# History of FDA Guidance on Drug Evaluation in Older Adult Patients

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**Center for Drug Evaluation and Research**
**Office of Translational Sciences**
**Office of Clinical Pharmacology**

# Disclaimer

- **This presentation reflects the views and opinions of the presenter and does not represent the views, opinions, and policies of the Food and Drug Administration.**
- **This presenter declares no conflict of interest.**

# Outline

- Background
- Development of regulations, guidelines, and guidances in the US - history and current status
- Enrollment of older adults in clinical trials
- Take-home messages
- Acknowledgements


3

# Background

Older adult patients are the main consumers of medications. This is the fundamental difference between geriatric patients and pediatric patients.

For the current thinking of the FDA on certain topics, the FDA communicates with the stakeholders via guidance documents.

Drug product label or “package insert” is an important tool to communicate critical information of the drug product to prescribers or health-care providers.

# Regulatory Development in the US

1985 — 21 CFR 314.50

21 CFR Ch. I (4-1-86 Edition)
Subpart B—Applications

§ 314.50 Content and format of an application.

(5) *Clinical data section.* A section describing the clinical investigations of the drug, including the following:

(v) An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications. Evidence is also required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended, and modifications for specific subgroups (for example, pediatrics, geriatrics, patients with renal failure).

1988 — Guideline NDA's Stat & Clin sections

1989

GUIDELINE FOR THE STUDY OF DRUGS LIKELY TO BE USED IN THE ELDERLY

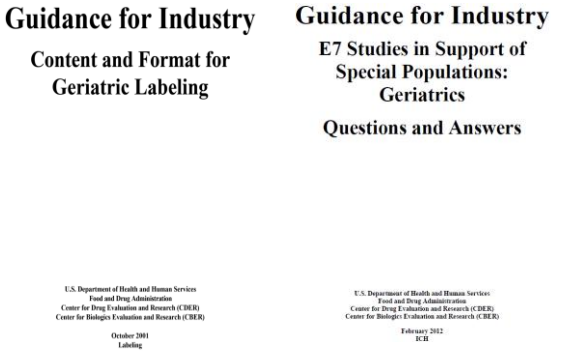
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

1994


1997 — Geriatric Use Subsection in Precaution section of product label

1998 — Demographic Rule requires effectiveness & safety data of age, gender, racial subgroups

2001




2012




Time not drawn to scale

# Regulatory Development in the US

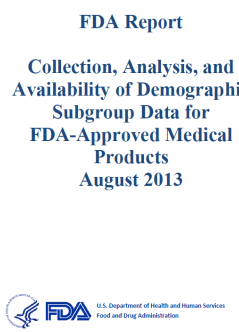
2012 2013 2014 2015 2016 2020

Time not drawn to scale

**SEC. 907. REPORTING OF INCLUSION OF DEMOGRAPHIC SUBGROUPS IN CLINICAL TRIALS AND DATA ANALYSIS IN APPLICATIONS FOR DRUGS, BIOLOGICS, AND DEVICES.**

(a) REPORT.—

(1) IN GENERAL.—Not later than 1 year after the date of enactment of this Act, the Secretary, acting through the Commissioner, shall publish on the Internet Web site of the Food and Drug Administration a report, consistent with the regulations of the Food and Drug Administration pertaining to the protection of sponsors' confidential commercial information as of the date of enactment of this Act, addressing the extent to which clinical trial participation and the inclusion of safety and effectiveness data by demographic subgroups


FDA Report

Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products

August 2013

U.S. Department of Health and Human Services
Food and Drug Administration

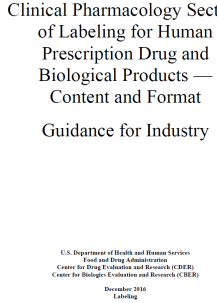

FDA Report

FDA ACTION PLAN TO ENHANCE THE COLLECTION AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA

August 2014


Make Available Clinical Trial Data that Supported NDA or BLA Approvals in Drug Trials Snapshots

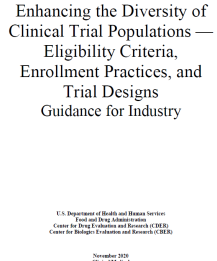
Example: Drug X


Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

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)

December 2016
Labeling


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

Guidance for Industry

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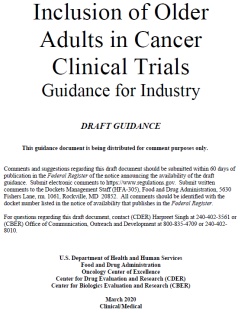
November 2020
Clinical/Medical


Inclusion of Older Adults in Cancer Clinical Trials

Guidance for Industry

*DRAFT GUIDANCE*

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U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
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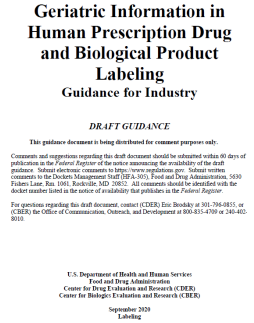
March 2020
Clinical/Medical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**Guidance for Industry**

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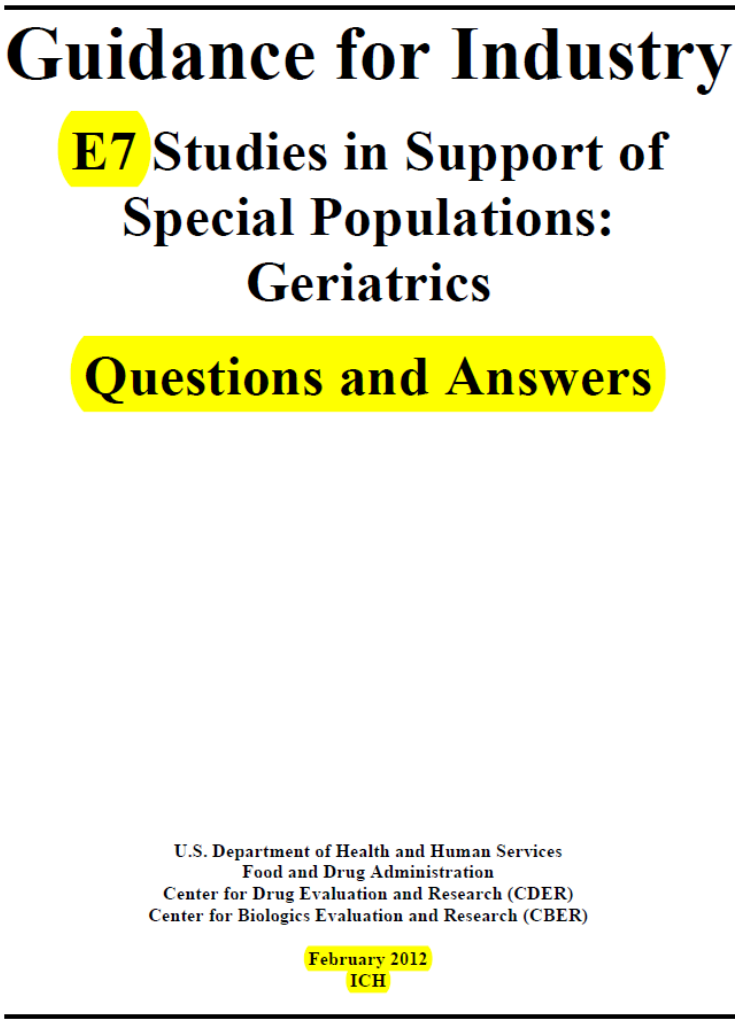
# ICH E7 Update 2012




