STAY SAFE MN

Ethical Framework for Allocation of Monoclonal Antibodies during the COVID-19 Pandemic

1/12/2022

This framework has been updated since 12/23/2021 to reflect changes to considerations for weighted random selection and clinical prioritization characteristics, including changing the clinical prioritization standard from the "MASSBP" to the "M-MASS."

Introduction

Since November 2020, the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) to permit the emergency use of investigational monoclonal antibody (mAb) therapies for the treatment of mild to moderate COVID-19 in adult and pediatric patients. The currently authorized mAbs are:

- Casirivimab/imdevimab (Regeneron) EUA issued Nov. 21, 2020[1]
- Bamlanivimab/etesevimab (Eli Lilly) EUA issued Feb. 9, 2021[2]
- Sotrovimab (GlaxoSmithKline LLC) EUA issued Oct. 8, 2021[3]

The FDA issued an EUA on Nov. 9 for the use of bamlanivimab alone for treatment of COVID-19. 2020.[4] As of April 16, 2021; however, this EUA has been revoked.[5] This revocation was issued due to concerns about the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone, resulting in the increased risk for

[1] U.S. Food and Drug Administration (FDA). Nov 21, 2020. Letter to Yunji Kim, PharmD, Regeneron Pharmaceuticals, Inc. (www.fda.gov/media/143891/download)

[2] U.S. Food and Drug Administration (FDA). Feb 9, 2021. Letter to Christine Phillips, PhD, RAC, Eli Lilly and Company. (www.fda.gov/media/145801/download)

[3] U.S. Food and Drug Administration (FDA). Oct 8, 2021. Letter to Debra Lake, GSK LLC (www.fda.gov/media/149532/download)

[4] U.S. Food and Drug Administration (FDA). Nov 9, 2020. Letter to Christine Phillips, PhD, RAC, Eli Lilly and Company. (www.fda.gov/media/143602/download)

[5] U.S. Food and Drug Administration (FDA). April 16, 2021. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab. (www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab)

treatment failure. The FDA therefore determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use.

In May and June of 2021, the FDA issued updated eligibility criteria for mAb treatment for both casirivimab/imdevimab (Regeneron) and bamlanivimab/etesevimab, and authorized the addition of a subcutaneous route of administration for casirivimab/imdevimab (Regeneron) as an alternative when intravenous infusion is not feasible and would lead to delay in treatment.[6]

On July 30, 2021, the FDA updated the EUA for casirivimab/imdevimab (Regeneron) to authorize use of this product for post-exposure prophylaxis (PEP) in some patients.[7] On Sept. 16, 2021, the FDA updated the EUA for bamlanivimab/etesevimab to authorize use of this product for PEP in the same patient population as that for PEP using the Regeneron product, and with specific guidance that bamlanivimab/etesevimab would only be authorized for continued use in states where prevalent COVID-19 variants are susceptible to the mAb.[8]

With respect to treatment uses, the FDA has noted in the EUAs for the currently authorized mAbs:

"Based on the totality of scientific evidence available to FDA, it is reasonable to believe that… " these monoclonal antibody therapies "… may be effective in treating mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age or older weighing at least 40kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and that, when used under the conditions described in this authorization, the known and potential benefits… when used to treat COVID-19 in such patients outweigh the known and potential risks of such product(s)."[9]

The patient eligibility criteria listed in the EUA for the authorization of each of the currently authorized monoclonal antibody therapies are identical. For that reason, this document covers each of these therapies under the umbrella term "mAb." Notably, these mAbs are not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. The U.S. government has secured supplies of these investigational antibody therapies for distribution to states. Infusion facilities may order directly from the U.S. Department of Health and Human Services as needed.

Allocation and administration of these mAbs for treatment are **time-sensitive**, as the EUA for each specifies that infusions be administered as soon as possible after a positive COVID-19 test result and **within 10 days of**

[6] FDA. June 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab). (www.fda.gov/media/145611/download)
See also FDA. May 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. (www.fda.gov/media/145802/download)

[7] FDA. July 30, 2021. Letter to Yunji Kim, PharmD, Regeneron Pharmaceuticals, Inc. (www.fda.gov/media/145610/download)

[8] FDA. September 16, 2021. Letter to Christine Phillips, PhD, RAC, Eli Lilly and Company/ (https://pi.lilly.com/eua/bam-and-ete-eua-fda-authorization-letter.pdf)
See also FDA. September 15, 2021. Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions. (www.fda.gov/media/151719/download)

