ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications

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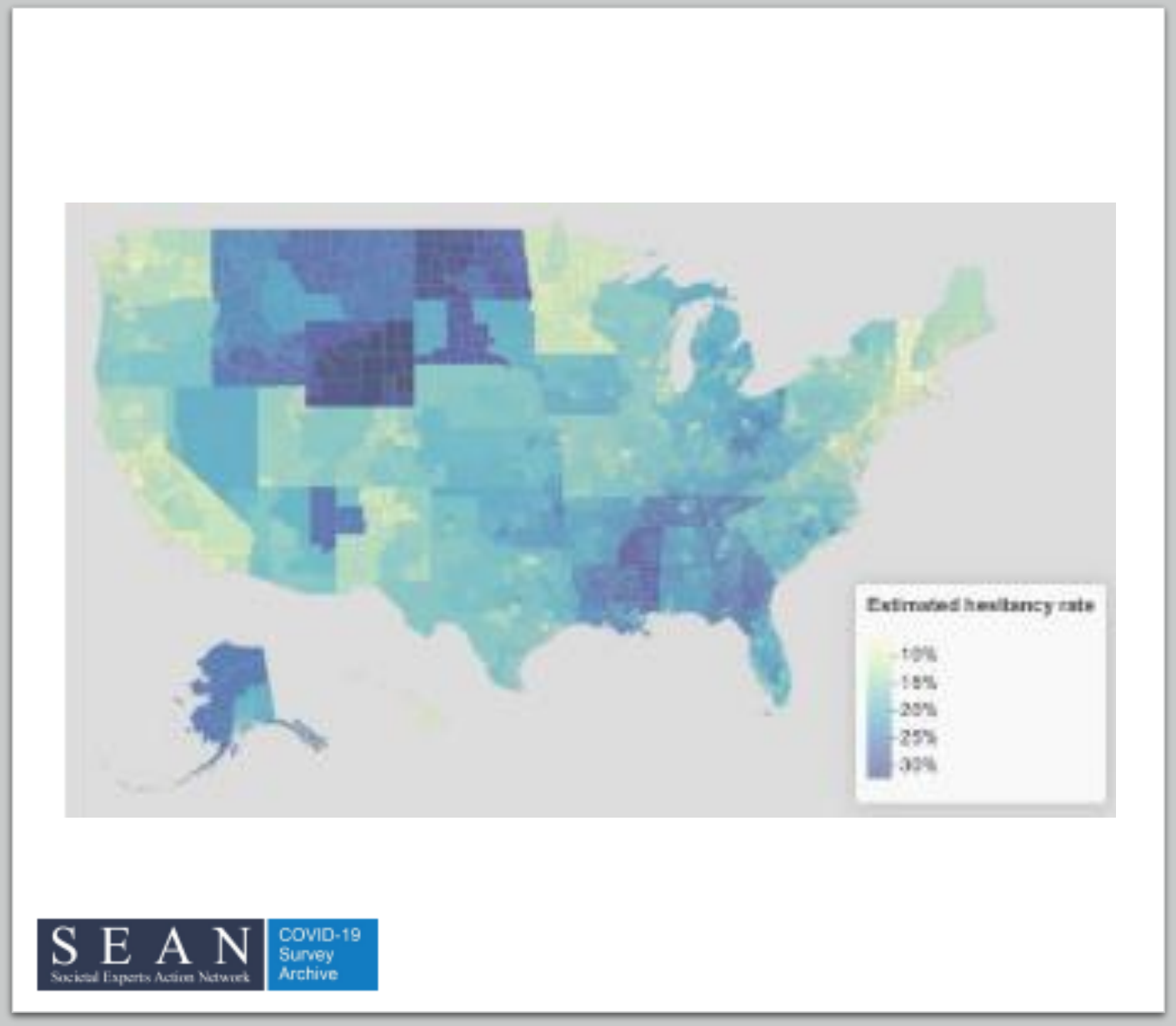
ACTIV-6 – Why?

- There is no FDA approved standard of care for COVID-19 patients with mild-to-moderate disease
- Current treatment options require infusion
- Vaccine hesitancy remains high
- Vaccine access globally is low



