

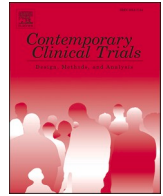


Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Contemporary Clinical Trials

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

Design of the Healthcare Worker Exposure Response and Outcomes (HERO) research platform

Anne Friedland^a, Adrian F. Hernandez^a, Kevin J. Anstrom^a, Mei Lin Chen-Lim^b, Lauren W. Cohen^a, Judith S. Currier^c, Christopher B. Forrest^b, Ryan Fraser^a, Elizabeth Fraulo^a, Anoop George^d, Eileen Handberg^e, Jennifer Jackman^a, Jayne Koellhoffer^f, Daryl Lawrence^g, Renee Leverty^a, Patty McAdams^a, Brian McCourt^a, Brenda Mickley^a, Syed Hasan Naqvi^h, Emily C. O'Brien^a, Rachel Olson^a, Clyde Praterⁱ, Russell L. Rothman^g, Elizabeth Shenkman^f, Jack Shostak^a, Kisha Batey Turner^g, Laura Webb^a, Chris Woods^a, Susanna Naggie^{a,*}, on behalf of the HERO Research Program

^a Duke Clinical Research Institute, Duke University, Durham, NC, United States of America

^b Children's Hospital of Philadelphia, Philadelphia, PA, United States of America

^c University of California Los Angeles, Los Angeles, CA, United States of America

^d Temple University Hospital, Philadelphia, PA, United States of America

^e University of Florida, Gainesville, FL, United States of America

^f Doylestown Health, Doylestown, PA, United States of America

^g Vanderbilt University Medical Center, Nashville, TN, United States of America

^h University of Missouri, Columbia, MO, United States of America

ⁱ Williamson Medical Center, Franklin, TN, United States of America

ARTICLE INFO

Keywords:

COVID-19
Healthcare workers
Registry
Study platform
Hydroxychloroquine
Pragmatic trial

ABSTRACT

Background: The SARS CoV-2 virus has caused one of the deadliest pandemics in recent history, resulting in over 170 million deaths and global economic disruption. There remains an urgent need for clinical trials to test therapies for treatment and prevention.

Design: An online research platform was created to support a registry community of healthcare workers (HCWs) to understand their experiences and conduct clinical studies to address their concerns. The first study, HERO-HCQ, was a double-blind, multicenter, randomized, pragmatic trial to evaluate the superiority of hydroxychloroquine (HCQ) vs placebo for pre-exposure prophylaxis (PrEP) of COVID-19 clinical infection in HCWs. Secondary objectives were to assess the efficacy of HCQ in preventing viral shedding of COVID-19 among HCWs and to assess the safety and tolerability of HCQ.

Methods: HCWs joined the Registry and were pre-screened for trial interest and eligibility. Trial participants were randomized 1:1 to receive HCQ or placebo. On-site baseline assessment included a COVID-19 nasopharyngeal PCR and blood serology test. Weekly follow-up was done via an online portal and included screening for symptoms of COVID-19, self-reported testing, adverse events, and quality of life assessments. The on-site visit was repeated at Day 30.

Discussion: The HERO research platform offers an approach to rapidly engage, screen, invite and enroll into clinical studies using a novel participant-facing online portal interface and remote data collection, enabling limited onsite procedures for conduct of a pragmatic clinical trial. This platform may be an example for future clinical trials of common conditions to enable more rapid evidence generation.

* Corresponding author at: 200 Morris Street, Durham, NC 27701, United States of America.

E-mail address: Susanna.naggie@duke.edu (S. Naggie).

<https://doi.org/10.1016/j.cct.2021.106525>

Received 22 April 2021; Received in revised form 24 June 2021; Accepted 2 August 2021

Available online 8 August 2021

1551-7144/© 2021 Elsevier Inc. All rights reserved.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus emerged in late 2019 and spread rapidly across the globe, resulting in the worst pandemic in nearly a century [1]. Healthcare workers (HCW) bore a heavy disease burden early in the pandemic. An analysis from the United States and United Kingdom showed that frontline HCWs demonstrated at least a three-fold increased risk of testing positive for SARS-CoV-2 compared to individuals in the general community [2]. In addition to exposure to patients and colleagues with COVID-19, critical shortages of personal protective equipment (PPE) put HCW at risk of infection early in the pandemic [3].

