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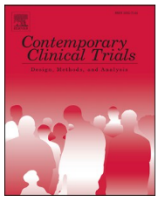

Eligibility criteria and clinical trials: An FDA perspective

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A B S T R A C T

Introduction: Randomized clinical trials are regarded as the gold standard for evaluating the effectiveness and safety of interventions. The US Food and Drug Administration (FDA) has made efforts to promote inclusive eligibility criteria. The objective of this study is to identify common trends in eligibility criteria and identify patterns of exclusion criteria among different diseases.

Methods: The authors evaluated the inclusion and exclusion criteria of 38 pivotal clinical trials representing 38 novel drugs approved between 2014 and 2017. Additionally, the authors reviewed the demographic characteristics of participants enrolled across 38 trials.

Results: Eighty two percent of trials in our study excluded participants based on hepatic related criteria and 79% trials excluded participants based on renal related criteria and specific infectious diseases. For trials in conditions that affected both men and women, there were no exclusions based on gender and race. More than 90% of trials excluded pregnant, lactating women and women not on adequate contraception. Of the 36,644 patients enrolled in trials for which both men and women were eligible, 62% were men.

Conclusions: The most frequent exclusion criteria were pregnancy, lactation/breastfeeding, renal and hepatic abnormalities, and specific infectious diseases. The preponderance of men in our study likely indicates that factors other than exclusion criteria affect enrollment. The lower representation of women may have been influenced by two large cardiovascular trials that included 75% men. Our study marks an important step in the ongoing efforts of the Agency to increase inclusivity in clinical trials by understanding common clinical trial eligibility criteria patterns.

1. Introduction

Marketing approval of new therapeutic products by United States (US) Food and Drug Administration (FDA) relies largely on randomized controlled trials (RCTs) which are considered the "gold standard" to determine safety and efficacy. It is important that the participants in these trials represent the population that will ultimately receive the therapeutic product. Including appropriate eligibility criteria in clinical trials is necessary to ensure that participants have the condition under study, that they are able to comply with study requirements, and that their participation in the trial does not put them at risk of potentially avoidable adverse events. However, some eligibility criteria have become commonplace in clinical trials, leading to exclusions that may not always be scientifically justified. There have been policy efforts by the FDA to broaden patient eligibility criteria to ensure that diverse populations are included in clinical trials and that inclusion and exclusion criteria are scientifically justified to avoid unnecessary exclusions. For example, in 2019, the FDA issued guidance titled "Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies Guidance for Industry" [1].

In addition, Section 610 of the Food and Drug Administration Reauthorization Act (FDARA) of 2017 required the agency to convene a public meeting to discuss clinical trial eligibility criteria to inform a guidance on this subject [2]. Under this mandate, FDA with Duke-Robert J. Margolis, MD, Center for Health Policy, held a public workshop titled, "Evaluating Inclusion and Exclusion Criteria in Clinical Trials" [3]. Following the workshop, a draft guidance was published by the Agency titled "Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry" [4]. In preparation for the workshop, we sought to identify common trends in eligibility criteria and identify patterns of exclusion criteria among protocols for different diseases. We reviewed the exclusion criteria in a sample of clinical trials submitted to FDA for marketing approval of novel drugs. Novel drugs are either new molecular entities (NMEs) under new drug applications (NDAs) or new therapeutic biologics under biologics license applications (BLAs) [5]. We also reviewed the demographic characteristics of the participants enrolled across the clinical trials in our study.

2. Methods

In preparation for the workshop, we approached clinical review staff

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in the Office of New Drugs (OND) to select between 1 and 3 NDAs or BLAs that were approved by FDA between 2014 and 2017. Each reviewer identified one pivotal clinical trial used to support the marketing application of their selected NDA or BLA. Each reviewer then analyzed the inclusion and exclusion criteria from that pivotal trial. Eleven reviewers agreed to participate. The reviewers were provided with a template listing different categories of common exclusion criteria. The exclusion criteria were grouped by organ system such as renal, liver, cardiac, infectious disease, hematology, malignancy, pulmonary disease, and sub-categories were created based on laboratory parameters commonly listed in eligibility criteria (e.g., serum creatinine, estimated glomerular filtration rate (eGFR), creatinine clearance (CrCl)).

