Real World Evidence and Monoclonal Antibody (mAb) COVID Project

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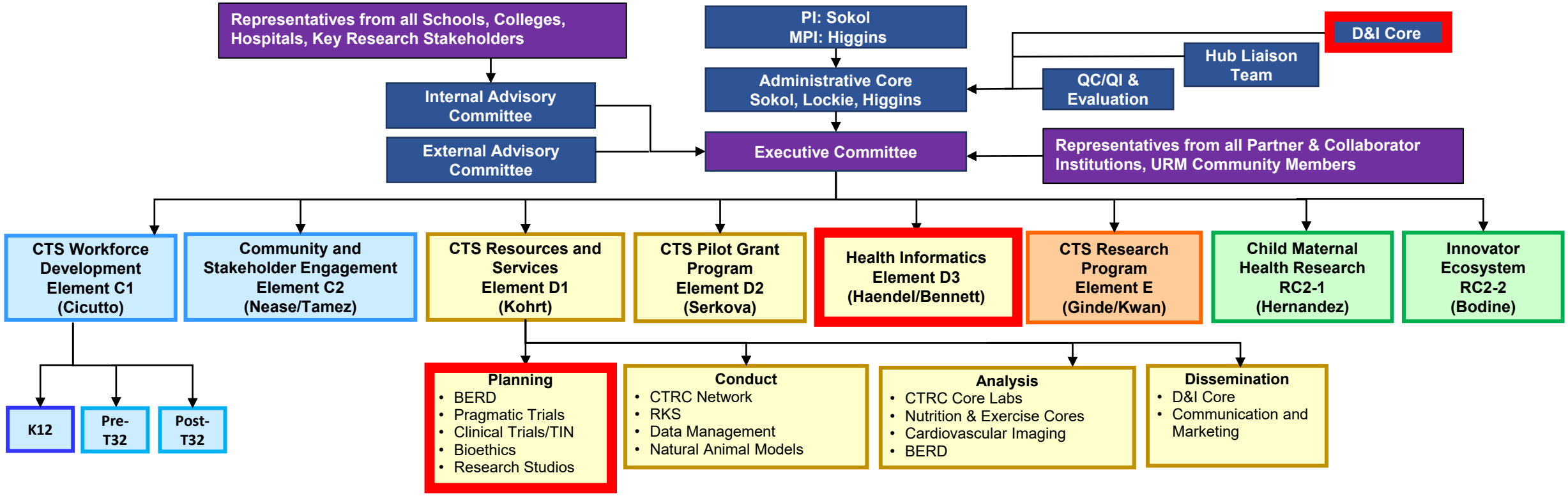

Representatives from all Schools, Colleges, Hospitals, Key Research Stakeholders
PI: Sokol
MPI: Higgins
D&I Core
Hub Liaison Team
QC/QI & Evaluation
Administrative Core
Sokol, Lockie, Higgins
Internal Advisory Committee
External Advisory Committee
Executive Committee
Representatives from all Partner & Collaborator Institutions, URM Community Members
CTS Workforce Development Element C1 (Cicutto)
Community and Stakeholder Engagement Element C2 (Nease/Tamez)
CTS Resources and Services Element D1 (Kohrt)
CTS Pilot Grant Program Element D2 (Serkova)
Health Informatics Element D3 (Haendel/Bennett)
CTS Research Program Element E (Ginde/Kwan)
Child Maternal Health Research RC2-1 (Hernandez)
Innovator Ecosystem RC2-2 (Bodine)
K12
Pre-T32
Post-T32
Planning
BERD
Pragmatic Trials
Clinical Trials/TIN
Bioethics
Research Studios
Conduct
CTRC Network
RKS
Data Management
Natural Animal Models
Analysis
CTRC Core Labs
Nutrition & Exercise Cores
Cardiovascular Imaging
BERD
Dissemination
D&I Core
Communication and Marketing

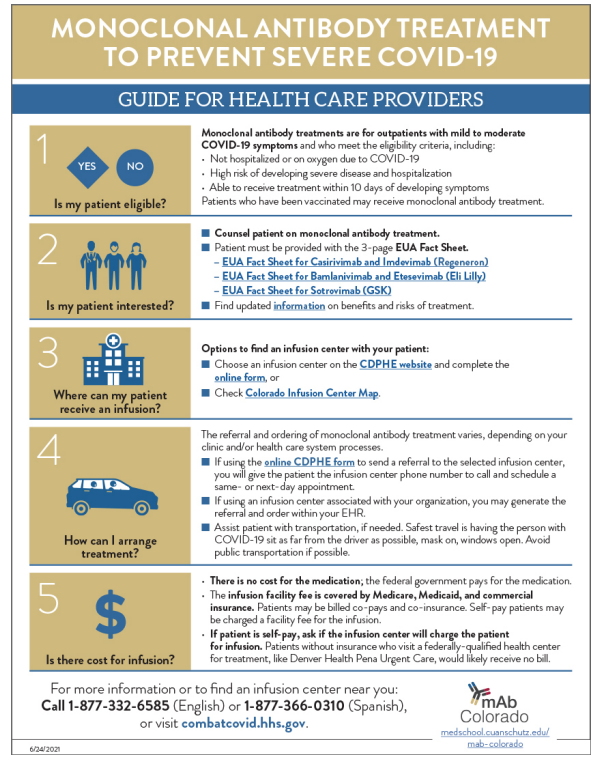
Strategic Goals

mAb Colorado

- **Goal 1**: Assess barriers and facilitators to use of mAbs statewide
- **Goal 2**: Develop, implement, and evaluate innovative strategies statewide to optimize equitable mAb access
- **Goal 3**: Determine the real-world effectiveness and safety of mAb (and other antiviral) treatment in high-risk COVID-19 outpatients

Barriers and Facilitators to Use of mAbs

- **Community awareness** of the need for timely testing and effective treatment available for all (not just the wealthy and connected)
- **Clinician education** about monoclonal antibody treatment for COVID-19 including strength of evidence, eligibility criteria, and how to access treatment
- Clear guidance on implementation and use of **referral processes**
- Addressing **inefficiencies in relying upon individual providers** to identify eligible patients, discuss treatment, find a treatment location, and complete a referral
- Assurances regarding **costs of care** especially for the **uninsured**

