Inclusion of Older Adults in Cancer Clinical Trials

Guidance for Industry

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

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I. INTRODUCTION

This guidance provides recommendations regarding the inclusion of older adult patients in clinical trials of drugs[2] for the treatment of cancer. For the purpose of this guidance, older adults are those 65 years of age and older. Specifically, this guidance includes recommendations for including an adequate representation of older adults in cancer clinical trials to better enable evaluation of the benefit-risk profile of cancer drugs in this population. Most cancer trials do not have an upper age limit for exclusion; however, adults 75 years of age and older are underrepresented in cancer clinical trials.[3] The guidance emphasizes the particular importance of including adults 75 years of age and older in cancer clinical trials. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, responsible for the development and oversight of cancer clinical trials.

Enrolling an adequate representation of the range of patients in a clinical trial that may be exposed to a drug after approval is important. It provides the ability to understand the drug's benefit-risk profile across the patient population likely to use the drug in clinical practice (e.g., to identify whether there are differences in the benefits and/or risks of the drug in different populations). Including information in the labeling describing use in older adults may help promote the safe and effective use of these products in older adults and better inform treatment decisions in clinical practice.[4]

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[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
[2] For the purposes of this guidance, references to drugs includes drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).
[3] Singh H, Kanapuru B, Smith C, et al., 2017, FDA Analysis of Enrollment of Older Adults in Clinical Trials for Cancer Drug Registration: A 10-Year Experience by the U.S. Food and Drug Administration, JCO, 35:15 suppl, 10009-10009.
[4] See the draft guidance for industry *Geriatric Information in Human Prescription Drug and Biological Product Labeling* (September 2020). When final this guidance, will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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II. BACKGROUND

Adults 65 years of age and older, and especially those 75 years of age and older, are underrepresented in cancer clinical trials despite representing a growing segment of the population of cancer patients.[5,6] Therefore, obtaining more information is important to better inform treatment decisions for older adults with cancer. Cancer is a disease generally associated with age, with the number of cancer cases projected to multiply due to a rapidly aging U.S. population.[7] FDA is engaged with stakeholders to improve the representation of older adults in cancer trials.

The issue of older adults being underrepresented in clinical trials persists in oncology despite FDA's efforts to increase their inclusion in clinical trials. FDA has encouraged the inclusion of older adults in clinical trials, including through interaction with sponsors and through several guidance documents.[8,] In addition, FDA published a series of guidances that encourages sponsors to broaden cancer clinical trial eligibility criteria to enhance the generalizability of trial results and the ability to understand the drug's benefit-risk profile across the patient population likely to use the drug in clinical practice. One guidance in the series, *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020) is particularly relevant to older adults. This guidance encourages the inclusion of patients with organ dysfunction and with prior or concurrent malignancies, as appropriate, to better reflect the population that will use the drug in clinical practice. It also includes specific recommendations regarding the inclusion of patients with renal, cardiac, and hepatic dysfunction and of patients with prior or concurrent malignancy, all of which may increase with age.

Differences may exist between younger and older adult patients in drug response and toxicity due to age-related physiologic changes. For example, the pharmacokinetics of the drug, or the pharmacodynamic response to the drug, or both may vary between younger and older adult

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[5] Singh H, Kanapuru B, Smith C, et al., 2017, FDA Analysis of Enrollment of Older Adults in Clinical Trials for Cancer Drug Registration: A 10-Year Experience by the U.S. Food and Drug Administration, JCO, 35:15 suppl, 10009-10009.

[6] Smith BD, Smith GL, Hurria A, et al., 2009, Future of Cancer Incidence in the United States: Burdens Upon an Aging, Changing Nation, JCO, 27(17): 2758-65.

[7] Levit L, Singh H, Klepin H, Hurria A, 2018, Expanding the Evidence Base in Geriatric Oncology: Action Items from an FDA-ASCO Workshop, JNCI, 110(11): djy169.

[8] See the guidance for industry *Studies of Drugs Likely to be used in the Elderly* (November 1989), *E7 Studies in Support of Special Populations: Geriatrics* (August 1994) and *E7 Studies in Support of Special Populations: Geriatrics Questions and Answers* (March 2012) and *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs (November 2020).*

patients. In addition, older adults often have comorbidities and may be taking concomitant medications that could impact the efficacy of the cancer drug and may also impact the incidence and the severity and seriousness of an adverse reaction. It is important that the spectrum of older adults included in clinical trials are representative of the intended population, including those with physiological decline (e.g., frailty). Furthermore, there may be important differences in efficacy in older adult patients compared to the younger or general population, and information describing such differences should be conveyed to patients and healthcare providers where appropriate.

