Contemporary Clinical Trials Communications 9 (2018) 135–142

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Temporal trends and characteristics of clinical trials for which only one racial or ethnic group is eligible

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ARTICLE INFO

Keywords:
Clinical trials
Eligibility requirements
Neighborhood characteristics
Protocols

ABSTRACT

Background: Increasing diversity in clinical trials may be worthwhile. We examined clinical trials that restricted eligibility to a single race or ethnicity.

Methods: We reviewed 19,246 trials registered on ClinicalTrials.gov through January 2013. We mapped trial ZIP-codes to U.S. Census and American Community Survey data. The outcome was whether trials required participants to be from a single racial or ethnic group.

Results: In adjusted analyses, the odds of trials restricting eligibility to a single race/ethnicity increased by 4% per year (95% CI 1.01–1.08, p = .024). Behavioral (5.79% with single race/ethnicity requirements), skin-related (4.49%), and Vitamin D (6.14%) studies had higher rates of single race/ethnicity requirements. Many other trial-specific characteristics, such as funding agency and region of the U.S. in which the trial opened, were associated with eligibility restrictions. In terms of neighborhood characteristics, studies with single race eligibility requirements were more likely to be located in ZIP-codes with greater percentages of those self-reporting the characteristic. For example, 35.2% (SD = 24.9%) of the population self-reported themselves as Black or African American in ZIP-codes with trials requiring participants to be Black/African American, but only 5.9% (SD = 6.9%) self-reported themselves as Black/African American in ZIP-codes with trials that required Asian ethnicity. In ZIP-codes with trials requiring Asian ethnicity, 24.6% (SD = 16.2%) self-reported as Asian. In ZIP-codes with trials requiring Hispanic/Latino ethnicity, 33.3% (SD = 28.5%) self-reported as Hispanic/Latino. Neighborhood level poverty rates and reduced English language ability were also associated with more single race eligibility requirements.

Conclusions: In selected fields, there has been a modest temporal increase in single race/ethnicity inclusion requirements. Some studies may not fall under regulatory purview and hence may be less likely to include diverse samples. Conversely, some eligibility requirements may be related to health disparities research. Future work should examine whether targeted enrollment criteria facilitates development of personalized medicine or reduces trial access.

1. Introduction

There has been increasing emphasis on ensuring diversity in clinical trials such that clinical trial results are more generalizable to a broad population [1,2]. However, diverse trials can increase heterogeneity in estimators, which reduces power to detect treatment effects [3,4]. In contrast, less diverse samples reduce variability at the expense of increasing bias with respect to the applicability of study findings to a wider group. This represents a classic bias-variance trade-off [5]. Less diverse samples reduce variability at the expense of increasing bias with respect to the applicability of study findings to a wider group. More diverse samples reduce bias, but at the expense of making studies less likely to achieve their primary endpoints.

Federal agencies have issued policy statements recommending that diverse populations be included in clinical trials [6–8]. Diverse clinical trials not only allow for investigating the generalizability of therapies when applied to a broader population, they allow for planned hypothesis testing for identification of subgroups in which therapies are particularly beneficial [9].

To date, the degree to which diversity is increased in clinical trials has been hampered by incomplete reporting of racial, ethnic, and sex distributions of participants in clinical trials [10]. However, inclusion of

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https://doi.org/10.1016/j.conctc.2018.01.004
Received 10 August 2017; Received in revised form 19 December 2017; Accepted 16 January 2018
Available online 31 January 2018
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diverse samples in clinical trials does seem achievable [11–13], and there is some evidence that diversity in clinical trials is slowly improving [10].

Still, there may be situations where eligibility restrictions may be necessary to meet a study's specific aims. With the rise of "personalized medicine" and genetic screening, there is increased recognition that racial and genetic differences would impact the response to many therapies [9]. In addition, certain behavioral interventions may be adapted to improve health outcomes in certain underserved minority groups [14].

Given potentially conflicting goals of generalizability versus personalized medicine in the setting of an increasingly diverse patient population, understanding patterns of clinical trial eligibility based on race seems important. We used the ClinicalsTrials.gov database to examine studies that require participants to be from one racial or ethnic group, and describe whether there are certain clinical trial characteristics that are associated with these eligibility criteria. As stated on the website, the ClinicalTrials.gov database has over 100,000 registered clinical trials from around the world sponsored by the National Institutes of Health, other public agencies, and private organizations. The National Library of Medicine of the National Institutes of Health (NIH) currently has responsibility for ClinicalTrials.gov. In 2004, members of the International Committee of Medical Journal Editors wrote joint statements requiring clinical trials be prospectively registered for the study results to be considered for publication in their clinical journals [15]. Since that time, the United States Health and Human Services has expanded requirements for public registration of clinical trials [16]. For these reasons, ClinicalTrials.gov likely provides the most comprehensive database of clinical trial inclusion and exclusion requirements [17,18].

As an exploratory study, we examined the relationship of racial exclusions with trial level descriptive fields available in ClinicalTrials.gov such as funders, eligible ages, phase of study, among other characteristics. We also examined neighborhood level characteristics of the centers opening trials, such community racial and ethnic demographics, as well as the poverty rates and English-fluency characteristics of neighborhood residents.

