Running Efficient and Cost-Effective Online Trials Utilizing Patient Reported Outcomes

Hydroxychloroquine experience:
1) post-exposure prophylaxis RCT (n=821)
2) preemptive early treatment RCT (n=491)
3) pre-exposure prophylaxis RCT (n=1483)

David Boulware, MD, MPH, CTropMed
Professor of Medicine
University of Minnesota
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A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19


Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19
A Randomized Trial
Caleb P. Skipper, MD; Katelyn A. Pastick, BSc; Nicole W. Engen, MS; Ananta S. Bangdiwala, MS; Mahsa Abassi, DO, MPH; Sarah M. Lofgren, MD; Darlisha A. Williams, MPH; Elizabeth C. Okafor, BSc; Matthew F. Pullen, MD; Melanie R. Nicol, PharmD, PhD; Alanna A. Nascene, BA; Kathy H. Hullsie, PhD; Matthew P. Cheng, MD; Darlette Luke, PharmD; Sylvain A. Lother, MD; Lauren J. MacKenzie, MD, MPH; Glen Drobot, MD; Lauren E. Kelly, PhD; Ilan S. Schwartz, MD, PhD; Ryan Zarychanski, MD, MSc; Emily G. McDonald, MD, MSc; Todd C. Lee, MD, MPH; Radha Rajasingham, MD; and David R. Boulware, MD, MPH

Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial
Radha Rajasingham, Ananta S. Bangdiwala, Melanie R. Nicol, Caleb P. Skipper, Katelyn A. Pastick, Margaret L. Axelrod, Matthew F. Pullen, Alanna A. Nascene, Darlisha A. Williams, Nicole W. Engen, Elizabeth C. Okafor, Brian I. Rimi, Ingrid A. Mayer, Emily G. McDonald, Todd C. Lee, Peter Li, Lauren J. MacKenzie, Justin M. Balko, Stephen J. Dunlop, Katherine H. Hullsie, David R. Boulware, and Sarah M. Lofgren; on behalf of the COVID PREP team
1. How did we do this?
2. What is the role for the future?

How can we use remote internet-based trials to answer pragmatic clinical questions?
**Project Start**

- **March 9**: Project started
- **March 10**: IRB submission
- **March 11**: FDA IND submission
- **March 12**: Trial database design
- **March 15**: IRB Approval
- **March 16**: Database finalized
- **March 17**: Canadian collaboration discussions begin
- **March 20**: FDA IND safe to proceed
- **March 21**: PET protocol modification
- **March 22**: PET first participant enrolled
- **March 24-25**: Health Canada and Canada IRB approval

**First Subject Enrolled**

- **March 17**: First subject enrolled

**2 of 3 Trials Completed**

- **May 3**: 2 of 3 trials completed
Two Stage RedCAP Survey
1) Screening → Email
2) Enrollment

Verify Receipt of Medicine

Patient Reported Outcomes

Email or SMS w/ Twilio integration into RedCAP

Screening Online Questionnaire
- Email covid19@umn.edu or go to www.covidpep.umn.edu if you have been exposed to or diagnosed with COVID19
- You will be sent an email with information about our clinical trial
- A URL link will be provided for you to take the online screening survey

Medication Shipped
- Study medicine will be shipped overnight to your address
- Study medicine should arrive by 10:30am (Mon-Sat)
  - If you enroll after ~12pm on Sat or Sun, it will arrive Tue.
- Take 4 tablets of the study medicine with some food or milk

Online Survey (Day 1)
- You will receive an email with a link to an online survey from covid19@umn.edu. If not received, check your spam folder.
- Take the second dose of 3 tablets 6-8 hours after the first.
- Take other medicines >= 4 hours apart from the study medicine

Study Days 2-4
- You should take 3 tablets each morning
- If you develop upset stomach, you may separate the pills, for example 1 at breakfast, 1 at lunch, and 1 at dinner.
- We will send a brief Day 3 survey

Online Survey (Day 5)
- You will receive an email with a link to an online survey
- This should be the same day you finish the study medicine
- A brief follow up survey will also be sent on Day 10 to ask if you have any COVID19 symptoms

End of Study Survey (Day 14)
- You will receive an email with a link to an online survey
- Unless you have developed symptoms, this marks the end of the study. We will ask if you wish to participate in future studies.
- If you were hospitalized or have pending tests, we will reach out to you every 2 weeks.
Automated RedCAP Screening

• Two part enrollment
  – Screening #1; Consent & Enrollment #2

• Screening: Used Branched RedCAP logic
  – Self-assessment of inclusion/exclusion criteria
  – Most criteria were not publicly posted
  – Could not change answers (i.e. exclusion criteria)
  – Verified working email

• Calculated hidden field variable to determine eligibility
  – Automated self-screening process
  – If eligible, follow up email had URL for enrollment
Efficient Screening Process
N=6924 screened

Enrollment:
N=821 prophylaxis RCT
N=491 enrolled treatment RCT
Time from Enrollment to Drug Delivery

Two-thirds of participants enrolled outside of weekday daytime hours (875/1312)
Follow Up

• PEP Trial received automated emails: Day 1, 3, 5, 10, 14

• PrEP Trial (12 weeks) used weekly messages

• ~75% Completed Follow Up well
• ~15% Needed additional prompts
  – Follow Up Email
  – SMS Text Messages
  – Phone Calls

• ~10% Lost to Follow Up
  – Should have explained ITT analysis better.
Remote Blood Collection

Whole Blood Collection: Neoteryx Microsampling Kits
Melanie Nicol PharmD, PhD led this for our team.

~$25; Analyte needs to be stable for ~24 hours

Endpoints

Simple, Straightforward

Patient Reported Outcomes (PROs)
Patient-Reported Outcomes (PROs)

• Are you experiencing COVID-19 symptoms?
  – Checklist of symptoms, and free text.
  – Visual analog scale 0-10 of overall symptom severity

• Since starting the study medicine, have you had any side effects?
  – Checklist of common HCQ side effects, and free text.

• Have you been hospitalized since enrolling in this study?

• Day 5 & 14 Targeted list of medicines
• Day 14 assessed adequacy of blinding
Role for Virtual Trials

• Pandemics
  – Patient Reported Outcomes (PROs) – U of MN trials; ACTIV-6
  – Clinician Reported Outcomes (ClinROs) -- UK Recovery Trial

• Not for FDA registrational trials

• Good Safety profile of medicines
  – No need for laboratory safety monitoring, or
  – Limited subgroup with safety monitoring

• Ability to Recruit
  – Rare & Neglected Diseases (Motivated participants)
  – Strategy Trials (Motivated investigators)
Strengths

• Pragmatic RCTs to answer clinically relevant questions
• Low cost
• Focused data collection
• Enable broad participation
  – Locations not near major medical centers
Challenges

• Inclusion / Exclusion criteria
  – Simple, Patient Reported
  – Can submit documents by email

• Informed Consent
  – Assessment of Comprehension
  – Consent to Access Medical Records

• Need Straightforward Surveys
  – User Acceptable Testing beforehand

• Rely on honest participants
  – Blinding and randomization = Key
Lessons Learned From Conducting Internet-Based Randomized Clinical Trials During a Global Pandemic