VA Cooperative Studies Program #2038

COVID-19 Pharmacotherapy Effectiveness in the VA Healthcare System (COPE-VA)

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September 21, 2023

U.S. Department of Veterans Affairs
Veterans Health Administration
Cooperative Studies Program

- I have no disclosures.

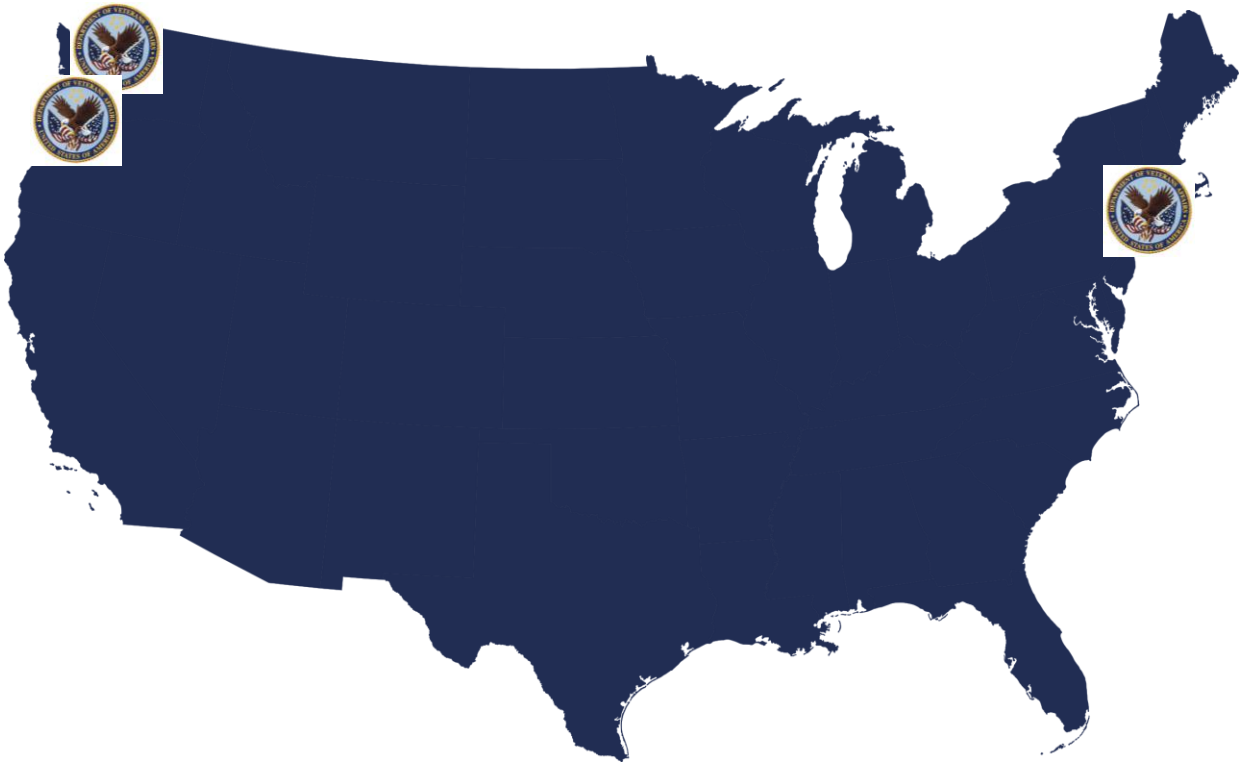
Objectives

- Understand how target trial emulation principles are applied to observational data to make causal inference about COVID-19 antiviral effectiveness.
- Recognize the benefits and limitations of currently recommended pharmacotherapies for treatment of mild-to-moderate COVID-19.
- Describe evidence from observational studies conducted within the Veterans Health Administration regarding the effectiveness of nirmatrelvir-ritonavir and molnupiravir in preventing short- and long-term COVID-19–related outcomes.

Outline

- COPE-VA platform
- Efficacy and limitations of outpatient COVID-19 antivirals
- Utilization in Veterans Health Administration (VHA)
- Motivation for real-world evidence and the role of target trial emulation methodology
- Effectiveness of nirmatrelvir-ritonavir and molnupiravir in COPE-VA studies
- Future directions

COPE-VA Background



BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY
BARDA

FDA U.S. FOOD & DRUG ADMINISTRATION

COPE-VA Background

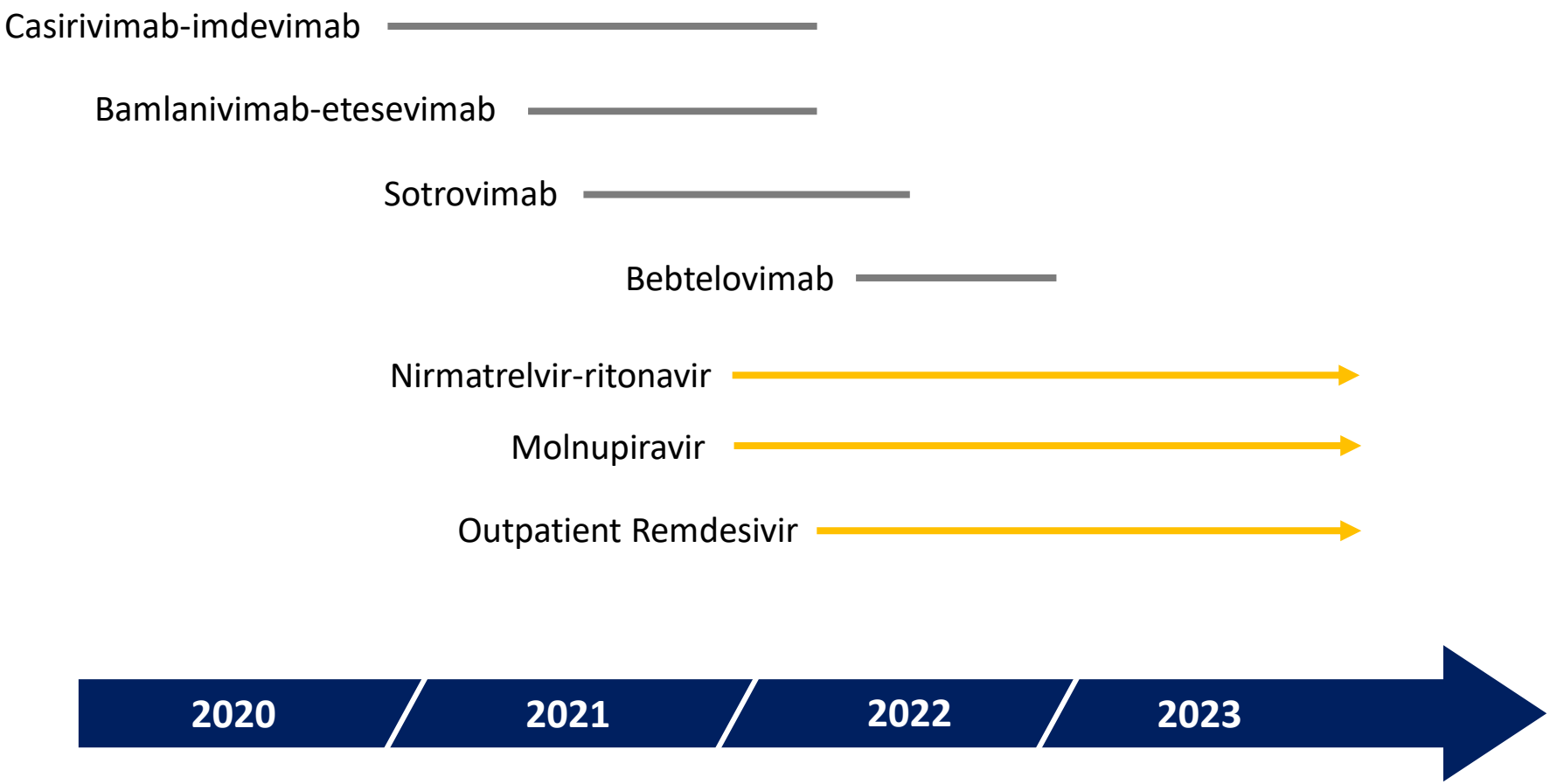
Aim 1: Build a platform for effectiveness and comparative effectiveness studies

- Describe trends and factors related to prescription of pharmacotherapies for treatment of mild to moderate COVID-19
- Inform clinical, operational, and research partners on strategies for optimizing use of COVID-19 pharmacotherapies
- Build common framework sharing similar population, design, and methodology

Aim 2: Determine effectiveness and comparative effectiveness of current and novel therapies

- Conduct observational studies emulating randomized trials of COVID-19 pharmacotherapies

EUA/Approval Timeline



NIH Recommendations for Outpatient COVID-19 Treatment

Preferred therapies. Listed in order of preference:

- Ritonavir-boosted nirmatrelvir (AIII)
- Remdesivir (BIIa)

Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:

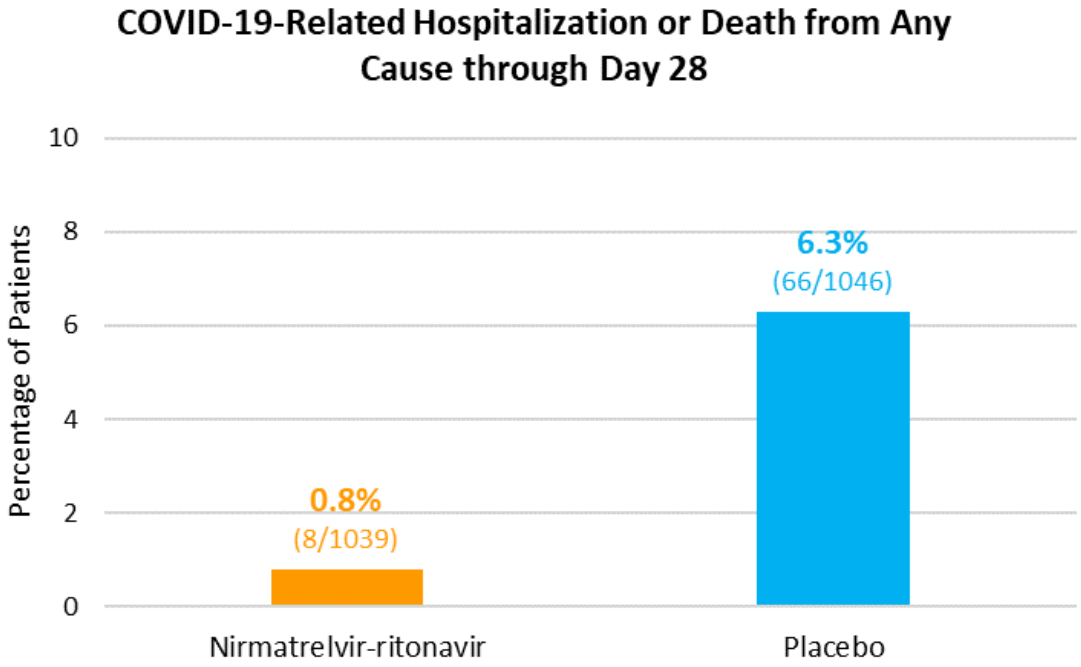
- Molnupiravir (CIIa)

