
Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**July 2020
Clinical/Medical**

Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002*

*Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>
and/or*

*Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002*

*Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
<https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances>*

**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**July 2020
Clinical/Medical**

Contains Nonbinding Recommendations

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	2
III.	RECOMMENDATIONS	3
A.	Patients with organ dysfunction	3
	1. <i>Renal function recommendations</i>	3
	2. <i>Cardiac function recommendations</i>	4
	3. <i>Hepatic function recommendations</i>	5
B.	Patients with prior or concurrent malignancy	5

**Cancer Clinical Trial Eligibility Criteria:
Patients with Organ Dysfunction or Prior or Concurrent
Malignancies
Guidance for Industry¹**

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products² regulated by CDER and CBER for the treatment of cancer.³ Specifically, this guidance includes recommendations regarding the inclusion of patients with organ dysfunction or with prior or concurrent malignancies. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and

¹ This guidance has been prepared by the Oncology Center of Excellence, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² For the purposes of this guidance, references to drugs and drug and biological products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

³ Topics of the other three guidances are related to eligibility criteria for patients with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infections; for patients with brain metastases; and regarding minimum age considerations for inclusion of pediatric patients.

Contains Nonbinding Recommendations

lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.^{4,5}

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice and should be considered to avoid jeopardizing patient safety.

Trial design and methodological approaches are important considerations when enrolling a broader population and are addressed elsewhere^{6,7} and are not addressed in this guidance because the considerations are not specific to enrolling patients with organ dysfunction or prior or concurrent malignancies.

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.

II. BACKGROUND

Patients with organ dysfunction are often excluded from clinical trials, regardless of knowledge of the metabolic pathways and excretory routes of the investigational drug. The life-span of the general population is increasing and thus includes increasing numbers of patients with co-morbid renal disease, cardiac disease, and hepatic dysfunction. Additionally, as life-span of the general population increases, a greater number of patients are anticipated to have prior or concurrent malignancies. By excluding individuals from cancer clinical trials who have major organ dysfunction or previous or concurrent cancers, trial recruitment may favor younger patients, which may not be fully representative of the population for whom the drug will be indicated. Designing cancer clinical trials that include patients with organ dysfunction and prior or concurrent malignancies and including this information in the labeling promotes the safe and effective use of these products across a broader patient population likely to use the drug in clinical practice.

⁴ Beaver JA, Ison G, Pazdur R, 2017, Reevaluating Eligibility Criteria- Balancing Patient Protection and Participation in Oncology Trials, *NEJM*, 376:1504-1505.

⁵ Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, *JCO*, 35(33): 3737-3744.

⁶ See the draft guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (June 2019). When final, this guidance will represent the FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁷ Jin S, Pazdur R, Sridhara R, 2017, Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015, *JCO*, 35(33): 3745-3752.

III. RECOMMENDATIONS

Thoughtful consideration should be given to the potential inclusion of patients with organ dysfunction or prior or concurrent malignancies in cancer clinical trials. The following recommendations for eligibility criteria for patients with organ dysfunction in cancer clinical trials focus on renal function, cardiac function, and hepatic function. This guidance also includes recommendations for eligibility criteria for patients with cancer who have prior or concurrent malignancies.

A. Patients with organ dysfunction

When pharmacokinetics (PK) and major routes of elimination in humans are not well understood, it is reasonable to enroll only patients with relatively preserved organ function (primarily renal and hepatic) in cancer clinical trials. As data on toxicity, including nonclinical and clinical toxicity, PK, and/or pharmacodynamics (PD) become available during drug development, protocols should be revised to include patients with compromised organ function where safe parameters regarding dosage adjustments have been determined.⁸

1. Renal function recommendations

- Eligibility criteria should be based on a contemporary, widely accepted, and clinically applicable equation that estimates glomerular filtration rate or a measure of glomerular filtration rate rather than an absolute serum creatinine concentration. The equation used for a particular patient population should remain consistent throughout the investigational drug development process.
- Sponsors should provide adequate justification for the inclusion/exclusion of patients with various degrees of renal impairment based on the stage of product development, safety profile of the product, understanding of the effect of renal impairment on the elimination of the drug, and the safety of study procedures in patients with renal impairment.
- Patients with renal impairment should be included in trials of investigational drugs when the available nonclinical and clinical data indicate that inclusion of patients with renal impairment would not place patients at unreasonable risk and/or adequate steps can be taken to mitigate potential risks. When there is an expectation that the systemic exposure will increase in patients with renal dysfunction, inclusion of such patients may be facilitated by prospective dose adjustment to produce similar systemic exposures to those seen in patients with relatively preserved kidney function.⁹

⁸ Lichtman S, Harvey R, Smit M, et al., 2017, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology – Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group, *JCO*, 35(33): 3753-3759.