We reviewed the responses from the clinical reviewers to ensure that the template was populated consistently. We then compiled the data from all reviewers and ranked the exclusion criteria by frequency across all trials in our study. Adjusted analyses were done to account for appropriate exclusions. For instance, in the analysis of eligibility criteria that excluded patients with liver function abnormalities, we excluded trials of drugs for liver diseases (e.g. hepatitis).

Additionally, we used Clinical Study Reports (CSRs), medical reviews, and the U.S. National Library of Medicine website Clinicaltrials.gov to obtain the demographic characteristics such as age, gender, and race of the patients who participated in the trials. Clinical trials generally reflect self-identified gender of participants, hence, for the purposes of this paper, we refer to participants as men and women (gender) rather than male and female (sex). We also compared the demographics of our study population to the demographic data from FDA's Drug Trials Snapshots, 2015–17 [6]. Drug Trials Snapshots were introduced in 2015 to provide data on who participated in the pivotal clinical trials used to approve a particular novel drug and stratify the data by gender, race, age and ethnicity subgroups.

3. Results

Our study consisted of 38 pivotal clinical trials representing 38 novel drugs approved between 2014 and 2017. Two trials supported drugs approved in 2014, 14 trials supported drugs approved in 2015, 13 trials were for drugs approved in 2016, and 9 trials supported drugs approved in 2017. Of the 38 clinical trials, 29 were for NDAs and 9 were for BLAs. Thirty-two out of 38 were Phase 3 clinical trials, 4 were Phase 2, and 2 trials were Phase 1/2.

Of the 38 trials in our study, one trial only enrolled pediatric patients from 3 to 15 years of age. Two trials included both pediatric and adult participants. One trial had a minimum enrollment age of 16 years, two additional trials had minimum enrollment ages of 20 and 50 years respectively. The remaining 32 trials in our study enrolled participants 18 years of age or older. Three trials addressed sex-specific indications - ovarian cancer, generalized hypoactive sexual desire disorder and osteoporosis in postmenopausal women.

Our study included clinical trials from a range of therapeutic areas. The distribution of trials by therapeutic area in our study (See Fig. 1) differed slightly from the distribution of trials by therapeutic areas for all novel drugs approved by FDA between 2014 and 2017 (one trial for an imaging agent was excluded). Among the 38 clinical trial protocols reviewed in our study there were no exclusion criteria based on gender other than for the three sex-specific indications. There were no exclusion criteria based on race or ethnicity. Ninety five percent of trials in our study excluded pregnant women, 92% excluded lactating or breastfeeding women (34% excluded breastfeeding women specifically) and 82% excluded participants not using adequate contraception. Adequate contraception was generally defined across protocols as using two or more methods of contraception. Seventy-nine percent of protocols allowed for the exclusion of participants based on the investigator's discretion. Examples of such exclusions included medical conditions or circumstances that the investigator determined might compromise the subject's ability to comply with the study protocol or pose an unacceptable risk, or biochemistry or hematology results not within the laboratory's reference range and deemed by the investigator to be clinically significant. Of the 37 protocols for adult participants, 13 specified an upper age limit for enrollment that ranged from 55 to 99 years with a median of 75.

Exclusion criteria related to hepatic and renal dysfunction were present in 79% and 82% of the trials respectively (Fig. 2). Forty-seven percent of trials excluded participants with abnormal creatinine clearance and 13% excluded participants with abnormal estimated glomerular filtration rates. Most protocols used 60 ml/min as the cut off value for exclusion. Elevations of AST, ALT and bilirubin were the most common reasons for excluding patients with liver dysfunction. (Table 1).

