Inclusion of Older Adults in Cancer Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Oncology Center of Excellence
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 aged 65 years 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. The guidance emphasizes the particular importance of including adults over age 75 years in cancer clinical trials. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, responsible for the development and oversight of clinical trials.

Enrolling an adequate representation of the range of patients in a clinical trial that may be exposed to a drug after approval can maximize the generalizability of the trial results. 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, risks, or both of the drug in different populations). Including information in the labeling describing use in older adults helps to promote the safe and effective use of these products and better informs treatment decisions in clinical practice.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Oncology Center of Excellence, 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).

II. BACKGROUND

Adults aged 65 years and older, and especially those over age 75, are underrepresented in cancer clinical trials despite representing a growing segment of the population of cancer patients.[3,4] Therefore, developing more information is important to better inform treatment decisions for older adults with cancer. Cancer is a disease associated with age, with the number of cancer cases projected to multiply due to rapid aging of the U.S. population.[5] FDA is engaged with stakeholders to improve the representation of older adults in cancer trials.

The issue persists in oncology despite FDA's efforts to increase the inclusion of older adults in clinical trials. FDA has encouraged the inclusion of older adults in clinical trials, including through several guidance documents.[6] In addition, FDA published a series of draft guidances that would encourage sponsors to broaden cancer clinical trial eligibility criteria to maximize 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 draft guidance in the series, *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies*,[7] is particularly relevant to older adults. The draft guidance would encourage 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. The draft guidance includes specific draft 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 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 patients. In addition, older adults often have comorbidities and may be taking concomitant medications that could impact the efficacy of either the cancer drug or other drug(s) they are taking, and may also impact the incidence and the severity of adverse events. 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

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[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] 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.

[5] 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.

[6] See the guidance for industry *Guideline for the Study of Drugs Likely to Be Used in the Elderly* (November 1989), guideline for industry *Studies in Support of Special Populations: Geriatrics* (ICH E7) (August 1994), guidance for industry *Content and Format for Geriatric Labeling* (October 2001), guidance for industry *E7 Studies in Support of Special Populations: Geriatrics Questions and Answers* (February 2012), and draft guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (June 2019). 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.

[7] March 2019. When final, this guidance will represent the FDA's current thinking on this topic.

in efficacy in older 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.[8] FDA's guidance for industry *Content and Format for Geriatric Labeling* describes the content and format of geriatric use information in labeling for human prescription drug and biological products to guide their safe and effective use in geriatric patients. In addition, FDA's Drug Trials Snapshots[9] is an effort to make demographic data, including age, more available and transparent by providing consumers with information about the demographic profile of the clinical trial participants for new molecular entities and biologics approved in 2015 and later. Demographic information may also be available on FDA's website within the posted product approval information. In particular, Snapshots can highlight differences 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.

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.[10] Older adults, including those with frailty, should be enrolled in all phases of clinical trials, when they can be safely and ethically enrolled.

Sponsors of cancer trials should consider the age demographics 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.

A strategy regarding inclusion of older adults should be informed by any known information for older adults, including for example, prevalence of the condition, diagnosis and treatment patterns, prior relevant studies, and differences in outcomes related to safety or efficacy. The draft guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* includes draft 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.

[8] See 21 CFR sections 201.56(d)(4), 201.57, and 201.80.

[9] Available at https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots

[10] 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/.

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

B. Clinical Trials

- *Trial design*

  Sponsors should make every effort to enroll older adults in their pivotal randomized trials. To encourage and facilitate the enrollment of older adults in cancer trials, FDA is available to discuss flexible approaches to trial design and analysis. For example, it may be acceptable to design a trial with stratification based on age, so that analyses can focus on benefits and risks among older adults. Alternatively, an open-label safety study can enroll and analyze an older adult population separately in a parallel arm of a trial. In some cases, the older adult arm(s) can be actively accruing at the time of NDA or BLA submission.

  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, a modified ITT (MITT) consists only of the patients under 75 years of age. The trial would use hierarchical testing, and the primary analysis would be conducted in the MITT population, with subsequent analyses in the ITT population to provide safety and efficacy information about all patients. If the size of the older patient population is adequate and hypothesis driven, results in the older population can also be analyzed separately.

  Distinctive benefit-risk considerations should be considered during drug development for older adults. We recommend that sponsors consider perspectives of older adults, including those of patients and patient and caregiver partners, clinicians, and advocacy groups, during the design of the clinical trial protocol to ensure patient preferences are incorporated in clinical trial activities, when possible, to facilitate enrollment of older adults as well as improve identification of meaningful endpoints and overall trial design.[11]

[11] See draft guidance for industry *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic.

- *Develop recruitment strategies targeted to older adults*

  In general, most cancer trials do not have an upper age limit for exclusion, however, older adults, particularly adults 75 years and older continue to be underrepresented in these trials. 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 over 75 years, 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 and content of informational material for the trial, caregiver support, accommodations needed for impairment (e.g., visual, mobility, cognitive, etc.), and travel and other logistics.

  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 recruitment of geriatric oncologists and oncologists with expertise in treating older adults.

- *Consider collecting additional information for older adults*

  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, such as functional status and cognitive function, or frailty measures and a comprehensive assessment of comorbidities should be considered during trial design.[12] 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.[13]

- *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 health care professionals with expertise in treating older adults) may facilitate older patients completing the trial.

[12] Singh H, Beaver JA, Kim G, Pazdur R, 2016, Enrollment of Older Adults on Oncology Trials: An FDA Perspective, JGO, 8: 149-50.

[13] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

- *Develop and report more discrete age subgroups*

  Because outcomes of cancer patients aged 65 and older may vary by age, sponsors should identify subgroups within the population of patients aged 65 and older for analysis, as relevant, to best understand the drug's benefits and risks in older adults. For example, subgroups such as age 65 years to 74 years and 75 years and older may be relevant. A particular need exists for evidence in patients older than 75 years. Reporting clinical trial data from older adults in a more standardized and granular way can be more clinically useful.[14] 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 world data in an observational study or registry. In certain situations, FDA may require postmarket studies and clinical trials.[15] 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 section of the labeling.

[14] See footnote 12.

[15] See the draft guidance for industry *Postmarketing Studies and Clinical Trials- Implementation of Section 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.