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Guidance Document Submission

Dr. Janet Woodcock  
Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993-0002

Dr. Richard Pazdur  
Oncology Center of Excellence  
Food and Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993-0002

Dear Drs. Janet Woodcock and Richard Pazdur, and colleagues at the FDA,

The American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) formally submit the following draft guidance documents for consideration by the Food and Drug Administration (FDA). The content and strategies to modernize eligibility criteria for oncology clinical trials build upon recommendations developed by a consortium of stakeholders composed of patient advocates, drug/biotech manufacturers, investigators, and regulators.

In 2016, ASCO and *Friends* began a joint project to develop and advance specific strategies to change the exclusionary nature of cancer clinical trial eligibility criteria on the following topics: 1) Brain Metastases, 2) HIV/AIDS, 3) Organ Dysfunction, 4) Prior and Concurrent Malignancies, and 5) Minimum Age for Enrollment. An ASCO-*Friends* joint research statement and four supporting manuscripts containing consensus recommendations based on the review of evidence, consideration of the patient population, and consultation with the research community were published in the *Journal of Clinical Oncology* on October 2, 2017. Since the publication of these recommendations, ASCO and *Friends* have been working to advance their broad implementation.

To further bolster that effort, recommendations outlined in the published manuscripts have been adapted to serve as the foundation for the five FDA draft guidance documents enclosed in this submission. The recommendations aim to maximize the generalizability of clinical trial results while also maintaining the safety of clinical trial participants. FDA guidance will assist sponsors in designing more representative trials, and we hope FDA seriously considers adopting the proposed set of guidance documents. We believe that the rationale for excluding patients from eligibility for a cancer clinical trial should be clearly articulated and should be based on the specific therapy under investigation and the study population to help improve trial accrual, ensure optimal patient access, and maximize information learned during the clinical trial.

We look forward to engaging with you to discuss these recommendations further and welcome any questions or comments you may have regarding the proposed guidance documents enclosed in this submission. Thank you for your consideration of these proposed guidance documents and your continued dedication to ensuring cancer clinical trials are scientifically sound, broadly accessible and representative of the intended use population of the intervention under study.

Sincerely,

Richard L. Schilsky, MD, FACP, FSCT, FASCO  
Senior Vice President and Chief Medical Officer  
American Society of Clinical Oncology

Ellen V. Sigal, PhD  
Chairperson and Founder  
Friends of Cancer Research

# Cancer Clinical Trial Eligibility Criteria: Brain Metastases

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## I. INTRODUCTION

A clinical trial's eligibility criteria are essential components of the trial and serve an important role in protecting the safety of trial participants as well as defining the characteristics of the patient population under study to better interpret the trial's outcomes.

These criteria may be inclusionary or exclusionary and together help guide selection of patients who may derive the greatest benefit with the lowest acceptable risk from the treatment(s) being tested in the study. Because study agents and trial objectives differ, eligibility criteria should be developed that take into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational agent, and the ability to recruit trial participants from the patient population in order to meet the objectives of the clinical trial. However, some inclusion and exclusion criteria have become commonly accepted over time, duplicated or used as template for subsequent trials without clear scientific or clinical rationale.

As we seek to modernize eligibility criteria to more accurately reflect the population of patients with cancer who will use the investigational agent once approved, it is important to assess whether the historical use of overly restrictive eligibility criteria may impair clinical trial accrual and completion, jeopardize the generalizability of trial results, and prevent patients from accessing investigational interventions that have potential to provide clinical benefit.<sup>1</sup>

## II. BACKGROUND

The goal of broadening oncology trial eligibility criteria is to maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the broad patient population likely to use the agent in clinical practice without jeopardizing patient safety. This guidance is intended to guide sponsors and assist institutional review boards (IRB) and institutions responsible for review and oversight of human subject research under the Department of Health and Human Services (HHS) or FDA regulations, or both.

Because broadening oncology trial eligibility criteria may result in a more heterogeneous trial population, the design and analysis of the clinical trial with expanded eligibility criteria will need to be considered.<sup>2</sup> This guidance does not discuss general clinical trial design issues or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials*,<sup>3</sup> *E10 Choice of Control Group and Related Issues in Clinical Trials*,<sup>4</sup> and the

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<sup>1</sup> Kim, Bruinooge, Roberts, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. (2017) *JCO* 35:33, 3737-3744.

<sup>2</sup> Jin, Pazdur, Sridhara. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. (2017) *JCO* 35:33 3745-3752.

<sup>3</sup> Guidance for Industry. E9 Statistical Principles for Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). September 1998

<sup>4</sup> Guidance for Industry. E 10 Choice of Control Group and Related Issues in Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May 2001

draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*.<sup>5</sup>

Every year, approximately 70,000 patients living with cancer in the United States will eventually develop brain metastases. The incidence of brain metastases is increasing in specific cancer subtypes, particularly affecting patients with melanoma and cancers of the lung and breast. However, patients with brain metastases have frequently been excluded from clinical trials due to restrictive exclusion criteria. The exclusion criteria commonly used generally encompass either all patients with any history of brain metastases, such that all such patients are excluded, or a subgroup of patients, such as those with active brain metastases, but may allow patients with treated and clinically stable brain metastases to participate. Given the high incidence of patients who present with brain metastases, the systematic exclusion of these patients from clinical trials may mean that one half to one third of intended-use disease populations are not included in the assessment of the agent's efficacy or safety. Moreover, the exclusion of these patients limits the sponsor's ability to learn about the safety and effectiveness of the agent in patients with brain metastases even though such patients are likely to receive such therapies following approval. In order to maximize generalizability of study results, enrollment criteria should strive for inclusiveness, unless compelling concerns for safety or efficacy restrict the inclusion of specific populations with brain metastases.