⁹ Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials, Workshop Report, July 2018, workshop date April 16, 2018, available at <https://www.fda.gov/oc/2018/08-22-18-FDAsummary.pdf?1534970149> (accessed June 23, 2020).

Contains Nonbinding Recommendations

- Sponsors should address the need for and timing of studies to evaluate the effect of dialysis on drug clearance and the need for dosage adjustment for patients on dialysis.

If there is adequate representation of patients with varying degrees of renal impairment, as well as data sufficient to adequately describe the impact of renal impairment on PK of the drug, population pharmacokinetic (popPK) analyses of data from phase 2 or phase 3 clinical trials may be sufficient to characterize the impact of renal function.

2. *Cardiac function recommendations*

- Inclusion of patients with cardiovascular dysfunction may be possible when available nonclinical and clinical data, including PK and PD data, indicate that inclusion of these patients does not expose them to unreasonable risk.
- Patients with significant clinical cardiac abnormalities (e.g., clinical heart failure, unstable angina) should be excluded, especially in early-phase studies.
- Inclusion criteria should require 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).
- Ejection fraction (EF) measurement:
 - EF measured by either echocardiography or multigated acquisition scan is acceptable for determining cardiac EF for eligibility criteria purposes.
- QTc Prolongation:¹⁰
 - Sponsors should assess the effects of a drug on QTc during early clinical development.
 - Sponsors should determine whether a maximum QTc interval is necessary as a clinical trial eligibility criterion based on whether there is a specific known risk of QTc prolongation, either through non-clinical (e.g., hERG) or clinical trial data.

¹⁰ See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005) and the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs – Questions and Answers (R3)* (June 2017) for additional information regarding QTc prolongation.

Contains Nonbinding Recommendations

3. *Hepatic function recommendations*

Unlike other organ systems, liver biochemical testing does not provide sufficient evidence of adequate liver drug metabolic function. While 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,^{11,12} are adopted as markers of hepatic metabolism in dedicated PK studies, hepatic metabolism may also be influenced by cancer and inflammation, even in the setting of normal scoring. To gauge hepatic drug transformation capacity, pre-existing liver disease, as well as epidemiological, genetic, environmental, and historical variables (e.g., chronic alcohol use and a past history of adverse drug reactions) should be ascertained. Impaired hepatic blood flow, in particular when portal hypertension is evident, is critical to assessing how the liver metabolizes drugs.

- Inclusion of patients with severe hepatic impairment should be discussed with FDA.
- Patients with mild and moderate hepatic impairment¹³ (defined as the equivalent of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 1 toxicity), as well as those with aspartate transaminase (AST) and alanine transaminase (ALT) elevations defined as grade 3 by the NCI CTCAE (> 5 to 20 x ULN (upper limit of normal)), may be asymptomatic and able to tolerate doses equivalent to patients with normal hepatic function.
- Inclusion of patients with mild to moderate hepatic impairment may be appropriate when the available nonclinical and clinical data, including PK and PD data, indicate that inclusion of these patients does not present an unreasonable risk to patients.

B. Patients with prior or concurrent malignancy

Patients with prior malignancies of the same or different tumor type and patients with concurrent malignancies of the same or different tumor type (referred to as *prior or concurrent malignancies* in this guidance) whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational drug should generally be eligible for enrollment in clinical trials. For example, in initial dose finding or preliminary activity-estimating or proof-of-concept studies, patients with a history of prior or concurrent malignancies should not be excluded.

¹¹ See the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

¹² See the Protocol Template for Organ Dysfunction Studies, updated February 5, 2020 for the NCI criteria, available at https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm (accessed June 23, 2020).

¹³ Talal AH, Venuto CS, Younis I, 2017, Assessment of hepatic impairment and implications for pharmacokinetics of substance use treatment, *Clin Pharmacol Drug Dev*, 6: 206-212.