Title

Current status of inclusion of older groups in evaluations of new medications: Gaps and implementation needs to fill them

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Publication Date

2024-04-10

DOI

10.1111/jgs.18912

Peer reviewed

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Manuscript IDJAGS-0369-SA-Mar-24

Special Article:

Current Status of Inclusion of Older Groups in Evaluations of New Medications: Gaps & Implementation Needs to Fill Them

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Word Count: Abstract: 204 Manuscript: 2816

Four Figures

Running Title: Clinical trial enrollment: now and future

Funding Source: none

This manuscript is based on a presentation at the 2023 American Geriatrics Meeting in Long Beach, CA

Key Points

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- Older adults have been under-represented in clinical trials of medications for disorders that are prevalent but not unique to older adults despite efforts to enroll representative patient populations.
- Recent legislation mandates “representative” enrollment in clinical trials and that representativeness be defined by prevalences of the treatment indication in clinical populations
- To achieve the goal of representative clinical trial enrollment, current and continually updated data on disease prevalences are needed and expansion of resources for clinical trial conduct will be required.

Why does this matter?

Without the enrollment of older adults that are representative of clinical populations in clinical trials, clinicians will continue to be faced with uncertainty as to the safety and efficacy of new drugs for older adults.

IMPACT statement: this work is original

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ABSTRACT

Under-representation of subgroups of the population in clinical trials has been and continues to be a problem despite goals of academia, industry, and government. Older adults are among the groups that are under-represented in trials of medications that they are likely to receive once marketing approval has been received. Recent legislation that mandates that clinical trial participants be representative of patient population has been passed and creates hope that greater numbers of older adults will be enrolled in clinical trials and that they will be representative of "typical" geriatric patients. However, there is the need for collection of current data on disease prevalences with granularity as to age, gender, and race as well as geriatric co-morbidities to assess the representativeness of clinical trial participants relative to patient populations. Consensus on definitions and collection of data relevant to geriatric patient populations are needed to evaluate effects of comorbidities, frailty, cognitive and physical function. There will also be a need for expansion of the geriatric research workforce, facilities for research both in academic centers but also in the community and long-term care facilities, and for engagement with and involvement of communities that have been traditionally under-represented to conduct clinical trials that enroll truly representative patient populations.

Key Words: clinical trials, underrepresentation, participation to patient ratio

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Background

The first "Guideline for the study of drugs likely to be used in the elderly" was published in 1989.[1] It clearly stated that "Drugs should be studied in all age groups, including the geriatric, for which they will have significant utility". This concept was universally endorsed in 1994 with the International Conference on Harmonization(ICH) E7 that stated a "meaningful number" of geriatric patients in the age groups 65 and older and 75 and older is important. [2] These documents stated the importance of clinical testing programs adhere to harmonized guidelines based on ethical and scientific principles so that the international development of valuable innovative drugs is achieved with maximum efficiency. Harmonization in relation to medicines for geriatric populations was considered important because of the increasing population of elderly in Europe, Japan, and the USA and the frequent occurrence of underlying diseases, concomitant drug therapy and the consequent risk of drug interactions in the elderly. In 2010 and 2012, the ICH7 guidelines were supplemented with questions and answers that repeated the need for enrollment of representative numbers of older adult patients and that 100 older patients were unlikely to be sufficient to determine older age-related differences in responses. The document also suggested presenting data for four age subgroups to assess consistency of treatment efficacy and safety with non-older adult patients. These 4 older age subgroups were: adults below 65 years of age, adults 65-74 years of age, adults 75-84 years of age and those 85 years and older. [3 4] These guidances emphasized studying patients ≥ 75 years of age, avoiding arbitrary upper age limits in

