Lessons from Virtual Trials in time of a Pandemic: Minnesota Hydroxychloroquine experience

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Oct 30, 2020

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Lessons from Virtual Trials in time of a Pandemic: Minnesota 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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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

3 June 2020
17 July 2020
17 Oct 2020

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

Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial FREE

Radha Rajasingham, MD ✉, Ananta S Bangdiwala, MS,

How did we do this?
Lessons learned

Cryptococcal Meningitis Clinical Trials in Africa

CROI HIV Conference
March 9-12, 2020
Boston, MA

Great Team

(with 4 days of free time: March 9-12)

Co-investigator: Sarah Lofgren MD

Co-investigator: Caleb Skipper MD

Co-investigator: Matthew Pullen MD

Co-investigator: Radha Rajasingham MD

Medical Monitor: Mahsa Abassi DO, MPH

Pharmacologist: Melanie Nicol PharmD, PhD

Biostatistician: Kathy H. Hullsiek PhD

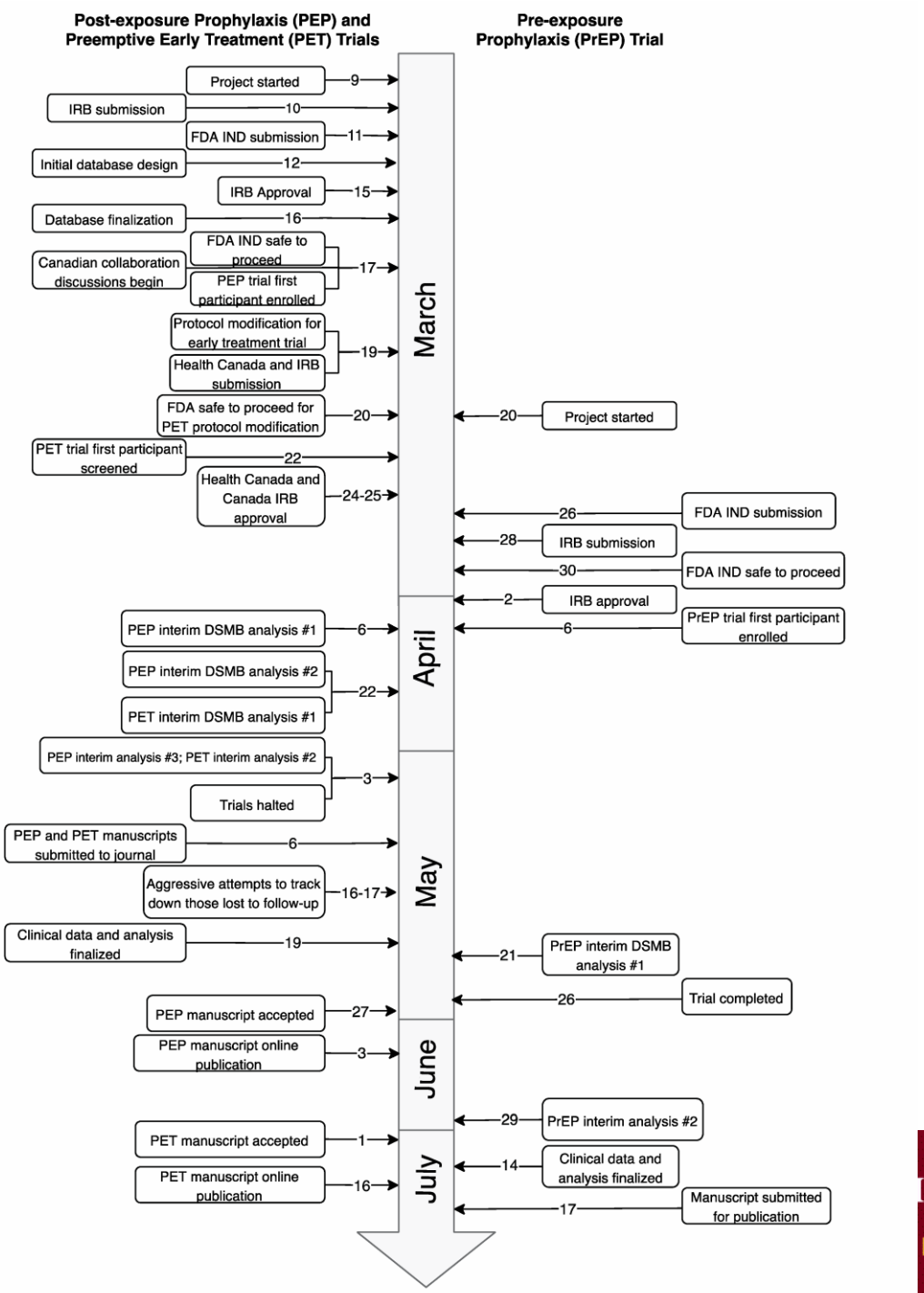
Associate Statistician: Ananta Bangdiwala MS

Associate Statistician: Nicole Engen MS

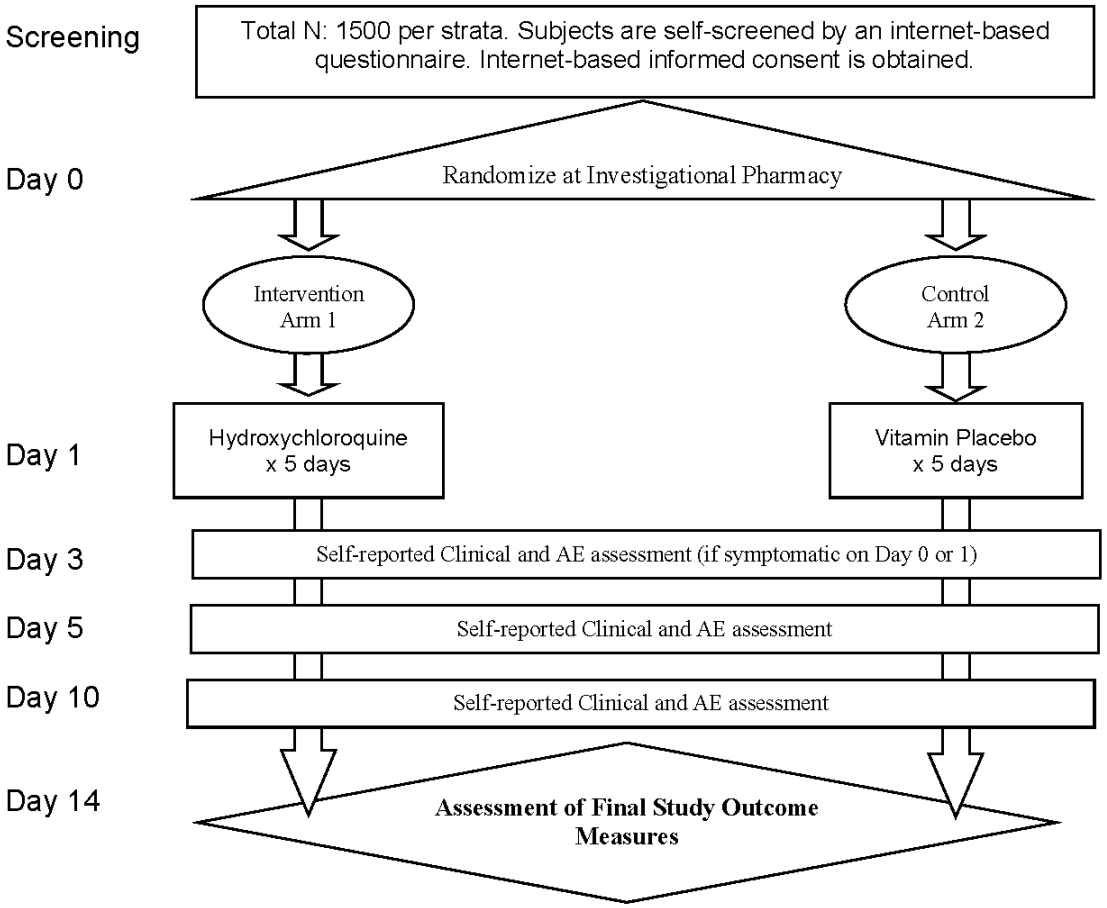
Research Associate: Katelyn Pastick, MD student

