COVID-19 Trials: Who Participates and Who Benefits?

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Objectives: The coronavirus disease 2019 (COVID-19) pandemic has disproportionately afflicted vulnerable populations. Older adults, particularly residents of nursing facilities, represent a small percentage of the population but account for 40% of mortality from COVID-19 in the United States. Racial and ethnic minority individuals, particularly Black, Hispanic, and Indigenous Americans have experienced higher rates of infection and death than the White population. Although there has been an unprecedented explosion of clinical trials to examine potential therapies, participation by members of these vulnerable communities is crucial to obtaining data generalizable to those communities.

Methods: We undertook an open-label, factorial randomized clinical trial examining hydroxychloroquine and/or azithromycin for hospitalized patients.

Results: Of 53 screened patients, 11 (21%) were enrolled. Ten percent (3/31) of Black patients were enrolled, 33% (7/21) of White patients, and 50% (6/12) of Hispanic patients. Forty-seven percent (25/53) of patients declined participation despite eligibility; 58%(18/31) of Black patients declined participation. Forty percent (21/53) of screened patients were from a nursing facility and 10% (2/21) were enrolled. Enrolled patients had fewer comorbidities than nonenrolled patients: median modified Charlson comorbidity score 2.0 (interquartile range 0–2.5), versus 4.0 (interquartile range 2–6) for nonenrolled patients ($P = 0.006$). The limitations of the study were the low participation rate and the multiple treatment trials concurrently recruiting at our institution.

Conclusions: The high rate of nonparticipation in our trial of nursing facility residents and Black people emphasizes the concern that clinical trials for therapeutics may not target key populations with high mortality rates.

Key Words: frailty, older adults, SARS-CoV-2, treatment, trial participation

As of April 2, 2021, there were 1553 international trials on the treatment of coronavirus disease 2019 (COVID-19) recruiting,[1] and an additional 1148 had been completed. The explosion of research into the treatment of COVID-19 has yielded four treatments that have positive effects on survival or hospital length of stay: remdesivir,[2] dexamethasone,[3] severe acute respiratory coronavirus 2 (SARS-CoV-2) monoclonal antibodies bamlavinimab and casirivimab/imdevimab,[4,5] and baricitinib.[6] Many other potential therapies remain to be tested, however. Testing these therapies in a timely fashion will require a large and diverse population to participate in trials, but the majority of those with COVID-19 will never enroll in a randomized controlled trial.[7]

COVID-19 disproportionately sickens and kills individuals with underlying illness.[8,9] Both the number and nature of comorbidities, such as asthma, hypertension, chronic kidney disease, obesity, and diabetes mellitus, increase the risk of severe disease

Key Points

- Coronavirus disease 2019 mortality has disproportionately affected older adults, residents of nursing facilities, and racial and ethnic minority individuals in the United States.
- Our open-label, factorial randomized clinical trial examining hydroxychloroquine and/or azithromycin for hospitalized patients screened 53 patients and enrolled 11.
- We found a high nonparticipation rate among nursing facility residents and Black individuals.
- Effective treatments for coronavirus disease 2019 may not have the desired impact on mortality if populations that are most at risk of death do not participate in therapeutics trials.

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This article includes unlabeled/investigational uses of hydroxychloroquine and azithromycin for the treatment of COVID-19 and the status of these is disclosed herein.

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and death.[10–12] In addition, increasing age is a key risk factor for severe COVID-19 disease and mortality both globally[13,14] and in the United States.[15] As of February 16th, 2022, in the United States >650,000 individuals older than age 65 years have died from COVID-19, 74% of the national death count.[16] Frailty, defined as a "syndrome of dysregulated energetics" resulting in slowing, fatigue, decreased muscle mass, strength, and physical activity, also is emerging as a risk factor for severe COVID-19 disease.[17]

Across many parts of the world, nursing facilities have borne the brunt of mortality secondary to COVID-19.[18–20] In the United States, estimates suggest that 40% of COVID-19 deaths are linked to nursing facilities while accounting for just 7% of cases.[21] Although residents of nursing facilities may be a primary target of effective COVID-19 treatments to reduce the mortality burden, these groups often have been underrepresented in clinical treatment trials.[22]

Black/African American, Hispanic, and indigenous populations, also underrepresented in clinical trials, have been disproportionately affected by the COVID-19 pandemic in the United States; 41% of deaths from COVID-19 have occurred in non-White populations, although these individuals make up only 28% of the population. The Black community accounts for 18% of the deaths but only 13% of the US population, while disproportionately fewer deaths (59%) have occurred among non-Hispanic Whites, who constitute 72% of the population.[23,24] In this article, we use the lens of our COVID-19 treatment trial to reflect on the question of whether potentially effective treatments will be studied in the populations most severely affected.