### **III. DEVELOPMENT AND REGULATORY CONSIDERATIONS**

The inclusion of patients with brain metastases in clinical trials should be done in a way that contributes to a greater understanding of the safety and efficacy profile of the treatment under study. Inclusion of patients with brain metastases early in drug development should be the default position when studying an agent that intends to treat a population with a high incidence of brain metastases, such as patients with melanoma and cancers of the lung and breast. However, there may still be instances where there is a strong rationale for exclusion. In such cases, these factors need to be explicitly addressed in the trial design.

Three distinct populations of patients with brain metastases exist: patients with brain lesions that have been treated and are clinically stable; active brain metastases, i.e., patients with new and/or progressive brain metastases at the time of study entry; and those with leptomeningeal disease.<sup>6</sup> Approaches and considerations for the inclusion of each population in clinical trials are described below.

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<sup>5</sup> ICH Harmonized Guideline: Estimands and Sensitivity Analysis in Clinical Trials E9(R1). [Draft] Current Step 1 version dated 16 June 2017

<sup>6</sup> Lin, Prowell, Tan, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Brain Metastases Working Group (2017) *JCO* 35:33, 3760-3773

## **A. Approaches for inclusion of patients with treated and/or stable brain metastases**

### *1. Definition*

- Patients who have received prior therapy for their brain metastases and whose central nervous system (CNS) disease is radiographically stable.

### *2. Recommendations*

- Patients with treated/stable brain metastases should be included in prospective trials of all phases unless there is reliable and compelling evidence to exclude such patients.
- In diseases where brain metastases are frequent, patients with brain metastases should be included early in drug development in either separate cohorts or same cohort with a subset analysis to assess efficacy or toxicity.
- Inclusion of patients with brain metastases should not be dependent on whether the drug's pharmacological properties predict penetration of the brain-blood barrier.
- Patients with a known history of brain metastases should obtain baseline CNS imaging at the start of the trial to document CNS tumor measurements and disease stability.
- If after local treatment, patients exhibit pseudo-progression, they should be re-evaluated and reenrolled in the trial later if the CNS disease is not considered progressive.
- These recommendations do not apply to trials designed specifically for primary brain cancers (e.g. GBM), or trials designed specifically for brain metastases.

### *3. Recommendations by specific areas of concerns*

- Drugs associated with increased risk of bleeding: consider excluding patients with clinically evident CNS hemorrhage on scans and/or on concurrent therapeutic doses of anticoagulation.
- Drugs that may lower seizure threshold: consider excluding patients with seizures over past month.
- Drugs with potential cytochrome interactions: consider excluding patients on enzyme-inducing antiepileptic drugs, with appropriate washout on the basis of drug half-life, and depending on whether the agent is metabolized by the same enzymes.
- Concerns on interpretation of CNS adverse events: consider requiring stable to decreasing corticosteroid dose over 1 week before study entry.
- Investigational agents whose efficacy may be compromised by concurrent corticosteroids: consider excluding patients requiring corticosteroid use that exceeds prespecified threshold.
- Poor prognosis: consider excluding patients with poor performance status or short anticipated life expectancy.

## **B. Approaches for inclusion of patients with active brain metastases**

### *1. Definition*

- Patients with new and/or progressive brain metastases at the time of study entry

### *2. Recommendations*

- Patients with active brain metastases should not be automatically excluded but should be considered eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.
- There may be situations where CNS-specific toxicities are a known concern. In these cases, exclusion may be justified, especially early in drug development.

### *3. Strategies for inclusion of patients with active brain metastases in clinical trials: trial design, investigational agent and characteristics of disease*

- Trial design:
  - Including patients with brain metastases in clinical trials will depend on the design and intent of the trial, and the status of the agent in clinical development.
  - Phase 1 dose-finding study
    - Strategies may include enrolling patients in a separate expansion cohort early in clinical development, taking into consideration prior safety and efficacy data from similar drugs in class (if available). Additionally, dose-limiting toxicity (DLT) definitions and reporting should be prospectively designed and tailored to patients with brain metastases.
  - Single-arm initial efficacy study
    - Strategies may include enrolling patients in a separate cohort or enrolling patients in the overall study with a prespecified subset analysis for both safety and efficacy.
  - Randomized studies with a time-to-event endpoint
    - Several study design and mitigation strategies could be implemented for including patients with brain metastases in later-phase studies.<sup>6</sup> Some of these include: enrolling patients in a parallel exploratory cohort contributing supporting safety and efficacy data but not included in formal assessment of the primary efficacy endpoint, conducting pre-specified sensitivity and subset analyses, capping enrollment of patients with active brain metastases within a trial, designating brain metastases as a stratification factor, and incorporating early stopping rules for excess toxicity in patients with brain metastases.

- Investigational agent: Characterize the profile of the investigational agent being studied and weigh the evidence available.
  - The inclusion of patients with brain metastases early in drug development will facilitate the collection of data that will inform inclusion/exclusion decisions in later-phase trials.
  - A few factors to consider include: mechanism of action, expected CNS penetration, preclinical and clinical data, and CNS-specific toxicity
- Disease characteristics: the following characteristics would influence the risk-benefit of including patients with brain metastases in trials and affect the amount of preliminary data required to consider inclusion: differences in tumor type regarding propensity for specific toxicities, the expected efficacy of local therapies, the disease pace, and expected survival rates.

### **C. Approaches for inclusion of patients with leptomeningeal metastases**

#### *1. Definition*

Patients with metastases in the leptomeningeal space, rather than in the parenchyma. Leptomeningeal disease (LMD) is a clinical diagnosis that is defined as positive CSF cytology and/or unequivocal radiologic or clinical evidence of leptomeningeal involvement.

#### *2. Recommendations*

- Patients with LMD should not be automatically excluded but should be considered eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy.
- Inclusion in early-phase trials of drugs with anticipated CNS activity when relevant in the specific disease type under study and there is strong scientific rationale for likelihood of benefit based on molecular pathways or histology as well as preclinical data. Consideration of CSF pharmacokinetic measurements is encouraged.
- Inclusion in later-phase trials would be useful in providing access to investigational agents and generating additional safety and efficacy data.

