ASCO/FOCR/ FDA Modernizing Eligibility Criteria Project

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Disclosure Information

I am an employee of the Federal Government and have no financial relationships to disclose.

I will not be discussing off-label and/or investigational use of named products in my presentation.

Goal of Clinical Trials

- Understand the risks and benefits of a therapy in a specific population/ disease setting.
- To facilitate ability to generalize study findings and ideally apply to all patients with the disease(s) studied.
  - Eligibility criteria are key component.

Eligibility criteria goals

- Define the patients who may potentially receive therapy within a given trial
- Facilitate clinical trial accrual
- Permit patient access to investigational agents
- Protect patients treated on trial (or by excluding from trial)
- Yield trial results that are generalizable to the broader US population.

Disadvantages of excessive eligibility criteria

- Limiting accrual to clinical trials due to excessive rigidity
- Lack of generalizability outside of specific study
- Limited guidance on how to deliver therapy to a heterogeneous population, post-approval.

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Modernizing Eligibility Criteria Project

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SPECIAL ARTICLE

Modernizing Eligibility Criteria for Molecularly Driven Trials

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A B S T R A C T

As more clinical trials of molecularly targeted agents evolve, the number of eligibility criteria seems to be increasing. The importance and utility of eligibility criteria must be considered in the context of the fundamental goal of a clinical trial: to understand the risks and benefits of a treatment in the intended-use patient population. Although eligibility criteria are necessary to define the population under study and conduct trials safely, excessive requirements may severely restrict the population available for study, and often, this population is not reflective of the general population for which the drug would be prescribed. The American Society of Clinical Oncology Cancer Research Committee, which comprises academic faculty, industry representatives, and patient advocates, evaluated this issue. Evaluation results were mixed. Most physicians agreed that excessive eligibility criterias slow study enrollment rates and prolong the duration of enrollment; however, this hypothesis was difficult to validate with the data examined. We propose the organization of a public workshop, with input from regulatory bodies and key stakeholders, with the goal of developing an algorithmic approach to

Recommended Approach to Eligibility Criteria Consideration

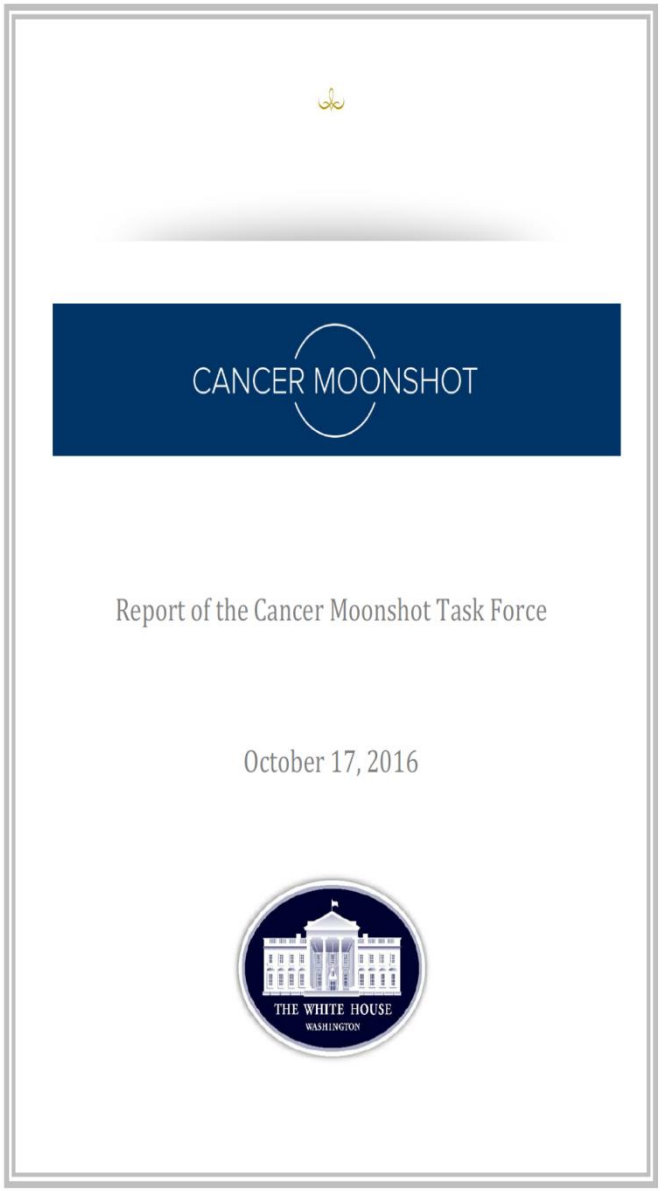
Category	Question for Consideration
Relationship to scientific objective	Does the eligibility criterion support the scientific hypothesis?
	Could the scientific goal be achieved without including this particular eligibility criterion?
Generalizability	Will the results of the study be applicable to a patient not enrolled on the study?
	Are the eligibility criteria too restrictive for practical clinical use?
Patient safety and drug toxicity	Is patient safety being adequately protected and does this eligibility criterion contribute to this?
	Are potential drug toxicities and mechanism of action being accounted for and does limiting or including this criterion support or hinder the scientific goal?
Continual review on a regular basis	At what point should eligibility criteria be re-justified during protocol development and during enrollment?
	Should a trial close due to poor accrual or be allowed to reduce/relax eligibility criteria as a first step?