Research Associate: Elizabeth Okafor, MD/PhD student

Research Associate: Alanna Nascene, Clinical Research Coordinator (RPII)



Trial Design of Post-Exposure Prophylaxis



If hospitalization occurs, this SAE will be followed for up to 90 days

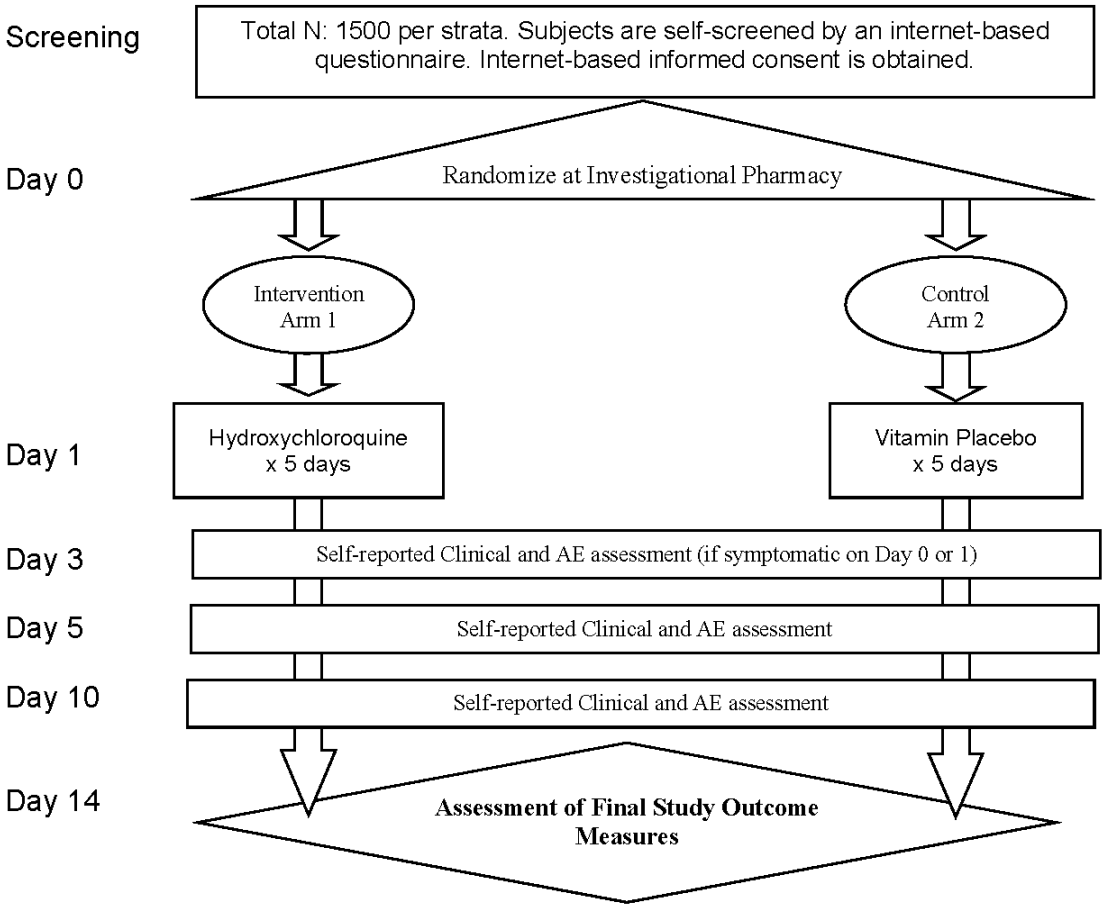
Assumptions:

Statistically Powered for 50% reduction in illness

10% illness rate of symptomatic infection

20% lost to follow up with internet based virtual trial

Trial Design of Post-Exposure Prophylaxis



If hospitalization occurs, this SAE will be followed for up to 90 days

Actuality:

Statistically Powered for 50% reduction in illness

~14% illness rate of symptomatic infection

~9.4% lost to follow up with internet based trial (n=77)

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.

