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ROADMAP TO 2030 FOR DRUG EVALUATION IN OLDER ADULTS

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Abstract (word limit 250): Changes that accompany older age can alter the pharmacokinetics (PK), pharmacodynamics (PD), and likelihood of adverse effects of a drug. However, older adults, especially the oldest or those with multiple chronic health conditions, polypharmacy or frailty, are often underrepresented in clinical trials of new drugs. Deficits in the current conduct of clinical evaluation of drugs for older adults and potential steps to fill those knowledge gaps are presented in this communication. The most important step is to increase clinical trial enrollment of older adults who are representative of the target treatment population. Unnecessary eligibility criteria should be eliminated. Physical and financial barriers to participation should be removed. Incentives could be created for inclusion of older adults. Enrollment goals should be established based on intended treatment indications, prevalence of the condition, and feasibility. Relevant clinical pharmacology data need to be obtained early enough to guide dosing and reduce risk for participation of older adults. Relevant PK and PD data as well as patient-centered outcomes should be measured during trials. Trial data should be analyzed for differences in PK, PD, effectiveness, and safety arising from differences in age or from the presence of conditions common in older adults. Postmarket evaluations with real-world evidence and drug labeling updates throughout the product lifecycle reflecting new knowledge are also needed. A comprehensive plan is needed to ensure adequate evaluation of the safety and effectiveness of drugs in older adults.

1. Background:

The U.S. Food and Drug Administration (FDA) hosted a virtual public workshop entitled "Roadmap to 2030 for New Drug Evaluation in Older Adults" on March 23, 2021.[1] This workshop brought together national and international stakeholders from academia, government agencies, the pharmaceutical industry, and patients to discuss inclusion of older adults in clinical trials. The focus was on strategies to ensure a database adequate to evaluate the safety and efficacy of drugs used in this population. This manuscript was developed from the information and suggestions collected from the presentations, panel discussions and live audience survey at the workshop, followed by reflection on the feedback received.

The importance and urgency of adequate evaluation of drugs in older adults.

The population in the US, Europe and many other industrialized nations is aging. The fastest rate of growth is in people aged 85 years and older, both in the U.S. and worldwide. The U.S. Census Bureau projects that by 2034 the number of people who are 65 years of age and older will outnumber children under the age of 18 years.[2] By 2060, approximately one quarter of the population will be 65 years or older. Increasing age is often accompanied by physiologic changes and the accumulation of medical conditions.[3] The older adult population is a major consumer of prescription medications. The ten most common chronic health conditions diagnosed in older adults include hypertension, high cholesterol, arthritis, ischemic heart disease, diabetes, chronic kidney disease, heart failure, depression, dementia and chronic obstructive pulmonary disease. Frailty, defined either by a frailty phenotype or by the accumulation of health and functional problems[4,5] also increases with increasing older age and has been associated with adverse health outcomes. In the 65 to 69 years age group, some estimate that 11% are frail and in the 85 to 89 years age group, 38% are frail.[6] Health conditions often occur in combination in older adults with 70% of people aged 65 or older having two or more chronic health conditions.[7]

With multiple chronic conditions comes polypharmacy, which is often defined as taking five or more drugs daily. From 1994 to 2014, the proportion of older adults taking five or more prescribed drugs, almost tripled, from 14% to 42%.[8] When over-the-counter medications and dietary supplements are included, the number of older adults regularly taking five or more drugs

or dietary supplements is 67%. Polypharmacy is important because it is the strongest risk factor for adverse drug events in older adults because of the increased risk of drug interactions and the cumulative effects of multiple drugs. Observational clinical and basic research have shown that polypharmacy, particularly with multiple drugs that have anticholinergic or antiadrenergic and sedative effects, increases adverse geriatric outcomes and frailty.[9,10] The pharmacology of multiple concurrent drug-drug and drug-disease interactions is still not well characterized, as most drug interaction studies investigate only two concurrent medications.

PK differences between younger and older adults have been relatively well characterized and doses of medications are routinely adjusted based on changes in factors such as renal function. However, less is known about the relationships between concentrations and responses or altered PD with aging. It is reasonable to assume that PD relationships are altered with aging as many systems including the nervous, cardiovascular, musculoskeletal, and immune system are affected by aging and older age is generally accompanied by lower physiologic reserve resulting in a decreased ability to respond to stressors. All of these factors can alter the benefit-risk balance for a medication in an older adult. The older adult population presenting for clinical care, however, is heterogeneous with significant inter-individual physiologic variability [11] resulting in part from differing presence or combinations of chronic health conditions and multiple medications, differing nutritional status, or frailty status.

A major clinical challenge in geriatric pharmacotherapy is achieving the optimal balance of benefit and risk for a medication regimen. Medications are important for preventing and treating illness and disability in older adults, but an important consideration is that adverse effects are more common in older adults. Understanding how changes in physiology, immunology, pharmacology, multimorbidity, nutritional status, polypharmacy, frailty, and impaired functional and cognitive status affect both efficacy and safety of medications is needed to inform decisions about the optimal use of drug therapy in older adults. Inclusion of older adults during drug development and clinical trials is essential for the evaluation of age-related effects on a drug's benefits and risks. If data are not collected on responses in older adults, prescribers, payers and older adult patients may not have adequate data to make decisions related to drug use in older

adults.

The history of relevant FDA regulations and guidances. (Fig 1)

The FDA has required reporting of data on older adults in New Drug Applications (NDA) since 1985 when it revised the regulations governing the new drug approval process, including the content and format sections of an NDA .[12,13,14] The FDA published the guideline on format and content of clinical and statistical sections of the NDA in 1988 that outlines an acceptable format for meeting the regulatory requirements in place at that time for reporting of age-related data.

The 1989 "Guideline for the Study of Drugs Likely to Be Used in the Elderly" provides recommendations for clinical trials for drug products seeking approval in the US. This seminal guideline recommended the inclusion of patients over 75 years of age with concomitant illness and treatments in clinical trials..

In 1994, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), comprised of the regulatory bodies of the European Union, Japan, and the U.S., published its E7 Guideline for studies in support of the older adult population. This guideline noted the characteristics of older adults warranting specific attention, such as concomitant illness and concomitant medications, and the importance of altered PK from renal or hepatic impairments.[17] Of note, the ICH E7 guideline recommended a minimum of 100 patients over the age of 65 for inclusion in a clinical drug development program for drugs used in diseases not unique to, but present in, older adults. This guideline has since been expanded, calling for the inclusion in clinical development programs of even larger and more representative numbers of older participants over the entire age spectrum of the geriatric patient population, including those older than 85 years of age.