NIH. COVID-19 Treatment Guidelines. Nonhospitalized Adults: Therapeutic Management | COVID-19 Treatment Guidelines (nih.gov)

Nirmatrelvir-ritonavir: EPIC-HR

- Study participants:
  - Unvaccinated
  - Non-hospitalized
  - ≥18 years
  - COVID-19 symptom onset within 5 days
  - ≥1 risk factor for severe disease
- Treatment: nirmatrelvir-ritonavir x5 days
- Endpoint: COVID-19–related hospitalization or death from any cause through day 28

Hammond J, et al. *N Engl J Med*. 2022. DOI: DOI: 10.1056/NEJMoa2118542.



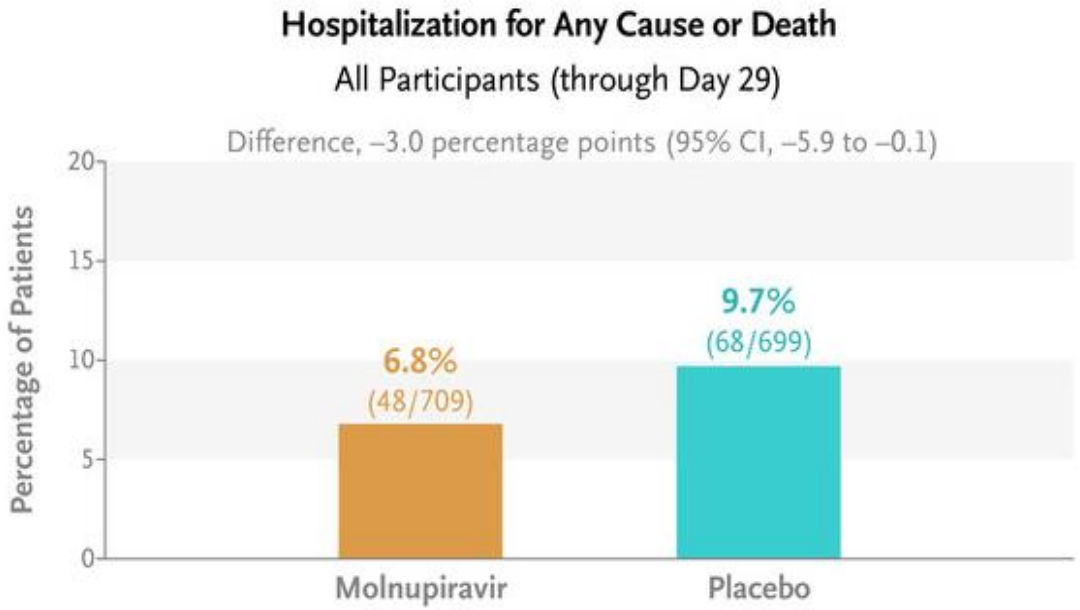
Risk difference **-5.6 percentage points** (95% CI, -7.2 to -4.0)

Hammond J, et al. *N Engl J Med*. 2022. DOI: DOI: 10.1056/NEJMoa2118542.

Molnupiravir: MOVe-OUT

- Study participants:
  - Unvaccinated
  - Non-hospitalized
  - ≥18 years
  - COVID-19 symptom onset within 5 days
  - ≥1 risk factor for severe disease
- Treatment: molnupiravir x5 days
- Endpoint: all-cause hospitalization or death through day 29

Bernal AJ, et al. *N Engl J Med*. 2022. DOI: 10.1056/NEJMoa2116044.



Risk difference **-3.0 percentage points** (95% CI, -5.9 to -0.1)

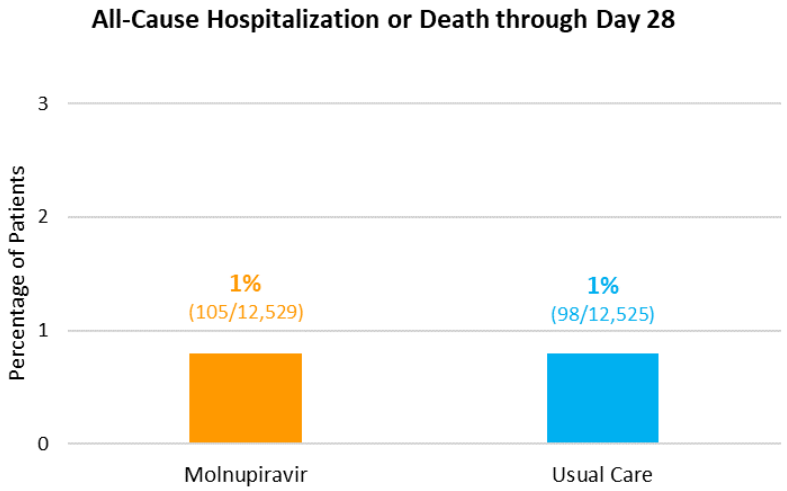
Bernal AJ, et al. *N Engl J Med*. 2022. DOI: 10.1056/NEJMoa2116044.

Molnupiravir: PANORAMIC

- Study participants:
  - Mostly vaccinated
  - Non-hospitalized
  - ≥50 years or ≥18 years with comorbidities
  - COVID-19 symptom onset within 5 days
- Treatment: molnupiravir x5 days
- Endpoint: all-cause hospitalization or death through day 28

Butler CC, et al. *Lancet*. 2022. DOI: https://doi.org/10.1016/S0140-6736(22)02597-1.

- No benefit for hospitalization or death



aOR 1.06 (95% CI, 0.81-1.41)

- Reduced time to self-reported recovery (9 versus 15 days)
- Reduced viral load

Butler CC, et al. *Lancet*. 2022. DOI: https://doi.org/10.1016/S0140-6736(22)02597-1.

Nirmatrelvir-ritonavir Adverse Effects

This Candy Is the Only Thing That Helped My Terrible "Paxlovid Mouth"

The antiviral treatment for COVID left a monstrous taste in my mouth. Cinnamon candies were my savior.

BY EMILY FARRIS

June 24, 2022

[This Candy Is the Only Thing That Helped My Terrible "Paxlovid Mouth" | Bon Appétit (bonappetit.com)]

Nirmatrelvir-ritonavir Contraindications

- Not recommended in patients with eGFR < 30 mL/min or severe hepatic impairment (Child-Pugh Class C)
- Many drug-drug interactions (ritonavir = potent CYP3A inhibition)
  - 37 contraindicated
  - 21 avoid concomitant use
  - 49 dose adjustment recommended
  - 6 therapeutic monitoring (e.g., warfarin, tacrolimus)

FDA. New Drug Application (NDA) 21788. March 16, 2023 Meeting of the Antimicrobial Drugs Advisory Committee Meeting (fda.gov)

Nirmatrelvir-ritonavir Drug-Drug Interactions

- Apixaban (atrial fibrillation)
- Metoprolol succinate
- Pantoprazole
- Sertraline
- Sildenafil (erectile dysfunction)
- Simvastatin
- Tamsulosin

Nirmatrelvir-ritonavir Drug-Drug Interactions

- Apixaban → decrease dose
- Metoprolol succinate
- Pantoprazole
- Sertraline
- Sildenafil → hold during treatment*
- Simvastatin → hold 12 hours before to 5 days after
- Tamsulosin → decrease dose

NIH. Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications. Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines (nih.gov)

University of Liverpool. COVID019 Drug Interactions. Liverpool COVID-19 Interactions (covid19-druginteractions.org)

Molnupiravir Adverse Effects

Not recommended during pregnancy or breastfeeding

SCIENCEINSIDER | HEALTH

A prominent virologist warns COVID-19 pill could unleash dangerous mutants. Others see little cause for alarm

Merck & Co.'s newly approved oral drug works by generating mutations, raising hypothetical fears

7 NOV 2021 · 12:35 PM · BY ROBERT F. SERVICE

VA Research Communications 2019. Photo: © iStock/NanoStockk, imaginima

VHA and Drug Distribution

- VHA serves more than 9 million enrolled Veterans each year at 171 medical centers and 1,113 outpatient sites of care
- COVID-19 pharmacotherapies under EUA are traditionally allocated across VHA pharmacies through a national distribution system coordinated by the Pharmacy Benefits Management Services (PBM)
- PBM also conducts surveillance to ensure prescription among eligible Veterans

Integrate Multiple Data Sources

- VA Corporate Data Warehouse
- Centers for Medicare and Medicaid Services
- VA Community Care program

SARS-CoV-2 Tests

- Laboratory-confirmed (nucleic acid amplification or antigen)
- Performed within VHA as well as outside VHA and documented in VHA clinical records
- First positive test results