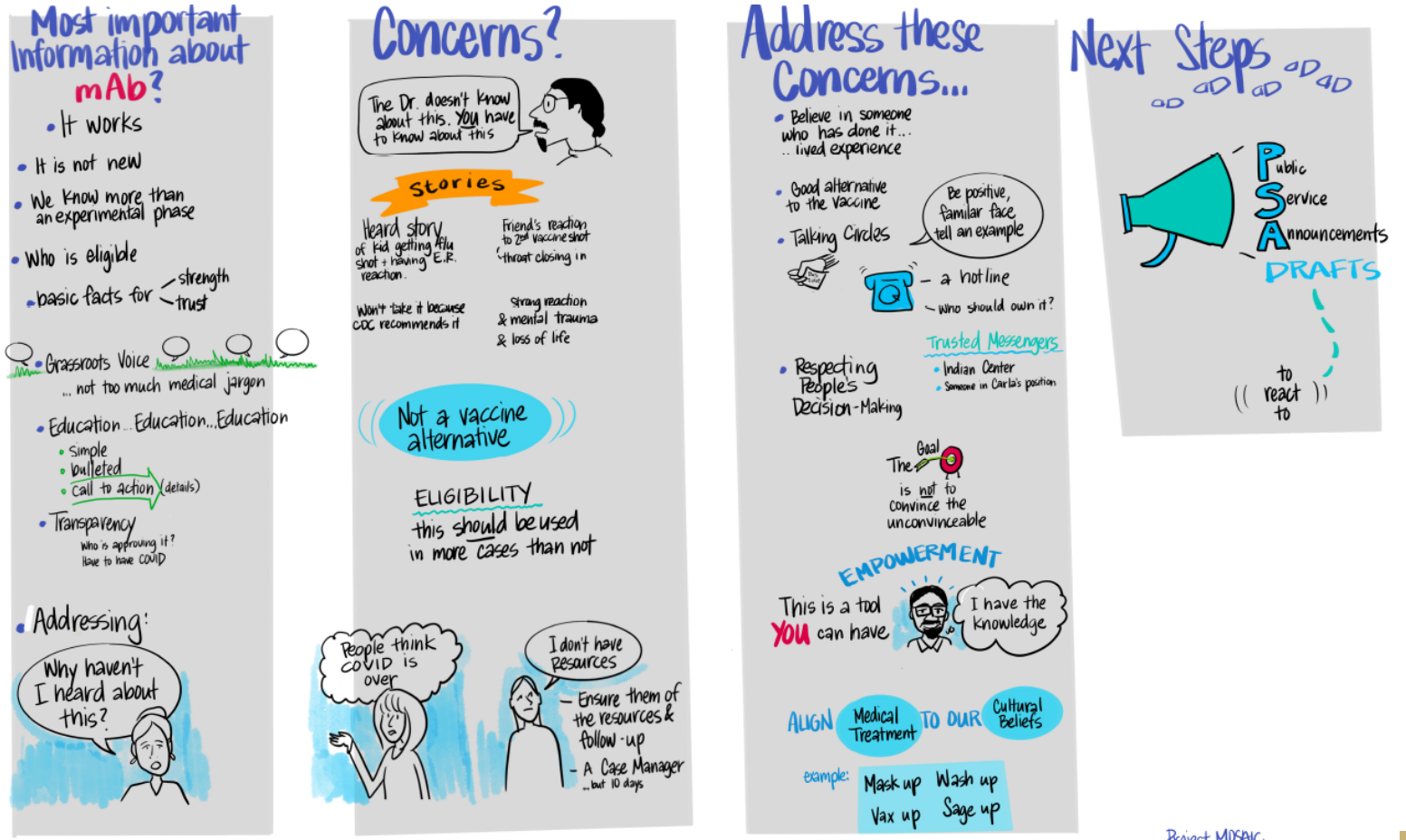


Kwan BM, Sobczak C, Gorman C, Roberts S, Owen V, Wynia MK, Ginde AA, Pena-Jackson G, Ziegler O, Ross DeCamp L. "All of the things to everyone everywhere": A mixed methods analysis of community perspectives on equitable access to monoclonal antibody treatment for COVID-19. PloS one. 2022 Nov 23;17(11):e0274043.

Kwan BM, Sobczak C, Beaty L, Wynia MK, DeCamp M, Owen V, Ginde AA. Clinician Perspectives on Monoclonal Antibody Treatment for High-Risk Outpatients with COVID-19: Implications for Implementation and Equitable Access. Journal of general internal medicine. 2022 Oct;37(13):3426-34.

Hamer MK, Alasmar A, Kwan BM, Wynia MK, Ginde AA, DeCamp MW. Referrals, access, and equity of monoclonal antibodies for outpatient COVID-19: A qualitative study of clinician perspectives. Medicine. 2022 Dec 16;101(50):e32191.

Community Engagement Studios: Native American Community



Credit: Kris Wittman, live illustrator

Community Engagement Studios: Hispanic/Latino Community

Credit: Kris Wittman, live illustrator

University of Colorado Anschutz Medical Campus

Webmail | UCD Access | Canvas | Quick Links |

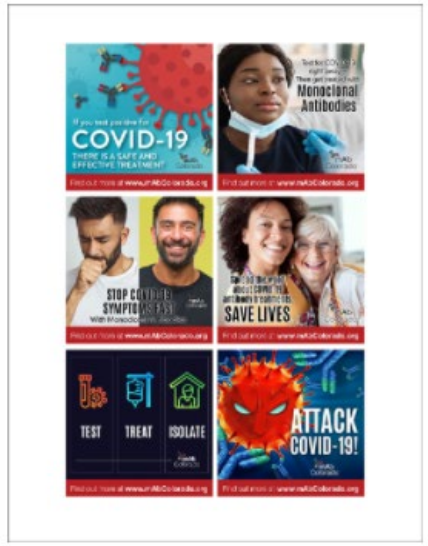
Community Messaging Materials

See below for materials you can share with members of your organization or community about monoclonal antibody (mAb) treatments for COVID-19.

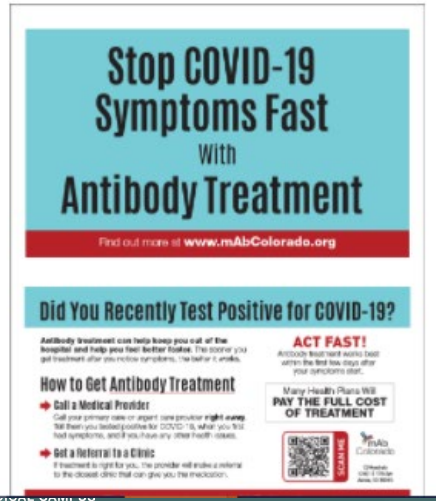
We are able to provide a limited number of printed materials mailed to you free-of-charge. If you would like to distribute printed materials to members of your organization or community, complete this order form.

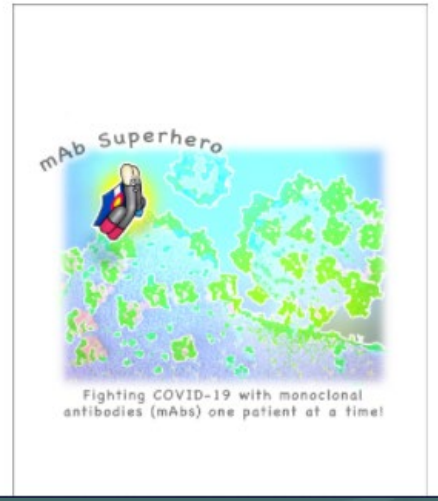
Download flyer versions in English and Spanish with basic information about mAb treatments. Can be printed front-to-back.

Download document versions in English and Spanish with answers to common questions about mAb treatments.



Download images to be shared as social media posts.





www.mAbColorado.org

¿Dio positivo para COVID-19? Actua Rapido

Puede sentirse mejor mas rápido si recibe un tratamiento con anticuerpos. Puede ayudar a mantenerlo fuera del hospital. El tratamiento con anticuerpos funciona mejor si usted es tratado dentro de los primeros días después de haber dado positivo para COVID-19.

Para obtener mas información acerca del tratamiento de anticuerpos siga estos pasos:

Llame a un proveedor médico de inmediato

- Llame a su proveedor de atención primaria o de atención urgente.
- Dígales cuándo tuvo los primeros síntomas de COVID-19.
- Dígales si tiene algún otro problema de salud.
- Pregúnteles si pueden ayudarle a obtener tratamiento con anticuerpos monoclonales.

Obtenga una referencia a una clínica

Si el tratamiento con anticuerpos es adecuado para usted, el proveedor hará una referencia a una clínica cercana a usted donde usted puede obtener el tratamiento. Le darán la dirección y el número de teléfono de la clínica.

