FDA U.S. FOOD & DRUG ADMINISTRATION

Modernizing Eligibility Criteria for Clinical Trials

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Outline

- Background
- ASCO FoCR Modernizing Eligibility Criteria Project
- Working Group Recommendations
- Regulatory Perspective
- Future Directions/Conclusions

Background

- Clinical Trials:
  - Understand risks/benefits
  - Develop safe and effective drugs
- Eligibility:
  - Safety/protection of patients
  - Define the study population

Background
Overly Restrictive Eligibility Criteria

- Major protocol-level barrier to patient enrollment
- Fail to capture the heterogeneous patient population that will ultimately receive the drug
- Duplication between and within drug development programs
- Impact includes: patients with HIV, brain metastases, prior malignancies, poor performance status, comorbidities/organ dysfunction (such as cardiac dysfunction), older adults, age <18

Cardiac Dysfunction Eligibility

- Exclusions on basis of cardiac disease may decrease enrollment of older patients by ~5%.
- Due to historical precedent patients must have EF of >45-50%
- Concern about cardiac effects leads to frequent ECG monitoring in early-phase trials (to determine QTc prolongation relationship)– often continued into later phases despite no cardiac risk

FDA analysis of Investigational New Drug Applications in 2015

- ~290 commercial IND submissions from 2015
  - 4% included pediatric patients
  - 60% required ECOG Performance status of 0-1
  - 77% excluded known, active or symptomatic CNS or brain metastases (47% allowed treated or stable brain metastases)
  - 84% excluded patients with known or active HIV (with only 2% allowing patients to enroll with adequate CD4 counts)
  - 74% excluded patients with history (or current) cardiovascular disease or risk (including angina pectoris, uncontrolled HTN, MI, CHF, arrhythmia)

Jin et al. JCO 2017

ES Kim et. al 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?

Kim et al., Modernizing Eligibility Criteria for Molecularly Driven Trials, JCO 2015

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ASCO-Friends Project Leadership

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Slide courtesy of Dr. Kim

ASCO-Friends of Cancer Research Modernizing Eligibility Criteria Project

- Multi-stakeholder working groups
  - Patient advocates
  - Clinical Investigators
  - Industry
  - Government (NCI and FDA)
  - Academics
  - Biostatisticians
  - Pharmacologists

- Brain Metastases
- Age <18
- HIV
- Organ Dysfunction/ Prior Malignancies

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Brain Metastases WG Recommendations

- Patients with treated and/or stable* brain metastases:
  - Routinely include in all phases, except where compelling rationale
- Patients with active (new or progressive) brain metastases:
  - No automatic exclusion, but one-size-fits all approach not appropriate.
  - History of disease, trial phase and design, and the drug mechanism and potential for CNS activity should determine eligibility.
- Patients with leptomeningeal disease:
  - Exclusion acceptable, although there may be situations that warrant inclusion in early phase trials. Defined clear language to avoid exclusion of patients with equivocal findings.

* No progression for at least 4 weeks after local therapy

Kim et al., Lin et al. JCO 2017

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 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.

Kim et al., Gore et al. JCO 2017

HIV+ WG 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 straightforward 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.

Kim et al., Uldrick et al. JCO 2017

Organ Dysfunction WG Recommendations

- WG recommendations were informed by an analysis of 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

Kim et al., Lichtman et al. JCO 2017

Prior Malignancies Recommendations

- Inclusion of patients with prior or concurrent malignancies is recommended, 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

Kim et al., Lichtman et al. JCO 2017

Cardiac Dysfunction Recommendations

- If an investigation therapy is not known to pose cardiac risks, arbitrary ejection fraction values should not be used to exclude
  - patients with EF <35% excluded in early-phase studies
- Investigator assessment of a potential participant's risk for heart failure with validated clinical classification system is recommended
- Concern about cardiac effects leads to frequent ECG monitoring in early-phase trials
  - Need for continued ECG monitoring and QTc interval eligibility criteria should be re-evaluated in later phases if cardiac risk not of concern
- Cardiovascular safety measures and close collaboration with cardiology recommended

Kim et al., Lichtman et al. JCO 2017

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Regulatory Considerations

- “protocol is required to contain . . . the criteria for patient selection and for exclusion of patients”[1]
- No detailed language regarding clinical trial eligibility criteria.
- Regulatory approval, however, must be predicated on data pertinent to the enrolled patients and relevant to the U.S. population and U.S. medical practice.[1]
- Penalizing companies would not be productive as it could restrict access to an effective drug.

[1]: 21 Code of federal regulations

Regulatory Considerations

- Potential for Expanded marketing claim
- Unnecessary postmarketing requirements/ commitments
- Address requirements to study drugs in children

Beaver, Ison, Pazdur, Reevaluating Eligibility Criteria – Balancing Patient Protection and Participation in Clinical Trials, NEJM 2017

Trial Design Considerations

- Expansion cohorts early in development
- 1^{o} population: pre-specified, more narrowly-defined
- Stratify enrollment
- Adaptive designs
- Companion protocol

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Expanded Eligibility: Risks/Benefits

Benefits

- Earlier access to investigational agents
- More complete safety and efficacy data
- Earlier identification of drugs that may not be effective
- Generalize to “real-world” patients
- Faster Accrual
- Efficacy in understudied population could differentiate between drugs of same class

Risks

- Variability of outcome (need larger sample size)
- Safety concerns may require separate cohorts or analysis
- Complicate attribution of AE
- Increased costs associated with additional cohorts
- Potential for additional procedures for increased safety monitoring
- Additional Resources required

From FoCR Annual Meeting November 2016

Current Status and Future Directions

- JCO 2017 published six papers
  - Joint statement
  - Working group manuscripts
- Promote implementation/Address Barriers
  - Develop methods to track implementation (ASCO)
  - Examine Additional Criteria (e.g. drug washout, concomitant meds/triggers for exclusion of the older adult, other cardiac risk factors?)
- FDA will work with sponsors to implement rational criteria

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