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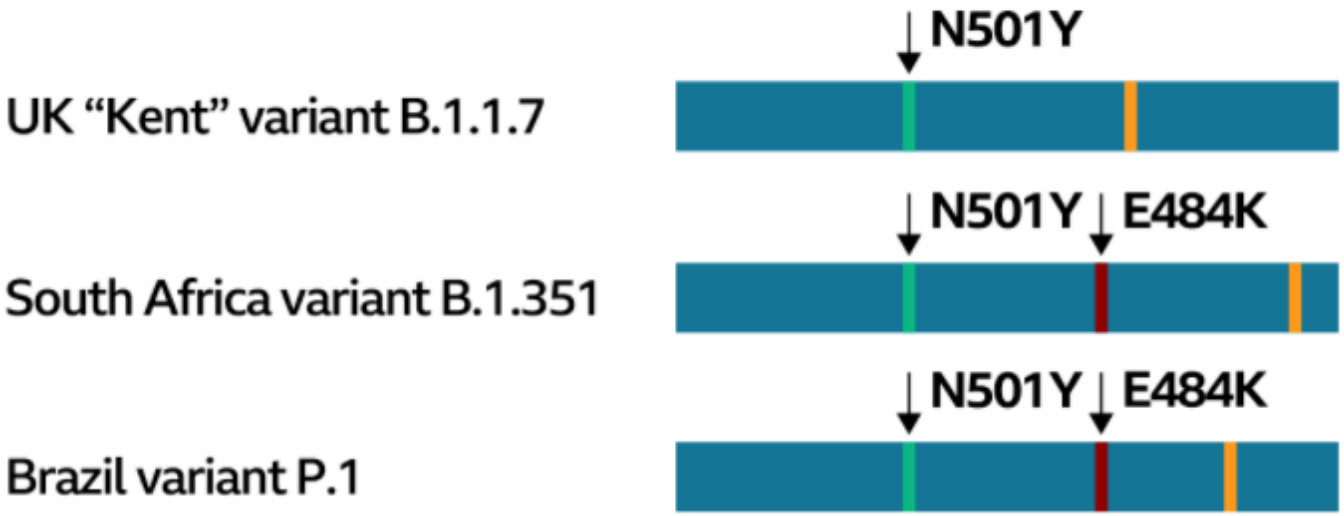
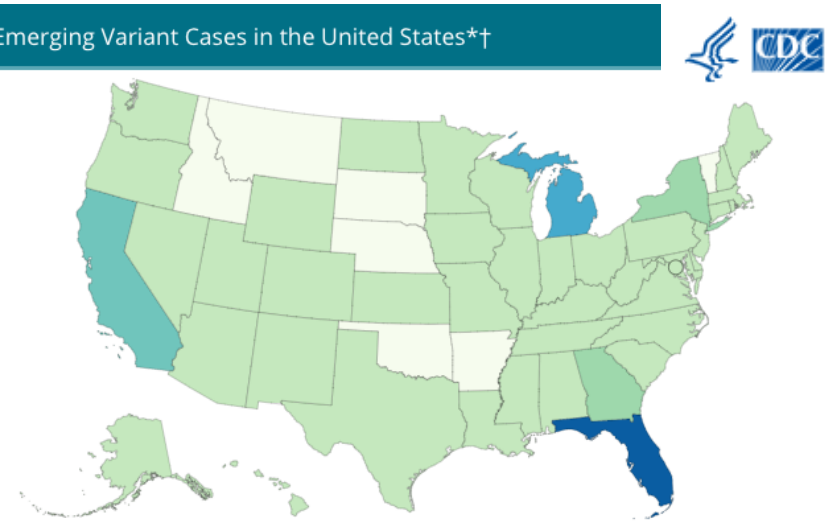
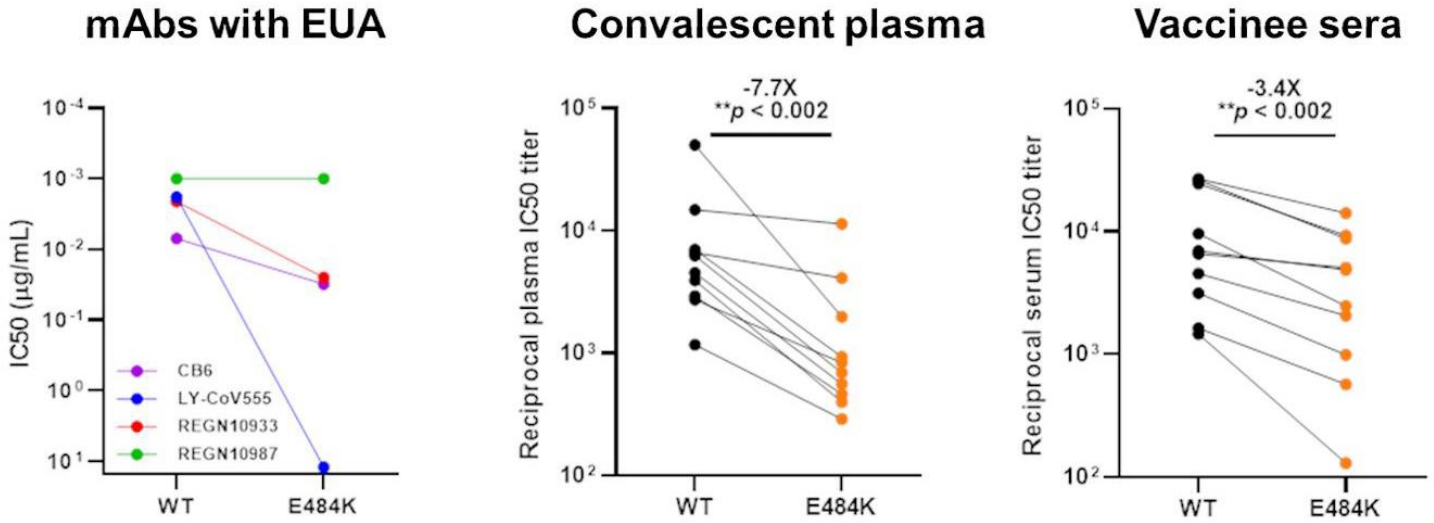
Viral Evolution