https://www.fda.gov/media/78220/download

- 100 patients are unlikely to be sufficient (aging Baby Boomers); include representative number of older adult patients
- Present data for 4 age groups to assess consistency of treatment efficacy and safety with non-older adult patients:
  - < 65
  - 65 – 74
  - 75 – 84
  - ≥ 85
- Emphasize studying patients ≥ 75 years of age.
- Avoid arbitrary upper age limits in clinical trials.
- Encourage inclusion of patients with concomitant illnesses.
- Prefer inclusion of older adult patients in the pivotal Phase 3 trials, not in separate trials.
- Study PK of older adult patients:
  - Entire spectrum of the older adult patient population to identify age-related differences not explained by other factors (renal and weight)
  - If enough number of patients in different age ranges (including patients ≥ 65 and ≥ 75 years) is included in the clinical trials, then population PK analysis could provide such data.
  - Or, a specific PK study comparing non-older adult and older adult participants in the same study (matched for relevant covariates such as weight and sex) could be performed.

Cerreta et al. *J Nutr Health Aging* 2015

# FDASIA's Section 907

**SEC. 907. REPORTING OF INCLUSION OF DEMOGRAPHIC SUBGROUPS IN CLINICAL TRIALS AND DATA ANALYSIS IN APPLICATIONS FOR DRUGS, BIOLOGICS, AND DEVICES.**

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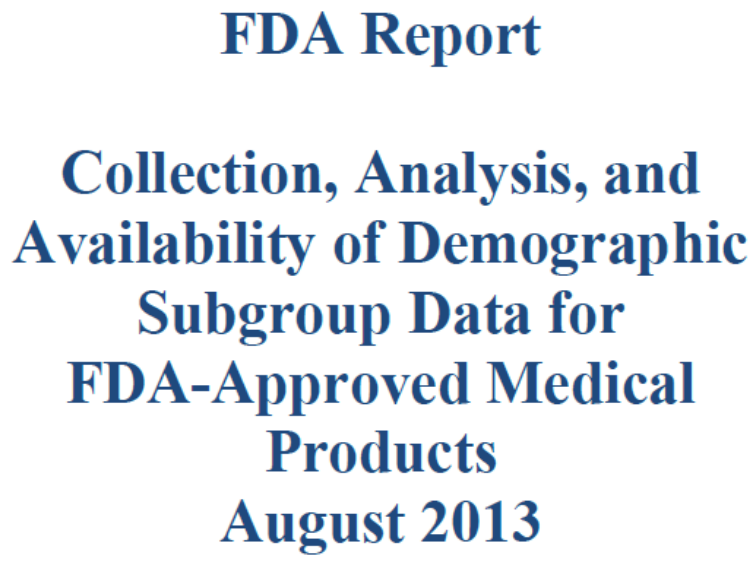
**FDASIA = Food and Drug Administration Safety and Innovation Act**
**In 2012, the Section 907 of FDASIA directed the FDA to issue a report within 1 year and an action plan in the following year to Congress.**

PUBLIC LAW 112–144—JULY 9, 2012 126 STAT. 1093

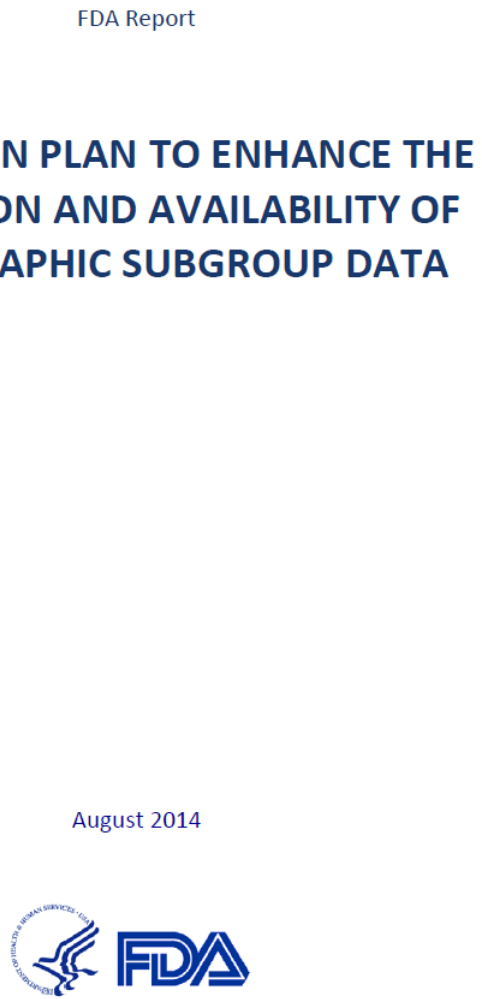
# The 2013 FDA Report to Congress




- **Describes the demographics and subset analyses for 72 approved applications in 2011 from:**
  - **CDER (24 drugs + 6 biologics)**
  - **CBER (5 biologics)**
  - **CDRH (37 devices)**