Along with concerns for their own safety, HCWs were forced to confront the daily toll of the pandemic as it claimed the lives of patients and colleagues. Lack of available testing and personal protective equipment (PPE) also increased anxiety early on. These factors combined to create significant mental health challenges for HCWs [4].

Emergency use authorization was eventually granted for protective vaccines; but, until then there was a desperate need for preventative strategies for COVID-19 transmission. One approach, commonly used with novel infections, has been to look at repurposing drugs with well-recognized safety profiles [5,6]. Anecdotal reports of successful treatment of patients with COVID-19 with the antimalarial drugs chloroquine and hydroxychloroquine (HCQ) emerged from China and other regions [7]. These reports were supported by *in vitro* data suggesting activity of HCQ against COVID-19 [8,9].

In addition, HCQ has been prescribed in the outpatient setting for treatment of autoimmune diseases for decades and has a good safety profile [29], with only rare case reports of QTc prolongation in this setting. Based on this, the American Rheumatologic Association (ARA) does not recommend baseline QTc assessment for patients initiating hydroxychloroquine, nor regular monitoring unless there is a baseline risk. We believed that the risk of QTc prolongation in a HCW population was similar or lower than patients with autoimmune disease and thus followed the ARA recommendation.

Based on the *in vitro* data, safety profile, and oral availability of the drug, HCQ generated substantial interest as a potential treatment and preventative therapy for COVID-19. Multiple studies were initiated to assess the safety and efficacy of HCQ for treatment and prophylaxis of COVID-19.

The Healthcare Worker Exposure Response and Outcomes (HERO) HCQ trial (HERO-HCQ) was one of the first trials to open to enrollment in the United States to test the safety and efficacy of HCQ as *pre-exposure prophylaxis* in frontline HCW. The HERO-HCQ trial was pragmatic, with a significant proportion of study activities occurring remotely via a participant-facing portal as well as strategic in-person visits to collect virologic and serologic samples. The HERO-HCQ trial leveraged both the HERO Registry as well as its relationship with The National Patient-Centered Clinical Research Network (PCORnet®) for site selection, recruitment, and engagement [4,10,11].

The primary objective of this trial was to evaluate the efficacy of HCQ to prevent SARS-CoV-2 clinical infection in HCWs. It additionally developed new timelines and methods for pragmatic trials, essential during emergency situations.

2. Methods

2.1. Trial setting

The HERO Registry (NCT04342806) was created to form a community of HCWs from across the United States, investigate issues, and offer the participants opportunities to access research projects, including clinical trials. The HERO Registry operates as a site-less, participant-facing registry, in which members complete surveys on a periodic basis, and are informed about opportunities for research participation. Recruitment for HERO-HCQ occurred at 34 Patient-Centered Clinical

Research Network (PCORnet) sites across the United States located in regions with HCW participating in the HERO Registry. The HERO Registry was used to facilitate recruitment and pre-screening of participants for the trial. The HERO Registry and HERO-HCQ trial were reviewed by the Duke University School of Medicine Institutional Review Board and approved by the Western Institutional Review Board (Pro00105274 and Pro00105284).

Inclusion and exclusion criteria are shown in Table 1. Of note, study PCR and serology results were batched and not used in real time to determine inclusion or exclusion. Participants with a positive SARS-CoV-2 PCR at enrollment were excluded from the primary efficacy analyses. The seroconversion analyses excluded the (small number of) participants with a positive SARS-CoV-2 nucleocapsid IgG at baseline.

2.2. Study schedule

After participants provided informed consent at the enrollment visit, on-site baseline assessments included a nasopharyngeal swab for SARS-CoV-2 and a blood sample to assess baseline SARS-CoV-2 antibody status. A quantity of study drug sufficient for 30 days was provided to the participant at the time of on-site enrollment. Weekly follow-up was performed via standardized questionnaires utilizing a direct to participant on-line portal. Weekly follow-up included self-reported screening for COVID-19 clinical signs/symptoms, self-reporting of COVID-19 testing and diagnosis (for participants and household contacts), diagnosis of other respiratory infections, self-reported medication changes, hospitalizations, non-infectious clinical events, adverse events and quality of life (QoL) assessments to assess emotional well-being. A call center provided support for missed visits to re-engage and remind participants to complete the questionnaires.