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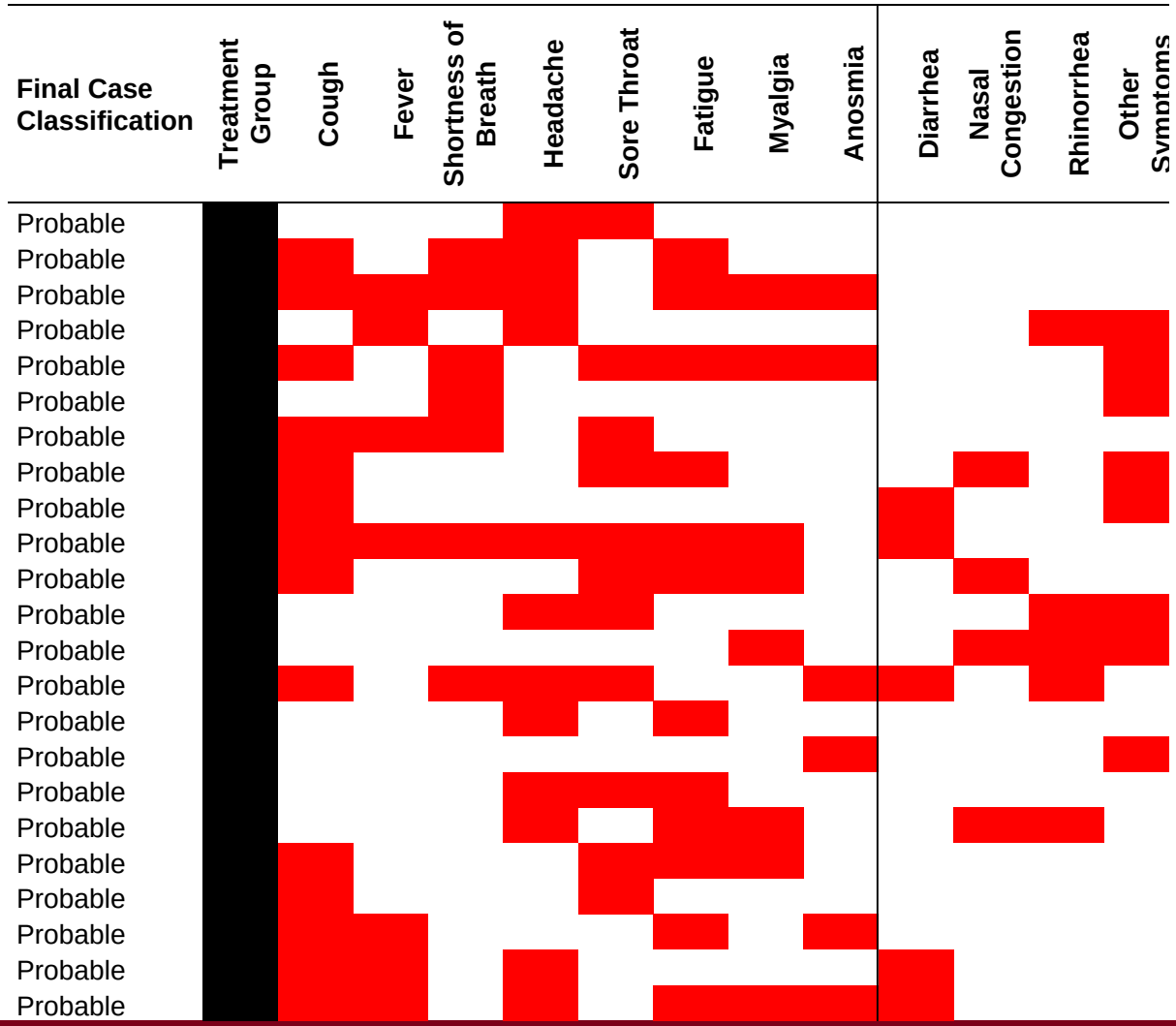
Patient-Reported Outcomes (PROs)

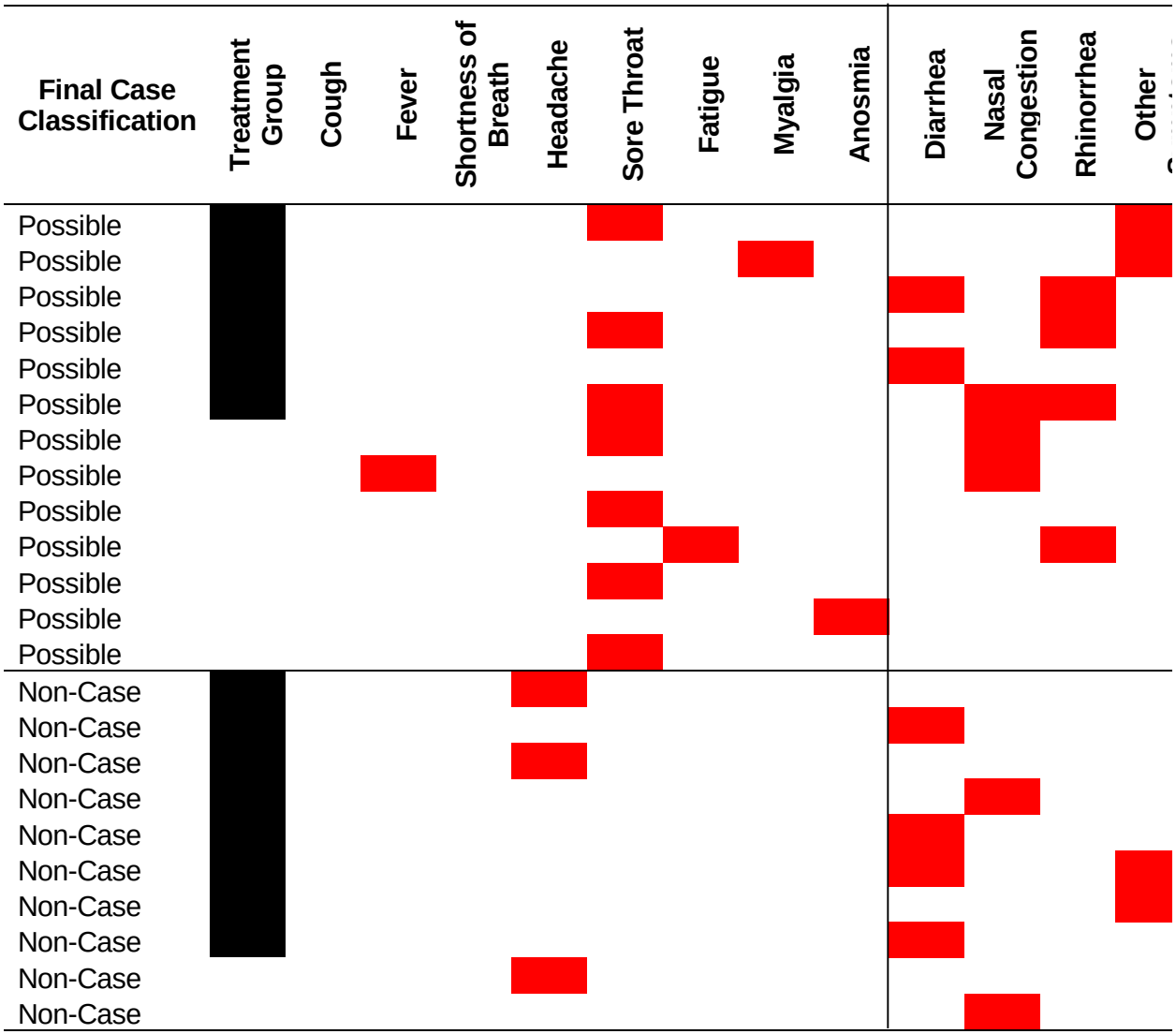
- **Are you experiencing COVID-19 symptoms?**
  - Checklist of symptoms, and free text.
  - Visual analog scale 0-10 of overall symptom severity
- **Since starting the study medicine, have you had any side effects?**
  - Checklist of common HCQ side effects, and free text.
- **Have you been hospitalized since enrolling in this study?**

- D5 & D14 Targeted list of medicines (including zinc)
- Day 14 assessed adequacy of blinding

Symptom Complex: Probable Cases



Symptom Complex: Possible Cases



U.S. Council of State and Territorial Epidemiologists: Probable COVID-19 Case Definition

At least 1 of the following:

- cough,
- shortness of breath, or
- difficulty breathing

OR

At least 2 of the following:

- fever (measured or subjective),
- chills,
- rigors,
- myalgia,
- headache,
- sore throat,
- new olfactory and taste disorder

OR

Epidemiologic Linkage

- Clinically compatible symptoms with one or more of the following exposures in the 14 days before onset of symptoms.

