Broadening/Modernizing Eligibility Criteria for National Cancer Institute (NCI) Sponsored Clinical Trials

Based on 2017/2021 Joint Recommendations from the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (Friends)

ASCO/Friends published recommendations in October 2017 to broaden clinical trial eligibility relating to brain metastases, minimum age, HIV infection, organ dysfunction, and prior and concurrent malignancies (Kim, ES, et al. J Clin Oncol 2017, PMID: 28968170). The NCI's Cancer Therapy Evaluation Program (CTEP) brought together NCI divisions, offices, and centers that sponsor NCI clinical trials to review and operationalize these published recommendations. Subsequently, CTEP together with input from pharmacology experts on the NCI's Investigational Drug Steering Committee, developed protocol template language for eligibility criteria from many of these recommendations into its Generic Protocol Template utilized by the Experimental Therapeutics Clinical Trials Network (ETCTN). CTEP announced to all CTEP-funded lead protocol organizations and investigators that future protocols submitted to CTEP as of September 2018 include the protocol inclusion criteria text found in this guidance document to broaden eligibility criteria, unless clinical or scientific rationale supported some type of modification. Pages 3-10 in this document describes NCI guidance, 2017 ASCO/Friends inclusion criteria protocol template recommendations, and NCI inclusion criteria protocol template recommendations.

In May 2021, ASCO/Friends published additional recommendations to broaden eligibility criteria relevant to washout periods, concomitant medications, prior therapies, laboratory reference ranges and test intervals, and performance status (Kim, ES, et al. Clin Cancer Res. 2021, PMID: 33563632), and this additional guidance from 2021 is included on pages 11-14. On page 15, NCI proposes to remove the exclusion criteria seen in some protocols relating to psychiatric illness. A bullet list with bookmarked hyperlinks to each modernized eligibility criterion can be found on page 2, which includes criteria from both ASCO/Friends 2017 and 2021 publications. NCI's Experimental Therapeutics Clinical Trials Network (ETCTN) and NCI's National Clinical Trials Network (NCTN) will utilize these modernized eligibility criteria in clinical trials going forward. These guidelines may be modified based on protocol-specific or drug development-specific needs under the condition that a scientific or clinically based rationale is provided specifically. Since eligibility criteria must be as broad as safely possible to achieve diverse and representative populations in future clinical trials, CTEP will continue to collaborate with investigators and industry partners in a shared responsibility to expand eligibility and access to trials.

The updated template is posted on the CTEP website:

- https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm

Eligibility Criteria:

2017 ASCO/Friends & NCI eligibility criteria and protocol template guidance	**2021 ASCO/Friends & NCI eligibility criteria guidance**
• Treated/stable brain metastases	• Washout periods
• New/progressive brain metastases for early phase trials	• Concomitant medications
• New/progressive brain metastases for later phase trials	• Prior therapies
• Patients younger than age 18 years	• Laboratory reference ranges and test intervals
• Patients with HIV, HBV, and HCV infection	• Performance status
• Prior/concurrent malignancies	• Psychiatric Illness/Social Situations
• Organ function: cardiac, liver, and kidney	

NCI Recommended Protocol Text and Guidance based on Joint ASCO/Friends Recommendations

Treated/stable brain metastases

Criterion	NCI Guidance	ASCO/Friends Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language

Patients with treated/stable brain metastases	These recommendations do not apply to:
	• Trials designed specifically for primary brain cancers, e.g., GBM.
	• Trials designed specifically for brain metastases
	  ○ Radiation
	  ○ Systemic agent for a specific disease with the specified trial objective of evaluating brain metastases response to treatment (lung, melanoma, breast)
		Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period.	Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression.
			
			(**Note:** in specific trials, it may be necessary to add a time factor regarding the follow-up brain imaging, but this should be as lenient as medically indicated.)

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New/progressive brain metastases for early phase trials

Criterion	NCI Guidance	ASCO/Friends Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal (LMD) disease ***– early-phase trials***	Consider inclusion of an LMD cohort in early phase trials of drugs with anticipated CNS activity when relevant in the specific disease type under study. Consideration of CSF pharmacokinetic measurements is encouraged in this context. <u>Guidance for inclusion in early-phase trials</u> Patients with active brain metastases should be included early in clinical development when there is strong scientific rationale for likelihood of benefit based on molecular pathways or histology as well as preclinical data. - For drugs/modalities with less robust preclinical information on potential CNS activity, inclusion of patients with active brain metastases should still be considered, particularly if brain metastases are common in the intended-use population. - The inclusion of a CNS-specific cohort can provide valuable dosing and preliminary efficacy data to either support or refute inclusion in later phase trials. The mechanism of action of the drug or predicted blood-brain barrier (BBB) penetration should not necessarily influence a decision to include such patients. In addition, preclinical studies of intact BBB penetration are not necessarily reflective of blood-tumor barrier penetration.	No template language provided for inclusion criteria. <u>Template for exclusion:</u> (If patients with LMD are to be excluded, the following wording is suggested to avoid unnecessary exclusion of patients with imaging-only equivocal findings.) No known LMD.	Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are 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.