### **D. Evidence to support exclusion of patients with brain metastases in oncology clinical trials**

The inclusion of patients with brain metastases in clinical trials where brain metastases are common in the intended-use population should be common practice; however, certain

characteristics would justify the exclusion of these patients from clinical trials. In these cases, the rationale for exclusion needs to be clearly addressed in the study design.

*1. Factors to take into consideration when seeking to exclude patients with brain metastases from clinical trials include:*

- Drug levels in the CNS: CNS penetration may affect efficacy of investigational agent.
- Inadequate preclinical models: lack of testing in intracranial tumor models
- Safety: patient frailty and susceptibility to adverse events, e.g., potential for bleeding, tumor flares, or seizures
- Adverse event reporting and attribution: challenge in distinguishing treatment-related adverse events from neurologic signs and symptoms related to CNS metastases
- Known or potential drug interactions
- Response assessment: limited ability to draw conclusions about CNS activity of investigational agent if CNS metastases are not considered target lesions
- Efficacy: may be affected by tumor microenvironment and inherent differences in tumor type, especially intracranial vs. extracranial disease
- Survival: patients with brain metastasis may have limited overall survival.
- Cost considerations: introducing additional cohorts or evaluations may add to the trial's cost.

**E. Baseline CNS screening concerns**

The inclusion of patients with brain metastases in clinical trials will decrease provider resistance or unwillingness to perform baseline CNS screenings that arise due to concerns that patients with identified asymptomatic lesions may not be able to enroll in a trial, or they may have to discontinue trial participation if a new or progressive lesion is identified. Inclusion of these patients will also promote greater knowledge regarding the impact of investigational agents in the CNS.

*1. Recommendations:*

- A baseline CNS imaging is recommended:
  - In populations where the risk of brain metastasis is high
  - If there are specific concerns related to inclusion of patients with brain metastasis
  - If one of the objectives of the study is to determine the impact of the investigational agent on CNS-related outcomes
- In patients with screen-detected brain metastasis, it is recommended to include them into clinical trials in the following ways:
  - Permit local therapy followed by immediate enrollment in study once acute treatment-related toxicities have resolved.
  - Enroll into separate pre-planned brain metastasis cohort.
  - Use statistical approaches, including stratification of randomization or capping, to allow enrollment of patients into the intent-to-treat study population.



- Baseline and surveillance CNS imaging on a protocol-defined schedule for patients with brain metastases identified at baseline. Required surveillance imaging could be considered throughout the study.
- Protocols could prospectively specify whether patients with isolated CNS progression, but responsive/stable extracranial disease, can remain on protocol therapy.
  - Concurrently allowed local CNS treatments should be prespecified explicitly in the protocol.
  - Intracranial and extracranial progression should be noted and recorded separately in the case report form if patient is able to continue in protocol.

**Cancer Clinical Trial Eligibility Criteria:  
Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus  
Infections**

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# Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections

## I. INTRODUCTION

A clinical trial's eligibility criteria are essential components of the trial and serve an important role in protecting the safety of trial participants as well as defining the characteristics of the patient population under study to better interpret the trial's outcomes.

These criteria may be inclusionary or exclusionary and together help guide selection of patients who may derive the greatest benefit with the lowest acceptable risk from the treatment(s) being tested in the study. Because study agents and trial objectives differ, eligibility criteria should be developed that take into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational agent, and the ability to recruit trial participants from the patient population in order to meet the objectives of the clinical trial. However, some inclusion and exclusion criteria have become commonly accepted over time, duplicated or used as template for subsequent trials without clear scientific or clinical rationale.

As we seek to modernize eligibility criteria to more accurately reflect the population of patients with cancer who will use the investigational agent once approved, it is important to assess whether the historical use of overly restrictive eligibility criteria may impair clinical trial accrual and completion, jeopardize the generalizability of trial results, and prevent patients from accessing investigational interventions that have potential to provide clinical benefit.<sup>7</sup>

## II. BACKGROUND

The goal of broadening oncology trial eligibility criteria is to maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the broad patient population likely to use the agent in clinical practice without jeopardizing patient safety. This guidance is intended to guide sponsors and assist institutional review boards (IRB) and institutions responsible for review and oversight of human subject research under the Department of Health and Human Services (HHS) or FDA regulations, or both.

Because broadening oncology trial eligibility criteria may result in a more heterogeneous trial population, the design and analysis of the clinical trial with expanded eligibility criteria will need to be considered.<sup>8</sup> This guidance does not discuss general clinical trial design issues or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles*

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<sup>7</sup> Kim, Bruinooge, Roberts, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. (2017) JCO 35:33, 3737-3744.

<sup>8</sup> Jin, Pazdur, Sridhara. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. (2017) JCO 35:33 3745-3752.

*for Clinical Trials,*<sup>9</sup> *E10 Choice of Control Group and Related Issues in Clinical Trials,*<sup>10</sup> and the draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.*<sup>11</sup>

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections can be chronically managed and hepatitis C virus (HCV) infections can be cured with contemporary anti-viral therapy. These viral infections may be associated with increased incidence of several malignancies. However, exclusion of patients with HIV, HBV, or HCV infections remains common in most studies of novel cancer agents. Expanding cancer clinical trial eligibility to be more inclusive of patients with treated HIV, HBV, or HCV is justified in most cases and may accelerate the development of effective therapies in cancer patients with these chronic infections. Eligibility criteria that address concurrent antiviral and other therapies and immune status related to HIV, HBV, or HCV infections should be designed in a manner that is appropriate for a given cancer, investigational agent and intended use population.<sup>12</sup>

### **III. RECOMMENDATIONS**

The HIV recommendations are focused on two areas: evaluation of immune function and criteria related to HIV therapy. Criteria for patients with evidence of chronic hepatitis B virus (HBV) or history/current hepatitis C virus (HCV) are also recommended.