PCR False neg rate on first day of symptoms is 38% (CI: 20-65%) with serial testing.

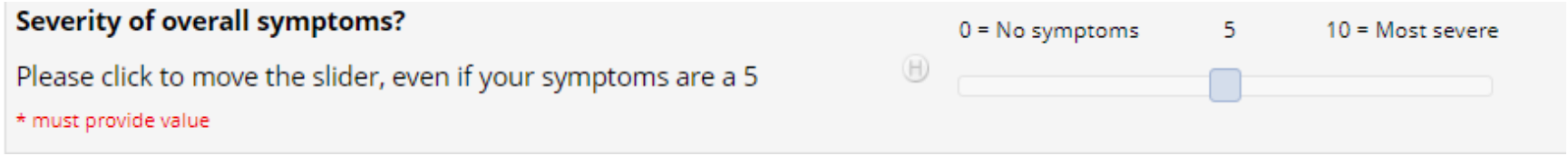
Kucirka LM et al. Annals of Internal Med. 2020

wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/

Visual Analog Scale

10cm scale on paper

0-10 continuous scale in RedCAP



Increment of 0.1 is captured

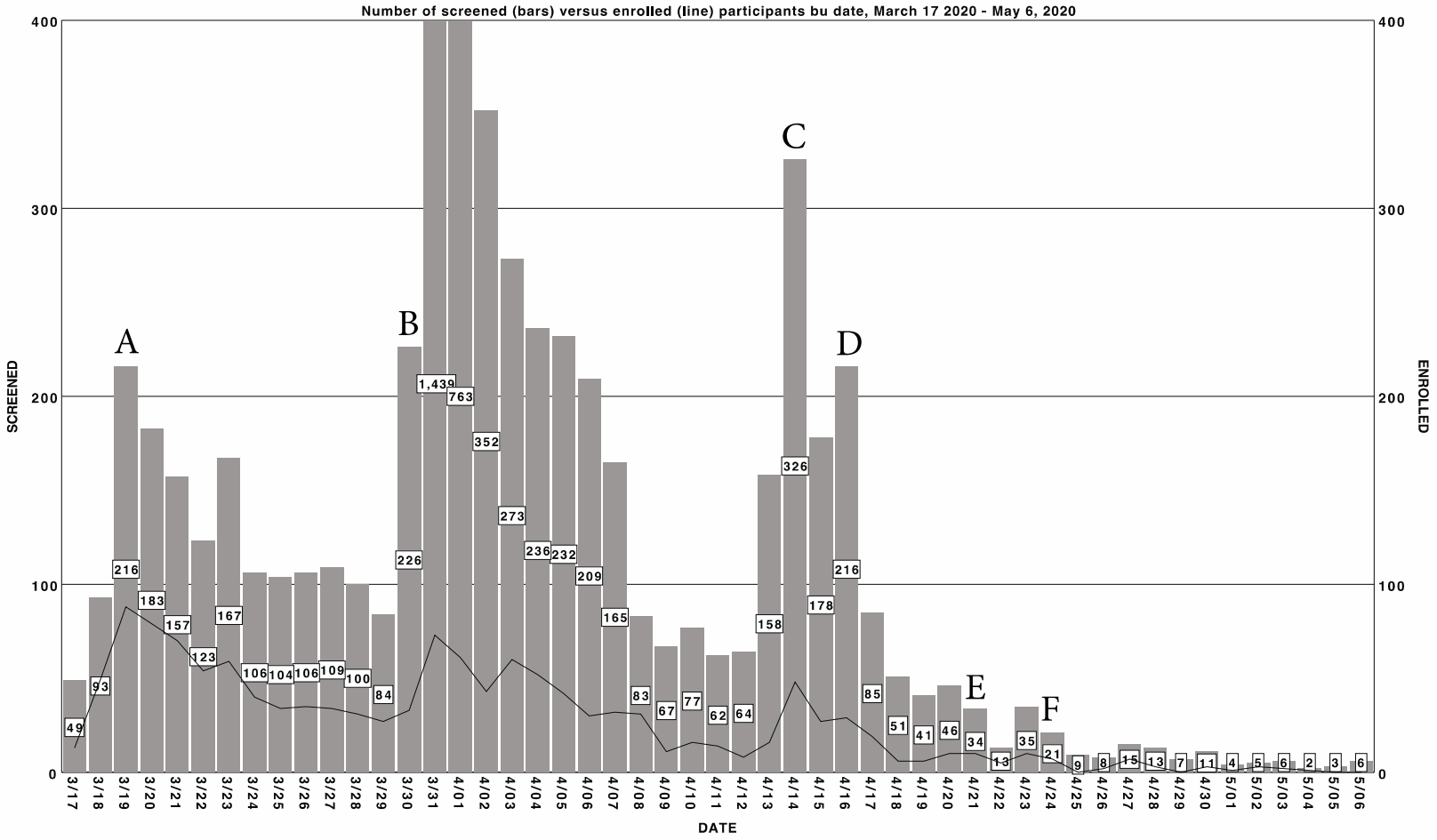
Subjective measure

Intra-person change over time.

>50,000 publications for Visual Analog(ue) Scale

Screening, Consent, & Enrollment

Screening Surveys



Adherence

	Hydroxychloroquine (N=414)	Placebo (N=407)	P-value
Reported Taking Any Study Medicine	349 (84)	351 (86)	
Reported 100% Study Medicine Adherence	312 (75)	336 (83)	0.01
Reasons Participants Did Not Take All Medication			
Study Medicine Side Effects	17 (4.1)	8 (2.0)	
Advised to not take Hydroxychloroquine	6 (1.4)	2 (0.5)	
Medicine not received from Fedex	9 (2.2)	2 (0.5)	
Took non-study Hydroxychloroquine	4 (1.0)	0 (0.0)	
Felt no longer at risk	5 (1.2)	3 (0.7)	
Other Reason	12 (2.9)	10 (2.5)	

Study not operating in a vacuum. Substantial media coverage during trial.