[9] U.S. Food and Drug Administration (FDA). Nov 21, 2020. Letter to Yunji Kim, PharmD, Regeneron Pharmaceuticals, Inc. (www.fda.gov/media/143891/download)
US Food and Drug Administration (FDA). Feb 9, 2021. Letter to Christine Phillips, PhD, RAC, Eli Lilly and Company. (www.fda.gov/media/145801/download)

symptom onset.[10,11] Consequently, communicating to health care systems, physicians, patients, and COVID-19 test sites the importance of rapid testing and referral for potential infusion is crucial. The EUA Fact Sheet states: "For treatment, intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and would lead to delay in treatment."[12]

For post-exposure prophylaxis (PEP) uses, the FDA notes:

"[I]t is reasonable to believe that [the authorized mAbs] may be effective for use as post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death, as described in the Scope of Authorization (Section II), and that, when used under [such condition]s, the known and potential benefits of [the authorized mAbs] outweigh the known and potential risks of such products."[13]

Allocation and administration of mAbs for PEP are also time-sensitive. The EUA states that mAbs should be administered for PEP "as soon as possible following exposure to SARS-CoV-2," without providing a more specific timeframe.[11] **This framework recommends administering mAbs for PEP within 10 days from exposure for eligible patients who are not expected to mount an adequate immune response – e.g., those with immunocompromising conditions or on immunosuppressive medications – and administering mAbs for PEP within five days from exposure for all other eligible patients.** Thus, communicating to health care systems, physicians, and relevant groups of patients about the option of accessing mAbs for PEP is crucial. For PEP, mAbs may be administered either via infusion or subcutaneous injection.[12]

On Sept. 3, 2021, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel issued guidance outlining clinical prioritization when there is insufficient capacity to meet need for mAbs.[14] This framework **recommends a somewhat different approach to allocation in scarcity, which is outlined below.** The NIH panel's guidance recommends prioritizing treatment uses of mAbs over all PEP. This MDH framework **prioritizes PEP for highly immunocompromised individuals** (as specified on Page 9) **along with treatment uses prior to 'escalation' in response to scarcity, over PEP for immunocompetent individuals,** for two reasons. First, highly immunocompromised individuals face extremely high risk of progression to severe COVID-19. Second, unlike immunocompetent individuals, immunocompromised patients who develop COVID-19 infection may progress to severe disease too quickly to reasonably allow them to access mAbs for treatment. Thus, to adequately protect this population, PEP for immunocompromised individuals should be managed differently than PEP for immunocompetent individuals. In addition, the NIH panel's guidance recommends prioritizing "unvaccinated or incompletely vaccinated individuals" over vaccinated ones in allocation of mAbs (as well as prioritizing vaccinated individuals who are immunocompromised). In allocating mAbs for treatment of COVID-positive patients, this MDH framework deviates from that guidance by permitting the **prioritization of both vaccinated and unvaccinated individuals who are at very high risk of progression to severe COVID-19**, even if they are not immunocompromised.

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[10] FDA. November 21, 2020. Provider Fact Sheet for Health Care Providers; EUA of casirivimab/imdevimab (www.fda.gov/media/145611/download)

[11] FDA. February 9, 2021. Provider Fact Sheet for Health Care Providers; EUA of bamlanivimab/etesevimab. (www.fda.gov/media/145802/download)

[12] FDA. July 30, 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) OF REGEN-COV™ (casirivimab and imdevimab). (www.fda.gov/media/145611/download)

[13] FDA. July 30, 2021. Letter to Yunji Kim, PharmD, Regeneron Pharmaceuticals, Inc. (www.fda.gov/media/145610/download)

[14] National Institutes of Health (NIH). September 3, 2021. The COVID-19 Treatment Guidelines Panel's Statement on the Prioritization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment or Prevention of SARS-CoV-2 Infection When There Are Logistical Constraints. (www.covid19treatmentguidelines.nih.gov/therapies/statement-on-the-prioritization-of-anti-sars-cov-2-monoclonal-antibodies/)

This document provides ethical guidance regarding the allocation of mAbs. When the first mAb – bamlanivimab – was first made available through an EUA, it was anticipated that supply would be insufficient to meet need. The Minnesota Department of Health (MDH) developed Interim Ethical Guidance for Monoclonal Antibody Administration with recommendations from the Minnesota COVID Ethics Collaborative (MCEC) and MDH's Science Advisory Team (SAT). That and subsequent versions of this guidance document are now superseded by this framework.

