Roadmap to 2030 for New Drug Evaluation in Older Adults:
An initial step to improve Representativeness of older age groups in drug development

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Disclaimer: The views presented in this presentation represent the personal opinion of the speaker and do not reflect the official positions of the United States Food and Drug Administration (FDA)– or UCSF

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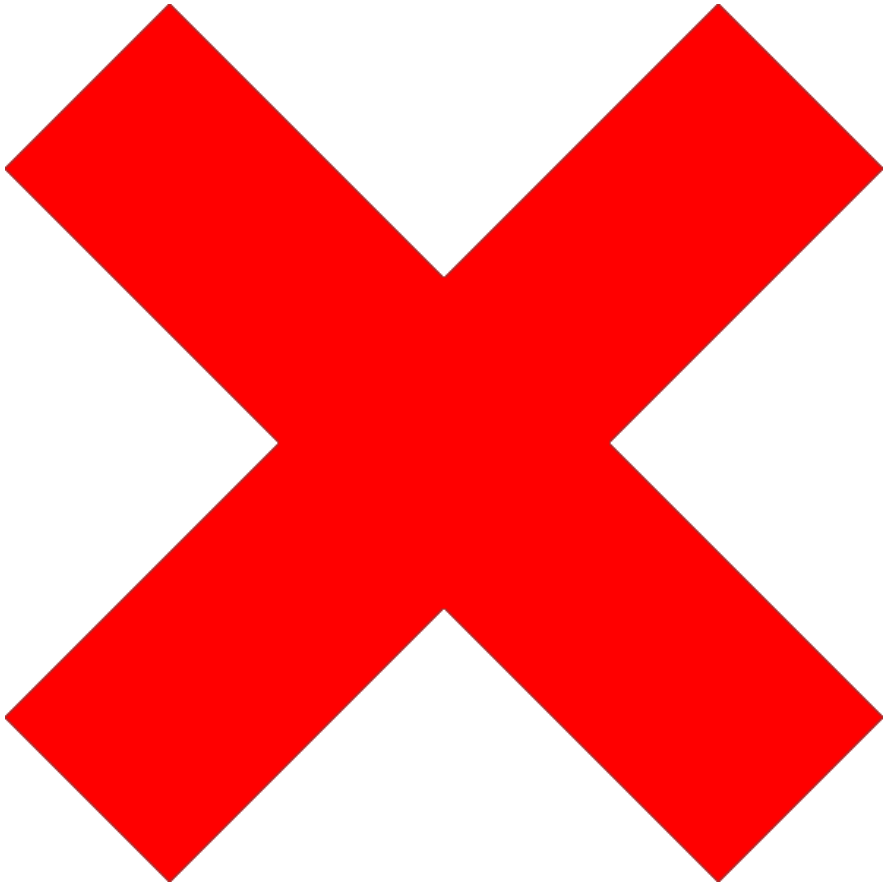
Outline

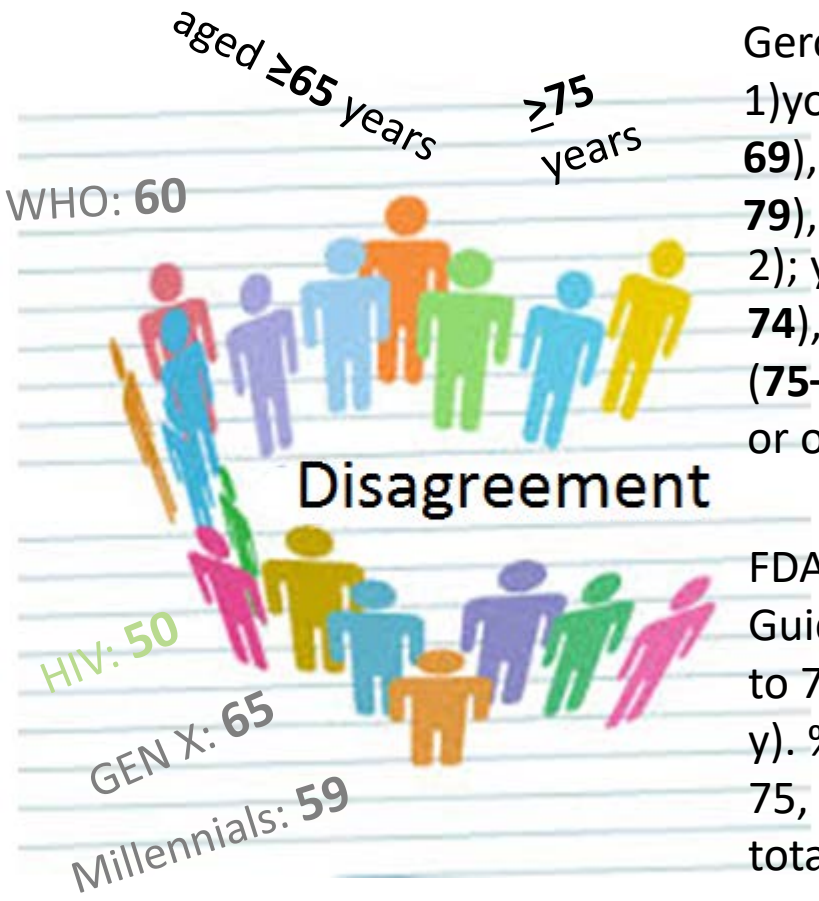
- Conclusion
- Rationale
- Examples
- Implementation Needs

Starting at the End
-- Conclusion

Enrollment *of older adults* in registration clinical trials of new drugs should be “in proportion” to their presence in the population with the treatment indication.