The genetic code for each of these variants is slightly different.







www.bbc.com/news/health-55659820

medRxiv preprint doi: https://doi.org/10.1101/2021.02.23.21252259;

Rationale

- > 80% of COVID-19 cases are diagnosed as an outpatient
- Testing “on the shelf” drugs has advantages during fast-paced pandemic:
  - Expedited timeline
  - Existing knowledge of safety profile
  - Possibly less expensive than newly developed drugs

- Question: Are there medications currently approved for other conditions that improve symptoms in non-hospitalized patients with mild to moderate COVID-19 symptoms?

Key Questions Facing Clinicians, Patients and Caregiver

How to help someone *feel better faster* with newly diagnosed mild-moderate COVID-19?

How to *prevent hospitalizations or death* in someone with newly diagnosed mild-moderate COVID-19?

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Study Objectives

Primary Objective

- To evaluate whether repurposed medications can:
  - Make outpatient participants with mild-to-moderate COVID-19 symptoms feel better faster
  - Reduce death and hospitalization, with the following evaluated from baseline through 14 days:
    - *Hospitalization*
    - *Death*
    - *Time to symptom freedom*
    - *Symptom count*

Secondary Objectives

- To evaluate clinical outcomes in a study drug arm versus placebo arm
  - *Using Modified COVID Ordinal Outcomes Scale on Days 1-14, Day 21, Day 28, and Day 90*
- To describe symptom resolution (3 consecutive days without symptoms)
- To describe participants' quality of life (QOL)
  - *Using Patient-Reported Outcomes Measurement Information System (PROMIS)-29 at baseline, Day 7, Day 14, Day 28, and Day 90 follow-up*

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Study Drug Selection

ACTIV-6 Repurposed Agents | *Scoring Criteria*

Scoring Criteria		No Go	0	1	2	3	4
Triage & Must-Have	**Safety**	Not approved for any other disease indication in proposed formulation	Previously approved for other disease indication, but lacks safety data in proposed dose			Adequate safety profile with suitable benefit/risk profile (with safety warning that needs to be adjudicated)	Strong safety profile [previously approved for other indication in broad patient populations (i.e., elderly, and/or patients with co-morbidities) and adequate amount of historical safety data]
	Route of Admin-istration	Difficult to administer (e.g., IV) or store (e.g., requiring specialized equipment)				Moderately difficult to administer (e.g., inhaled, intranasal, SubQ) and store (e.g., refrigerated / 4ºC)	Easy to administer (e.g., oral, metered-dose inhaler) and store (e.g., room temp)
Must-Have	**Rationale for MOA to be relevant to COVID-19**		Unknown	Weak	Moderate	Strong (reasonable rationale for use with COVID-19 and appropriate for outpatient setting)	
	Relevant Clinical Trial Data for Early COVID-19	Majority of clinical data shows no effect in outpatient setting	No data from outpatient trials	Data from one or more outpatient trials in **mechanistically relevant disease** with promising initial results	Mixed / inconclusive results from **outpatient uncontrolled trials and/or RCTs** in SARS CoV-2 or related virus	Overall promising initial results from **uncontrolled outpatient trials** for SARS CoV-2 or related virus	Overall highly promising initial results including data from **one or more outpatient RCTs** for SARS CoV-2 or related virus
	Real World Evidence		No evidence of efficacy from use in the clinical setting / no data to judge	Valid data from **one** RWE case study suggesting clinical efficacy	Valid data from **multiple** RWE case series suggesting clinical efficacy		
	Drug-drug Interaction	Major concern (clinically significant DDIs)	Insufficient / no data to judge	Minor concern / manageable drug interactions	None		
Nice-to-Have	**Preclinical Data**		No preclinical data / shows no effect	In vivo data in appropriate animal model			
	PK / PD		No PK/PD data / insufficient plasma levels	Sufficient plasma and / or tissue levels			
	Need for Scientific Clarity (i.e., strong public interest)		No expressed interest from the public / scientific community		Significant interest from the public / scientific community, with no current plans to study the agent in an adequately powered trial		

Note: Availability / scalability will be assessed after prioritization of any agent before official entry into the trial

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Study Design

Study Design

- Platform Protocol
  - Quickly test different medications using the same infrastructure
  - Used in wide range of settings
  - Integrated into routine COVID-19 testing programs and treatment plans
- Remote Study Visits
  - Participants use online system to complete study surveys and report adverse events or changes in clinical status
  - Unplanned in-person or remote study visits possible if deemed necessary by study investigator