Similar methods were used in a prior report of characteristics of trials that exclude based on English language ability [18]. This study primarily differs from the previous study in that our outcomes consist of whether studies have racial or ethnic eligibility restrictions, rather than English fluency eligibility criteria. Previously, we had found relatively high rates of inclusion criteria stating that participants were required to be fluent in English.

2. Methods

By using the ClinicalTrials.gov search algorithm available at the time, we downloaded information from 68,188 clinical trials located in the United States on January 31, 2013, shortly after receiving notification of funding for this work.

We used the sample() permutation command in R (R foundation for Statistical Computing, Vienna Austria) to randomly reorder trials and we examined the inclusion and exclusion criteria of the first 10,361 protocols. After reviewing the first set of trials, we noted which types of studies were more likely to have eligibility exclusions. We next enriched the sample by adding a more targeted group of 10,095 protocols in which we chose trials from categories that seemed more likely to have racial or ethnic eligibility restrictions, which broadly included behavioral, dietary supplement, gastric bypass, gene expression, pharmacodynamics, pharmacokinetics, skin, smoking, and Vitamin D search terms. We identified these areas as potentially having restrictions during prior exploratory and hypothesis generating pilot projects [17,18]. There were few enough gastric bypass surgery, skin, smoking, Vitamin D, and pharmacodynamic trials such that we could include all trials that matched the relevant search terms. For the behavioral, dietary supplement, gene expression, and pharmacokinetic trials, we included a random sample of the matched trials. We also examined 389 protocols that had the term "Caucasian" in the protocol. After eliminating duplicates across the three types of samples, we had 19,246 trials. Of these, 47 did not have eligibility criteria listed, so were removed from the sample. This gave us a final sample of 19,199 trials. Supplemental Figure 1 and Table 1 give more details on the sampling methods for trial inclusion.

Our protocol for the study initially called for both the random and enriched targeted sampling strategies. The rationale for including a random sample of trials was that the random sample would allow us to estimate an unbiased proportion with racial eligibility requirements. The rationale for including an enriched targeted sample was that we expected racial exclusions to be a small percentage of the total sample, and we would have more power to investigate associations with the targeted sample. While the prevalence of exclusions would be biased in our targeted sample, the relationships among variables and eligibility requirements (e.g. slopes from regressions) would be unbiased (as per Prentice and Pyke [19]).

This work was funded by a grant from the National Cancer Institute with the aim of examining racial and English fluency exclusions in clinical trials. The preliminary data used to design the study suggested that as few as 1% of studies might have racial restrictions; this was conservative with respect to English language restrictions as we subsequently discovered that rates were substantially greater than 1% [18]. Given that we estimated that racial exclusions might be low, we chose to examine a random sample (i.e. non-targeted based on trial criteria) of at least 10,000 studies such that we would have 90% power to detect odds ratios of 2.0 when comparing trial characteristics with (expected number = 100) and without exclusions (expected number = 9900). We assumed a 5% Type I error rate (2-sided) with a 25% rate of a clinical trial characteristics, such as the U.S. census defined region of the country (i.e. Northeast, Midwest, South, West, Multi-region), in studies that do not have exclusions. In other words, if 25% of trials without exclusions were opened in the Northeastern region of the United States, we would be able to detect an association of racial eligibility criteria with region if 40% of trials with exclusions were located in the Northeast region (40%/60%)/(25%/75%) = OR of 2.0). Hypothesis testing in the second set of enriched targeted trials was considered independent, with similar power.

We defined that a study required participants to be a member of a single race or ethnic group if the eligibility criteria in the inclusion and exclusion fields of ClinicalTrials.gov specified as such. Examples of specific inclusion criteria were requirements that participants be "Caucasian", "European Descent," or "African American." Three individuals coded the studies as described previously [18].

We used generalized Fisher's exact tests and t-tests to examine the relationship of studies requiring participants to be from a single race or ethnic group with trial characteristics for trials open in any year. Due to the sparseness of some of the cells, we felt that Fisher's Exact test would be more reliable; in cases in which the table or sample size was too large to calculate Fisher's Exact test, we instead used Chi-squared tests. ClinicalTrials.gov has fields detailing a trial's funding agency, study type (intervention versus observation), U.S. census defined region of the country, intervention type (e.g. device, drug, or genetic focus, among other types), phase (e.g. I, II, III), age group (children, adults, or all ages), and included genders. We excluded missing data when performing hypotheses tests, although we report the amount of missing data in tables.

We also examined the area level characteristics of clinical trials using ZIP-code level data of institutions either opening or sponsoring trials for those trials opened in 1995 or later. The Zoning Improvement Plan (ZIP) Code is a 5 digit system, with additional 4 digit subdivisions, used by the United States Post Office to geographically partition the United States for ease of mail delivery [20]. We matched the 5-digit ZIP-codes of institutions listed on ClinicalTrials.gov with ZIP-code level

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