Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Oncology Center of Excellence (OCE)
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to sponsors who are planning global clinical development programs for drugs[2] intended to treat cancer, on improving the evidence obtained from one or more multiregional clinical trials (MRCTs) intended to support a marketing application. This guidance expands on principles described in FDA's existing guidance documents related to this topic,[3,4] by providing additional recommendations for the planning, design, conduct, and analysis of an oncology MRCT that may facilitate FDA's assessment of applicability of the data to the U.S. population with the cancer being investigated and to U.S. medical practice.[5]

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 (OCE) in collaboration with the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drug* or *drugs* include both human drug products and biological products regulated by CDER and CBER, unless otherwise specified.

[3] See the guidance for industry: *E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data – Questions and Answers* (September 2006). We update guidances periodically. For the most recent versions of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See the guidance for industry: *E17 General Principles for Planning and Design of Multiregional Clinical Trials* (July 2018).

[5] See 21 CFR 314.106(b)(1).

II. BACKGROUND

FDA guidance defines a multiregional clinical trial (MRCT) as "a trial that is conducted in more than one region under a single protocol," with "region" defined as a geographical region, country, or regulatory region.[6] The paramount consideration for FDA when evaluating such oncology trials is whether the results are applicable to the intended use population in the U.S., and to U.S. standard oncological care. Therefore, when planning a multiregional clinical development program (CDP), which includes all clinical trials intended to support approval in the U.S., including pivotal trials, the evidence generated should be derived from study populations that enable the results to be interpretable in the context of U.S. patients with the disease or condition and U.S. medical practice.

In oncology MRCTs, there has been decreasing proportion of U.S. participants included in these trials; this can limit the assessment of treatment effect consistency between U.S. enrolled participants and the effect observed for the overall study population in the MRCT. Additionally, the distribution of demographic characteristics or clinical characteristics of participants enrolled in these trials may differ significantly from the U.S. population such that foreign data may not be appropriate to support an FDA regulatory decision.[7] These and other factors can impact FDA's assessment of the generalizability and applicability of the results from such trials to the U.S. population or to U.S. medical practice.

FDA has identified a need for additional guidance to address questions raised by sponsors and other interested parties about demographic representativeness of the U.S. population in oncology MRCTs.[8,9] FDA is providing more detailed recommendations for MRCTs conducted to provide the evidence to support the safe and effective use of cancer drugs in the U.S. population. FDA recognizes the challenges that sponsors may face in designing trials that must meet the requirements of various regulatory agencies. The recommendations herein are intended to help sponsors improve the planning, design, conduct, and analysis of oncology MRCTs to simultaneously achieve the efficiency that MRCTs can provide while also generating the data necessary to evaluate the trial's results in the context of U.S. patients who have the cancer for which the drugs are being developed.

While not all CDPs may be appropriate to conduct in a multiregional fashion, in the appropriate setting, well-designed and executed multiregional CDPs that include MRCTs can:

- facilitate the investigation of new drugs in a study population that may vary in risk factors for the disease or how it is treated. This can help generate evidence to support the safe and effective use of the drug in multiple regions with diverse patient populations.

[6] See footnote 4.

[7] See 21 CFR 312.120 and 21 CFR 314.106.

[8] See the guidance for industry: *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

[9] See Fashoyin-Aje L, Beaver J, and Pazdur R, 2021, Promoting Inclusion of Members of Racial and Ethnic Minority Groups in Cancer Drug Development, JAMA Oncol, 7(10):1445-1446.

- enable early identification of factors that may predict regional differences in outcomes that could inform the design of MRCTs; this can increase the likelihood of success and better tailor treatments to the intended use population.

- improve the feasibility of conducting trials for drugs intended to treat rare diseases or diseases that may be rare in one region but occur more commonly in others; this can facilitate earlier access to drugs that address an unmet medical need in the region where the disease is rare.

- promote multiple efficiencies in the clinical development process by reducing the number of trials conducted separately in each region; this can potentially enable parallel marketing application submissions to global regulatory authorities and expedite access to innovative drugs for all.

For these reasons, multiregional oncology trials are encouraged in the appropriate context. Marketing application submissions that rely on data from MRCTs can provide the basis for FDA approval,[10,11] provided that such data are applicable to the U.S. patient population and U.S. medical practice and other criteria for approval are met. FDA's determination of the applicability of the data to U.S. patients in the context of U.S. medical practice includes an assessment of the impact of both intrinsic and extrinsic factors[12] on study outcomes. Therefore, when planning, designing, conducting, and analyzing MRCTs, sponsors should carefully consider the factors that may impact the trials' outcomes.