Muchos planes de salud pueden **pagar el costo total del tratamiento**

El tratamiento con anticuerpos funciona contra la variante delta COVID-19

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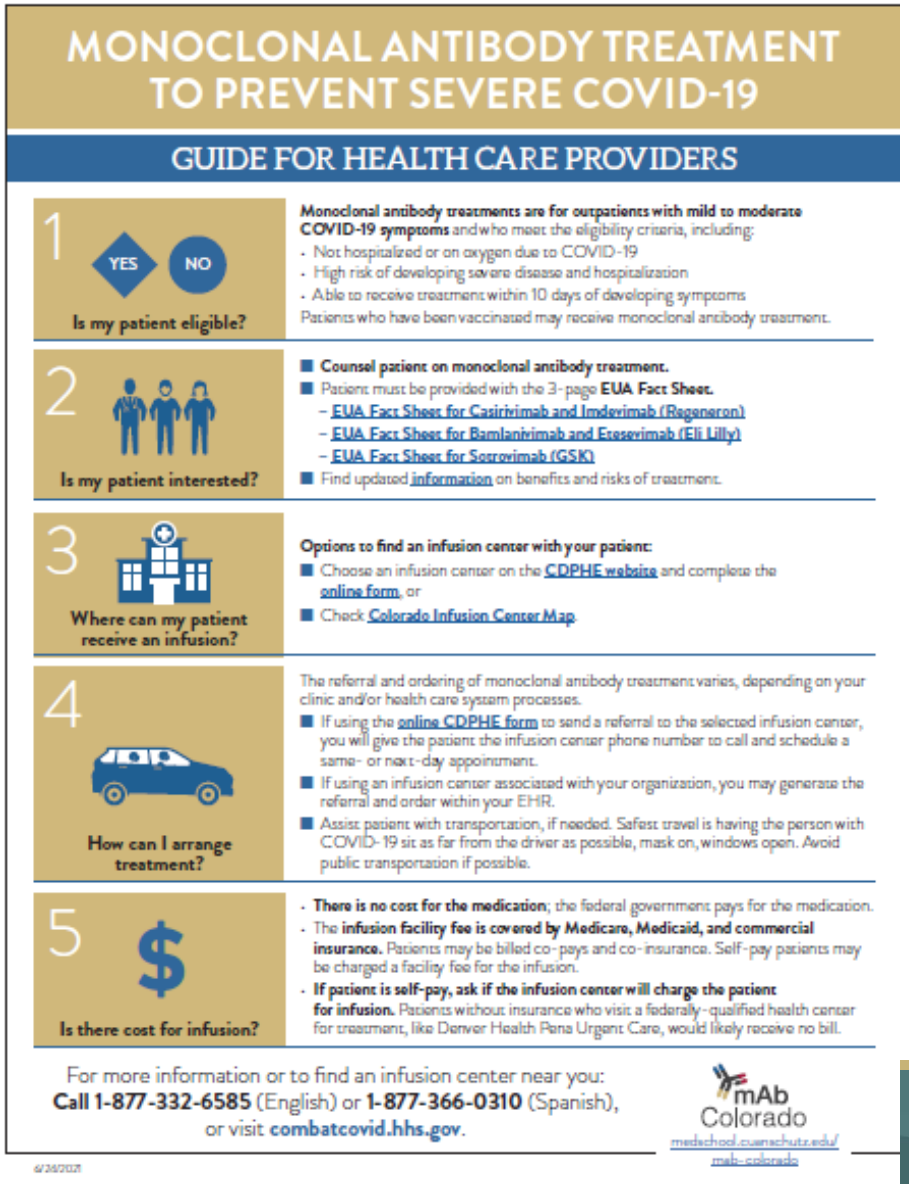
Health Care Provider Messages & Materials



MONOCLONAL ANTIBODY TREATMENT TO PREVENT SEVERE COVID-19

GUIDE FOR HEALTH CARE PROVIDERS

1 Is my patient eligible? (YES / NO)

Monoclonal antibody treatments are for outpatients with mild to moderate COVID-19 symptoms and who meet the eligibility criteria, including:

- Not hospitalized or on oxygen due to COVID-19
- High risk of developing severe disease and hospitalization
- Able to receive treatment within 10 days of developing symptoms

Patients who have been vaccinated may receive monoclonal antibody treatment.

2 Is my patient interested?

- **Counsel patient on monoclonal antibody treatment.**
- Patient must be provided with the 3-page **EUA Fact Sheet.**
  - EUA Fact Sheet for Casirivimab and Imdevimab (Regeneron)
  - EUA Fact Sheet for Bamlanivimab and Etesevimab (Eli Lilly)
  - EUA Fact Sheet for Sotrovimab (GSK)
- Find updated information on benefits and risks of treatment.

3 Where can my patient receive an infusion?

Options to find an infusion center with your patient:

- Choose an infusion center on the CDPHE website and complete the online form, or
- Check Colorado Infusion Center Map.

4 How can I arrange treatment?

The referral and ordering of monoclonal antibody treatment varies, depending on your clinic and/or health care system processes.

- If using the online CDPHE form to send a referral to the selected infusion center, you will give the patient the infusion center phone number to call and schedule a same- or next-day appointment.
- If using an infusion center associated with your organization, you may generate the referral and order within your EHR.
- Assist patient with transportation, if needed. Safest travel is having the person with COVID-19 sit as far from the driver as possible, mask on, windows open. Avoid public transportation if possible.

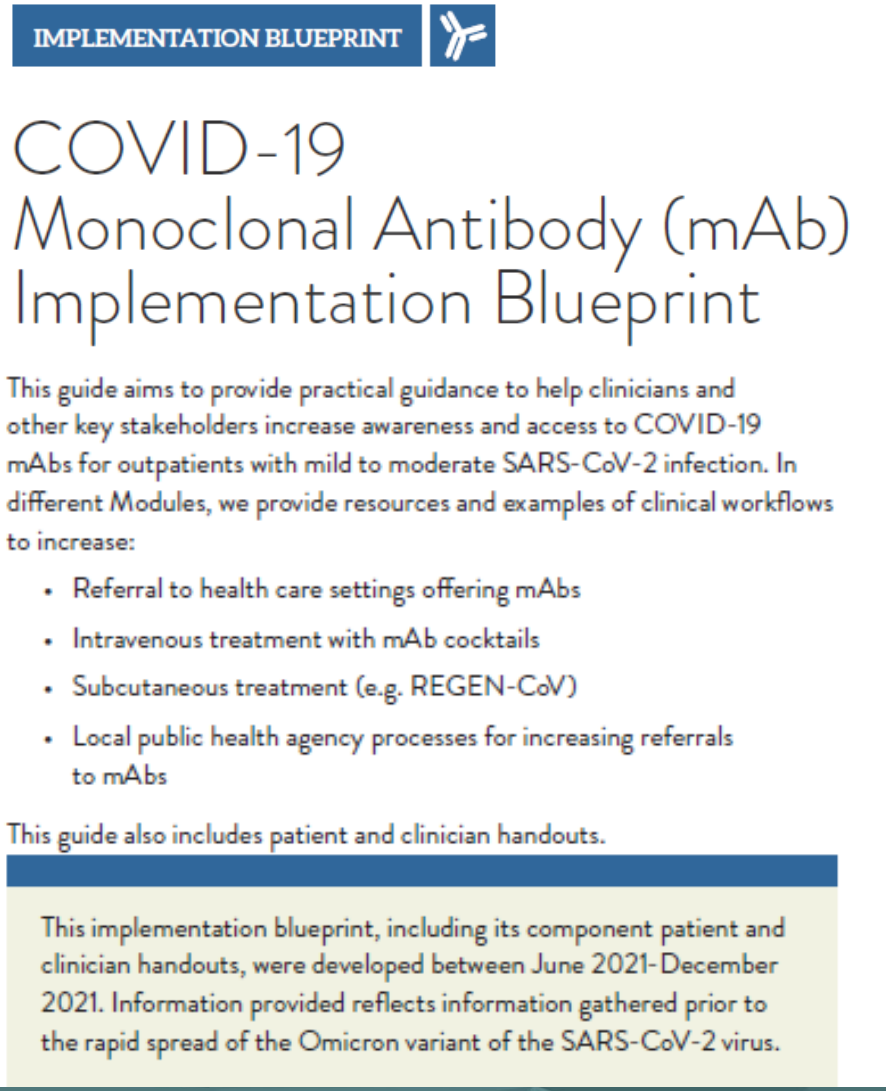
5 Is there cost for infusion?

