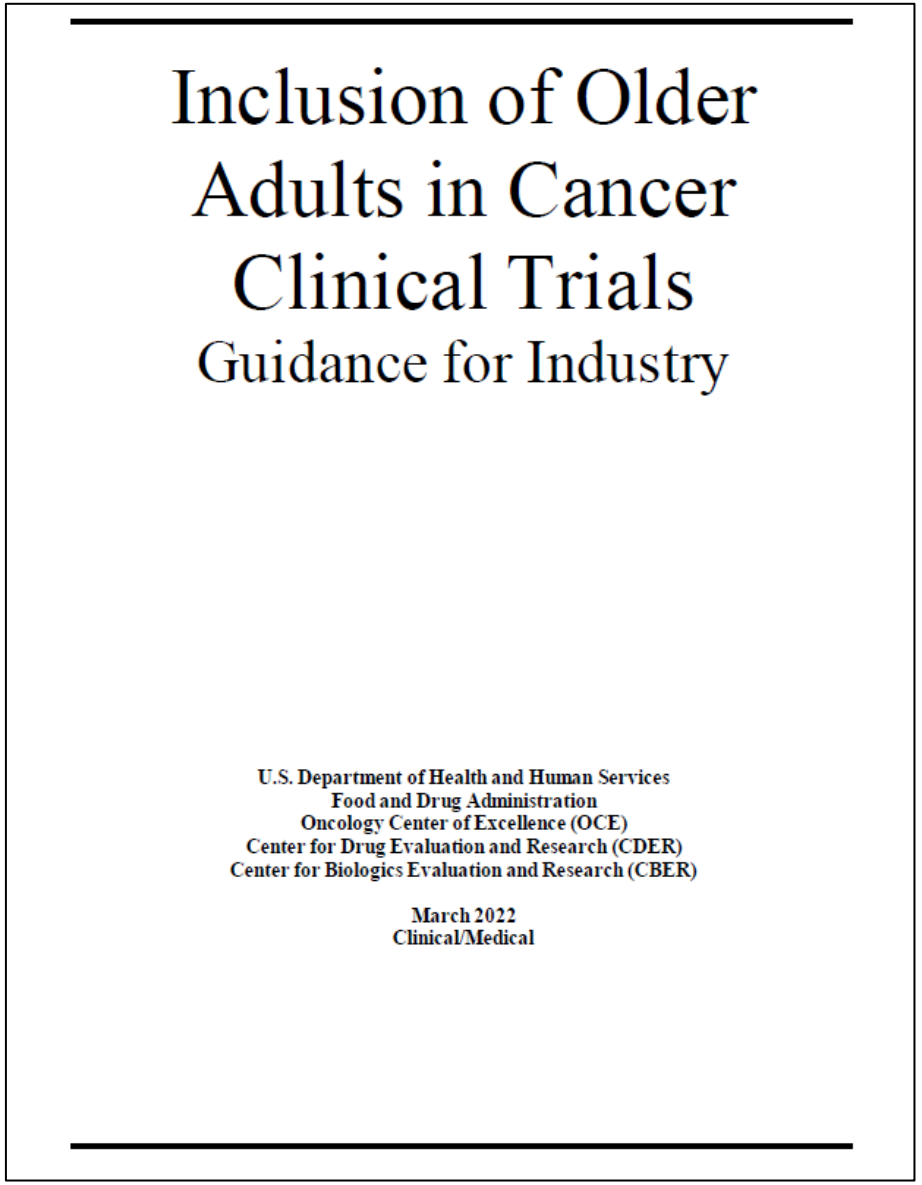
Background

- Geriatric patients are defined as patients 65 years of age and older
- Like pregnant individuals, medicines approved for specific indications in adults are also approved geriatric populations unless specifically contraindicated
- Importance of including geriatric patients
  - Impact of comorbidities on efficacy and safety (organ dysfunction)
  - Higher incidence of concomitant therapy and higher risk of drug interactions
  - Increasing number of geriatric patients in U.S.
- Labeling should provide information on any differences in:
  - Safety
  - Effectiveness
  - Pharmacodynamics and/or pharmacokinetics

Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry (2020)

Inclusion of Older Adults in Cancer Clinical Trials (2022)

- Geriatric patients important to study
  - Cancer is generally associated with age
  - Inclusion can increase generalizability
  - Efficacy and safety may differ
- Trial Designs
- Recruitment approaches
- Additional data collection
  - Adverse event monitoring and management
  - Post-marketing data may be needed


Inclusion of Older Adults in Cancer Clinical Trials

Guidance for Industry

U.S. Department of Health and Human Services
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March 2022
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Enhancing Diversity in Clinical Trials