U.S. Department of Health and Human Services
Food and Drug Administration

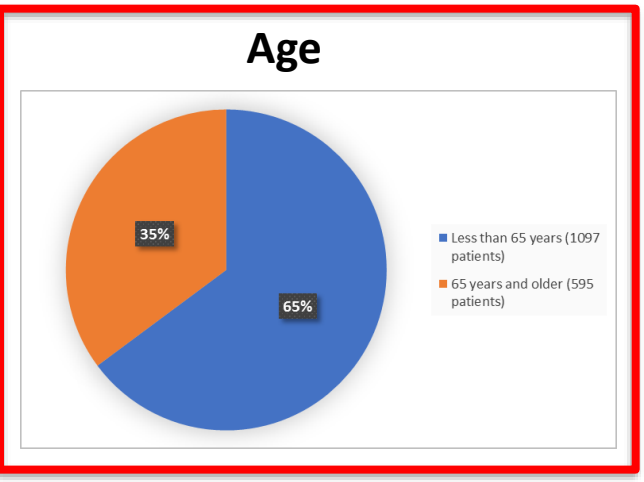
# The 2014 FDA Action Plan to Congress

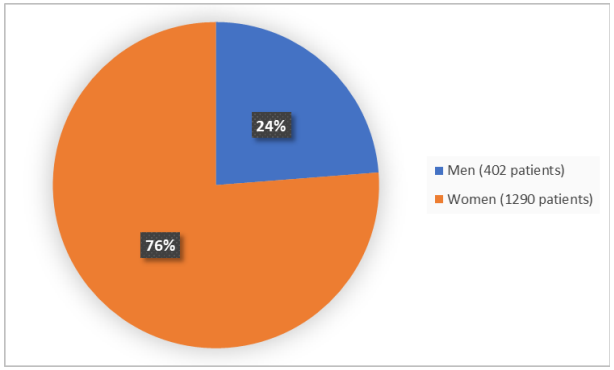


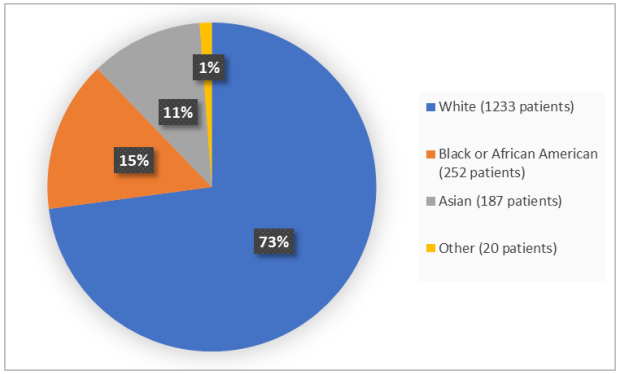

- **Has 3 priorities:**
  - **Quality: improve the completeness and quality of demographic subgroup data analyses**
  - **Participation: identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation**
  - **Transparency: making demographic subgroup data more available and transparent**
- **To include the subgroup data analyses in:**
  - **product labeling**
  - **information distributed to patients and healthcare providers**

# Make Available Clinical Trial Data that Supported NDA or BLA Approvals in Drug Trials Snapshots

## Example: Drug X




**Suggestions:**

- **Data on all age subgroups (not just < 65 or ≥ 65 years) will be very helpful.**
- **Update with data from supplements.**

# Labeling for Clinical Pharmacology

Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

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)

December 2016
Labeling

- **Section 12 of product label, Specific Populations**

*4. Specific Populations*

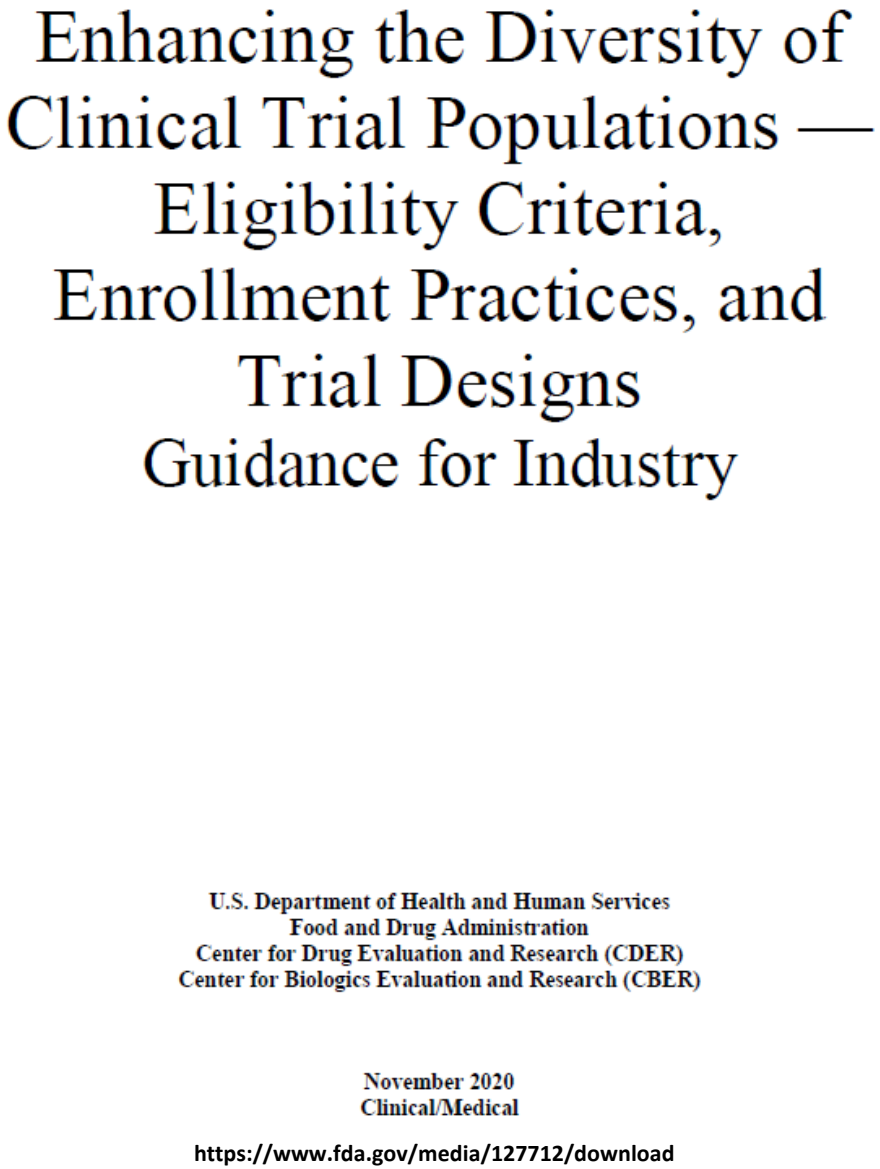
This heading should include results of studies or analyses that evaluate the potential for PK differences in subpopulations defined by age, sex, race/ethnicity, renal function, hepatic function, and pregnancy. We recommend that the following subheadings be used for consistency unless the specific population was not assessed: Geriatric Patients, Pediatric Patients, Male and Female Patients, Racial or Ethnic Groups, Patients with Renal Impairment, Patients with Hepatic Impairment, and Pregnant Women. Additional subheadings representing other specific

