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Report on Research Compliance Volume 17, Number 5. April 23, 2020 Draft Guidance to Increase Seniors in Cancer Trials a 'Good First Step'

By Theresa Defino

Study sponsors should be making additional efforts to enroll older individuals in cancer trials, incorporating such strategies in study design and recruitment methods, and as part of postmarket studies. This is because those 65 and older are underrepresented in pre-market research, according to new draft guidance published by the Food and Drug Administration (FDA).[1]

Open for comment until later this month, at least one advocacy group is encouraged by the draft guidance but notes that even more needs to be done, including legislatively. Still, despite being in draft form, the proposed guidance can prove instructive to investigators as they design studies and to institutional review boards as they ponder whether research reflects the intended beneficiaries.

"It's a very good first step," Susan Peschin, president and CEO of Alliance for Aging Research, said of the draft guidance. "It sends a strong message to oncology clinical development programs that they should be deliberate in their recruitment efforts to enlist a group of older adults that reflects the intended population for the treatment being studied and evaluated." The alliance is an advocacy and lobbying group "dedicated to accelerating the pace of scientific discoveries and their application to vastly improve the universal human experience of aging and health."

The draft guidance isn't FDA's first attempt at promoting the enrollment of older individuals, which it defines as aged 65 and older, with particular concern given to recruiting those over age 75. It was issued by FDA's Oncology Center of Excellence, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

FDA: Underenrollment 'Persists'

The first part of the draft guidance makes the case for including the elderly; then it offers some recommendations for doing that.

As FDA notes, 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," and those in these age groups "are under-represented in cancer clinical trials." This issue, FDA said, "persists" despite the agency's efforts to date.

Having diverse and "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," FDA explained. "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."

Specifically, younger and older individuals may evidence different responses 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," FDA said.

Additionally, "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," the draft guidance states. "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 patients compared to the younger or general population, and information describing such differences should be conveyed to patients and healthcare providers where appropriate."

Previous Guidance Also Addressed Seniors

And, from a practical perspective, FDA points out that information about older adult use must already be included in labeling, "unless clearly inapplicable." If sponsors aren't collecting this data during trials, adding it to labeling would be nearly impossible.

The agency also points out that older adults should be enrolled in all phases of trials.

Accomplishing this requires planning from the start, according to FDA—and the agency is also willing to help. Officials from 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."

The agency already issued draft (though never finalized) guidance documents to "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."

In particular, FDA cited its March 2019 draft guidance, Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies, as "particularly relevant to older adults."[2]

According to the new draft guidance, last year's specifically encouraged the inclusion of research subjects "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 included "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."

Similarly, FDA issued draft guidance, Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs,[3] which the new draft guidance said offers "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."

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," FDA said.

For clinical research, FDA offered recommendations related to trial design, recruitment strategies, the collection of additional information about older adults, consideration of adverse event monitoring and management, and development and reporting on more discrete age subgroups.

Convenient Locations Increase Enrollment

To ensure that sponsors include older adults in "pivotal randomized trials," FDA said it was willing to consider

certain "flexible approaches to trial design and analysis." A trial "with stratification based on age" could allow analysis to "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," FDA said.

Also as part of trial design, FDA officials "recommend that sponsors consider perspectives of older adults, including those of patients and patient and caregiver partners, clinicians, and advocacy groups…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."

FDA pointed out that while there are obstacles to enrolling older individuals, they can be overcome.

"Possible challenges with recruiting older adults that could be mitigated, particularly among patients over 75 years, include: location 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."

Aside from its own recommendations, FDA said it "encourages sponsors and clinical trial cooperative groups to develop strategies to recruit patients that are reflective of the intended population."

FDA's concluding recommendations addressed postmarket data collection. "Ideally, adequate information on older adults should be captured in the premarket clinical trials. However, if older adults are not adequately represented in premarket clinical trials, it may be appropriate to develop a plan to collect data on older adults in the postmarket setting," FDA said. "This could be accomplished with postmarketing trials examining a broader population, or through collection of real-world data in an observational study or registry."

The agency noted that in "certain situations" it may mandate studies and clinical trials that are postmarket. "Sponsors should prospectively discuss their plan for collecting additional information in the postmarket setting with the CDER or CBER review division or office," FDA said, adding, "Postmarket data may provide clinically useful information that, when appropriate, can be added to the geriatric use section of the labeling."

More Transparency, Details Urged

Peschin, with the alliance, told *RRC* the draft guidance was unexpected but welcome.

"We appreciate that the Oncology Center of Excellence recommends inclusion of older adults in all stages of clinical development, and that the [draft] guidance addresses the need for sponsors to develop recruitment strategies specific to older adults," Peschin said. "We also support the recommendations to use geriatric assessment tools within trials, and to prospectively discuss postmarket studies."

The draft guidance also may have an impact within FDA, she said, as it "sends a broader message to other divisions within CDER and other FDA centers that, for conditions that disproportionately impact older adults, their representation in clinical trials matters to the agency."

In addition to what FDA is recommending, Peschin said more transparency is needed for how drugs and devices perform once they are in use.

"We would like to see the agency require the publication of postmarket studies on older adult patients so that the public may benefit from the additional knowledge gained, not just the sponsor and agency," she said. "Postmarket data may impact patient decision-making regarding risk-benefit as well as treatment choice."

She added that although the group supports FDA's "recommendation to develop and report on age subgroups," the agency needs to provide more details.

"For example, there are studies going on in areas such as heart valve disease and atrial fibrillation that include older adults 90 and above. Metabolism and immune system response [change] with age, so further subgrouping in oncology may be warranted," Peschin said. "Additionally, measures that can gauge biological age are likely more useful than chronologic age since humans vary in rates of aging biologically. Ultimately, we would like to see an FDA-wide guidance like this for all medical products meant to treat conditions that primarily impact older adults."

Peschin: Mandate Older Adult Enrollment

At the point that *RRC* spoke to Peschin, she wasn't sure whether the group would comment on the draft guidance. "We are considering a comment that would praise the effort and offer some constructive feedback," she said.

Looking beyond FDA, Peschin has previously advocated for legislative mandates to include older individuals in clinical trials. That position is likely still necessary, as guidance is limited in its impact and does not have the force of law.

As Peschin put it, "FDA guidance is not a mandate, only a reflection of FDA's thinking on a given issue. A mandate will be needed to ensure that clinical trials enlist adequate proportions of older adults equivalent to their representation in the condition-specific patient population."

Should Congress give FDA the authority to mandate enrollment of older adults, it could deny applications that don't comply, she added.

RRC asked Peschin what investigators and sponsors could do now to improve this situation. "Typically, sponsors have focused on the disease-specific communities for recruitment," she said. "There is a large and thriving aging network that has yet to be engaged on clinical trial recruitment."

The comment deadline for the draft guidance is May 5. Any extension of a deadline is announced in the *Federal Register.* Organizations that need more time may still comment past that date, as FDA allows commenting on "any guidance at any time."

1 FDA, "FDA In Brief: FDA Encourages Inclusion of Older Adult Patients in Cancer Clinical Trials," news release, March 5, 2020, https://bit.ly/3a3Il2i.
2 Cancer Clinical Trial Eligibility Criteria: Patients With Organ Dysfunction or Prior or Concurrent Malignancies; Draft Guidance for Industry; Availability, 84 Fed. Reg. 9,129 (March 13, 2019) .
3 Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry; Availability, 84 Fed. Reg. 26,687 (June 7, 2019) .