A visit at approximately 30 days after randomization was completed on-site to assess study drug adherence and any subsequent clinical or safety events. A nasopharyngeal swab for SARS-CoV-2 and a polymerase chain reaction (PCR) test and a blood sample were obtained for SARS-CoV-2 antibody.

A remote end of study visit was conducted approximately 60 days after randomization via the direct to participant portal or call center to assess for any subsequent clinical or safety events.

2.3. Intervention

As shown in Fig. 1, participants were randomized 1:1 to receive HCQ or placebo. Participants randomized to the HCQ arm received a 600 mg loading dose of study drug twice on the first day, followed by 400 mg daily for 29 days. This dose was chosen based on *in vitro* studies reporting a wide range of EC50 for COVID-19 and known variability of absorption and tissue distribution into the lung [8,9,12]. All study drug doses were oral self-administrations. Study drug was supplied as 200 mg tablets.

Participants randomized to the placebo had the same dosage schedule and number of tablets as the HCQ arm. The placebo is similar in appearance to the study drug and packaged and labeled in a masked manner.

2.4. Outcomes

The primary outcome was clinical infection with COVID-19, defined as new-onset of fever, cough or dyspnea and confirmed SARS-CoV-2 positive test result via local PCR testing OR suspected (fever, cough or dyspnea) COVID-19 disease without confirmation testing due to local restrictions (in the absence of a negative test) measured up to 30 days after randomization.

Two secondary objectives assessed the efficacy of HCQ in preventing viral shedding of COVID-19 among HCWs and the safety and tolerability of HCQ in this study population.

Secondary outcomes included (1) viral shedding of SARS-CoV-2 and

Table 1
HERO-HCQ inclusion and exclusion criteria.

Inclusion criteria
An age of 18 years or older
Currently working in any environment in which there is a risk of exposure to patients with COVID-19 infections (“healthcare worker”) including, but not limited to, the following example work exposures:
At risk for COVID-19 infection through one or more of the following work exposures:
a) in the Intensive Care Unit or
b) in the Emergency department or
c) in Emergency Services or
d) in a COVID-19 hospital unit/ward or
e) in respiratory services or
f) in a COVID-19 testing location or
g) in a clinical or research laboratory handling COVID-19 patient samples or
h) in an inpatient hospital unit / area with potential COVID-19 cases or
i) in a long-term care, assisted living or skilled nursing facility or
j) in outpatient care or
k) in dental offices or
l) in home healthcare or
m) in health services for incarcerated populations or
n) in dialysis centers
Exclusion criteria
Prior diagnosis of COVID-19 infection
Participation in another COVID-19 prophylaxis trial within 30 days of consent
Respiratory illness with new-onset fever (Temperature > 100 F) or ongoing cough or dyspnea within 14 days
Known allergy to HCQ or chloroquine
Congenital prolonged QTc syndrome
Current or planned use of QTc prolonging drugs (e.g., procainamide, disopyramide, mexiletine, flecainide, propafenone, amiodarone, sotalol, cimetidine, dronedarone, dofetilide, levofloxacin, ciprofloxacin, moxifloxacin) and other contra-indicated medications
End stage renal disease
Pre-existing retinopathy
Current or planned use of HCQ for any indication
Current or planned use of chloroquine or azithromycin for treatment or prevention of COVID-19
Known cirrhosis or severe liver disease
History of severe skin reactions such as Stevens-Johnson or toxic epidermal necrolysis
History of psoriasis or porphyria
Ventricular arrhythmias requiring medical treatment
Severe coronary disease or heart failure / cardiomyopathy with ongoing symptoms
Current or planned use of anti-seizure drugs
History of Glucose-6-phosphate dehydrogenase deficiency