Defining “Older Age” – A Universal Definition





Gerontologists: 1)young old (**60 - 69**), middle old (**70-79**), very old (**80+**); 2); young-old (**65-74**), middle-old (**75–84**), oldest-old or old old (**85+**)*

FDA 2020 Labelling Guidance: ≥65 **or** (65 to 74, 75-84, and 85+ y). % ≥ 65 years and ≥ 75, **OR** total ≥ 65 and total ≥ 75 y

*ICH (65-74; 75-84 and 85+ years).

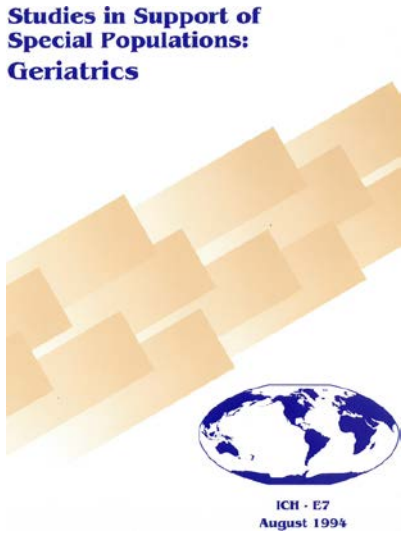
Where is there Agreement?

1989

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

"Drugs should be studied in all age groups, including the geriatric, for which they will have significant utility.

1974



ICH E7 "meaningful number" of geriatric patients; ≥ 65 years; important ≥ 75 years

2016

21st Century Cures Act, **consideration of age** as an inclusion variable in human research, to identify criteria for **justification for any age-related exclusions,** provide data on the **age** of participants in clinical research studies. **Acceptable reasons for excluding individuals based on age ..disease or condition does not occur in the excluded age group, or the research topic is not relevant to the excluded age group.**

2020

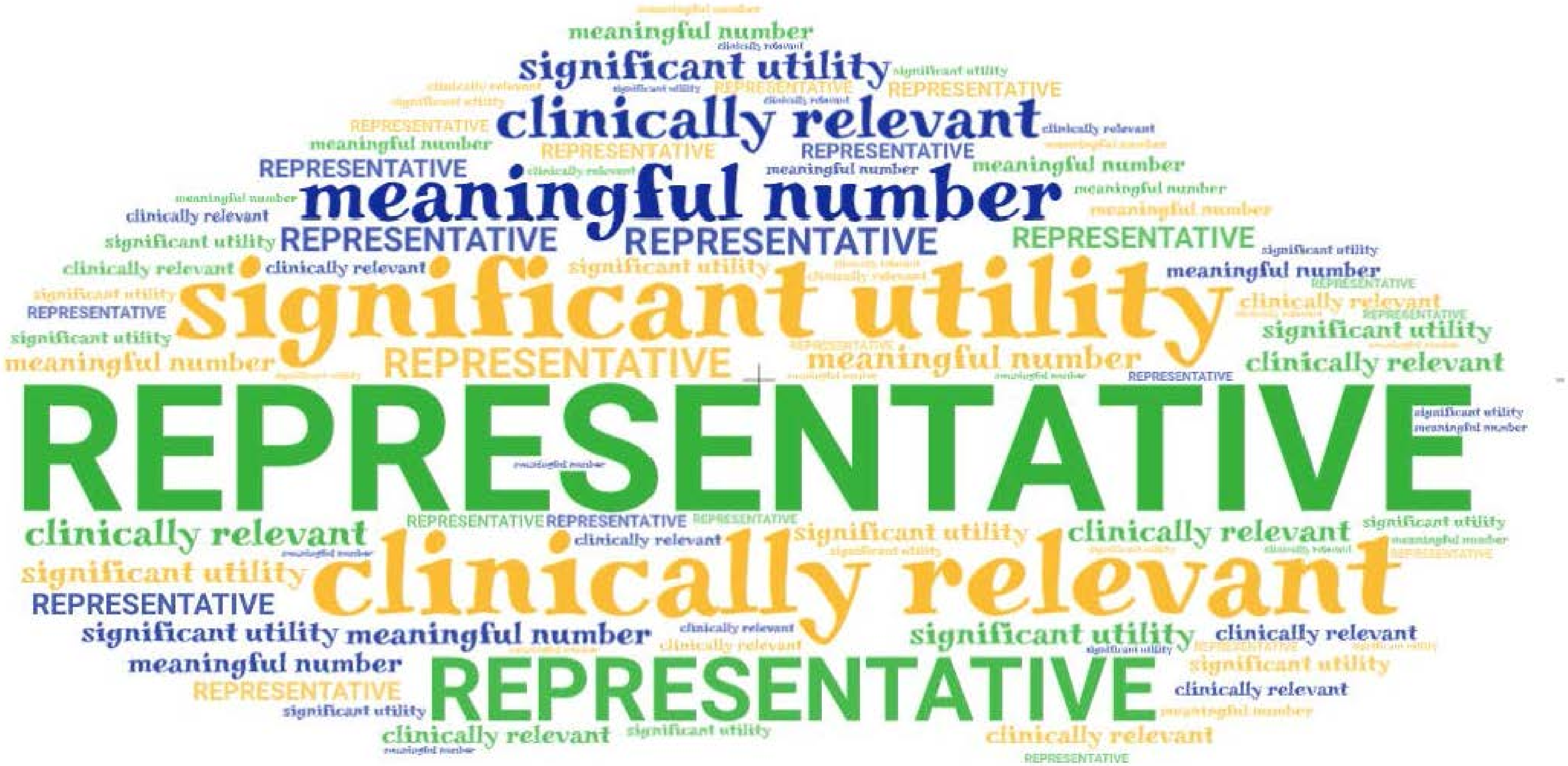
Sponsors **should enroll participants who reflect the characteristics of clinically relevant populations** with regard to age, sex, race, and ethnicity