Methods

We performed a pragmatic, open-label, factorial randomized clinical trial of hydroxychloroquine plus or minus azithromycin for hospitalized patients across four hospital sites in North Carolina and Iowa.

Participants

The study was designed to enroll the broadest possible group of participants, including many individuals who were ineligible for other treatment trials resulting from comorbidities. Patients were initially screened by the hospitals' COVID-19 trial team and referred to us with the following inclusion criteria: older than 12 years, hospitalized with COVID-19 infection confirmed by a validated nucleic acid amplification assay (in the 14 days prerandomization), and symptoms attributable to COVID-19 infection. Symptoms were defined as an illness of any duration that included any lower respiratory symptoms (cough, shortness of breath, wheezing), or any documented $SpO_2 \leq 94\%$ on room air, or supplemental oxygen, or pulmonary infiltrates on chest imaging (chest x-ray or computed tomography of the chest). The exclusion criteria included a history of hypersensitivity to either of the study drugs, liver cirrhosis, corrected QT interval > 500 ms, enrollment in another COVID-19 treatment trial, recent (<180 days) use of hydroxychloroquine, or death anticipated within 48 hours of enrollment. Participants were recruited from two health systems: Duke Health in North Carolina (Duke University Hospital, Duke Regional Hospital, and Duke Raleigh Hospital) and UnityPoint Health (Iowa Regional Medical Center and Iowa Lutheran Hospital) in Des Moines, Iowa.

Randomization, Interventions, and Follow-Up

Enrolled patients were randomly assigned in a 1:1 ratio to standard-of-care treatment or standard-of-care treatment plus hydroxychloroquine 800 mg on day 1 followed by 600 mg daily for another 4 days. Patients eligible to receive azithromycin (no receipt in the previous 7 days and no contraindications) were also randomized in a 1:1 ratio to receive azithromycin 500 mg once, followed by 250 mg/day for another 4 days, or no azithromycin. This resulted in four treatment groups: standard of care alone, standard of care plus hydroxychloroquine, standard of care plus azithromycin, standard of care plus hydroxychloroquine plus azithromycin.

The standard care for COVID-19 was at the discretion of the treating physicians. The use of glucocorticoids, immunomodulatory drugs, antibiotic agents, and/or antiviral agents was permitted outside an experimental treatment trial, but concurrent participation in another treatment trial was not permitted. Remdesivir was available only through a clinical trial at the time. The trial received institutional review board approval at all of the sites and was registered with clinicaltrials.gov (NCT04335552).

The study opened on April 14, 2020, and the first participant was enrolled on April 17, 2020. Because of the emerging evidence on the lack of hydroxychloroquine efficacy for COVID-19 and potential adverse effects, study enrollment was terminated on June 5, 2020.

Results

For 8 weeks, 53 patients were screened and 11 (21%) enrolled in the study, all at the North Carolina sites. Table 1 compares the demographics and characteristics of the 53 patients who were screened in our study. Fifty-one percent (27/53) were male, with an average age of 56 years, 23% (12/53) were Hispanic, and 59% (31/53) were Black. This screened population was somewhat different from the overall patient population admitted with COVID-19 during that time. From April 14 to June 5, 2020, 262 patients were admitted to the North Carolina hospital sites. Fifty-eight percent (152/262) were male, 32% (83/262) were Hispanic, 32% (84/262) were Black, and the average age was 56 years old.

The majority of enrolled patients were male (73%, 8/11) and Hispanic (55%, 6/11). Enrolled patients were younger than nonenrolled patients (mean age 55 vs 67 years, $P = 0.033$), more likely to be Hispanic (54% vs 14%, $P = 0.015$), and less likely to be Black ($P = 0.018$). Ten percent (3/31) of Black patients were enrolled, compared with 33% (7/21) of White patients and 50% (6/12) Hispanic patients.