- **There is no cost for the medication**; the federal government pays for the medication.
- The **infusion facility fee is covered by Medicare, Medicaid, and commercial insurance.** Patients may be billed co-pays and co-insurance. Self-pay patients may be charged a facility fee for the infusion.
- **If patient is self-pay, ask if the infusion center will charge the patient for infusion.** Patients without insurance who visit a federally-qualified health center for treatment, like Denver Health Pena Urgent Care, would likely receive no bill.

For more information or to find an infusion center near you:
Call 1-877-332-6585 (English) or **1-877-366-0310** (Spanish),
or visit **combatcovid.hhs.gov**.

mAb Colorado
medschool.cuanschutz.edu/mab-colorado

6/28/2021



IMPLEMENTATION BLUEPRINT

How to Use This Document

This implementation blueprint includes common resources and specific modules. Modules can be reviewed individually.

Modules:

- Referral to mAb Treatment Sites
- Intravenous Treatment
- Subcutaneous Treatment (only REGEN-CoV)
- Local Public Health Processes

Appendix:

Educational Resources
Sample Discharge Instructions
Sample Standing Orders

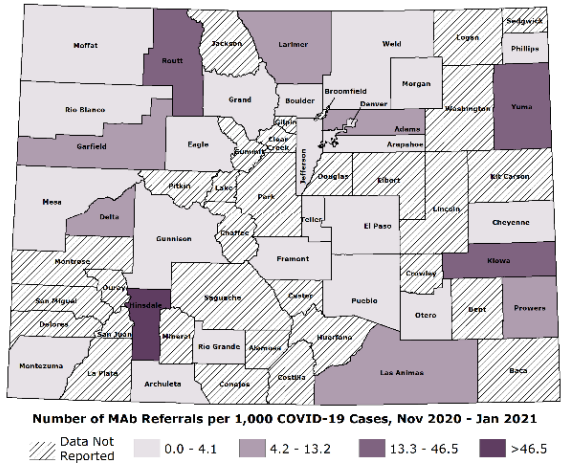
COVID-19 Monoclonal Antibody (mAb) Implementation Blueprint

This guide aims to provide practical guidance to help clinicians and other key stakeholders increase awareness and access to COVID-19 mAbs for outpatients with mild to moderate SARS-CoV-2 infection. In different Modules, we provide resources and examples of clinical workflows to increase:

- Referral to health care settings offering mAbs
- Intravenous treatment with mAb cocktails
- Subcutaneous treatment (e.g. REGEN-CoV)
- Local public health agency processes for increasing referrals to mAbs

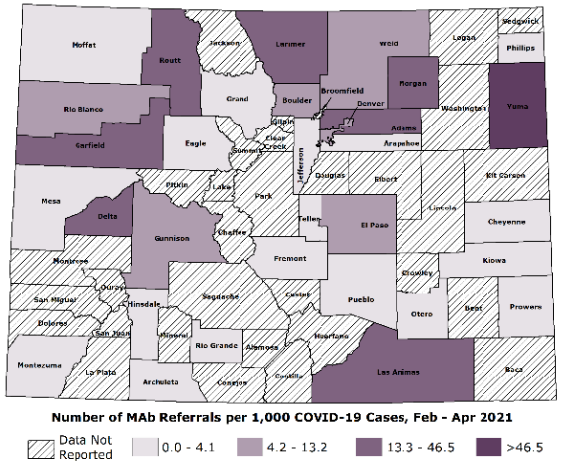
This guide also includes patient and clinician handouts.

This implementation blueprint, including its component patient and clinician handouts, were developed between June 2021-December 2021. Information provided reflects information gathered prior to the rapid spread of the Omicron variant of the SARS-CoV-2 virus.



Number of MAb Referrals per 1,000 COVID-19 Cases, Nov 2020 - Jan 2021

Data Not Reported | 0.0 - 4.1 | 4.2 - 13.2 | 13.3 - 46.5 | >46.5



Number of MAb Referrals per 1,000 COVID-19 Cases, Feb - Apr 2021

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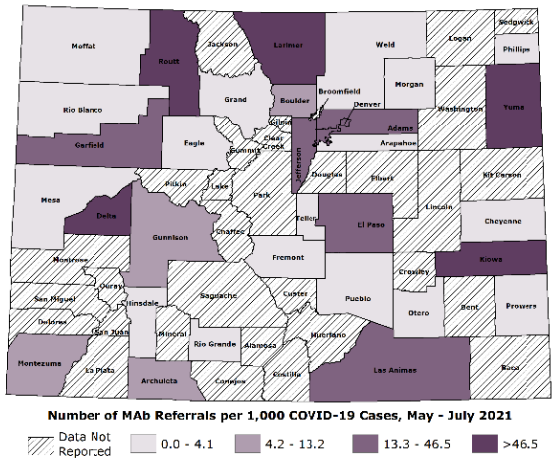

Number of MAb Referrals per 1,000 COVID-19 Cases, May - July 2021

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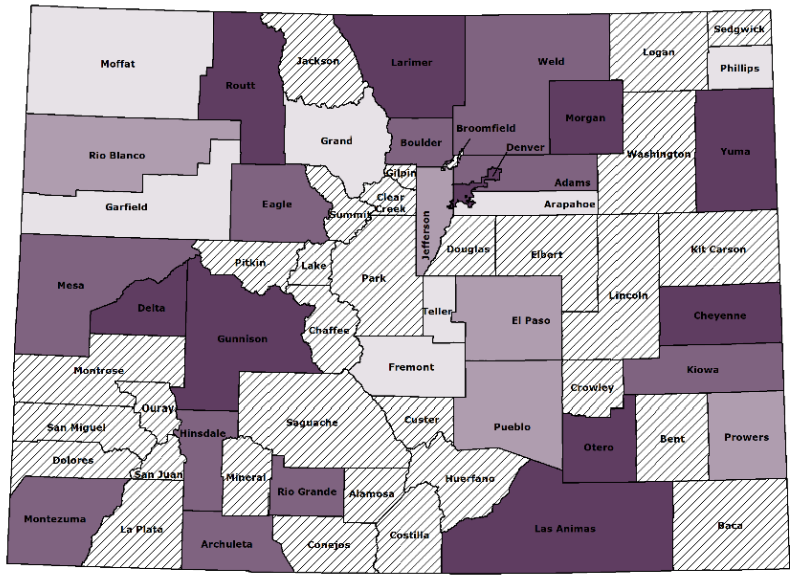
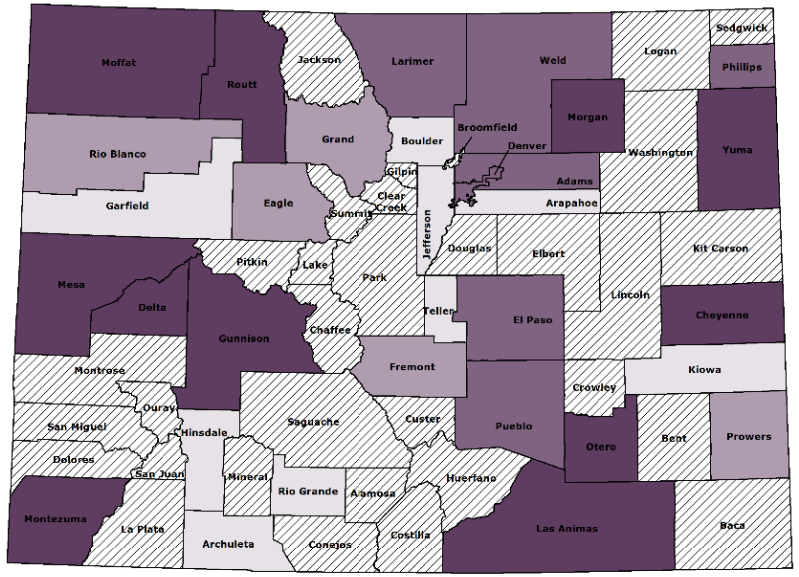
Pre (Top) vs Post (Bottom) mAb Colorado Dissemination