Patients with malignancies were commonly excluded from participation. Sixty-three percent of non-oncology trial protocols excluded

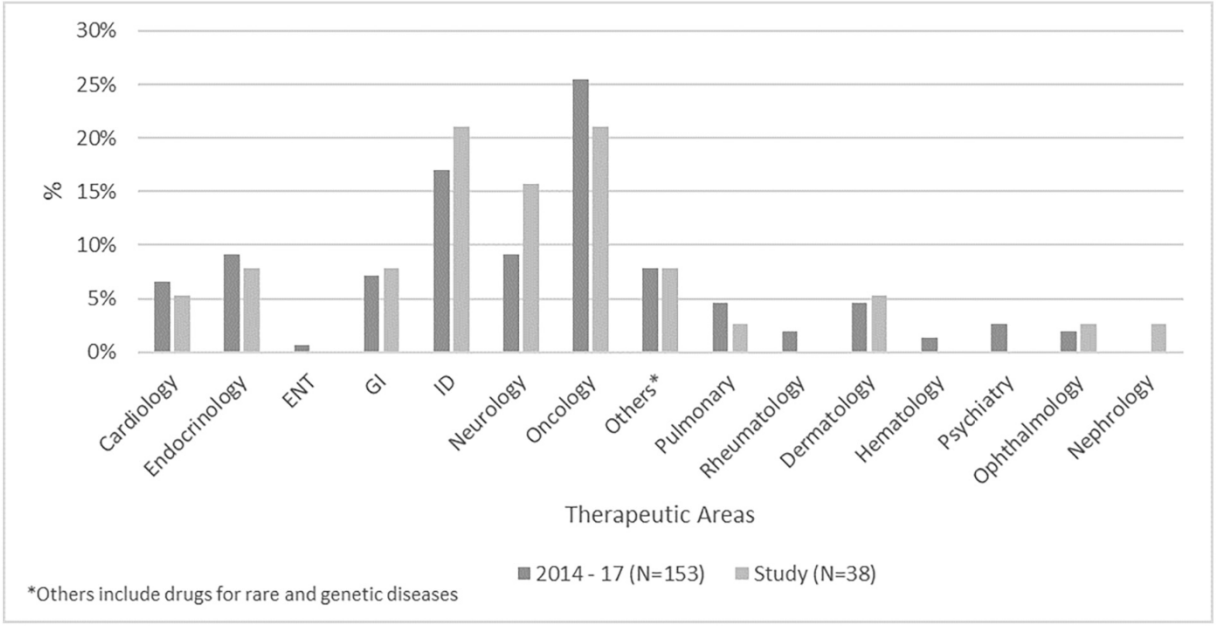

Fig. 1. Comparison of novel drug approvals by therapeutic area in our study to all novel drugs approved by FDA from 2014 to 2017.