Diversity in Clinical Trials

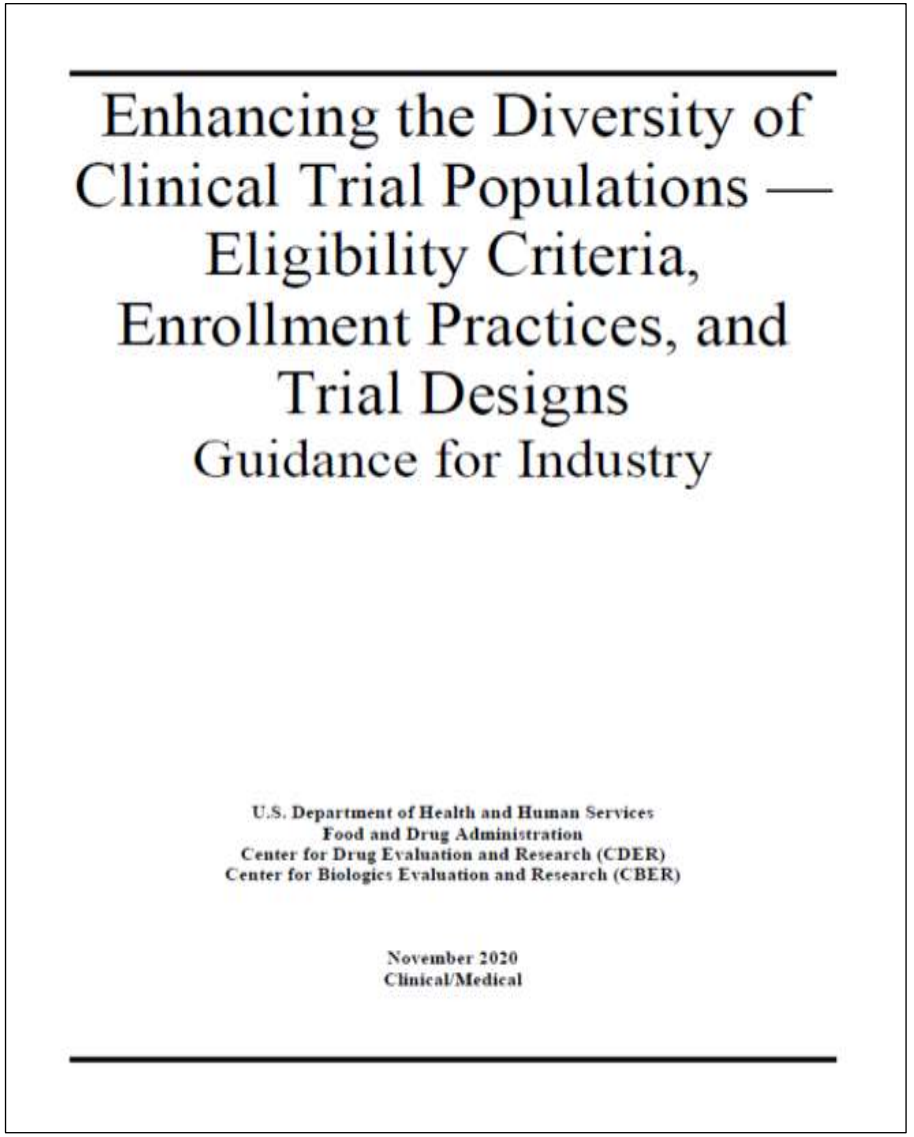
"The U.S. population has become increasingly diverse, and ensuring meaningful representation of racial and ethnic minorities in clinical trials for regulated medical products is fundamental to public health"

--FDA Commissioner Robert M. Califf, M.D.

- FDA working to ensure public health of the whole public
- Trials should reflect the population most likely to use the drug
- Certain groups continue to be underrepresented in many clinical trials.

Enhancing Diversity of Clinical Trial Populations (2020)

- Broadening eligibility criteria
  - Inclusive trial practices
- Trial Design and Methodological Approaches
- Broadening Eligibility Criteria Using Enrichment Strategies
- Decreasing burden for participation
- Enrollment and retention that enhance inclusiveness
- Rare disease considerations


Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs

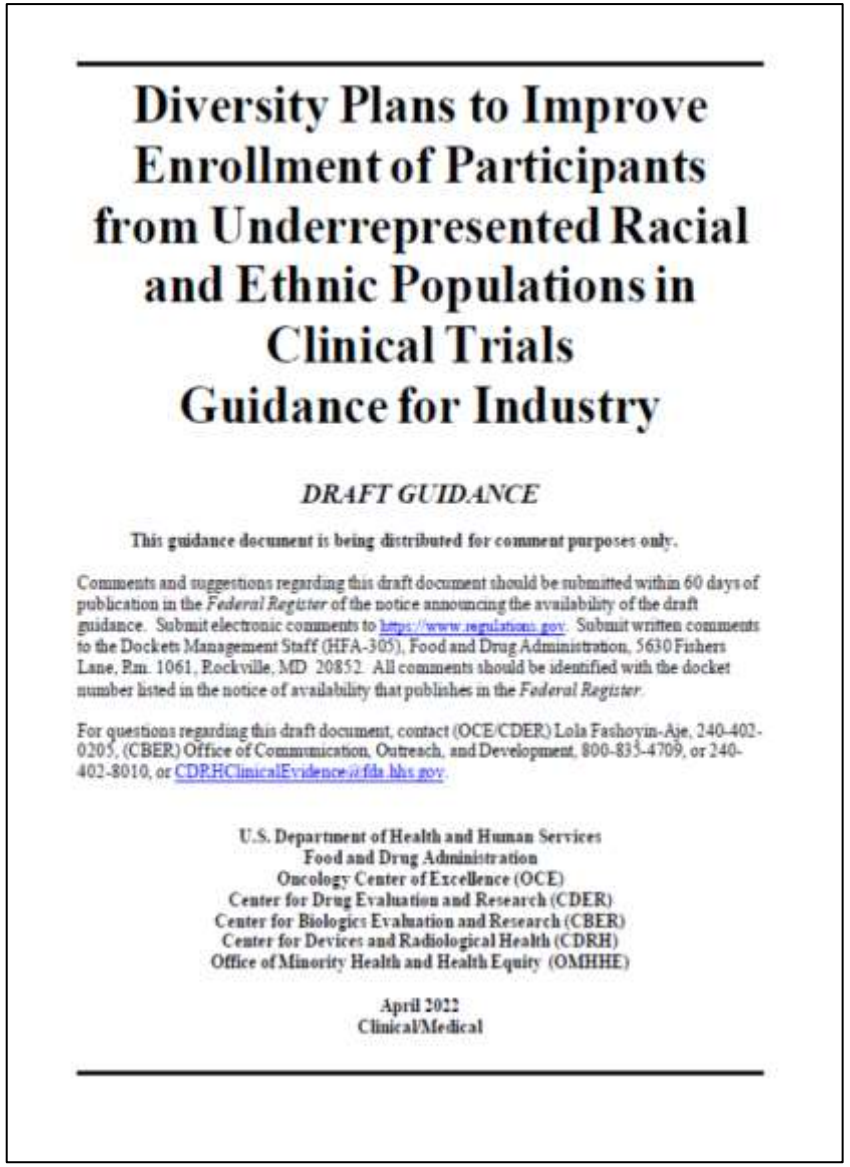
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2020
Clinical/Medical

Diversity Plans Draft Guidance (2022)

- CDER/CBER/OCE/CDRH/OMHHE joint guidance
- Diversity plan is recommended:
  - IND is required and/or clinical studies are intended to support a marketing submission
  - IDE is required and/or clinical studies are intended to support a device marketing submission
- Diversity plan should be submitted as early as practicable but generally no later than advice requested for pivotal trials (e.g., EOP2)
- Describes content of the plan
  - Overview of disease; Scope of product development program; Goals for enrollment of underrepresented racial and ethnic participants; Specific plan to enroll and retain diverse participants; Status updates as applicable



Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials
Guidance for Industry

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For questions regarding this draft document, contact (OCE/CDER) Lola Fashoyin-Aje, 240-402-0205, (CBER) Office of Communication, Outreach, and Development, 800-835-4709, or 240-402-8010, or CDRHClinicalEvidence@fda.hhs.gov.

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Center for Devices and Radiological Health (CDRH)
Office of Minority Health and Health Equity (OMHHE)

April 2022
Clinical/Medical

Diversity and Decentralized Clinical Trials

- A clinical trial where some or all the trial-related activities occur at a location separate from the investigator's location
- Potential benefits
  - Patient convenience (avoiding travel to sites, time off work, etc.)
  - Improved participation and diversity
  - Potentially improves enrollment (rare or sporadic diseases)
- Challenges
  - Increased need for innovative training and tracking strategies
  - Compliance issues

Summary

- Children, pregnant and lactating individuals and geriatric populations should have access to medicines with information to support their safe and effective use
  - When drugs are approved for specific indications in adults, this includes pregnant and lactating individuals and geriatric populations unless specifically contraindicated
  - When drugs are approved for adults, pediatric populations are not automatically approved
- Drug development should be designed to include specific populations when use is expected in these populations
  - Unique ethical considerations for both children and pregnant individuals enrolled in clinical trials
- Early planning needed to ensure adequate participation of specific populations
- U.S. population has become increasing diverse and clinical trials should reflect the population most likely to use the drug

Challenge Question

Specific populations that should be considered for enrollment in clinical trials during drug development include:

- A: Pediatric populations
- B: Pregnant and lactating populations
- C: Geriatric populations
- D: All of the above
- E: A and B only

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Thank You