Number of MAb Referrals per 1,000 COVID-19 Cases, Aug - Oct 2021

Data Not Reported | 0.0 - 4.1 | 4.2 - 13.2 | 13.3 - 46.5 | >46.5



Number of MAb Referrals per 1,000 COVID-19 Cases, Nov - Dec 2021

Data Not Reported | 0.0 - 4.1 | 4.2 - 13.2 | 13.3 - 46.5 | >46.5

Average weekly mAb referral rates by Colorado county over time (November 2020-December 2021)

RWE Rationale

- **Problem:** How to apply knowledge about COVID-19 therapeutics from a prior era of the pandemic to current practice

- **Solution:** Develop scalable infrastructure for real-time, implementation and real-world effectiveness data for authorized outpatient antiviral treatments

- **Long-term goal:** Create a model for rapidly generating high quality real-world evidence in pandemics and other future public health emergencies

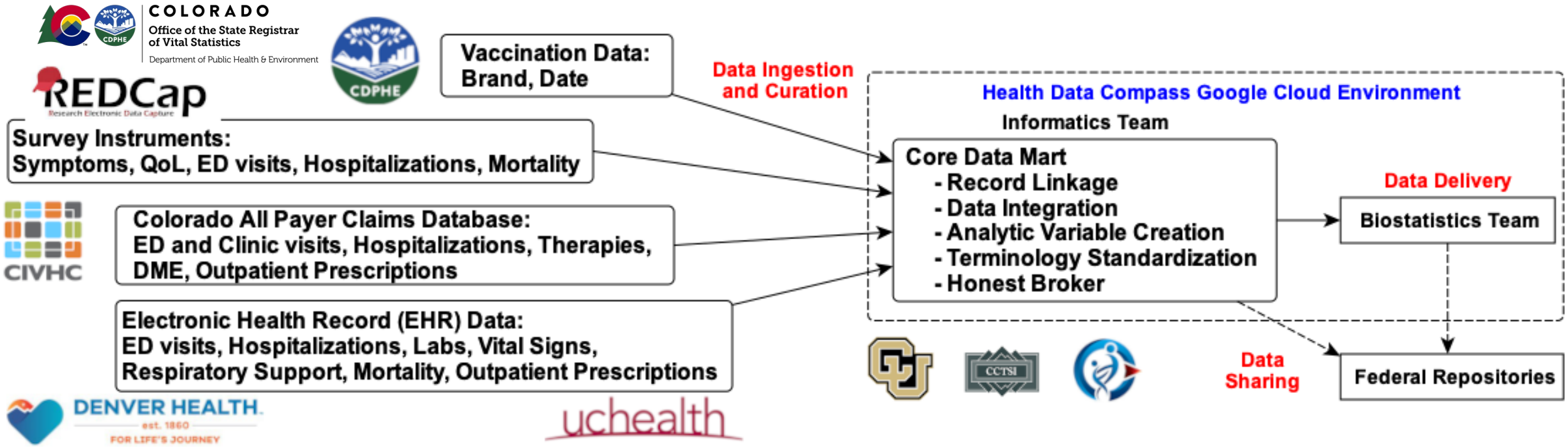
Knowledge Gaps in COVID-19 Therapeutics

- Ongoing real-time, real-world effectiveness data
  - New treatments with limited clinical trial data
  - Efficacy (early clinical trials) → Effectiveness (real-world evidence)
  - Changes in pandemic—new variants, treatments, vaccination
  - Effectiveness in key subgroups—age, comorbidities, vaccination status (prioritization decisions)
  - Outcomes beyond hospitalization and mortality
    - Time to resolution of symptoms
    - Long COVID

➢ **Inform regulatory, policy, and public health decisions**

➢ **FDA, BARDA, ASPR, White House, CDC, DoD, VA, NIH, WHO others**

Innovative Informatics Pipelines



Leveraging Existing CCTSI/NCATS and Local Technology and Team Investments

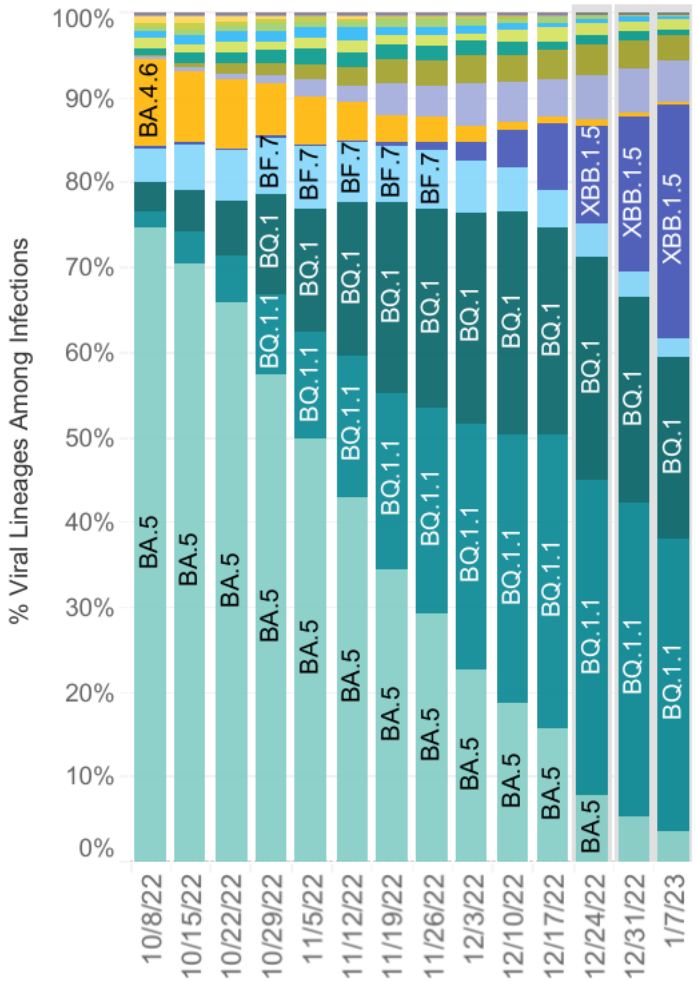
REDCap	Health Data Compass
Data transfer and versioning, data collection, access control and logging	Honest broker, Google Cloud tools, EUREKA compute environment

