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

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18 June 2021

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Hydroxychloroquine experience:

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

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COVID-19 RCTs

3 June 2020

17 July 2020

17 Oct 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

D.R. Boulware, M.F. Pullen, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E.C. Okafor, C.P. Skipper, A.A. Nascene, M.R. Nicol, M. Abassi, N.W. Engen, M.P. Cheng, D. LaBar, S.A. Lother, L.J. MacKenzie, G. Drobot, N. Marten, R. Zarychanski, L.E. Kelly, I.S. Schwartz, E.G. McDonald, R. Rajasingham, T.C. Lee, and K.H. Hullsiek

Annals of Internal Medicine

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. Hullsiek, 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

Clinical Infectious Diseases

MAJOR ARTICLE

Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial

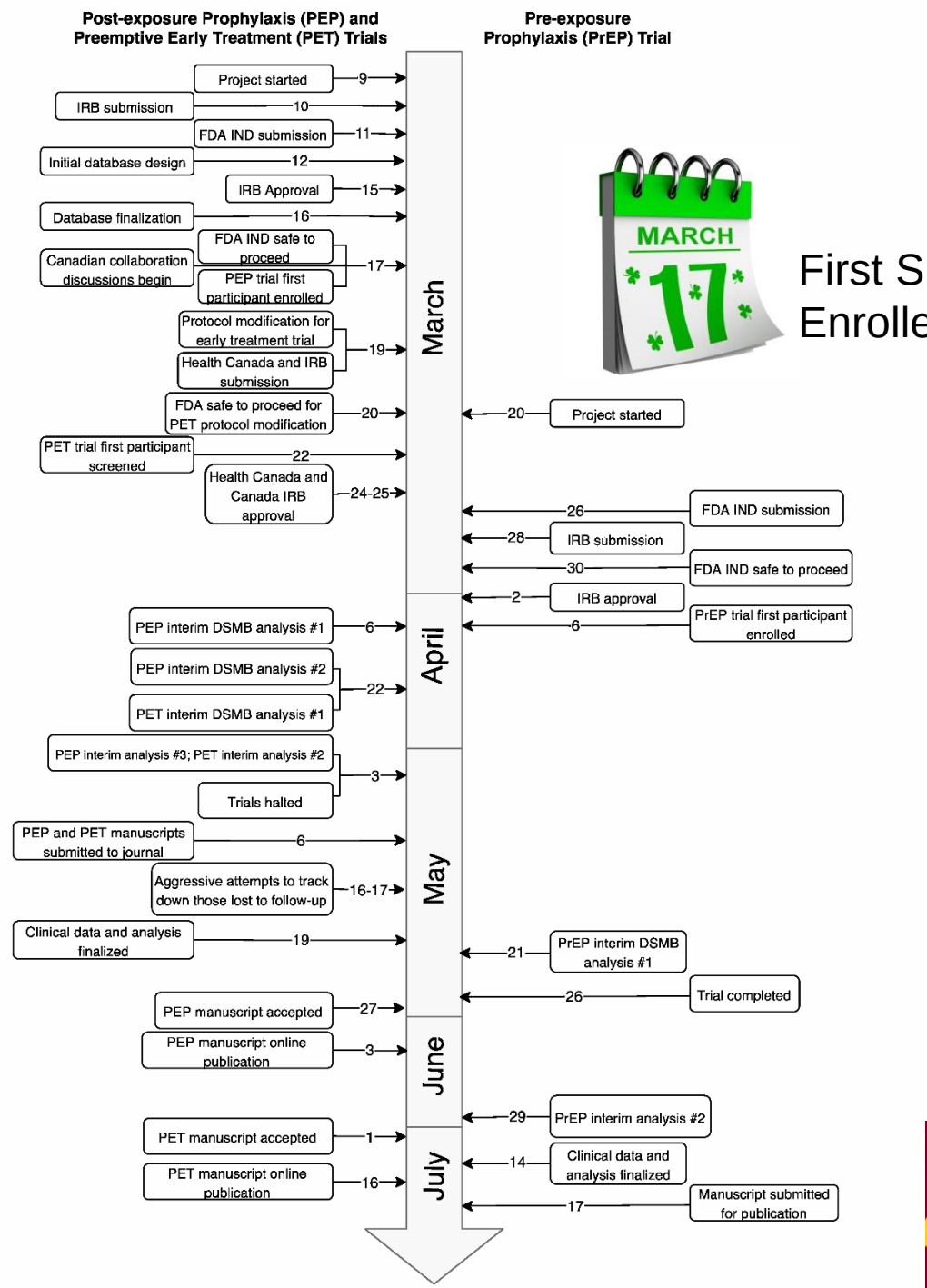
Radha Rajasingham,[1,©] Ananta S. Bangdiwala,[1] Melanie R. Nicol,[1] Caleb P. Skipper,[1] Katelyn A. Pastick,[1,©] Margaret L. Axelrod,[2] Matthew F. Pullen,[1] Alanna A. Nascene,[1] Darlisha A. Williams,[1] Nicole W. Engen,[1] Elizabeth C. Okafor,[1] Brian I. Rini,[2] Ingrid A. Mayer,[2] Emily G. McDonald,[3] Todd C. Lee,[3] Peter Li,[4] Lauren J. MacKenzie,[5] Justin M. Balko,[2] Stephen J. Dunlop,[1,6] Katherine H. Hullsiek,[1] David R. Boulware,[1,a] and Sarah M. Lofgren[1,a]; 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