#### **A. Recommendations for patients with HIV infection**

1. Immune criteria recommendations
  - Eligibility based on CD4+ T-cell counts
    - Patients with CD4+ T-cell counts  $\geq 350$  cells/uL should generally be eligible for any study if otherwise eligible.
      - Lower CD4+ count eligibility is often appropriate for patients with curable malignancies or for interventions with a high probability of efficacy in a given tumor.
  - Eligibility based on history of AIDS-defining opportunistic infections
    - Patients with NO history of AIDS-defining opportunistic infections (or only remote AIDS-defining opportunistic infections; i.e., none in the past year in patients on stable effective antiretroviral therapy [ART]) should generally be eligible for any study if they meet all other inclusion and exclusion criteria.

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<sup>9</sup> Guidance for Industry. E9 Statistical Principles for Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). September 1998

<sup>10</sup> Guidance for Industry. E 10 Choice of Control Group and Related Issues in Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May 2001

<sup>11</sup> ICH Harmonized Guideline: Estimands and Sensitivity Analysis in Clinical Trials E9(R1). [Draft] Current Step 1 version dated 16 June 2017

<sup>12</sup> Uldrick, Ison, Rudek, et al: Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV working group. (2017) *JCO* 35:33, 3774 – 3780.

- Patients WITH a history of AIDS-defining opportunistic infections may be eligible, depending upon the time frame and cancer type:
  - For many studies, patients should be included if they have not experienced an opportunistic infection within the past 12 months.
  - For studies of patients with AIDS-defining cancers (e.g., Kaposi's sarcoma, aggressive B-cell lymphoma, and invasive cervical cancer) with curative potential, exclusion of patients with uncontrolled opportunistic infections may be appropriate.
  - Patients on prophylactic antimicrobials need not be excluded, although specific agents may be excluded for drug-drug interactions or overlapping toxicities.

## 2. HIV therapy criteria recommendations

- Timing of ART initiation – Criteria specifying timing of initiation of ART should be provided based on study goals and take into consideration patients recently diagnosed with HIV or patients not on effective ART.

Examples include the following:

- For non-curative therapies: To ensure that effective ART is tolerated and that toxicities are not confused with study drug toxicities, trial participants should be on established ART for at least four weeks and have HIV a viral load less than 400 copies/mL prior to enrollment
- For therapies with curative potential: Participants should have no documented multidrug resistance that would prevent effective HIV therapy and should agree to adhere to ART based on protocol defined treatment guidelines
- Exclusion of specific ART agents – It may be necessary/appropriate to exclude certain ART agents based on predicted drug-drug interactions that may affect absorption, distribution, metabolism, and excretion of the study drug or potential overlapping toxicities.
  - Although many drug-drug interactions occur with CYP3A4, other metabolic routes and drug transporters may be involved. Recommend assessment of the absorption, distribution, metabolism, and excretion data known to date for the anticancer agent. Contraindicated agents are then rationally selected based on drug-drug interaction potential using known sources (see Table 2 below). Recommend providing tables of contraindicated agents that include ART and other drugs. For sensitive CYP3A4 substrates, concurrent strong CYP3A4 inhibitors (ritonavir and cobicistat) or inducers (efavirenz) should be contraindicated.

Otherwise eligible HIV study participants should be switched to an alternate effective antiretroviral therapy regimen before study participation.

- Consider exclusion of ART agents based on toxicity (e.g., tenofovir [renal dysfunction], atazanavir [QT prolongation], efavirenz [depressed mood]).
- Exceptions to concurrent ART – Although effective ART is generally recommended, exceptions to concurrent ART should be considered in both development of eligibility criteria and conduct of studies.<sup>13</sup>
  - In first-line studies of curable malignancies where cancer therapy requires prioritization, investigators should have discretion to include patients not currently on ART.
  - Treatment interruption or deferred initiation of ART is appropriate in curable malignancies when ART may compromise intended full-dose oncology therapy with investigational agent(s).
  - Treatment interruptions for toxicity management.
  - Treatment interruptions to meet scientific objectives of the study.

## **B. Eligibility of patients with evidence of chronic Hepatitis B Virus (HBV) infection or patients with current or history of Hepatitis C Virus (HCV) infection**

1. Liver function criteria
  - Liver function criteria should generally be the same as that for the general population.
  - For patients with hepatocellular carcinoma, Child-Pugh score use is appropriate.
2. Criteria related to HBV and HCV therapy
  - HBV: For participants with serologic evidence of chronic hepatitis B virus infection, the HBV viral load should be undetectable and participants should be on suppressive therapy, if indicated.<sup>14</sup>
  - HCV: Patients with a history of hepatitis C virus infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
3. Exceptions to liver function and HBV/HCV criteria
  - AST/ALT and bilirubin criteria may be less stringent in hepatocellular carcinoma and cholangiocarcinoma studies.
  - HBV viral load data may not apply to studies in hepatocellular carcinoma, where the viral load may be elevated due to the underlying malignancy.

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<sup>13</sup> Uldrick and Little. How I treat classical Hodgkin lymphoma in patients infected with human immunodeficiency virus. (2015) Blood 125:1226-1235.

<sup>14</sup> Reddy, Beavers, Hammond, et al. American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy. (2015) Gastroenterology 148:1, 215-219.

**Table 1. References for management of concurrent HIV<sup>15</sup>**

***Management of Concurrent HIV***

[Department of Health and Human Services \(DHHS\) Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents](#)

Includes preferred up to date recommendations for preferred ART regimens.

Physicians should be familiar with broad guidelines of HIV care that includes DHHS recommendations for Laboratory Monitoring includes:

- Baseline and 3 monthly CD4+ monitoring
- Baseline and 3 monthly HIV viral load monitoring; or 2 months follow up after initiation or change of ART

[Department of Health and Human Services \(DHHS\) Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents](#)

Physicians who treat HIV infected patients on clinical studies should also be aware of guidelines for administration of concomitant antimicrobial prophylaxis in this patient population, including:

- Prophylaxis against *Pneumocystis pneumonia* (PCP) with trimethoprim/sulpamethoxizole or alternative agent if CD4+ count <200 cells/uL; or at any CD4+ count if study drug(s) have potential immunosuppressive effects
- Prophylaxis against HSV/VZV prophylaxis for patients with recurrent HSV infections or in studies of agents with immunosuppressive effects
- Prophylaxis against atypical mycobacterial infection with azithromycin 1200 mg weekly if CD4+ count less than 50 cells/uL

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<sup>15</sup> Uldrick, Ison, Rudek, et al: Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV working group. (2017) JCO 35:33, 3774 – 3780.