JAMA Network Open

Original Investigation | Public Health

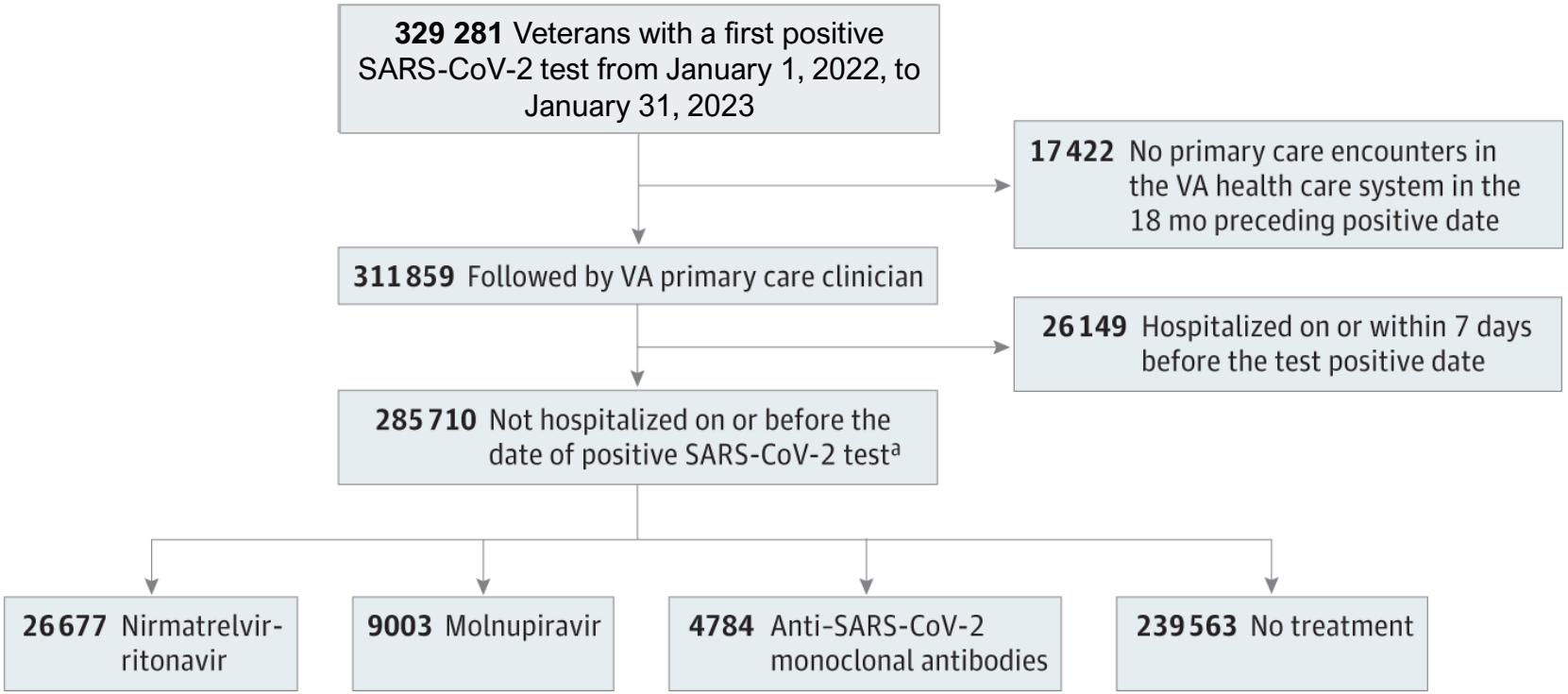
Early Adoption of Anti–SARS-CoV-2 Pharmacotherapies Among US Veterans With Mild to Moderate COVID-19, January and February 2022

Kristina L. Bajema, MD, MSc; Xiao Qing Wang, MPH; Denise M. Hynes, MPH, PhD, RN; Mazhgan Rowneki, MPH; Alex Hickok, MS; Francesca Cunningham, PharmD; Amy Bohnert, PhD, MHS; Edward J. Boyko, MD, MPH; Theodore J. Iwashyna, MD, PhD; Matthew L. Maciejewski, PhD; Elizabeth M. Viglianti, MD, MPH, MSc; Elani Streja, PhD; Lei Yan, PhD; Mihaela Aslan, PhD; Grant D. Huang, MPH, PhD; George N. Ioannou, BMBCh, MS

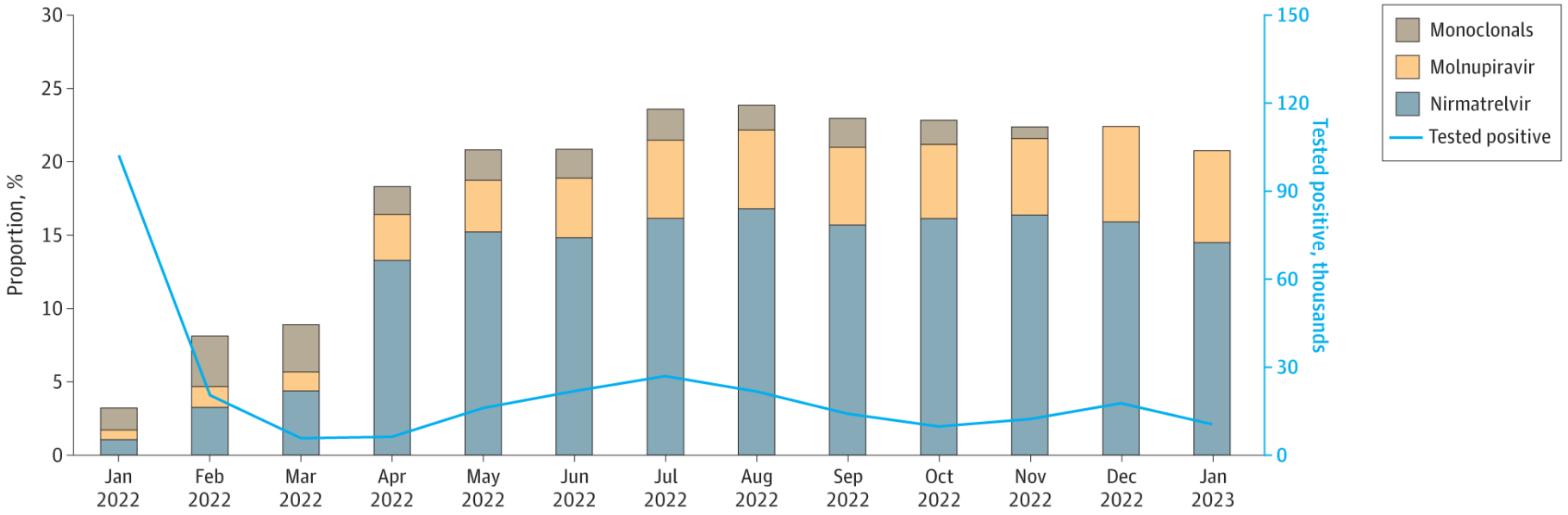
Original Investigation | Infectious Diseases

Anti–SARS-CoV-2 Pharmacotherapies Among Nonhospitalized US Veterans, January 2022 to January 2023

Lei Yan, PhD; Elani Streja, PhD; Yuli Li, MS; Nallakkandi Rajeevan, PhD; Mazhgan Rowneki, MPH; Kristin Berry, PhD; Denise M. Hynes, MPH, PhD, RN; Francesca Cunningham, PharmD; Grant D. Huang, MPH, PhD; Mihaela Aslan, PhD; George N. Ioannou, BMBCh, MS; Kristina L. Bajema, MD, MSc



Yan L, et al. *JAMA Network Open* 2023. DOI: 10.1001/jamanetworkopen.2023.31249



Yan L, et al. *JAMA Network Open* 2023. DOI: 10.1001/jamanetworkopen.2023.31249

- Regional differences by Veterans Integrated Services Network (VISN) in the relative use of different pharmacotherapies
- Older Veterans with a higher burden of underlying conditions as well as persons of Black race and Hispanic ethnicity were more likely to receive treatment
- Unvaccinated, rural were less likely to receive treatment

Yan L, et al. *JAMA Network Open* 2023. DOI: 10.1001/jamanetworkopen.2023.31249

Motivation for Real-World Evidence of COVID-19 Pharmacotherapy Effectiveness

- Clinical trials were conducted primarily among unvaccinated subjects
- Most trials were conducted before the Omicron variant emergence
- Trials were conducted among persons with a first episode of COVID-19
- Clinical trials did not directly compare different pharmacotherapies
- Impact on post-acute sequelae of COVID-19 was not examined

Target Trial Emulation

- Not always able to conduct a randomized trial to answer the causal question of interest
- To effectively use real-world data for causal inference, a study should be carefully designed to emulate a hypothetical randomized trial
- Apply design principles from randomized trials:
  - Eligibility
  - Treatment strategy and assignment
  - Follow-up
  - Outcomes
  - Causal contrast
  - Analysis plan

Labrecque and Swanson. Eur J Epidemiol 2017. DOI: 10.1007/s10654-017-0293-4
Hernán MA and JM Robins. *Am J Epidemiol* 2016. DOI: 10.1093/aje/kwv254

Target Trial Emulation Framework: Eligibility

Target Trial Specification	Target Trial Emulation
• First positive SARS-CoV-2 test between January 1 and July 31, 2022 • Enrolled adult Veterans with VHA primary care visit in the last 18 months • Alive and not hospitalized through the day following the positive test and no hospitalization on or before the day of randomized assignment to treatment or no treatment • No prior COVID-19 treatment • ≥1 risk factor for progression to severe COVID-19 • No contraindications to medication use • Symptomatic infection	• Same • Not included

Target Trial Framework: Treatment Strategy

Target Trial Specification	Target Trial Emulation
• Randomized to treatment with nirmatrelvir-ritonavir or no treatment within 5 days of symptom onset	• Used treatment within 5 days of the test-positive date rather than within 5 days of symptom onset

Target Trial Framework: Treatment Outcomes

Target Trial Specification	Target Trial Emulation
Primary • Any hospitalization or death through day 30 • Any hospitalization or death from days 31-180 Secondary • ICU admission through day 30 • Mechanical ventilation through day 30	• Same

Target Trial Framework: Follow-up

Target Trial Specification	Target Trial Emulation
• For each person, follow-up started on the day of randomization to nirmatrelvir-ritonavir or no treatment and continued until day 180 after treatment	• Same • For untreated patients, an index was assigned which was the same interval (paired) from the date of testing positive as the treated match (treatment interval)