The National Academies of SCIENCES ENGINEERING MEDICINE

2020" Inclusion Across the older agespan"

NIH National Institutes of Health
Turning Discovery Into Health

EMA: European Medicines Agency Clinical Trials Regulation (EU) No 536/2014



meaningful number
significant utility
clinically relevant
REPRESENTATIVE
meaningful number
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significant utility
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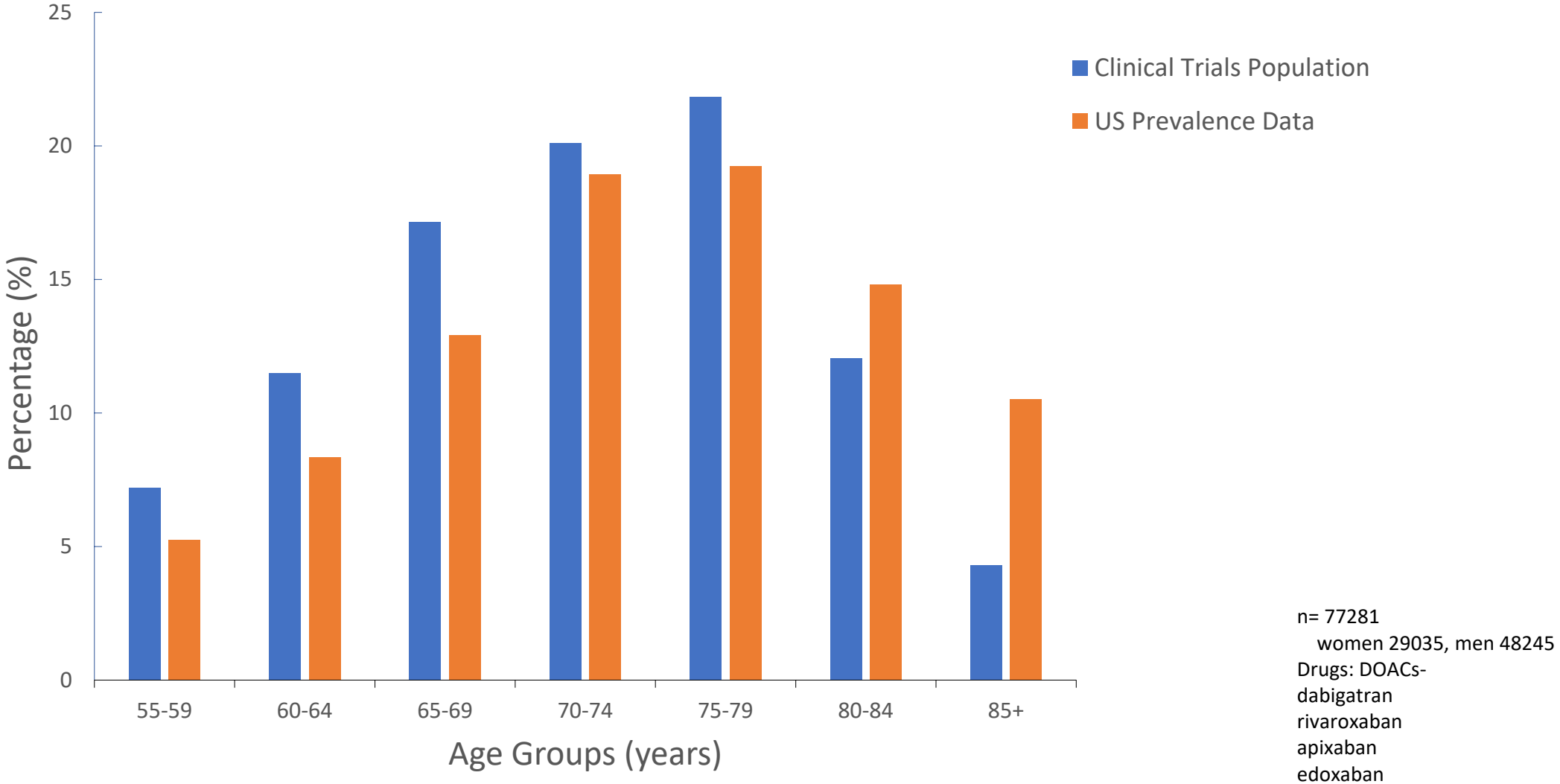
meaningful number
REPRESENTATIVE
clinically relevant
clinically relevant
significant utility
REPRESENTATIVE
significant utility meaningful number
meaningful number
REPRESENTATIVE
clinically relevant

