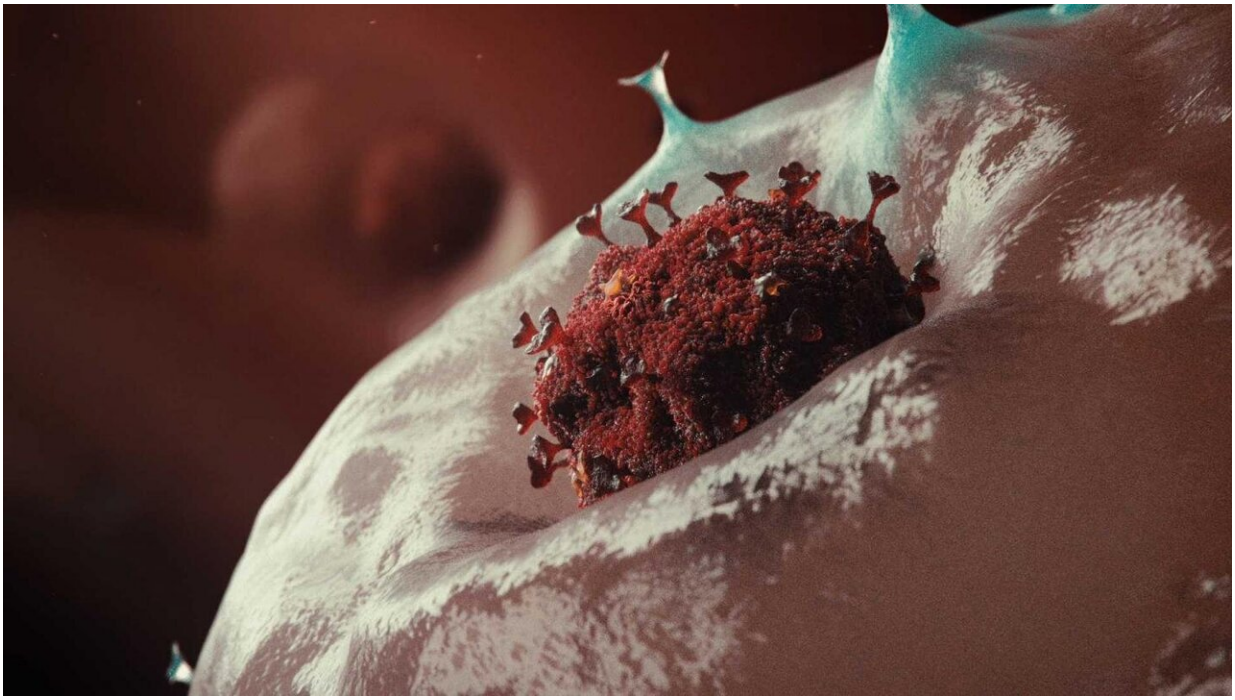
Modified clinical trial protocol created in response to urgency of COVID-19 pandemic

May 19 2020



A new paper published online in the Annals of the American Thoracic Society describes a nimble, pragmatic and rigorous multicenter clinical trial design to meet urgent community needs in the face of the COVID-19 pandemic. Credit: ATS

A new paper published online in the *Annals of the American Thoracic Society* describes a nimble, pragmatic and rigorous multicenter clinical trial design to meet urgent community needs in the face of the

COVID-19 pandemic.

In "Hydroxychloroquine vs. Azithromycin for Hospitalized Patients With Suspected or Confirmed COVID-19 (HAHPS): Protocol for a Pragmatic, Open Label, Active Comparator Trial," Samuel Brown, MD, MS, and co-authors report on the design of a clinical trial, now underway, that they were able to quickly establish and adopt in community and academic hospitals throughout Utah comparing hydroxychloroquine and azithromycin as potential COVID-19 treatments.

"We developed the trial in response to local pressures for widespread, off-label use of these medications," said Dr. Brown, director of pulmonary and critical care research at Intermountain Healthcare in Salt Lake City, who oversees the Center for Humanizing Critical Care at Intermountain Medical Center. "This, and past experience with Ebola, underscored the need for nimble, timely, rigorous controlled trials in a pandemic setting."

The researchers hope to recruit up to 300 study participants with varying degrees of COVID-19 severity from within the Intermountain Healthcare and University of Utah health systems.

The study design differs from that of other randomized, controlled trials in that it does not have a placebo arm. "Placebos can take weeks or months to manufacture and distribute and generally require a research pharmacy to manage," Dr. Brown explained. "We were able to launch quickly because we didn't have to wait for the placebo manufacture. We were also able to start the trial at hospitals that don't have research pharmacies, including many community hospitals. It's really been an all-hands-on-deck effort."

In place of a placebo, the investigators chose to use a comparator

drug—the antibiotic azithromycin. Because the drug showed anti-inflammatory pulmonary effects and other potential benefits in some previous trials, they felt it might have efficacy, and have a very low likelihood of harm due to its established safety profile.

The study is a prospective, randomized, open-label, active comparator trial of hydroxychloroquine versus azithromycin among hospitalized patients with confirmed or suspected COVID-19. Study participants in the hydroxychloroquine arm receive 400mg twice a day for one day, followed by 200mg twice daily for four days.

Participants in the azithromycin study arm receive 500mg on the first day, plus 250mg daily on days two through five. These patients are monitored remotely on a daily basis while receiving the study medication for adverse events and possible introduction of other medications that may result in cardiac problems.

Study participants are observed for 14 days, at which point their progress or decline are assessed (primary endpoint) based on the WHO COVID Ordinal Outcomes Scale. Secondary endpoints are calculated at 28 days based on whether they are hospital-free, ventilator-free and ICU-free.

A formal statistical analysis plan will be written prior to the initial formal interim analysis. New information may come to light that makes it necessary to modify the study protocol and analyses, due to the rapidly evolving state of knowledge about the COVID-19 pandemic.

The authors concluded: "Faced with the prospect of massive statewide expansion of clinical use of untested therapies with unknown risk/benefit profiles in COVID-19 and operating within the context of global placebo-controlled trials being launched in parallel, we initiated a pragmatic trial intended to both provide treatment options in a structured environment, with informed consent and formal safety monitoring, and to contribute

to knowledge about which treatment strategies may be of use in subsequent waves of COVID-19 activity."

More information: Samuel M Brown et al. Hydroxychloroquine vs. Azithromycin for Hospitalized Patients with Suspected or Confirmed COVID-19 (HAHPS): Protocol for a Pragmatic, Open Label, Active Comparator Trial, *Annals of the American Thoracic Society* (2020). DOI: 10.1513/AnnalsATS.202004-309SD

Provided by American Thoracic Society