EHR RWE Platform: Brief Methods

Observational cohort—EHR data with statewide vaccine, variant, hospitalization, and mortality data

- Three health systems—regular, real-time data feeds
- Eligibility: Positive SARS-CoV-2 test prior to hospitalization (or treated with authorized antiviral)
- Propensity matching for control selection
  - Up to 2-3 untreated controls for every 1 mAb/antiviral-treated patient
  - Pre-treatment factors : age, sex, race/ethnicity, insurance status, obesity, immunocompromised, # other comorbid conditions, vax status, time
- Outcomes
  - Primary: 28-day hospitalization
  - Secondary: 90-day hospitalization, 28- and 90-day mortality, 28-day ED visits, severity of hospitalization

Clinical Challenges



- **Bebtelovimab** lossed antiviral activity: BQ.1, BQ.1.1, XBB
  - Not authorized by FDA
  - NIH panel recommends against use

- Preferred therapies
  - **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
  - **Remdesivir (BIIa)**
- Alternative therapy
  - **Molnupiravir (CIIa)**

  Only when preferred therapies not available, feasible, or clinically appropriate

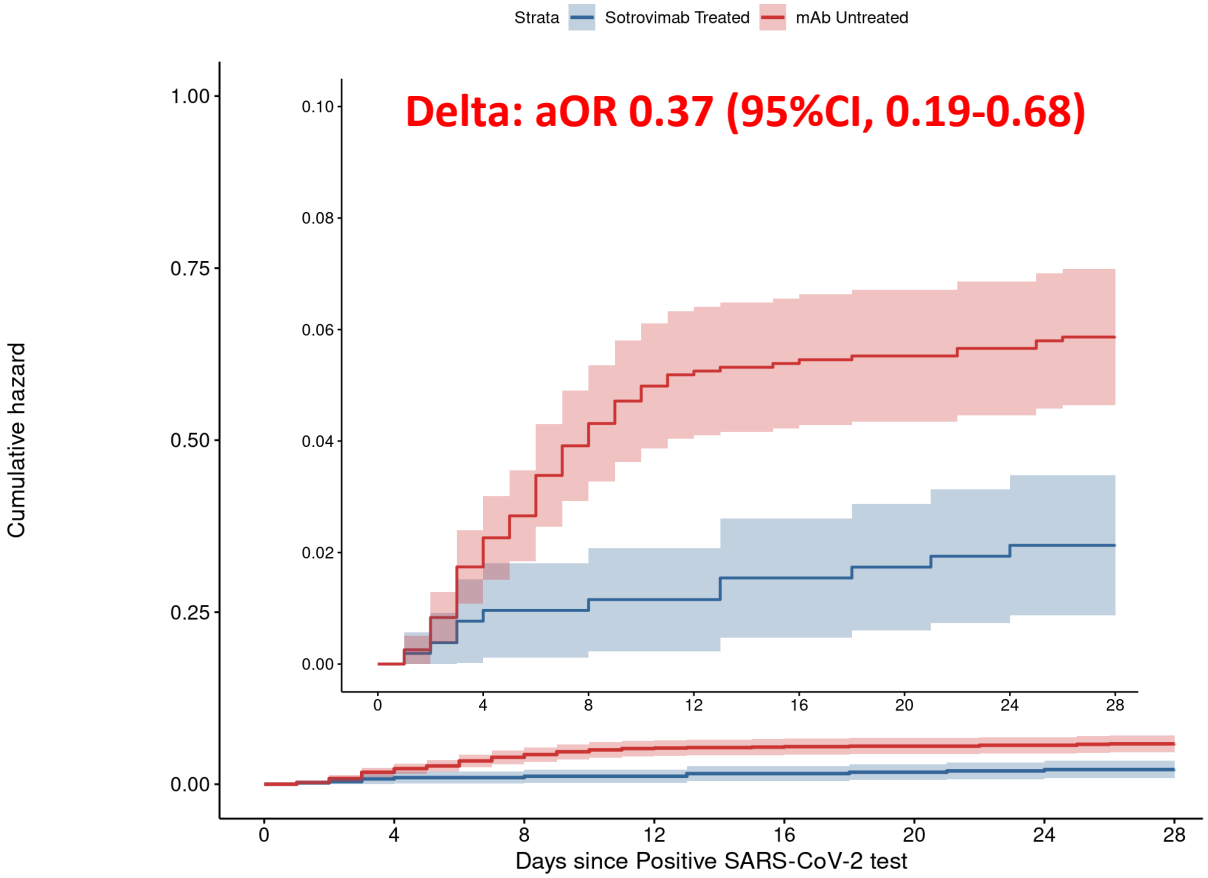
https://covid.cdc.gov/covid-data-tracker/#variant-proportions

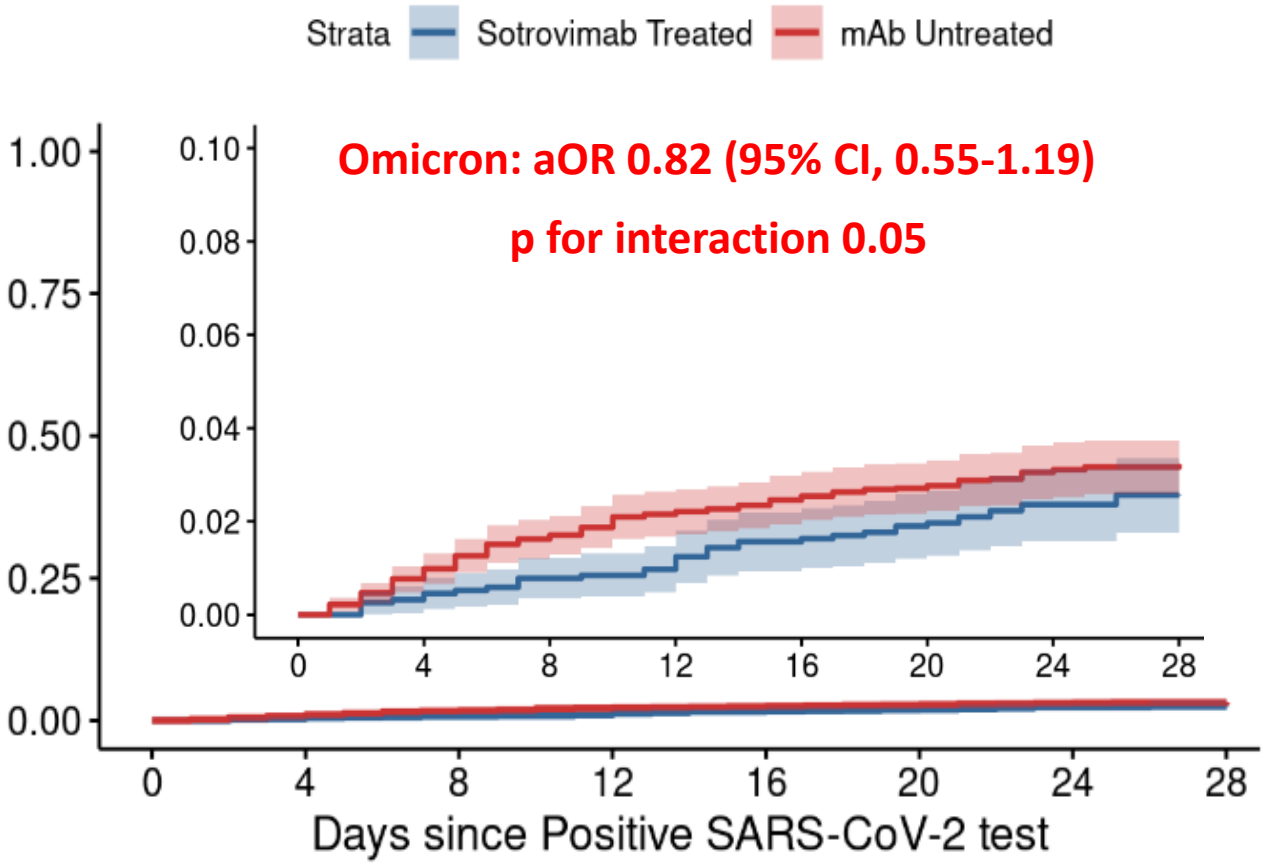
Example: Sotrovimab-Omicron RWE

Aggarwal NR et al, *Int J Infect Dis* 2022 (PMID: 36229005)