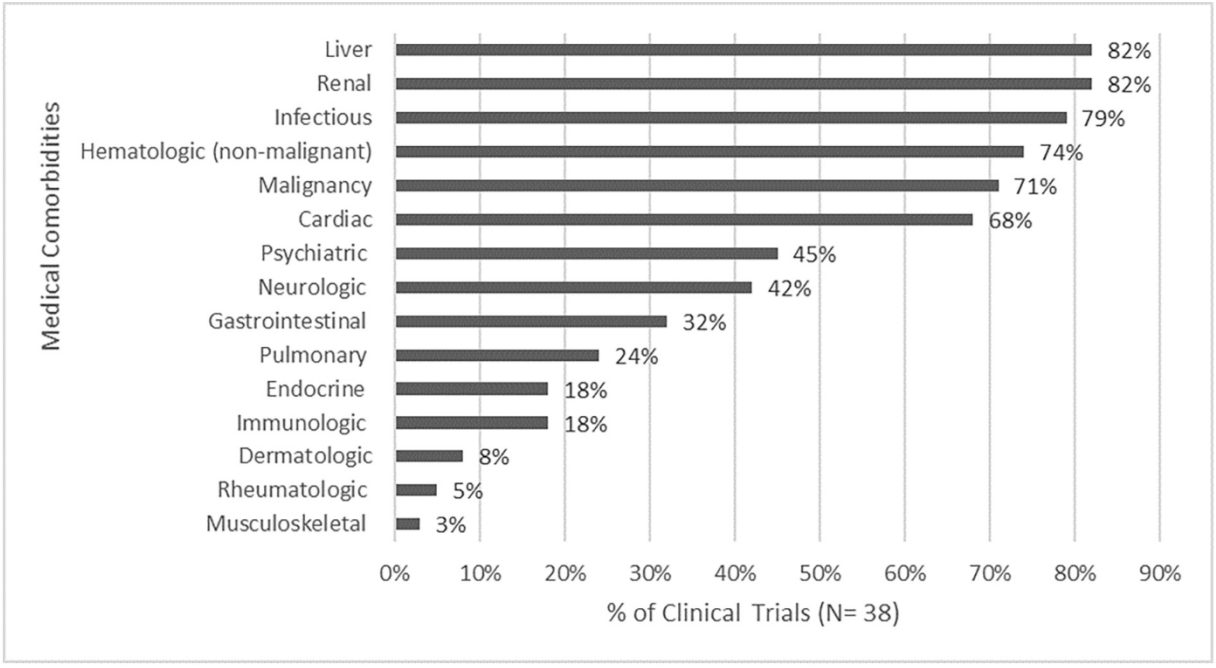

Fig. 2. Frequency distribution (%) of medical co-morbidities listed in the exclusion criteria in our study.

Table 1
Liver, renal and infection related exclusions.

Criteria	Trials with exclusion/Total Trials
Renal Related Exclusions:	%
Any renal related criterion	31/38 (82%)
Abnormal CrCl or eGFR[a]	22/38 (58%)
Abnormal Serum creatinine[b]	14/38 (37%)
Other renal	5/38 (24%)
Liver Related Exclusions:	
Any liver related criterion	26/33[c] (79%)
Abnormal Aspartate Aminotransferase Test (AST)	22/33 (67%)
Abnormal Alanine Aminotransferase Test (ALT)	22/33 (67%)
Abnormal Total bilirubin	15/33 (45%)
Other liver	13/33 (39%)
Infection Related Exclusions:	
Any infection related exclusion	30/38 (79%)
HIV/AIDS	22/37[d] (59%)
Positive tests for Hepatitis B	18/38 (47%)
Positive tests for Hepatitis C	18/35[e] (50%)

[a] CrCl/eGFR: 47% of trials had an exclusion based on CrCl, 13% excluded based on eGFR. Majority used a cutoff of <60 ml/min

[b] Serum Creatinine: > 1.5–2.0 mg/dL or 1.5× upper limit of normal AST and ALT exclusion range: 2-10× upper limit of normal. Equal number of studies excluded participants for 2, 2.5 or 3× upper limit of normal.

[c] 5 trials of drugs indicated for liver disease were excluded.

[d] 1 trial of drug indicated for HIV/AIDS was excluded.

[e] 3 trials of drugs indicated for Hepatitis C were excluded.

participants with an active malignancy within the past 2 to 5 years. Exceptions were made for carcinoma in situ or basal cell carcinoma. Substance abuse was also a common reason for exclusion. Fifty percent of the protocols excluded participants with substance abuse (ranging from use within last 3 months to 2 years).

Overall, exclusion criteria for BLAs and NDAs were similar except for renal related exclusions. In our study, 90% of NDA protocols excluded participants with renal abnormalities as compared to 56% of BLA protocols.

3.1. Participant demographics

We analyzed the demographic information of all participants (N = 40,892) across the 38 trials in our study. The mean age of the participants was 51 years (range 1–100 years). Detailed age break-down information for participants 65 years and older was available for 30 trials and thirteen trials presented information regarding participants 75 years of age and older. Out of 30 trials for which detailed age break-down was available, 42% participants were 65 years and older and out of 13 trials for which information was available, 16% were 75 years and older. Among the 35 trials that included both men and women, 62% of the participants were men.

