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Evaluating Demographic Representation in Clinical Trials: Use of the Adaptive Coronavirus Disease 2019 Treatment Trial (ACTT) as a Test Case

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Background. Clinical trials initiated during emerging infectious disease outbreaks must quickly enroll participants to identify treatments to reduce morbidity and mortality. This may be at odds with enrolling a representative study population, especially when the population affected is undefined.

Methods. We evaluated the utility of the Centers for Disease Control and Prevention's COVID-19–Associated Hospitalization Surveillance Network (COVID-NET), the COVID-19 Case Surveillance System (CCSS), and 2020 United States (US) Census data to determine demographic representation in the 4 stages of the Adaptive COVID-19 Treatment Trial (ACTT). We compared the cumulative proportion of participants by sex, race, ethnicity, and age enrolled at US ACTT sites, with respective 95% confidence intervals, to the reference data in forest plots.

Results. US ACTT sites enrolled 3509 adults hospitalized with COVID-19. When compared with COVID-NET, ACTT enrolled a similar or higher proportion of Hispanic/Latino and White participants depending on the stage, and a similar proportion of African American participants in all stages. In contrast, ACTT enrolled a higher proportion of these groups when compared with US Census and CCSS. The proportion of participants aged ≥65 years was either similar or lower than COVID-NET and higher than CCSS and the US Census. The proportion of females enrolled in ACTT was lower than the proportion of females in the reference datasets.

Conclusions. Although surveillance data of hospitalized cases may not be available early in an outbreak, they are a better comparator than US Census data and surveillance of all cases, which may not reflect the population affected and at higher risk of severe disease.

Keywords. ACTT; COVID-19 clinical trials; representation evaluation.

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Historically, ethnic and racial minorities, women, children, and older adults have been underrepresented in clinical research due to multiple factors at the participant, investigator, and organizational levels [1–3]. This issue persists despite efforts to conduct more inclusive human subjects research [4–6]. During the coronavirus disease 2019 (COVID-19) pandemic, some of these same groups were disproportionately affected as measured by higher hospitalization and mortality rates [7–10]. Despite this burden of disease, published reports have raised concerns that these populations were underrepresented in COVID-19 clinical trials [11–15].

Representation in clinical trials is generally defined as enrollment of participants proportional to those affected by the disease [16]. Representation helps to ensure the generalizability of the results, in addition to determining the safety and efficacy of a therapeutic intervention [17, 18]. Clinical trials undertaken during outbreaks of emerging infectious diseases must enroll rapidly to identify treatments to reduce morbidity and mortality. This may be at odds with the goal of representative enrollment initially because the risk profile for the disease may be unknown, leading to enrollment proportional to the population census, which may not be representative of those affected by the disease. Timely enrollment necessitates selection of experienced trial sites in high-incidence areas, which may preclude participation from individuals living in underserved urban settings and in rural areas.

Ensuring that a clinical trial enrolls a representative study population depends on both the fidelity of the trial demographic data and epidemiologic data collected outside of the trial. While real-time availability of accurate surveillance data was limited early in the COVID-19 pandemic, we hypothesized that for most emerging infectious diseases, national disease surveillance data would be the best comparator for such monitoring because it captures data on those most impacted by the disease. We speculated that the optimal comparator for an inpatient trial would be national surveillance data on people who are hospitalized with the disease. In this study, we utilized data from the United States (US) Census and 2 COVID-19 surveillance systems to evaluate representation in the Adaptive COVID-19 Treatment Trial (ACTT), a series of 4 randomized, double-blind, placebo-controlled clinical trials that evaluated novel therapeutics in adults hospitalized with COVID-19 [19–22].

METHODS

Clinical Trial Data

ACTT enrolled 4074 adults in the US and international sites in 4 stages: ACTT-1 (21 February 2020 through 19 April 2020; n = 1062) [19], ACTT-2 (8 May 2020 through 30 June 2020; n = 1033) [20], ACTT-3 (5 August 2020 through 21 November 2020; n = 969) [21], and ACTT-4 (1 December 2020 through 13 April 2021; n = 1010) [22] (Figure 1). The majority (3509 [86.1%]) of participants were enrolled at 69 US sites in 26 states and the District of Columbia (Supplementary Table 1). Eligibility criteria for each stage of ACTT are shown in the Supplementary Methods.