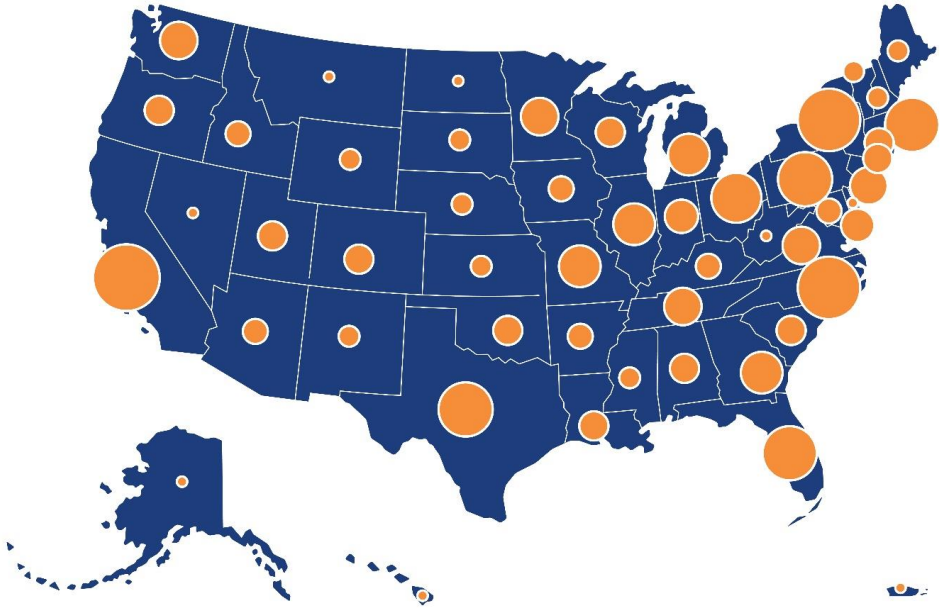
Overall Goal:

ACTIV-6 access in every state via sites or remotely

pcornet

The National Patient-Centered Clinical Research Network

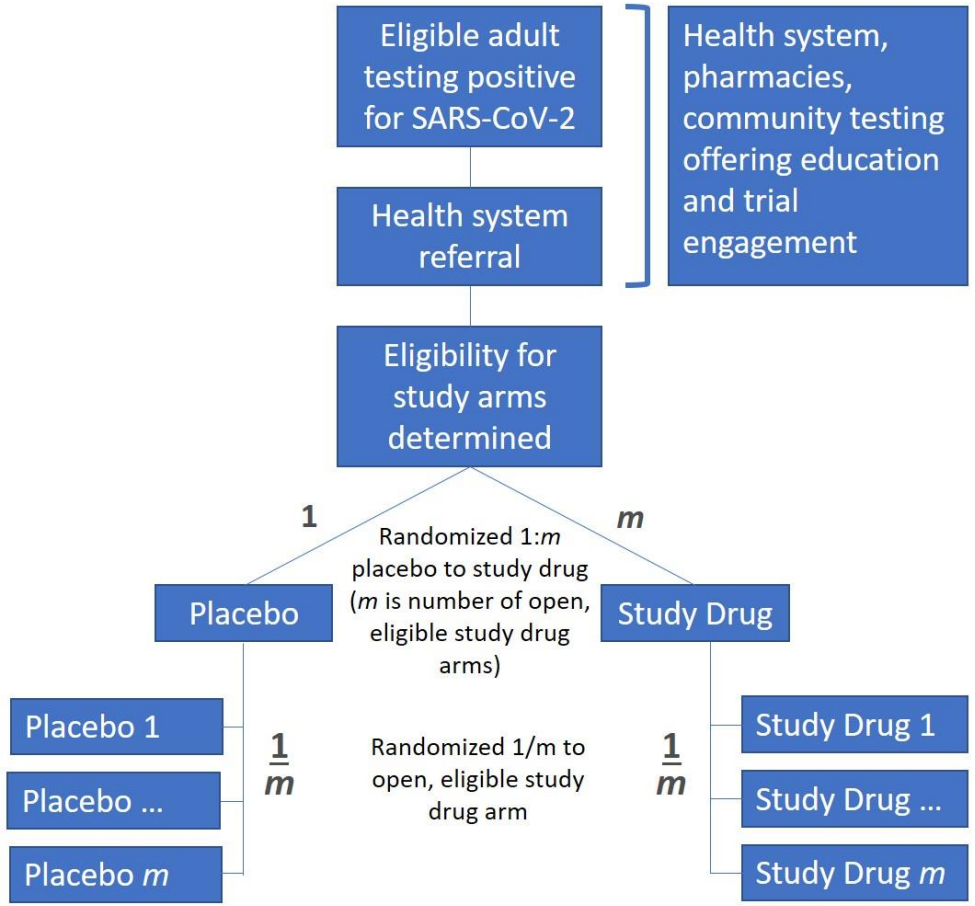
TRIAL INNOVATION NETWORK



Randomization

- If only one study drug under study, patients randomized 1:1 between study drug and placebo
- If multiple study drugs, patients randomized among study drugs for which they are eligible and placebo with equal probability (1:1)
  - *2-step randomization process:*
    - Participant randomized 1:m, placebo to active study drugs. Participants carry this "placebo" versus "study drug" randomization into the next step.
    - Participant randomized among the m active study drugs for which they are eligible.
- Sites will be informed of participants' study drug arm but not whether participant is allocated to placebo or study drug