3.2. Demographics of study participants compared to demographics from Drug Trials Snapshots, 2015–17

Among the trials in our study that included both men and women (n = 35), 38% of the participants were women compared to 48% in trials for novel drugs approved between 2015 and 2017 identified in Drug Trial Snapshots. Forty two percent of our study population was over 65 years of age compared to 30% in the Snapshots data, and 81% of our study population was white compared to 77% from the Snapshots data (See Fig. 3).

4. Discussion

We undertook this study to better understand common trends in clinical trial eligibility criteria particularly with respect to exclusion criteria. We also reviewed the demographic trends of patients who participated in the trials.

The most common exclusions across the trials in our study were for kidney and liver disease. Eighty two percent of the clinical trials in our study had a renal related exclusion and 79% had liver related exclusions. A systematic sampling review conducted by Spall et al. at University of Toronto found that in 81% of RCTs, participants were excluded due to comorbidities related to kidney, liver, infectious disease, cardiac, or hematological-oncological disease [7]. We postulate that the rationale for excluding patients with renal and hepatic impairment is concern over decreased drug clearance, potential increased drug exposure that

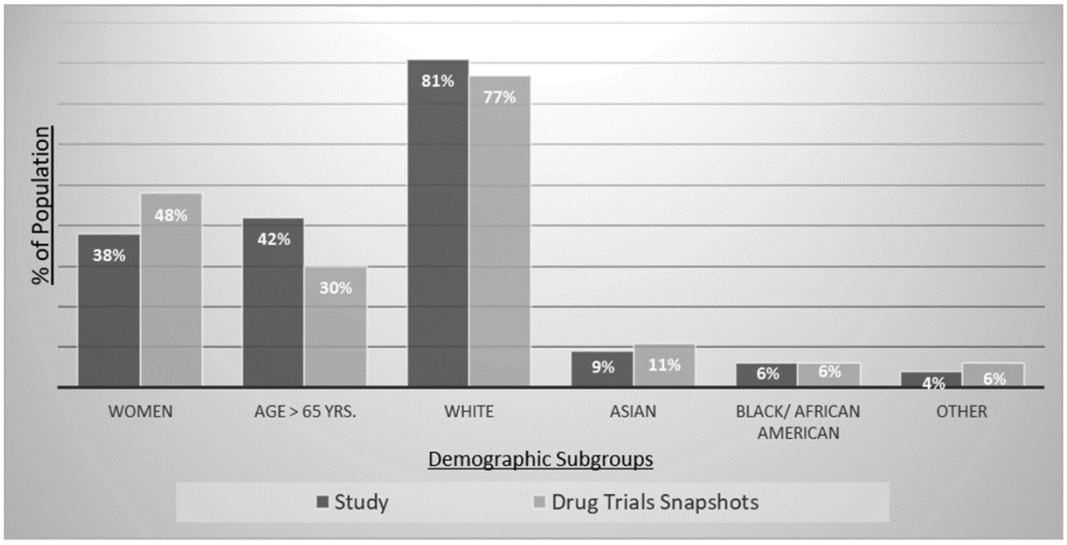

Fig. 3. Comparison of patient demographics in our study (38 novel drug approvals) to patient demographics from Drug Trials Snapshots* (113 novel drug approvals).
*Data from Drug Trial Snap Shots Summary Reports from 2015-2017.

may result in toxicity, and altered drug metabolism for liver impairment. However, most protocols in our study did not specify the reason for excluding patients with renal and liver impairment. Recent FDA guidance on cancer clinical trial eligibility recommends that sponsors provide adequate justification for including or excluding patients with varying degrees of renal impairment [1]. The FDA guidance on enhancing the diversity of clinical trial populations also offers recommendations to address the issue of excluding participants with organ dysfunction, such as, using an appropriate specific measure of organ dysfunction so that it does not result in unnecessarily excluding those with milder dysfunction [4].

