Introduction: Session 1

Characterizing Risk Factors for Severe COVID-19 to Inform Participant Eligibility Criteria for Enrollment

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Underlying Medical Conditions Associated with Higher Risk

Including:

- Cancer, hematologic disorders and malignancies
- Chronic kidney disease
- Chronic lung diseases
- Down syndrome, dementia, neurodisability

- Primary immunodeficiencies
- Solid organ or blood stem cell transplantation
- Use of immunosuppressive medications

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

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CDC Data Sources

- Systematic Review
- Meta-Analyses
- Cohort Studies
- Case Series
- Case Control Studies
- Longitudinal Studies

What has changed?

Overlapping factors:

- Vaccination

- Prior infection

- Variants

Who is Currently "High Risk"?

FDA

NIH Tier	
1	• **Immunocompromised individuals** not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Immunocompromising Conditions below); or • **Unvaccinated individuals at the highest risk of severe disease** (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
2	• **Unvaccinated individuals not included in Tier 1** who are at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• **Vaccinated individuals at risk of severe disease** (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)

https://www.covid19treatmentguidelines.nih.gov/overview/prioritization-of-therapeutics/

Goals

- Redefine eligible patient populations based on baseline factors or underlying medical conditions to inform trial design (placebo-controlled versus placebo controlled with add-on to SOC).

    For example:

    – Define subgroups of NIH Tier 2 and 3 that may be appropriate for placebo-controlled trials based on specific risk factors or underlying medical conditions.

Author	Publication Source	Date Published	Study Start	Study End	Pre/Post-Omicron	Study type	Data source
Adeji et al.	MMWR	Sep-22	Apr-20	Jun-22	Pre and Post Omicron	Cross-sectional study	Premier (PHD-SR)
Andreano et al.	Epidemiol Prev	Jan-21	Apr-20	Apr-20	Pre-Omicron	Retrospective cohort	Public databases
Arbel et al.	N Engl J Med	Sep-22	Jan-22	Mar-22	Pre and Post Omicron	Retrospective cohort	EHR
Bierle et al. (MASS score)	J Prim Care Community Health	May-21	Nov-20	Dec-20	Pre-Omicron	Observational cohort	EHR
Bierle et al. (MASS score)	J Infect Dis	Feb-22	Jul-21	Sep-21	Pre-Omicron	Observational cohort	EHR
Bohrmann et al.	JAMA	May-23	Jan-06	Feb-21	Pre and Early Omicron	Prospective cohort	UK Biobank
Bramante et al. (COVID-OUT)	N Engl J Med	Aug-22	Dec-20	Jan-22	Pre and Post Omicron	Decentralized, DB, PC, RCT	Placebo and failed arms
Butler et al. (PANORAMIC)	Lancet	Dec-22	Dec-21	Apr-22	Post-Omicron	Open-label, platform, RCT	Placebo arm
Leung et al.	Emerg Infect Dis	Jan-23	Mar-20	Nov-21	Pre and Post Omicron	Retrospective cohort	Public databases
Ebell et al. (LOCH risk score)	J Am Board Fam Med	Sep-22	Mar-20	Sep-21	Pre and Post Omicron	Systematic review	EHR
Ganesh et al. (MASS score)	J Infect Dis	Oct-21	Nov-20	Feb-21	Pre-Omicron	Observational cohort	EHR
Han et al.	Br J Haematol	Aug-22	Jan-21	Dec-21	Post-Omicron	Retrospective cohort	EHR
Havers et al.	JAMA Intern Med	Sep-22	Jan-21	Apr-22	Pre and Post Omicron	Cross-sectional study	COVID-NET
Johnson et al. (MASS score)	Mayo Clin Proc Inn Qual Out	Apr-23	Nov-20	Jun-22	Pre and Post Omicron	Retrospective cohort	EHR
Kompaniyets et al.	Prev Chronic Dis	Jul-21	Apr-20	Mar-21	Pre-Omicron	Cross-sectional study	Premier (PHD-SR)
Kojima et al.	Clin Infect Dis	May-23	Mar-21	Aug-22	Post-Omicron	Prospective cohort	IVY Network
Link-Gelles et al.	MMWR	Nov-22	Sep-22	Nov-22	Post-Omicron	Observational cohort	ICATT
Morello et al. (4CMS)	Minerva	Dec-22	Apr-20	Jan-21	Pre and Early Omicron	Observational cohort	Medical records
Naggie et al. (ACTIV-6, HD IVM)	JAMA	Feb-23	Feb-22	Jul-22	Post-Omicron	Decentralized, DB, PC, RCT	Placebo and failed arms
Nyberg et al.	Lancet	Mar-22	Nov-21	Jan-22	Delta and Omicron	Retrospective cohort	UKHSA linked to vaccine status
Pisaturo	Front Aging Neurosci	Jun-21	Feb-20	Jan-21	Pre-Omicron	Observational case-control	
Quanjel et al.	Nature Machine Intelligence	May-20	May-22	May-22	Pre-Omicron	Retrospective cohort	Medical records
Skarbinski et al.	Lancet	Jun-22	Jul-21	Jan-22	Delta and Omicron	Retrospective cohort	EHR (Kaiser Permanente Northern California KPNC)
Yan et al.	Nature Machine Intelligence	May-20	Jan-20	Feb-20	Pre-Omicron	Observational cohort	Medical records
Yek et al.	MMWR	Jan-22	Dec-20	Oct-21	Pre-Omicron	Retrospective cohort?	Premier (PHD-SR)

Approach for Discussion: Determine Eligibility for Enrollment in Outpatient COVID-19 Trials

Mild-moderate COVID-19

Age ≥75 years OR
Severe immunocompromise
(at least one of the following)?*
*Regardless of vaccination status or prior COVID-19
- CAR-T cell therapy, HCST, SOT, or receipt of transplant-related immunosuppressive drugs within 2 years
- Hematologic malignancy, myeloma, or related disorder (e.g., myelodysplastic syndrome, myelofibrosis)
- Chemotherapy or radiotherapy for solid organ cancer in last 12 months
- High-dose steroids (i.e., equivalent of ≥20 mg prednisone for ≥14 days)
- Immunomodulators, including alkylating agents, antimetabolites, anti-TNF or anti-CD20 drugs (e.g., 6MP, AZA, MMF, MTX, rituximab, infliximab, ustekinumab)
- HIV w/ CD4 <200
- Primary immunodeficiency (e.g., DiGeorge, Wiskott-Alrich, SCID, CVID)
- Sickle cell disease
- Chronic liver disease (e.g., Child-Pugh Class A, B or C cirrhosis)
- Down syndrome
- Dementia or neurocognitive disability (e.g., Parkinson's disease)

Three or more of the following conditions:
- No prior COVID-19, completion of vaccine series, or booster within last 6 months
- Age 65-74 years
- BMI ≥35 (or >95th percentile in adolescents)
- Type 1 or type 2 diabetes mellitus
- Cardiovascular disease (including HTN if age >55)
- Chronic lung disease (including bronchiectasis, CF, COPD, ILD, PHTN, PE, moderate-to-severe asthma)
- Chronic kidney disease (eGFR <30)

No

Yes

No

Two conditions? →No→ **One condition or none?**

Yes

Yes

Highest risk
(≥~1% risk of progression to severe COVID-19 or death)

"Intermediate" risk
(~0.5 to <1% risk)

Standard risk
(<~0.5% risk)

Add-on placebo-controlled trial:
Study drug + SOC vs placebo + SOC

Placebo-controlled trial:
Study drug vs placebo

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Study drug vs placebo