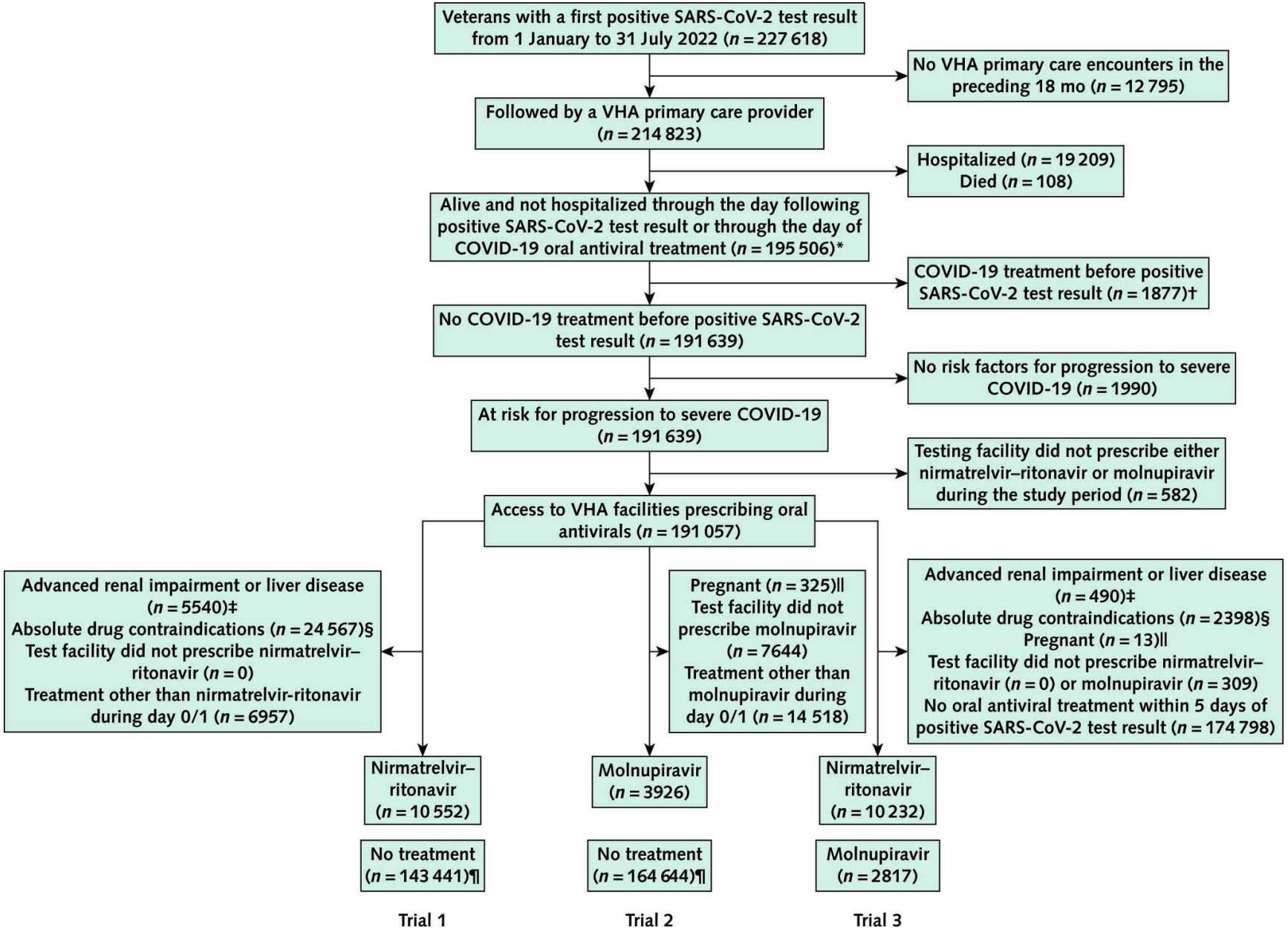
Target Trial Framework: Causal Contrasts

Target Trial Specification	Target Trial Emulation
• Intention-to-treat effect	• Same

Emulated Three Trials

- Retrospective cohort study to emulate 3 target trials of COVID-19 antivirals among symptomatic, non-hospitalized adult
  - Trial 1: nirmatrelvir-ritonavir vs no treatment
  - Trial 2: molnupiravir vs no treatment
  - Trial 3: nirmatrelvir-ritonavir vs molnupiravir

Bajema KL, et al. *Ann Intern Med.* 2023. DOI: 10.7326/M22-3565


Veterans with a first positive SARS-CoV-2 test result from 1 January to 31 July 2022 (n = 227 618)
No VHA primary care encounters in the preceding 18 mo (n = 12 795)
Followed by a VHA primary care provider (n = 214 823)
Hospitalized (n = 19 209)
Died (n = 108)
Alive and not hospitalized through the day following positive SARS-CoV-2 test result or through the day of COVID-19 oral antiviral treatment (n = 195 506)*
COVID-19 treatment before positive SARS-CoV-2 test result (n = 1877)†
No COVID-19 treatment before positive SARS-CoV-2 test result (n = 191 639)
No risk factors for progression to severe COVID-19 (n = 1990)
At risk for progression to severe COVID-19 (n = 191 639)
Testing facility did not prescribe either nirmatrelvir–ritonavir or molnupiravir during the study period (n = 582)
Access to VHA facilities prescribing oral antivirals (n = 191 057)
Advanced renal impairment or liver disease (n = 5540)‡
Absolute drug contraindications (n = 24 567)§
Test facility did not prescribe nirmatrelvir–ritonavir (n = 0)
Treatment other than nirmatrelvir-ritonavir during day 0/1 (n = 6957)
Pregnant (n = 325)‖
Test facility did not prescribe molnupiravir (n = 7644)
Treatment other than molnupiravir during day 0/1 (n = 14 518)
Advanced renal impairment or liver disease (n = 490)‡
Absolute drug contraindications (n = 2398)§
Pregnant (n = 13)‖
Test facility did not prescribe nirmatrelvir–ritonavir (n = 0) or molnupiravir (n = 309)
No oral antiviral treatment within 5 days of positive SARS-CoV-2 test result (n = 174 798)
Nirmatrelvir–ritonavir (n = 10 552)
Molnupiravir (n = 3926)
Nirmatrelvir–ritonavir (n = 10 232)
No treatment (n = 143 441)¶
No treatment (n = 164 644)¶
Molnupiravir (n = 2817)
Trial 1
Trial 2
Trial 3

Matching in nested sequential trials

Within each nested trial day, matching occurs among eligible, alive, not hospitalized