Is the Current Enrollment of Older Adults Representative ?

Disease Prevalence vs. Clinical Trial Enrollment

Ex. Prevention of Stroke in Patients with Non-Valvular Atrial Fibrillation (NVAF)

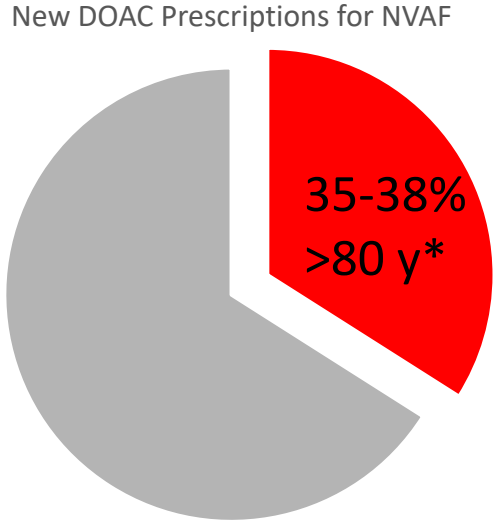


n= 77281
women 29035, men 48245
Drugs: DOACs-
dabigatran
rivaroxaban
apixaban
edoxaban

Relevance: Post Marketing "Real" World Data"- New Prescriptions for Direct-acting Oral Anticoagulants

Lip, et al Stroke 2018 + 2019 correction
n=466,991 -1/12013-9/30/2015

			Warfarin	Dabigatran
			100,977	36,990
			76	73
			10%	17
			33%	36
			20%	20
			38%	27
Lower dose	*24%* *(vs 5% in trial)*	*21%* *(21% in trial)*	*n.a.*	*16%*

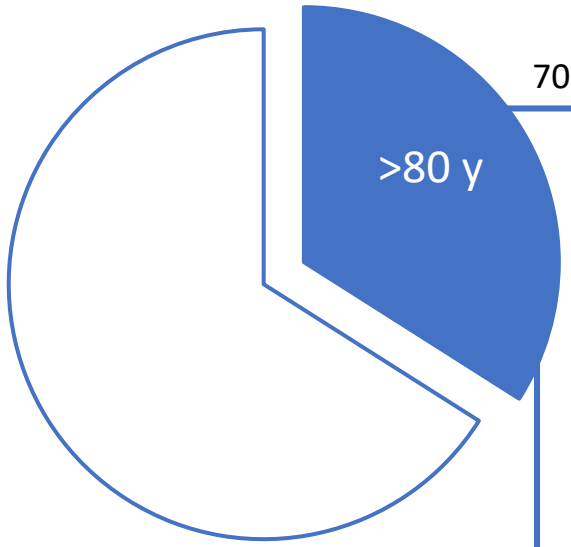


*in Proportion to Prevalence

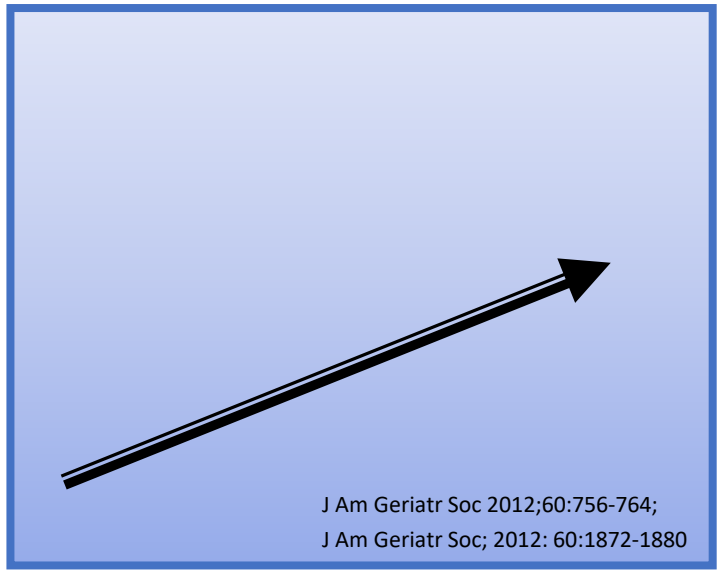
* Of 108,852 total apixaban and 153,002 of rivaroxaban; of 167,413and 37, 724 dabigatran