Overall Flow:
Direct to Participant via Site or Anywhere



Inclusion Criteria

- Willing and able to provide informed consent
- ≥30 years
- Confirmed SARS-CoV-2 infection by any authorized or approved PCR or antigen test collected within 10 days of screening
- Two or more current symptoms of acute infection for ≤7 days. Symptoms include the following:
  - *Fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell*
- Willing and able to complete study questionnaires for up to 90 days

Exclusion Criteria

- Prior COVID-19 diagnosis (>10 days from screening)
- Hospitalization for COVID-19
- Known allergy/sensitivity or any hypersensitivity to components of the study drug or placebo
- Known contraindication to study drug, including prohibited concomitant medications

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Study Analyses

Objectives and Endpoints

	OBJECTIVES	REPORTED ENDPOINTS
Primary	To evaluate the **effectiveness** of repurposed medications [(study drug(s)] in **non-hospitalized participants with mild to moderate COVID-19**	• The OR describing the overall treatment effect on symptoms and clinical events over the 14 days • The overall risk difference for hospitalization and death • Mean and median time to symptom freedom

Primary Analysis

SYMPTOM BURDEN SCALE

- Fatigue
- Dyspnea
- Fever
- Cough
- Nausea
- Vomiting
- Diarrhea
- Body aches
- Chills
- Headache
- Sore throat
- Nasal symptoms
- New loss of sense of taste or smell
- Other COVID-related symptom