This document was developed by MDH working with MCEC and the SAT. The document addresses relevant past guidance developed at MDH, key ethical values, and how allocation should occur both under conditions of scarcity and conditions of sufficient supply regarding: (1) allocation to hospitals and health systems throughout the state and (2) allocation among patients within each infusion or injection facility (which will initially be affiliated with hospitals).

This framework recommends this ethical guidance be operationalized using a centralized system called the Minnesota Resource Access Platform (MNRAP). This centralized approach promotes consistency among institutions and systems across the state of Minnesota, which is ethically important because it:

- Enhances transparency and the trustworthiness of pandemic response throughout the state;
- Fosters a common standard of care and access, and so helps to ensure fairness; and
- Promotes equity in allocation for all Minnesotans, whether or not they are affiliated with a health system.

After adopting this framework in February 2021, and after requests from a small number of health care systems, MDH decided to permit some health systems to opt out of using MNRAP to allocate mAbs on the condition that these systems demonstrate that their allocation process meets the ethical requirements of this framework and is at least as fair and equitable as MNRAP. These conditions include that opted-out systems accept unaffiliated patients without disadvantaging them, and that they implement their own weighted random selection process when their system is in scarcity, as defined either by insufficient doses or appointment slots to meet demand. The weighted random selection process should account for the same clinical and nonclinical factors as outlined in this guidance (refer to "Escalating approaches to scarce resource allocation" below for those specific requirements). Opted-out systems should also meet additional reporting requirements set by MDH to demonstrate their respective systems are performing as intended. **Given the current state of mAb supply, mAbs may need to be rationed due to scarcity. Thus, all systems that have not opted out of MNRAP should use MNRAP for all mAbs allocation decisions, and not supplement MNRAP with allocation processes internal to their respective systems.** In other words, all patients for facilities that have not opted out of MNRAP should be run through the MNRAP system.

Past guidance and ethical values

This document draws upon substantial ethical guidance that had already been developed for public health emergencies in the state of Minnesota, well before the COVID-19 crisis began. This established ethical guidance was created in two projects, sponsored by and completed in partnership with MDH:

- Minnesota Pandemic Ethics Project (www.health.state.mn.us/communities/ep/surge/crisis/panethics.html)
- Ethical Considerations for Crisis Standards of Care (www.health.state.mn.us/communities/ep/surge/crisis/panethics.html)

The development of that ethical guidance involved significant stakeholder consultation and wide community engagement. Community engagement forums included discussion of allocation objectives, criteria for allocation, and strategies to promote equity in access and address health disparities. In the COVID-19 pandemic, as in other public health emergencies, response should focus on the overall benefit to the population, to **try to save the most lives possible while also respecting rights and promoting fairness across our population.**

Ethical values guiding COVID-19 response

This ethical framework for COVID-19 response is grounded in the **fundamental ethical commitments** that the response to a pandemic will pursue Minnesotans' common good in ways that:

- Are accountable, transparent, and worthy of trust.
- Promote solidarity and mutual responsibility.
- Respond to needs respectfully, fairly, effectively, and efficiently.

To honor these fundamental value commitments, pandemic response must promote Minnesotans' common good by balancing **three ethical objectives**:

- Protect the population's health by reducing mortality and serious morbidity.
- Respect individuals and groups.
- Strive for fairness and protect against systematic unfairness and inequity.

Allocation of scarce resources should maximize the number of lives saved, taking into account both risk and expectation of benefit, while respecting individuals and groups and protecting against inequity.

As production of mAbs increases and more facilities offer infusion and injection appointments, supply and appointments may become sufficient to meet need. **When the inventory of mAbs and availability of appointments are sufficient or when mAbs become commercially available with sufficient appointment slots** (i.e., moving out of the process and centralized allocation approach outlined below), standard clinical ethical values guiding competent medical care, shared decision-making with patients, and appropriate stewardship of medications apply.

Determining whether supply of mAbs is sufficient or scarce

MDH should determine whether mAbs are in sufficient or scarce supply at least weekly, by region within Minnesota. Determining scarcity depends on the number of courses of mAbs available (inventory) and the number of appointment slots available to administer the mAbs (capacity), including in health systems that have opted out of the MNRAP platform. To determine scarcity, MDH should project the need for mAbs for the coming week (both for PEP and for treatment of COVID-19-positive patients), by considering the number of patients treated with mAbs in the previous week and adjusting for trends in case incidence rates as well as demand. MAbs should be considered to be in scarce supply statewide when either the number of courses available or the infusion and injection appointments available are less than 125% of the projected number of doses of mAbs needed for the coming week. MAbs should be considered to be in sufficient supply when both medication quantity and available infusion/injection appointments meet or exceed 125% of MDH's projection of need. Projections of demand relate to the allowable level of clinical prioritization (refer to "Stage 1: Clinical prioritization" below), e.g., demand would be calculated only from patients with a clinical prioritization score of X (when X=the current level of prioritization) or higher, and not of ALL patients seeking treatment. Only when it is expected that supply will not meet demand for patients deemed high risk under the clinical prioritization criteria below should a weighted random selection process be considered.