In 1998, the FDA established the Geriatric Use subsection, as a part of the PRECAUTIONS section, in the labeling for human prescription drugs to include more comprehensive information about the use of a drug or biological product in persons aged 65 years and above.[20]

In 1998, the FDA issued a final rule (the ''Demographic Rule'') requiring presentation of safety and effectiveness data in an NDA by gender, age, and race.[21]

In 2001, the FDA published a guidance on the labeling of drug products for older adults. In 2012, Section 907 of the FDA Safety and Innovation Act (FDASIA) directed the FDA to develop a report on the inclusion of demographic subgroups in clinical trials and data analysis in applications for drugs, biologics, and devices within 1 year. In August 2013, the FDA released a report describing demographics and subset analyses included in 72 applications for drugs, biological products, and medical devices approved in 2011.[24] Section 907 of FDASIA also directed the FDA to publish an Action Plan to enhance the collection and availability of demographic subgroup data from NDAs and BLAs.

To enhance transparency, the FDA implemented the Drug Trials Snapshots program. Drug Trials Snapshots present the participation of patients in trials that supported the approval of new drugs by age, sex, and race, and highlight whether there was any difference in benefits or side effects among these subgroups. It is important to note, however, that Drug Trials Snapshots are published only for approved new molecular entities and original biological products, but not for indication expansions. It should also be appreciated that Drug Trials Snapshots do not include information on the majority of trials, as most drugs are never approved. In 2018, The European Medicines Agency made recommendations about instruments to assess baseline frailty status to supplement chronologic age as a demographic characterization factor in order to support a better understanding of the benefit-risk of a drug in older adults.

In 2020, the FDA issued 3 guidances related to the inclusion of older adults in clinical trials. The FDA issued a final guidance on improving the diversity of clinical trial populations to better reflect the population of patients who will use the drug if approved, including older adults who had been excluded from clinical trials without clinical or scientific justification. The FDA also published draft guidance on the adequate representation of older adults to better assess the benefit-risk profile of cancer drugs in this population, especially adults over age 75 years.[19,27] Finally, the FDA published draft guidance to assist applicants in determining the appropriate placement and content of geriatric information in prescription drug labeling. It recommends inclusion of additional information on geriatric age subgroups in drug product labeling if important differences exist in responses in older age subgroups with suggested age groupings

(65-74, 75-84, and higher than 85 years of age) depending on the data. This draft guidance further recommends the inclusion of the number and percentage of drug-exposed age subgroups and age subgroup specific data on the level of evidence for effectiveness and safety in drug product labeling.

2. The gaps in the new drug evaluation in older adults (Table 1)

Insufficient enrollment of older adults in trials and inadequate identification of factors in older adults predictive of alterations of PK, PD, efficacy, and safety.

The paucity of clinical trial participation of very old adults with the greatest burden of multiple medical conditions and geriatrics syndromes limits our understanding of these factors on responses to drugs in older adults. The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) searched the ClinialTrials.gov database for registration trials with respect to potential age-related exclusion criteria. Out of 8702 phase 3 trials initiated between 2010 and 2021, 61% did not have specific chronological upper age exclusions. This was consistent with findings from an informal survey of IQ member companies which demonstrated that 80% (41/51) of recent controlled registration trials did not have any upper age restriction on inclusion. Results of an informal survey of member companies suggested that limited inclusion may have arisen more often from practical factors, such as lack of information about trial participation, mistrust, limited mobility or challenges to informed consent, than from comorbidities and co-medications. Nonetheless, the concern is that older participants in clinical trials may not represent the breadth of health conditions in the older adult population.

An exploratory study was conducted to assess the age distribution of adults enrolled in registration clinical trials for 45 new molecular entities that were FDA-approved from 2010 through 2019 in 7 therapeutic indications relevant to older adults: diabetes, depression, heart failure, insomnia, non-small cell lung cancer, osteoporosis, and prevention of stroke in patients with non-valvular atrial fibrillation. A participant to prevalence ratio (PPR) was calculated as the proportion of adults within a particular age subgroup that participated in the clinical trials divided by the estimated proportion of adults within the corresponding age group in the disease

population.[30] The proportion of adults in the clinical trials was considered to be comparable to the corresponding age group of estimated proportion of adults in the prevalence disease population if the PPR was between 0.8 and 1.2. The lowest PPRs for the seven therapeutic indications examined generally occurred in the older age groups. Illustrative results for the 2 therapeutic indications with the largest numbers of trial participants are shown in Figure 2. This underrepresentation was seen beginning at age 75 for type 2 diabetes trials, and beginning at age 80 years for the trials for the prevention of stroke in patients with non-valvular atrial fibrillation. This under-enrollment of older adults has been commented upon previously.

The coronavirus disease 2019 (COVID-19) pandemic highlighted the issue of underrepresentation of older adults in clinical trials, especially of older adults residing in skilled and long-term care facilities. A recent analysis of drug trials for COVID-19[32] concluded that 23% excluded older adults based on a chronologic age restriction, and an additional 53% had indirect age-related exclusions for comorbidities, functional impairments (e.g., vision, hearing, or mobility impairments), lack of access to internet or information technology, or other broad, poorly defined or supported exclusions. In vaccine trials, 61% had a chronologic upper age restriction, while 39% had indirect age-related exclusions. Thus, 100% of vaccine trials were at high risk for excluding older adults.[32-36] Notably, older adults residing in nursing homes were not included, despite having disproportionate morbidity and mortality from Covid-19 infection.[32] Thus, because of lack of data, the labeling of many products legally sold in the US relating to a host of therapeutic areas may provide little information to guide prescribing in very old or frail adults or those with multimorbidity or polypharmacy.

Lack of accepted criteria for "representative" population for clinical trial enrollment.

There is general agreement that registration trial enrollment should be representative of the target post-approval treatment population, but there are no specific or measurable criteria for meeting this goal. As reviewed above, the FDA guidance on inclusion of older adults in clinical trials states that a) "drugs should be studied in all age groups, including the geriatric, for which they will have significant utility" (note: originally stated in the 1977 guideline: General Considerations for the Clinical Evaluation of Drugs[37] but restated and further explained in the 1989 guideline), b) that PK differences should be evaluated, for drugs likely to be used in the

elderly, c) older patients should be included in clinical trials in "reasonable" numbers, and d) exclusions deemed prudent for safety and ethical reasons in early studies need not necessarily be maintained in Phase 3. All these statements are in the 1989 guideline for study of drugs likely to be used in the elderly; the challenge is how to implement these principles.