- **Rationale:** *In vitro* data suggest that sotrovimab was the only mAb that maintained antiviral activity (early 2022)
  - Sotrovimab IC50: Ancestral < BA.1 < BA.2
  - Other antivirals available
- **Cohort:** 12/26/21-03/10/22 for SARS-CoV-2+ collection date
  - >96% omicron variant (BA.1)
  - Prior to emergence of BA.2 (<2%)
  - Cas/imd and bam/ete use suspended 12/28/21 at UCHealth
- 1:2.4 propensity matching (full cohort: n=30,247)
  - n=5,205; 1,542 sotrovimab-treated, 3,663 controls (mAb-untreated)
- Primary endpoint: 28-day hospitalization

Cumulative Risk of Hospitalization





Sotrovimab: RWE Conclusions

- Sotrovimab effective in preventing hospitalization and death for delta
  - Similar effectiveness as cas/imd for delta
- Sotrovimab appears to lose effectiveness for omicron (BA.1)
- *In vitro* data for sotrovimab shows less potency against BA.2 than BA.1
  - Data supports U.S. FDA decision to pause distribution/use of sotrovimab (3/25/22)

Example: Symptom Recovery

(first author: Sarah Jolley, MD)

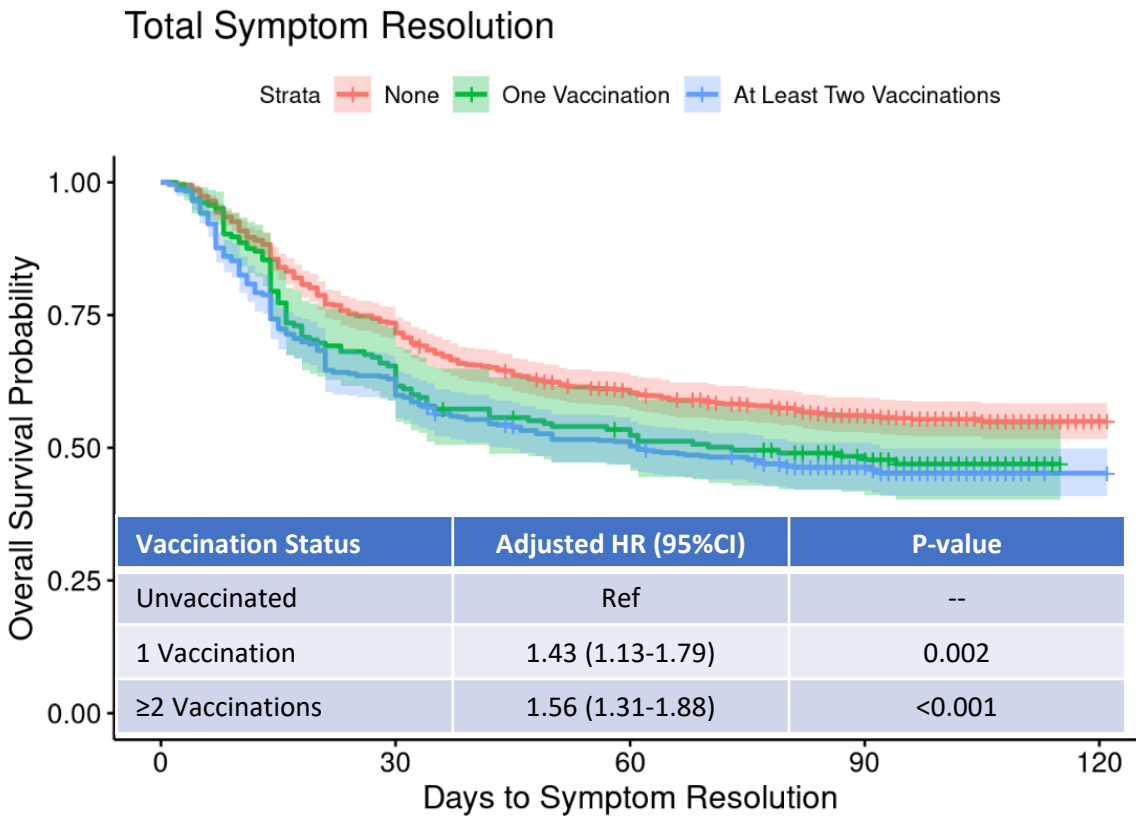
Survey data collection for **1,840 patients** (April 2021-January 2022)

- 569 received mAb treatment; 1,271 did not receive mAb treatment
- Longitudinal surveys through 3 months after COVID-19 onset
- Focus on secondary endpoints: acute and longer-term **symptom recovery**, quality of life, and patient experience

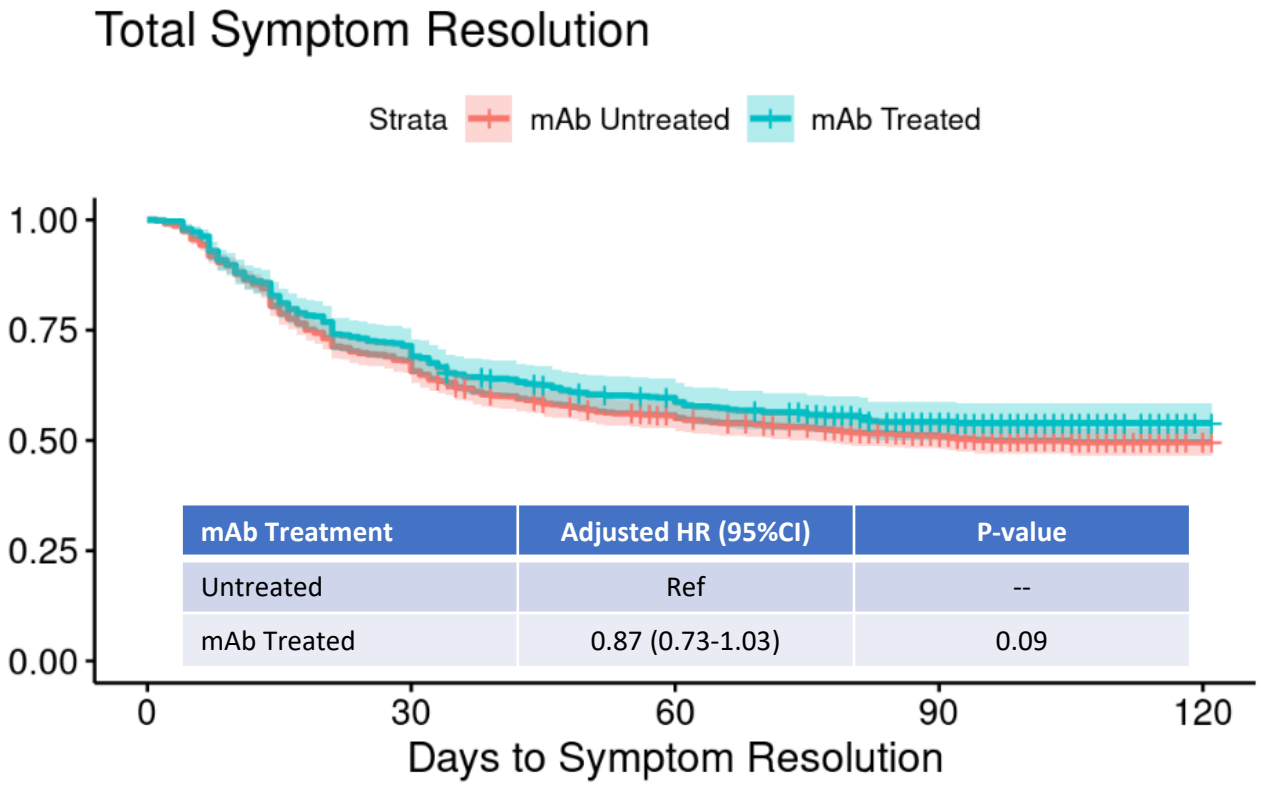
Table 4. Adjusted Odds Ratio for 28-day hospitalization

