CTAC Strategic Planning Working Group (SPWG): Update on the Implementation of the Recommendations

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November 10, 2021

Topics for this Session

- Overview of the progress toward the initial implementation of the Strategic Planning Working Group recommendations
- Focus on the recommendation to broaden eligibility criteria to increase patient access to trials
  - Presentation of the CTEP Analysis of Implementing ASCO-Friends Broadened Eligibility Criteria in CTEP-Sponsored Trials (*Denicoff)*
  - Discussion (*all*)

    Are there additional steps that NCI should be taking at this time related to broadening eligibility criteria?

NCI Strategic Vision for Clinical Trials: 2030 and Beyond

Develop **flexible**, **faster**, **simpler**, **less expensive**, **high-impact** clinical trials that seamlessly integrate with clinical practice

- Streamline processes for trial design and execution
- Focus on essential endpoints
- Decrease regulatory hurdles and broaden trial access
- Increase efficiency of data collection

NCI Clinical Trials and Translational Research Advisory Committee Strategic Planning Working Group Overview

Re-assess strategic vision for clinical trials system for 2030 and beyond

Review and address necessary clinical trials infrastructure

Developed
15 recommendations and
3 operational initiatives

Themes:

- Trial Complexity and Cost
- Decentralized Trial Activities
- Promoting Accrual and Access
- New Data Collection Approaches
- PRO Data for Clinical Trials
- Operational Burden
- Statistical Issues
- Workforce Outreach and Training

Initial Implementation

Focus of Recommendations Selected for Initial Implementation

- Streamlining Clinical Trials
  - Limiting Data Elements Collected
  - Using EHRs to Support Clinical Trials
- Decentralized Trial Activities
  - Local/remote Conduct of Study Procedures
  - Telehealth Use in Clinical Trials
- Patient Access to Trials
  - Broaden Eligibility Criteria
  - Conduct Trials that Support Minority and Underserved Patient Needs

Streamlining Clinical Trials: Recommendation

Limiting Data Elements Collected

Rationale: Logistical complexity and data collection burden of NCI clinical trials increases costs and disincentivizes site participation

Recommendation: Limit clinical trial data collection in late phase trials to essential data elements

Limiting Data Elements Collected: Progress

- Analysis of recent NCTN Phase III protocols underway to gain an understanding of the current extent of data collection
- Expert Group will be convened in early 2022 to review findings and provide guidance on ways to limit data collection, e.g.
  - Which data elements are critical? Are there some that could be limited?
  - Could the frequency of collection of some data elements be reduced?
- Membership to include CTAC members, NCI clinical trials investigators, biostatisticians, and patient advocates as well as representatives from FDA, industry, CROs etc.

Streamlining Clinical Trials: Recommendation

Using EHRs to Support Clinical Trials

Rationale: Manually building and validating study-specific documents in local EHR and CTMS systems results in duplicative, burdensome, expensive, and nonproductive activity

Recommendation 1: Engage EHR and CTMS vendors to create mechanisms for automatically integrating study-specific documents into local implementations of their products

Rationale: Lack of EHR data element standardization and interoperability with clinical trial systems complicates extraction of clinical trial data from EHRs

Recommendation 2: Resolve the logistical and data quality challenges of extracting clinical trial data from electronic health records

Using EHRs to Support Clinical Trials: Progress

- Funded administrative supplements to P30 CCSG grants to develop approaches to automatically integrate study-specific documents into local CTMS and EHR systems [MD Anderson Consortium & Big 10 Consortium (IUSCCC)]

- Gathering information on internal and external initiatives addressing EHR study builds and/or data extraction from EHRs, e.g.
  - Alliance ICAREdata project
  - UCSF OneSource
  - TransCelerate eSource and Digital Data Flow
  - Leukemia and Lymphoma Society integrated electronic infrastructure for “Beat AML” study including EHR to electronic data capture

- Anticipate a presentation to CTAC in March 2022 summarizing findings and implications

Decentralized Trial Activities: Recommendation

Local/Remote Conduct of Study Procedures

Rationale: Local or remote conduct of select study procedures would increase trial efficiency and patient convenience

Recommendation: Identify study procedures modified due to COVID-19 to be performed locally or remotely that can be adopted as standard clinical trial practice

Local/Remote Conduct of Study Procedures: Progress

- CTEP is assessing which trial procedure modifications due to the pandemic can be continued

- Planning interviews with a sample of NCI clinical trials stakeholders to probe:
  - Costs and benefits of the modified procedures
  - Internal and external obstacles to continuation of the modified procedures
  - Steps required to enable continuation of the modified procedures

Decentralized Trial Activities: Recommendation

Telehealth Use in Clinical Trials

Rationale: Convenience of telehealth can improve clinical trial access

Recommendation: Expand the use of telehealth in clinical trials

Telehealth Use in Clinical Trials: Progress

- Conducted NCORP survey on telemedicine use during pandemic and community sentiment about continuation
- Reviewing data on state-level licensing and reimbursement policies, status of national physician and nurse cross-state licensing compacts
- Need pilot studies in a carefully-chosen setting where licensing and reimbursement policy are permissive to evaluate potential to enhance participation by rural and underserved populations
- NCI Workshop on telehealth for cancer care and clinical trials planned for January 2022