Table 1. Characteristics of screened participants

Screening outcome (n)	Nonenrolled (42)	Enrolled (11)	*P*
Demographics			
Age, y, mean (SD)	67 (18)	55 (13)	0.03
Race (%)			0.02
Black	28 (67)	3 (27)	—
Multiple races	0	1 (9)	—
White	14 (33)	7 (63)	—
Non-Hispanic (%)	36 (86)	5 (46)	0.02
Male sex (%)	19 (45)	8 (73)	0.20
Nursing facility resident (%)	19 (45)	2 (18)	0.20
Comorbidities (%)			
Hypertension	33 (79)	6 (55)	0.22
Anticoagulant	7 (17)	1 (9)	0.88
BMI, kg/m^2, mean (SD)	32 (10)	38 (11)	0.09
Diabetes mellitus	22 (52)	5 (46)	0.94
Asthma	2 (5)	2 (18)	0.39
Coronary artery disease	10 (24)	2 (18)	1
Chronic heart failure	8 (19)	1 (9)	0.67
Stroke	9 (21)	1 (9)	0.62
PVD	2 (5)	0	1
Dementia	13 (31)	1 (9)	0.28
COPD	2 (5)	0	1
Autoimmune disease	1 (2)	0	1
ESRD (%)	2 (5)	0	1
Solid tumor malignancy (%)	7 (17)	0	0.34
Modified Charlson comorbidity index (IQR)	4 (2–6)	2 (0–2.5)	<0.01
Baseline WHO score (%)			
Hospitalized, mechanical ventilation or ECMO	4 (10)	0	
Hospitalized, non-invasive ventilation	2 (5)	0	
Hospitalized, supplemental oxygen	24 (57)	10 (91)	
Hospitalized, no supplemental oxygen	12 (29)	1 (9)	

Modified Charlson Comorbidity Index: age, chronic heart failure, PVD, stroke, dementia, COPD, autoimmune disease, diabetes mellitus, chronic renal impairment, solid tumor malignancy, leukemia, chronic liver disease (no screened participants had liver disease). Full Charlson Comorbidity Index also includes peptic ulcer disease, myocardial infarction, and hemiplegia. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; IQR, interquartile range; PVD, peripheral vascular disease; SD, standard deviation; WHO, World Health Organization.

The median modified Charlson comorbidity score among enrolled patients was 2.0 (interquartile range 0–2.5), versus 4.0 (interquartile range 2–6) for nonenrolled patients (P = 0.006; Table 1). Among patients who did not enroll, 31% (13/42) had dementia; 17% (7/42) had an active malignancy; and 19% (8/42) had heart failure. In the enrolled group, only 9% (1/11) had dementia, no patients had a malignancy, and 9% (1/11) had heart failure. Patients with dementia and diabetes mellitus who resided in nursing facilities were overrepresented in nonenrolled compared with enrolled participants (P = 0.0098; Fig.). No enrolled patients required noninvasive ventilation or mechanical ventilation, compared with 15% (6/42) in the nonenrolled group.

Of the total screened cohort, 47% (25/53) of the patients declined enrollment, 26% (14/53) were excluded based on ineligibility for the trial, 6% (3/52) were unable to provide consent, and 21% (11/53) were enrolled (Table 2). Patients who declined participation were older than those who enrolled (64 years old, standard deviation 19 years). Fifty-eight percent (18/31) of Black patients declined participation in the study despite eligibility compared with 25% (3/12) of Hispanic patients. Fifty-seven percent (8/14) of patients with dementia and 75% (3/4) of patients on mechanical ventilation declined participation. Of the 14 screened patients who were not eligible for enrollment, 29% (4/14) had a corrected QT interval > 500 ms, 29% (4/14) were not expected to survive 48 hours, and 29% (4/14) were hospitalized for reasons other than symptoms attributable to COVID-19 and not enrolled at investigator discretion.

Overall, 40% (21/53) of the screened patients were from a nursing facility. Nursing facility residents made up 45% (19/42) of the nonenrolled patients and 18% (2/11) of the enrolled patients. Nonenrolled nursing facility residents declined participation in 47% (9/19) of cases and were ineligible or unable to provide consent in 53% (10/19) of cases.

Discussion

The majority of patients considered for this study (79%) either declined participation or were not eligible. Those who declined participation (47%) met the eligibility requirements and were hospitalized for severe COVID-19. Enrolled patients had fewer comorbidities than nonenrolled patients and were less likely to have been residents of nursing facilities. Despite the fact that the majority of screened patients (58%) were Black and there