Identifying drugs likely to be used in the elderly or older adults requires defining "elderly" or "older adult" and determining the prevalence of the therapeutic indication in these "older adults". Currently, there is no uniform definition of "older adult" or comprehensive data on the prevalence of disorders in older adults. The multiple proposed chronologic age definitions for older age (ICH E7 , Clinical Pharmacology & Therapeutics dosing for all ages white paper, WHO (World Health Organization)[39], FDA geriatric labelling guidance 2020) are not based on evidence linking them to either the trajectory or presence of physiological changes that alter drug PK, PD, safety or efficacy, nor have they been related to either the prevalence of conditions that are the treatment indication for new drugs (utility) or that are most common in older adults. While various entities gather data on clinical diagnoses and epidemiologic studies may gather data on geriatric syndromes and function, data are often presented in aggregate for adults over age 60 or 65 years (Centers for Disease Control and Prevention[40], and FDA Drug Trials Snapshots[41], National Institute on Aging (NIA)-funded nationally representative studies[42]) and may not be updated regularly.[43] Health care databases may be proprietary and not publicly accessible (Veterans Administration Medical Centers, Optum Labs). Thus, there are no current comprehensive data with sufficient granularity on the prevalence of health-related disorders in age subgroups of older adults to define a "representative or reasonable reflection of the chronologic age of the target treatment population" or to classify a drug as "likely" or "unlikely" to be used in the elderly". The need for such data will become more widely recognized as the New England Journal of Medicine (NEJM) has recently announced the requirement for a Supplementary Table on the representativeness of study participants for manuscripts reporting on clinical trials.[44]

There is also wide variation in biologic function observed in individuals of the same chronologic "old" age. Multiple chronic medical conditions, polypharmacy, changes in physical and cognitive function, and decreased functional reserve are present in significant proportions of

older adults and how these factors affect responses to drugs need to be determined. Consensus is needed on preferred methods for assessment or measurement of multimorbidity, polypharmacy, physical function, nutritional status, frailty, or cognitive function, and other measures, including age-related immunocompromise, that would contribute to creating a representative heterogeneous older adult cohort. Without these definitions and metrics, it will be difficult to accurately assess whether clinical trial enrollment is representative of the older adult population likely to receive the drug for the treatment indication upon marketing approval.

Absence of patient-centered endpoints important to older adults.

"Hard outcomes" such as mortality and cardiovascular events or surrogate outcomes (e.g., low density lipoprotein levels) are often used in clinical trials, but may not capture other outcomes that matter to older adults, such as symptom burden, and effects on cognition, physical function, and health-related quality of life.[44] For example, the neurocognitive effect of statins were not evaluated before the original approvals but were only considered during real world clinical usage.[45] Of note, health-related quality of life has been shown to decrease when treatment interferes with cognition in older adults.[46] Priorities of some older adults may also shift from increased length of life to increased quality of life, particularly for those who are frail, experiencing multimorbidity or with limited life expectancy receiving burdensome treatments.[46] Information available to guide optimal drug selection and dosing in product labelling is often limited, especially with regard to evidence needed to weigh the potential impact on endpoints of importance to older adults such as cognition, physical function or falls. For example, information about fall risk is often not consistently included as an assessment in trials and is not usually described in labeling in the context of advanced age, frailty, multimorbidity or polypharmacy, although cumulative effects of sedative and anticholinergic drugs and/or multiple drugs have been associated with falls. [48,49]Additional issues considered by geriatricians and patients such as time to benefit relative to time to potential adverse effects and drug burden are not addressed.

Inadequate PD data in older adults.

Age-related PD changes may be more important than age-related PK changes that can be managed with dose adjustment, but age-related PD changes are less well characterized than age-related PK changes. PD studies have demonstrated age-related changes that can alter the characteristics and clinical presentation of diseases in older adults as well as responses to drugs. Reproducible age-related decreases occur in beta-adrenergic mediated changes in heart rate, cardiac output, vasodilation, in decreased baroreflex responses, and in increased ventricular wall and arterial wall stiffness with preservation of non-endothelial nitric oxide mediated responses. These age-related changes are likely responsible for the different types of cardiovascular disorders observed in older adults compared to younger adults, such as diastolic vs. systolic hypertension and heart failure with preserved ejection fraction vs. heart failure with decreased ejection fraction. These age-related changes also contribute to the risks of adverse events such as postural hypotension after administration of vasodilators, blood pressure lowering drugs or intravascular volume depletion with diuretics in older adults. Another consistent PD alteration in older adults is increased sensitivity to central nervous system (CNS) effects of drugs resulting in increased risk of falls or cognitive impairment. Some potential mechanisms for this increased sensitivity include changes in the blood brain barrier, age or disease related reduction in baseline performance, reduced effect of compensatory mechanisms or changes in receptor density or function.[50-52] In contrast, the effect of age on the development of acute tolerance and the intensity and time course of drug withdrawal of CNS-active drugs is not well documented nor has the potential cumulative psychotropic burden been considered during clinical drug evaluations.

Other issues.

(1) Ethical and Practical Issues.

Ethical issues in conducting research include informed consent, beneficence, respect for autonomy, justice and confidentiality and privacy. Consent and beneficence (in the context of research that researchers should have the welfare of the research participant as a goal of any clinical trial or research) issues are particularly relevant to enrollment of older adults in clinical trials. Cognitive impairment increases in prevalence at older ages with estimates that approximately 30 percent of adults over age 80 living independently in the community may have low cognitive performance. An individual's ability to consent to research needs to be considered

as do legal and ethical issues regarding surrogate consent. There is wide variation in county, state, and individual institution policies regarding surrogate consent. The COVID-19 pandemic has increased acceptability of electronic consent by individuals or surrogates and may lead to more universal policies These policies must ensure that ethical considerations for those with cognitive impairment are addressed adequately.. Beneficence (in the context of preventing harm to patients), may influence reluctance toward research in non-academic settings. On the other hand, the principle of justice requires fair treatment of individuals and equitable allocation of resources. Ethical framing has shifted from the position of protecting older adults by excluding them from research to protecting older adults by including them in research necessary to ensure safe and effective drug therapy.[54,55] The ethical framework necessary to support inclusion of older adults in clinical research needs to continue to be developed and refined to honor these ethical principles and remove unnecessary barriers to research participation.