Definitions

Demographic data for ACTT were collected by participant self-report or from a legally authorized participant representative. The race categories included American Indian or Alaska Native; Asian; Native Hawaiian or other Pacific Islander (hereafter Asian or Pacific Islander); Black or African American; White; multiple races; or not reported. The ethnicity categories include Hispanic or Latino; not Hispanic or Latino; and unknown or not reported (hereafter "unknown"). Age groups included 18–39 years, 40–64 years, and ≥65 years. Sex was defined as male or female. Additional details can be found in the Supplementary Methods.

Reference Datasets

US Census

The 2020 Decennial Census Redistricting Data [23] were used to extract Census counts by race and ethnicity for the population aged ≥18 years for each state and the District of Columbia. The Vintage 2020 Population Estimate [24] was used for age and sex population proportions as 2022 data have not been released.

COVID-NET

The Centers for Disease Control and Prevention (CDC) COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) [25] is a population-based active surveillance system that collects county-level data about individuals who were hospitalized and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test positive within 14 days of admission. It collects data from approximately 250 acute care hospitals in 14 states. We used COVID-NET data from 12 of the 14 states where there were 24 ACTT sites (Supplementary Table 1, Supplementary Figure 1, and Supplementary Methods).

CDC COVID-19 Case Surveillance System

The CDC COVID-19 Case Surveillance System (CCSS) [26] is a passive surveillance system that captures notifiable disease reports about individuals in an inpatient or outpatient setting who are SARS-CoV-2 test positive. CDC CCSS data were used to evaluate 45 ACTT sites not captured by COVID-NET (Supplementary Table 1 and Supplementary Figure 2). Supplemental Table 2 presents a comparison of the three reference datasets.

Statistical Analysis

We calculated and compared the proportion of participants by sex, race, ethnicity, and age groups in each stage of ACTT using a Pearson χ^2 test.

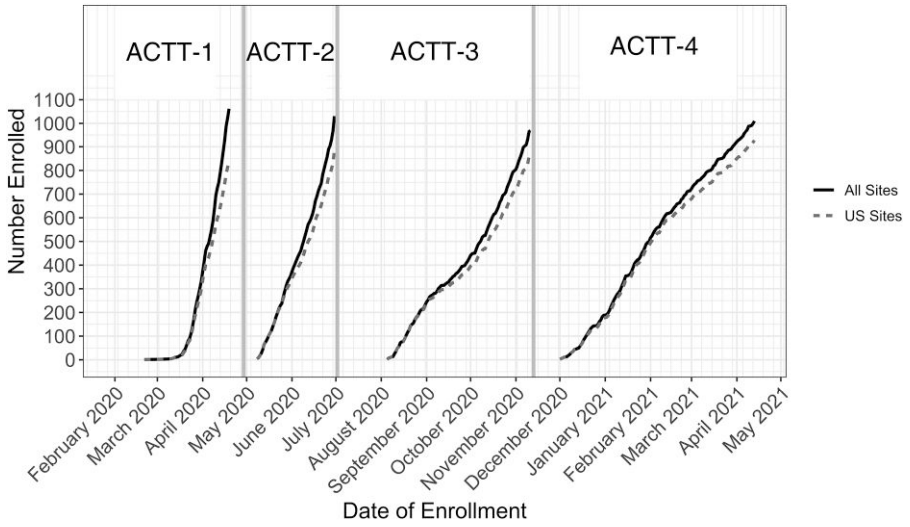

Figure 1. Number of participants enrolled by month and stage of the Adaptive COVID-19 Treatment Trial (ACTT) and site location. Abbreviation: US, United States.