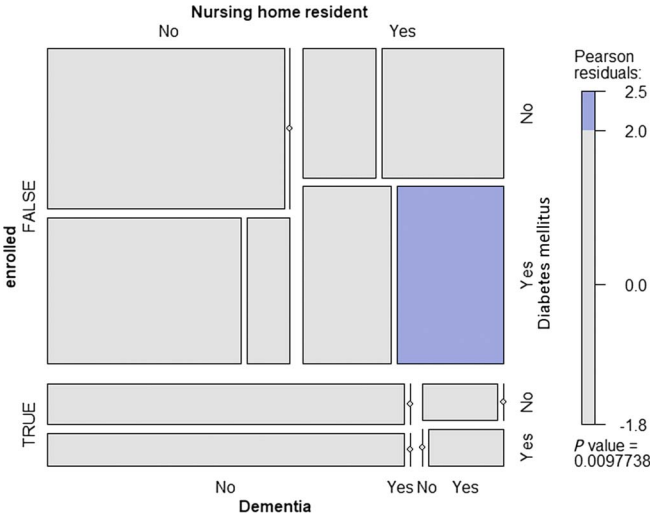

Fig. Risk factors by enrollment status.

Table 2. Study screening outcomes

Screening outcome	N = 53 (%)
Enrolled	11 (21)
Declined enrollment	25 (47)
Not eligible for enrollment	
QTc ≥500	4 (8)
<48 h expected survival	4 (8)
Investigator discretion	4 (8)
Recent HCQ use	1 (2)
Alternative COVID-19 trial	1 (2)
Consent not obtained	3 (6)

COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; QTc, corrected QT interval.

is an overall high mortality from COVID-19 among Black communities in the United States, the participation rate among Black patients in our study was particularly low (10%) compared with other ethnic and racial minorities. The majority of Black patients screened (18/31, 58%) did not enroll because they declined to participate. The findings from our study may reflect a number of factors.

First, in North Carolina at the time of our study recruitment, the pandemic was predominately affecting congregate facilities, such as nursing facilities and prisons, and most of the hospitalized patients were from these groups.[25] Ineligibility in the nursing facility group for our study was high, reflecting the overall frailty of this group and a higher burden of underlying illness. The high declined proportion in the nursing facility group likely also reflects challenges in obtaining informed consent from nursing facility residents because of cognitive impairment, the ability to engage in informed consent, and the complexities around family members as proxy decision makers.[26] In this vulnerable population there may be questions around quality of life, with patients and their families weighing the risks and benefits of a novel treatment with considerations of the patients' overall goals of care.

A second reason for low participation in our trial may be the overall declining participation rate in scientific trials in the United States.[27] There have been a number of reasons postulated for this: a proliferation of research studies, political polls, and surveys (indistinguishable from scientific inquiry) during the past 2 decades that have produced an oversurveyed population; decreased volunteerism in the United States and other wealthy democracies reflecting the unwillingness to participate in scientific research; and increasing study complexity, participant time requirements, and onerous informed consent processes.[27]

The high nonparticipation rate among Black participants in our study and clinical trials across the United States may in part relate to a long history of injustice and racist exploitation by American physicians and scientists toward Black people.[28] The distrust in the healthcare system and clinical research derives from past unethical studies such as the Tuskegee Study of Untreated Syphilis in the Negro Male, in which researchers withheld syphilis treatment in Black American men to understand the natural history of the disease.[29] The legacy of such studies continues to impede COVID-19 therapeutics and vaccine trial recruitment.[30–32]

Our study reflected the high burden of severe COVID-19 infection in nursing facility residents, with 45% of the screened cohort from this population. In North Carolina, the mortality burden among this group has mirrored national statistics, with 50.6% of deaths from nursing and residential facilities.[33] Mortality also has been high in North Carolina among older people, with 80% of deaths occurring in the older than 65 years age group, despite this group only accounting for 13% of cases. Despite this, only 10% of nursing facility patients screened were enrolled in our study. Low participation rates in this frail, sick population reduces the generalizability of any study results; it may well be that interventions effective in healthier populations may not reduce morbidity or mortality in this population, and assessments of the impact of novel therapeutics need to be tempered by the possibility that frail, older adults whose baseline functional status is marginal may not benefit from these therapeutics.

Older adults have historically been excluded from participation in clinical trials. In 2017, the National Institutes of Health attempted to address this inequality by issuing new policy guidelines requesting grant applicants to provide a rationale to restrict study enrollment based on age.[34] During the COVID-19 pandemic trial, however, inclusivity of older adults has continued to be a challenge. A recent study reviewing the available clinical trials (from October 1, 2019 to June 1, 2020) found that adults older than age 65 years were not able to participate in 50% of COVID-19 treatment trials and 100% of vaccine trials.[35] Two major COVID-19 treatment trials, the Adaptive COVID-19 Treatment Trial (ACTT-1) and the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, did not exclude participants based on age; however, they listed exclusion criteria that may have reduced participation by frail older adults. In RECOVERY, patients were excluded if they had a medical condition that in the opinion of their physician precluded participation; this constituted 15% of participants prerandomization.[3] The ACTT-1 excluded people with transaminases >5 times the upper limit of normal and impaired renal function (stage IV chronic kidney disease or dialysis).[2] These criteria likely excluded frail older adults and those with increased comorbidities. Data on whether trial participants were nursing facility residents were not published.