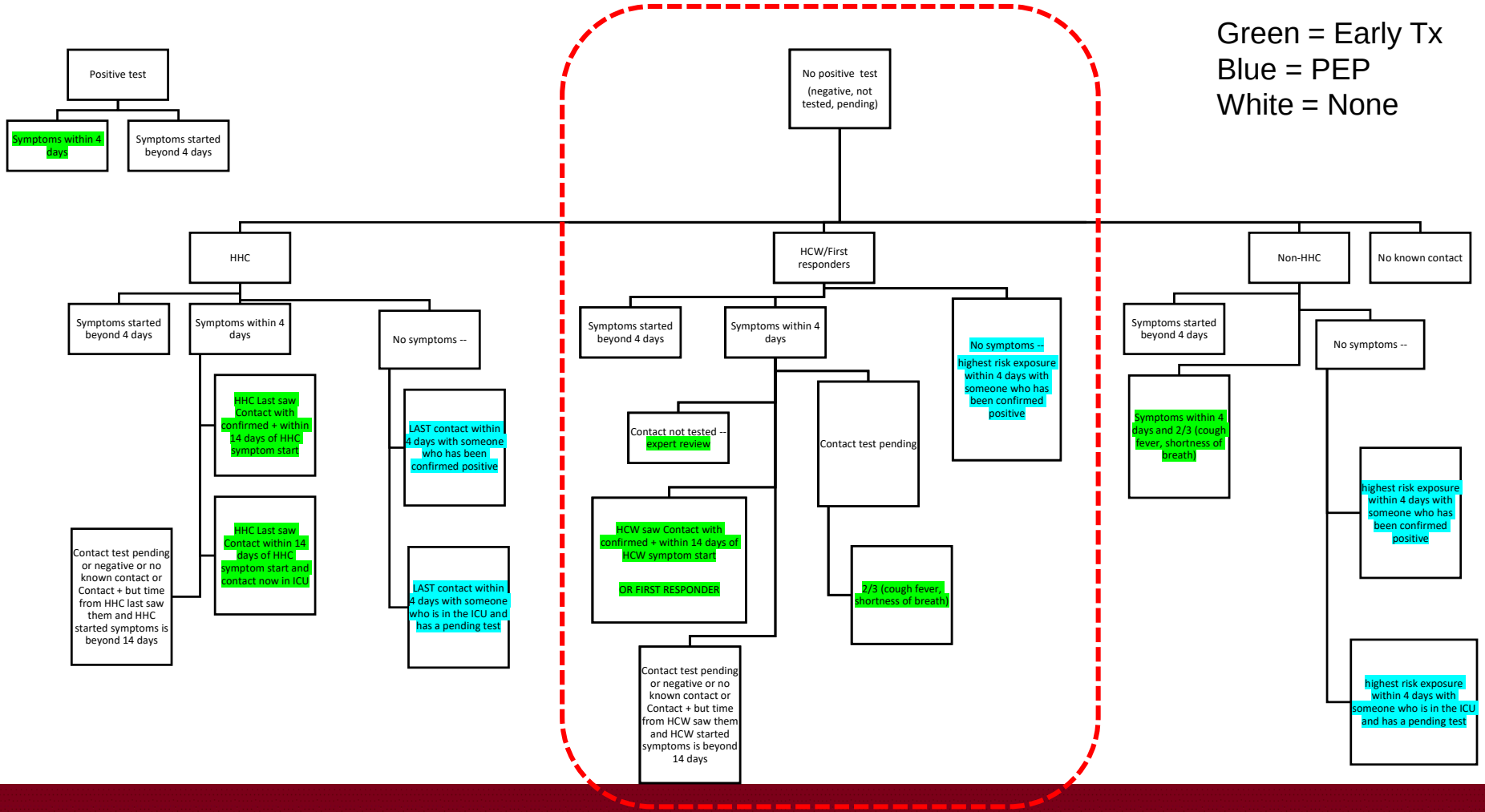
Automated RedCAP Survey

- Two part enrollment
  - Screening #1; Consent & Enrollment #2
  - Verified working email
  - Could not change answers

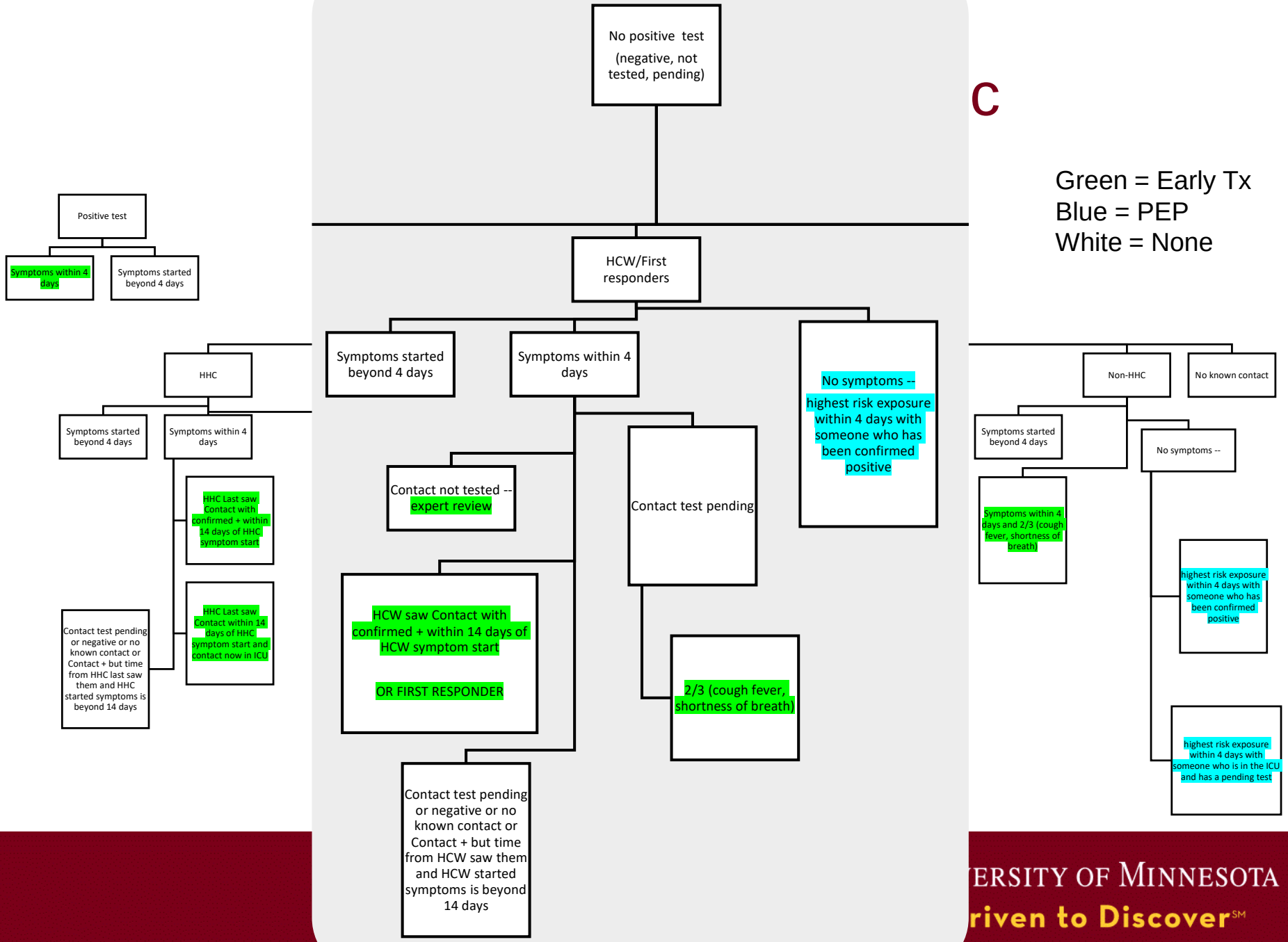
- Screening: Used Branched RedCAP logic
  - Assessed inclusion/exclusion criteria
  - Most criteria were not publicly posted