2 of 3 Trials Completed



First Subject Enrolled

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

Two Stage RedCAP Survey
1) Screening → Email
2) Enrollment

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, 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 covidfaq@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

Verify Receipt of 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

Patient Reported Outcomes

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

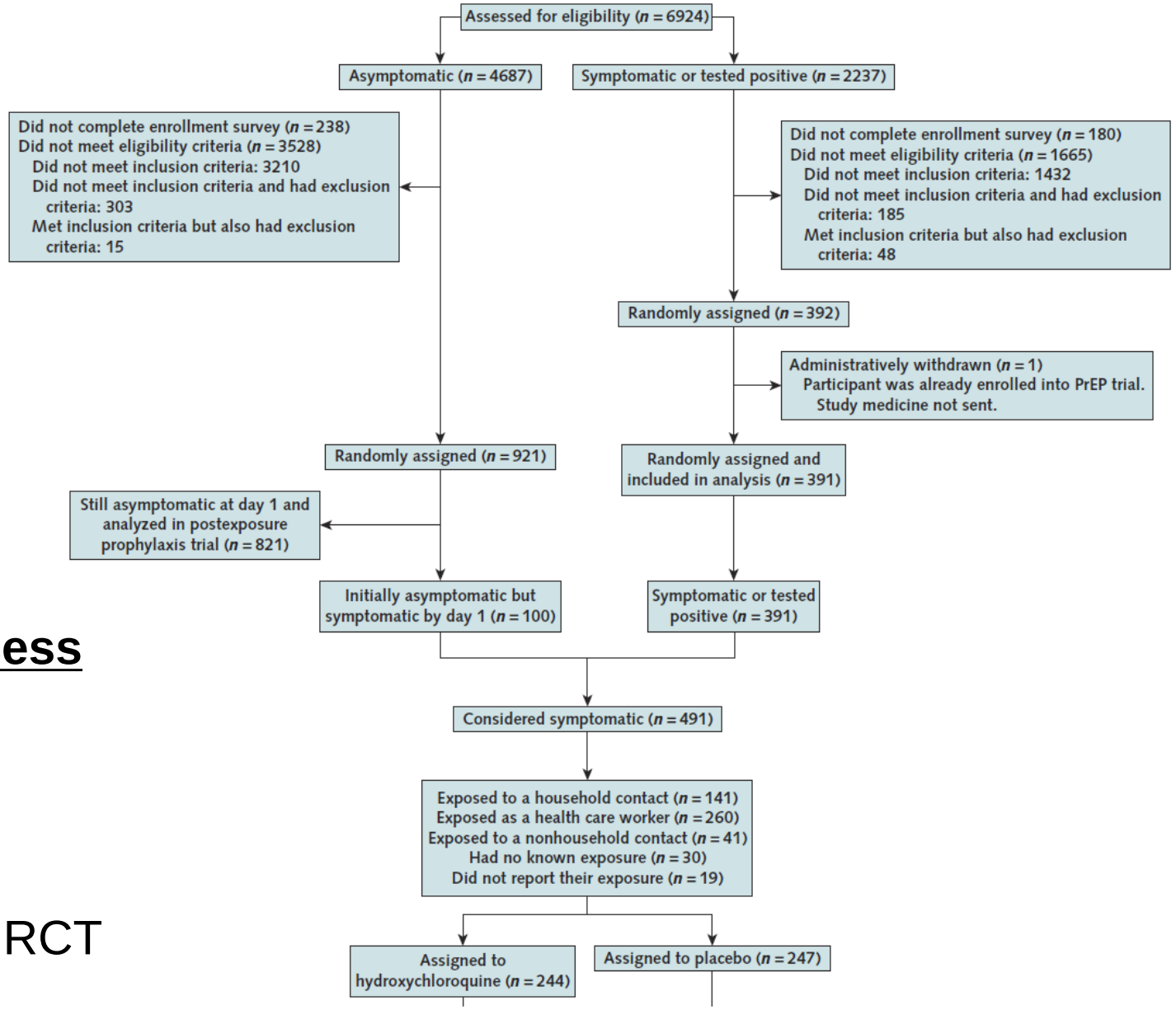
Email or SMS w/ Twilio integration into RedCAP

