

Reducing Trial Barriers: Broadening Eligibility Criteria, Improving Informed Consent Language, and Providing National Coverage Analyses for NCI Network Clinical Trials

*Andrea Denicoff, MS, RN, ANP
Head, NCTN Clinical Trials Operations
Clinical Investigations Branch, CTEP, DCTD, NCI*



a National Cancer Institute program

Clinical Trials Advisory Committee (CTAC)
Meeting
November 1, 2017

Outline

1. Review ASCO and Friends of Cancer Research joint recommendations on broadening eligibility criteria
 - Describe implementation plan within CTEP Trials
2. Describe revisions to NCI's Informed Consent Document Template
 - Includes new Common Rule requirements
3. Describe effort to provide National Coverage Analyses of NCI's Network trials

Broadening Eligibility Criteria to Make Clinical Trials More Representative

Joint Recommendations of the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (Friends)

Manuscripts published as *Journal of Clinical Oncology* Special Series. October 2, 2017 at ascopubs.org/journal/jco

ASCO-Friends Project Overview

- Prioritized assessment of specific eligibility criteria in 4 major areas:
 1. Brain Metastases
 2. Minimum Age
 3. HIV/AIDS
 4. Organ Dysfunction, Co-morbidities, Prior and Concurrent Malignancies
- Formed multi-stakeholder working groups including:
 - Patient advocates
 - Clinical investigators
 - FDA medical reviewers
 - NCI medical officers
 - Drug and biotech manufacturers
 - Pharmacologists
 - Biostatisticians

ASCO-Friends Brain Metastases Recommendations

- Patients with treated and/or stable brain metastases:
 - Stable = no progression for at least 4 weeks after local therapy
 - Routinely include in all phases, except where compelling rationale
- Patients with active (untreated or progressive) brain metastases:
 - No automatic exclusion
 - A one-size-fits-all approach is not appropriate. Factors such as history of the disease, trial phase and design, and the drug mechanism and potential for CNS interaction should determine eligibility.
- Patients with leptomeningeal disease:
 - In most trials, exclude, although there may be situations that warrant a cohort of such patients in early phase trials

ASCO-Friends Minimum Age Recommendations

- Initial dose-finding trials:
 - Pediatric-specific cohorts should be included when there is strong scientific rationale (based on molecular pathways or histology and preclinical data)
- Later-phase trials:
 - Trials in diseases and therapeutic targets that span adult and pediatric populations should include pediatric patients with the specific disease under study
 - Patients aged 12 years and above should be enrolled in such trials
 - Patients under 12 years may also be appropriate

ASCO-Friends HIV+ Recommendations

- Cancer patients with HIV infection who are healthy and low-risk for AIDS-related outcomes should be included
- HIV-related eligibility criteria should be straight-forward and focus on:
 - Current and past CD4 and T-cell counts
 - History (if any) of AIDS-defining conditions
 - Status of HIV treatment
- Treated using the same standards as other patients with co-morbidities, and anti-retroviral therapy should be considered a concomitant medication

ASCO-Friends Organ Dysfunction Recommendations

- Informed by an analysis of Kaiser dataset of 13,000 patients newly diagnosed in 2013-2014
- Renal function should be based on creatinine clearance (calculated by Cockcroft-Gault or MDRD)
 - Liberal creatinine clearance (e.g., >30 mL/min) should be applied when renal excretion not significant
 - Follow established dose modification strategies.
- Hepatic Function
 - Current tests are inadequate, particularly drug metabolism capability
 - Employ standard clinical assessments relative to institutional normal ranges

ASCO-Friends Prior and Concurrent Malignancies Recommendations and Cardiac Testing

- Prior Malignancy
 - Patients eligible if prior therapy at least 2 years prior and no evidence of disease
- Concurrent Malignancy
 - Patients eligible if clinically stable and not requiring tumor-directed therapy
- Cardiac testing
 - If no known cardiac risks, ejection fraction tests should not be exclusionary
 - Investigator assessment with a validated clinical classification system
 - If no cardiac risks, ECG should be eliminated in later phases

ASCO-Friends Initiative Next Steps (as of October 2017)