**Table 2. References for preventing drug-drug interactions<sup>16</sup>**

*Available Antiretroviral Agents and Relevant Pharmacology to Avoid Drug-Drug Interactions*

[Rudek et. al 2011 \*Lancet\* Review of Antineoplastic agents in patients with cancer who have HIV/AIDS](#)

Includes tables on Drug Interaction potential of antiretroviral agents

[Uptodate Systemic Therapy for Malignancies in Patients on Antiretroviral Therapy](#)

Includes Table of relevant drug-drug interactions

[University of Liverpool HIV Drug Interaction Website](#)

[Searchable database](#)

[POZ List of HIV Medications](#)

[Comprehensive list of ART with dosing information and photos of medications](#)

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<sup>16</sup> Uldrick, Ison, Rudek, et al: Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV working group. (2017) *JCO* 35:33, 3774 – 3780.



# Cancer Clinical Trial Eligibility Criteria: Patients with Renal, Cardiac, or Hepatic Dysfunction

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# Cancer Clinical Trial Eligibility Criteria: Patients with Renal, Cardiac, or Hepatic Dysfunction

## I. INTRODUCTION

A clinical trial's eligibility criteria are essential components of the trial and serve an important role in protecting the safety of trial participants as well as defining the characteristics of the patient population under study to better interpret the trial's outcomes.

These criteria may be inclusionary or exclusionary and together help guide selection of patients who may derive the greatest benefit with the lowest acceptable risk from the treatment(s) being tested in the study. Because study agents and trial objectives differ, eligibility criteria should be developed that take into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational agent, and the ability to recruit trial participants from the patient population in order to meet the objectives of the clinical trial. However, some inclusion and exclusion criteria have become commonly accepted over time, duplicated or used as template for subsequent trials without clear scientific or clinical rationale.

As we seek to modernize eligibility criteria to more accurately reflect the population of patients with cancer who will use the investigational agent once approved, it is important to assess whether the historical use of overly restrictive eligibility criteria may impair clinical trial accrual and completion, jeopardize the generalizability of trial results, and prevent patients from accessing investigational interventions that have potential to provide clinical benefit.<sup>17</sup>

## II. BACKGROUND

The goal of broadening oncology trial eligibility criteria is to maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the broad patient population likely to use the agent in clinical practice without jeopardizing patient safety. This guidance is intended to guide sponsors and assist institutional review boards (IRB) and institutions responsible for review and oversight of human subject research under the Department of Health and Human Services (HHS) or FDA regulations, or both.

Because broadening oncology trial eligibility criteria may result in a more heterogeneous trial population, the design and analysis of the clinical trial with expanded eligibility criteria will need to be considered.<sup>18</sup> This guidance does not discuss general clinical trial design issues or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles*

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<sup>17</sup> Kim, Bruinooge, Roberts, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. (2017) JCO 35:33, 3737-3744.

<sup>18</sup> Jin, Pazdur, Sridhara. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. (2017) JCO 35:33 3745-3752.

*for Clinical Trials,*<sup>19</sup> *E10 Choice of Control Group and Related Issues in Clinical Trials,*<sup>20</sup> and the draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.*<sup>21</sup>

Patients with organ dysfunction are often excluded from clinical trials, regardless of knowledge of the metabolic pathways and excretory routes of the agent under investigation. The general population is aging and thus includes increasing numbers of patients with renal disease, hepatic dysfunction, and cardiac disease due to co-morbid illnesses. Where pharmacokinetics (PK) and major routes of elimination in humans are not well understood, it is reasonable to enroll patients with normal organ function (primarily renal and hepatic) on cancer clinical trials. As data on toxicity, PK, and pharmacodynamics (PD) become available during drug development, protocols should be revised to include patients with compromised organ function where safe parameters have been determined.<sup>22</sup>

### III. RECOMMENDATIONS

#### A. Renal function recommendations

Both calculated creatinine clearance (CrCl) and serum creatinine values are commonly used to measure renal function. However, serum creatinine does not accurately reflect renal function and CrCl should be the standard measure of renal function.

- Eligibility criteria assessments should use assessment of kidney function via CrCl, rather than serum creatinine concentrations.
- The Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) equations are reasonable standards for estimating creatinine clearance.
- A consistent measure of renal function should be applied throughout the drug development process.
- Inclusion of patients with renal dysfunction could be liberalized in the following specific settings:
  - If renal toxicity and clearance of the investigational agent are not of concern, then CrCl values of > 30 mL/min should be used for inclusion.

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<sup>19</sup> Guidance for Industry. E9 Statistical Principles for Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). September 1998

<sup>20</sup> Guidance for Industry. E 10 Choice of Control Group and Related Issues in Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May 2001

<sup>21</sup> ICH Harmonized Guideline: Estimands and Sensitivity Analysis in Clinical Trials E9(R1). [Draft] Current Step 1 version dated 16 June 2017

<sup>22</sup> Lichtman, Harvey, Smith, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. (2017) JCO 35:33, 3753-3759.

- When established dose modifications allow for safe and effective administration of the drug and are not likely to change outcomes, these modifications should be incorporated into the protocol (e.g., carboplatin, methotrexate, capecitabine).
- When the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of patients with renal dysfunction is safe.

## **B. Cardiac function recommendations**

Accuracy of ejection fraction (EF) measured by either echocardiography or multigated acquisition scan is acceptable for determining cardiac ejection fraction. However, there is no clearly established minimum cardiac ejection fraction predictive of anticancer agent cardiotoxicity.

