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Broadening Eligibility Criteria to Make Clinical Trials More Representative

Joint Project of the American Society of Clinical Oncology and Friends of Cancer Research

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Disclosures

- Research Funding
  - AstraZeneca
  - Hoffmann La Roche

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Overview

- Background
- FOCR-ASCO collaboration
- FOCR-ASCO recommendations
- Next steps

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Clinical Trial Eligibility Criteria

- Essential component of clinical trials
  - Define the characteristics of population under study
  - Protect safety of study population
- Frequently overly restrictive
  - Limit accrual
  - Prevent patients from accessing investigational interventions that may provide clinical benefit
  - Limit the ability to understand the therapy's benefit-risk profile across a broad patient population
  - Jeopardize generalizability of trial results

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Potential Limitations of Traditional Eligibility Criteria

- Developed through experience with cytotoxic chemotherapy
- Often duplicated from prior trials using standardized templates
- Not appropriate for specific patient populations targeted by the evolving novel therapeutic agents

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FDA ADMINISTRATION

PUBLIC WORKSHOP:

EVALUATING INCLUSION AND EXCLUSION CRITERIA IN CLINICAL TRIALS

WORKSHOP REPORT

The National Press Club • Washington, DC • April 16, 2018

Barriers *to*

Patient Enrollment in Therapeutic Clinical Trials for Cancer

A Landscape Report

ACS CAN April 11, 2018

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FRIENDS OF CANCER RESEARCH ANNUAL MEETING

November 2016 - Washington DC

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The American Society of Clinical Oncology's Blueprint for Transforming Clinical and Translational Cancer Research

Neal J. Meropol, *University Hospitals Case Medical Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*
Mark G. Kris, *Memorial Sloan-Kettering Cancer Center, New York, NY*
Eric P. Winer, *Dana-Farber Cancer Institute, Boston, MA*

J Clin Oncol 30:690-691, 2012

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Modernizing Eligibility Criteria for Molecularly Driven Trials

Edward S. Kim, David Bernstein, Susan G. Hilsenbeck, Christine H. Chung, Adam P. Dicker, Jennifer L. Ersek, Steven Stein, Fadlo R. Khuri, Earle Burgess, Kelly Hunt, Percy Ivy, Suanna S. Bruinooge, Neal Meropol, and Richard L. Schilsky

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ASCO-Friends of Cancer Research Project Overview

- **Prioritized assessment of specific eligibility criteria:**
  - Brain Metastases, Minimum Age, HIV/AIDS, Organ Dysfunction, and Prior and Concurrent Malignancies
- **Formed multi-stakeholder working groups**
  - Patient advocates
  - Clinical investigators
  - FDA medical reviewers
  - Drug and biotech manufacturers
  - Biostatisticians
  - Pharmacologists

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What is the goal?

- **Challenge assumptions & past practice**
- **Create new culture – only exclude where safety warrants**
- **Not just publication of recommendations, but <u>implementation</u>**

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ASCO-Friends Recommendations Development

- Working Groups developed consensus recommendations as four separate manuscripts.
  - Recommendations presented at November 2016 Friends' Annual Meeting and highlighted in Moonshot Task Force report.
  - Representatives from the NCTN participated in the 2016 meeting providing examples of ongoing efforts within the NCTN groups to appropriately expand eligibility criteria
- ASCO and Friends developed joint statement including summary recommendations and discussion of implementation.
  - ASCO Board of Directors and Friends' leadership approved the statement.
- Manuscripts published as *Journal of Clinical Oncology* Special Series.
  - November 20, 2017 Vol 35, Issue 33 at ascopubs.org/journal/jco

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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.

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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.

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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.

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Organ Dysfunction Recommendations

- Informed by an analysis of Kaiser dataset of 13,000 newly diagnosed patients in 2013-2014.

Table 2. Kaiser Permanente Northern California 2013 to 2014: Lowest Glomerular Filtration Rate at Cancer Diagnosis

	% of Patients (N = 13,000)						
Cancer Site	< 30 mL/min	30-39 mL/min	40-49 mL/min	50-59 mL/min	30-59 mL/min	< 60 mL/min	≥ 60 mL/min
Breast	1.4	2.3	5.9	10.7	18.9	20.3	79.7
Colorectal	2.4	4.0	6.9	11.3	22.2	24.6	75.4
Lung	2.6	4.7	9.0	11.4	25.1	27.7	72.3
Bladder	9.1	9.5	10.9	16.3	36.7	45.9	54.1

NOTE. Calculated using Cockcroft-Gault equation.