- Initiate implementation projects
 - Education and awareness campaigns for sponsors, investigators, IRBs, patients, etc.
 - NCI and Network Group endorsements
 - Tools for sponsors, investigators, and IRBs
- Consider new working groups to make recommendations for additional eligibility criteria
 - Project leadership emphasizes that concrete steps toward implementation of the existing recommendations must take priority

Implementation in CTEP Network Clinical Trials

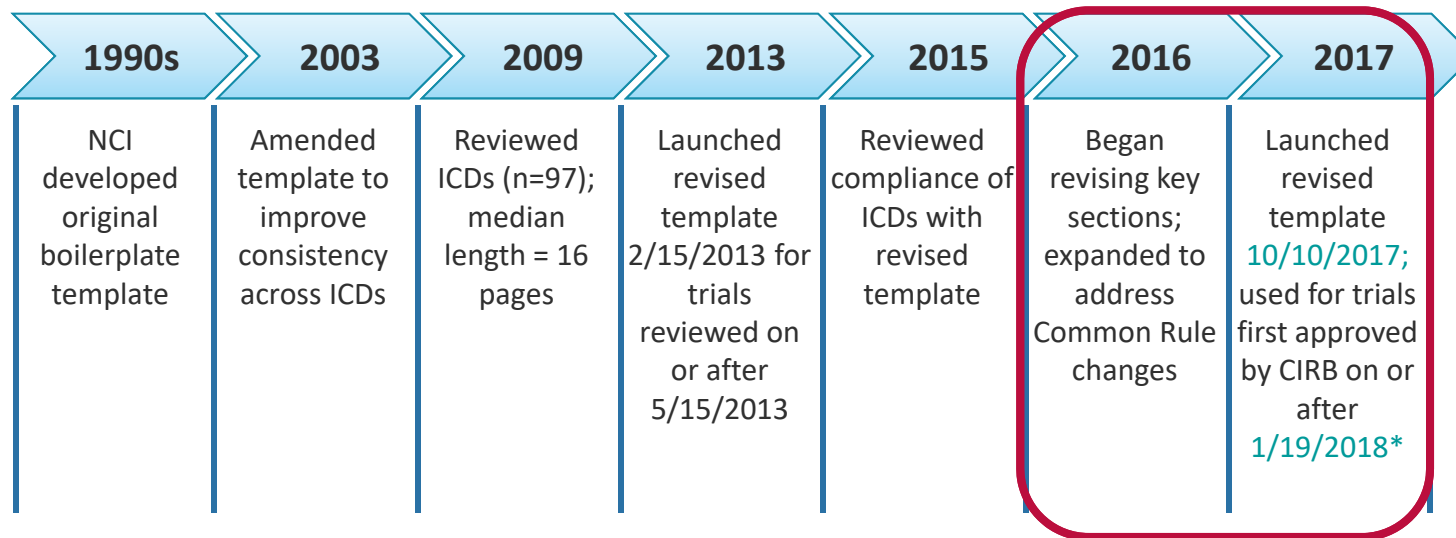
- ETCTN: Early Therapeutics Clinical Trials Network
 - Incorporate ASCO-Friends recommendations in new centralized protocol authoring with eligibility criteria as part of protocol template
 - Collaborate with NCI's Clinical Trials Reporting Program (CTRP) to structure eligibility to improve downstream impact on trial searching
- NCTN: NCI National Clinical Trials Network
 - NCTN Groups - continue to expand use of broadened eligibility criteria across disease and scientific committees
 - Network Accrual Core Team (ACT) Eligibility Task Force - Network Operations Leaders, Site Investigators, Research Coordinators and Patient Advocates involved in dissemination

Broadening Eligibility: Challenges to Implementation

- Trial collaborations with industry will require discussions to balance safety and overly strict exclusion criteria
 - FDA's role will be important
- PIs and study teams will need to remain committed to considering eligibility, avoid re-use of prior more restrictive criteria from older trials
- Site investigators and their research teams will need to modify site processes to identify and screen potential clinical trials participants
- To be successful, it will require increased awareness and commitment to broaden eligibility criteria across all stakeholder groups

Revisions to NCI's Informed Consent Document Template

NCI Informed Consent Template Timeline



***Note:** If the implementation of changes to the Common Rule is delayed, NCI will provide additional instructions about use of the October 2017 ICD Template