Additionally, a determination of scarcity or sufficiency should consider the entire week, avoiding a determination of scarcity that is based only on scarcity on the weekend due to the paucity of providers offering appointments on the weekend. A weighted random selection process should not be triggered based only on the fact that some patients who are clinically eligible cannot find appointments during Saturday or Sunday. The practical and ethical burdens of running a statewide weighted random selection process outweigh these interests, though patients whose clinical eligibility window expires during the weekend should be urged to seek access through an emergency department or their usual provider. Facilities should be encouraged to provide adequate access and appointments on weekends as well as weekdays.

Ethical criteria for distribution and allocation of mAbs

Ethical strategy for distribution throughout the state

The EUAs originally specified that each pharmaceutical manufacturer will provide supplies of mAbs to the federal government for distribution directly to hospitals by authorized distributors. However, the federal government, which controls distribution throughout the country, eventually allowed facilities to order doses directly from the distributors. Under that approach, MDH has authority and responsibility for determining ethical standards for allocation of mAbs by facilities within the state of Minnesota, consistent with the conditions set forth in the EUAs. Hospitals and health care systems will create and/or designate facilities to administer the infusions and/or injections to patients on an outpatient basis. In each region, hospitals and health care systems will determine which facilities will provide mAbs to patients. Each region should have several locations designated for mAb infusions/injections, taking into account geographic factors and populations' needs in order to promote equitable access.

In mid-September 2021, the federal government announced it would revert to controlling allocation of mAbs to the states, rather than allowing hospitals to order doses directly from distributors, given the need to manage inventory in response to significant increases in use of mAbs associated with the surge in cases. Under this plan for distribution, the federal government will control distribution throughout the country, working in cooperation with state health departments. MDH has authority and responsibility for determining allocation of mAbs within the state of Minnesota, consistent with the conditions set forth in the EUA. This will be accomplished as follows:

- Within regions, MDH will allocate doses of mAbs to facilities proportionate to their weekly infusion/injection capacity and use of mAbs. Only facilities that have a care setting that is appropriate for mAb infusion/injection (referred to throughout this document as "infusion/injection facilities") will be eligible to receive mAbs. MDH may modify this allocation plan based on a facility's capacity to deliver infusions/injections during a given allocation period.
- All infusion/injection sites must complete the federally required weekly reporting of both inventory and number of patient courses (or doses) used in the seven-day reporting period to be eligible for state allocation. Failure to accurately report these data affects the entire state allocation the federal government will grant Minnesota.
- In each region, hospitals and health care systems will determine which infusion/injection facilities will provide mAbs to patients. Each region should have several locations designated for mAb infusions/injections, taking into account geographic factors and populations' need in order to promote equitable access.

Regional Health Care Coalitions may ask facilities to redistribute doses between infusion/injection facilities in the same region, but facilities should not independently redistribute doses. **This also means systems and facilities should not distribute doses to facilities outside the state without express permission from MDH.**

Ethical strategy for allocation among patients

Because mAbs will be administered in ambulatory care settings and treatment is time-sensitive, **MDH should work with health systems and other partners to promote communication to the diverse communities in the state about this resource and the importance of early testing and treatment as well as the option for PEP for some patients.**

When patients receive a positive COVID-19 test result, the **provider or health system** that is informing them of their test result (via the system's electronic portal or otherwise) should also:

- Inform them about the availability of these investigational treatments (note that the provider need not prescreen patients who will access mAbs through MNRAP, as the MNRAP system will do that), and
- Alert them to the importance of seeking access to this treatment as soon as possible following a positive test result and within 10 days of symptom onset,[15] and
- Inform them of the process of seeking access to it via the centralized MNRAP screening website or opt-out facilities, and
- Encourage them to contact their primary care provider quickly about symptom onset and positive test results, and
- Inform them that close contacts who may have been exposed to them (e.g., family members) should consider contacting their doctor and/or MNRAP rapidly for post-exposure prophylaxis (PEP) use of mAbs within five days of exposure (or 10 days if the exposed individual is immunosuppressed).