Real World Population: >80 y
Multimorbidity-> Polypharmacy, Frailty

New DOAC Prescriptions for NVAF



70% ≥ 5 Rx



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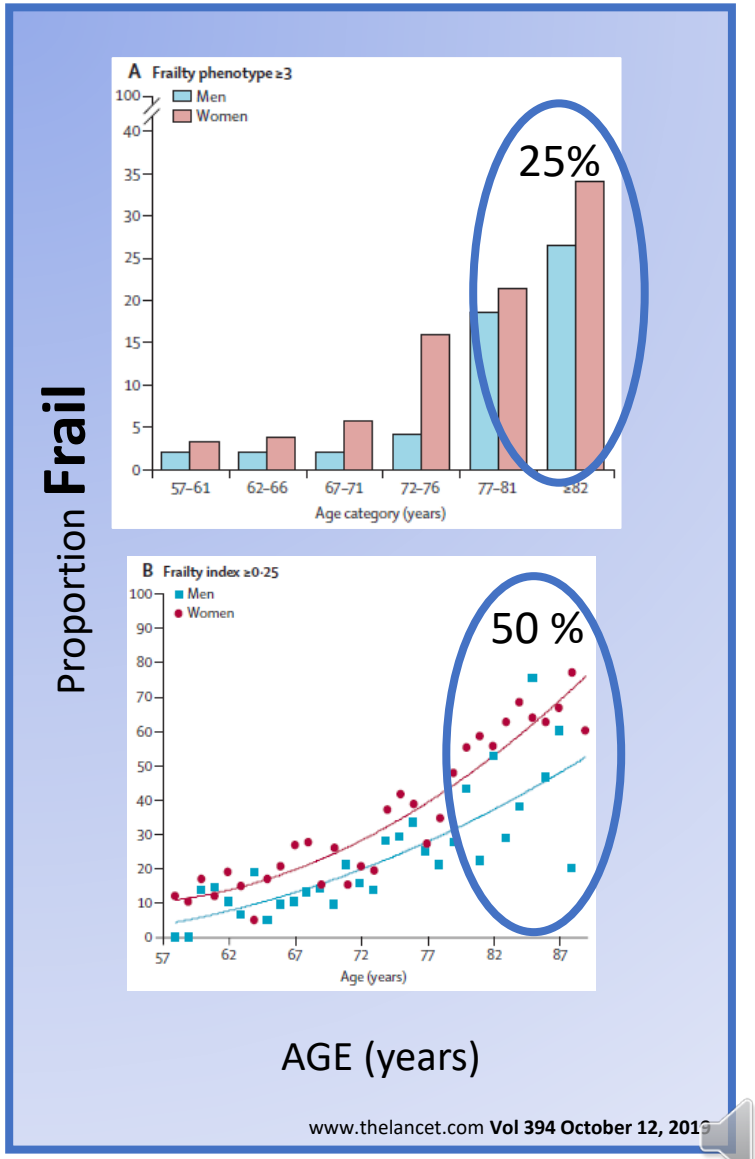
Number of **Medical Conditions**

Older AGE



Consequences of Non-representative Population in DOAC Trials

- Unknown Safety and Efficacy Profile in **ONE-THIRD** of population that receives the drugs during initial clinical use (those with multiple medical conditions, polypharmacy, geriatric syndromes)

- Post marketing use data (uncontrolled experiments) or Real World Data:

  Efficacy: *Probably* qualitatively similar to results in Registration Trials *at full doses*