69 clinical trials, encouraging inclusion of patients with concomitant illnesses, inclusion of older adult
70 patients in pivotal Phase 3 trials rather than separate trials, studying the pharmacokinetics (PK) of older
71 adult patients that could be done with sparse sampling population PK analyses if enough patients in
72 different age ranges were included in the trials, and studying the entire spectrum of the older adult
73 patient population to identify age-related differences not explained by other factors (renal and weight).
74 In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) law mandated that
75 within one year, the FDA report publicly on the extent to which clinical trial participation and the
76 inclusion of safety and effectiveness data by demographic subgroups including sex, age, race, and
77 ethnicity is included in new drug applications submitted to the FDA.[5] In response, the FDA established
78 the Drug Trials Snapshots that originally presented data on approved new drug applications for each
79 year with age breakdowns by multiple older age groups, by sex, and by race. The 2015 report provided
80 data on patients >65, ≥75 and ≥ 80 years of age, but only data aggregated for patients ≥65 years of age
81 have been reported since 2015.[6]

82 Yet, under-representation of subgroups of the population in clinical trials has continued and is present in
83 NIH trials as well as in pharmaceutical industry trials. The NIH has noted under-representation of
84 women and racial minorities, as well as older adults in clinical trials that are not specific to disorders in
85 those groups. [7] An analysis of NIH-funded clinical trials in 2016 comparing the mean age of trial
86 participants to the mean age of manifestation of the conditions found that only trials on prostate cancer

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came close to matching the age of the affected population. [7] The analysis also found that older adults were often excluded from trials altogether with 27 percent of the studies having arbitrary upper age caps, and many studies had exclusion criteria that would indirectly exclude many older adults. A workshop titled "Inclusion Across the Lifespan" was convened in June 2017 and a new NIH policy issued in December 2017 that requires clinical study applications submitted to NIH to include a plan for enrolling individuals across the lifespan.[8] However, in a follow-up analysis presented at a workshop in 2020, it was stated that NIH-funded investigators were still "not meaningfully including older adults and children."[9]

The continued inequity in clinical trial participants led to FDA guidance on enhancing clinical trial diversity in 2020 with suggestions for further changes in eligibility criteria, enrollment practices, and trial design to achieve greater clinical trial diversity. [10] The lack of enrollment of older adults in cancer trials received special attention in academia, professional organization, the scientific and lay literature leading to draft guidance for industry on inclusion of older adults in cancer trials in 2020.[11] The NIA has begun collecting individual level data on participants in clinical research but analyses have yet to be published. A recent statement from the NIA Directors stated in a blog post on November 1, 2023 that moving forward: "NIA will prioritize funding requests with proposed planned enrollment that are 1) representative of the population affected by the disease, condition, or health experience; and 2) appropriately inclusive of racial and ethnic groups; participants across the lifespan; as well as other

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populations experiencing health disparities, including sexual and gender minority, persons with disabilities, or socioeconomically disadvantaged and geographically underrepresented populations."[12]

In parallel to the recognition of the failure to enroll representative older adults into pivotal clinical trials, has come the recognition of the under-representation of other populations—especially racial minorities and women. [6] The National Academies of Science, Education, and Medicine reported in 2021 that pregnant and lactating individuals, sexual- and gender-minority populations, and racial and ethnic subgroups of women remain underrepresented in clinical trials. [13] And perhaps most importantly, that the racial and ethnic diversity of clinical trials has had little change in diversity over time. [13]

Where are the Biggest Gaps with regards to participation of Older Adults in Clinical Trials?

The Roadmap to 2030 for New Drug Evaluation in Older Adults Workshop was held by the FDA in 2021.[14] The objectives included reviewing current data on the inclusion of older adults in clinical trials in select key therapeutic areas, identifying gaps in drug evaluation in older adults, and exploring approaches to closing existing gaps. As part of the preparation for this workshop the enrollment of older adults in clinical trials of new drug applications and biologics license applications approved by the FDA for marketing from 2010 through 2019 was analyzed.[15] The age distribution of clinical trial participants enrolled in registration trials for heart failure, insomnia, non–small cell lung cancer (NSCLC),