We compared de-identified data on sex, race, ethnicity, and age from participants enrolled at the US ACTT sites with US Census data, and CDC COVID-NET and CCSS data from the same geographic area and time. Results are presented separately for all comparator datasets as the geographic locations included in the estimates differ by comparator (Supplementary Table 1). We determined the percentage of cumulative enrollments by subgroup for each stage of ACTT and calculated the corresponding Clopper-Pearson 95% confidence intervals (CIs). We determined whether the corresponding reference data were contained in the ACTT 95% CI and, if they were not, the differences were considered statistically significant. Data are presented as forest plots displaying the ACTT enrollment cumulative proportion and 95% CI, and the reference data estimate and 95% CI. Analyses by state are presented in the Supplementary Figures 3–10 and Supplementary Material. No multiple comparison adjustments were performed. Analyses were performed using R version 4.1.3 software [27].

Patient Consent Statement

This secondary analysis of de-identified ACTT data was conducted as a quality assurance, quality improvement project. A description of the project was reviewed by the National Institutes of Health Office of Institutional Review Board Operations and by the CDC's National Center for Immunization and Respiratory Diseases. These offices determined that the project did not qualify as human subjects research as defined by federal regulations and therefore the activities proposed did not require institutional review board review or approval.

RESULTS

The demographic characteristics of the 3509 adults enrolled in the US ACTT sites varied by trial stage (Table 1). The proportion of American Indian or Alaska Native participants enrolled increased from 0.1% in ACTT-1 to 1.9% in ACTT-4. ACTT-1 had the highest proportion of Asian and Black or African American participants (8.8% and 25.9%, respectively), whereas ACTT-2 had the lowest enrollment of Asian (3.6%) and Black or African American (17.6%) participants. Hispanic or Latino enrollment varied across stages with similar enrollment in ACTT-3 (29.5%) and ACTT-4 (31.8%), the lowest enrollment in ACTT-1 (27%), and the highest enrollment in ACTT-2 (52.1%). The proportion of female participants in ACTT increased from 35.7% in ACTT-1 to 43.4% in ACTT-3. Participants in ACTT-2 tended to be younger (30.2% were aged ≥65 years) than those enrolled in ACTT-1, ACTT-3, or ACTT-4 (36.2%, 38.6%, and 33.5%, respectively).

ACTT Representation Compared With US Census Data

Compared with US Census data, the proportion of participants aged ≥65 years enrolled in ACTT was significantly higher than in the US population; the proportion of participants aged 18–39 years was significantly lower (Figure 2). A significantly higher proportion of Black or African American and Hispanic or Latino participants were enrolled in ACTT when compared to US Census data. A similar proportion of all other races were enrolled in ACTT except for White participants. A lower proportion of White participants were enrolled in ACTT-1 and ACTT-2 than in the US population, whereas a higher proportion were enrolled in ACTT-3. There was a higher proportion of participants with unknown race in ACTT-1 and ACTT-2 than reported in the US Census data. A significantly lower proportion of female participants were enrolled in ACTT than in the US population.

Table 1. Demographic Characteristics of Enrolled Participants at United States Adaptive COVID-19 Treatment Trial Sites

Characteristic	ACTT-1 (n = 837)		ACTT-2 (n = 885)		ACTT-3 (n = 860)		ACTT-4 (n = 927)		χ^2 *P* Value[a]
US participant	837	(100.0)	885	(100.0)	860	(100.0)	927	(100.0)	
Race									<.0001
American Indian or Alaska Native	1	(0.1)	8	(0.9)	11	(1.3)	18	(1.9)	
Asian	74	(8.8)	32	(3.6)	32	(3.7)	39	(4.2)	
Native Hawaiian or Pacific Islander	4	(0.5)	11	(1.2)	9	(1.0)	5	(0.5)	
Black or African American	217	(25.9)	156	(17.6)	160	(18.6)	188	(20.3)	
White	427	(51.0)	487	(55.0)	583	(67.8)	588	(63.4)	
Multiple races	3	(0.4)	…	…	5	(0.6)	4	(0.4)	
Unknown	111	(13.3)	191	(21.6)	60	(7.0)	85	(9.2)	
Ethnicity									<.0001
Not Hispanic or Latino	561	(67.0)	408	(46.1)	588	(68.4)	605	(65.3)	
Hispanic or Latino	226	(27.0)	461	(52.1)	254	(29.5)	295	(31.8)	
Not reported	22	(2.6)	4	(0.5)	5	(0.6)	10	(1.1)	
Unknown	28	(3.3)	12	(1.4)	13	(1.5)	17	(1.8)	
Age									<.0001
18–39 y	96	(11.5)	137	(15.5)	108	(12.6)	89	(9.6)	
40–64 y	438	(52.3)	481	(54.4)	420	(48.8)	527	(56.9)	
≥65 y	303	(36.2)	267	(30.2)	332	(38.6)	311	(33.5)	
Sex									.00775
Female	299	(35.7)	342	(38.6)	373	(43.4)	384	(41.4)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: ACTT, Adaptive COVID-19 Treatment Trial.