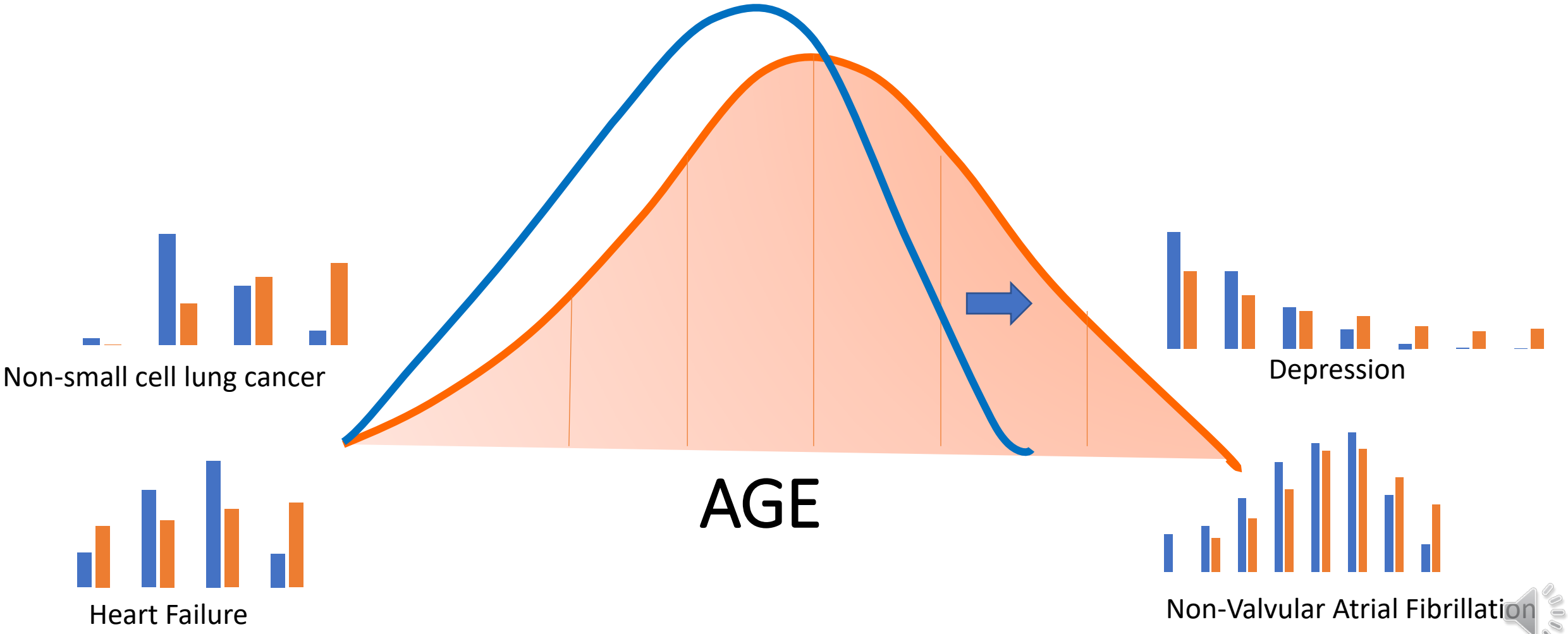
  Safety: Major Bleeding Rates **2-4X higher** than reported in Registration Trials

  Dosing: Significant fraction receiving doses that were not definitively tested

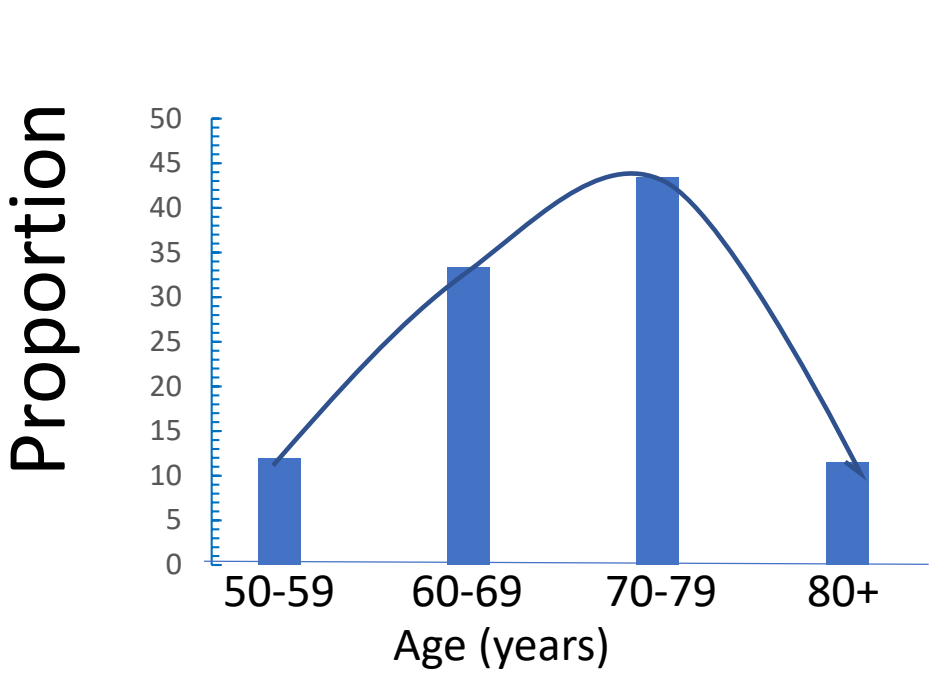
*Today: 2 of 4 agents currently appear in the "American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults"**