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nonvalvular atrial fibrillation (NVAF) stroke prevention, osteoporosis, and type 2 diabetes or adults was compared with the age distribution of the U.S. population with the disease or disorder (prevalent population). The participation to prevalence ratio (PPR) was calculated as the Percentage of Patients by Age (Sub)Group Among Trial Participants/Percentage of Patients by Age (sub)Group Among US Prevalent Population with a PPR of 0.8-1.2 considered adequate representation. These trials enrolled almost 230,000 participants and all had under-representation of the oldest age groups. Trials for heart failure, NVAF stroke prevention, osteoporosis, and sleep disorders had PPRs below 0.8 for ages 80 years and above. Heart failure trials had a PPR of about 0.2 for patients 80 years and older. Trials for type 2 diabetes had PPRs below 0.8 for ages 65-74 years of age and was about 0.2 for ages 75 and older. For all but the diabetes trials, the inclusion of older patients from 60 to 75 years of age was reasonably close to the corresponding prevalence of the treatment indication in older adults. Illustrative prevalence and PPR data for the NVAF stroke prevention and heart failure trials are shown in Fig 1. Other major gaps identified at the workshop were the under-representation of older adults with frailty, multimorbidity or polypharmacy in clinical trials, the lack of accepted criteria for benchmark “representative” populations for clinical trial enrollment, the unknown effect of aging on pharmacodynamics and of chronic conditions on pharmacokinetics and pharmacodynamics, efficacy, and safety in older adults, and absence of patient-centered endpoints important to older adults. [16]

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The upcoming paradigm shift to *representative patient population enrollment into Clinical Trials*

Despite guidances over the past few decades and universal endorsement of the principle of enrolling representative populations into clinical trials of new therapeutic agents, this goal has not been achieved. Many have hypothesized that only requirements and not ideals would accomplish this goal. The COVID pandemic brought a focus on the disproportional burden and death rates of minoritized groups and older adults. A glaring lack of inclusion of minorities and older adults in trials of COVID vaccines and therapies was widely publicized.[13,17] This created an environment ready for legislation to improve clinical trial conduct and diversity. On December 29, 2022, President Biden signed into law "The Consolidated Appropriations Act of 2023". [18] Included in the omnibus bill is the Food and Drug Omnibus Reform Act of 2022 ("FDORA"), with provisions to promote diversity in clinical trial enrollment, encourage the growth of decentralized clinical trials, and streamline clinical trials. This finally provides a legal mandate for clinical trial participants to be representative of clinical populations. Sections related to clinical trial participation are summarized in Figure 2. Implementation will require achieving consensus and actions on several key issues for all populations and for geriatrics in particular. These include:

1) How to Define and Evaluate Representativeness
2) Consensus on definitions for medical and health-related conditions and co-morbidities
    a. Standardizing definitions and measurement for key geriatric conditions (such as frailty)

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3) Addressing patient-level barriers and motivators to clinical trial participation

***1) Defining Representativeness: Age-stratified prevalence data*.** The legislation suggests basing the diversity plan on the "Estimated prevalence or incidence in the U.S. of the disease or condition for which the drug or device is being investigated *if such estimated prevalence or incidence is known or can be determined based on available data"*. The prevalence ratio (PPR) defined above as the percentage of patients by age group among clinical trial participants to the percentage of patients by age group among U.S. prevalent population is a logical approach. Advantages of this approach is that it would meet the overall goal of providing the information on safety and efficacy in a representative population before a drug or new chemical entity comes to market. In contrast to requiring blanket inclusion of older patients (or pediatric patients), it would not mandate enrollment of older patients in trials of agents that are unlikely to be used in this age group and expose them to unnecessary risks. Additionally, age is universally measured the same way. Disadvantages of this approach is that numbers in subgroups enrolled may be insufficient for comparative analyses, only the "healthiest in the age group" may be enrolled, or those hypothesized to be at greatest risk may not be enrolled in sufficient numbers for subgroup analyses. However, if multimorbidity is present in 2/3 to ¾ of older adults this is likely to be present in age-representative enrolled participants. Depending on whether the definition of frailty is based on phenotype or accumulation of disorders, 25-50% of older adults 75 years of age and above will have this condition and the likelihood of representation may be somewhat lower. Therefore, the

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possibility of specific sample size targets for subgroups of interest may also need to be incorporated in evaluations of enrollment plans.