(2) Perceptions about Research Participation.

Risk assessment of research participation may be viewed differently by older adults as compared to their health care providers or caregivers.[56] Providers of health care for older adults in both community and long-term care settings may be hesitant to refer patients for research participation and may serve as "gatekeepers". Older adults also often have both formal "caregivers" from long-term care services and informal caregivers such as family or friends who assist with medications, transportation, communication, and influence perceptions. Their concerns about research participation may prevent older adults from accessing clinical trials.

(3) Residential Care Facilities.

There are several million Americans residing in residential care facilities with nursing homes providing long-term care services to the largest proportion of the oldest adults. There has been some limited enrollment of long-term care residents in clinical trials of drugs for dementia and osteoporosis. However, nursing home residents and those over age 85 years have been largely absent from trials of drugs for most other categories such as cardiovascular diseases that are the most common diagnoses in these older adults and for sedatives and antipsychotics that have a high risk for unwanted CNS effects. Vaccine clinical trials are rarely performed in nursing home

residents despite nursing home residents being at greatest risk of morbidity from infection. The tragic impact of the COVID-19 pandemic on the population residing in long-term care and assisted living settings highlights the need for clinical trials to assess the benefits and risks of drugs in these populations, and to make them available to those in greatest need. Countering the need for data is the insufficient staff, administrative, and other resources for research within the residential care facilities and assisted living sites.

(4) Availability of Product Dosage Sizes/Strength or Formulations.

Reductions in dosage recommendations are often needed for older adults based on estimated decreases in renal drug clearance and/or metabolism and elimination by other routes. Conversely, increases in doses may be needed for effective immunization due to diminished immune responses with aging.[58] If limited numbers of dosage strength are approved for marketing, it will be difficult to adjust dosages appropriately. Swallowing disorders also increase with older age, therefore some large size capsules or tablets may be difficult for some older adults to ingest.

3. **The way forward - potential solutions to fill the gaps. (Table 1)**

Obtaining clinical pharmacology and disease prevalence data to guide the enrollment, dosing, and risk mitigation for older adults in later trials

Drug development should follow a rational sequence, so that the information obtained in earlier studies can be used to guide the design of later studies. Clinical pharmacology data are often critical for trial design questions such as selecting the appropriate dose(s) to be tested in older adults, as well as the need for restrictions on comedications in the safety and efficacy trials. Early consideration of the PD profile is important as certain effects, such as the potential to increase risk of falls or the impact of drugs with CNS effects or anticholinergic effects that affect cognitive function can produce greater or cumulative effects in older adults. Obtaining these data before the initiation of the clinical safety and efficacy trials is critical for assessing risk and determining the strategy to address balancing the inclusion of representative older adults and protection of the trial participants.

In early phase trials, after initial tolerability, safety, PK/PD evaluation in younger adults, inclusion of older adults should be considered especially if the drug is likely to be used in older adults after approval. The absorption, distribution, metabolism and excretion information of a new drug can help evaluate the need for clinical evaluation of the impact of hepatic or renal dysfunction on the PK of the drug and to anticipate PK changes in older adults. The evaluation of potential drug-drug interactions in older adults should expand beyond the traditional focus of PK-based interaction between two drugs. It is important to consider potential PK and/or PD interactions of multiple drugs likely to be co-prescribed for the typical older adults with the target diseases, with particular emphasis on neurological or cardiovascular effects. Approaches that may be useful in characterizing the impact of various age-related physiological changes on PK of a new drug and predicting the potential for drug-drug interactions and the impact of polypharmacy include Model-informed drug development (MIDD) approaches such as physiologically based pharmacokinetic (PBPK) modeling, and quantitative systems pharmacology (QSP). Applying population-based modeling and simulation approaches such as population PK and PD to early clinical data may also provide insights around drug variability. Integrating early clinical data with MIDD approaches can be useful to inform dosing and safety monitoring for the inclusion of older adults in later stage clinical development.

Key information needed to assure adequate representation of older adults with the treatment indication for which a drug is being evaluated in clinical trials is data on the prevalence of the target indication across the older age-span. The prevalence data should inform sample size targets for the enrollment of older adults in clinical efficacy and safety trials. The criteria for adequate sample size of older adults enrolled in registration clinical trials has progressed from thinking that a specific number, such as 100 older adults, would be sufficient enrollment to detect age-related differences to recognizing that no single number for age subgroup enrollment would be appropriate for all new drug evaluations. Stakeholders generally agree on the concept that enrolled trial participants should reflect or be representative of the patient population with the intended treatment indication with the caveat that if there are concerns regarding safety or efficacy in a subgroup such as older adults, they may need to be “over-represented.” Research

efforts are needed to determine the best ways to design trials to capture or analyze the heterogeneity of treatment or unwanted effects.

Achieving inclusion of representative older adults and collection of relevant data in efficacy and safety trials

As noted in earlier sections, there is no current uniform definition of "representative" older adults but chronologic age is surely the starting point. As suggested above, the initial step in trial design should include an epidemiologically-based assessment of the age distribution of the population with the target treatment indication to inform on expected use. If enrollment targets mirror this distribution, participants are also likely to have the clinical characteristics found in the ultimate treatment group. Thus, enrollment targets and analyses based on the age distribution in the population with the disease may be preferable to attempting a universal definition of "older" age for either enrollment or assessment of the adequacy of enrollment in trials. To approach similar distributions of participants in clinical trials for drugs likely to be used in older adults and the intended treatment population, the following considerations will need to be addressed.

i. Eliminating unnecessary eligibility criteria

Perhaps the single step with the most impact toward reaching the goal of inclusion of representative older adults in efficacy and safety trials would be to eliminate eligibility criteria that currently make "typical" older adults ineligible. In general, older age alone should not be an exclusion criterion. In addition, exclusion of older adults (or, any adults) with concomitant medical conditions or use of drugs that are present in a large percentage of older adults is inappropriate if the goal of a clinical trial is to demonstrate the effectiveness and safety of a drug that is likely to be prescribed for these older adults after marketing approval. Broader inclusion criteria will result in greater generalizability.