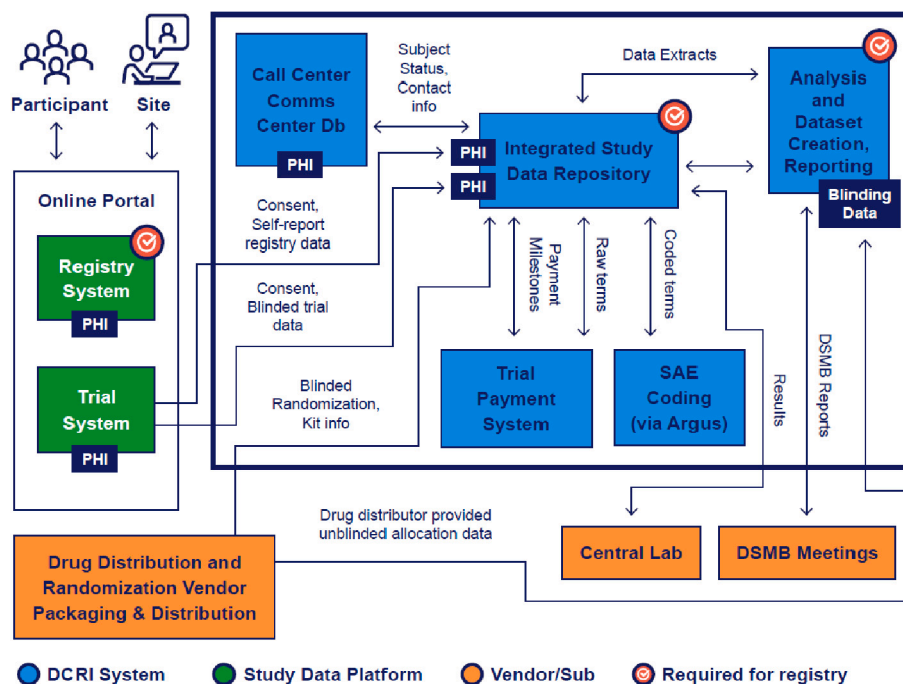


Fig. 1. HERO-HCQ participant flow diagram.

(2) safety and tolerability as determined by subject reported serious adverse events (SAEs) and HCQ-associated Events of Special Interest (ESIs). SAEs and ESIs were assessed up to 60 days after randomization.

Early discontinuers, (including those lost to follow-up) were included in the non-event group, unless they had a qualifying event for the primary analysis prior to being lost to follow-up, in which case there were included in the event group.

Exploratory outcomes included (1) SARS-CoV-2 seroconversion at 30 days, (2) COVID-19 complications including hospitalization, intensive care unit (ICU) level care or need for invasive ventilation, (3) days sick or lost work-time, (4) self-reported health and well-being obtained from the Patient-Reported Outcomes Measurement Information System (PROMIS) Emotional Distress-Anxiety-Short Form, a single-item Burnout Measure, Patient Health Questionnaire (PHQ-2), (5) patient-reported clinical infections among household contacts and other impacts on the HCW's household [13–22,24].

See Table 2 for the assessment schedule.

Fig. 2 depicts the participant experience and data collection.

2.5. Participant recruitment and consent

Recruitment occurred at 34 designated sites across the United States. The HERO Registry was used to pre-screen participants who self-reported interest in the study. Registry participants were able to opt-in for interest in the HERO-HCQ and other clinical trials through the registry portal. Participants who opted-in were shared with sites in that region for initiation of contact for the clinical trial. Participants who appeared eligible based on demographics, clinical characteristics, and self-reported interest were either sent an e-mail invitation or contacted directly by the site study team. Sites were also provided a variety of digital and print tools to help raise awareness and facilitate enrollment.

Institutional Review Board (IRB)-approved consent forms describing the study agent, procedures, and potential risks were provided to participants via the portal. Sites were provided flexibility for consent method so that consent was obtained both in person and through the on-line portal using e-consent, depending on the site. Documentation of informed consent was required prior to starting any study procedures. An explanation of the study and extensive discussion of the potential risks and benefits of participation were provided to potential participants by the investigator (or a delegate) and any questions were