	Adjusted Models			
	OR	95% CI	p-value	LRT p-value
Treatment Status				
mAb Untreated	NA			NA
mAb Treated	0.31	(0.19, 0.50)	<0.001	
Vaccine Status				
No Vaccination	NA			<0.001
One Vaccination	0.42	(0.21, 0.79)	0.011	
At Least Two Vaccinations	0.33	(0.20, 0.55)	<0.001	

Symptom Recovery: Vaccination and mAbs



Vaccination Status	Adjusted HR (95%CI)	P-value
Unvaccinated	Ref	--
1 Vaccination	1.43 (1.13-1.79)	0.002
≥2 Vaccinations	1.56 (1.31-1.88)	<0.001



mAb Treatment	Adjusted HR (95%CI)	P-value
Untreated	Ref	--
mAb Treated	0.87 (0.73-1.03)	0.09

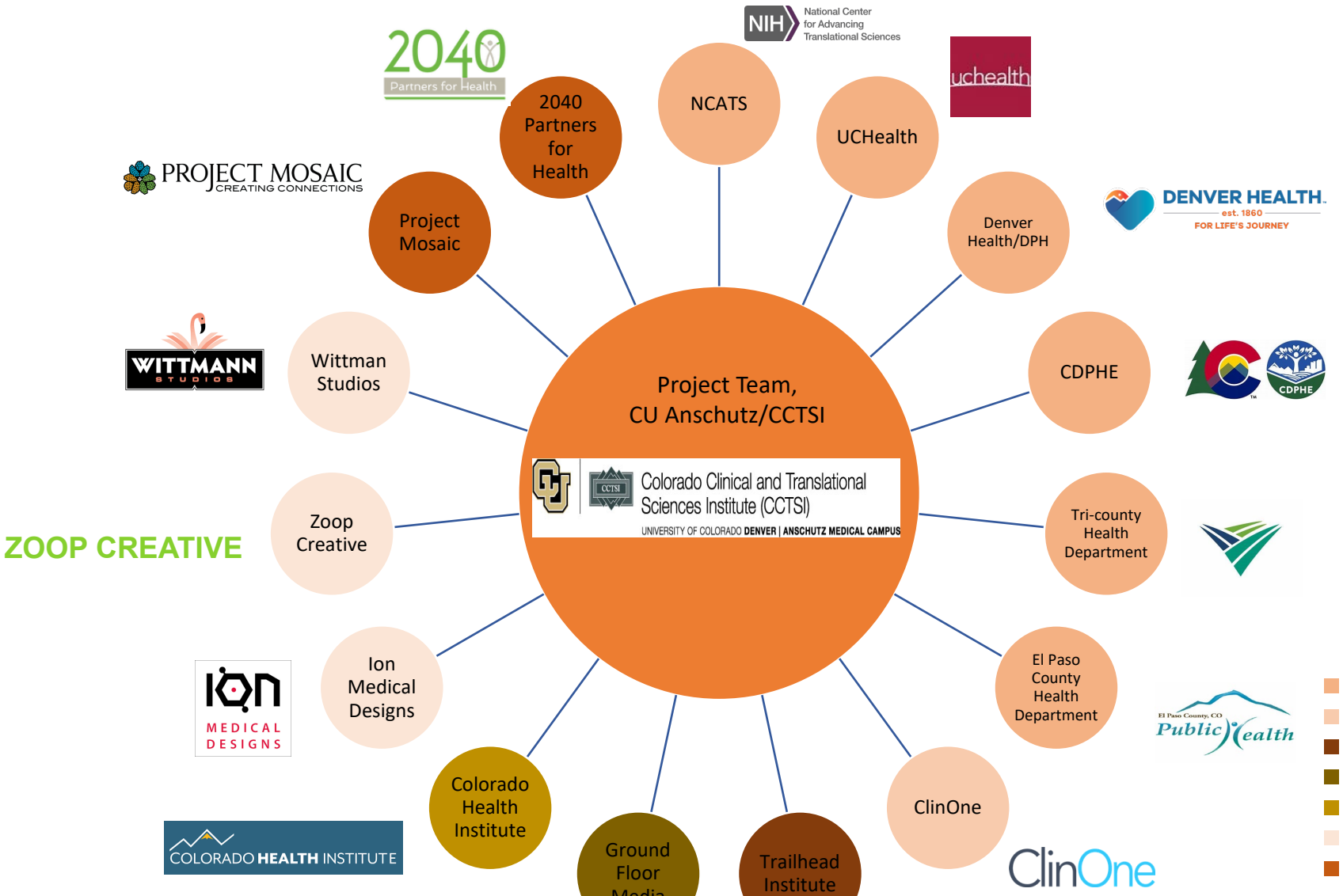
RWE Manuscripts (2022)

- Initial mAb effectiveness: CHEST published (Wynia, Beaty)
  - Dec 2021: FDA presentation; Jan 2022: Pre-print, SIG presentation; Oct 2022: publication
- Sotrovimab-delta: JID published (Aggarwal, Beaty)
- Treatment failure: BMC ID published (Douin, Wogu)
- Sotrovimab-omicron: IJID published (Aggarwal, Beaty)
- Paxlovid: pre-print 8/22. **Accepted** Lancet ID (Aggarwal/Molina, Beaty)
- Symptom resolution/PASC: **Submitted** JAMA IM (Jolley, Roberts)
- Bebtelovimab RWE: **Submitted** JID (Molina, Kennerly)
- Remdesivir RWE: manuscript drafting (Molina/Webb, Kennerly)
- Survey Equity/Experience data: analysis in progress (Fish, Roberts)
- Pregnancy: analysis in progress (Douin, Jackson)
- ED SC Regeneron: analysis in progress (Wendel, Wogu)
- Allocation: analysis in progress (TBD, Mengli)
- Vaccination after COVID (TBD, Roberts)
- Near horizon: defining hospitalizations *for* COVID; **long-term outcomes**; methods papers

Presentations (2022)

- USG COVID Therapeutics Leadership Group (SIG)
  - White House, BARDA, FDA, CDC, NIH, DoD, VA
  - Individual agency presentations
- WHO outpatient therapeutic steering committee
- VA RWD steering committee
- NCATS RWD symposium/unmeeting

mAb Colorado Partners



mAb Colorado team

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Informatics Lead

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