*Disclaimer: Speaker was NOT on the Publications committee

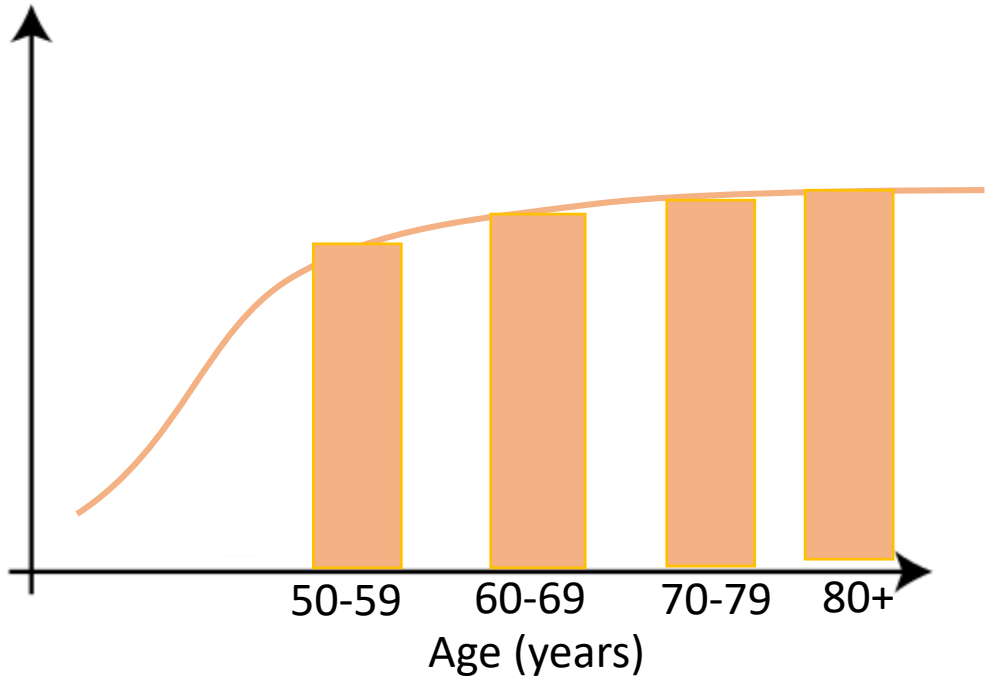
Goal: Clinical Trial Population in Proportion to Target Treatment Population



Target Population Proportional Enrollment
Ex. osteoporosis



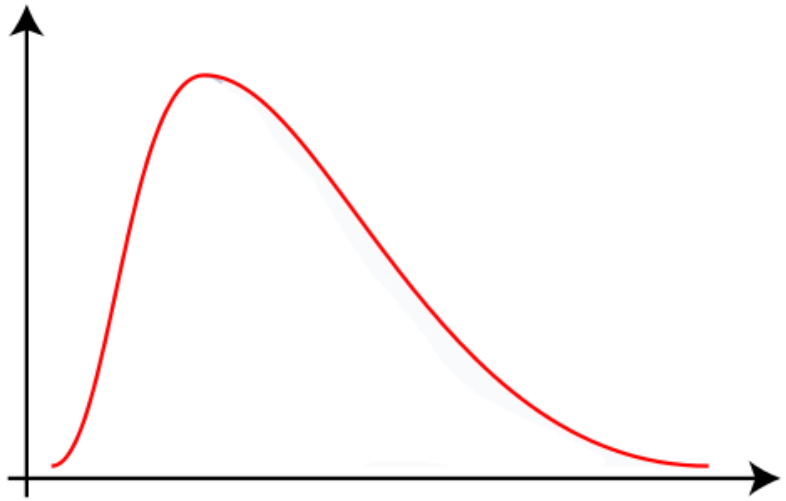
Registration Trial Enrollment (2010-2020)