a. Geriatric Patients

Descriptions and results of PK studies and analyses conducted in subjects 65 years of age and older should be presented under this subheading. Results should be compared to those obtained in younger adult populations where possible. Analyses related to age can be included with age as a categorical variable or as a continuous variable. In some cases, it may be relevant to use age breakpoints other than 65 years. For example, if exposures are found to be much higher in patients older than 80 years, it would be appropriate to use 80 years of age as a breakpoint to describe the results. If appropriate, ranges of ages could also be included to describe the results.

https://www.fda.gov/media/74346/download

# Enhance Clinical Trial Population Diversity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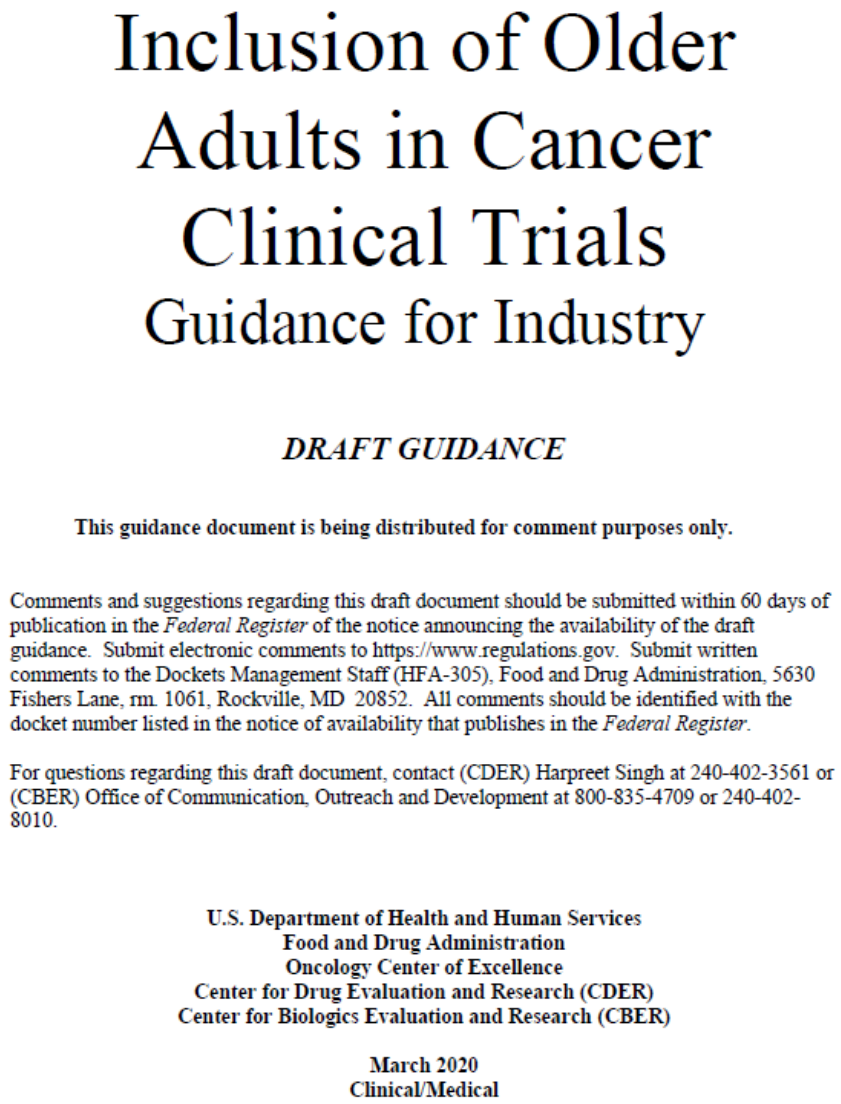
Center for Biologics Evaluation and Research (CBER)

November 2020
Clinical/Medical

https://www.fda.gov/media/127712/download

- **Inclusive trial practices**
  - **Relevant population: age, sex, race, and ethnicity**
- **Trial design and methodology**
  - **Early characterizing of drug metabolism and clearance**
  - **Adaptive trial design**
- **Inclusion of older adult populations**

# Inclusion of Older Adults in Cancer Trials



Inclusion of Older Adults in Cancer Clinical Trials

Guidance for Industry

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For questions regarding this draft document, contact (CDER) Harpreet Singh at 240-402-3561 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