Geriatric (i.e., older adult) use information must be included in labeling, unless clearly inapplicable.[9] FDA's draft guidance for industry: *Geriatric Information in Human Prescription Drug and Biological Product Labeling* (September 2020)[10] assists applicants in determining the appropriate placement and content of geriatric information in labeling so that the information is clear and accessible to health care practitioners and includes content that guides the safe and effective use in geriatric patients. In addition, FDA's Drug Trials Snapshots[11] provides consumers with relevant information about the demographic profile of participants in key clinical trials that supported the original approval of new molecular entities and new biological products since 2015. Snapshots can also highlight differences, if applicable, in benefits and side effects among demographic groups, including, for example, differences based on age when a clinical trial includes a representative population of older adults. Demographic information may also be available on FDA's website within the posted product approval information.[12]

III. RECOMMENDATIONS

Clinical trials should include study populations reflecting the intended population that may receive the intervention being evaluated, if approved. In general, to achieve an unbiased estimate of treatment effect in the general population, sponsors should develop a strategy to enroll diverse populations, including different age groups, that are consistent with the intended use population. For most cancers, clinical trials should include a representative population of older adults.[13] Older adults, including those with physiological decline, should be enrolled in all phases of clinical trials when they can be safely and ethically enrolled.

Sponsors of cancer trials should consider the expected age range of their target population early in development. CDER and CBER are available to discuss plans for enrollment of older adults in cancer clinical trials, particularly when enrollment of adequate representation of older adults may be challenging.

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[9] See 21 CFR sections 201.56(d)(4), 201.57(c)(9)(v), and 201.80(f)(10).
[10] When final, this guidance will reperesent the FDA's current thinking on this topic.
[11] Available at https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots
[12] See Drugs@FDA.
[13] One source of data that may be considered when estimating the incidence of a cancer in older adults is the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, SEER Incidence database, available at https://seer.cancer.gov/data/.

A strategy regarding inclusion of older adults should include all known information including for example, prevalence of the condition, diagnosis and treatment patterns, prior relevant studies, and differences in outcomes related to safety or efficacy. The guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020) includes recommendations for inclusive trial practices, trial design and methodological approaches, and other study design and conduct considerations for improving enrollment that sponsors should consider regarding older adults.

To understand potential age-related differences that may be relevant to the clinical development of a cancer drug, FDA recommends the following:

A. Early Clinical Development

- Sponsors should enroll older adults, if appropriate, in early phase studies to obtain information on safety, exposure, and response to better inform the study design and dose selection of later phase studies.

- Sponsors should evaluate drug interactions early in drug development to allow enrollment of older adults who may otherwise be excluded because of their concomitant medication use.

- Sponsors should document co-morbidities and make every effort to safely include these patients as well as those with organ dysfunction and prior/concurrent malignancies.[14]

B. Clinical Trials

- *Trial design*

  Sponsors should make every effort to enroll a representative population of older adults in their pivotal randomized trials. To facilitate the enrollment of older adults in cancer trials, sponsors may consider flexible approaches to trial design, such as age-based stratification or analyses based on hypothesized efficacy differences in older adults compared to the younger adults participants (≤65 years) to allow a focused benefit/risk assessment. If the pivotal trials are not able to enroll a representative sample of older adult patients, alternative trial designs should be proposed. This may include an open-label safety study that can enroll and analyze an older adult population separately in a parallel arm of a trial. Additional considerations for this particular trial design can be found in the guidance for industry *Placebos and Blinding in Randomized Controlled Cancer Trials for Drug and Biological Products* (August 2019). In some cases, the older adult arm(s) can be actively accruing at the time of new drug application (NDA) or biologics license application (BLA) or supplement submission.

[14] See guidance for industry *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020).

An example of a possible trial design approach is a randomized controlled trial that enrolls younger and older adults and stratifies by age. The intent-to-treat (ITT) population consists of all enrolled patients, with the primary study hypothesis evaluating effectiveness in randomized patients under 75 years of age. Using a hierarchical testing strategy, after the primary analysis in patients under 75 years of age, subsequent analyses would be done in the ITT population to provide safety and efficacy information about all patients. If the size of the older patient population is adequate and powered to address the hypothesis, results in the older population can also be analyzed separately.