If the patient does not have a regular primary care provider, the provider or test facility informing them of their test result should also inform them about how they can access care promptly.

Since providers and health systems may not know when patients who qualify for PEP have been exposed to COVID-19, communication will be essential to let patients know that they may be eligible for PEP if and when they are exposed and how to use MNRAP to access mAbs rapidly for this purpose. Communication to patients who are immunosuppressed is particularly important, as the consequences of exposure to COVID-19 in this population may be dire, heightening the importance of PEP.

Escalating approaches to scarce resource allocation

Recognizing that inventory or capacity may not be sufficient to meet demand for mAbs for prolonged periods of time, health systems should implement escalating strategies for prioritizing allocation relative to the depth of resource scarcity. The approach is as follows: first, implement an approach that prioritizes allocation to those at very high risk of severe COVID-19 outcomes (defined as any of: hospitalization, ICU admission, or death). Second, if scarcity continues to deepen such that mAb access cannot be provided to those groups that have a modified Monoclonal Antibody Screening Score (M-MASS) score of 4 or more OR patients who are pregnant (as explained in the Clinical Prioritization plan below), proceed to an instant-read weighted random selection approach.

[15] FDA. November 21, 2020. Provider Fact Sheet for Health Care Providers; EUA of casirivimab/imdevimab (www.fda.gov/media/149534/download)
FDA. February 9, 2021. Provider Fact Sheet for Health Care Providers; EUA of bamlanivimab/etesevimab. (www.fda.gov/media/145802/download)

Stage 1: Clinical prioritization

Under circumstances where demand for mAbs from clinically eligible patients is expected to outstrip supply (including inventory and capacity), two substantial changes to mAb allocation should occur. First, PEP **should be restricted only to patients that are highly immunocompromised, in order to** prioritize allocation to higher-risk PEP patients and infected patients actively showing symptoms and at high risk for severe COVID-19 outcomes who need treatment. Other patients who are clinically eligible for PEP should actively monitor for symptoms and, if those develop and they test positive for COVID-19, they may be eligible for mAbs for treatment. For purposes of mAb allocation for PEP, immunocompromised status includes:

- Hematologic and solid tumors on active therapy;
- Hematopoietic stem cell or solid organ transplant on immunosuppressants;
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome);
- HIV/AIDS with CD4 less than 200.

One exception is that congregate settings such as long-term care, correctional facilities, and shelters for people experiencing homelessness with supplies of mAbs on hand will still be permitted to provide PEP to all eligible patients (including during outbreaks) if they have staff available to provide PEP on-site without requiring an appointment through MNRAP. This exception recognizes that an outbreak in a congregate setting places multiple individuals at high risk of infection.

The second major approach in escalating prioritized allocation to mAbs is that sites should begin deprioritizing access for clinically eligible patients with the lowest clinical risk. **These patients should not be EXCLUDED**, but only given access to appointments after higher-risk patients have been scheduled. This strategy is meant to ensure that all higher risk patients are allocated mAbs before lower risk patients have access.

As of 1/11/2022, MDH uses the modified Monoclonal Antibody Screening Score (M-MASS) for MNRAP, which is a score adapted from Mayo Clinic's published studies.[16,17] The M-MASS is calculated as follows, on a scale of 0-19: age 65 years and older (2 points), BMI 35 kg/m^2 and higher (2), diabetes mellitus (2), chronic kidney disease (3), cardiovascular disease in a patient 55 years and older (2), chronic respiratory disease in a patient 55 years and older (3), hypertension in a patient 55 years and older (1), and immunocompromised status (4). The original MASS score assigned immunocompromised status 3 points; however, after consultation with clinical advisers and review of data from the University of Minnesota, MDH modified the scoring system to update the weighting from 3 points to 4 points.

Additionally, patients who are pregnant are clinically prioritized, independent of their M-MASS score. Pregnancy was not included in the MASS score as developed by the Mayo Clinic, but data on pregnancy and the risk of severe COVID-19 was used to determine a weighting that would provide relatively equivalent access to treatment in relation to the MASS scoring system. The Science Advisory Team (SAT) has recommended, and MDH has directed, that sites deprioritize low M-MASS scores for non-pregnant people in response to appointment scarcity. This means MNRAP has been instructed to begin by deprioritizing access for non-pregnant patients with a M-MASS of 0, and to further be ready to deprioritize M-MASS=1, M-MASS=2, and M-MASS=3 as scarcity deepens.