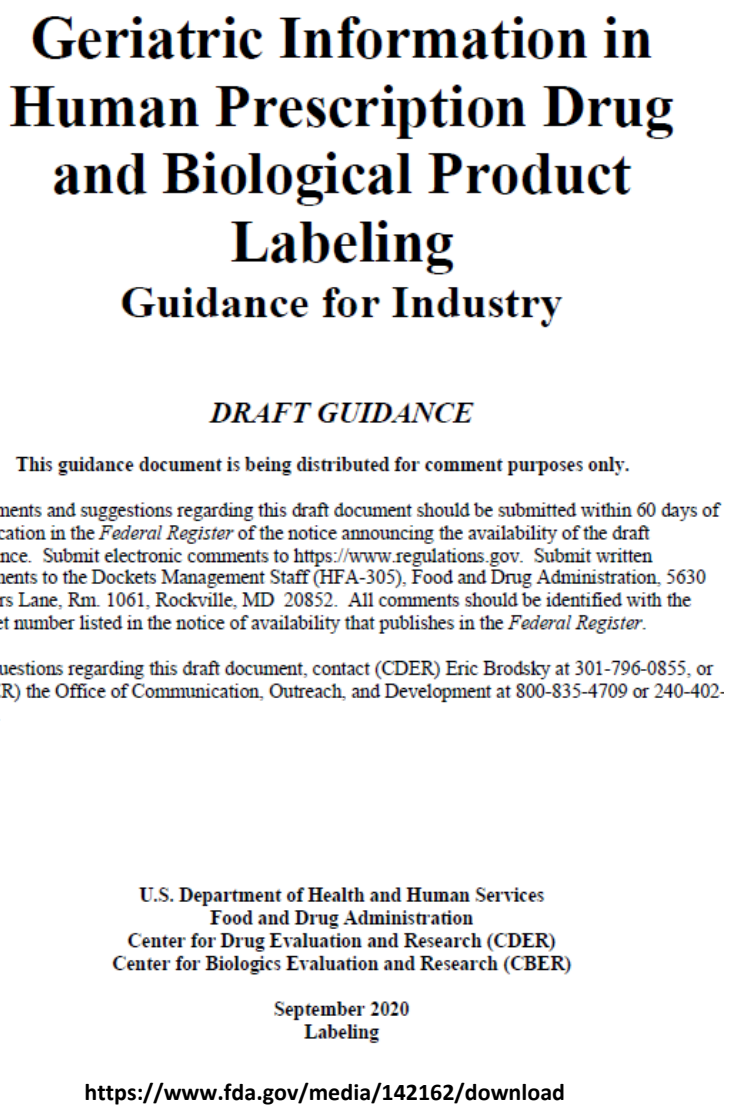
**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Oncology Center of Excellence**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**March 2020**
**Clinical/Medical**

**https://www.fda.gov/media/135804/download**

- **Adequate representation of older adults is necessary to determine the benefit-risk profile of cancer therapeutics in this population:**
- **Early clinical development**
  - **Enroll older adults in early phase trials, study drug-drug interactions**
- **Clinical trials**
  - **Trial design, recruitment strategies, collect additional information, safety monitoring strategies, reporting in discrete age groups**
- **Collection of post-marketing data thru additional trials, registries, and or real world data**

# Guidance on Geriatric Labeling



**Geriatric Information in Human Prescription Drug and Biological Product Labeling**

**Guidance for Industry**

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

September 2020
Labeling

https://www.fda.gov/media/142162/download

- Update of the 2001 geriatric labeling guidance
- This guidance discusses:
  - FDA's initiatives to ↑ quantity and quality of drug information for patients ≥ 65 years of age
  - Geriatric age subgroups:
    - 65 – 74
    - 75 – 84
    - ≥ 85
    - Or continuous function of age
  - Label based on sufficiency of data to detect differences in safety and or effectiveness between geriatric and younger adult patients
  - 3 drug approval scenarios:
    - Use in adult patients including geriatric patients
    - Geriatric-specific indication
    - Not approved in geriatric patients but approved in younger adults

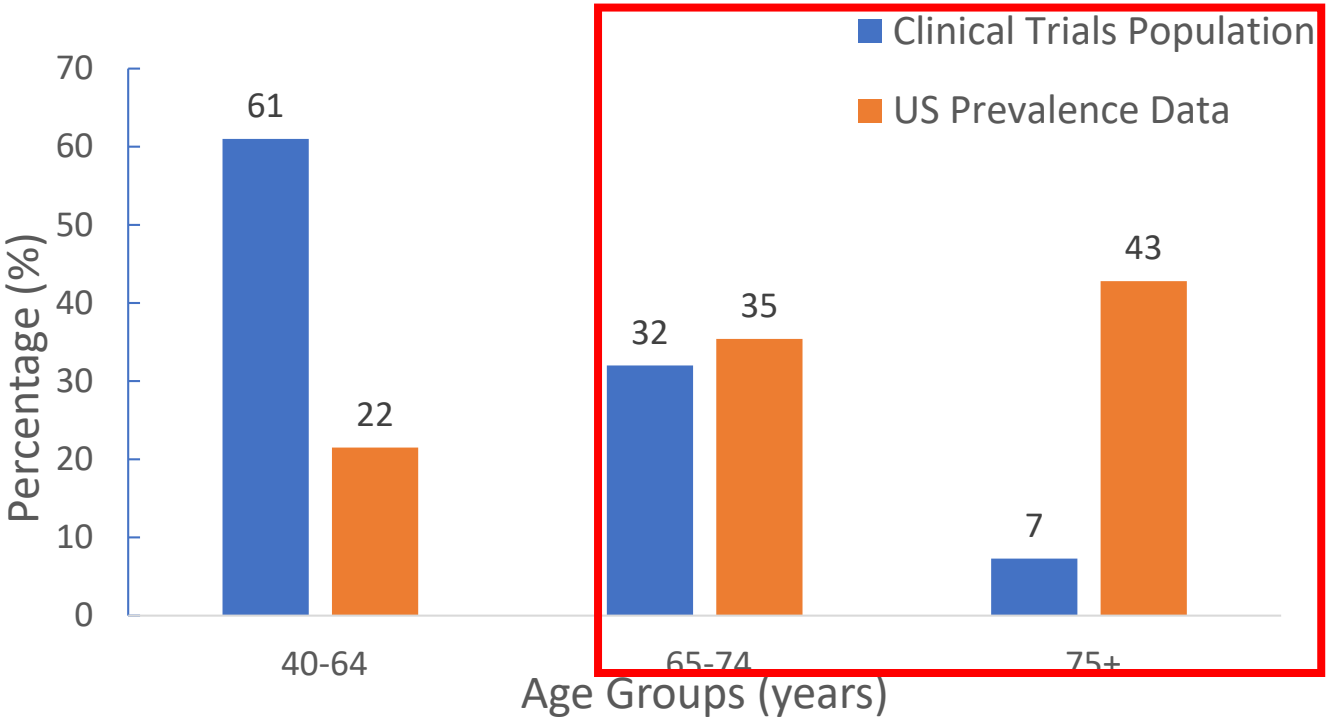
# Enrollment of Older Adults in Clinical Trials