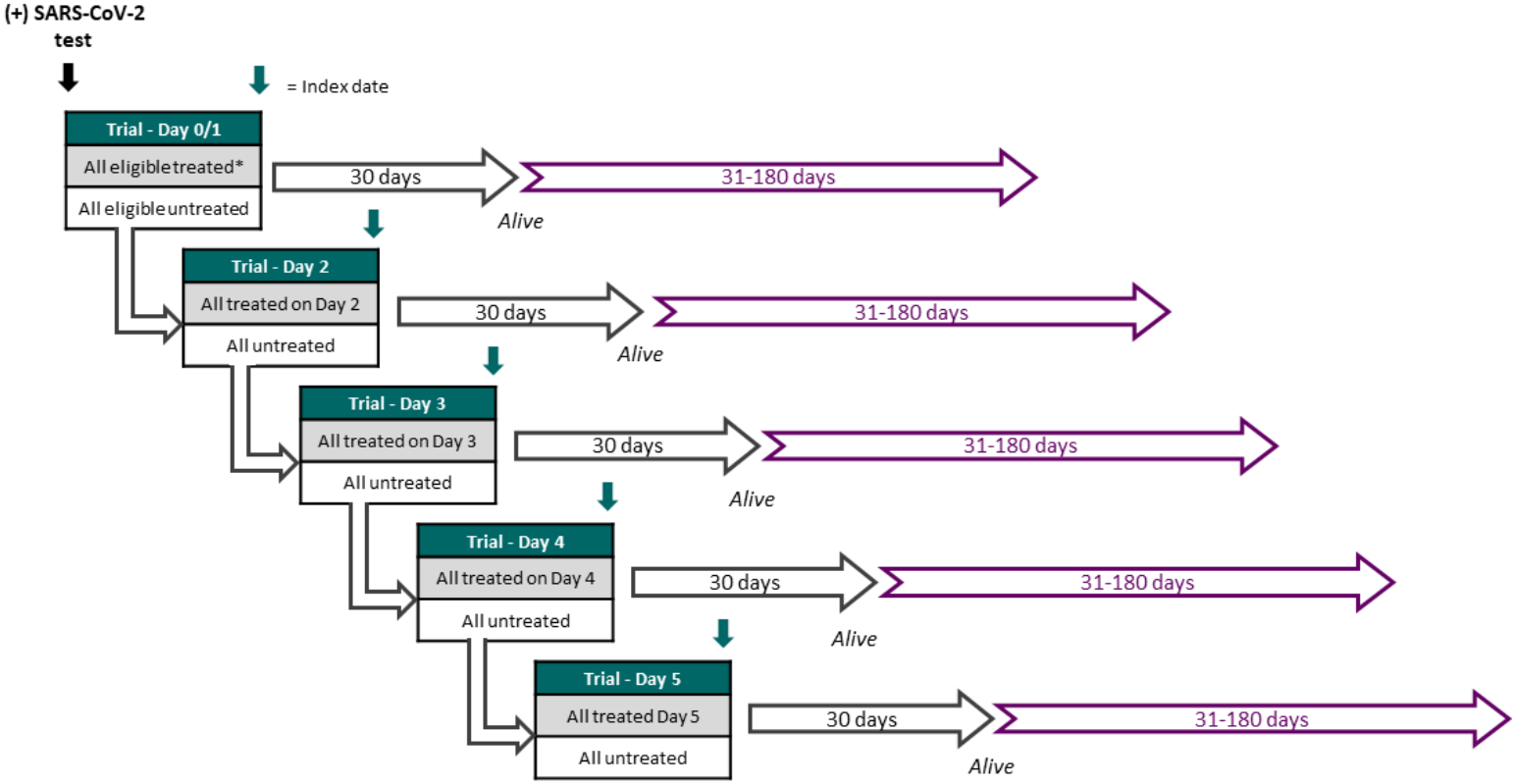
Up to 1:4 ratio

+

Exact-matching
NIH tier
VISN
Facility complexity
±7 days of positive test

+

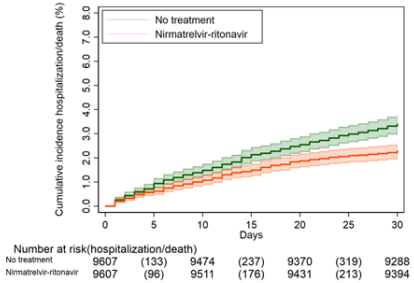
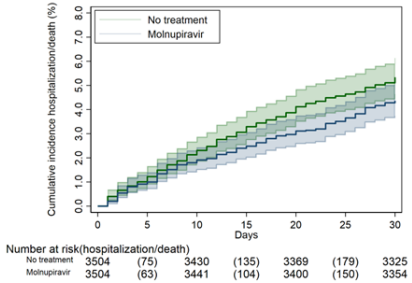
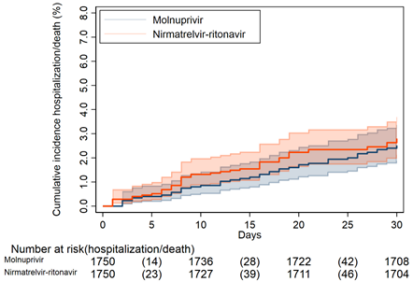
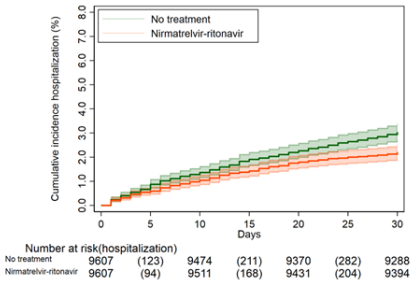
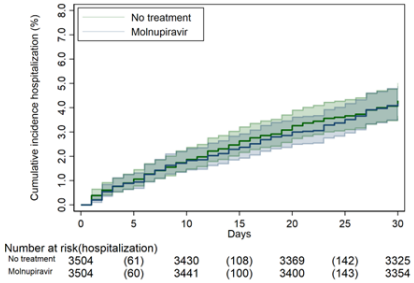
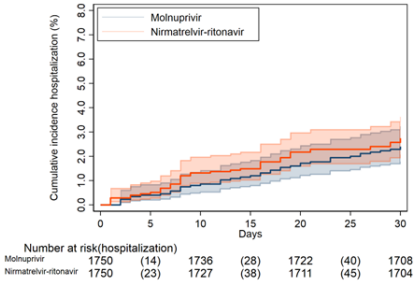
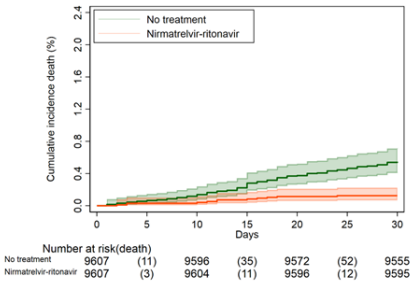
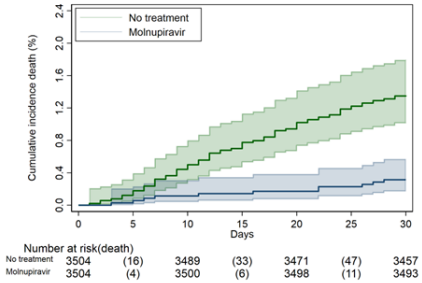
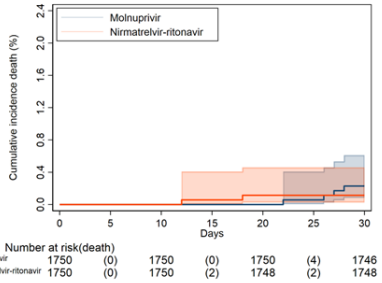
Propensity-score matching
24 demographic, geographic, and clinical variables



Matched Patient Population Across 3 Trials

- 86-91% male
- Median ages 66-70 years
- 7-9% Hispanic, 15-19% Black, 63-69% White
- Median 4-5 medical conditions
- 11-18% not vaccinated
- >90% treated within 0/1 day of positive test

30-day Hospitalization or Death

	Trial 1: Nirmatrelvir-ritonavir vs. no treatment	Trial 2: Molnupiravir vs. no treatment	Trial 3: Nirmatrelvir-ritonavir vs. molnupiravir
Hospitalization or death			
Hospitalization			
Death			

Trial 1: 30-day Outcomes

	Incidence (95% CI), events per 1000 persons			
	Nirmatrelvir-ritonavir	**No Treatment**	**Risk Difference (95% CI)**	**Risk Ratio (95% CI)**
Hospitalization or death	23.00 (20.19 to 26.20)	34.17 (31.42 to 37.15)	-11.16 (-15.30 to -7.03)	0.67 (0.58 to 0.79)
Hospitalization	22.07 (19.31 to 25.20)	30.32 (27.68 to 33.20)	-8.25 (-12.27 to -4.23	0.73 (0.62 to 0.85)
Death	1.25 (0.71 to 2.20)	5.47 (4.55 to 6.58)	-4.22 (-5.45 to -3.00)	0.23 (0.13 to 0.41)
ICU admission	2.50 (1.67 to 3.72)	4.90 (3.85 to 6.24)	-2.40 (-3.95 to -0.85)	0.51 (0.32 to 0.81)
Mechanical ventilation	0.83 (0.42 to 1.66)	3.02 (2.26 to 4.03)	-2.19 (-3.23 to -1.14)	0.28 (0.13 to 0.58)

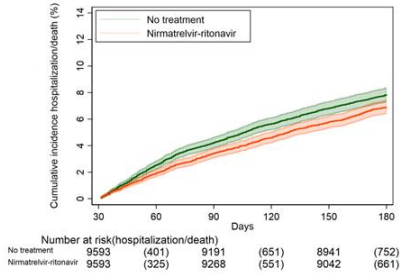
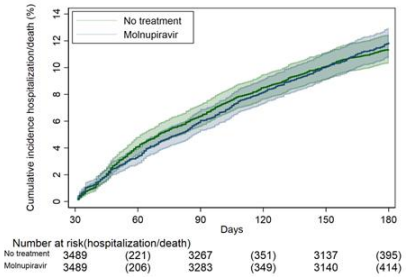
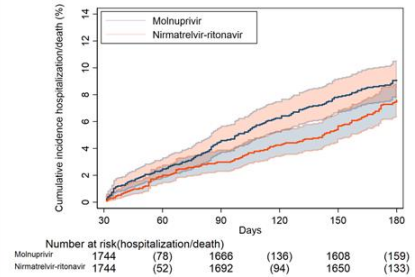
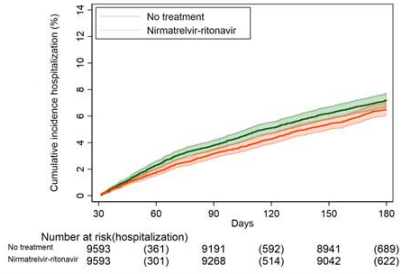
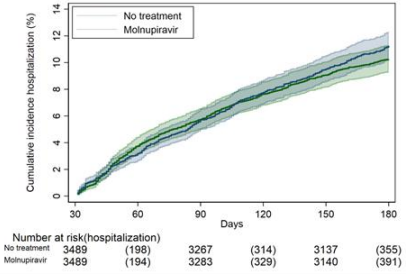
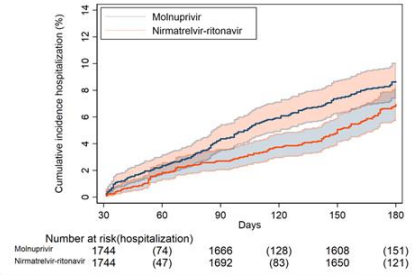
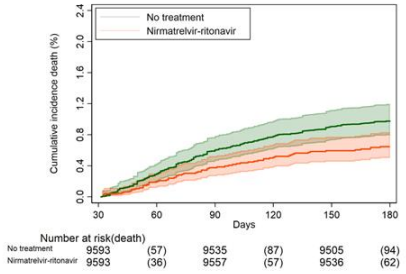
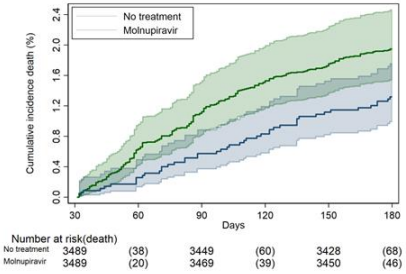
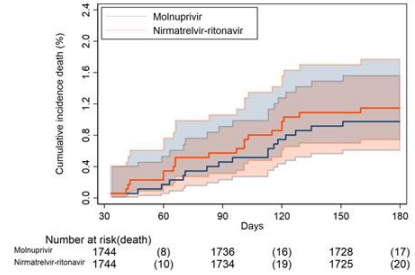
Trial 1: 30-day Outcomes

	Incidence (95% CI), events per 1000 persons			
	Nirmatrelvir-ritonavir	**No Treatment**	**Risk Difference (95% CI)**	**Risk Ratio (95% CI)**
Hospitalization or death	23.00 (20.19 to 26.20)	34.17 (31.42 to 37.15)	-11.16 (-15.30 to -7.03)	0.67 (0.58 to 0.79)
Hospitalization	22.07 (19.31 to 25.20)	30.32 (27.68 to 33.20)	-8.25 (-12.27 to -4.23	0.73 (0.62 to 0.85)
Death	1.25 (0.71 to 2.20)	5.47 (4.55 to 6.58)	-4.22 (-5.45 to -3.00)	0.23 (0.13 to 0.41)
ICU admission	2.50 (1.67 to 3.72)	4.90 (3.85 to 6.24)	-2.40 (-3.95 to -0.85)	0.51 (0.32 to 0.81)
Mechanical ventilation	0.83 (0.42 to 1.66)	3.02 (2.26 to 4.03)	-2.19 (-3.23 to -1.14)	0.28 (0.13 to 0.58)

Trial 2: 30-day Outcomes

	Incidence (95% CI), events per 1000 persons			
	Molnupiravir	**No Treatment**	**Risk Difference (95% CI)**	**Risk Ratio (95% CI)**
Hospitalization or death	43.66 (37.37 to 50.96)	53.37 (48.40 to 58.81)	-9.70 (-18.04 to -1.37)	0.82 (0.68 to 0.98)
Hospitalization	41.67 (35.53 to 48.81)	42.67 (38.13 to 47.71)	-1.00 (-9.05 to 7.05)	0.98 (0.81 to 1.18)
Death	3.14 (1.74 to 5.66)	13.56 (11.31 to 16.24)	-10.42 (-13.49 to -7.35)	0.23 (0.13 to 0.43)
ICU admission	7.71 (5.29 to 11.21)	7.30 (5.52 to 9.66)	0.40 (-3.10 to 3.91)	1.06 (0.66 to 1.68)
Mechanical ventilation	3.14 (1.74 to 5.66)	3.38 (2.43 to 4.70)	-0.24 (-2.40 to 1.93)	0.93 (0.47 to 1.83)

31-180-day Hospitalization or Death

	Trial 1: Nirmatrelvir-ritonavir vs. no treatment	Trial 2: Molnupiravir vs. no treatment	Trial 3: Nirmatrelvir-ritonavir vs. molnupiravir
Hospitalization or death			
Hospitalization			
Death			

Trial 1: 31-180-day Outcomes

	Incidence, events per 1000 persons		
	Nirmatrelvir-ritonavir	**No Treatment**	**Hazard Ratio or Subhazard Ratio[1] (95% CI)**
Hospitalization or death	59.32	67.99	0.87 (0.79 to 0.96)
Hospitalization	55.82	62.26	0.90 (0.79 to 1.02)
Death	5.40	8.22	0.66 (0.49 to 0.89)

[1]Derived from proportional hazards regression that accounted for the competing risk for death, presented for hospitalization outcomes.