[16] Bierle et al., Monoclonal Antibody Treatment of Breakthrough COVID-19 in Fully Vaccinated Individuals with High-Risk Comorbidities. 2021 MedRxiv (www.medrxiv.org/content/10.1101/2021.10.19.21265222v1)

[17] Razonable, R. R., Ganesh, R., & Bierle, D. M. (2022). Clinical Prioritization of Antispike Monoclonal Antibody Treatment of Mild to Moderate COVID-19. In Mayo Clinic Proceedings (Vol. 97, Issue 1, pp. 26–30). Elsevier BV (doi.org/10.1016/j.mayocp.2021.11.017)

- After Dec. 1, 2021, sites that have opted out of MNRAP and are running their own screening processes are encouraged to use the same M-MASS scoring system and deprioritization of non-pregnant M-MASS=0 patients as implemented by MNRAP. If scarcity deepens and deprioritization of non-pregnant M-MASS=1, M-MASS=2, or M-MASS=3 is implemented by MNRAP, opted-out sites using the M-MASS scoring systems should be prepared to do the same.
- Under the above approach, MNRAP will track all patients that have been deprioritized for access and, at the end of each daily allocation cycle, allocate any available appointments to these deprioritized patients in order of clinical priority, randomizing access for similarly rated patients (refer to "Employing an end-of-day holdback or reserve" below). To promote fairness across systems, opted-out sites should be prepared to do the same.
- If supply is too scarce to allow allocation to all patients M-MASS=4 or higher OR pregnant, then allocation will be managed via weighted random selection as described below. M-MASS of 4 was recommended by the Science Advisory Team as the point beyond which patients are judged to have a high risk (i.e., 10% or higher) of severe COVID-19 outcomes.

This clinical prioritization does not apply to patients aged younger than 18 years. Pediatric patients should continue to be referred as before.

Stage 2: MNRAP's instant-read weighted random selection approach

If medication inventory or infusion/injection appointments for mAbs are in scarcity (as defined above) and the clinical prioritization strategy described above is insufficient to ameliorate the issue (i.e., if supply is too scarce to allow allocation to all patients with M-MASS=4 or higher or pregnant), the resource will be allocated to patients 18 years of age and older via a **weighted random selection mechanism, using the centralized MNRAP screening website** managed by MDH (unless the patient is accessing mAbs through an opt-out health care system, which will run its own weighted random selection process). The weighted random selection process operated by a facility or system that has opted out of MNRAP should meet the requirements of this framework, be at least as fair and equitable as MNRAP, and be approved by MDH. These conditions include that opted-out systems accept unaffiliated patients without disadvantaging them compared to patients who normally access care through the facility or system. **Patients younger than 18 will be directed to pediatric providers** who will determine whether mAbs may be safe and effective for them, given considerations specific to patients in this population, but otherwise will not participate in any weighted random selection process.

The details of this weighted random selection approach are provided below, though the concept itself is straightforward. Every day, a base chance of receiving mAbs will be calculated given known supply and predicted demand for the resource. Until supply is exhausted for the day, everyone will have at least this chance of receiving the resource, if clinically eligible. At the discretion of MDH, certain groups, detailed below (such as clinically prioritized patients, critical workers in high-risk settings, and residents of long-term care facilities) may have higher priority in allocation for reasons explained below. This higher priority will be operationalized in MNRAP as a better chance at receiving the scarce resource because their chances of success in the weighted random selection are weighted higher than the base chances (i.e., certain groups have better chances of success in allocation than others). The weighted random selection will give everyone one initial chance plus one overnight chance (refer to "Employing an end-of-day holdback or reserve" below) for PEP and the same for treatment.

Among the options considered for structuring MNRAP, MDH chose to adopt a weighted random selection process because it provides instant decisions regarding allocation in most cases, and thus best promotes access to this time-sensitive therapy while also promoting fairness and equity as recommended in this ethical framework. It is weighted to operationalize prioritized access for specific groups, as detailed below.

Priority for clinically eligible patients who are critical workers in high-risk settings (CWHRS)

MDH may elect to prioritize clinically eligible critical workers in high-risk settings (CWHRS). These are "individuals whose occupations are in essential industries and who cannot avoid a high risk of exposure to COVID-19."[18] **There are two primary reasons for prioritizing CWHRS** in allocation of some scarce health resources. First, CWHRS have an **instrumental value** to the pandemic response – that is, by virtue of the role they play, their health and well-being is important to response efforts. This is why they are called critical workers – because they provide essential services.[19] Second, CWHRS are owed duties of **reciprocity** (i.e., to the extent that they face heightened risk in service of the public, they are owed a duty of protection in return). Thus, the ethical rationale for prioritizing these workers in resource allocation relates to their specific job function in pandemic response and does not involve a view that some individuals have greater social value than others. Notably, individuals who perform these job functions may be paid workers or volunteers. Job duties and related exposure risk are what matter ethically, not whether the individual is paid or their social standing. Given the reasons for prioritizing CWHRS for allocation of resources, the priority should be grounded in both the significance of the services that the worker provides and the worker's risk of occupational exposure to COVID-19.