- Eligibility criteria should reflect a conservative approach to cardiac safety measures, so that patients with significant clinical cardiac abnormalities (e.g., clinical heart failure, unstable angina, or EF < 35%) are excluded, especially in early-phase studies.
- Inclusion of patients with cardiovascular dysfunction may be possible when the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of these patients is safe.
- Ejection Fraction (EF) values:
  - EF values should not be used in isolation to exclude patients from trials. Trials should recommend investigator assessment of a potential participant's risk for heart failure with a validated clinical classification system (e.g., the New York Heart Association Functional Classification).
- QTc Prolongation:
  - If QTc prolongation is not identified as a concern in first-in-human studies, QTc interval eligibility criteria in phase IB and later trials should be re-evaluated, and ongoing ECG monitoring may not be required.
- Cardiovascular safety measures and close collaboration with cardiology should be considered, particularly when investigating compounds or regimens where trial-emergent cardiac contractility toxicity is a factor (e.g., trastuzumab or sunitinib).

## **C. Hepatic function recommendations**

Current clinically available hepatic function testing does not fully describe liver function, particularly drug metabolism capability (i.e., there is no reliable test comparable to the relationship between creatinine and renal drug clearance). Estimates of hepatic function

that incorporate clinical variables as well as functional and laboratory values, such as the Child-Pugh and Model for End-Stage Liver Disease scoring systems, may more closely align with hepatic metabolism.<sup>23</sup> Hepatic metabolism may also be influenced by cancer and inflammation, even in the setting of normal test results. More reliable measures to predict both phase I and phase II hepatic metabolism function are needed.

1. Patients with mild to moderate hepatic impairment
  - Patients with mild and moderate hepatic impairment (defined as the equivalent of CTC grade 1 toxicity), as well as those with aspartate transaminase (AST) and alanine transaminase (ALT) elevations defined as grade 3 by the National Cancer Institute Common Terminology Criteria for Adverse Events (> 5 to 20 x ULN [upper limit of normal]), may be asymptomatic and able to take doses equivalent to patients with normal hepatic function.
  - Inclusion of patients with mild to moderate hepatic dysfunction may be acceptable when the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of these patients is safe.
2. Patients with severe hepatic impairment
  - Intolerance of labelled doses by patients with severe hepatic impairment is often the result of poor performance status rather than an alteration in PK measures.<sup>24,25</sup> Another complicating factor in patients with liver dysfunction is that an investigational agent may cause liver toxicity and therefore may exacerbate underlying liver dysfunction.

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<sup>23</sup> Albarmawi , Czock, Gauss, et al: CYP3A activity in severe liver cirrhosis correlates with Child-Pugh and model for end-stage liver disease (MELD) scores. *Br J Clin Pharmacol* (2014). 77:160-169.

<sup>24</sup> Ramalingam SS, Kummar S, Sarantopoulos J, et al: Phase I study of vorinostat in patients with advanced solid tumors and hepatic dysfunction: A National Cancer Institute Organ Dysfunction Working Group study. *JCO* (2010) 28:4507-4512.

<sup>25</sup> Shibata, Chung, Synold, et al: Phase I study of pazopanib in patients with advanced solid tumors and hepatic dysfunction: A National Cancer Institute Organ Dysfunction Working Group study. *Clin Cancer Res* (2013). 19:3631-3639.

**Cancer Clinical Trial Eligibility Criteria:  
Patients with Prior or Concurrent Malignancies or Comorbidities**

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# Cancer Clinical Trial Eligibility Criteria: Patients with Prior or Concurrent Malignancies or Comorbidities

## I. INTRODUCTION

A clinical trial's eligibility criteria are essential components of the trial and serve an important role in protecting the safety of trial participants as well as defining the characteristics of the patient population under study to better interpret the trial's outcomes.

These criteria may be inclusionary or exclusionary and together help guide selection of patients who may derive the greatest benefit with the lowest acceptable risk from the treatment(s) being tested in the study. Because study agents and trial objectives differ, eligibility criteria should be developed that take into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational agent, and the ability to recruit trial participants from the patient population in order to meet the objectives of the clinical trial. However, some inclusion and exclusion criteria have become commonly accepted over time, duplicated or used as template for subsequent trials without clear scientific or clinical rationale.

As we seek to modernize eligibility criteria to more accurately reflect the population of patients with cancer who will use the investigational agent once approved, it is important to assess whether the historical use of overly restrictive eligibility criteria may impair clinical trial accrual and completion, jeopardize the generalizability of trial results, and prevent patients from accessing investigational interventions that have potential to provide clinical benefit.<sup>26</sup>

## II. BACKGROUND

The goal of broadening oncology trial eligibility criteria is to maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the broad patient population likely to use the agent in clinical practice without jeopardizing patient safety. This guidance is intended to guide sponsors and assist institutional review boards (IRB) and institutions responsible for review and oversight of human subject research under the Department of Health and Human Services (HHS) or FDA regulations, or both.

Because broadening oncology trial eligibility criteria may result in a more heterogeneous trial population, the design and analysis of the clinical trial with expanded eligibility criteria will need to be considered.<sup>27</sup> This guidance does not discuss general clinical trial design issues or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles*

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<sup>26</sup> Kim, Bruinooge, Roberts, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. (2017) JCO 35:33, 3737-3744.

<sup>27</sup> Jin, Pazdur, Sridhara. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. (2017) JCO 35:33 3745-3752.

*for Clinical Trials,*<sup>28</sup> *E10 Choice of Control Group and Related Issues in Clinical Trials,*<sup>29</sup> and the draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.*<sup>30</sup>

The general population is aging and thus includes increasing numbers of patients with prior or concurrent malignancies or comorbidities. Diagnoses of more than one malignancy are not unusual, occurring in approximately 15% of patients. By excluding individuals with previous or concurrent cancers or comorbidities, trial recruitment favors younger patients. Furthermore, when clinical trials include older patients, geriatric-specific baseline data are almost never obtained. Explicitly including patients with prior and concurrent malignancies rather than removing prior and concurrent malignancies as an exclusion may have a positive effect on accrual.<sup>31</sup>

### **III. RECOMMENDATIONS**

#### **A. Prior or concurrent malignancy recommendations**

Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen should be included.