# Selected New Drug Approvals

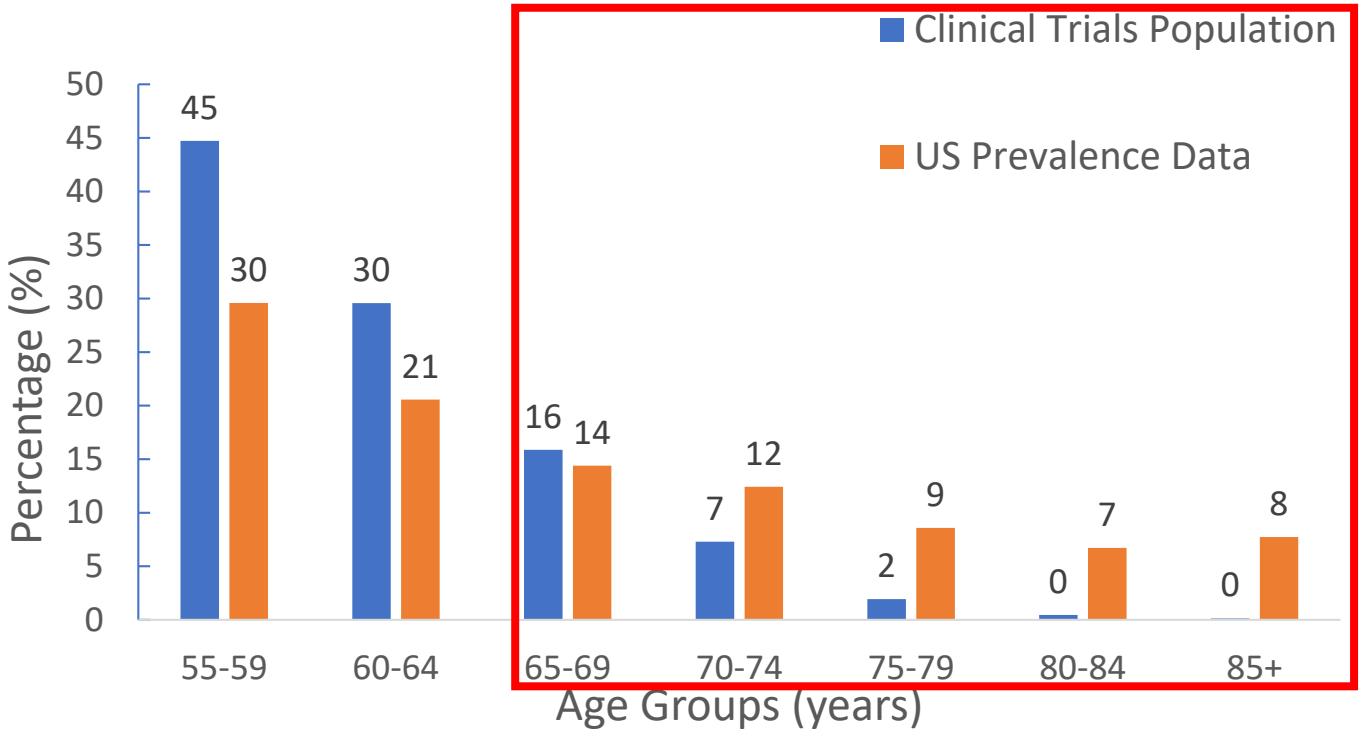
- **Therapeutic Indications:**
  - **Depression**
  - **Heart failure**
  - **Insomnia (trouble staying asleep)**
  - **Non-small cell lung cancer (NSCLC)**
  - **Osteoporosis**
  - **Prevention of stroke associated with non-valvular atrial fibrillation (NVAF)**

- **We searched internal clinical trials data that supported the approval of NDAs or BLAs of these medications between 2010 and 2019.**
- **We derived the prevalence data (from CDC-NHANES, NCI-SEER, NIA, and published literatures) for these indications as comparators for the corresponding clinical trial data.**
- **The prevalence data are from community dwelling older adults.**
- **The dates of some prevalence data may not exactly align with the timing of trials. Also, some granularity in the data are limited such as age cutoffs.**