Priority for CWHRS in allocation of scarce resources is not absolute and must be balanced against other rationing priorities. It is vital to protect critical workers, since doing so helps to protect the public. However, the ethical values grounding this guidance, and past guidance developed in the state based on those values, also recommend that some individuals be prioritized for access to resources based upon their health needs, completely independent of their work roles. A balance must be struck between these two strategies for protecting the public's health.

MDH should issue guidance about whether, at any given point in the pandemic, a priority for CWHRS is warranted. In doing so, MDH should consider if case rates, or patterns of infections, ground significant concerns that the ability to provide essential services (or particular essential services) may be undermined by possible workforce shortages, then considerations of instrumentality justify prioritizing CWHRS (or the particular groups of CWHRS facing risks of workforce shortages). If CWHRS (or particular categories of CWHRS) face heightened risk in service of the public, then considerations of reciprocity may also justify prioritizing CWHRS (or the relevant groups of CWHRS). **MDH should issue guidance regarding prioritization for CWHRS (or specific groups of CWHRS)**; the judgment about whether or which workers should receive priority should not be left to treating clinicians. If variants of the virus create a surge in COVID-19 cases, then MDH should consider activating a priority for CWHRS.

If a priority for CWHRS is activated, the centralized MNRAP screening website will screen patients to determine if they are a critical worker in a high-risk setting. Facilities may confirm this information prior to infusion/injection, but their process of confirmation should accommodate workers (e.g., volunteers) who may not have documentation of their role.

Priority for clinically eligible patients who are health care workers

If MDH determines that health care workers are in a shortage that increases risks to patients, MDH should also consider issuing guidance about whether health care workers who are clinically eligible to receive mAbs and interact with COVID-19-positive patients will receive prioritized access to mAbs. **Under this priority, MDH may, based on the workforce situation, adopt non-clinical prioritization offering a higher chance for clinically-eligible**

[18] National Academies of Sciences, Engineering, and Medicine. 2020. Framework for Equitable Allocation of COVID-19 Vaccine. Washington, DC: National Academies Press. (doi.org/10.17226/25917) p 12

[19] Executive Order 20-48. April 30, 2020. (www.leg.mn.gov/archive/execorders/20-48.pdf)

health care workers treating COVID-19 patients to be allocated mAbs if the resource is available. Individuals who are eligible for this priority will be identified through the centralized MNRAP screening process. This level of priority may justified by profound instrumentality considerations in times of severe shortage of health care workers. During a surge in cases, hospitalizations, and deaths, widespread illness and rates of required quarantine among these particular workers may impair the health system's ability to provide care for patients. **MDH should assess whether this priority is needed statewide or if shortages affect particular regions. MDH should also regularly evaluate the need for this priority and sunset it when it is no longer needed to preserve health care capacity**. During periods in which health care workers directly interacting with COVID-19 patients continue to be in short supply and this increases risk to patients (e.g., because health care systems report high absentee and/or sick rates; normal operation nurse-to-patient ratios are not maintainable; beds or ventilators are not fully able to be staffed), this provision should remain. **It is critical that this exception be ended when it is no longer needed to address workforce shortages, as appropriate sunsetting will maximize access for others and maintain trust in the broader allocation process.**

Priority for clinically eligible patients who are residents in skilled nursing and long-term care facilities

Residents of **skilled nursing facilities (SNF) or other long-term care (LTC) facilities,** such as assisted living or group homes, should receive prioritized access to mAbs. This does not imply that these facilities will directly administer mAbs to patients, but that such patients should have access to the therapy. Because mAbs are authorized for use in outpatient settings, it represents an important potential countermeasure for residential care facilities, given increased risk of poor outcomes for patients in these settings. MDH should determine whether a priority based on the M-MASS score adequately addresses the risks faced by these patients, or whether an additional level of priority is needed.