A major hindrance to this approach is that currently published data on disease prevalences often do not contain the detailed age information need to allow comparisons across the older age span and publicly available sources may not be regularly updated. National health data are collected at varying intervals but are often reported for broader age groupings and merge all data for older adults. In contrast, the standards for reporting of U.S. ethnicity and race are standardized across government agencies (specifically at minimum: ethnicity: Hispanic or Latino or not-Hispanic or Latino; race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White[19]).

- *Data Needs: Collection, Warehouse and Access to granular U.S. age and disease prevalence data (Fig 3)*

2) Consensus for Definitions of medical and health-related conditions and co-morbidities.

Currently most clinical trials collect data and report on individual medical conditions and may analyze data for effects on subgroups with the individual co-morbid condition. Co-morbid conditions are not reported at an individual participant or age group level. Definitions for medical conditions may not be uniform in clinical care records or survey data and may not be comprehensively collected or reported.

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The legislation states that non-demographic factors, "including co-morbidities" are important to consider. Co-morbid conditions are present in the majority of older adults but multiple approaches to defining medical co-morbidities exist and consensus is needed for which are most informative for older age groups or therapies for specific conditions.

- *Implementation Need: Standardized disease/condition and multiple co-morbid condition definitions and nationally representative prevalence data stratified by age*

a) Defining Representativeness based on Function**.** Disease-specific functional status and outcomes are used routinely for many clinical trials as are medical quality of life measures. However, functional assessment of daily activities or independent daily activities have yet to be incorporated into U.S. guidances, either for baseline assessment or for assessment of drug/therapeutic effects. Alterations in these functions may be highly important to people and may be especially affected by drugs with effects on the central nervous system.

- *Implementation Need: Collection and analysis of standardized functional status data*

3) Addressing patient-level barriers and motivators to clinical trial participation.

Recommendations to alter trial design and conduct to address the lack of "typical" older patients with multiple chronic conditions in evaluations of new therapies have been made by academicians, journals, politicians, professional societies and the government. [7,16,20-27] Many suggestions focus on

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decentralization of clinical trials with use of internet recruitment, consent, and virtual visits as well as less frequent research encounters to relieve transportation challenges, as well as community-based trials and engagement efforts to achieve broader racial participation. [7,16,20,21,28]

Age is one of the most-cited barriers to the use of telemedicine as well as with inability to access internet-enabled devices or broadband internet in homes. [29] Older adults may also have hearing and vision disorders, as well as financial constraints that may present challenges for virtual clinical trial enrollment and conduct.[30] Thus, it is not clear that a move to decentralization and virtual platforms would enhance enrollment of representative older adults without provisions for internet access, training on virtual and video platforms, provision of real-time support, closed captioning, and low vision interfaces. Even if such provisions were made, our recent national survey found that 2/3 of adults with multimorbidity would prefer clinical trials that included in-person visits and about ½ would not join a clinical trial that had video or telephone only visits.[31] Suggestions for changes in clinical trial design and conduct are unlikely to have the desired outcome unless they align with the preferences of currently under-represented older people with multiple medical conditions. A recent viewpoint concluded that "At present, evidence for the advantages of decentralized clinical trials, including health equity–related benefits, consists primarily of anecdotal reports, uncontrolled studies, and expert opinion."[32]

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- *Implementation Need: Determine and Adopt Clinical Trial conduct preferences of "representative" older adults*

Other missing Pieces—Infrastructure: the clinical research workforce and networks. (Fig 4)

Most of this paper has dealt with issues related to under-representation of older adults in clinical trials but a lack of racial and ethnic diversity in clinical trial populations also exists. The barriers to overcome inadequate recruitment of diverse patient groups may differ somewhat from older patients. Lack of knowledge about clinical trials, trust, and opportunity/accessibility, differing language requirements, lack of research personnel diversity may need to be addressed, and community engagement may need to play a larger role.[28] [13] [33]