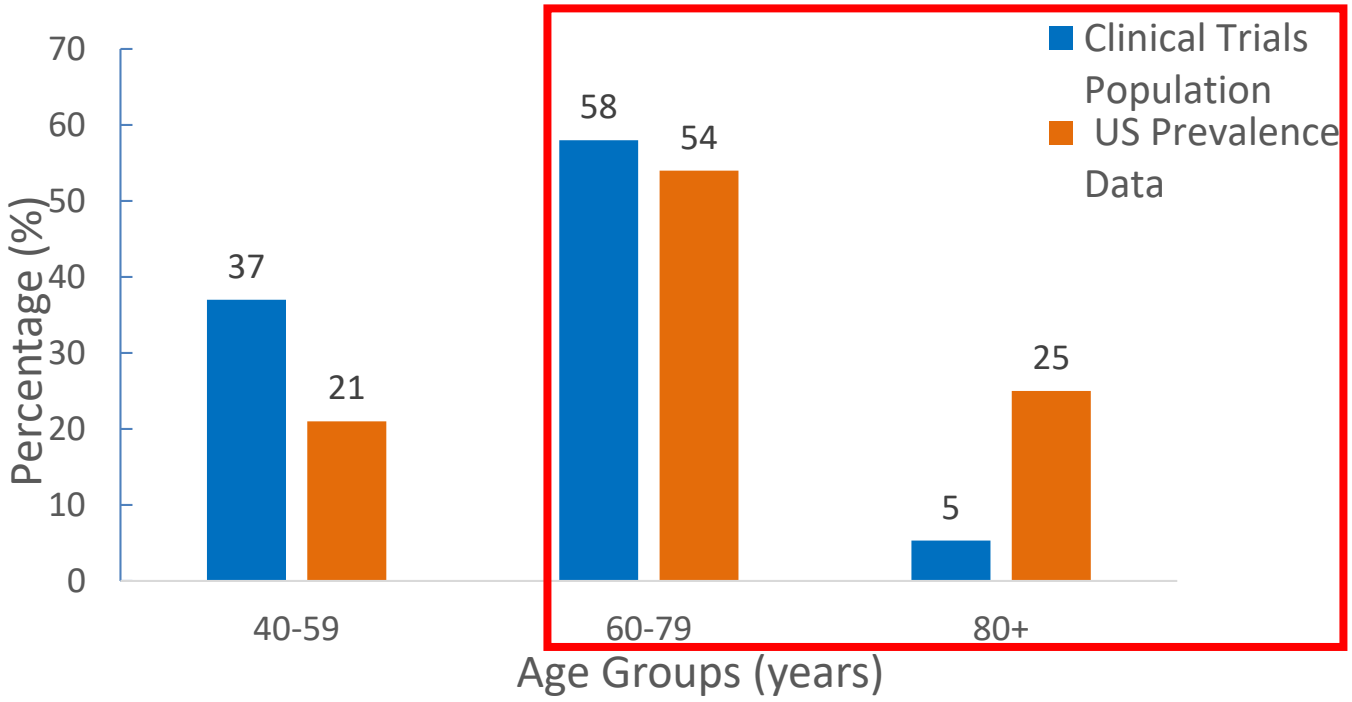
# Non-Small Cell Lung Cancer



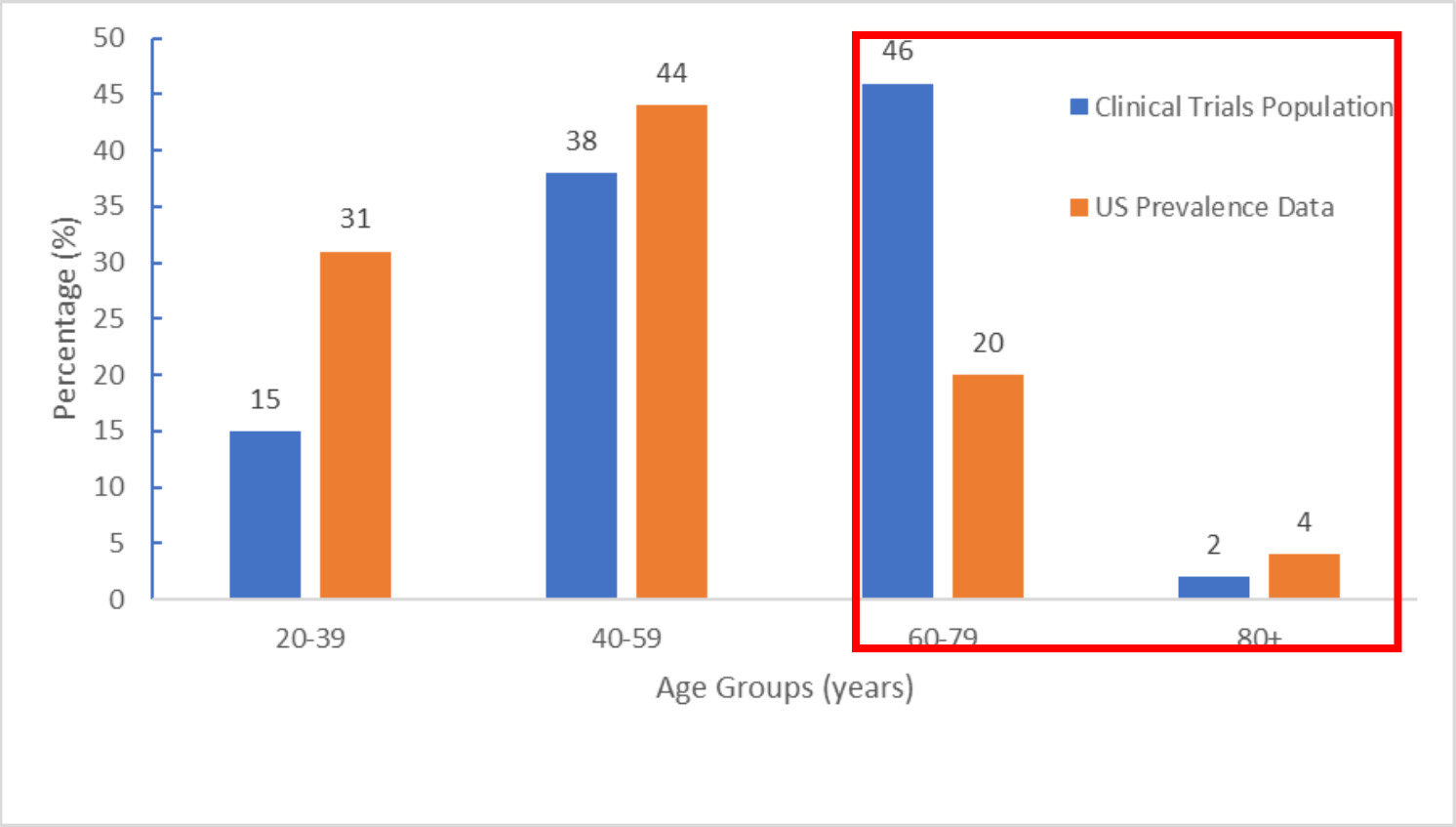
# Depression


Clinical Trials Population
US Prevalence Data
Percentage (%)
50
45
40
35
30
25
20
15
10
5
0
45
30
30
21
16
14
7
12
2
9
0
7
0
8
55-59
60-64
65-69
70-74
75-79
80-84
85+
Age Groups (years)