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New/progressive brain metastases for later phase trials

Criterion	NCI Guidance	ASCO/Friends Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease – ***later-phase trials***	When possible, inclusion of an LMD cohort in later-phase trials may be useful to provide access to investigational agents and to generate additional safety and efficacy data. <u>Guidance for inclusion in later-phase trials:</u> - Ideally, data from earlier-phase trials, in concert with the strength of the scientific rationale and preclinical data, can inform decisions on inclusion of patients with active brain metastases in later-phase trials. - When such data are not available, a few potential trial designs could allow patients with active brain metastases to enroll, either as a parallel cohort or as a defined subset within the larger clinical trial.	No template language provided for inclusion criteria. <u>Template for exclusion:</u> (If patients with LMD are to be excluded, the following wording is suggested to avoid unnecessary exclusion of patients with imaging-only equivocal findings.) No known LMD.	Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are 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.

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Patients Younger than Age 18 Years

Criterion	NCI Guidance	ASCO/Friends Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Patients younger than age 18 years	Pediatric-specific cohorts should be included in early-phase trials when there is strong scientific rationale for likelihood of benefit, based on molecular pathways or histology as well as preclinical data. Investigators and their industry collaborators are encouraged to discuss the inclusion of pediatric patients in the drug development plan early in the development process; and determine when it is relevant to study the agent in pediatric cancers. For studies that plan to include patients age younger than age 18, a pediatric oncologist co-investigator must be involved with the study and be responsible for writing the pediatric version of the informed consent.	a) Adolescent/pediatric patients age *[protocol author to insert age minimum and maximum specific to the study under consideration]* will be included after enrollment of adult patients after safety and toxicity in the adult population have been established. Participating sites will be notified when adolescent/pediatric patient enrollment may begin. b) Adolescent/pediatric patients age *[protocol author to insert age minimum and maximum specific to the study under consideration]* will be included starting one dose cohort behind the current adult cohort in which there are no dose-limiting toxicities identified. Participating sites will be notified when enrollment onto the adolescent/pediatric stratum may begin. c) Adolescent/pediatric patients age *[protocol author to insert age minimum and maximum specific to the study under consideration]* will be included in age- specific cohorts that will be staggered starting one dose cohort behind the current adult cohort in which there are no dose- limiting toxicities identified. Participating sites will be notified when each adolescent/pediatric cohort enrollment may begin. d) Adolescent/pediatric patients age *[protocol author to insert age minimum and maximum specific to the study under consideration]* are included in this trial in a separate cohort that will accrue simultaneous to the adult cohort *[specify age 18 and older or protocol-specific upper age limit]*.	No template language needed as the lower age limit should be added to the eligibility criteria. ASCO/Friends template language offers potential options for certain studies.

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HIV and Hepatitis Infection

Criterion	NCI Guidance	ASCO/Friends Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Patients with HIV infection	HIV-related eligibility criteria should be straightforward and focus on: - Current and past CD4 and T-cell counts - History (if any) of AIDS-defining conditions - Status of HIV treatment Patients with HIV infection should be treated using the same standards as other patients with co-morbidities. Anti-retroviral therapy should be considered a concomitant medication.	HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.	HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
For patients with evidence of chronic hepatitis B virus (HBV) infection and/or patients with a history of hepatitis C virus (HCV) infection	Patients with HBV and/or HCV should be treated using the same standards as other patients with co-morbidities. Therapy should be considered a concomitant medication.	None provided	For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) 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.

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Prior or Concurrent Malignancies

Criterion	NCI Guidance	ASCO/Friends Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Prior or concurrent malignancies	Patients with prior or concurrent malignancies should be eligible, especially when the risk of the malignancy interfering with either safety or efficacy endpoints is very low.	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.	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 are eligible for this trial.

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Organ Function: Cardiac, Liver, and Kidney

Criterion	NCI Guidance	ASCO/Friends Inclusion Criteria Template Language	NCI Inclusion Criteria Template Language
Cardiac function	Investigator assessment of a potential participant's risk for heart failure should use a validated clinical classification system (e.g., the New York Heart Association Functional Classification). Patients with active cardiac disease may be eligible after assessment of cardiac function by a cardiologist.	None provided	Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification[1]. To be eligible for this trial, patients should be class IIB or better. [1] *See page 10 for reference*.
Liver function	Liver function tests used to determine eligibility should be assessed relative to institutional normal ranges, not a universal cutoff point. These are guidelines that may be modified based on protocol-specific or drug development-specific needs.	None provided	Total Bilirubin: ≤ institutional upper limit of normal (ULN) AST(SGOT)/ALT(SGPT): ≤3 × institutional ULN
Kidney function	For agents for which renal excretion is not a major route of clearance and for which renal toxicity is not an issue, the threshold for creatinine clearance should be >30 mL/min.	Patients with creatinine clearance >30 mL/min (measured using Cockcroft-Gault equation or the estimated glomerular filtration rate from the Modification of Diet in Renal Disease Study) are included in the study. Established dose-modification strategies can allow safe and effective administration.	**ETCTN and Phase I trials** GFR* ≥60 mL/min/1.73m2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73m2. OR **NCTN trials (mostly large phase II and III trials)** GFR* ≥50 mL/min/1.73m2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73m2. **: GFR can be measured directly or estimated using the site's institutional standards.*

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The New York Heart Association (NYHA) Functional Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

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Washout Periods

Criterion	ASCO/Friends Recommendation
Washout periods PMID: 33563635	1. Time-based washout periods should be removed from protocol eligibility criteria in most cases. Any inclusion of time-based washout periods should be scientifically justified and clearly specified. 2. Relevant clinical and laboratory parameters should be used in place of time-based washout periods to address safety considerations. 3. Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.