Patient Access to Trials: Recommendation

Broaden Eligibility Criteria

Rationale: Higher rates of chronic comorbidities in minority and underserved populations limit their participation in clinical trials

Recommendation: Broaden eligibility criteria to address distinctive medical problems experienced by minority and underserved patients

Broadening Eligibility Criteria: Progress

- CTEP implementation of ASCO/Friends recommendations underway – Andrea Denicoff will provide update today
- Considering pilot studies to further broadening eligibility criteria (e.g. performance status)

Patient Access to Trials: Recommendation

Conduct Trials that Support Minority and Underserved Patient Needs

Rationale: Clinical trials often do not adequately address cancer treatment needs of minority and underserved populations

Recommendation: Address the distinctive medical problems experienced by minority and underserved patients during cancer treatment

Patient Access to Trials: Progress

- Connecting Underrepresented Populations to Clinical Trials (CUSP2CT)
  - Designed to implement and evaluate outreach and education interventions to increase referral of racial/ethnic populations to NCI-supported clinical trials
  - Anticipate 4 to 6 U01 awards and one U24 Coordinating Center
  - RFA-CA-21-057 (U01) and RFA-CA-21-058 (U24)

- Plan discussions with M/U NCORPs regarding issues arising in safety-net settings; Exploring two concepts:
  - Cancer care delivery research (CCDR) studies and additional resources needed for the conduct of clinical trials in safety-net settings
  - Clinical studies addressing aspects of cancer treatment that are of specific concern for minority and underserved patients

Workforce: Emerging Issues

Analyze current outreach and training support for the oncology workforce

Staff attrition during COVID

- Plan to assess more systematically through Cancer Centers survey and possibly in-depth investigator interviews
- Findings will be shared with CTAC to determine whether any actions are warranted

Demographic breadth of NCI investigator workforce

- Plan to collect data to inform workforce and training discussions

CTAC SPWG Implementation Leads

- Seeking CTAC members to serve as “champions” for each SPWG recommendation currently in active implementation
  - Provide input to implementation team activities
  - Review findings
  - Participate in CTAC reporting and discussion

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CTEP Analysis of Implementing ASCO-Friends Broadened Eligibility Criteria in CTEP-Sponsored Trials

Andrea Denicoff, MS, RN

Clinical Investigations Branch,

Cancer Therapy Evaluation Program (CTEP), DCTD

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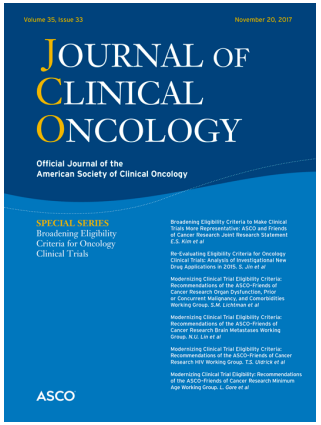
CTAC Meeting
November 10, 2021

1. *Describe CTEP Analysis*
2. *Provide pilot project plans*
3. *Gather feedback*

Background

- **2017**: ASCO/Friends publish broadened eligibility criteria to include patients with:
  - Brain metastases
  - Prior and concurrent malignancies
  - HIV infection
  - Organ dysfunction, and
  - Patients younger than age 18 years



Kim, ES, et al. J Clin Oncol 2017, PMID: 28968170

- **2018**: NCI created protocol template language based on ASCO/Friends guidance: https://ctep.cancer.gov/protocoldevelopment/docs/NCI_ASCO_Friends_Eligibility_Criteria.pdf

- **2021**: NCI analysis of broadened criteria used in CTEP trials presented during a poster discussion at ASCO Annual Meeting
  - Authors: A. Denicoff, S. Percy Ivy, Kathy Worthington, Jinxiu Zhao, Nita Seibel, Grace Mishkin, Meg Mooney, and Richard F. Little J Clin Oncol 2021 39:15_suppl, 6518

Methods: Evaluating CTEP Protocols for Consistency with Broadened Eligibility

- Protocols first approved by CTEP between 11/1/2018 and 4/30/2020 were assessed for consistency with the new eligibility criteria template
- Eligibility criterion were abstracted from protocols and compared with the NCI template language and the ASCO/Friends guidelines
- All criterion were reviewed by 2 or more NCI clinicians (Medical Oncology and Nurse Practitioner) and 2 information specialists (PhD and MS)
  - Weekly meetings over a year were held to conduct reviews
  - Protocols with a pediatric focus or in malignancies primarily seen in adults, were not relevant for the lower age criterion analysis
- Criteria Scoring:
  - Implemented new criteria = Yes or No
  - Not Addressed = Specific eligibility criteria missing from protocol, thus presumed to allow inclusion

Methods: Examples of Eligibility Criteria Template

Criterion	Protocol Template Language
HIV infection	HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
Cardiac function	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. To be eligible for this trial, patients should be class 2B or better.

