

November 15, 2024

Dr. Lola Fashoyin-Aje, Oncology Center of Excellence
Dr. Sandra Casak, Center for Drug Evaluation and Research
Mr. James Myers, Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

RE: ACRO comment submission:
*Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical
Development Programs*
[FDA-2024-D-3163]

Dear Dr. Fashoyin-Aje, Dr. Casak, and Mr. Myers,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and clinical technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support a majority of all biopharmaceutical sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO members have extensive breadth and depth of experience in operationalizing global clinical development programs (CDPs) on behalf of sponsors – including identifying potential regions, countries, and individual sites for clinical studies. In addition to ACRO member expertise in managing multiregional clinical trials (MRCTs) that are part of global CDPs, ACRO advances diversity, equity and inclusion in the clinical research ecosystem through its Diversity and Inclusion Committee.

General Comments and Recommendations:

ACRO thanks the Agency for releasing the draft guidance on *Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs*. We welcome this guidance and the acknowledgment of the need to balance the numerous benefits and efficiency gains of MRCTs with ensuring applicability of the evidence generated to US patients and US clinical practice.

ACRO appreciates the need for applicability of clinical trial results to real-world populations. We agree that reflecting the intended populations within the clinical trial population is key. However, there are multiple factors which result in the need for a highly complex set of decisions regarding region and site selection for inclusion in clinical trials. Examples of these include the following:

- **Statistical considerations for oncology studies:**
Robust prespecified planning of statistical analyses will mean that there are constraints on the ability of clinical study teams to increase or decrease subpopulations within trials. The increasing use of Bayesian methodologies within oncology programs is adding further complexities to statistical plans and decisions around patient allocations to individual countries.
- **Simultaneous global regulatory submissions:**
ACRO members are asked to develop clinical trial plans which meet the need of regulators across multiple regions. This is so that, subject to meeting regulatory requirements, new medicines can be made available to patients in multiple regions as quickly as possible.
- **Standard of care:**
As noted in the guidance, the standard of care varies in different countries. When a certain medicine is included in the clinical trial protocol but is not available in a country, this may exclude the country from inclusion in a study, or require the sponsor to provide the standard of care medicine as part of the trial (which increases complexity of the trial from a number of aspects). This may also impact the potential patient population in terms of including patients who are naïve to certain treatment modalities, which may be relevant.
- **Biomarker status:**
Different countries will have different approaches to biomarker testing which may impact selection decisions.
- **Availability of investigators and patients for new studies:**
ACRO members have reported a generalized issue with saturation of clinical trial sites for oncology studies in the US. US sites are turning down the opportunity to participate in studies. This means that sponsors and CROs need to conduct studies across different regions in order to ensure sufficient patient numbers. While sponsors may consider research-naïve sites in the US for oncology trials there are several concerns that make sponsors hesitant to include such sites. For example, new sites may require significant training, recruitment rates are often uncertain, a track record of good compliance may be absent, and there may be a need for more intensive monitoring.

Because of concerns about US clinical trial site capacity, ACRO would support activities to enable capacity building in the US in terms of numbers of sites, the capability of sites to conduct trials, and the capability of sites to engage patients from diverse populations. In addition, flexibility in the use of decentralized models through the use of local health care professionals could potentially assist with the site capacity.

Line-specific comments:

Section III A. U.S. Population Representativeness in the MRCT (Lines 163-185)

ACRO notes the recommendation regarding adequate regional representativeness and the use of “a strategic allocation approach that is based, in part, on the incidence or prevalence of the cancer in the U.S., with regions characterized on the basis of major geographical regions (e.g., Africa, Asia, Europe, North America) rather than single countries.” We note the guidance’s elaboration that “strategic allocation” of study

participants can take two forms. Equal allocation is defined as “allocation of equal numbers of subjects to each region” and that proportional allocation is defined as “allocation of subjects to regions in proportion to size of region and disease prevalence.”:

- “For trials of drugs intended to treat cancers that are common in the U.S. such as colorectal cancer or breast cancer, FDA recommends *equal allocation* of study participants across the selected major geographical regions, including North America.” and that “For trials of drugs intended to treat cancers that occur much less commonly in the U.S. compared to regions outside the U.S. (e.g., squamous cell esophageal cancer), FDA recommends a *proportional allocation* approach.” [lines 169-172]
- “For trials of drugs intended to treat cancers that occur much less commonly in the U.S. compared to regions outside the U.S. (e.g., squamous cell esophageal cancer), FDA recommends a *proportional allocation* approach. Key considerations in assessing the appropriateness of this approach would be whether the drug’s effect may be altered based on factors that may differ across regions such as disease etiology (e.g., viral etiology in hepatocellular carcinoma) or disease subtype (e.g., keratinizing vs. non-keratinizing nasopharyngeal carcinoma), or differences in treatments received before the clinical investigation. However, when using a proportional allocation approach, there still may be important differences across the trial population (e.g., different risk factors in major geographical regions) that may lead to a narrower indication that reflects the population studied.” [lines 174-185]

As noted earlier, there are multiple factors which result in the need for a highly complex set of decisions regarding region and site selection for inclusion in clinical trials. ACRO thanks the Agency for the flexible approach reflected through many sections of this draft guidance as this flexibility is vital in helping sponsors navigate the complexity of oncology global clinical development programs in the US. ACRO asks the Agency to consider explicitly applying this flexible approach to the guidance discussion of “strategic allocation” and the document’s specific recommendations regarding the application of the concepts of “equal allocation” and “proportional allocation.”

Section III B Considerations for U.S. and Foreign Site Selection (Lines 219-227)

ACRO notes that “Sponsors are encouraged to select clinical sites with investigators who have experience conducting clinical trials intended to support regulatory submissions” and that “While investigators lacking such experience should not necessarily be excluded from participation as site investigators, sponsors should ensure that inexperienced investigators and research staff have the resources to aid in adherence to the protocol and to good clinical practice.”

In order to be consistent with the aim of ensuring demographic representativeness within trials, ACRO would recommend consideration of the wider context of historical and current barriers to participation, in particular limited numbers of investigators who can help enroll underrepresented subgroups. ACRO supports the requirement that “inexperienced investigators and research staff have the resources to aid in adherence to the protocol and to good clinical practice” but would recommend that the use of inexperienced investigators is not discouraged. As such ACRO would recommend an amendment to line 224-227 to read “Sponsors should ensure that inexperienced investigators and research staff have the resources to aid in adherence to the protocol and to good clinical practice.”



ACRO thanks the Agency for this opportunity to comment on draft Guidance on *Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs*.

Please do not hesitate to contact ACRO if we can provide further details or answer any questions (knoonan@acrohealth.org).

Respectfully submitted,

A handwritten signature in dark blue ink that reads "Karen A. Noonan". The signature is written in a cursive, flowing style.

Karen A. Noonan
Senior Vice President, Global Regulatory Policy