Another finding was the difference between the exclusions based on disease criteria between NDAs and BLAs. Fifty six percent of BLAs excluded patients based on renal dysfunction compared to 90% of NDAs. This difference is likely attributed to the fact that unlike drugs, most biologics in our study were monoclonal antibodies which generally are not excreted through the kidneys and would not present a problem with drug accumulation and toxicity. These findings would need to be confirmed in a larger sample of clinical trials including NDAs and BLAs.

There were no exclusion criteria based on race and gender in our study (except those studies that were for sex-specific indications). However, we found that 95% of trials excluded pregnant women, 92% excluded lactating or breastfeeding women (34% excluded breastfeeding women specifically) and 82% excluded participants not using adequate contraception. Including pregnant women in clinical trials is complicated from both scientific and ethical perspectives. Pregnant women have historically been excluded from clinical trials. In an effort to address this issue, the agency has published numerous guidances [8–10] offering guidelines and considerations for including pregnant and lactating women in trials. The 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to identify gaps in knowledge and research specific to this group [11,12]. The Office of Women's Health at FDA served on the PRGLAC Taskforce which put out a series of recommendations to the US Department of Health and Human Services (HHS) for development of safe and effective therapies for pregnant and lactating women [12].

Twelve trials in our study excluded participants based on an upper age limit. Excluding elderly patients has been observed in studies for heart failure [13], cancer [14], and ischemic heart disease [15,16]. A systematic review looking at RCTs conducted from 1998 to 2015 found that 29% of the trials specified an upper age limit cut off, out of which 92.8% did not offer an explanation for the age cut off [17]. FDA has made efforts to promote the inclusion of elderly patients in clinical trials. Two guidances on eligibility criteria offer recommendations for including elderly patients [1,4].

Out of the 30 trials for which detailed age break-down was available, 42% of participants were 65 years of age or older. Out of the 13 trials that reported on participants 75 years of age and older, 16% were 75 or older. In addition to protocols that specified age cut offs, other reasons that prevented elderly patients from enrolling in trials might have included limited mobility, transport issues, potentially harmful drug interactions and comorbidities.

Ninety-two percent of trials in our study excluded children. The Agency has been at the forefront of encouraging the industry to conduct more pediatric studies by way of the Pediatric Exclusivity Provision Act (PREA) of the Best Pharmaceuticals for Children Act (BPCA) [18]. Companies that conduct studies in children as requested by the Agency are offered an additional six months of marketing exclusivity through PREA of the BPCA. BPCA also provides a contract mechanism through the National Institute of Health (NIH) to fund pediatric studies [18].

We compared the demographic data in our study of 38 trials to 113 trials supporting novel drugs approved between 2015 and 2017 as reported in Drug Trials Snapshots. Women represented 38% of the trial population in our study compared to 48% in Drug Trials Snapshots (Fig. 3). These differences are likely due to the fact that our study included one pivotal trial each for 38 novel drug approvals where as Drug Snapshots captured data from all pivotal clinical trials for 113 novel drug approvals. The lower percentage of women in our study may also have been influenced by two large cardiovascular trials in our study that included 19,587 participants of which 75% were men. One of the two trials supported marketing approval of a therapeutic to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction, and the other trial was for a therapeutic to reduce the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis. It has been reported in previous research that women are underrepresented in cardiovascular trials for certain indications such as heart failure, coronary artery disease, and acute coronary syndrome [19].

Lastly, it should be pointed out that under representation of specific

populations in clinical trials is not exclusively a function of the exclusion criteria and may be influenced by an array of contributing factors. A study conducted to identify critical barriers to minority participation in trials found financial burden, time commitment, transportation, compensation and logistics, mistrust of process and fear, and lack of awareness as some of the barriers to participation [20].

Our study was limited by a small sample of 38 trials. We also did not explore the rationale for the exclusion criteria in each trial in our study. Further investigation of this important issue is needed. While designing eligibility criteria for clinical trials, inclusion and exclusion criteria should be evaluated closely to ensure that every criterion is scientifically justified, and populations are not unnecessarily excluded.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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