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

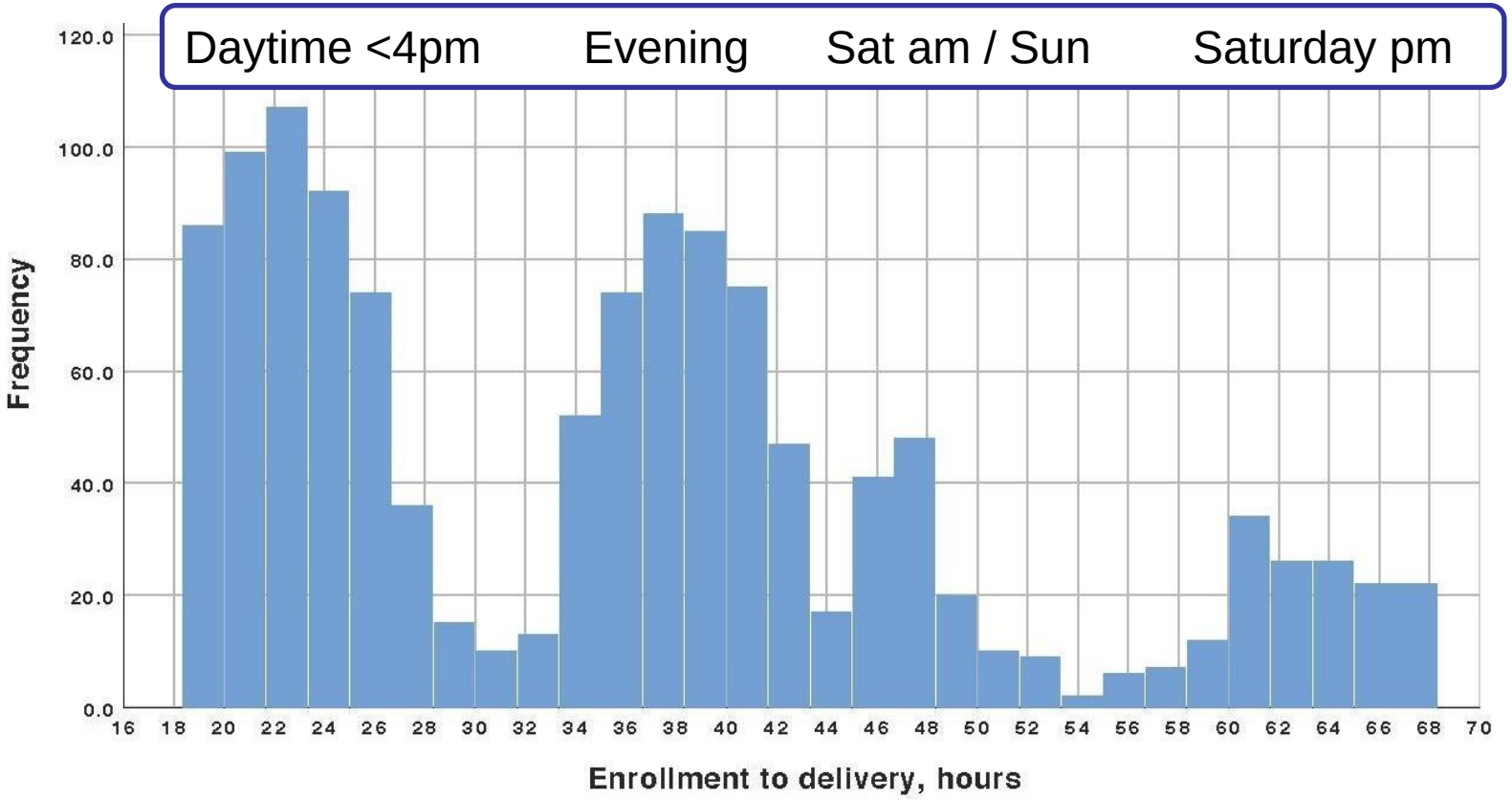


Efficient Screening Process

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 → **Antibody Studies**
Pharmacokinetics

Melanie Nicol PharmD, PhD led this for our team.

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

Rajasingham R, et al. *Clin Infect Dis* 2021

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

For More Information

Open Forum Infectious Diseases

REVIEW ARTICLE

Lessons Learned From Conducting Internet-Based Randomized Clinical Trials During a Global Pandemic

Matthew F. Pullen,[1] Katelyn A. Pastick,[1] Darlisha A. Williams,[1] Alanna A. Nascene,[1] Ananta S. Bangdiwala,[2] Elizabeth C. Okafor,[1] Katherine Huppler Hullsiek,[2] Caleb P. Skipper,[1] Sarah M. Lofgren,[1] Nicole Engen,[2] Mahsa Abassi,[1] Emily G. McDonald,[3] Todd C. Lee,[3] Radha Rajasingham,[1] and David R. Boulware[1,2]

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