NCI Informed Consent Template Revision: Process

- **Internal revision process in 2016**
 - Revised key sections identified through prior evaluations, including costs, extra tests, and general integration of biomarker research
- **Stakeholder review in 2016**
 - Distributed Revision #1 to prior working group members, Groups, and other NCI entities
 - Received 29 responses; reviewed and reconciled comments and edits
- **Final Revisions to the [Common Rule](#), January 2017**
 - Released by OHRP on January 19, 2017 and effective January 19, 2018
 - NCI implemented changes to the consent template to comply with the Final Rule requirements¹
 - Conducted iterative review with plain language specialist and finalized Revision #2
- **Stakeholder review in 2017**
 - Circulated Revision #2 & received 18 responses; reviewed and reconciled comments and edits
- **Final revised template published, October 2017**

NCI Informed Consent Template Revision: Key Changes

- Formatting changes to improve usability for ICD authors
- Compliance with new OHRP Common Rule requirements
 - New “Overview and Key Information” section at the beginning of the ICD
 - More information about storage and potential use of identifiable information or identifiable biospecimens
- Additional information and examples for trials with genomic testing
- Clarification of “Costs” and “Exams, Tests, and Procedures” sections to address potential billing and insurance coverage issues
 - Better delineation between routine, clinically indicated tests and procedures that may be done more frequently than usual but are still billable, and tests and procedures done for research purposes that are not billable
- Improvements to readability and language to facilitate patient understanding

NCI Informed Consent Template Revision: New OHRP Common Rule Requirements

- Regulatory language on the new Key Information section from the Final Rule to revise the current 45CFR 46, Subpart A (Common Rule):
 - Final Rule language at § II.116(a)(5)(i): “Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research.”
- Official guidance has not been published, but the commentary accompanying publication of the Final Rule described the expectations for this new section:
 - “In general, we would expect that to satisfy § II.116(a)(5)(i), the beginning of an informed consent would include a concise explanation of the following: (1) the fact that consent is being sought for research and that participation is voluntary; (2) the purposes of the research, the expected duration of the prospective subject’s participation, and the procedures to be followed in the research; (3) the reasonably foreseeable risks or discomforts to the prospective subject; (4) the benefits to the prospective subject or to others that may reasonably be expected from the research; and (5) appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject.”

NCI Informed Consent Template Revision: Key Dates

- **October 10, 2017:** Revised Informed Consent Template is published on the CTEP website
- **January 18, 2018:** Protocols that have an approval (either Approval Pending Modification or full Approval) by the CIRB before this date **do not need to use** the revised Informed Consent Template.
 - However, protocols that have not yet activated **can** begin using the revised Informed Consent Template for submissions from this point forward
- **January 19, 2018:** Protocols that are **initially approved** by the CIRB on or after this date **must use** the revised Informed Consent Template, which includes those studies that receive an “Approval Pending Modification” from NCI’s CIRB.

NCI Informed Consent Template Revision: Website and Email Address

- Revised template is available on the CTEP website at:
https://ctep.cancer.gov/protocoldevelopment/informed_consent.htm
 - Or use the short URL: <https://go.usa.gov/xn32M>
- We expect this template to be a “living document”
 - We expect additional revisions based on new needs and changes in the science
 - Provide suggestions for changes to the email box we have created:
NCICTEPComments@mail.nih.gov
- Thanks to all stakeholders for continued feedback and input!

Reducing Trial Barriers: National Coverage Analyses of NCI Network Trials

Clinical Trials National Coverage Analyses

- A National Coverage Analysis (NCA) is a review of all tests, procedures, and interventions associated with a clinical trial to determine which ones are ‘billable’ and which are ‘not billable’ to a third party payer.
- CMS [National Coverage Determination \(NCD\) for Routine Costs in Clinical Trials](#) (310.1) is used as a core resource to create NCAs
 - Excerpts from “routine costs” in clinical trials include:
 - “Items or services that are typically provided absent a clinical trial”
 - “Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service in particular, for the diagnosis or treatment of complications”