Irrespective of diversity issues, the infrastructure for clinical trials and research needs to be expanded. The numbers of sites and investigators and staff able to conduct clinical trials of high quality needs to be increased if transportation and access issues are to be minimized. Networks may need to be created in order to include potential participant pools not present in any one geographic area or to allow participation across the continuum of care in the community, hospital, and long-term care sites. Simplified institutional requirements and inter-institutional agreements are needed to facilitate collaboration. Time for clinician participation and rewards for involvement in clinical trials need to be created. Clinical research and trial participation needs to be promoted at all levels within the health care

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system but also in the community. Facilities must also be welcoming and able to accommodate all populations of patients with differing physical and medical challenges.

SUMMARY

There is universal agreement that clinical trials should be representative of the clinical population that will be treated with the tested therapies and that this goal has not been met with adequate representation of older adults, or for racial or ethnic people. The 2023 Omnibus Bill now provides the legal impetus to conduct trials that are representative of clinical populations but will require efforts and investment of everyone involved in clinical research to implement changes to achieve this goal.

Acknowledgments. Dr. Schwartz credits her involvement in NASEM panels, an Oakridge fellowship at the FDA, and participation in the AGS national meeting in 2023 as well as interactions with many colleagues in AGS, UCSF and the FDA as contributing to the concepts presented in this paper.

Elements of Financial/Personal Conflicts. Author Schwartz: Has received research funding (grants) from the NIH and the FDA and holds stock in Pfizer, Amgen, Inspire Therapeutics, Ingeneron, Medtronic, Edwards, ThermoFisher, Inari; none of which are relevant to this manuscript.

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Author Contributions: Drs. Schwartz contributed to the concept and design and preparation of the manuscript.

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Figure Legends

Figure 1. Recent enrollment by age subgroups in clinical trials of medications for heart failure (upper left panel) and stroke prevention in patients with non-valvular atrial fibrillation (lower left panel) are shown in orange and the prevalence of these conditions in the U.S. by age group in green as visual examples to assess age representation. On the right, these same data are presented quantitatively with the solid horizontal bars indicating the (clinical trial) participant to (U.S. patient) prevalence ratio (PPR). The shaded green area indicates PPR's of 0.8-1.2 that are usually considered adequate representation. Data from Reference [15]

Figure 2. Summary of older-age relevant sections of the Consolidated Appropriations Act, 2023, Chapter 1 Clinical Trial Diversity

Figure 3. Data needs to achieve representative patient enrollment in clinical trials includes initial and continually updated disease prevalence and clinical trial enrollment data and analysis.

Figure 4. Infrastructure needs to achieve representative patient enrollment in clinical trials includes expansion of the workforce with administrative support and community collaborators, places to conduct the work, programmatic support with uniform platforms and protocols, and promotion at all levels of society.

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Figure 1.

Visual

70

Quantitative Metric

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Heart

50 Failure

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U.S. Prevalence Trial Enrollment