III. RECOMMENDATIONS

Sponsors should ensure that the results of their CDP, including the MRCT, will be applicable to the U.S. population that will take the drug if approved and to U.S. medical practice. Sponsors should carefully consider whether a CDP conducted using a multiregional approach is appropriate in the context of scientific, clinical, and other factors. For example, known differences in the prevalence, presentation, etiology, or severity of a cancer may exist across countries or regions and can impact applicability to the U.S. population and to U.S. medical practice. Sponsors should at a minimum, take into account the following factors, when assessing the appropriateness of a CDP that includes multiregional clinical trials for a particular drug and clinical setting:

- patient-related factors (e.g., exposure to disease risk factors, genetic ancestral background).

[10] For MRCTs that are not conducted under an investigational new drug application (IND), see 21 CFR 312.120.

[11] For MRCTs that are not conducted under an IND, see the guidance for industry and FDA staff: *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions* (March 2012).

[12] See footnotes 3 and 4.

- disease-related factors (e.g., prevalence of disease subtypes, the frequency and distribution of certain molecular drivers of oncogenesis in the population).

- healthcare system factors (e.g., access to health care, including specialized oncology care, cancer screening practices, availability and affordability of cancer treatments)[13,14,15,16] which can impact prior treatments received and available treatments following the clinical investigation.

- socio-cultural factors (e.g., diets, cultural beliefs regarding use of "alternative" therapies to treat cancer).

Because the above referenced factors have the potential to impact the clinical outcome of an MRCT, sponsors should carefully evaluate them as part of the feasibility assessment for their CDP. The recommendations below address a non-exhaustive list of issues that sponsors should consider when planning a multiregional CDP to ensure that the results of the MRCT(s) are applicable to the U.S. population and to U.S. medical practice.

A. U.S. Population Representativeness in the MRCT

To permit an assessment of the intrinsic and extrinsic factors[17] that may affect clinical outcomes, careful consideration of the trial population enrolled is paramount. Given that differences in outcomes within subgroups of individuals enrolled across regions may only become apparent after the trial is complete and fully analyzed, sponsors planning a MRCT intended to support approval of an oncologic drug should plan to enroll a sufficient number of U.S. participants in the trial to help ensure that the evidence generated supports a robust assessment of the safety and effectiveness of the drug in U.S. patients with the disease and in the context of U.S. standard of care practices and treatments.

- If the sponsor's intent is to conduct a multiregional CDP, early-stage (i.e., pharmacokinetic/pharmacogenomic, dose-finding, activity-estimating) studies should be conducted in a population that reflects the diversity of the intended regions to be represented in the trial, to the extent possible. These studies can help identify early signals of differential drug effects across the population. For example, such studies could provide preliminary information regarding the impact of factors such as

[13] Zhou W and Christiani D, 2011, East Meets West: Ethnic Differences in Epidemiology and Clinical Behaviors of Lung Cancer Between East Asians and Caucasians, Chin J Cancer, 30(5):287-292.

[14] Wong KCW, Hui EP, Lo KW, Lam WKJ, Johnson D, Li L, Tao Q, Chan KCA, To KF, King AD, Ma BBY, and Chan ATC, 2021, Nasopharyngeal Carcinoma: An Evolving Paradigm, Nat Rev Clin Oncol, 18(11):679-695.

[15] Bickenbach K and Strong VE, 2012, Comparisons of Gastric Cancer Treatments: East vs. West, J Gastric Cancer, 12(2):55-62.

[16] Barrios C, de Lima Lopes G, Yusof MM, Rubagumya F, Rutkowski P, and Sengar M, 2023, Barriers in Access to Oncology Drugs – A Global Crisis, Nat Rev Clin Oncol, 20(1):7-15.

[17] See footnotes 3 and 4.

pharmacokinetics, diet, use of alternative medicines, pharmacogenetics, race, age, ethnicity, and sex on clinical outcomes and can inform the design of a future MRCT. However, because the impact of intrinsic and extrinsic factors on a drug's effects may not be identifiable in these early studies due to their small sample sizes, the absence of observed differences should not be considered adequate justification to limit the conduct of a trial to a single non-U.S. country or region.

- FDA recognizes that a thoughtfully designed multiregional CDP can facilitate enrollment of foreign participants with diverse genetic ancestral backgrounds (e.g., Indigenous American, African, Asian, and European ancestries), that may be scientifically and clinically relevant to the U.S. population. However, because there may be limitations or challenges in characterizing an individual on the basis of genetic ancestry,[18] sponsors should aim to enroll an adequately representative subgroup of U.S. participants in a MRCT to allow for a robust assessment of the drug's safety and efficacy in this subgroup relative to the overall MRCT study population. Sponsors should prospectively plan the distribution of clinical sites in a MRCT to achieve enrollment of a population that adequately represents the U.S. population affected with the cancer indication being studied.