Criteria for safe enrollment and monitoring of older adults with common medical conditions such as hypertension (present in as many as 80% of adults over age 65 years), hyperlipidemia (present in at least half of adults over age 65 years), coronary heart disease (present in 20-50% of adults over age 65 years), or diabetes (present in 20-40% of adults over age 65 years) should be incorporated into clinical trial designs. If these conditions are clinically controlled and stable, their presence should not lead to exclusion of enrollment. An exception would be treatment with

drugs predicted to be contraindicated for use in combination with the drug(s) being tested due to safety concerns. When specific concerns exist regarding potentially adverse effects in older adults such as effects on cognition or falls, these should be assessed and monitored during the trial as safety and adverse event measurements. Identifying and reporting patterns of co-morbidities in participants would also assist in evaluating the "representativeness" of the trial population in relation to patients likely to receive the drug after marketing approval.

ii. Removing barriers and creating incentives to inclusion of older adults in clinical trials

Eliminating unnecessary eligibility criteria is a critical step, but this approach alone is unlikely to be sufficient to achieve a study sample whose health and demographic characteristics mirror real-world populations of older adults to whom the drug will ultimately be prescribed. It is also necessary to actively seek recruitment of study participants such as older medically complex patients who are likely to use the drug evaluated in the study but have been difficult to recruit and retain in traditional randomized clinical trials. Studies of barriers to enrollment of representative populations, as well as evidence-based recruitment and retention strategies, and potential changes in clinical trial designs to make them user-friendly for older age participants have been recently reviewed extensively and provide valuable insights for investigators planning to enroll older patients.[61-63]

Sedrak at al, conducted a systematic review of barriers and interventions relevant to participation of older adults in cancer trials. [61] Their findings are relevant to participation of older adults in any clinical trial. They identified 4 categories of barriers: system, provider, patient, and caregiver, and discussed how current cancer research infrastructure must be modified to accommodate the needs of older adult patients. The authors noted that addressing the barriers alone will not be adequate to solve the evidence gap in geriatric oncology. It is also necessary to expand current cancer and aging research beyond standard clinical trials. A number of pragmatic approaches have been suggested that include designing trials that allow participation of older and/or frail adults where they live with home visits or data collection using phone, internet, or digital tools, use of community-based sampling centers, and use of real-world data collected during routine clinical care from electronic records.

Bowling et al, have provided both a framework for communicating challenges to inclusion of older adults in clinical research and recommended practical solutions.[62]. This framework consists of the 5Ts (Target Population, Team, Tools, Time, and Tips). Among the challenges identified were lack of training in aging research, lack of knowledge of geriatric syndromes or common age-related impairments, lack of familiarity with measures relevant to the needs of older adults, and inflexible and complex study protocols. Additional obstacles are the "typical" single disease clinical trial focus that excludes people with diseases other than the one for which the treatment indication is being sought and skepticism that mechanisms of disease differ in younger versus older adults. Finally, geriatric health care professionals who are experienced in caring for these patients and balancing benefits and risk considerations in a framework of overall function and patient goals have been minimally involved in the drug evaluation process. The corresponding recommended solutions emphasize incorporating geriatric experts into the study team, using measures of function and patient reported outcomes, and practical strategies for accommodating those with comorbidities and age-related limitations. Recent FDA draft guidance on core patient-reported outcomes in cancer clinical trials includes physical function outcomes and illustrates how outcomes important to older adults could be addressed in regulatory guidance.

The above addresses barriers and solutions targeted at trial design and performance. Solutions must also address the reluctance of health care providers to either refer or enroll patients in research trials, the lack of involvement of health care partners in research efforts to date, the lack of access of researchers to information on potentially eligible patients or their caregivers, the administrative obstacles that may lie at the level of institutional review boards and health care systems, the lack of public awareness of the value of research and unfavorable public perceptions regarding research and possibly the pharmaceutical industry, and the lack of sufficient infrastructure in settings such as residential care facilities. Engagement of providers and caregivers in addition to potential participants may also be essential to successful trial recruitment and conduct with older adults. These challenges and their potential solutions are beyond the scope of this communication but are acknowledged as a part of the ecosystem that needs to be addressed in order to achieve enrollment of older adults in relevant clinical research and trials.

iii. Targeting adequate and feasible sample size for age subgroups with intended indications

It seems apparent that guidance on more representative enrollment is needed to approach the goal of having clinical trial participants be of similar ages and medical status to the clinical patient population that will receive the agents after marketing approval. Ideally, sample sizes for the age subgroups should be adequate to detect differences in effectiveness or safety that may warrant a different treatment decision. Data on the disease prevalence in different age subgroups and knowledge/hypotheses on age-related differences can be helpful. This goal must be balanced by the challenges of identifying and enrolling large numbers of some patient subgroups and recognizing the potential impact of decreased cognitive or physical function on the ability to fully participate through study completion. The FDA 2020 draft guidance "Evaluating the Safety of New Drugs for Improving Glycemic Control" recommends specific targets for the safety studies during phase 3 trials for patients with 1) stage 3/4 chronic kidney disease, 2) established cardiovascular disease, and 3) older age. For other treatment indications, adequate representation of frequent concomitant conditions and across the complete patient age span would likely have different targets that should be established during the trial design phase to reflect the potential treatment population and trial design requirements.

iv. Obtaining PK, relevant PD data, and patient-centered endpoints

It is critical to obtain data on drug concentrations and PD effects in late stage clinical trials. Sparse PK sampling and population PK analyses to evaluate the effect of age on PK have become common practice in drug development. What is needed is the consideration of age-related changes in sleep patterns, immune responses, basal inflammatory and coagulation status, muscle function, gait and balance, and increased sensitivity to central nervous system acting drugs or anticholinergic interventions in trial design, specific trial measurements, and analysis of data on responses to drugs. PD measures in older adults should include CNS and cognitive effects for any new drugs targeting the central nervous system and any drugs with anticholinergic properties. Data on objective measures of physical function and falls, including their medical consequences (bone or brain injuries), should also be collected during trials of agents from these drug categories and assessment of postural effects on blood pressure should be included during trials of drugs affecting intravascular volume or arterial or venous tone or

modulating baroreceptor reflexes. Effects to be monitored during both drug initiation and discontinuation should be specified. There is a need to routinely collect and report data on how to discontinue drugs and effects of discontinuation as deprescribing becomes incorporated into clinical practice to decrease polypharmacy. Assessment of both efficacy-related and off-target PD effects are needed. Development of approaches for PD analyses that are not for the primary outcome of clinical studies may be critically important.