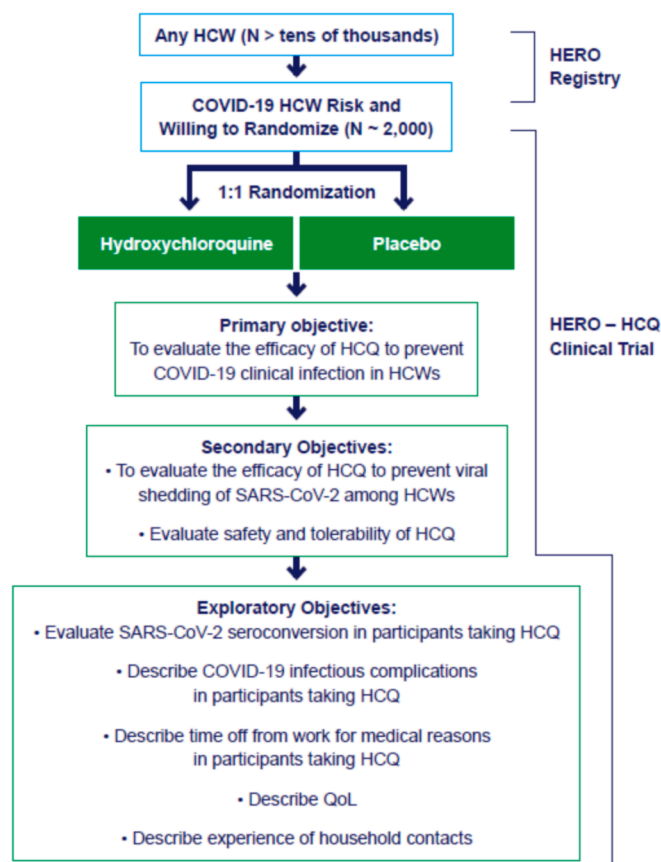


Fig. 2. HERO-HCQ operational diagram.

answered either by telephone or in person at the entry visit. Participants self-reported their past medical history and medications on the HERO registry. There was no other source documentation obtained including medical or hospital records, although medical records could be reviewed for SAE or ESI reporting.

Table 2
HERO-HCQ Schedule of Assessments.

	Baseline: Oneiste (Day 0)	Follow-up: Remote (Day 7 ± 2 days)	Follow-up: Remote (Day 14 ± 2 days)	Follow-up: Remote (Day 21 ± 2 days)	Follow-up: Onsite (Day 30 + 5 days)	Final Visit: Remote (Day 60 + 5 days)
Trial Procedures						
Consent	X					
Demographic Information	X					
Eligibly criteria confirmed	X					
Randomization	X					
Receipt of study drug or placebo	X					
Continued use of study drug	Continuous					
Clinical Assessments						
Medical history	X					
Concomitant medications of interest	X		X		X	X
Temperature	X					
COVID-19 Questionnaire		X	X	X	X	X
Quality of life questionnaires	X		X		X	X
SAEs and events of special interest		Continuous via participant portal and at onsite visits				
Biospecimen Collection						
Nasopharyngeal swab for COVID-19	X				X	
Blood collection for exploratory analysis	X				X	

2.6. Randomization

Randomization occurred on-site at the level of the individual participant. Eligible participants were randomized via the study website in a 1:1 ratio to either HCQ or matching placebo. Randomization was stratified by clinical site using a permuted block design with random block sizes.

2.7. Sample size

The original sample size of approximately 15,000 randomized participants was selected to yield high statistical power for testing the primary outcome of clinical infection with SARS-CoV-2 under reasonable assumptions about the control-group event rate. Assuming that the usual risk of SARS-CoV-2 infection was 5%, this sample size provided greater than 80% power to detect a 1% absolute decrease (20% relative decrease) in the HCQ group compared to the placebo group. These calculations assume a two-sided Type I error rate of 0.05 with 1:1 randomization and were based on a two group continuity corrected chi-square test. In July 2020, due to slower than expected enrollment and emerging evidence from other trials, the study protocol was amended to reduce the total sample size to 2000, which would provide 80% power to detect a 50% relative decrease in the risk for the HCQ group compared to the placebo group assuming that the placebo group risk was 5% [25]. The study had an interim analysis plan to assess for futility after the first 1000 participants had completed their 30 day visit. In addition, interim examination of clinical endpoints and enrollment occurred weekly following enrollment of the first participants. The interim analysis occurred as planned after the first 1000 participants and the DSMB recommended continuation of the study.

2.8. Statistical methods

Statistical comparisons were performed using two-sided significance tests. The primary endpoint was clinical infection with SARS-CoV-2. For the primary outcome of clinical infection with SARS-CoV-2, comparisons between treatment arms were presented as differences in proportions with 95% confidence intervals using the Miettinen-Nurminen method and a *p*-value calculated using the Fisher's exact test. A secondary analysis was based on a logistic regression model with an indicator variable for the treatment group.