- FDA guidance describes several approaches to regional allocation in the planning of a MRCT and for subpopulation analyses.[19] As a general consideration for what may be considered adequate regional representativeness, FDA recommends a strategic allocation approach that is based, in part, on the incidence or prevalence of the cancer in the U.S.,[20] with regions characterized on the basis of major geographical regions (e.g., Africa, Asia, Europe, North America) rather than single countries.

  - 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*[21] of study participants across the selected major geographical regions, including North America.

  - 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*[22] approach. Key

[18] For the purposes of this guidance the term *genetic ancestry* refers to information about the people that an individual is biologically descended from, including their genetic relationships.

[19] See footnote 4.

[20] Examining incidence and prevalence information in national registries and databases (e.g., the Surveillance, Epidemiology, and End Results (SEER) Program) can aid in determining an appropriate sample allocation approach.

[21] See footnote 4. For the purposes of this guidance *equal allocation* is defined as allocation of equal numbers of subjects to each region.

[22] See footnote 4. For the purposes of this guidance *proportional allocation* is defined as allocation of subjects to regions in proportion to size of region and disease prevalence.

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.

- It may be acceptable for a sponsor to conduct an MRCT that will enroll a substantial proportion of participants in a single foreign geographical region if such a trial is conducted as part of an overall program that includes one or more additional pivotal trials in the premarket setting that will enroll a population that is representative of the U.S. population. Such an approach should be discussed with FDA in early clinical development, preferably prior to initiating any of the pivotal studies.

B. Considerations for U.S. and Foreign Site Selection

- In general, if planning a single oncology MRCT to support approval, FDA recommends that such a trial be conducted across major geographical regions (e.g., across several continents) rather than predominantly in a single country or in a single geographical region (e.g., Asia).

- When discussing the trial design and trial population characteristics with FDA, sponsors should provide justification for the selected geographical regions and the sample size allocation distribution across the geographical regions. Information to be included in the briefing documents to aid FDA's assessment of the sponsor's justification should include, but is not limited to, a description of differences and similarities across the proposed geographical regions with respect to patient-, disease-, and healthcare system-related factors.

- During the MRCT planning stage when determining which major geographical regions (and countries within these regions) to include in the MRCT, sponsors should review available data and information to understand whether regional differences or similarities exist (i.e., with respect to patient-, disease-, and healthcare system-related factors) for the regions under consideration. When evaluating such data and information, an important consideration is whether the data and information are based on a population that represents the current demographic and clinical characteristics of the population with the disease, and the current treatment landscape in the U.S. to avoid drawing erroneous conclusions.

- Sponsors should consider whether individual clinical trial sites have a record for complying with applicable laws and regulations covering good clinical practice.[23] Sponsors are encouraged to select clinical sites with investigators who have experience conducting clinical trials intended to support regulatory submissions; for non-U.S. sites, this could include clinical trial sites in International Council on Harmonization (ICH) regions.[24] 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.

- Sponsors should consider how each clinical trial site may contribute to achieving demographic representativeness for the overall trial's study population. As appropriate, sponsors should explore the possibility of establishing clinical trial sites in non-traditional settings (e.g., community hospitals, community cancer centers) as an approach that can help improve opportunities to enroll a representative study population. As an additional measure, sponsors should consider a clinical site's past track record in enrolling participants with specific demographic characteristics in oncology clinical trials when selecting clinical trial sites.

- Clinical trial sites are subject to onsite inspections should FDA deem such inspections to be necessary.[25] If circumstances beyond the sponsor's control lead to potential challenges in FDA accessing a site, sponsors should promptly notify the appropriate FDA oncology review division.

C. Disease, Available Treatment, and Medical Product Considerations

- Sponsors should consider regional differences in the disease characteristics such as incidence, prevalence, risk factors, age at presentation, distribution of cancer histologies, available treatments, etc., when deciding whether the CDP should follow a multiregional approach. If a cancer subtype is the predominant presentation of the disease in the U.S., sponsors should select clinical trials sites that will permit the evaluation of the investigational agent in a substantial proportion of patients with that cancer subtype.

- Assessment of available standard of care treatment at foreign sites should include an evaluation of the availability of treatments to include in the control arm of an MRCT; this information should be provided to FDA during the planning stages of the trial. Treatments included in the control arm of the MRCT should reflect standard of care in the U.S. to ensure that the trial results are applicable to the U.S. population. FDA recognizes that the standard of care in foreign sites may not align with the U.S. In these circumstances, sponsors should consider whether the control arm can include pre-

[23] See the guidance for industry: *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

[24] See International Council on Harmonization membership at https://www.ich.org/page/members-observers.