[a] *P* values from Pearson χ^2 tests to compare the distribution of demographic variables across the 4 ACTT trials.

ACTT Representation Compared With CDC COVID-NET Data

There was a similar proportion of participants aged ≥65 years enrolled in ACTT-3 and reported by COVID-NET, while there was a lower proportion of this subpopulation enrolled in ACTT-1, ACTT-2, and ACTT-4 when compared with COVID-NET (Figure 3). In contrast, the proportion of participants aged 40–64 years enrolled in ACTT was significantly higher than the proportion detected by COVID-NET. There was a similar proportion of 18- to 39-year-old participants enrolled in ACTT as reported to COVID-NET. There was a higher proportion of Hispanic or Latino participants in ACTT-2 and ACTT-4 than in COVID-NET, while the proportion of Hispanic or Latino participants were similar between ACTT-1 and ACTT-3 and COVID-NET. The proportion of patients in COVID-NET with unknown ethnicity was higher than in ACTT-3 and ACTT-4 but was similar in ACTT-1 and ACTT-2. For every stage of ACTT, the proportion of American Indian or Alaska Native, Asian or Pacific Islander, and Black or African American participants was similar to the proportion detected by COVID-NET. There was a higher proportion of White participants enrolled in ACTT-2 and ACTT-3 compared with COVID-NET, whereas the proportion of this subpopulation in ACTT-1 and ACTT-4 was similar to COVID-NET. The proportion of patients in COVID-NET with unknown race was statistically significantly higher than in ACTT. The proportion of female participants enrolled in ACTT was significantly lower than the proportion of females identified by COVID-NET.

ACTT Representation Compared With CCSS Data

A significantly higher proportion of participants enrolled in ACTT were aged 40–64 years and ≥65 years when compared to those reported to CCSS; however, CSS included both hospitalized and nonhospitalized patients (Figure 4). In contrast, a significantly lower proportion of participants enrolled in ACTT were aged 18–39 years when compared to CCSS. The proportion of Hispanic or Latino participants enrolled in ACTT was significantly higher than the proportion reported to CCSS. However, a significantly higher proportion of the patients reported to CCSS had unknown or undocumented ethnicity and race compared with those enrolled in ACTT. Compared to CCSS data, there was a higher proportion of Black or African American participants and White participants in ACTT. Similarly, the proportion of Asian and Pacific Islander participants was significantly higher than reported to CCSS for all stages of ACTT except for ACTT-4, when the proportions were similar. A similar proportion of American Indian or Alaska Native participants were enrolled in all stages of ACTT except for ACTT-1 when none of the 45 ACTT sites enrolled participants from this population. The proportion of female participants enrolled in ACTT was significantly lower than the proportion of female patients reported to CCSS.