The design of the development program should reflect any important differences in a drug's benefit-risk balance in older adults compared to younger adults. In the design of the clinical development program, we recommend that sponsors consider perspectives of older adults, seeking input from patients and advocacy groups, as well as input from those caring for older adults such as clinicians and caregivers. This information can inform the design of the clinical trials, such as in assuring meaningful endpoints are selected, as well as in the conduct of the trial, such as in facilitating enrollment and retention of older adults.[15]

- *Develop recruitment strategies targeted to older adults*

  Clinical trials do not have an upper age limit for exclusion, however adults 75 years of age and older, continue to be underrepresented. FDA encourages sponsors and clinical trial cooperative groups to develop strategies to recruit patients that are reflective of the intended population. Possible challenges with recruiting older adults that could be mitigated, particularly among patients 75 years of age and older, include: location of clinical trial sites (e.g., sites in community-based settings may be more accessible to older adults than sites located in urban academic centers), format (e.g. digital) and content of informational material for the trial, caregiver support, accommodations needed for impairment (e.g., visual, mobility, etc.), and travel and other logistics. Where feasible, remote monitoring approaches should be considered.

  Sponsors should discuss specific goals for enrollment of older adults with clinical investigators and keep the clinical trial sites updated on the progress of enrolling older adults in the trial. Sponsors should discuss the importance of enrolling older adults during study training provided to the clinical sites. In addition, sponsors should consider getting input on trial design, trial conduct and recruitement strategies from geriatricians, geriatric oncologists, social and behavioral scientists with expertise in treating older adults. Additional input from patient advocates/navigators should also be sought.

- *Consider collecting additional information for older adults*

[15] See guidance for industry *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020).

Sponsors should prospectively consider information that should be collected for older adults that will be clinically informative and will provide an understanding of clinical outcomes in older adults. For example, in addition to collection of age and performance status, elements from geriatric assessment tools (e.g. functional status, cognitive function), and a comprehensive assessment of comorbidities should be considered during trial design.[16] Incorporating a patient reported outcome instrument(s) in cancer trials may encourage older adults to participate in clinical trials and the information obtained may inform future research.[17]

- *Consider additional strategies in adverse event monitoring and management*

  Older adult patients' experience with adverse events may differ from younger patients. Developing strategies to capture and manage adverse events in older patients (e.g., supportive care measures, involvement of geriatric oncologists and other health care professionals with expertise in treating older adults) may facilitate older patients completing the trial.

- *Report more discrete age subgroups*

  Because outcomes may differ by increasing age group in patients 65 years of age and older, sponsors should identify further age subgroups to understand the drug's benefits and risks.[18] For example, subgroups such as age 65 years to 74 years of age and 75 years of age and older may be relevant. A particular need exists for information in patients 75 years of age and older. Sponsors may consider combining data across trials of similar design to ensure adequate representation of older adults across discrete age subgroups. Reporting clinical trial data from older adults in a more standardized and granular way can be more clinically useful[19]. FDA's guidance for industry *Integrated Summary of Effectiveness* (October 2015) includes recommendations regarding subpopulation assessment and reporting in the NDA or BLA that are applicable to subgroups of older adults in cancer trials (see section III.D of that guidance).

C. Postmarket

- Ideally, adequate information on older adults should be captured in the premarket clinical trials. However, if older adults are not adequately represented in pre-market clinical trials, it may be appropriate to develop a plan to collect data on older adults in the postmarket setting. This could be accomplished with post-marketing trials examining a broader population, or through collection of real

[16] Singh H, Beaver JA, Kim G, Pazdur R, 2016, Enrollment of Older Adults on Oncology Trials: An FDA Perspective, JGO, 8: 149-50.
[17] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).
[18] See the guidance for industry *E7 Studies in Support of Special Populations: Geriatrics Questions and Answers* (March 2012).
[19] See footnote 16.

world data in an observational study or registry. In certain situations, FDA may require postmarket studies and clinical trials.[20] Sponsors should prospectively discuss their plan for collecting additional information in the postmarket setting with the CDER or CBER review division or office. Postmarket data may provide clinically useful information, that when appropriate, can be added to the *Geriatric Use* subsection of the labeling or other parts of the labeling.[21]

[20] See section 505(o)(3)(B) of the FD&C Act and draft guidance for industry *Postmarketing Studies and Clinical Trials-Implementation of 505(o)(3) of the Federal Food, Drug and Cosmetic Act* (October 2019). When final, this guidance will represent the FDA's current thinking on this topic

[21] See draft guidance for industry: *Geriatric Information in Human Prescription Drug and Biological Product Labeling* (September 2020). When final this guidance, will represent the FDA's current thinking on this topic.