A standard set of health outcome measures for older adults has been proposed for the following variables that have not been routinely assessed in clinical trials: total number of drugs, baseline cognition, history of delirium, vision and hearing impairment, frailty, falls, and baseline activities of daily living.[67] Tools are available for the measurement or screening of geriatric syndromes (see National Institutes of Health (NIH) Toolbox, among others). However, determination of the definitions to be used and the preferred tools for measurements of cognition, delirium, multimorbidity, polypharmacy, frailty, gait and balance, functional status, and health-related quality of life for people with multiple chronic conditions in clinical trials are needed.

Increased emphasis should be given to ensuring that the endpoints that matter most to older adults (e.g., endpoints related to patients' quality of life) are considered in the drug evaluation process when older adults are part of the target population to be treated. Cognitive function and physical function are especially important to older adults as reflected in conceptual models for what matters most to older adults such as the 5Ms for Mind (cognitive function), Mobility (physical function), Medications, Multicomplexity, and Matters to Me. A list of outcomes relevant to older adults developed by the International Consortium for Health Outcomes Measurement includes: participation in decision making, autonomy and control, mood and emotional health, loneliness and isolation, pain, activities of daily living, frailty, time spent in hospital, overall survival, [caregiver] burden, polypharmacy, falls, place of death mapped to a 3-tier, value-based health care framework.[67]

Analyses to detect differences in PK, PD, effectiveness and safety and to derive recommendations based on age and conditions common in older adults

Analyses need to be conducted across the entire older age span and based on relevant comorbid conditions. The subgroup analyses should be conducted on the data from individual clinical trials and, when appropriate, on integrated data from multiple trials that might allow the best estimation of effects and allow better detection of differences. The objectives of these analyses are to evaluate whether there are any differences in the PK, PD, effectiveness, and/or safety in the relevant subpopulations that might warrant a different treatment decision (such as dose adjustment, or the need to avoid certain drug in a particular subgroup). Forest plots can be a concise and informative visual presentation to illustrate the results of subgroup analyses, although it is important to avoid misinterpretation of the plots (e.g., when the confidence interval for a subgroup crosses the no effect point, it does not necessarily indicate a lack of effect in the subgroup because the confidence interval may be too wide due to small sample size).

The FDA recommends assessment of dose-response relationships in demographic subgroups such as older adults. Exposure-response analyses can provide complementary information and it is a good practice to include them as part of routine evaluation. In addition to performing univariate analyses for age, population exposure-response analyses should also be conducted taking into consideration the interplay between age and other factors such as sex, body weight, race, hepatic and renal function. In addition to analyses based on age subgroups, it may be helpful to treat age as a continuous variable in the analyses. Given the heterogeneity of the older adult patient population and the clinical contexts, not all clinically relevant scenarios can be empirically explored. Modeling approaches may provide an opportunity to elucidate subgroup differences, especially when there are multiple influencing factors. It is likely that more adverse events and deaths will occur in clinical trials when older adults, especially when very old patients, are enrolled. Ideally, adverse events including deaths in the treatment group(s) should be compared with matched control groups for all patients and the different age subgroups. If no control group is available, it may be helpful to look at the data from trials for other drugs studied in the same population.

Continued evaluation based on real-world evidence (RWE).

After a drug is approved, it is important to continue the evaluation of its safety and the effectiveness through the real-world evidence (RWE). Although all efforts should be made to

ensure that clinical trials reflect the population most likely to use the drug following market approval, gaps almost always exist between clinical trials and the real world. Real-world data (RWD) such as data derived from electronic health records, medical claims and billing data, and product and disease registries, may be used to fill some of these information gaps when combined with appropriate methods to place the findings in the appropriate context for reliable evidence. One example is FDA's Sentinel initiative. This is the FDA's national electronic system for safety monitoring of FDA-regulated medical products.[72,73] However, as of April 2021, only 7% of individuals tracked in Sentinel are adults over age 75 years because the vast majority of the data comes from private payer databases. The FDA Adverse Event Reporting System (FAERS) is a database that contains individual case safety reports (ICSRs) of AEs of drugs. As older adults are generally more susceptible to adverse drug events as compared to younger adults, the draft FDA document "Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff" stresses that ICSRs that describe AEs in the geriatric patient population warrant special consideration.[74] A recent example was the occurrence of severe urogenital infections observed with the introduction of SGLT2-inhibitors. These were probably not seen in trials because of the exclusion of representative older adults with diabetes (and decreased renal function and prior infections), the patients most at risk for these infections.[75] RWD with proper study design to enable the development of RWE can also be useful in the evaluation of the effectiveness of drugs. Graham et al. compared stroke, bleeding, and mortality risks in patients with nonvalvular atrial fibrillation enrolled in US Medicare and treated with nonvitamin K antagonist oral anticoagulants (NOACs).[76] The study confirmed the efficacy of NOACs for preventing strokes seen in the individual NOAC trials, but also described important differences between the NOACs for major GI bleeding in patients with mean ages older than in the registration trials. Khozin et al. studied the real-world outcomes of patients with metastatic non-small cell lung cancer treated with programmed cell death protein 1 inhibitors in the year following FDA approval. Their analyses suggested that patients aged >75 years at immunotherapy initiation did not have worse overall survival than younger patients.[77]

The use of RWD for clinical research or regulatory decision making is challenging. As many RWD sources were not built for research purposes, there could be issues related to the data

quality and completeness. Data elements for an individual may exist in different electronic systems that lack interoperability. Databases may be limited to selected geographic regions or types of patients and lack diversity. The data may also not be granular enough to be able to detect common adverse events including those that affect quality of life. Research using RWD often suffers from potential confounding and bias due to a multitude of factors, including changes in treatment practices over time, changes in covered enrollee pools over time, changes in data content, coding, or completeness over time, and lack of randomization in many cases, among other factors. Finally, critical information on symptoms and diseases are not fully standardized although communities of practice such as the Observational Health Data Sciences and Informatics (OHDSI) program have formed to address such issues. Careful selection of the RWD sources, well-designed study protocols, and innovative analytic approaches and control for confounding will be critical to ensuring the validity of the conclusions derived from RWD.[79,80]