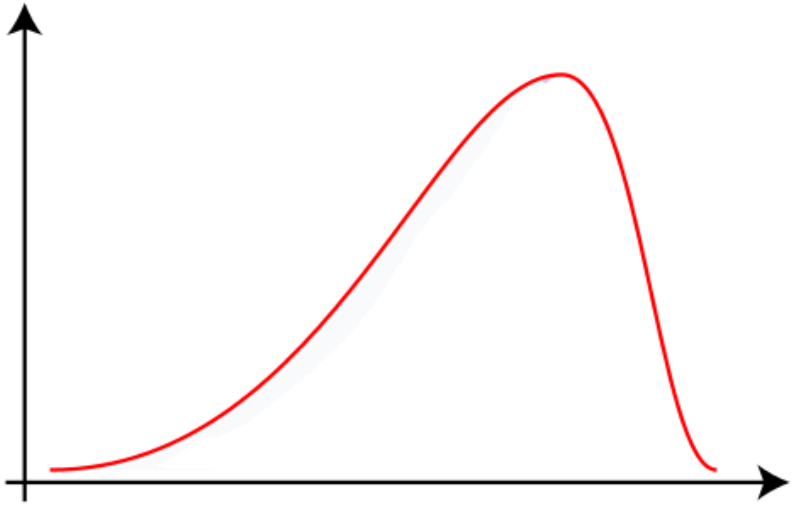
Prevalence-based Enrollment

Distribution will differ by Indication

Proportions adjusted to Distribution

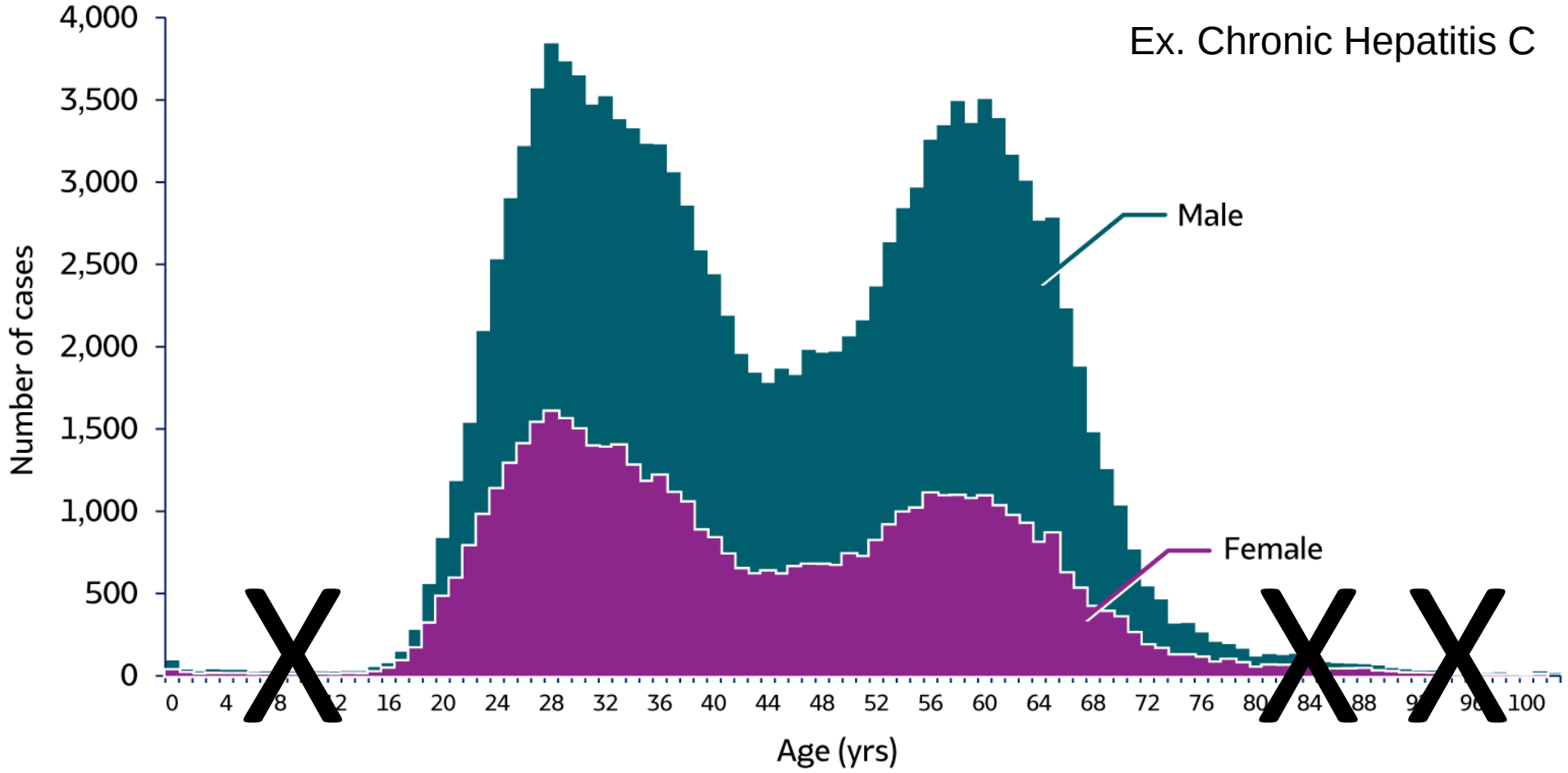


Childhood Diseases



Older Age Diseases

Approach may also identify when studying age subgroups may *not* be representative



Source: Number of newly reported* chronic hepatitis C cases† by sex and age — United States, 2018 (N=137,713) https://www.cdc.gov/hepatitis/statistics/2018surveillance/HepC.htm#Figure3.8

Implementing Representative Patient Enrollment- Needs

Premarketing Clinical/Registration Trials

Prevalence Data

Develop/Publish/Warehouse population distribution models

Census (population)

Diseases, conditions- Community and Residential

Clinical Trial Data

Guidances

Design + Evaluation

Representative quantiles, *exceptions*, allowable variation, time periods for re-defining

Incorporate into sample size and subgroup estimates

Policies- incentives, penalties, accountability

Periodic Re-evaluations

Population and Clinical Trials

Update Prevalence data

Assess clinical trial enrollment

subgroups and conditions, key variables identified

Human Power--Working Group, Committee, Office, or Task Force-broad representation

Conclusion-**R**epresentative **P**atient **E**nrollment (RPE)

Enrollment goals in registration clinical trials of new drugs should be based on the proportion of *older adults* in the population with the treatment indication.

Representative Patient Enrollment and evaluation will provide the necessary information for clinicians to optimize use of new drugs in older adults at the start of clinical use.

Now is the time to build the steps to achieve this goal.

Thanks to the FDA Offices of Clinical Pharmacology and New Drugs, as well as CDER for organizing this workshop and to Fellows Shenggang Wang, Yue Huang, Julie Hsieh who prepared the landscape analyses