2.9. Secondary endpoints

The statistical comparisons of the randomized arms with respect to serious adverse events and events of special interest used chi-square or other appropriate 2-sample methods. For time-to-event endpoints, Cox proportional hazards regression models were used to estimate the hazard ratio associated with the HCQ intervention. These analyses were supplemented using log-rank tests with event curves presented as Kaplan-Meier estimates.

2.10. Preplanned subgroup analysis

A set of analyses were included to explore whether intervention effects on the primary and secondary outcomes are consistent across subgroups of interest defined according to baseline characteristics. Planned sub-groups included age, sex, race/ethnicity, occupation and COVID-19 risk factors. A logistic regression model, similar to the models discussed above, was included for each subgroup analysis, with additional terms identifying subgroup membership and intervention by subgroup interaction. A post-hoc supplemental analysis was conducted using the Mantel-Haenszel method with the enrolling site as a stratification factor. The treatment effect was reported using the common odds ratio and the associated 95% confidence interval.

2.11. Data monitoring

The data safety monitoring board (DSMB) reviewed safety data weekly and the full DSMB met bi-weekly to review safety and enrollment data. Uniquely, the DSMB communicated directly with the submitted safety reports to the Food and Drug Administration (FDA) when there was a safety signal or when a serious and unexpected adverse reaction (SUSAR) occurred.

3. Discussion

By using the HERO Registry platform and community, we were able to quickly launch a randomized, double-blind, placebo-controlled parallel group superiority study to evaluate the efficacy of HCQ for COVID-19 PrEP in HCWs. There are numerous novel aspects of this design, including the recruitment strategy using a HCW registry, the patient-facing online portal interface limiting the need for frequent in-person visits, and the reliance on patient-reported outcomes in a large pragmatic PrEP trial.

The registry and randomized trial were approved by the IRB 12 and 21 days after initial contact from the funder regarding the trial, and the first participant was randomized one week after the trial received IRB approved. This study's pragmatic nature and leverage of a pre-existing registry allowed us to start enrolling participants remarkably quickly. The registry enrollment reached 12,500 participants within 35 days after the initial launch on 4/10/2020, creating a large recruitment population. Among registry participants enrolled by July 2020, the mean age was 42 years, 78.9% were white, 76.4% were female, and nearly 1/3 worked in settings at high risk for COVID-19 exposure (e.g., ICUs, EDs, COVID-19 unit) [4]. It serves as an example of trial designs that are amenable to rapid start-up during a public health crisis.

The HERO-HCQ trial is novel in several ways. First, the trial recruited from the HERO Registry. Participants of the registry could express their interest in trial participation, screen for eligibility online, and then be directed to a local PCORnet trial site. Second, the trial is largely pragmatic, with only two in-person site visits at entry and end of study drug dosing period, with all other data collection reported by participants via the Registry platform, significantly lowering the cost and infrastructure required to support the trial. This strategy of embedding the trial within the registry and using the registry for recruitment is unique and proved to be extremely effective in the early stages of the trial. The remote, HCW-facing portal improved convenience and minimized the burden of participation for HCWs and limited exposure and infrastructure required at the sites, which was critical as institutions struggled with supporting research early in the pandemic, an issue that remains a challenge even now. The trial also utilized a unique safety reporting process, whereby the DSMB reported directly to the FDA when a safety signal was detected or a SUSAR occurred.

The HERO-HCQ trial has unique features not found in other published PrEP studies. Due to the high rates of asymptomatic infection, all participants underwent COVID-19 PCR and serologic testing at entry and at end of therapy, as opposed to relying solely on self-reported COVID-19 outcomes, which were almost exclusively related to symptomatic disease. This will provide important clinical information on the epidemiology of COVID-19 infection in HCWs including cases of asymptomatic infection. It will also provide valuable data on rates of COVID-19 seroconversion, which will provide a better understanding of the true infection rates over the study period in the setting of having patient reported clinical disease outcomes. One weakness of other pragmatic PrEP trials, is the dependence on local testing strategies to make microbiologic diagnoses of SARS-CoV-2 infection. The availability of SARS-CoV-2 seroconversion in HERO-HCQ is a critical piece of additional information to understand the significance of the suspected clinical cases.