Labeling for Older Adults Throughout the Product Lifecycle

In some respects, it is possible to view drug product labeling as a "living document" due to requirements that NDA holders update the labeling. Specifically, 21 CFR 201.56(a)(2) states that "labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading." Considerations associated with use that may impact the older adult population may not be evaluated or communicated in labeling at the time of approval, such as if a tablet may be crushed or split. Updated draft guidance on geriatric labeling was recently issued to promote consistent placement of relevant information about drug use in geriatric patients. As there may be information gaps for older adult populations, the draft guidance has specific language to indicate when there are insufficient data to detect differences between older and younger adult patients, which aligns with the regulatory goal of labeling that is truthful and not misleading by avoiding any misleading implications that the drug is safe and effective in an unstudied population ((see, e.g., 21 CFR 201.56(a)(2)). For some products, information related to drug discontinuation or anticholinergic or sedative effects may be essential for safe and effective prescribing in an older adult population.[81]

Improving collection and communication of age-related information in labeling throughout the product lifecycle is necessary to support decision-making by patients and healthcare providers or

caregivers. One mechanism could, if appropriate under applicable legal and regulatory requirements, be establishment of a post-marketing requirement (PMR) or post-marketing commitment (PMC).[82] This mechanism could address gaps in knowledge related to under-representation of older adults in clinical trials that may impact safety or effectiveness. It can assess clinical differences in safety, effectiveness, PK or PD in specific age groups, in older patients with prevalent related conditions, such as impaired renal function, or potential drug interactions that may be significant in the older patient population. Data collected through this mechanism may support updated labeling for older adults.

Data availability is one of the gaps that has received focus, but lack of timely submission of new information for inclusion in labeling may also be a barrier for ensuring safe and effective use in older adults. As prescribing practice for a product may evolve with use, sources such as practice guidelines or drug information resources from clinical support database vendors may be developed and serve as a resource for clinicians, but this information may not be fully considered or submitted by sponsors for review and inclusion in labeling. Aligning labeling with current evidence and highlighting essential information would allow labeling to be a more effective primary information source for stakeholders. Further consideration of the feasibility of ensuring timely labeling updates and communication of these changes to healthcare providers and patients would be worthwhile.

Engaging all stakeholders

- Closing the gaps in clinical trial enrollment of older adults will require engagement of multiple stakeholders, including researchers and scientific societies, regulatory bodies, healthcare providers, older adults and caregivers, and healthcare payers.[83] Best practices for addressing the ethical and practical issues in increasing enrollment of older adults in clinical trials are emerging and require broader dissemination in the research, practice, and patient communities. Recent examples of forums bringing together multiple stakeholders to address inclusion of older adults in clinical research include the National Academies of Science, Engineering and Medicine's workshop on Drug Research and Development for Adults Across the Older Age Span, National Institutes of Health's Inclusion Across the Lifespan II workshop and the National Institute on Aging Research

Centers Collaborative Network's Inclusion of Older Adults in Clinical Research workshop[85]. These efforts shared knowledge and offered recommendations informed by broad stakeholder input, including older adults, and proceedings are available to guide future research endeavors. It has been suggested that if payers sought direct evidence of benefit before covering drug therapies for their beneficiaries, it could incentivize inclusion of representative older adults in drug evaluation research. To accommodate any necessary dose adjustment for older adults or to address the need for patients with swallowing difficulties, additional formulation/dose strengths may be needed and discussions among drug developers, regulators, healthcare providers, and patient/caregiver groups may be helpful.

4. Proposed action plan (Figure 3)

In the past several decades, FDA has developed guidances, Manual of Policies and Procedures, and Good Review Practice recommendations related to drug evaluation in older adults. FDA has also taken initiatives such as Drug Trials Snapshots to improve the transparency of clinical trials' demographic participation. Considerable progress has been made in improving the enrollment of older adults in clinical trials and conducting the relevant subgroup analyses to assess the safety and effectiveness of drugs in older adults. For example, age groups of 65 – 75 years were fairly well represented in proportion to the prevalence of the treatment indication for a number of trials in the recent decade.[89] The questions around drug utilization in older adults are recognized given the efforts within scientific and patient advocate communities. Still, information gaps exist, and more work is needed.

At the FDA public workshop "Roadmap to 2030 for New Drug Evaluation in Older Adults"[1], FDA received valuable feedback and many suggestions from the presentations, panel discussions and live audience surveys. It was suggested that the FDA should establish a working group, which would be tasked with developing a comprehensive strategic plan to ensure adequate evaluation of the safety and effectiveness of drugs in older adults if they are part of the target population likely to use the drug. The working group should first identify the gaps in the current drug evaluation in older adults and then develop strategies to fill those gaps. The authors believe that such strategies could include but are not limited to (1) development of additional

guidances and internal advice (or updating existing ones) on how to achieve inclusion of the full range of older adult patients, including avoiding unnecessary exclusions for concomitant illnesses and concomitant medications (2) communication and outreach to stakeholders, and (3) support for additional research related to drug evaluation in older adults. A particular concern is the excessive exclusion of older patients because of concomitant illness or multiple drug therapies when such exclusion is not necessary. Assessing the impact of these factors is a critical aspect of evaluating drugs used in older adults.

To determine the best strategies to improve drug evaluation in older adults, FDA should consider additional research (including potential collaborations with external experts) to identify the diseases and/or drug classes in which age (or other factors such as comorbidities and polypharmacy) will make a clinically meaningful difference in terms of PD, safety, and/or effectiveness of drugs. These diseases and drug classes can then be the focus of efforts in developing specific recommendations on the evaluation of drugs in older adults.

Many stakeholders are involved in drug development and evaluation in addition to the FDA. For example, within the federal government, CDC tracks prevalence of diseases and changes in treatment patterns, the NIH has a crucial research role, and CMS plays a critical role in determining and providing coverage for new therapies. It is important to note that Medicare accounts for a significant portion of federal spending. It will be very beneficial if the federal agencies can work together to facilitate the generation of sufficient evidence to guide utilization of treatments in the large and growing population of older adults. To further improve drug evaluation in older adults, FDA and other federal agencies should collaborate with all stakeholders, including patients, caregivers of patients, patient advocacy groups, clinical investigators, academic institutions, healthcare providers and organizations, industry, and other international regulatory bodies. Our society will need to build an ecosystem to improve drug evaluation in older adults while considering the burden and cost of drug development and risks to trial participants and the risks to patients if appropriate evidence is not generated. It is essential that all stakeholders work together to further improve drug evaluation in older adults.