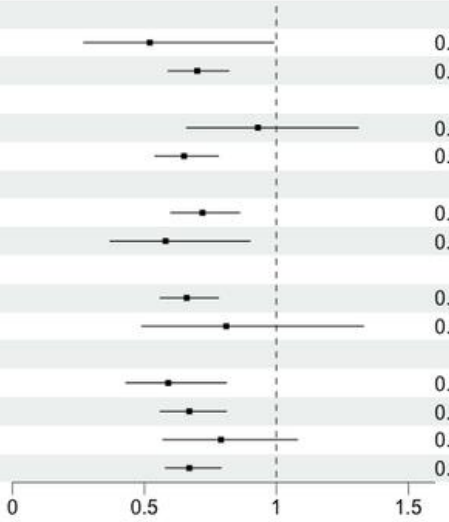
Trial 2: 31-180-day Outcomes

	Incidence, events per 1000 persons		
	Molnupiravir	**No Treatment**	**Hazard Ratio or Subhazard Ratio[1] (95% CI)**
Hospitalization or death	104.76	100.27	1.04 (0.92 to 1.19)
Hospitalization	98.94	90.02	1.10 (0.95 to 1.29)
Death	11.05	16.39	0.67 (0.48 to 0.95)

[1]Derived from proportional hazards regression that accounted for the competing risk for death, presented for hospitalization outcomes.

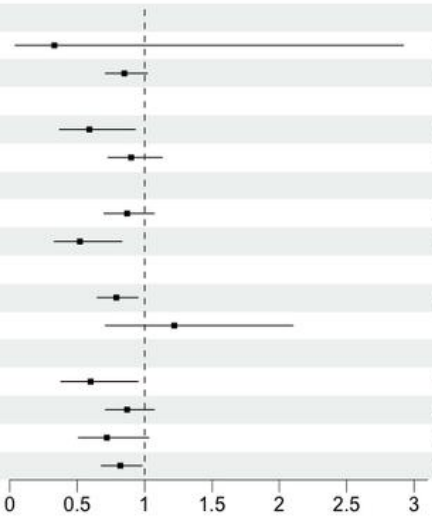
Trial 1 Subgroup Analysis: 30-day Hospitalization or Death

Subgroup	Nirmatrelvir-ritonavir Incidence (95% CI)*	No Treatment Incidence (95% CI)*	Risk Difference (95% CI)	Relative Risk (95% CI)	P interaction
Age, years					<0.001
18-64	7.93 (4.51 to 13.92)	15.31 (10.76 to 21.74)	-7.38 (-14.17 to -0.59)	0.52 (0.27 to 0.99)	
≥65	26.67 (23.29 to 30.53)	38.21 (34.88 to 41.85)	-11.54 (-16.54 to -6.53)	0.70 (0.59 to 0.82)	
COVID-19 vaccination status					<0.001
Unvaccinated	30.03 (22.63 to 39.76)	32.27 (26.19 to 39.70)	-2.24 (-12.85 to 8.38)	0.93 (0.66 to 1.31)	
Primary or booster	20.57 (17.58 to 24.05)	31.84 (28.65 to 35.36)	-11.27 (-15.89 to -6.65)	0.65 (0.54 to 0.78)	
Immunocompromised					<0.001
No	21.20 (18.37 to 24.45)	29.39 (26.48 to 32.61)	-8.19 (-12.48 to -3.90)	0.72 (0.60 to 0.86)	
Yes	44.44 (30.40 to 64.54)	77.21 (59.37 to 99.83)	-32.76 (-58.20 to -7.33)	0.58 (0.37 to 0.90)	
Timing of treatment, days					<0.001
0/1	22.56 (19.68 to 25.86)	34.05 (31.18 to 37.18)	-11.49 (-15.78 to -7.20)	0.66 (0.56 to 0.78)	
2-5	29.01 (18.56 to 45.08)	35.75 (28.18 to 45.26)	-6.74 (-21.98 to 8.50)	0.81 (0.49 to 1.33)	
Symptoms					<0.001
0	18.17 (13.67 to 24.10)	30.76 (26.66 to 35.47)	-12.60 (-19.36 to -5.83)	0.59 (0.43 to 0.81)	
≥1	24.39 (20.99 to 28.33)	36.25 (32.42 to 40.52)	-11.86 (-17.32 to -6.40)	0.67 (0.56 to 0.81)	
Treatment ≤5 days symptom onset*	27.33 (20.58 to 36.19)	34.79 (29.84 to 40.52)	-7.46 (-16.80 to 1.88)	0.79 (0.57 to 1.08)	
Overall	23.00 (20.19 to 26.20)	34.17 (31.42 to 37.15)	-11.16 (-15.30 to -7.03)	0.67 (0.58 to 0.79)	



Trial 2 Subgroup Analysis: 30-day Hospitalization or Death

Subgroup	Molnupiravir Incidence (95% CI)*	No Treatment Incidence (95% CI)*	Risk Difference (95% CI)	Relative Risk (95% CI)	P interaction
Age, years					<0.001
18-64	3.82 (0.53 to 26.91)	11.45 (4.54 to 28.57)	-7.63 (-20.58 to 5.32)	0.33 (0.04 to 2.92)	
≥65	48.59 (41.59 to 56.71)	57.23 (51.63 to 63.39)	-8.63 (-17.97 to 0.71)	0.85 (0.71 to 1.02)	
COVID-19 vaccination status					<0.001
Unvaccinated	48.46 (32.07 to 72.60)	82.78 (63.96 to 106.51)	-34.32 (-62.15 to -6.50)	0.59 (0.37 to 0.93)	
Primary or booster	40.07 (33.40 to 48.01)	44.51 (39.21 to 50.03)	-4.23 (-13.28 to 4.81)	0.90 (0.73 to 1.13)	
Immunocompromised					<0.001
No	39.72 (33.34 to 47.28)	45.88 (40.82 to 51.53)	-6.16 (-14.83 to 2.52)	0.87 (0.70 to 1.07)	
Yes	65.57 (42.59 to 99.68)	125.41 (96.52 to 161.40)	-59.85 (-98.86 to -20.81)	0.52 (0.33 to 0.83)	
Timing of treatment, days					0.013
0/1	43.42 (36.86 to 51.09)	54.99 (49.64 to 60.87)	-11.56 (-20.41 to -2.72)	0.79 (0.65 to 0.95)	
2-5	46.01 (27.85 to 75.10)	37.58 (28.30 to 49.73)	8.44 (-15.49 to 32.36)	1.22 (0.71 to 2.10)	
Symptoms					0.003
0	27.19 (18.12 to 40.61)	45.41 (36.71 to 56.05)	-18.22 (-32.81 to -3.63)	0.60 (0.38 to 0.95)	
≥1	49.90 (42.03 to 59.16)	57.25 (50.62 to 64.69)	-7.35 (-18.15 to 3.45)	0.87 (0.71 to 1.07)	
Treatment ≤5 days symptom onset*	45.99 (33.76 to 62.37)	63.48 (53.31 to 75.44)	-17.49 (-35.51 to 0.52)	0.72 (0.51 to 1.03)	
Overall	43.66 (37.37 to 50.96)	53.37 (48.40 to 58.81)	-9.70 (-18.04 to -1.37)	0.82 (0.68 to 0.98)	