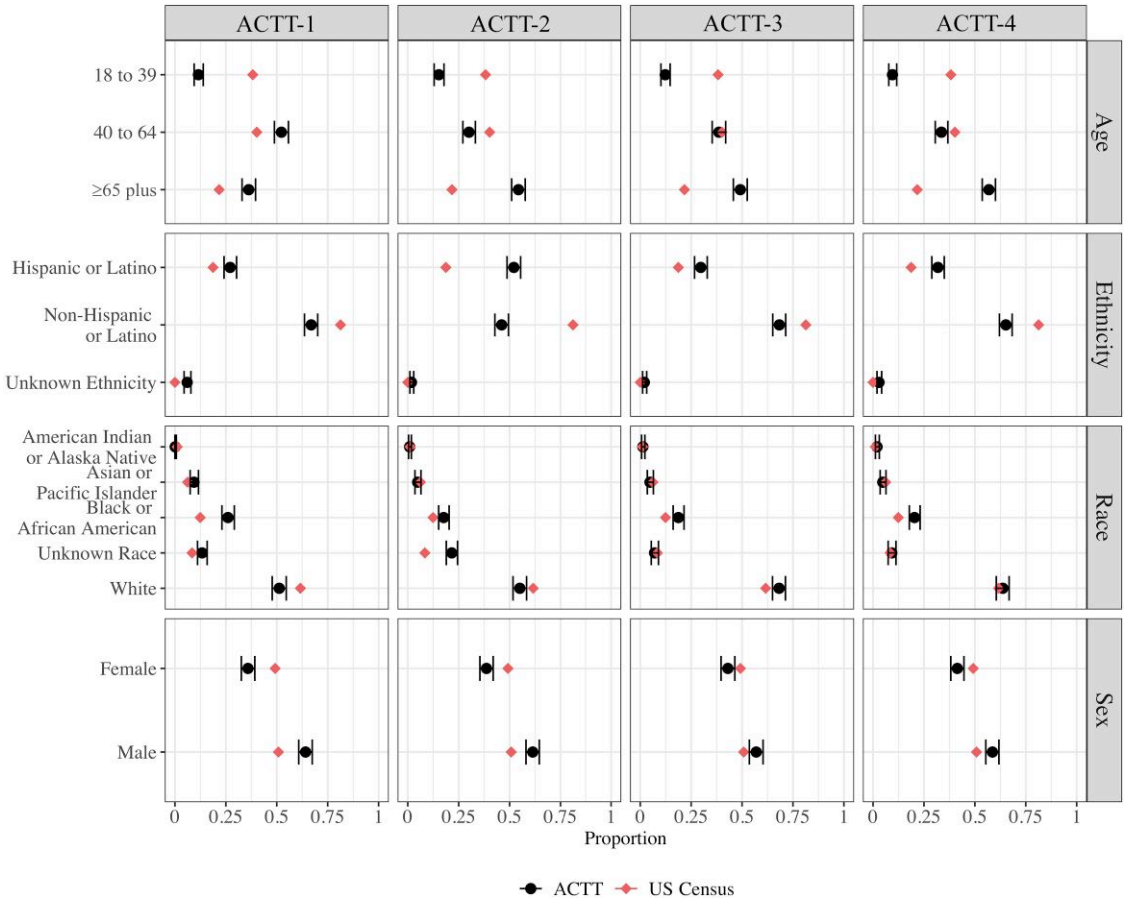

Figure 2. Demographics of participants enrolled in United States (US) Adaptive COVID-19 Treatment Trial (ACTT) sites compared with the US Census. The US Census proportion corresponds to the 2020 estimate and was presented for each stage of ACTT. Circles and error bars represent ACTT proportions and associated 95% confidence intervals (CIs); Diamonds correspond to US Census reported values and estimates. Differences were considered statistically significant if the US Census proportion was not contained within the ACTT enrollment CI.

Analyses by state are provided in Supplementary Figures 3–10.

DISCUSSION

The conclusion that ACTT achieved appropriate representation of ethnic and racial minorities, women, and older adults depended greatly on which dataset was used for comparison and the stage of ACTT examined. Despite including participants from relatively limited geographic areas, COVID-NET had characteristics that made it a superior comparator. Both ACTT and COVID-NET included only hospitalized individuals whereas the CCSS included both outpatients and hospitalized individuals. COVID-NET provided complete data on race and ethnicity compared to CCSS. COVID-NET data may be a better comparator because it records cases by county versus state level, which may be a more precise comparator for the catchment area of an individual trial site. When compared with COVID-NET, ACTT representation largely mirrored the demographics of US patients hospitalized with COVID-19 with respect to traditionally underrepresented groups: older adults, Hispanic or Latino, and Black or African American. In contrast, our comparison with US Census data highlighted its inability to serve as a comparator to assess whether trial enroll proportionally to those most impacted by the disease.