- Calculated hidden field variable to determine eligibility
  - If eligible, follow up email had URL for enrollment

RedCAP Branched Logic



Green = Early Tx
Blue = PEP
White = None


C
Green = Early Tx
Blue = PEP
White = None
No positive test (negative, not tested, pending)
HCW/First responders
Symptoms started beyond 4 days
Symptoms within 4 days
No symptoms -- highest risk exposure within 4 days with someone who has been confirmed positive
Contact not tested -- expert review
Contact test pending
HCW saw Contact with confirmed + within 14 days of HCW symptom start
OR FIRST RESPONDER
2/3 (cough fever, shortness of breath)
Contact test pending or negative or no known contact or Contact + but time from HCW saw them and HCW started symptoms is beyond 14 days
Positive test
Symptoms within 4 days
Symptoms started beyond 4 days
HHC
Symptoms started beyond 4 days
Symptoms within 4 days
HHC Last saw Contact with confirmed + within 14 days of HHC symptom start
HHC Last saw Contact within 14 days of HHC symptom start and contact now in ICU
Contact test pending or negative or no known contact or Contact + but time from HHC last saw them and HHC started symptoms is beyond 14 days
Non-HHC
No known contact
Symptoms started beyond 4 days
No symptoms --
Symptoms within 4 days and 2/3 (cough fever, shortness of breath)
highest risk exposure within 4 days with someone who has been confirmed positive
highest risk exposure within 4 days with someone who is in the ICU and has a pending test
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Enrollment

- eConsent via RedCAP
  - FDA guidance on eConsent Dec 2016
- Assessed comprehension before allowing signing
- Collected
  - Address, Email, Phone number
  - Next-of-kin contact (if hospitalized)
- Should have collected:
  - If phone number was mobile or not
  - Preferred follow up method (SMS vs. Email)
  - Social media contact info (to assess vital status)

Exclusions

Rationale	Total records (n)	Recommended Response
Deemed ineligible by automated internal survey logic	6924	Pilot survey logic before launching trial
Incomplete enrollment form	44	Carefully review each enrollment for valid completion of key fields;
Duplicate screening forms	14	Screen all new enrollees against full database, looking for duplication in identifying fields
Participant did not meet criteria	6	Continual review of internal survey logic, especially after updates
Participant located outside US or Canada	1	Screen all new enrollee addresses; require valid US zip code for enrollment form submission
Potential fraud	1	Monitor enrollee emails for domains potentially linked to groups with interest in private trial data

Logistics

Logistics

QC then Export dataset from RedCAP

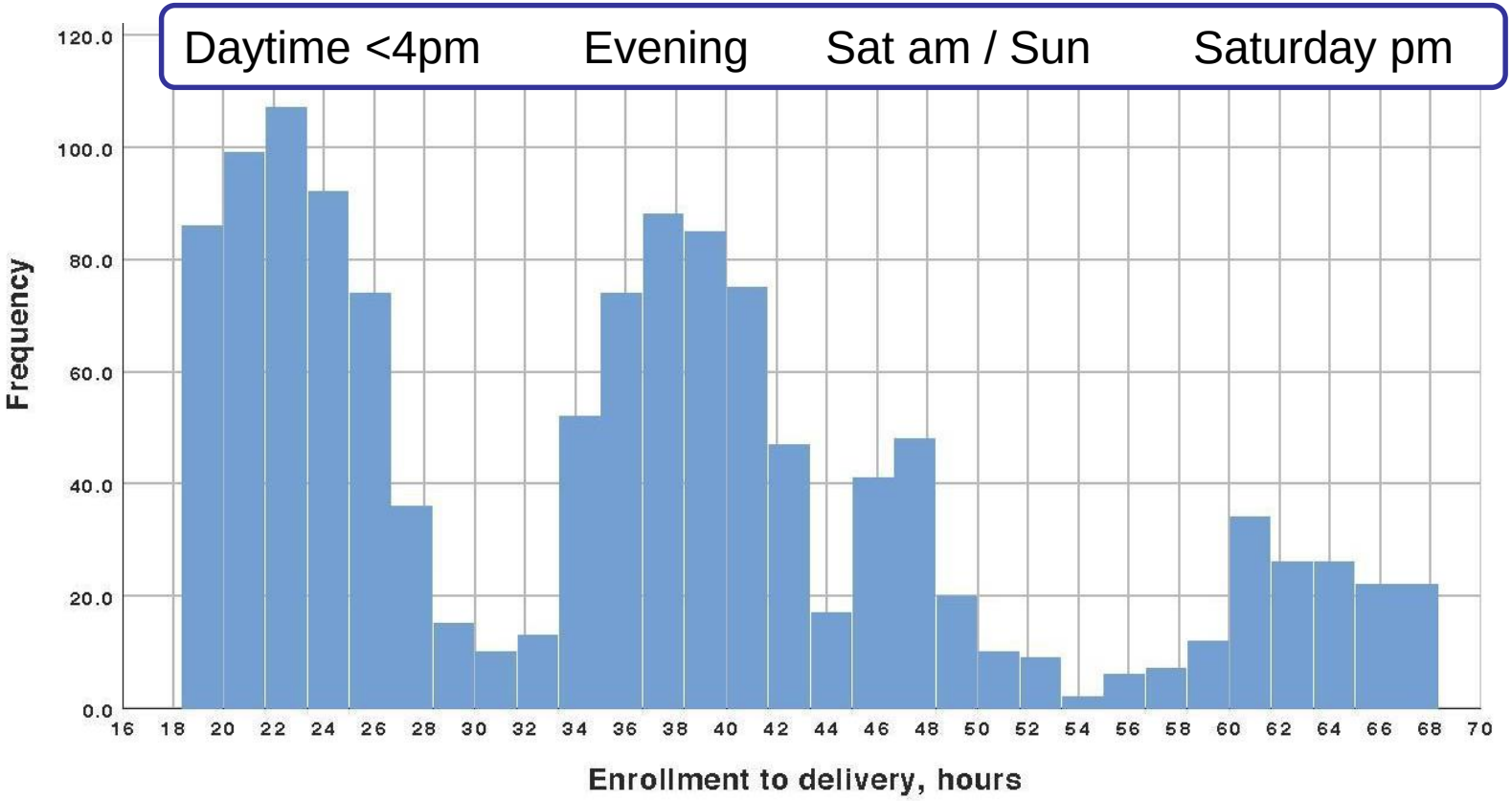
MSWord mail merge for generating a prescription => PDF

Secure email sent to Pharmacy

Randomized at Research Pharmacy

Fedex Ship Manager software => generate Fedex labels

Time from Enrollment to Drug Delivery



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

Follow Up

- Received automated emails on Day 1, (3), 5, 10, 15
- PrEP Trial used weekly messages
- ~75% Completed Follow Up well
- ~15% Needed additional prompts
  - Follow Up Email
  - SMS Text Messages (Twilio integrated into RedCAP)
  - Phone Calls

~10% Lost to Follow Up

Remote Blood Collection

Whole Blood Collection: Neoteryx Microsampling Kits → PK, Serology

Melanie Nicol PharmD, PhD led this for our team.