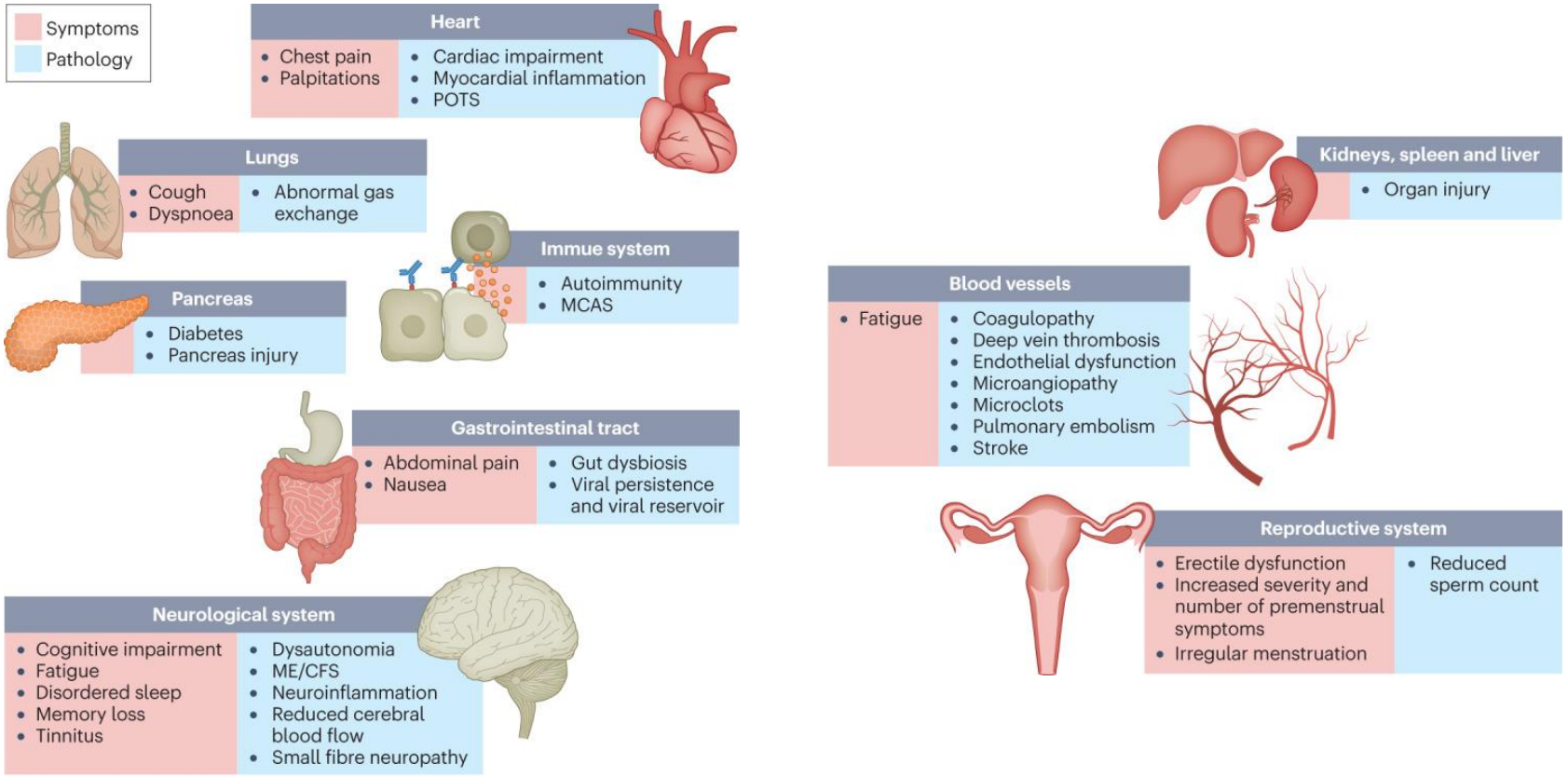
Main Conclusions

- Nirmatrelvir–ritonavir was effective at preventing 30-day all-cause mortality, hospitalization, ICU admission, and mechanical ventilation
- Risk reduction associated with molnupiravir was limited to all-cause mortality
- Additional mortality benefit was observed from days 31-180 for both antivirals

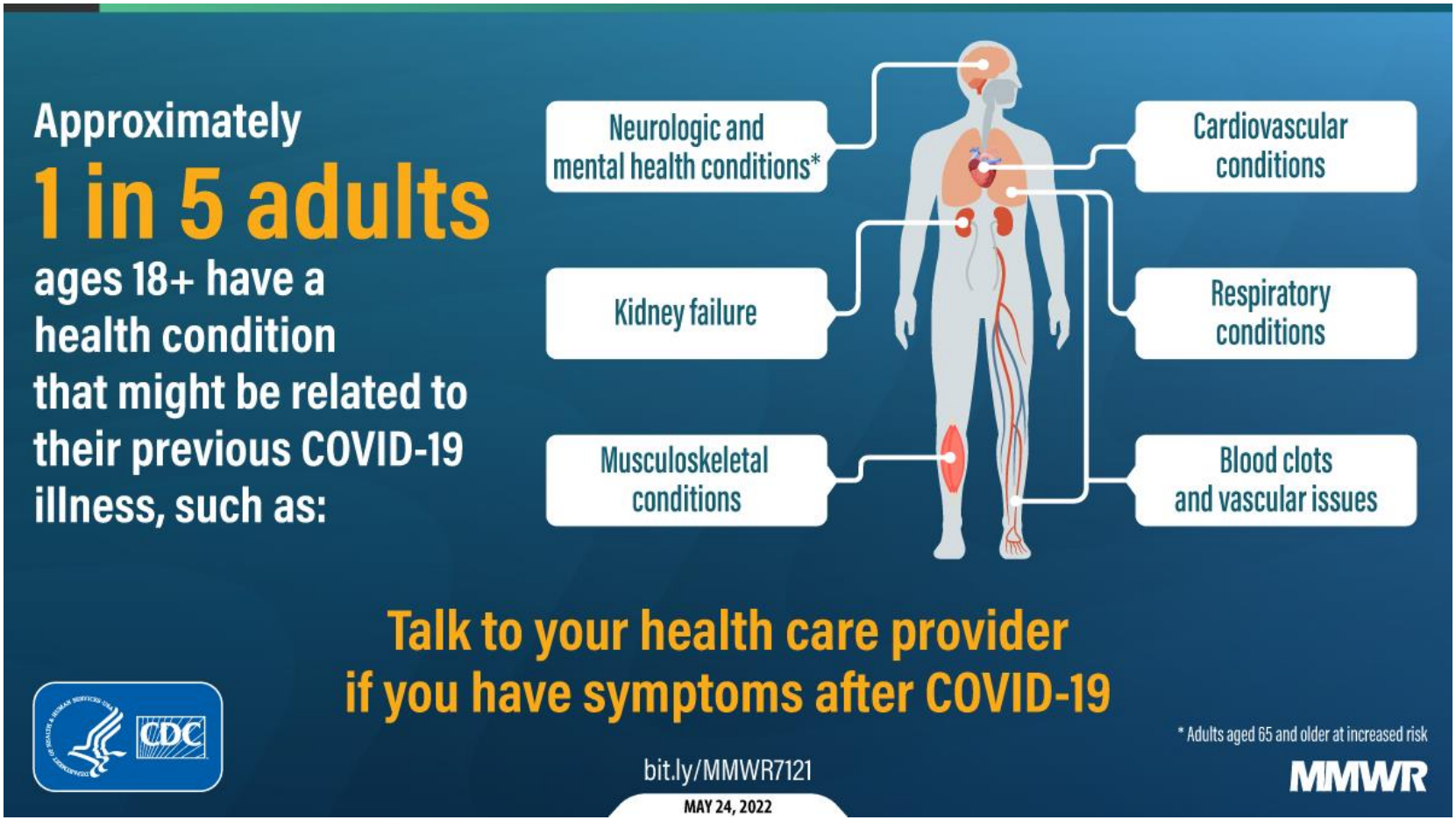
Limitations

- Not able to ascertain COVID-19–related symptom onset in most patients
- Not designed to capture prior infections
- Capture of outpatient COVID-19 treatments and outcomes (particularly hospitalizations) may be incomplete
- Residual confounding
- Could not verify whether Veterans who were prescribed antiviral medications completed treatment as recommended

Post COVID Conditions



Davis HE, et al. *Nat Rev Microbiol* 2023. DOI: https://doi.org/10.1038/s41579-023-00896-0



Bull-Otterson, et al. *MMWR* 2022. DOI: http://dx.doi.org/10.15585/mmwr.mm7121e1

Post-COVID conditions and symptoms

Cardiac

Acute coronary syndrome

Cardiac dysrhythmias

Cardiovascular disease

Chest pain

Heart failure/cardiomyopathy

Hypertension

Myocarditis and pericarditis

Pulmonary

Respiratory symptoms

Asthma

COPD/emphysema

Renal

Thromboembolic

Venous thromboembolism

Pulmonary embolism

Gastrointestinal

Gastrointestinal symptoms

Gastrointestinal disorders

Neurologic

Cerebrovascular disease

Dementia

Dysautonomia

Smell/taste disturbance

Headache

Sleeping disorders

Mental health

Depression

Other mood disorders

Anxiety

PTSD

Substance-related disorders

Musculoskeletal

Myalgias and myositis

Endocrine

Diabetes

General

Malaise and fatigue

Postviral fatigue

Erectile dysfunction

Davis HE, et al. *Nat Rev Microbiol* 2023. DOI: https://doi.org/10.1038/s41579-023-00896-0
Bull-Otterson, et al. *MMWR* 2022. DOI: http://dx.doi.org/10.15585/mmwr.mm7121e1
Al-Aly, et al *Nature* 2021. DOI: 10.1038/s41586-021-03553-9

Data and Information Sharing

- Collaborate with VA COVID-19 Observational Research Collaboratory (CORC)
- CORC is building a research data repository, some resources created by COPE-VA will be shared with CORC
- Bidirectional knowledge sharing between analysts on both projects

https://www.research.va.gov/corc/default.cfm

Future Directions

- Incorporate prior infections
- Risk prediction modeling
- Apply target trial emulation principles to treatments for other respiratory infections
- Time zero (index date) methodology

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  - *RSV, influenza*
  - *Oseltamivir, vaccine effectiveness*
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Time zero = index date

Within each nested trial day, matching occurs among eligible, alive, not hospitalized