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20

10

0

40-59 60-79 80+

25

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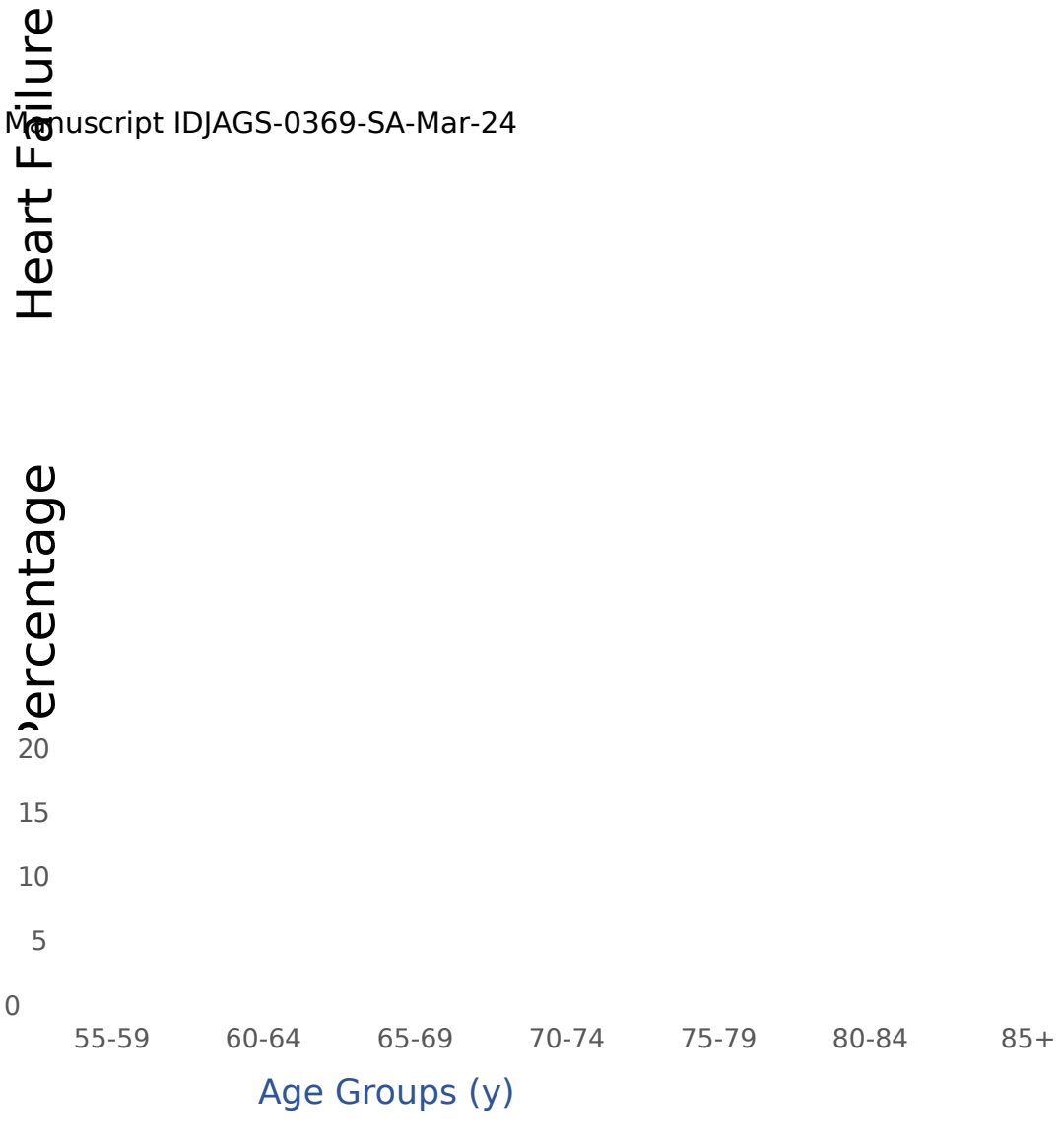

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Participant to Prevalence Ratio

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Figure 2

SEC. 3601.

DIVERSITY ACTION P

STUDIES....required

Goals for enrollment, ..