While the HERO-HCQ trial, like other remote PrEP trials, relies largely on self-reported outcomes, the in-person study visits at

enrollment and day 30 (end of treatment period) for assessments including SARS-CoV-2 nasopharyngeal PCR and serologic testing provides additional microbiologic data. This distinguishes the HERO-HCQ trial from other PrEP and post-exposure prophylaxis trials, which were conducted entirely remotely [25,26]. Important clinical questions remain concerning rates of asymptomatic infection in HCW and rates of seroconversion. This study's PCR and serologic testing will provide important epidemiologic information on SARS-CoV-2 exposure and asymptomatic infection in HCWs and what, if any, role HCQ plays on these outcomes.

There are also limitations of the trial. First, for both the HERO registry and the HERO-HcQ trial females, Caucasians and nurses were over-represented. African American and Hispanic populations, which have been disproportionately affected by the pandemic, were underrepresented, in addition to HCWs aside from physicians and nurses. The HCW population is generally younger and better educated with fewer comorbidities than the general population.

It is possible that elderly patients may have difficulty with the online portal. Studies addressing this question have been limited by small sample size and lack of description of specific portals. A summary of prior papers on the topic showed that overall, the most prominent barriers were concerns about safety/privacy and internet access and capability. The most common facilitators were technical assistance and family/provider advice [30]. More longitudinal studies and nuanced understanding of older adult portal experience, with identification of access barriers and facilitators is necessary. These factors reduce the generalizability of both the trial and registry.

In conclusion, the HERO Registry and HERO-HCQ trial demonstrate many aspects of pragmatic design including remote registry based screening and recruitment, patient-facing on-line portal, and reliance on self-reported outcomes, which proved very effective and should be considered for use in the design of future clinical trials. In fact, this patient-facing on-line portal is now being used to monitor for self-reported safety events in participants receiving COVID-19 vaccines via Emergency Use Authorization (EUA). The need to rapidly scale up clinical trials during a public health emergency and to ensure safety for participants and research staff highlights the strengths of pragmatic trial design.

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.

Acknowledgements

The HERO Registry & Trial: Healthcare Worker Exposure Response and Outcomes are funded by the Patient Centered Outcomes Research Institute (PCORI), Contract Number COVID-19-2020-001.