Importance to Cancer Moonshot

Strategic Goal 3– Accelerate Bringing New Therapies to Patients: Plans for Year 2 & Beyond

1. **Modernize eligibility criteria for clinical trials**

   "In coordination with the American Society of Clinical Oncology, Friends of Cancer Research, and other stakeholders, FDA will evaluate clinical trial entrance criteria that may unnecessarily restrict clinical trial access—such as brain metastases, HIV status, organ dysfunction, and age restrictions (e.g., pediatrics)—to better assess when restrictions are warranted for specific clinical trials to protect patient safety. … Moving forward, FDA will work with sponsors to improve the use of science-based, clinically relevant eligibility criteria to allow greater patient access to clinical trials while maintaining patient safety."



What are the goals?

- Challenge assumptions & past practice
- Create new culture – only exclude where safety warrants
  - Shape the perception/attitudes/practice of clinical trial eligibility
  - Create new language to use
  - Active discussion during trial design & FDA pre-IND meetings to justify exclusions or differences between trial participants and overall patient population with the indicated disease
- Not just publication of recommendations, but implementation

Modernizing Trial Eligibility Workshop

- Convened May 2016
- FDA, ASCO, FOCR, NCI, clinical investigators, statisticians, pharmacolotists, Industry, Patient Advocates
- Prioritized assessment of 4 eligibility criteria (forming working groups):
  - HIV
  - Brain metastases
  - Minimum age (pediatrics)
  - Organ dysfunction/ Comorbidities/ Prior malignancies

ASCO-Friends-FDA Project Leadership

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Brain Metastases WG Recommendations

- Patients with **treated or stable brain metastases**:
  - Routinely include in all phases, except where compelling rationale for exclusion.
- Patients with **new/active/progressive brain metastases**:
  - 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**:
  - Still appropriate to exclude from most trials, due to poor prognosis.

HIV/AIDS WG Recommendations

- HIV patients should be included unless reason to believe drug may interfere with control of HIV infection
- HIV-related eligibility criteria should focus on:
  - Current and past CD4 and T-cell counts
  - History (if any) of AIDS-defining conditions such as opportunistic infections
  - Status of HIV treatment
- Healthy HIV-positive patients (based upon factors above) that are included in cancer clinical trials should be treated using the same standards as other patients with co-morbidities, and anti-retroviral therapy should be considered a concomitant medication.

Minimum Age WG Recommendations

- Initial dose-finding trials:
  - Pediatric-specific cohorts should be included when there is strong scientific rationale (based on molecular pathways or histology and/or preclinical data)

- Later-phase trials:
  - Trials in diseases 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

Organ Dysfunction/ Comorbidities, Prior Malignancies WG Recommendations

- **Renal function** should be based on creatinine clearance (calculated using the Cockcroft-Gault formula) rather than serum creatinine levels.
  - Liberal creatinine clearance eligibility criteria should be applied when renal excretion is not a significant component of a drug's pharmacokinetics or when known dose modification strategies allow for safe and effective administration.
  - Conservative criteria for known nephrotoxic drugs remain appropriate.

Organ Dysfunction/ Comorbidities, Prior Malignancies WG Recommendations

- **Hepatic or Cardiac dysfunction**
  - No recommended changes to current criteria
  - Future studies should include specific cohorts for these categories of patients
  - Inclusion of **geriatric patients** usually appropriate

Organ Dysfunction/ Comorbidities, Prior Malignancies WG Recommendations

- **Prior malignancies**
  - Liberalize exclusions with regard to timing and type of prior cancers
  - Also may include patients with current/concomitant malignancies that are not life-threatening in short term
- WG still discussing specific recommendations and considering:
  - Cancer types
  - If previous therapies were curative
  - If cancer not cured, but stable
  - Time lapse between previous therapy and trial

Next Steps

- Publish findings
  - Working group manuscripts & ASCO-Friends Statement – Spring 2017
- Promote implementation
  - Creating standards for EC language that is inclusive
  - Working with trial sponsors to embed recommendations
  - Developing metrics to track implementation
  - Documenting results where recommendations are used
  - Addressing practical issues that may arise
- Examine additional eligibility criteria
  - Drug washout periods
  - Concomitant medications
  - Other triggers for exclusion of elderly patients

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

- Pragmatic phase 2 study with FDA-approved, targeted agents
- Incorporates general and drug-specific eligibility criteria
- Prior malignancy:
  - No exclusion or time limit for patients with prior malignancies
- HIV+
  - General criteria- included except where clinician decides to exclude
  - Drug specific- pembrolizumab and olaparib exclude
- Performance status (PS):
  - General eligibility: 0-2 eligible
  - Drug specific: Pembrolizumab or regorafenib PS 0-1.

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TAPUR Study Eligibility Criteria cont'd

- Brain Mets- eligible as long as patient is:
  - Not progressive and not on treatment
  - Has not experienced a seizure or had significant change in neuro status within 3 months
  - Off steroids for at least 1 month
- Patients must have organ function as defined:
  - AST and ALT < 2.5 X ULN (or < 5X ULN for those with hepatic mets)
  - Serum Cr ≤1.5 X ULN or calculated ≥ 50 mL/min/ 1.73 m^2
- Pediatric population:
  - Current TAPUR eligibility require age ≥ 18 years
  - Plans to lower minimum age to 12 year where pediatric dose defined.

Urgency of the Project: 5 Years Down the Road

- Have we begun to change protocols and perception?
- Are protocols enrolling more patients?
- Industry conducting studies with broader eligibility?
- Are young investigators writing protocols with broad eligibility?
- FDA approval of drugs in these populations, or labeling recommendations for drug administration to these populations?

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- Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007):
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- Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (2009):
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics
  - www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf - 289k - 2014-08-01
- Be on the look out for upcoming guidances:
  - Guidance for Industry and Reviewers Measuring Symptoms, Physical Signs, and Functioning in Hematology and Oncology Clinical Trials (being drafted)

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