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A Telehealth-Based Randomized Controlled Trial: A Model for Outpatients Trials of Off-Label Medications During the COVID-19 Pandemic

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Trial registration

The study was registered at clinicaltrials.gov: NCT04363203

In response to the COVID-19 pandemic, many clinical trials have been initiated but few are focused on outpatient drugs. Although there is a need to test off-label medications in the outpatient setting, recruitment is challenging because the desire to limit transmission of infection in clinic and hospital facilities has led to the establishment of virtual care and

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Declaration of competing interests

The authors declare that there is no conflict of interest.

drive-through testing, restricting in-person access to potential trial participants. These challenges may partially account for why only a limited number of outpatient treatments have been evaluated during the pandemic.

The VA Remote and Equitable Access to COVID-19 Healthcare Delivery Trial (VA-REACH)

We designed and launched a double-blinded, placebo-controlled, 3-arm (1:1:1) randomized control trial to examine the efficacy of hydroxychloroquine[1–3] or azithromycin for the reduction of symptoms and prevention of disease progression (hospitalization) in Veterans with COVID-19 in the outpatient setting.[4] VA-REACH was designed to recruit a national cohort of Veterans at low risk for adverse cardiac events. We leveraged the data resources of the VA to implement the trial remotely without direct participant contact. Azithromycin was included as a separate arm due to emerging data on its potential antiviral properties and clinical benefit.[5–7] The trial was launched on April 29, 2020. Protocol details are provided in Table 1.

Recruitment strategy

VA laboratory data[8] were reviewed for positive COVID-19 cases based on PCR (Supplement Figure S1). Given that azithromycin and hydroxychloroquine can both cause QT prolongation, the enrollment criteria were designed to only recruit participants at very low risk for a cardiac event. In accordance with American College of Cardiology recommendatons,[9] we designed enrollment criteria that ensured a Tisdale score <6 (Table 1). The VA medical record was examined to determine baseline symptoms (fever, cough, dyspnea). These three symptoms were selected based on their prevalence in early reports of COVID-19 clinical manifestations.[10] One of these documented symptoms was required for enrollment. Potential participants with symptoms that started >5 days prior to chart review were excluded because the goal was to enroll patients early in their disease. Figure S2 in the supplement outlines steps in the recruitment strategy. Potential participants received a mailed overnight recruitment package that included study information and consent forms. Postal tracking information allowed the team to be alerted at the time the package was delivered. After delivery, research staff waited two hours before calling potential participants. Upon calling, research staff determined interest in participation, assessed eligibility, and obtained phone consent. After obtaining consent, the study team randomized the participant to a study drug arm, alerted a clinician investigator to create a prescription, and notified the pharmacy to dispense the blinded study medication.

Daily symptom checklists and adverse data collection

Baseline comorbidities could be extracted from national VA data. The telephone-based interview allowed for confirmation of days of symptoms at enrollment, a review of drug allergies, and other enrollment criteria. Symptom data and adverse event data collection were conducted by surveys using an automated daily text/email strategy. If a participant did not answer the texted/emailed survey for two consecutive days, we planned to call them and collect data over the phone. If a participant was unreachable, the VA medical record was reviewed to determine if they were hospitalized in the VA. If no data were available, the plan

was to call the participant's emergency contact to collect information on potential hospitalization in non-VA settings (see supplement for data collection tools).

Sample size and power

For the outcome of symptom duration, we required 300 participants to power our study appropriately. For full details see supplement.

Trial launch

On April 29, 2020, 65 cases were identified from the prior two days using COVID-19 laboratory data. Given inclusion criteria to ensure participant safety, only 12 of the 65 cases were retained after VA data and chart exclusions. The average Tisdale score for the 12 potential participants was 1, suggesting it was feasible to identify participants at low risk of cardiac arrhythmia. All 12 cases were sent the consent package with overnight postal delivery. Of the 12 packages, 10 potential participants received the package—one stated he was no longer staying at the address listed in the medical record and one did not answer the telephone. Among the 10 potential participants, two expressed interest in participation but only one met inclusion criteria. The participant was consented and enrolled in the trial. The participant reported daily symptoms via the text/email strategy, reported no adverse events, and reported at day 30 via text that he was not hospitalized. This was confirmed in the medical record. On May 4, 2020, the San Francisco VA was asked to place the trial on hold by VA research leadership due to concerns regarding lack of national coordination of the trial with the VA Office of Research and Development, inadequate communication with local providers, and sensitivities around the use of hydroxychloroquine (see supplement for full details). Although the VA-REACH trial was not completed, the design and launch were novel and provide an approach to efficiently and safely recruit participants in health systems without compromising research staff safety during a pandemic.