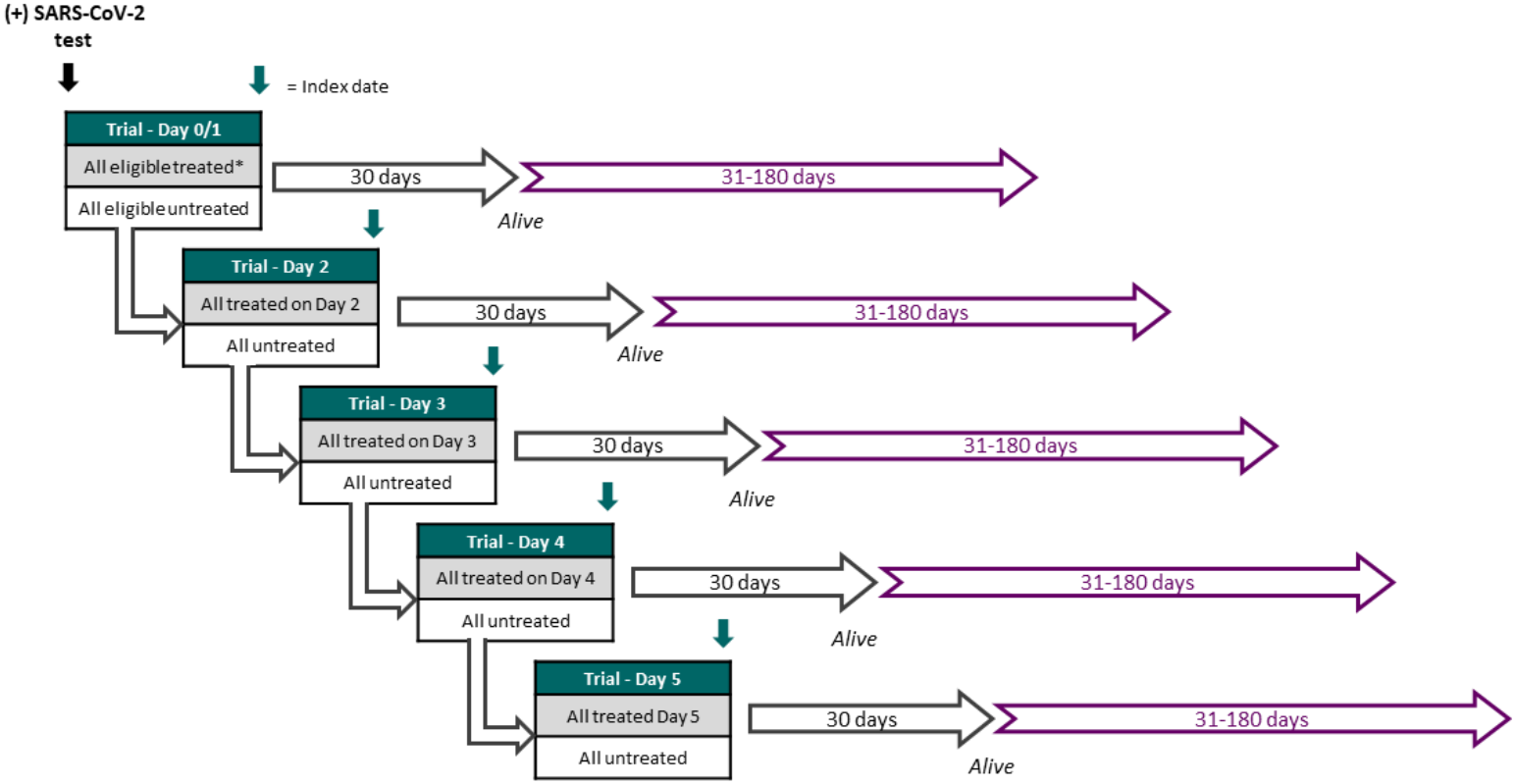
Up to 1:4 ratio

+

Exact-matching
NIH tier
VISN
Facility complexity
±7 days of positive test

+

Propensity-score matching
24 demographic, geographic, and clinical variables



Time zero = test date

Within each nested trial day, matching occurs among eligible, alive, not hospitalized

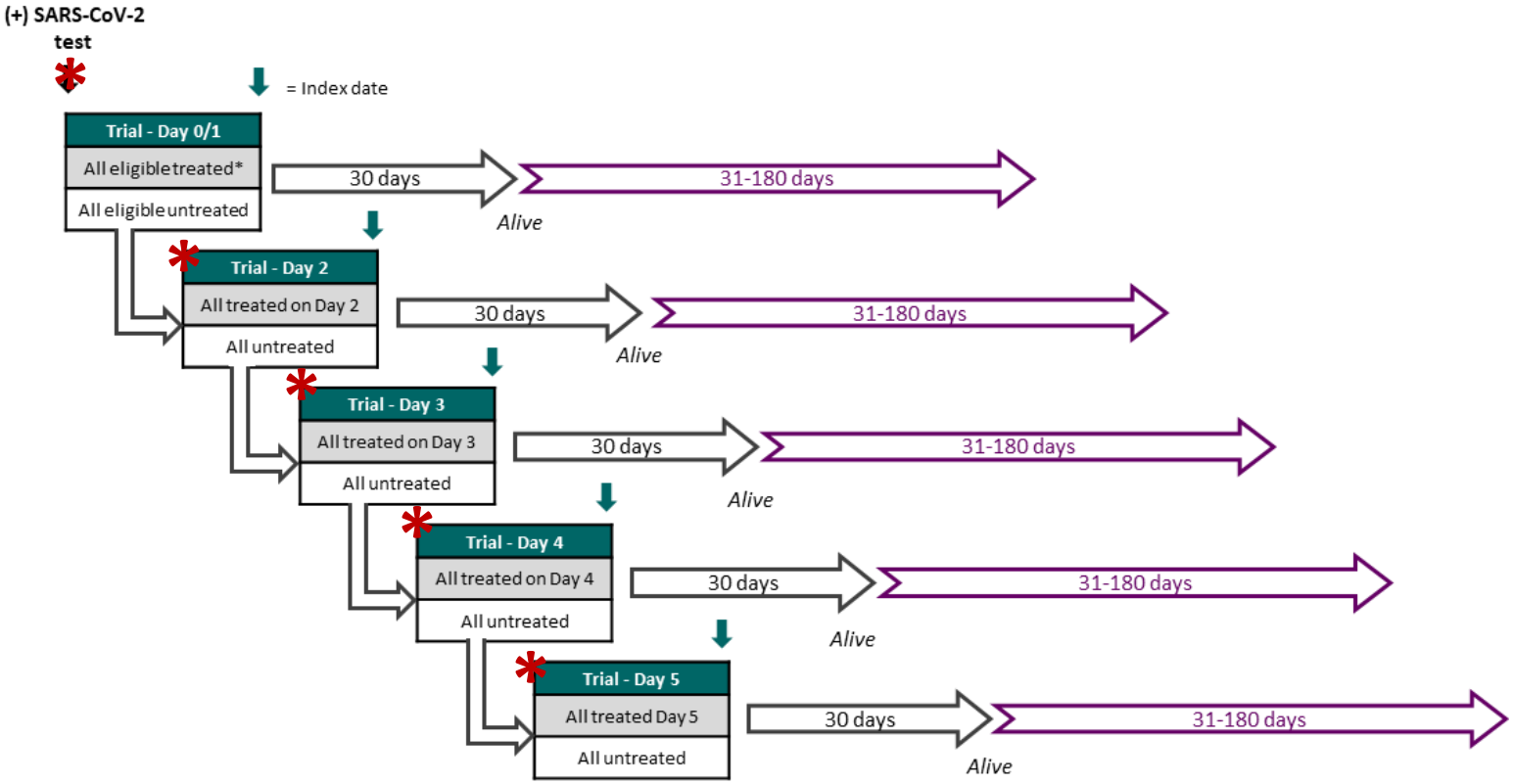
Up to 1:4 ratio

+

Exact-matching
NIH tier
VISN
Facility complexity
±7 days of positive test

+

Propensity-score matching
24 demographic, geographic, and clinical variables



Time zero = treatment date (treated) vs. test date (untreated)

Within each nested trial day, matching occurs among eligible, alive, not hospitalized

Up to 1:4 ratio

+

Exact-matching
NIH tier
VISN
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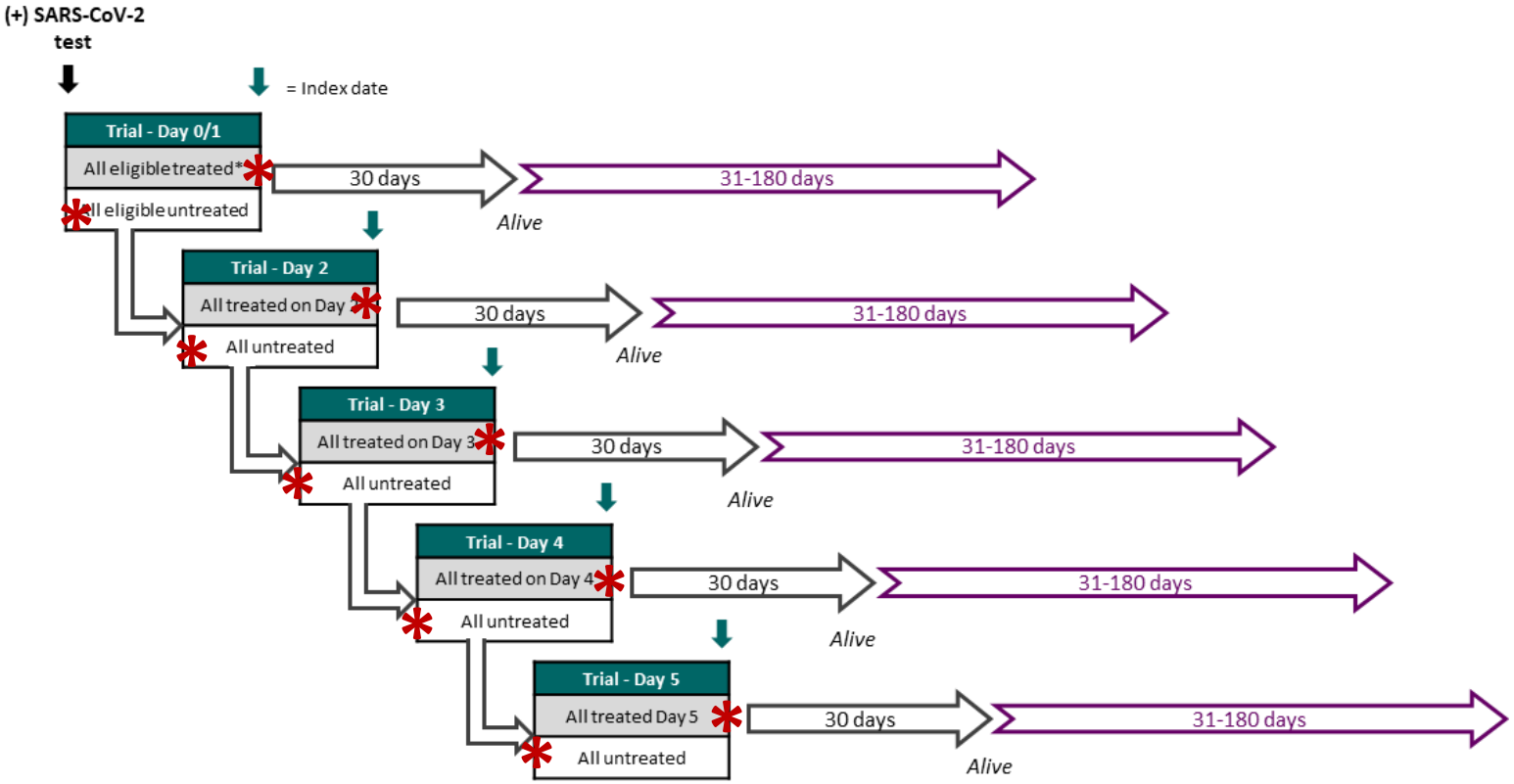

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