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Lichtman SM, Harvey RD, Smit M-A D, et al. J Clin Oncol 2017;33:3753-3759.

Organ Dysfunction Recommendations

- 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 and avoid imposing a universal cutoff point
- Cardiac function
  - If no known cardiac risks, ejection fraction tests should not be exclusionary
  - Investigator assessment of risk for CHF with a validated clinical classification system
  - If no cardiac risks found in early–phase trials, ECG should be eliminated in later phases

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Prior and Concurrent Malignancies Recommendations

- General Principal
  - Include patients when the risk of the prior or concurrent malignancy interfering with safety or efficacy endpoints is very low
- 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

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SWOG Phase III NSCLC Trials: Evolution of Selected Eligibility Criteria

- S9509
  - Phase III Trial of Paclitaxel plus Carboplatin versus Vinorelbine and Cisplatin in Untreated Advanced NSCLC
- S1400
  - Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer (LUNG-MAP)
- S1403
  - Randomized Phase II/III Trial of Afatinib Plus Cetuximab Versus Afatinib Alone In Treatment-Naïve Patients With Advanced, EGFR Mutation Positive NSCLC

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Evolving Eligibility Criteria in SWOG Phase III NSCLC Trials (1995 -2014)

CRITERIA	S9509	S1400	S1403
Brain metastases	No	Yes (treated)	Yes (asymptomatic)
Prior Malignancies	Skin (basal,squamous) In-situ cervical; all others > 5years	Skin, cervical (is) Stage I/II in CR Any NED > 5 years	Skin, cervical (is) Stage I/II in CR Any NED > 5 years
Liver function tests	Single criteria	Two criteria (with or without mets	Two criteria (with or without mets
HIV positive	No mention	Yes (controlled)	No

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Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015

Susan Jin, Richard Pazdur, and Rajeshwari Sridhara

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JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015

Susan Jin, Richard Pazdur, and Rajeshwari Sridhara

- FDA reviewed eligibility criteria for 2015 commercial IND applications (297)
- Brain metastases
  - 47% allowed treated or stable brain metastases
- Minimum age
  - 1/286 adult protocols permitted patients < 18 years of age ($\geq$ 16)
- HIV
  - 1.7% allowed HIV positive patients with stable disease and/or adequate CD4
- Serum creatinine
  - > 75% required $\leq$ 1.5 X ULN

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Next Steps

- Initiate implementation projects
  - Education and awareness campaigns for sponsors, investigators, IRBs, patients, etc.
  - NCI and Cooperative 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

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Implementation Activities

- **FDA Draft Guidances**
  - ASCO and Friends submitted recommended draft guidance language to FDA on August 8, 2018
    - Five documents addressing the topics reviewed by the ASCO-Friends work groups (brain metastases, HIV, organ dysfunction, prior/concurrent malignancies, and minimum age)
  - If FDA releases draft guidance documents on these topics, ASCO and Friends will announce when they are available and will develop comments for submission
- **Revised Version of NCI CTEP Generic Protocol Template**
  - CTEP staff worked with their Protocol Review Team, with input from NCI's Investigational Drug Steering Committee, to adapt the proposed revisions submitted by ASCO/Friends into the **NCI CTEP Generic Protocol Template**
  - A modified template was released on September 4, 2018 and posted on the CTEP website

  https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm
  - NCI's Experimental Therapeutics Clinical Trials Network (ETCTN) and NCI's National Clinical Trials Network (NCTN) will utilize these broadened eligibility criteria in clinical trials

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Dissemination Activities

- **NCTN Cooperative Group Dissemination**
  - All Cooperative Group Chairs have scheduled presentations of the ASCO-Friends recommendations at their 2018 meetings.
    - Alliance Spring Group meeting (May 12)
    - SWOG Fall Group meeting (October 5)
    - ECOG-ACRIN Fall Group meeting (October 25-27)
  - Modified NCI CTEP Generic Protocol Template is on the Agenda for the SWOG Committee Chairs Meeting October 6, 2018
  - Implementation plan to follow

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Conclusions

- Restrictive eligibility criteria constitute a barrier to successful completion of clinical trials
- Many groups are involved in efforts to appropriately broaden eligibility criteria
- ASCO – FOCR collaboration has proposed modifications in criteria in several areas: brain metastases, minimum age, HIV/AIDS, organ dysfunction, and prior and concurrent malignancies
- ASCO working to broadly disseminate the recommendations including working with the FDA on guidance documents on these areas
- Modified NCI CTEP Generic Protocol Template incorporating the ASCO – FOCR recommendations has been released

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