Discussion

The VA-REACH trial experience, albeit limited, supports the feasibility of combining the resources of a national health system to recruit participants in a manner that protects study staff from exposure to the virus and maximizes recruitment. This trial design did not rely on the variability of local case counts. As the pandemic moved from one location to another, the ability to track lab data across the country provided an opportunity for regular daily recruitment and facilitated outcome measurement and follow-up. Although this design is not suitable for medications delivered intravenously or those requiring inpatient monitoring, it may be suitable for the evaluation of other off-label outpatient medications.[11–12] VA-REACH had several advantages. Our staff were remotely based and were not at risk of being exposed to infection. One staff member worked part time on-site to facilitate postal delivery. We had access to national daily new positive tests supporting rapid recruitment. We leveraged health system data to rapidly identify eligible participants. The clinical trial methods were also convenient for patients, who did not have to drive to a facility. They participated fully in the trial from their home and reported outcomes using a simple phone-based application, facilitating complete and rapid data collection. Trial implementation challenges are discussed in Supplement Table S2.

In conclusion, there is a need to rethink clinical trial design in outpatient settings to support rapid evaluation of off-label medications. The COVID-19 pandemic has been disruptive to traditional clinical trial designs, offering us an opportunity (e.g. outbreak response) for using telehealth-based remote strategies. This approach may be considered in other settings including emergency scenarios and even routine study environments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

VA REACH Trial

Regulatory milestones	The FDA provided us an exemption letter for the use of azithromycin and hydroxychloroquine on March 31, 2020. The University of California San Francisco Institutional Review Board provided human subjects' approval on April 15, 2020.
Inclusion criteria	(a) first COVID-19 positive laboratory test (b) willingness to take the study drug(s) (c) able to be contacted by smart phone (d) willing and able to provide informed consent for participation in the study (e) presence of fever, cough, or shortness of breath within the last 24 hours
Exclusion criteria	Arrythmia, congestive heart failure, renal disease, electrolyte disturbance *
Randomization	Eligible, consented patients could be randomized to a 1:1:1 treatment allocation, stratifying by age (<65 versus ≥65 years), and using randomly permutated blocks (block size of 3) within four geographic areas (Pacific, Continental, Northeast, and Southeast)
Dosing	**Azithromycin**: 2×250mg by mouth (PO) in the AM on Day 1, followed by 250mg PO every day on Days 2–5 **Hydroxychloroquine**: 2×200mg PO in the AM and 2×200mg PO in the PM on Day 1, followed by 200mg PO in the AM and 200 mg PO in the PM on Days 2–5. **Placebo:** provided in identical bubble packs with same number of pills in all arms
Follow-up period	30 days from enrollment
End points	Primary: Days of symptoms (fever, cough, shortness of breath) Secondary: Any symptoms, all-cause hospitalization, all-cause ICU admission, all-cause death
Analysis	The primary efficacy outcome was the time to resolution of common COVID-19 symptoms (fever, shortness of breath, and cough). The secondary outcomes, which would be collected via national VA, included: all-cause hospitalization, all-cause ICU stay, all-cause death, COVID-19-specific hospitalization, COVID19-specific ICU stay, or COVID-19-specific death.The statistical analysis plan was for a blinded, intention-to-treat analysis using Cox regression. Hazard ratios for time until resolution of symptoms, hospitalization, or death were planned as was a per-protocol analysis.
Safety monitoring	Participants were provided with a study email and a study telephone number to contact a study clinician at any hour; participants were questioned daily about potential adverse events as described above using daily surveys and any positive responses would lead to further evaluation by a study clinician; general safety information and guidance about monitoring for potential side effects were provided to patients with the study medication. The patients were required to have a primary care physician in order to be enrolled in the study, and the primary care physician was sent a notification of participant enrollment and an explanation of the study details via VA email.

* **Exclusion Criteria based on National VA Data** (a) CKD with eGFR <30mL/min or on dialysis; (b) aspartate transaminase (AST) or alanine transaminase (ALT) >5 times the upper limit of normal; or cirrhosis; (c) hypersensitivity to chloroquine, hydroxychloroquine or other 4-aminoquinolines (e.g., amodiaquine), azithromycin or macrolides; (d) already taking hydroxychloroquine or azithromycin; (e) congestive heart failure with an ejection fraction (EF) <35%; or hospitalization for CHF in past 6 months; (f) AMI in past 2 years; (g) concomitant treatment with any QT prolonging drug; (h) inability to take oral medications; (i) history of cardiac arrest, ventricular fibrillation or ventricular tachycardia in past 5 years; (j) QT prolongation; (k) potassium <3.5 meq/L in any lab in past 2 years; (l) magnesium <1.5 meq/L; (m) any patient who has not had follow-up with their primary care doctors in past 2 years; (n) inability to follow-up (e.g. dementia or evidence of active psychosis in chart); (o) any patient diagnosed with G6PD deficiency; (p) any patient diagnosed with porphyria

Chart Exclusion Criteria(q) symptoms of cough, fever or SOB >5 days, not having an address (e.g., P.O. Box only) **Baseline Survey Exclusion Criteria**(r) Pregnant, breastfeeding, or interest in becoming pregnant in the next 3 months; (s) receive the majority of their care outside the VA; (t) participating in any other COVID-19 therapeutic trial