Methods: Example of Review Challenges

- Example of exclusion criteria from a phase II study in advanced solid tumor study:
  - Uncontrolled intercurrent illness including, but not limited to, ongoing or **active infection**, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, evidence of any acute or chronic viral illness or disease, or *psychiatric illness/social situations that would limit compliance with study requirements.*

Results: CTEP-Sponsored Protocols Reviewed (n=122)

Phase Category	Phase	Number of Protocols	Percentage
Early Phase	I	22	71%
	I/II	16	
	II	49	
Later Phase	II/III	7	29%
	III	28	
Grand Total		**122**	**100%**

Note: 102 (84%) had an IND (Investigational New Drug) with an industry collaborator.

Results: Protocols by Phase and Adult vs Pediatric

Phase Category	Phase	No. of Pediatric Protocols	No. of Adult Protocols	No. of Total Protocols
Early Phase	I	3	19	22
	I/II	2	14	16
	II	8	41	49
Late Phase	II/III	0	7	7
	III	5	23	28
Grand Total		**18**	**104**	**122**

Results: Lead Organization in Protocols Reviewed

Lead Organization	Number of Protocols
NCTN	69
ETCTN	44
Other Consortia	9
Grand Total	**122**

Results: Lead Disease in Protocols Reviewed

Major Disease Category	Number of Protocols
Solid tumors	90
Hematologic cancers	32
Grand Total	**122**

Age Criterion Results

- The CTEP portfolio spans both pediatric and adult trials
  - Trials are available for all relevant age groups
  - Where appropriate, adolescents and young adults (AYA) are included

- Of the 122 studies reviewed, 6 trials were considered relevant for age analysis; 3 were consistent with the age criterion
  - Many of the adult studies were in diseases not seen in pediatrics, e.g., prostate cancer, adult leukemias, etc.

Results of Broadened Criterion Implemented or Not

Broadened Eligibility Criteria Category	Liver function	Kidney function	Cardiac function	HIV	Prior/ Concurrent Malignancies	Treated / Stable Brain Metastases	New / Progressive Brain Metastases
No. of Analyzable Trials	122	122	122	122	122	86*	86*
Criteria Implemented = YES	87.7%	86.1%	58.2%	76.2%	34.4%	51.2%	15.1%
Criteria NOT Addressed	5.7%	4.9%	10.7%	17.2%	19.7%	32.5%	47.7%
Criteria Implemented = NO	6.6%	9.0%	31.1%	6.6%	45.9%	16.3%	37.2%

*Criterion not relevant for trials in non-metastatic disease and primary CNS cancers

CTEP Analysis Conclusions

- Our analysis identifies the need that as sponsors, we must conduct focused reviews of eligibility criteria to assure implementation.
- Eligibility guidelines without attention to specific template language is not enough to remove clinical trial barriers.
  - Criteria not addressed in protocols may allow but does not actively promote inclusion (e.g., brain metastases)
- NCI is committed to continuing to broaden eligibility criteria to expand opportunities for under-represented and diverse populations to participate in clinical trials.
  - Results have been discussed internally at NCI with next steps to conduct a pilot with focused reviews.

CTEP Pilot to Broaden Eligibility Criteria in Clinical Trials

Goal: CTEP Protocol Review Committee to conduct focused reviews of eligibility criteria (EC) and compare to ASCO/Friends EC and NCI protocol template language in NCTN and ETCTN protocols to further expand EC.

Pilot Implementation:

- CTEP will broadly announce pilot expectations for NCTN and ETCTN protocols
- Study teams will need to provide scientific and/or clinical rationale for protocols that have EC restricted in some way and NCI will review.
- CTEP Project Managers will review and track EC in protocols prospectively.
- Pilot will begin in early 2022 and include May 2021 ASCO/Friends further expanded EC, including:
    - Washout periods, concomitant medications, prior therapies, laboratory reference ranges and test intervals, and performance status

- Clinical Cancer Research, May 2021, Vol 27, No 9. PMID: 33563632 (includes 6 papers)

Discussion

CTAC Feedback & Discussion

- ASCO/Friends May 2021 papers recommend using minimal exclusion criteria. At the same time, there is an argument for adding expanded "inclusion criteria" to encourage enrolling investigators to consider patients who may have previously been excluded (e.g., explicitly stating that patients with treated brain metastases <u>are</u> eligible).
  - **Feedback requested:** should protocols generally include fewer, minimal criteria or more criteria emphasizing patients who can be included?
- NCI-supported trials take different approaches to criteria excluding participants with psychiatric or social conditions that may make it difficult to comply with the study requirements. NCI wants to ensure that these exclusion criteria do not contribute to implicit biases that inappropriately exclude certain groups.
  - **Feedback requested:** how does CTAC recommend this issue be approached?

Impact of Expanded Eligibility Criteria: Discussion

- Are there additional actions that NCI should take at this time?
- Should a pilot study be considered to expand select criteria further?
  - Should such a pilot be implemented as an additional arm on an existing study or as a free-standing study?
  - Which of the expanded eligibility criteria would be the most promising candidates for a pilot?

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