References

- [1] K. McIntosh, Coronavirus Disease 2019 (COVID-19): Epidemiology, Virology, and Prevention - UpToDate, *UpToDate*, 2021.
- [2] L.H. Nguyen, et al., Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study, *Lancet Public Health* (2020), [https://doi.org/10.1016/S2468-2667\(20\)30164-X](https://doi.org/10.1016/S2468-2667(20)30164-X).
- [3] X. Wang, X. Zhang, J. He, Challenges to the system of reserve medical supplies for public health emergencies: reflections on the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic in China, *Biosci. Trends* (2020), <https://doi.org/10.5582/BST.2020.01043>.
- [4] C.B. Forrest, et al., Impact of the early phase of the COVID-19 pandemic on US healthcare workers: results from the HERO registry, *J. Gen. Intern. Med.* (2021), <https://doi.org/10.1007/s11606-020-06529-z>.
- [5] J. Devillers, Repurposing drugs for use against Zika virus infection\$, *SAR QSAR Environ. Res.* (2018) <https://doi.org/10.1080/1062936X.2017.1411642>.
- [6] H. Sweiti, O. Ekwunife, T. Jaschinski, S.K. Lhachimi, Repurposed therapeutic agents targeting the Ebola virus: a systematic review, *Curr. Ther. Res. - Clin. Exp.* (2017), <https://doi.org/10.1016/j.curtheres.2017.01.007>.
- [7] H. Xue, et al., Hydroxychloroquine treatment in COVID-19: a descriptive observational analysis of 30 cases from a single center in Wuhan, China, *J. Med. Virol.* (2020), <https://doi.org/10.1002/jmv.26193>.
- [8] X. Yao, et al., In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), *Clin. Infect. Dis.* (2020), <https://doi.org/10.1093/cid/ciaa237>.
- [9] J. Liu, et al., Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro, *Cell Disc.* (2020), <https://doi.org/10.1038/s41421-020-0156-0>.
- [10] C.B. Forrest, et al., PCORnet® 2020: current state, accomplishments, and future directions, *J. Clin. Epidemiol.* (2021), <https://doi.org/10.1016/j.jclinepi.2020.09.036>.
- [11] R.L. Fleurence, et al., Launching PCORnet, a national patient-centered clinical research network, *J. Am. Med. Assoc.* (2014), <https://doi.org/10.1136/ama.jnl-2014-002747>.
- [12] S.E. Tett, Clinical pharmacokinetics of slow-acting Antirheumatic drugs, *Clin. Pharmacokinet.* (1993), <https://doi.org/10.2165/00003088-1993325050-00005>.
- [13] C. Maslach, S.E. Jackson, The measurement of experienced burnout, *J. Organ. Behav.* (1981), <https://doi.org/10.1002/job.4030020205>.
- [14] P.R. Gil-Monte, Factorial validity of the Maslach burnout inventory (MBI-HSS) among Spanish professionals, *Rev. Saude Publica* (2005), <https://doi.org/10.1590/s0034-89102005000100001>.
- [15] O. Kanste, J. Miettunen, H. Kyngäs, Factor structure of the Maslach burnout inventory among Finnish nursing staff, *Nurs. Health Sci.* (2006), <https://doi.org/10.1111/j.1442-2018.2006.00283.x>.
- [16] C.P. West, L.N. Dyrbye, J.A. Sloan, T.D. Shanafelt, Single item measures of emotional exhaustion and depersonalization are useful for assessing burnout in medical professionals, *J. Gen. Intern. Med.* (2009), <https://doi.org/10.1007/s11606-009-1129-z>.
- [17] B.M. Rohland, G.R. Kruse, J.E. Rohrer, Validation of a single-item measure of burnout against the Maslach Burnout Inventory among physicians, *Stress. Health* (2004), <https://doi.org/10.1002/smi.1002>.
- [18] S. Sen, et al., A prospective cohort study investigating factors associated with depression during medical internship, *Arch. Gen. Psychiatry* (2010), <https://doi.org/10.1001/archgenpsychiatry.2010.41>.
- [19] P.A. Pilkonis, et al., Item banks for measuring emotional distress from the patient-reported outcomes measurement information system (PROMIS®): depression, anxiety, and anger, *Assessment* (2011), <https://doi.org/10.1177/1073191111411667>.
- [20] P.J. Batterham, M. Sunderland, N. Carragher, A.L. Calear, Psychometric properties of 7- and 30-day versions of the PROMIS emotional distress item banks in an Australian adult sample, *Assessment* (2019), <https://doi.org/10.1177/1073191116685809>.
- [21] B.D. Schalet, et al., Clinical validity of PROMIS depression, anxiety, and anger across diverse clinical samples, *J. Clin. Epidemiol.* (2016), <https://doi.org/10.1016/j.jclinepi.2015.08.036>.
- [22] L.P. Richardson, et al., Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents, *Pediatrics* (2010), <https://doi.org/10.1542/peds.2009-2712>.
- [24] K. Kroenke, R.L. Spitzer, J.B. Williams, Patient health questionnaire (PHQ-9), *J. Gen. Intern. Med.* 16 (9) (2001) 606–613, <https://doi.org/10.1046/j.1525-1497.2001.016009606.x>.
- [25] D.R. Boulware, et al., A randomized trial of Hydroxychloroquine as Postexposure prophylaxis for Covid-19, *N. Engl. J. Med.* (2020), <https://doi.org/10.1056/nejmoa2016638>.
- [26] R. Rajasingham, et al., Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial, *medRxiv* (2020), <https://doi.org/10.1101/2020.09.18.20197327>.
- [29] I. Ben-Zvi, S. Kivity, P. Langevitz, et al., Hydroxychloroquine: from malaria to autoimmunity, *Clin. Rev. Allerg. Immunol.* 42 (2012) 145–153, <https://doi.org/10.1007/s12016-010-8243-x>.
- [30] D.K. Sakaguchi-Tang, A.L. Bosold, Y.K. Choi, A.M. Turner, Patient portal use and experience among older adults: systematic review, *JMIR Med. Inform.* 5 (4) (2017 Oct 16), e38, <https://doi.org/10.2196/medinform.8092>. PMID: 29038093; PMCID: PMC5662789.