Older adults were well represented in ACTT, reflecting that most patients hospitalized with COVID-19 were older adults with more severe disease, a key enrollment eligibility criterion [28, 29], whereas in other COVID-19 trials, older adults were underrepresented [12, 30]. Conversely, 18- to 39-year-olds were underrepresented in ACTT, using the CCSS comparator. This was anticipated because CCSS includes outpatients who tend to be younger and less likely to develop severe disease requiring hospitalization.

Female participants were underrepresented in ACTT even when compared to hospitalized patients detected by COVID-NET. This was not entirely unexpected since among adults hospitalized with COVID-19, women were less likely than men to have severe disease [31, 32], which may have

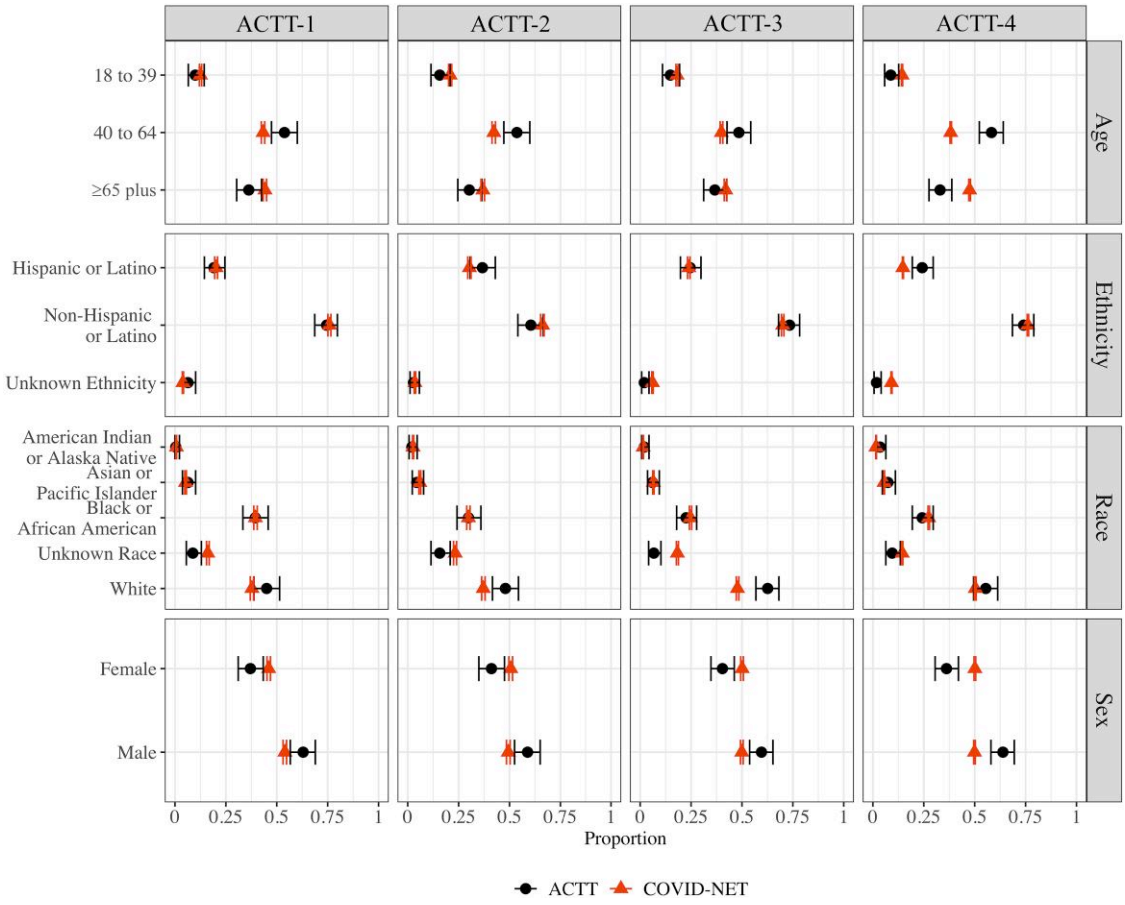

Figure 3. Demographics of participants enrolled in United States Adaptive COVID-19 Treatment Trial (ACTT) sites compared with participants reported to the Centers for Disease Control and Prevention's COVID-19–Associated Hospitalization Surveillance Network (COVID-NET). Circles and error bars represent ACTT proportions and associated 95% confidence intervals (CIs); triangles and error bars correspond to COVID-NET estimates and 95% CIs. Differences were considered statistically significant if the COVID-NET proportion was not contained within the ACTT enrollment CI.

impacted their trial eligibility. ACTT required a baseline level of disease severity and an anticipated hospital stay of at least 72 hours to allow the time necessary to evaluate the investigational study product. However, we cannot rule out other factors that may have contributed to female underrepresentation [1, 33].