This analysis has two primary limitations. The low overall participation rate of our trial, particularly from nursing facility residents, may be partially attributable to factors surrounding the study drugs themselves. At the time of recruitment, there was extensive public debate around the role and effectiveness of hydroxychloroquine as a treatment for COVID-19, and significant politicization on the issue before the publication of sound efficacy data.[36] Cognizant of these issues, our trial was suspended when there were early indicators from large trials (RECOVERY and the World Health Organization Solidarity Trial) of the lack of efficacy of hydroxychloroquine for COVID-19.[2,37] Nevertheless,

study recruitment may have been affected by concerns of hydroxychloroquine toxicity in frail nursing facility residents, particularly in combination with azithromycin. A second factor potentially affecting the trial participation rate was investigator bias from the hospital COVID-19 trials team. At the time our trial was recruiting, there were multiple treatment trials offered across the Duke Hospital network. Most of these trials precluded enrollment in other therapeutics trials. To decrease the burden on patients, the trials team determined the initial eligibility of each patient after reviewing medical records. If a patient was eligible for multiple trials, then a single trial was selected, and the respective study coordinator contacted to approach the patient. Patients were enrolled preferentially in the ACTT-1 trial (study drug remdesivir) over other trials. This process reduced enrollment in trials of drugs deemed less likely to be efficacious, limiting the potential to demonstrate efficacy.

Conclusions

The high rate of nonparticipation in our trial among those from nursing facilities and Black people emphasizes the concern that those who participate in treatment trials for COVID-19 may not reflect the populations who are most affected by severe disease and stand to benefit from effective treatment. As worldwide rollout of COVID-19 vaccine began, there was concern that distribution and access also were unlikely to be equitable.[38] As COVID-19 cases and deaths continue to rise rapidly in the United States and other parts of the world, disproportionately affecting older adults and racial and ethnic minorities, the question of whether any effective treatment will affect overall mortality given the population at risk, remains to be seen.