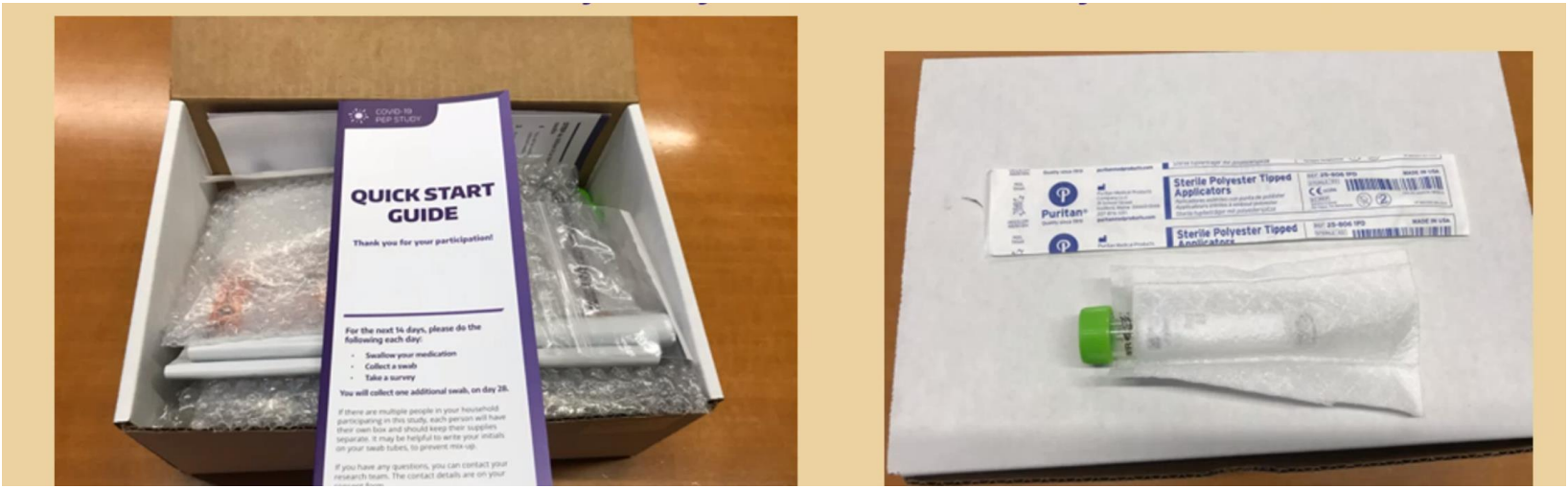
~$25

Analyte needs to be stable for ~24 hours

Rajasingham R, et al. *Clin Infect Dis* 2020

Remote Viral Collection

Self collection anterior nares mid-turbinate viral swabs
Univ. of Washington HCQ PEP Trial -- Ruanne Barnabas (PI)



Early Treatment Trial

Expectations for Future Trials

Time to Enroll for Early Treatment Trial

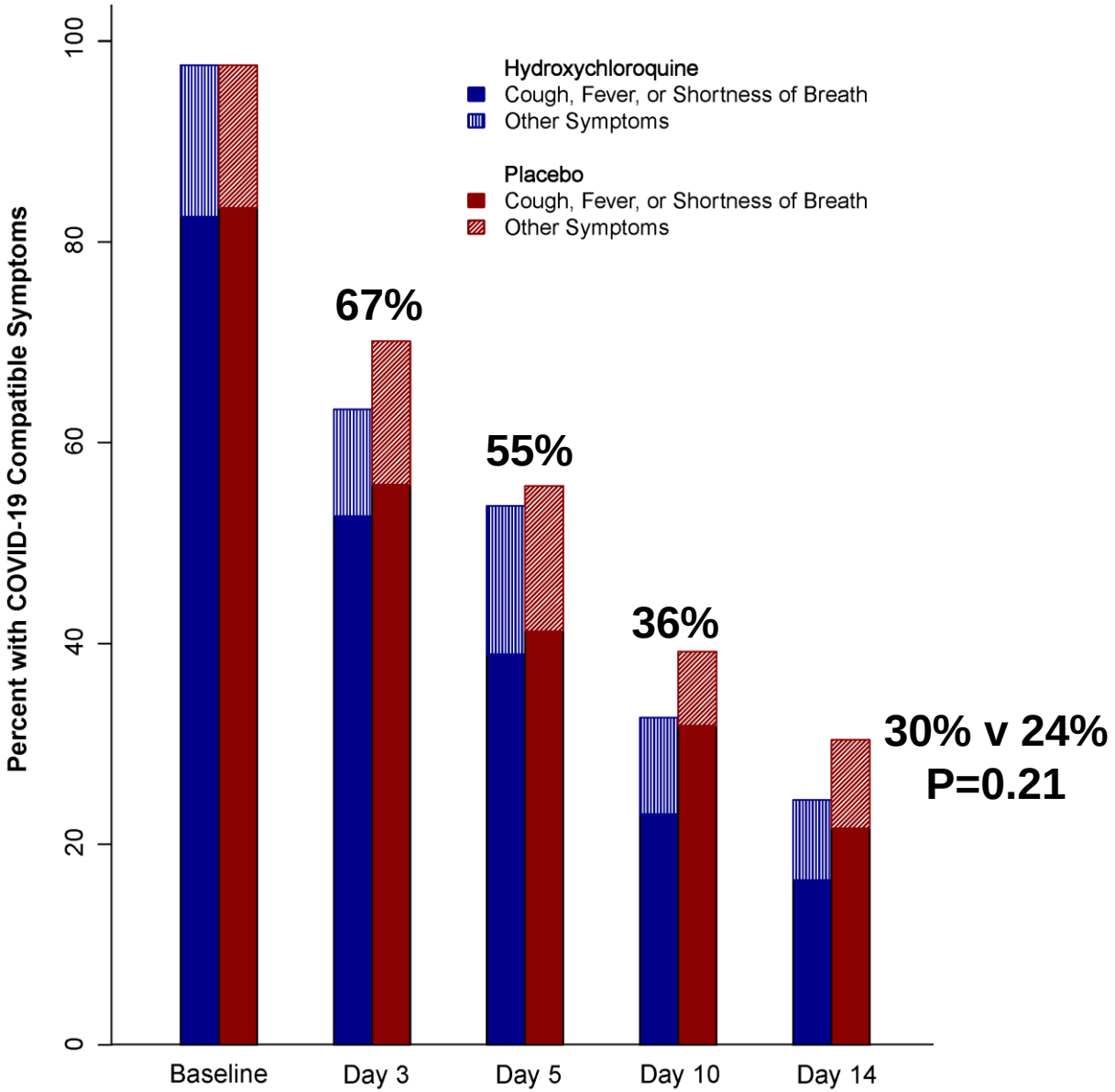
Exposure Group	N	Mean Days of Symptoms	Median Days of Symptoms	IQR
Lab Confirmed PCR+	145	2.2	2	0 – 3
Contact PCR+	196	1.3	1	0 – 2
Probable Case Only (Pending PCR)	82	1.0	0	0 – 2