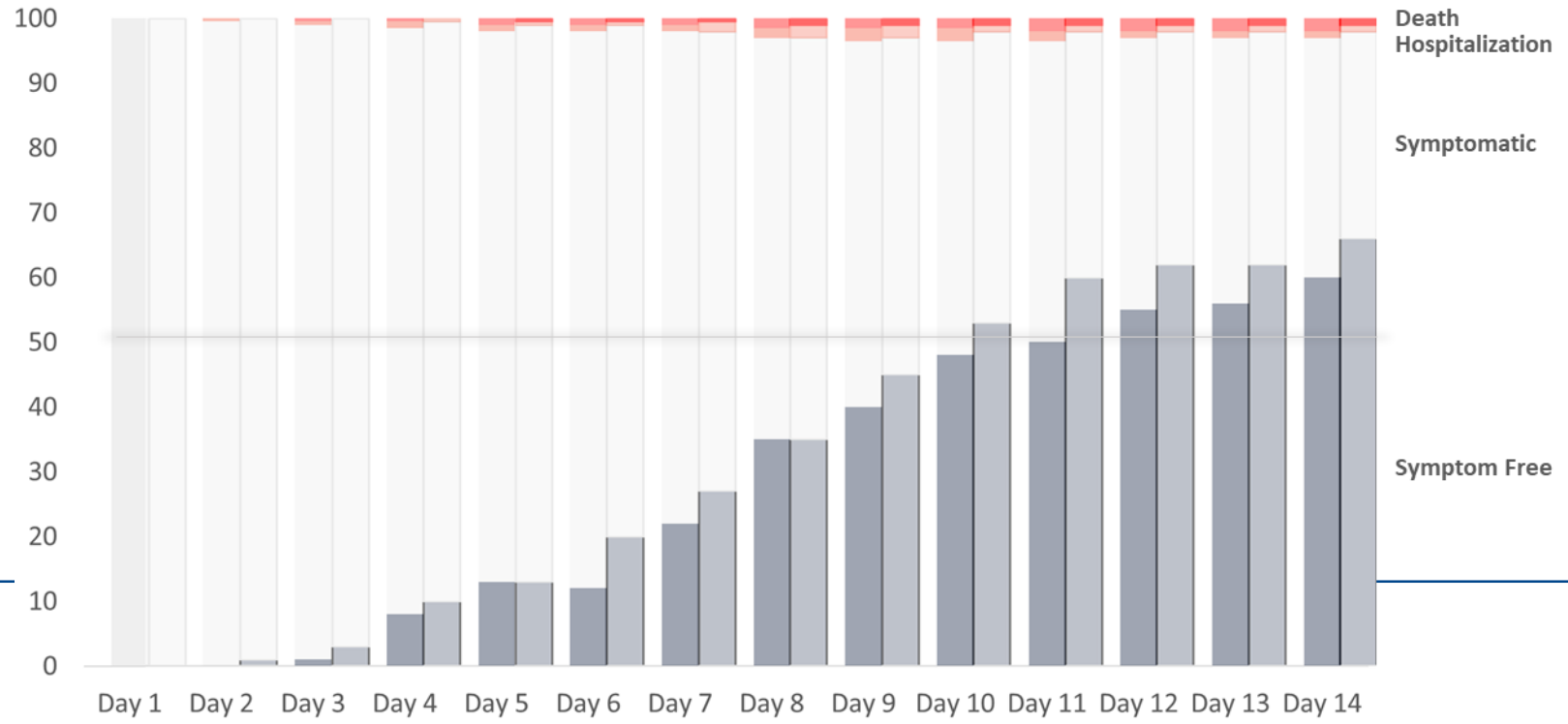
ASSESSING EFFECTIVENESS

- Overall effect for each study drug versus placebo will be quantified using the common odds ratio (cOR) from a proportional odds model
- The following will be reported, regardless of efficacy signal:
  - ❖ Mean and median time to symptom freedom (for quantifying benefit on symptoms)
  - ❖ Mean and median time to hospitalization or death (secondary outcomes)

Example report

MAIN RESULTS

The figure shows symptom freedom and event rates over the first fourteen days of observation. Overall, participants in the treatment group experienced significantly fewer symptoms, hospitalization and mortality (cOR=0.7, CI 0.6-0.8, p=0.0003). Specifically, median time to being free of symptoms was 2 days (CI 1.8 to 2.2) shorter in the treatment group than the control group, and the risk of hospitalization and mortality at day 14 was 0.9% lower (CI 0.1% to 1.4%).



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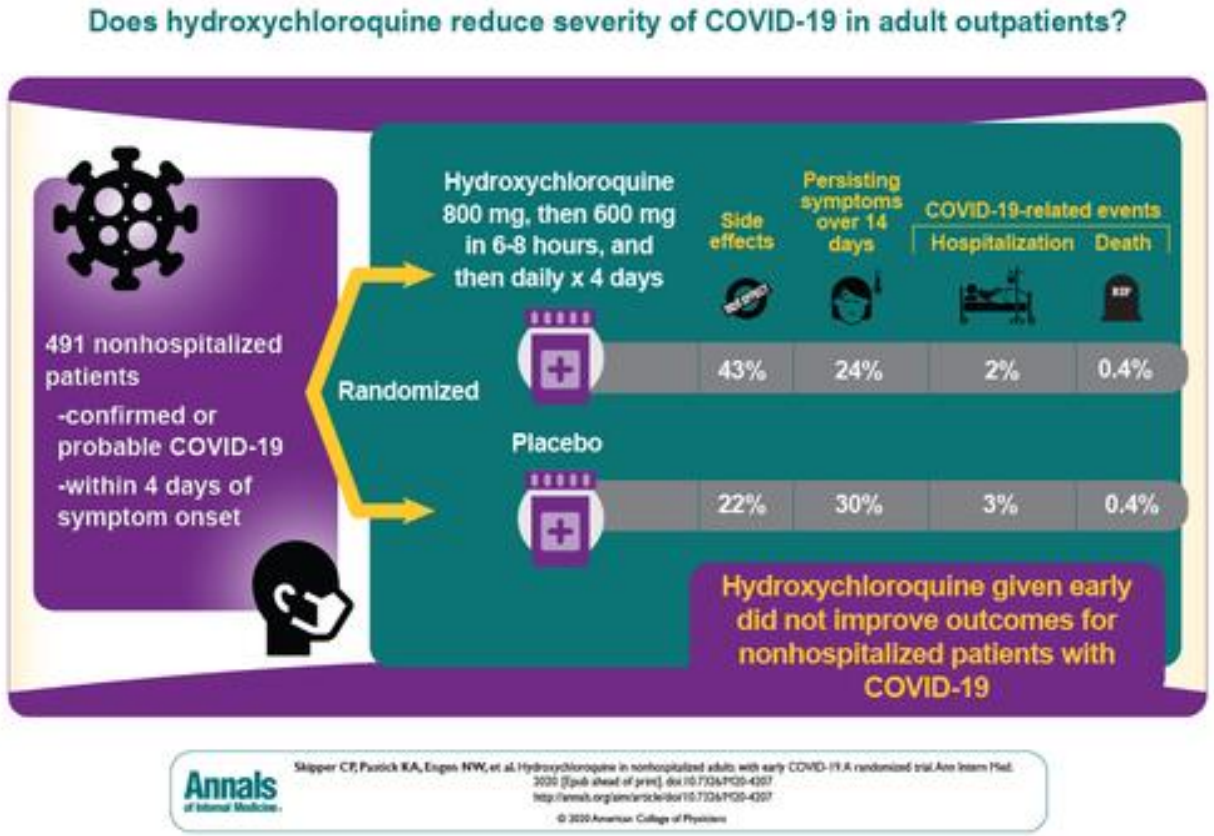
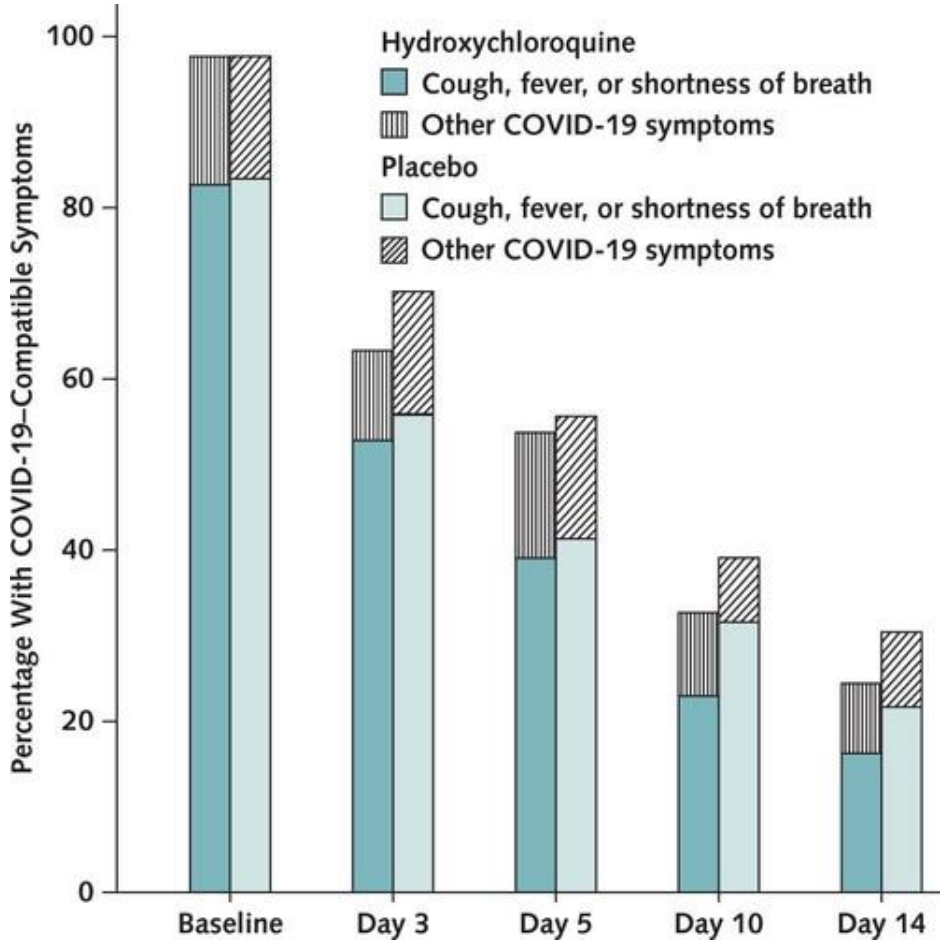
Example Publication





