

FDA Experience

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Hypothesis

- Inadequate representation of older adults patients in clinical trials
- ✓ In majority of clinical trials adults > 18 years are included in the eligibility criteria
- Why older adult patients are not enrolled?
- ✓ In majority of clinical trials exclusion criteria includes some comorbid conditions
- Are there other reasons for low enrollment of older adults patients?
- What can be done to increase enrollment of older adults patients?

Increasing Participation of Older Adults in Clinical Trials

- Without compromising safety
 - Expand eligibility to include patients with some comorbid conditions
 - What are the design options for such a trial and how to interpret the data from such a clinical trial?
 - Address other road blocks such as accessibility/feasibility for elderly patients to participate; educating patients and investigators, etc.
- *Among the total US population¹ 16.5% are estimated to be 65 years or older, 13.4% Black/African American and 50.8% female population; Proportion of older adult population varies with disease*

Examination of New Drugs and Therapeutic Biological Products FDA Approved in 2019²

- 48 products (NME) approved in various diseases (17/48 oncology and hematology products)
- Safety and efficacy evaluation based on trial data from a range of 56 to 11,273 patients
- Of the 48 products approved women participation in 40 products ranged from 10% to 91%; 6 products to treat diseases in only Women, 1 product to treat disease only in men and a product to treat Duchenne muscular dystrophy included only male children

Examination of 48 New Drugs and Therapeutic Biological Products FDA Approved in 2019²

- ≥ 65 years old participation ranged from 1% (*acute hepatic porphyria*) to 90% (*wet age-related macular degeneration*)
- 7 products approved had $\leq 10\%$ participation and 30 products approved had $\leq 30\%$ participation by ≥ 65 years old subjects
- In 8 of the products approved all patients were < 65 years of age; 1 product did not have age information
- Black/African American participation varied from $< 1\%$ to 91%; 24 (50%) of the products approved had $\leq 5\%$ African American participation

Experience in Cancer

Singh et al ASCO 2017 Meeting³

- Number of older age cancer patients is increasing over years
- 56% of cancer patients ≥ 65 years of age; 29% of cancer patients ≥ 75 years of age
- 10-year perspective based on 105 registrational trials with 224,766 patients:
 - 41% of cancer patients enrolled were ≥ 65 years
 - 12% of cancer patients enrolled were ≥ 75 years

NME oncology and hematology products approved in 2019²

- 17 products approved
- 9/17 products included $\geq 30\%$ of patients ≥ 65 years of age
- 5/17 products included $\leq 10\%$ of patients ≥ 65 years of age

Oncology and Hematology New Drug Products and Biological Therapeutics Approved in 2019* with < 10% of Patients ≥ 65 years²

Drug	FDA-approved use	N**	% Women	% Black	% ≥ 65 years
voxelotor	To treat sickle cell disease	182	59%	67%	0%
givosiran	To treat acute hepatic porphyria, a rare blood disorder	94	89%	< 5%	1%
crizanlizumab-tmca	To treat patients with painful complication of sickle cell disease	132	55%	91%	0%
luspatercept-aamt	For the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell transfusions	336	58%	< 5%	< 1%
pexidartinib	To treat adult patients with symptomatic tenosynovial giant cell tumor	120	59%	< 5%	6%

* Total 17 new oncology and hematology products approved;

**Included safety population in some cases;

NASEM Drug R & D for Adults Across Older Age Span Workshop

Randomized Cancer Trials Evaluating PD1/PDL1 Inhibitors (Courtesy Flora Mulkey, FDA)

- 22 Randomized Trials (NSCLC (9), Melanoma (6), Head & Neck (2), Renal Cell Carcinoma (4) , Urothelial Cancer (1))
- Total 14,951 patients enrolled
 - **43% of patients enrolled were ≥ 65 years; 10% ≥ 75 years**
 - 1% of enrolled patients were Black/African American
 - 33% Women
 - 25% from US

Points to consider to increase participation of older adult patients

- Prevalence of disease in the elderly population
- Access to care facility
- Frequency of outcome assessment; invasive or non-invasive outcome assessments
- Thoughtful consideration for exclusion criteria
 - Toxicity of the drug, any drug-drug interaction
- Design of the clinical trial

Clinical Trial Designs

- During early phase of drug development consider adding a small cohort of elderly patients to:
 - Better understand the safety and tolerability of the treatment
 - Dose selection and potential dose modifications
 - To study drug-drug interactions
 - Feasibility of outcome assessments
- During late phase of drug development in confirmatory studies different trial designs can be considered without compromising safety
- Post-marketing studies (clinical trial, registry, or RWD)

Trial Design Options

➤ Randomized Clinical Trial

- Population: defined by restricted eligibility criteria + expanded older age high risk population
- Stratification factors: restricted population and high risk population
- Primary analysis based on modified ITT population with only restricted population (modified ITT population, MITT)
- Hierarchical testing: ITT after MITT; high risk population can be tested separately if it is hypothesis driven and sample size is adequate

➤ Simultaneous RCT in restricted population and single arm cohort in the high-risk population

- RCT and single arm cohort analyzed separately
- Single arm high risk cohort – descriptive statistics

Key Considerations

- Who should be in the expanded, older age high risk population
 - What co-morbidities, drug-drug interactions, level of toxicity are acceptable?
- Randomized Control Trial
 - Proportion of patients in older age high risk group; limit number of patients in high risk stratum?
 - Primary hypothesis, Type I and Type II errors, number of events for the final analysis, benefit:risk assessment based on restricted population
 - Hierarchical testing feasible? – what if more events occur in the high risk stratum?
 - Consideration of safety assessment in the high risk population
- Single arm cohort of older age, high risk population
 - Could consider enrolling patients only in certain sites
 - Difficult to interpret toxic events, in particular deaths without a control arm in a single arm study
- Post-market studies
 - Reproducible outcome definition and assessment
 - Measures for safety evaluation, consistency in recording data

References

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