#### **B. Comorbidity recommendations**

The inclusion of baseline data on patients' comorbidities and function will make study results more applicable to a broader oncology population, and when included in the final study analysis, will help guide clinicians to treat patients with comorbidities with more precision.

Clinical trial designs should include functional assessment beyond performance status (e.g., using recommended performance assessment tools for older adults<sup>32</sup>) at baseline and throughout the study to better assess the safety and efficacy of an investigational agent in fit versus frail patients.

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<sup>28</sup> Guidance for Industry. E9 Statistical Principles for Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). September 1998

<sup>29</sup> Guidance for Industry. E 10 Choice of Control Group and Related Issues in Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May 2001

<sup>30</sup> ICH Harmonized Guideline: Estimands and Sensitivity Analysis in Clinical Trials E9(R1). [Draft] Current Step 1 version dated 16 June 2017

<sup>31</sup> Lichtman, Harvey, Smith, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. (2017) JCO 35:33, 3753-3759.

<sup>32</sup> Mohile, Dale, Somerfield, et. al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. (2018) JCO 36:22, 2326-2347.



# Cancer Clinical Trial Eligibility Criteria: Minimum Age

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# Cancer Clinical Trial Eligibility Criteria: Minimum Age

## I. INTRODUCTION

A clinical trial's eligibility criteria are essential components of the trial and serve an important role in protecting the safety of trial participants as well as defining the characteristics of the patient population under study to better interpret the trial's outcomes.

These criteria may be inclusionary or exclusionary and together help guide selection of patients who may derive the greatest benefit with the lowest acceptable risk from the treatment(s) being tested in the study. Because study agents and trial objectives differ, eligibility criteria should be developed that take into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational agent, and the ability to recruit trial participants from the patient population in order to meet the objectives of the clinical trial. However, some inclusion and exclusion criteria have become commonly accepted over time, duplicated or used as template for subsequent trials without clear scientific or clinical rationale.

As we seek to modernize eligibility criteria to more accurately reflect the population of patients with cancer who will use the investigational agent once approved, it is important to assess whether the historical use of overly restrictive eligibility criteria may impair clinical trial accrual and completion, jeopardize the generalizability of trial results, and prevent patients from accessing investigational interventions that have potential to provide clinical benefit.<sup>33</sup>

## II. BACKGROUND

The goal of broadening oncology trial eligibility criteria is to maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the broad patient population likely to use the agent in clinical practice without jeopardizing patient safety. This guidance is intended to guide sponsors and assist institutional review boards (IRB) and institutions responsible for review and oversight of human subject research under the Department of Health and Human Services (HHS) or FDA regulations, or both.

Because broadening oncology trial eligibility criteria may result in a more heterogeneous trial population, the design and analysis of the clinical trial with expanded eligibility criteria will need to be considered.<sup>34</sup> This guidance does not discuss general clinical trial design issues or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles*

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<sup>33</sup> Kim, Bruinooge, Roberts, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. (2017) JCO 35:33, 3737-3744.

<sup>34</sup> Jin, Pazdur, Sridhara. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. (2017) JCO 35:33 3745-3752.

*for Clinical Trials,*<sup>35</sup> *E10 Choice of Control Group and Related Issues in Clinical Trials,*<sup>36</sup> and the draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.*<sup>37</sup>

Historically, children have been excluded from first-in-human studies and all adult clinical trials, which specify 18 years as the minimum age of eligibility. In some cases, when drugs are specifically evaluated in the pediatric population, trials are undertaken after extensive testing in adults, well after the completion of one or more adult clinical trials, delaying access of these potentially promising new cancer drugs to the pediatric population. This delay encourages the use of off-label treatment without pediatric-specific information about dose, safety, efficacy and long-term effects. Moreover, the off-label use of these agents impedes the acquisition of such information because data are not systematically collected or evaluated in these situations, thus compromising the safety of childhood and adolescent patients.

Many of the historical concerns about including children early in oncology clinical trials do not apply in the current scientific and clinical environment of pediatric oncology and drug development.<sup>38</sup> For example, drug exposure in adolescents and adult patients has been shown to be similar for many drugs,<sup>39</sup> therefore enrollment of adolescents with cancer in adult trials should be based on either the histology under investigation or the molecular target of the drug where both the mechanism of action of the drug and the molecular derangement of the tumor are relevant.<sup>6,40</sup>

Although there are unique safety and/or efficacy signals in children and children may have different toxicity or drug tolerance and administration profiles compared with adult patients, it is preferable to evaluate new agents in the preapproval setting rather than relying on the off-label use of a new cancer agent in children.

Including pediatric patients in clinical trials provides assurances of appropriate regulatory and safety oversight from which meaningful data can be derived to inform safe and effective use of a new drug in a timely manner. Clinical trials for children have additional considerations that will need to be met, and sponsors are advised to consult the appropriate regulatory agency prior to initiation of such trials due to potential differences in requirements between FDA and other regulatory agencies.

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<sup>35</sup> Guidance for Industry. E9 Statistical Principles for Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). September 1998

<sup>36</sup> Guidance for Industry. E 10 Choice of Control Group and Related Issues in Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May 2001

<sup>37</sup> ICH Harmonized Guideline: Estimands and Sensitivity Analysis in Clinical Trials E9(R1). [Draft] Current Step 1 version dated 16 June 2017

<sup>38</sup> Gore et al., Modernizing Clinical Trial Eligibility: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Minimum Age Working Group. (2017) *JCO* 35:33, 3781-3787

<sup>39</sup> Momper et al., Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. (2013) *JAMA Pediatr* 167, 926-932

<sup>40</sup> Chuk et al., Enrolling Adolescents in Disease/Target-Appropriate Adult Oncology Clinical Trials of Investigational Agents (2017) *Clin Cancer Res* 23:1, 9-12

In this guidance, pediatric age groups are defined as neonates (newborns up to one month of age); infants (one month to two years of age); children (two to twelve years of age); and adolescents (twelve to seventeen years of age).