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Skipper CP, …., Boulware DR. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. Ann Intern Med. 2020 Oct 20;173(8):623-631. PMCID: PMC7384270.

Objectives and Endpoints

	OBJECTIVES	REPORTED ENDPOINTS
Secondary	To evaluate the **clinical outcomes** in participants in a study drug arm versus those in the placebo arm	• The OR describing the overall difference in clinical progression • The OR describing the difference in clinical progression at each measured time point. • The overall risk difference for hospitalization or death
	To evaluate **effects on acute care needs**	• The overall risk difference for any of urgent care, emergency care, hospitalization or death • Time to first urgent care, emergency care, hospitalization or death • Risk and time to event for each component of the composite
	To describe **symptom resolution**	• Directly measured mean and median time to 3 consecutive days symptom free

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Objectives and Endpoints

	OBJECTIVES	REPORTED ENDPOINTS
Secondary	To describe the **quality of life (QOL)** in participants in a study drug arm versus those in the placebo arm	• For each scale, the overall OR • For each scale, the OR and mean difference at D7, D14, D28, D90
Exploratory	To describe **long-term COVID-19-related symptoms** in participants in a study drug arm versus those in the placebo arm	• Directly measured mean and median symptom count

Independent Data and Safety Monitoring Decision Framework

Stopping thresholds for efficacy, safety, and futility after each 200 participants enrolled in an agent-specific arm based on overall benefit and clinical efficacy

- Stopping for efficacy, inferiority or equivalence will be based on the posterior probabilities, stopping for futility
- If overall efficacy is observed but there is no clear benefit on clinical events, a futility analysis on clinical benefit will be undertaken and the trial may continue if the predicted probability of success on clinical events is optimistic within the resources available to the platform in the context of external environmental factors (external data on available drugs; evolution of the pandemic)
- All futility analysis will use projected accrual at a defined calendar time