# Heart Failure

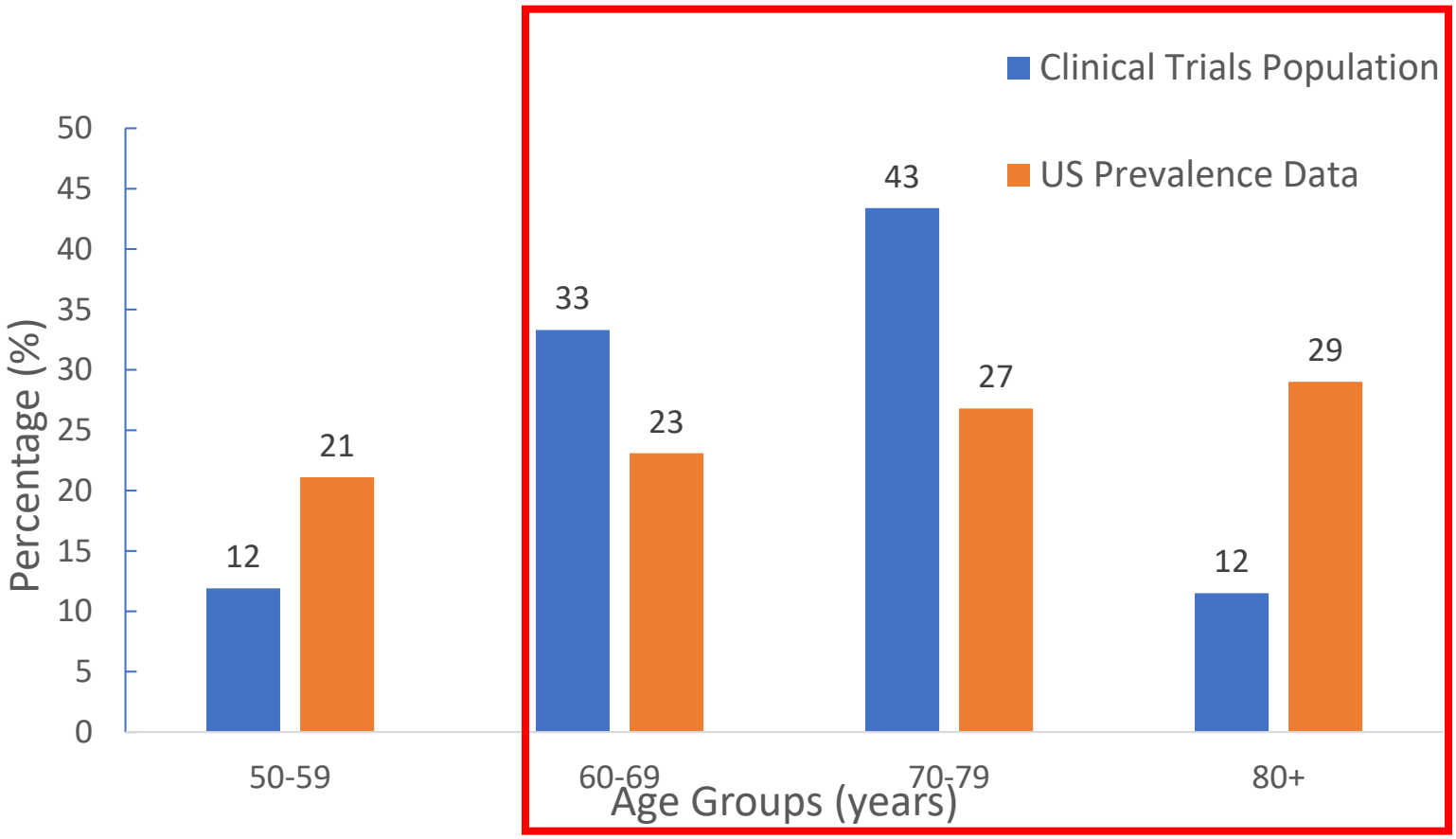


# Insomnia – Trouble Staying Asleep

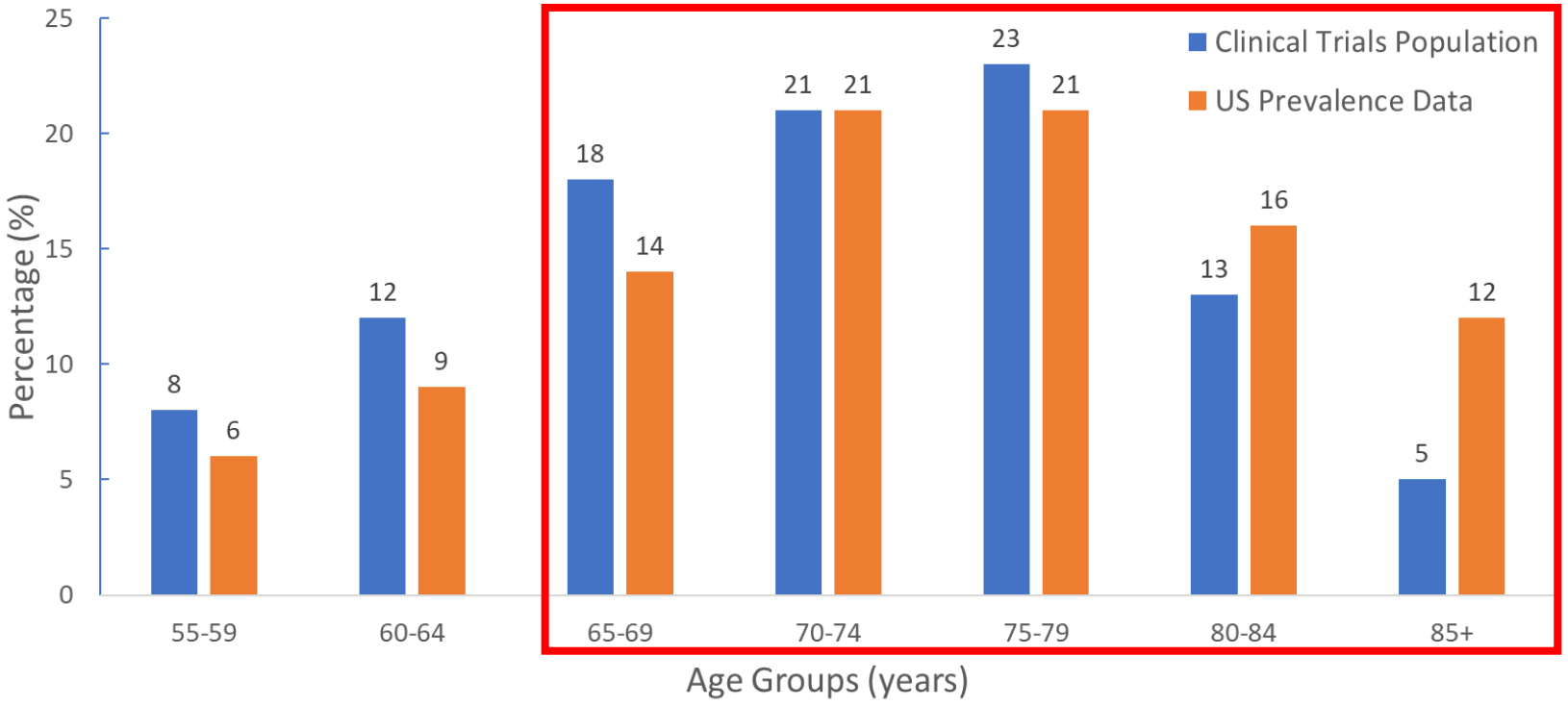



Additional safety for insomnia thus oversampled.

# Osteoporosis



# Prevention of Stroke Associated with NVAF



# Take-home Messages

- **Guidances exist to guide the inclusion of participants in clinical trials and labeling of drugs for use in older adults.**
- **Underrepresentation of the very old adults in clinical trials remains a challenge across multiple therapeutic areas.**

# Acknowledgements


- Yue Huang
- Julie Hsieh
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- Office of Clinical Pharmacology's Geriatrics Scientific Interest Group
- OCPers (current and former)
- Friends in the geriatrics field
- Older adult relatives and friends