ethnic demographics c

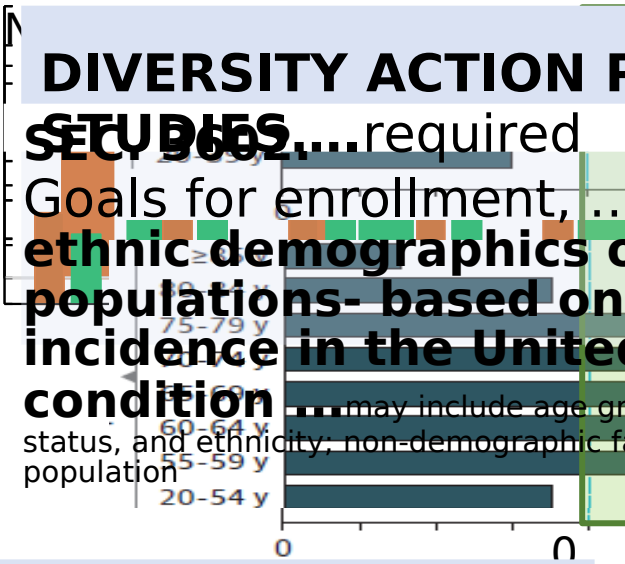
populations- based on

incidence in the Unite

condition ....may include age gr

status, and ethnicity; non-demographic f

population



Encouraging clinical study participation that reflects the prevalence of the disease or condition among demographic subgroups, where appropriate, and other topics, including...

- how and when to collect and present the prevalence or incidence data on a disease or condition by demographic subgroup, including possible sources for such data and methodologies for assessing such data...
- the establishment of goals for enrollment in clinical trials, including the relevance of the estimated prevalence or incidence, as applicable, in the United States of the disease or condition for which the drug or device is being developed..

SEC. 3603.

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Accountability
Annual clinical trial reporting on enrollment

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The Consolidated Appropriations Act, 2023

CHAPTER 1—CLINICAL TRIAL DIVERSITY AND MODERNIZATION

Some Pertinent Highlights

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Figure 3

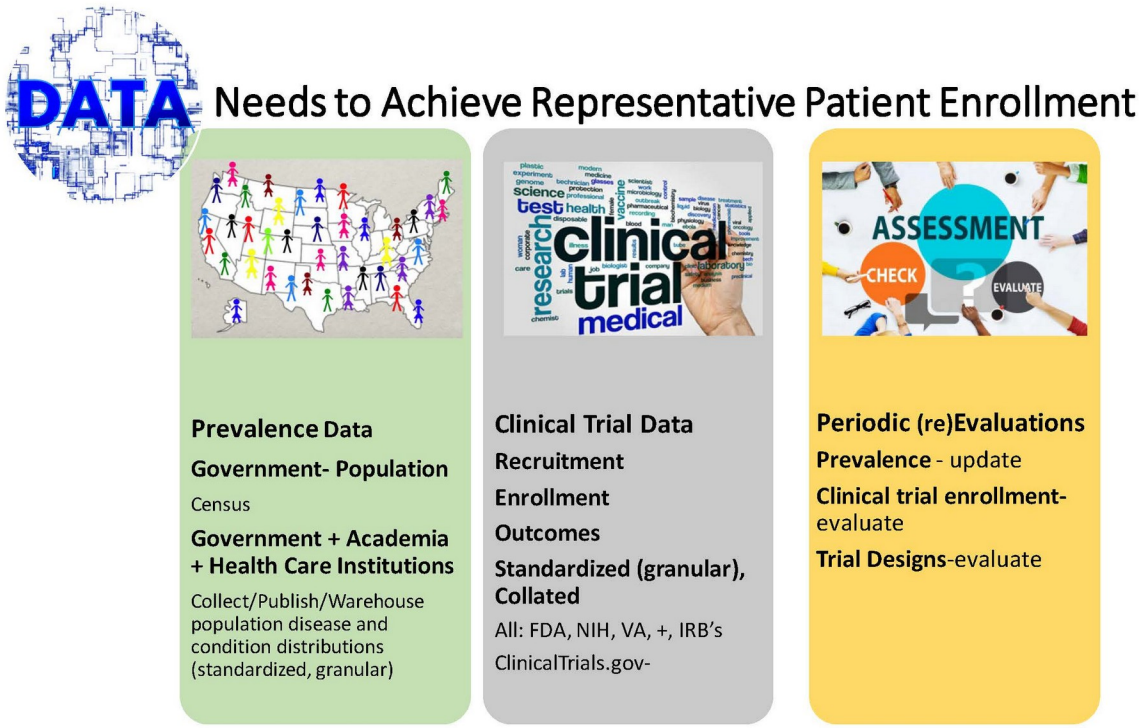

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Figure 4