<https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ncdver=2&fromdb=true>

Need for NCAs in NCI Network Trials

- All sites must comply with federal regulations to bill for routine care in clinical trials
 - This is a complex operational and regulatory challenge faced by academic and community sites
 - Each site has independently created CAs for NCI Network trials – this is inefficient and costly
 - Sites may decide not to open or participate in a national NCI CT if the financial burden to the institution or patient is found to be considerable
- 2015 ASCO-NCI Symposium identified the centralized creation of NCAs for national CTs as a potential solution
 - [Szczepanek CM et al](#), doi: 10.1200/JOP.2016.020313
- 2016 ASCO-AACI Workshop to address administrative and regulatory burden in cancer clinical trials endorsed using NCAs and supported NCI's pilot effort
 - [Vose JM et al](#), doi/abs/10.1200/JCO.2016.69.6781

Goals of NCI Pilot: Create NCAs in Network Trials

- Provide centralized resource to increase efficiency and decrease burden (financial and time) on institutions
- Increase transparency of NCI funding and if additional funding is available for NCI Network CTs
- Reduce or prevent patients from being billed for tests or services they believed would be covered by insurance/Medicare or the study
- Reduce or prevent inaccurate billing of research tests by the sites to Medicare and third party payers
- Increase awareness of Medicare coverage policy among organizations leading CTs
- Work with lead organizations to align required tests and exams within clinical care guidelines and medical necessity

NCA Pilot Process and Initial Results

- Coordinated by NCI's Cancer Trials Support Unit (CTSU)
- Formed a Coverage Analysis Working Group with representatives from all the NCTN & NCORP Groups, billing consultants, and NCI staff in late 2015
- Created NCAs for select Phase 2 and all Phase 3 NCTN and NCORP multisite trials that were newly or recently activated as of May 2016
 - NCAs are created by the CTSU, reviewed by the Group and trial PIs, and approved or revised
- Surveyed sites after 1 year
 - Over 230 respondents reported high satisfaction
 - Respondents wanted NCAs for more trials and wanted them to be posted sooner
- Results of pilot presented as 2017 ASCO poster:
 - Denicoff, Mishkin, Good, Patrichuk, et al, National Coverage Analyses for NCI Clinical Trials: A Pilot Project to Reduce Participation Barriers.
http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.6542#

Collaboration with CMS

- NCI's CTEP & DCP, CTSU and Billing Consultants worked with the CMS Coverage and Analysis Group to review NCA processes in aligning with CMS coverage policies and national clinical guidelines
- Presented NCA pilot in March 2017 to the Medical Directors of the Medicare Administrative Contractors (MACs)
 - Increased awareness among MACs of NCI's new NCA process
 - Highlighted challenges of implementing national trials across different MAC regions
 - Discussed possible alignment of MAC Local Coverage Determinations (LCDs) to support the medically necessary tests and services required in trials

Current Efforts with NCAs in NCI Network Trials

- Working with Groups to draft NCAs during protocol development with the goal of completing NCA prior to trial activation
- **January 2017:** NCAs posted on the CTSU website for **22 trials**
 - 17 NCTN trials and 5 NCORP trials
 - MATCH and LUNG-MAP counted as a single trial, with 20 NCAs for MATCH sub-studies and 6 NCAs for LUNG-MAP sub-studies
- **October 2017:** NCAs posted on the CTSU website for **67 trials**
 - 54 NCTN trials and 13 NCORP trials
 - MATCH and LUNG-MAP counted as a single trial, with 31 NCAs for MATCH sub-studies and 6 NCAs for LUNG-MAP sub-studies
- CTSU will begin working with ETCTN to develop NCAs

NCAs: Challenges to Implementation

- Protocols and informed consents have not consistently included information that provides clarity that tests and/or procedures are medically necessary versus a study data point
 - New directions to clarify are part of the NCI ICD Template update
- Investigators, Lead Protocol Organizations and study teams must be aware of and align protocols with national clinical care guidelines and/or recent published evidence in peer reviewed journal per CMS
- Clinical trial sites must review the NCAs and modify based on their regional Medicare Contractor local coverage determinations and other large regional insurance coverage policy variation

Summary

- Broadened eligibility criteria: implementing will require concerted efforts among all stakeholder groups
- Updates to NCI Informed Consent Template: living document that will continue to need input and updating to stay current
- National Coverage Analyses of NCI Network Clinical Trials: will require collaborations and early review of protocol's possible costs

Barriers to clinical trial accrual continue to arise and will continue to require multi-stakeholder collaborations to address them

Discussion