ACTT was able to achieve representation over time by adding trial sites serving highly affected populations, contrary to an early characterization of ACTT [13]. To do this, we added trial sites with more patient diversity, hired staff who recruit and enroll non-English-speaking patients, and translated the informed consent form into 9 languages. Hispanic or Latino participants were particularly well represented in ACTT; the proportion enrolled was similar or higher than that identified by COVID-NET. Enrollment by race in ACTT was similar to that reported by COVID-NET for ACTT-1 and ACTT-4, whereas there was a higher proportion of White participants enrolled in ACTT-2 and ACTT-3 despite efforts to enroll a racially diverse population.

Research study designs should include enrollment targets reflective of those affected by the disease, and researchers must monitor recruitment and find real-time solutions to overcome barriers. Notably, representative enrollment may be difficult to achieve if the product safety profile requires exclusion criteria that disproportionately affect certain groups. For example, participants with severe renal disease were ineligible to participate in ACTT, a criterion that has been previously documented to systematically exclude Black or African American participants [34, 35]. In addition, social determinants of health that disproportionately affect underserved communities, such as lack of healthcare insurance, economic instability, and limited healthcare literacy, contribute to both decreased access to healthcare and willingness to participate in research [36, 37]. In ACTT, we worked to limit barriers to enrollment by minimizing data collection including follow-up after initial hospital discharge and limiting eligibility restrictions. Importantly, all potential barriers to representative enrollment require consideration early in the trial design.