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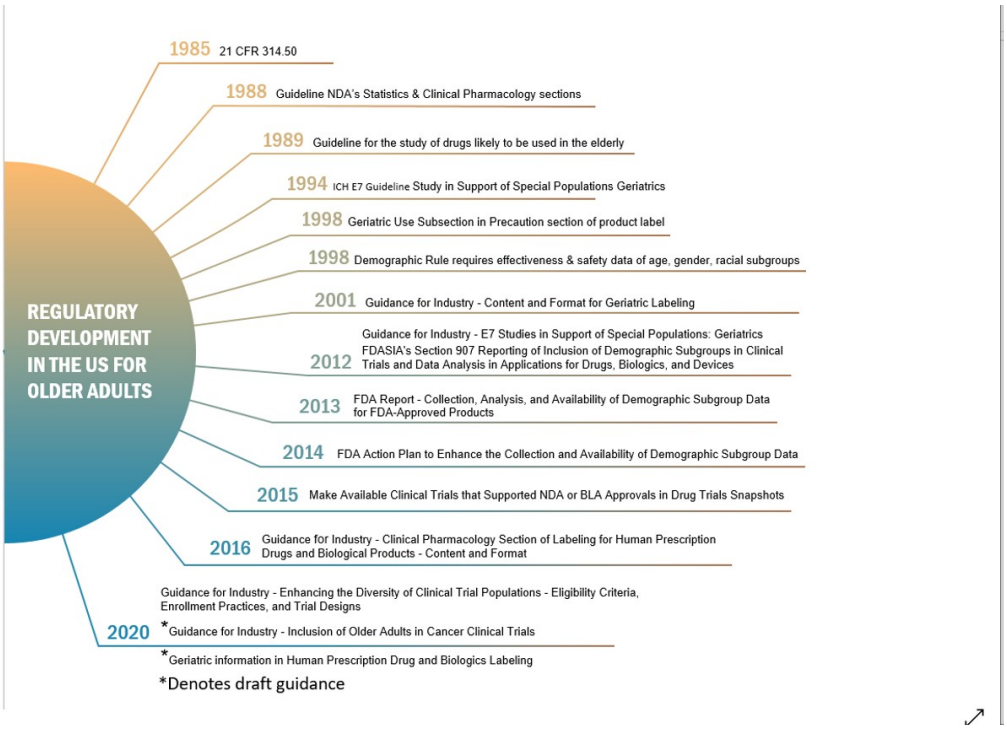
Figures Legends:

Figure 1. The history of relevant FDA regulations and guidances related to new drug evaluation in older adults

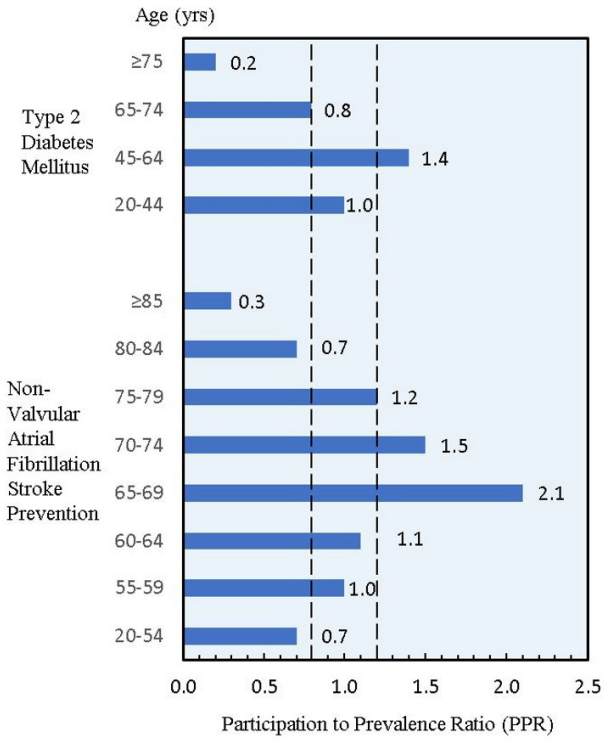
Figure 2. The ratio of older adults' participation in clinical trials relative to the corresponding prevalence disease population for two indications

The vertical axis represents the age groups of participants in clinical trials for the 2 indications. The horizontal axis represents the participation to prevalence ratio (PPR). PPR is calculated as the proportion of adults within a particular age subgroup that participated in the clinical trials divided by the estimated proportion of adults within the corresponding age group in the disease population.

Figure 3. Proposed action plan to improve new drug evaluation in older adults

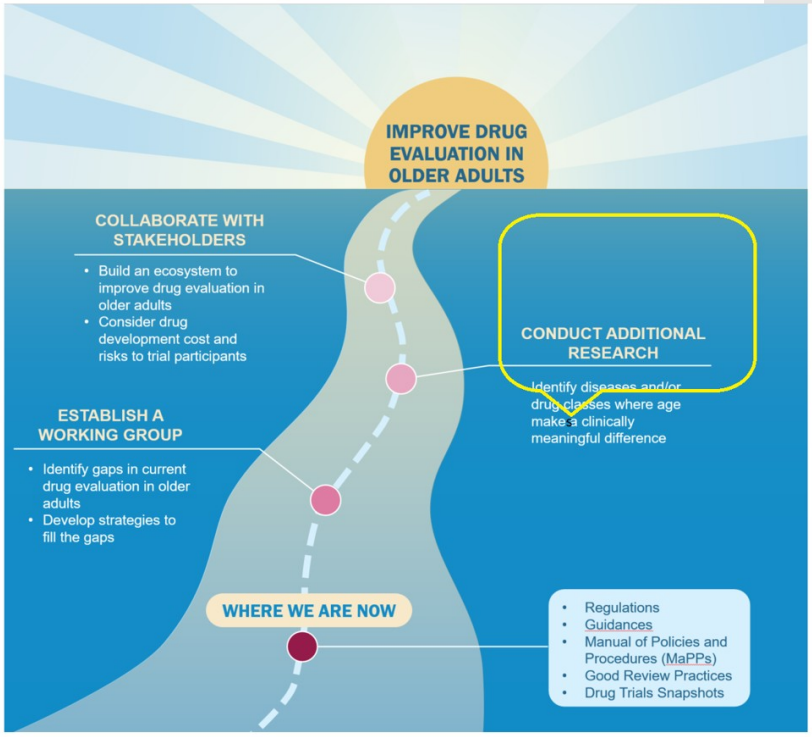


1058 Figure 1



1059 Figure 2

1060



1061 Figure 3