56% (236/423) enrolled within ≤1 day of symptom onset

Excluded n=1432 symptomatic of which ~55% had >4 days of symptoms

Skipper CP et al. *Annals of Intern Med* 2020
www.acpjournals.org/doi/10.7326/M20-4207

Covid-19 Symptom Duration



~3% Hospitalization rate in placebo group

Skipper CP et al. *Annals of Intern Med* 2020
www.acpjournals.org/doi/10.7326/M20-4207

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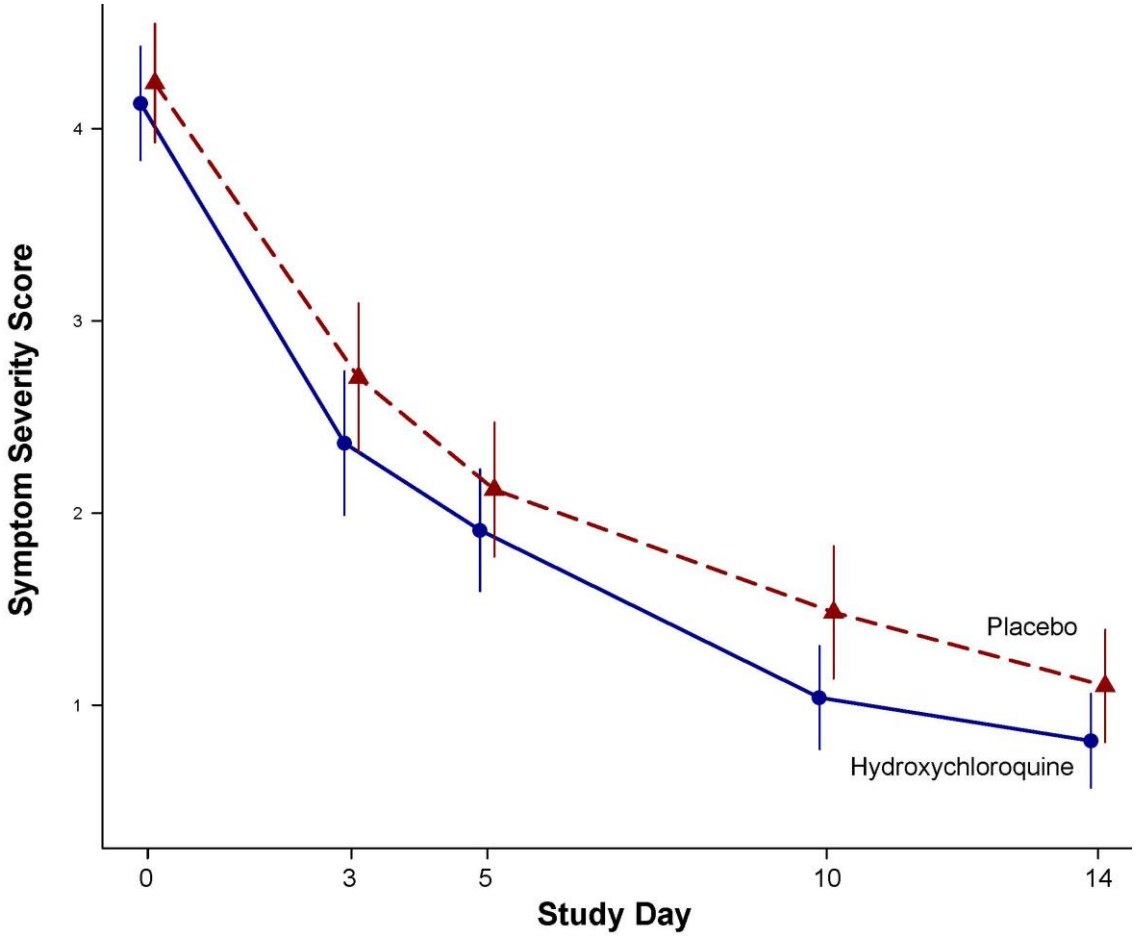
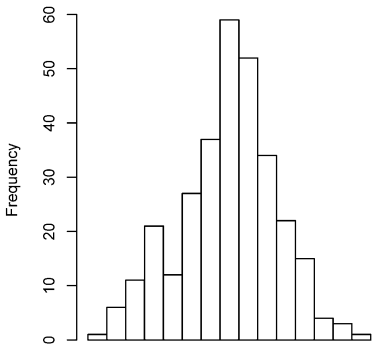
Change in Symptom Severity from Baseline



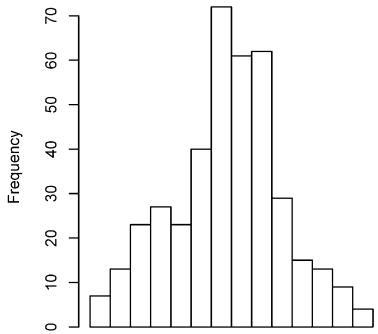
P=0.12

Skipper CP et al. *Annals of Intern Med* 2020
www.acpjournals.org/doi/10.7326/M20-4207

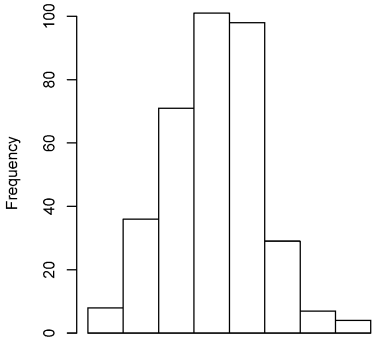
Change from Baseline Normally Distributed



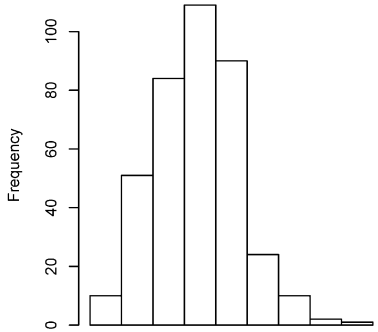
Study Day 3



Study Day 5



Study Day 10



Study Day 14

Absolute Scores
Right-handed skewed

Sensitivity Analysis with: log-link gamma-error generalized linear mixed model using absolute scores.

Skipper CP et al. *Annals of Intern Med* 2020
www.acpjournals.org/doi/10.7326/M20-4207

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- Minnesota Chinese Chamber of Commerce
- University of Minnesota
- Myself

Team Science

In collaboration with McGill U, U of Manitoba, & U of Alberta.

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Mahsa Abassi

Pharmacologist
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Caleb Skipper

Med Students:
Katelyn Pastick
Elizabeth Okafor

Research Associates:
Darlisha Williams
Alanna Nascene

Statisticians
Ananta Bangdiwala
Nicole Engen
Kathy Huppler Hullsiek