References

1. Cytel. Global coronavirus COVID-19 clinical trial tracker. https://www.covid-trials.org. Accessed April 2, 2021.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med* 2020;383:1813–1826.
3. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med* 2021;384:693–704.
4. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med* 2021;384:229–237.
5. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *N Engl J Med* 2021;384:238–251.
6. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 2021;384:795–807.
7. North CM, Dougan ML, Sacks CA. Improving clinical trial enrollment—in the Covid-19 era and beyond. *N Engl J Med* 2020;383:1406–1408.
8. Palmieri L, Vanacore N, Donfrancesco C, et al. Clinical characteristics of hospitalized individuals dying with COVID-19 by age group in Italy. *J Gerontol A Biol Sci Med Sci* 2020;75:1796–1800.
9. Neumann-Podczaska A, Al-Saad SR, Karbowski LM, et al. COVID 19—clinical picture in the elderly population: a qualitative systematic review. *Aging Dis* 2020;11:988–1008.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–1062.
11. Lee JY, Kim HA, Huh K, et al. Risk factors for mortality and respiratory support in elderly patients hospitalized with COVID-19 in Korea. *J Korean Med Sci* 2020;35:e223.
12. Centers for Disease Control and Prevention. COVID-19: people with certain medical conditions. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcovid-data%2Finvestigations-discovery%2Fhospitalization-underlying-medical-conditions.html. Published 2020. Accessed October 10, 2020.
13. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180:934–943.
14. Kluge HHP. Statement—older people are at highest risk from COVID-19, but all must act to prevent community spread. https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/statements/statement-older-people-are-at-highest-risk-from-covid-19,-but-all-must-act-to-prevent-community-spread. Published April 2, 2020. Accessed January 15, 2022.
15. Centers for Disease Control and Prevention. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:343–346.
16. Centers For Disease Control and Prevention. Weekly updates by select demographic and geographic characteristics. Provisional death counts for coronavirus disease 2019 (COVID-19). https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm. Published 2020. Accessed January 2, 2021.
17. Ma Y, Hou L, Yang X, et al. The association between frailty and severe disease among COVID-19 patients aged over 60 years in China: a prospective cohort study. *BMC Med* 2020;18:274.
18. Machado CJ, Pereira CCA, Viana BM, et al. Estimates of the impact of COVID-19 on mortality of institutionalized elderly in Brazil. *Cien Saude Colet* 2020;25:3437–3444.
19. Ciminelli G, Garcia-Mandicó S. COVID-19 in Italy: an analysis of death registry data. *J Public Health (Oxf)* 2020;42:723–730.
20. Barnett ML, Hu L, Martin T, et al. Mortality, admissions, and patient census at SNFs in 3 US cities during the COVID-19 pandemic. *JAMA* 2020;324:507–509.
21. Kamp J, Mathews AW. As U.S. Nursing-Home Deaths Reach 50,000, States Ease Lockdowns, June 16th, 2020. Available at: https://www.wsj.com/articles/coronavirus-deaths-in-u-s-nursing-long-term-care-facilities-top-50-000-11592306919. Accessed February 28, 2022.
22. Herrera AP, Snipes SA, King DW, et al. Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. *Am J Public Health* 2010;100(suppl 1):S105–S112.
23. Centers for Disease Control and Prevention. COVID data tracker: demographic trends of COVID-19 cases and deaths in the US reported to CDC. https://covid.cdc.gov/covid-data-tracker/#demographics. Published 2020. Accessed February 16, 2022.
24. Humes KR, Jones NA, Ramirez RR. Overview of race and Hispanic origin: 2010. https://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf. Published March 2011. Accessed January 15, 2022.
25. Brosseau C. Coronavirus NC: deaths in long-term care, nursing homes rise. *News & Observer,* May 30, 2020.
26. Harris R, Dyson E. Recruitment of frail older people to research: lessons learnt through experience. *J Adv Nurs* 2001;36:643–651.
27. Galea S, Tracy M. Participation rates in epidemiologic studies. *Ann Epidemiol* 2007;17:643–653.
28. Warren RC, Shedlin MG, Alema-Mensah E, et al. Clinical trials participation among African Americans and the ethics of trust: leadership perspectives. *Ethics Med Public Health* 2019;10:128–138.
29. Katz RV, Warren RC, eds.. *The Search for the Legacy of the USPHS Syphilis Study at Tuskegee*. Lanham, MD: Lexington Books; 2013.
30. Washington HA. *Medical Apartheid: The Dark History of Medical Experimentation on Black Americans from Colonial Times to the Present*. New York: Doubleday; 2006.
31. Warren RC, Forrow L, Hodge DA, et al. Trustworthiness before trust—Covid-19 vaccine trials and the Black community. *N Engl J Med* 2020;383:e121.

32. Hoffman J. 'I won't be used as a guinea pig for white people'. https://www.nytimes.com/2020/10/07/health/coronavirus-vaccine-trials-african-americans.htmlhttps://www.nytimes.com/2020/10/07/health/coronavirus-vaccine-trials-african-americans.html. Published October 7, 2020. Accessed January 15, 2022.
33. North Carolina Department of Health and Human Services. NC COVID-19 dashboard, outbreaks and clusters. https://Covid19.ncdhhs.gov/dashboard/outbreaks-and-clusters. Published 2020. Accessed September 20, 2020.
34. National Institutes of Health. Revision: NIH policy and guidelines on the inclusion of individuals across the lifespan as participants in research involving human subjects. https://grants.nih.gov/news/revision-nih-policy-and-guidelines-inclusion-individuals-across-lifespan-participants-research. Published December 26, 2017. Accessed January 15, 2022.
35. Helfand BKI, Webb M, Gartaganis SL, et al. The exclusion of older persons from vaccine and treatment trials for coronavirus disease 2019—missing the target. *JAMA Intern Med* 2020;180:1546–1549.
36. Stone W. Politics around hydroxychloroquine hamper science. https://www.npr.org/sections/health-shots/2020/05/21/859851682/politics-around-hydroxychloroquine-hamper-science. Published 2010. Accessed October 10, 2020.
37. Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed antiviral drugs for Covid-19—interim WHO Solidarity Trial results. *N Engl J Med* 2021;384:497–511.
38. OXFAM. Campaigners warn that 9 out of 10 people in poor countries are set to miss out on COVID-19 vaccine next year. https://www.oxfam.org/en/press-releases/campaigners-warn-9-out-10-people-poor-countries-are-set-miss-out-covid-19-vaccine. Published December 9, 2020. Accessed January 15, 2022.