[25] See 21 CFR 312.58, 312.68, 312.120, and 314.106.

specified physician's choice of treatment that includes the U.S. standard of care; the proportion of participants receiving the U.S. standard of care in the control arm of the MRCT should be sufficiently large to permit a robust evaluation of the safety and efficacy of the investigational agent compared to the U.S. standard of care.

- In some situations, treatment options that may be considered for the control arm, do not comprise the standard of care in the U.S. FDA recommends that the preferred U.S. standard of care is used in the MRCT, whenever possible, to facilitate the interpretation of study results in the context of current medical practice. FDA recognizes that the treatment landscape may evolve during the conduct of an MRCT. In these instances, FDA strongly recommends that sponsors discuss with FDA the feasibility of amending the protocol to incorporate the new standard of care as a control arm option.

- When designing a trial in the advanced disease setting, sponsors should consider available treatments received prior to eligibility determination for the MRCT. In cases where the outcome of interest is overall survival, available treatments following disease progression may also be important to consider as such treatments have the potential to impact the clinical outcome of the study. Information about available treatments should be provided to FDA during the planning stages of the clinical trial, along with the sponsor's assessment of whether regional differences in prior and subsequent treatments could impact the conduct of the trial (e.g., allowance of cross over), the results, and the interpretability of study results and ultimately, whether differences in available therapies could lead to results that are not applicable to the U.S. population or to U.S. medical practice.

D. Considerations for Analyses of Data from MRCTs

- The analysis plan should include an estimation of regional treatment effects and the basis for the proposed estimates. Sponsors should also pre-specify their approach to evaluate geographical regional effects and provide a rationale for the proposed approach.

- When analyzing the data from an MRCT, sponsors should provide an explanation of the differing results across important subgroups, including a description and assessment of the potential impact of trial conduct and data quality on any observed subgroup differences in treatment effects.

- FDA's assessment of the results of an MRCT includes a review of the effects demonstrated in the overall study population (i.e., the intent-to-treat population) as well as an exploration of subgroup effects. Although subgroup analyses are limited and thus generally exploratory, the subgroup of patients enrolled in the U.S. will be of particular interest in FDA's assessment of the results of an MRCT. However, when there are limitations in subgroup size, sponsors can elect to evaluate subgroup effects by pooling patients in the MRCT from countries or regions that share similarities across several factors including but not limited to patient demographic and clinical characteristics, medical practice, and available prior treatment. To the extent possible, sponsors should

pre-specify and provide justification for the pooling strategy in the statistical analysis plan.

- The safety assessment should also be conducted across subgroups in the MRCT to help identify potential safety signals that may suggest the need for alternative dosage or additional dose optimization.

E. Early Consultation with FDA and Other Regulatory Authorities

- Sponsors who plan to conduct any aspect of the CDP for an oncology drug outside the U.S. should consult with FDA early in clinical development to discuss the approach for obtaining data in a single MRCT with sufficient representation of U.S. patients to characterize the benefits and risks in the U.S. population, or in several trials with variable representation of U.S. patients. Early consultation with FDA promotes efficiency in drug development by minimizing the risk that additional studies may be required pre- or -post market, or that the data may be deemed not applicable to the U.S. population or U.S. medical practice, resulting in delays in providing access to innovative cancer therapies.

- When possible, sponsors are encouraged to seek input on their development program from FDA and other regulatory authorities concurrently or nearly concurrently.[26,27] This may facilitate review and discussion of the program across regulatory agencies prior to initiation to determine whether the proposed trial will meet their respective requirements. Alignment between regulatory authorities on key features of the overall clinical development plan to generate data from a representative study population, including the number of trials, and the design, analysis plan, and study population enrolled in the trial(s) can promote efficiency. However, despite these measures, in some cases it may be infeasible to conduct a single MRCT that complies with requirements and recommendations from the several global health authorities, and separate or additional trials may be needed.

- Sponsors should keep abreast of imminent changes in the treatment landscape of a cancer when planning their MRCT and take reasonable steps to include new standards of care into the trial to improve the applicability of trial results once completed. Sponsors should request a meeting with FDA when the treatment landscape changes during the conduct of the trial to determine the most efficient approach to incorporating the new treatment into an ongoing trial, when feasible.

[26] See the FDA-European Medicines Agency (EMA) Parallel Scientific Advice (PSA) Program at https://www.fda.gov/drugs/news-events-human-drugs/fda-ema-parallel-scientific-advice-psa-program-03162022.

[27] Thor S, Vetter T, Marcal A, and Kweder S, 2023, EMA-FDA Parallel Scientific Advice: Optimizing Development of Medicines in the Global Age, Ther Innov Regul Sci, 57(4):656-661.