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Concomitant Medications

Criterion	ASCO/Friends Recommendation
Concomitant medications PMID: 33563635	Concomitant medications use should only exclude patients from trial participation when clinically relevant known or predicted drug–drug interactions or potential overlapping toxicities will impact safety or efficacy.

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Prior Therapies

Criterion	ASCO/Friends Recommendation
Prior therapies PMID: 33563637	1. Patients are eligible for clinical trials regardless of the number or type of prior therapies and without a requirement to have received a specific therapy prior to enrollment unless a scientific or clinically based rationale is provided as justification. 2. Prior therapy (either limits on the number and type of prior therapies or requirements for specific therapies before enrollment) could be used to determine eligibility in the following cases: a. If the agents being studied target a specific mechanism or pathway that could potentially interact with a prior therapy. b. If the study design requires that all patients begin protocol-specified treatment at the same point in the disease trajectory. c. In randomized clinical studies, if the therapy in the control arm is not appropriate for the patient due to previous therapies received. 3. Trial designers should consider conducting evaluation separately from the primary endpoint analysis for participants who have received prior therapies.

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Laboratory Reference Ranges and Test Intervals

Criterion	ASCO/Friends Recommendation
Laboratory reference ranges and test intervals PMID: 33563636	1. Laboratory test results should only be used as exclusion criteria when scientifically justified and when abnormal test results confer safety concerns. 2. Laboratory reference values should account for potential normal variations due to race, ethnicity, age, sex, and gender identity (i.e., due to surgical and/or hormonal changes). 3. Routine reassessment of laboratory test-based exclusion criteria should be conducted during the course of clinical research and drug development as investigational agents progress from earlier- to later-phase clinical trials. 4. Increasing the intervals between protocol-specified tests should be considered to help reduce patient burden and increase ability to rely on routine clinical testing, especially in later cycles of treatment and over the evolution of the protocol from earlier- to later-phase clinical trials.

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Performance Status

Criterion	ASCO/Friends Recommendation	NCI Inclusion Criteria Template Language
Performance status PMID: 33563633	1. Patients with reduced PS (e.g., ECOG PS 2) should be included unless there is a scientific and/or clinical rationale for exclusion justified by established safety considerations. a. ECOG PS eligibility criteria should be based on the patient population in which the intervention is expected to be used in clinical practice. b. PS eligibility criteria should be continually reevaluated and modified throughout the clinical development process to reflect accumulated safety data of the investigational treatment. Decisions about PS eligibility criteria should be based on early clinical safety and efficacy data about the specific investigational agent or based on known data from other drugs in the same class with similar mechanism of action. Later-phase trials (e.g., phase II/III) should generally mirror the intended use population and ECOG PS 2 patients should be included, unless safety concerns have manifested in earlier-phase trials. The rationale for exclusion should be justified and stated explicitly. c. Incorporating the rationale for inclusion of a broader population into the protocol could help encourage investigators to enroll these patients. d. Performance status data should still be collected for use as a stratification factor, regardless of how it is incorporated into eligibility criteria. 2. Consider alternate trial designs, such as prespecified cohorts with lower PS that are exempt from the primary analysis, to encourage inclusion of these patients. These cohorts would generally be small in size and exploratory in nature and could be enrolled in an incremental way to enable an early stopping rule based upon safety data. Consideration of the data analysis approach for the broader eligibility cohort and subgroup analysis should be determined during the study design phase. Early discussion with FDA about enrollment of a broader population may have implications for marketing and post-marketing research requirements. 3. Additional assessments of functional status should be considered to better characterize the functional status of ECOG PS 2 patients and patients ages ≥65, such as activities of daily living (ADLs) and instrumental ADLs.	ECOG performance status[2] ≤2 (Karnofsky[2] ≥60%) [2] *See page 14 for reference.*

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Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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Psychiatric Illness/Social Situations

Criterion	NCI and CTAC Recommendation
Psychiatric illness and social situations CTAC Strategic Planning Working Group Update	1. Protocols should not have exclusion criteria for patients with psychiatric illness and social situations and should be as inclusive as possible. 2. Clinicians should use their clinical judgement and have discussions with potential trial participants to assess their ability to follow protocol requirements safely. Clinicians and site staff should work with patients to provide support needed to those interested in participating in clinical trials and avoid creating implicit bias disproportionately affecting underserved populations. 3. NCI wants to ensure that exclusion criteria do not contribute to inappropriately excluding certain groups of patients.

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