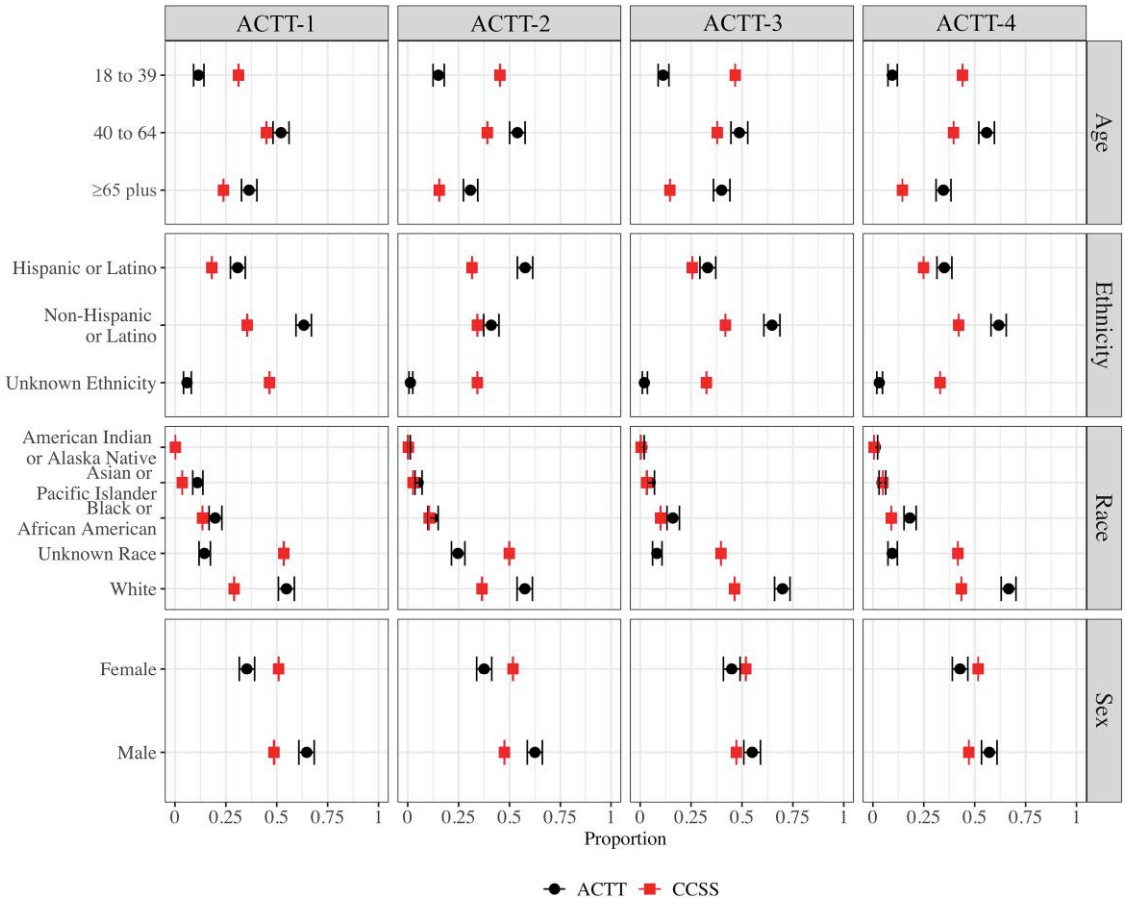

Figure 4. Demographics of participants enrolled in United States (US) Adaptive COVID-19 Treatment Trial (ACTT) sites compared with participants reported to the Centers for Disease Control and Prevention's COVID-19 Case Surveillance System (CCSS). Circles and error bars represent ACTT proportions and associated 95% confidence intervals (CIs); squares and error bars correspond to CCSS estimates and 95% CIs. This figure contains ACTT sites not covered by the COVID-19–Associated Hospitalization Surveillance Network, with the exception of New York and California (see Methods). Differences were considered statistically significant if the US Census proportion was not contained within the ACTT enrollment CI.

Achieving a representative study population may be difficult during the pandemic. The ability to achieve adequate representation is largely dependent upon timely and accurate demographic data both within and outside the trial. During study design, demographic enrollment goals and criteria for pausing enrollment of overrepresented demographic groups should be specified. This decision may have to be based on the US Census data until data sources that describe the populations most impacted by the infectious disease become available.

During the COVID-19 pandemic, reporting of both epidemiological data and results of clinical trials by race and ethnicity has been inadequate [14, 38, 39]. In ACTT, 96% of all participants had these data collected; unfortunately, comparator data had a higher proportion of unknown ethnicity and race among persons with COVID-19 reported to CCSS. While the ideal surveillance comparator data may not be available early in an outbreak, even passive surveillance data is important because US Census data may not reflect the population affected by an emerging infectious disease [40]. Active surveillance systems with more complete data, such as COVID-NET, may be ideal; however, they may have a limited geographic catchment area. When compared to COVID-NET, the most appropriate dataset for this assessment, ACTT enrolled participants whose demographics were most consistent with those of hospitalized participants with COVID-19. Designing and executing a recruitment strategy that makes representation a core element, and monitoring enrollment demographics, is important to achieve adequate representation. The selection of a comparator dataset to evaluate and monitor representation should be done in advance whenever possible to avoid potential selection bias. Representative clinical trial enrollment is essential to ensure generalizability to the populations for which interventions will be used.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the

authors, so questions or comments should be addressed to the corresponding author.

Notes

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