### **III. DEVELOPMENT AND REGULATORY CONSIDERATIONS**

The study of a drug in a specific pediatric population should be conducted when there is scientific rationale to suggest that children with a specific diagnosis or biological feature may benefit and when there is adequate nonclinical and clinical information to sufficiently mitigate patient risk. Rationale for excluding patients with characteristics should be clearly articulated and reflect expected toxicities associated with the therapy under investigation based on existing data. The inclusion of pediatric patients may require additional screening or monitoring or the engagement of additional expertise to manage safety issues specific to that patient population in clinical trials. Moreover, trials involving children should use a central IRB, especially when the institutional IRB does not have extensive experience in these types of studies. Additional regulatory requirements for research involving children may also be applicable.<sup>41</sup> Lastly, sponsors who perform studies in pediatric patient populations may also be eligible for additional incentives.

#### **A. Approaches for inclusion in oncology clinical trials**

- Sponsors should consider the inclusion of adolescents (ages 12-17) in disease- and/or target-appropriate adult oncology clinical trials at all stages of development.<sup>42</sup>
- Inclusion of pediatric patients is encouraged in early-phase trials that assess dose, safety, and pharmacokinetics (PK) in a variety of tumor types and in later phase trials that assess efficacy in diseases that span adult and pediatric populations.
- Sponsors seeking to include pediatric patient populations should evaluate pediatric formulation requirements based on the age, size, physiologic condition and treatment requirements to be studied.
- Types of evidence that could support inclusion of patients under age 12 are listed below, although other sources of evidence may also be appropriate. When more than one of these observations are present, the strength of the evidence increases. If no evidence is available or available support is weak, inclusion of pediatric patients may not be appropriate.
  - Clinical studies: Preliminary studies demonstrate pediatric patients will likely exhibit similar responses to the investigational drug based on a clinical efficacy endpoint. Assessment of long-term clinical impact and data from adult clinical programs may support conclusions of efficacy and safety.

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<sup>41</sup> 45 CFR 46 Subpart D; 21 CFR 50 Subpart D—Additional Safeguards for Children in Clinical Investigations; 45 CFR 46.111(b); 21 CFR 56.111(c)

<sup>42</sup> Guidance for industry. Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials. Food and Drug Administration, Center for Drug evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Oncology Center of Excellence (OCE). June 2018

- Nonclinical studies: *In vivo* and *in vitro* pediatric preclinical data may help increase confidence to support inclusion of pediatric patients. Modeling and simulation should be used to understand potential differences in PK and pharmacodynamic (PD) modelling (PK/PD). Animal xenograft studies of pediatric tumors would also provide enhanced supportive evidence.
- Predictive biomarkers
- *In silico* or mechanism-based *in vitro* evidence
- Evidence from other drugs in the same pharmacological class or with similar mechanism of action

The following are general recommendations for inclusion of pediatric patients in early-phase oncology clinical trials assessing dose, safety, and pharmacokinetics:

- For patients under 12 years of age, sponsors could consider enrolling an expanded population with patients under 12 years of age with the goal of including them in the safety analysis, but excluding them from the primary efficacy analysis, so as not to compromise assessment of the drug's efficacy. Strategies are discussed as follows:
  - Enroll restricted and expanded populations in the same clinical trial, conduct simultaneous clinical trials and analyze separately, or use an extended trial design to expand knowledge in particular populations.
  - Include adolescent/pediatric patients after enrollment of adult patients and after safety and toxicity in the adult populations have been established. This could be done in the following ways:
    - Include adolescent/pediatric patients starting one dose cohort behind the current adult cohort in which there are no dose-limiting toxicities identified.
    - Include adolescent/pediatric patients in age-specific cohorts that will be staggered starting one dose behind the current adult cohort in which there are no dose-limiting toxicities identified.
    - Include adolescent/pediatric patients in a separate cohort that will accrue concurrently with the adult cohort.

The following are general recommendations for inclusion of pediatric patients in later phase oncology clinical trials assessing efficacy:

- Once initial adult safety and toxicity data are known, it may be appropriate to use a staggered enrollment approach starting with older children.
- For diseases that span the pediatric and adult patient populations, patients 12 years of age and older should be included on the basis of the similarity in drug metabolism and excretion between adults and postpubertal adolescents.<sup>43</sup> Patients younger than age 12 years may also be included if clinically appropriate.

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<sup>43</sup> Guidance for industry. Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and the Oncology Center of Excellence (OCE). June 2018

- The minimum age of eligibility specified in late-phase trials should be tailored to the biology of the disease under study, the scientific objectives of the trial and the existing data regarding the mechanism of action and safety profile of the drug.

#### **B. Evidence to support exclusion of pediatric patients in oncology clinical trials**

- The exclusion of pediatric-specific cohorts should be guided by strong scientific rationale that can include non-clinical and clinical evidence from studies in adults, or data that suggests the molecular pathways or histology are biologically implausible in pediatric cancers.

#### **C. Benefit and risk determination and labeling**

- As per FDA guidelines, experimental interventions or procedures that present greater than low risk must offer a sufficient prospect of clinical benefit to justify exposure of a pediatric population to such risk.<sup>44</sup>
- Long-term clinical aspects may require follow-up in a prospective to evaluate the long-term safety and efficacy of treatment in pediatric patients. Safety data should be examined for any age-related differences.

Expanding the patient population in oncology clinical trials can result in the potential inclusion of additional information in the label's prescribing information. Labeling will reflect the overall benefits and risks of the drug in a pediatric population.

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<sup>44</sup> E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population