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Patient Engagement

Stakeholder Engagement

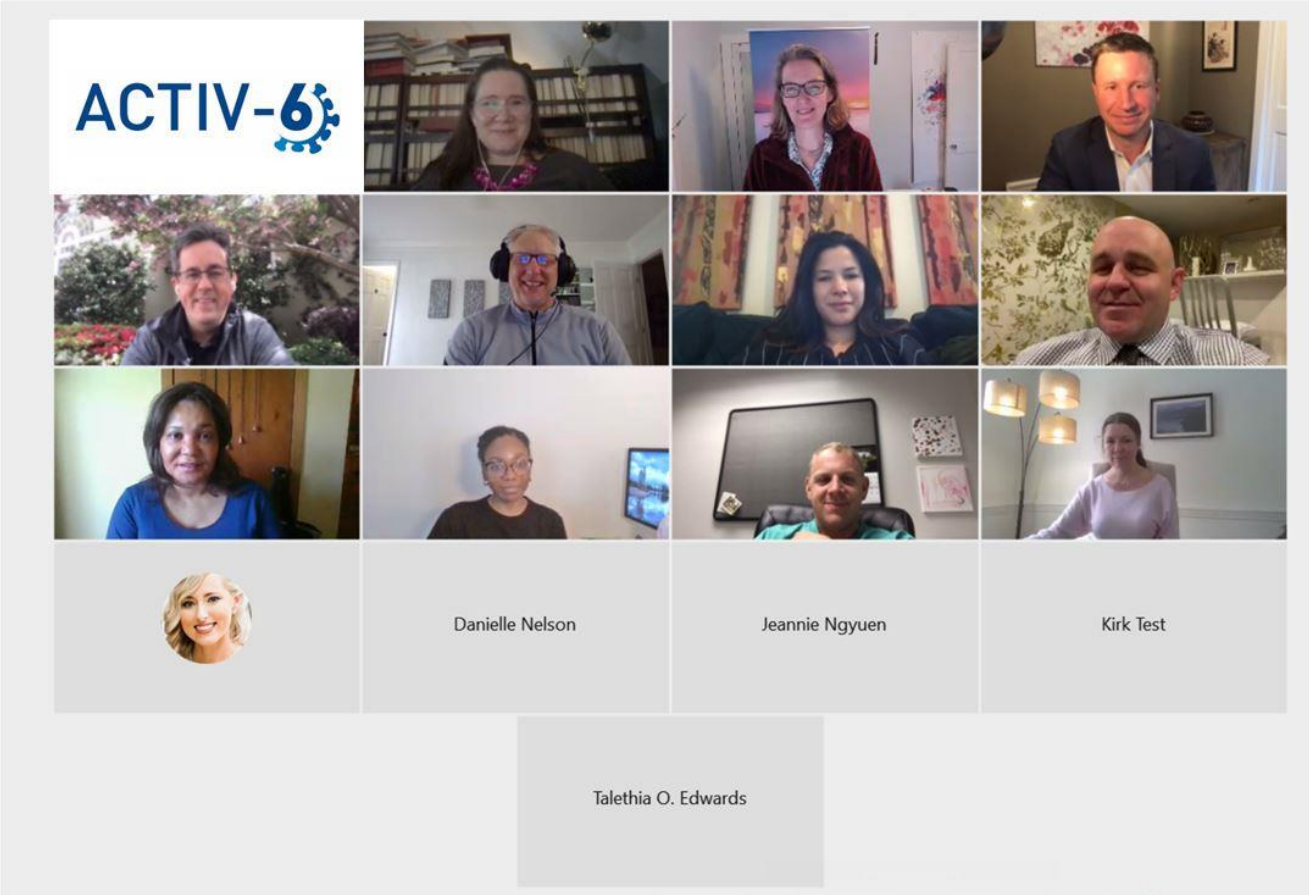
- COVID-19 has affected people in many ways
- Overall goal– Understand and incorporate the lived experience to address:
  - Meaningful outcomes
  - Recruitment and retention
  - Dissemination of results

Stakeholder Advisory Committee Charge

To provide input into critical elements and key areas of ACTIV-6 protocol and processes in order to support high-quality, efficient, patient-centered research that:

- Includes representative populations
- Is feasible and minimally burdensome for participants
- Drives higher rates of retention and compliance through enhanced value and improved participant experience
- Improves data quality through minimizing patient dropout and enhancing participant adherence to networks' protocols
- Enables dissemination of what's most important from different points of view

Stakeholder Advisory Committee is Going!



PCORnet Affiliation	Member Name
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GPC	Andrew Vasey
INSIGHT	Matthew William McCarthy
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OneFlorida	Danielle Nelson
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PaTH	Jonathan Arnold
REACHnet	Jeannie Nguyen
REACHnet	Joshua Denson

Facilitators

Megan Hamm, PaTH

Kathleen McTigue, PaTH

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Conclusion:
What does success look like?

- Informing and changing care!
- Any clear, proven answer for study drugs
  - Do any of the study drugs help participants feel better, faster, when compared with placebo?

  AND
  - Do any of the study drugs also improve clinical outcomes such as emergency department visits, hospitalization, and death?
  - Does early treatment of mild to moderate COVID-19 in the outpatient setting impact post-acute sequelae of COVID?

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