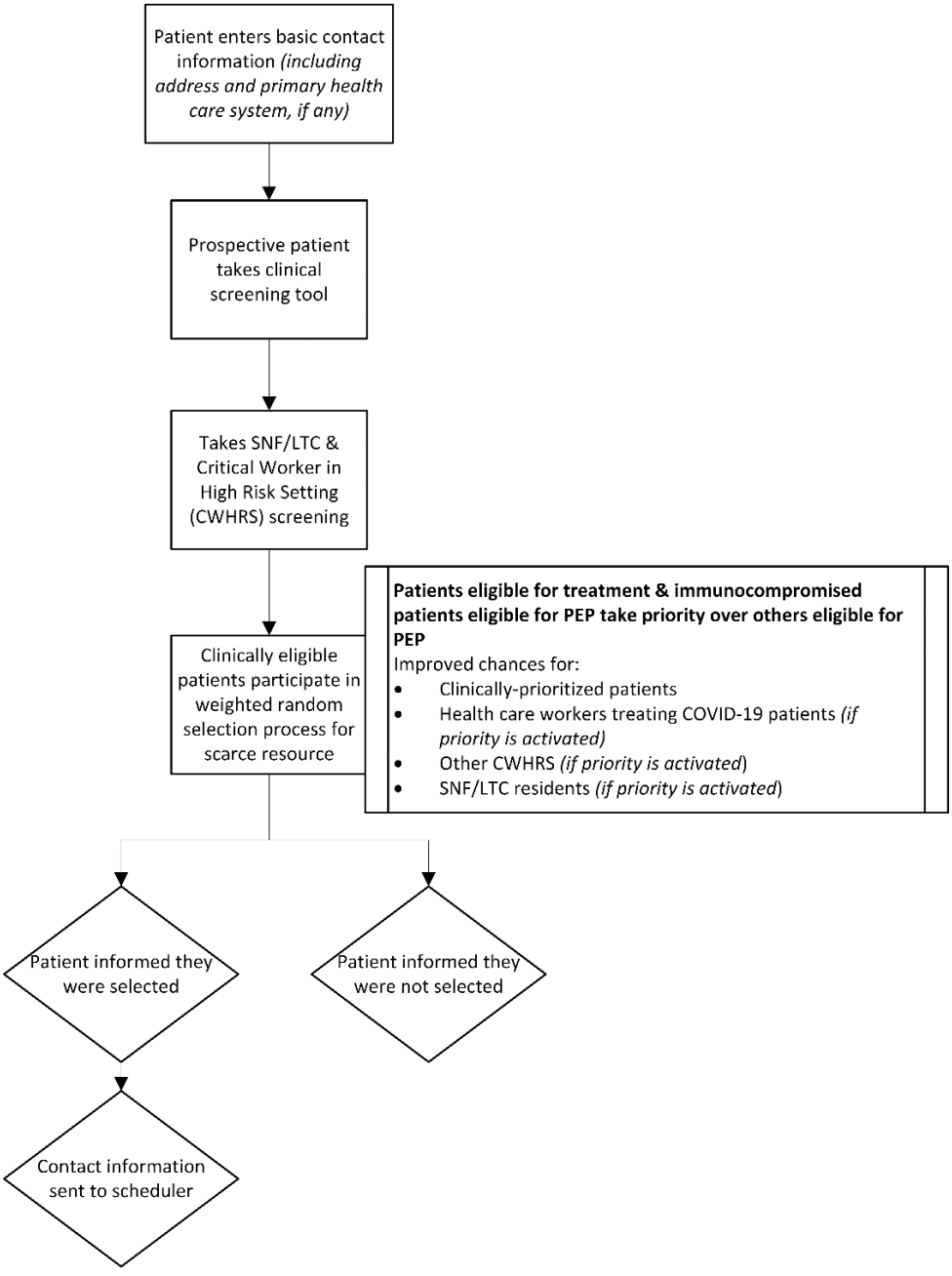
Access

Patients may seek access to mAbs as follows: Individuals should be referred by their primary care provider, health system, testing site, or an information campaign run by MDH directing them to a screening MNRAP website run by MDH (unless the patient is being cared for by a health care system that has opted out of MNRAP), which will ascertain provisional clinical eligibility and whether the patient is a health care worker who directly interacts with COVID-19 patients, a CWHRS more broadly, or a resident at SNF or LTC facilities. If a clinically eligible patient fits into none of these groups, they will be considered part of the general public. Patients will then participate in the weighted random selection process and will receive an immediate notification of whether they have been provisionally selected for allocation of mAbs. Selection is provisional, because confirmatory screening must be performed by providers at the infusion/injection facility in advance of the infusion/injection – either when the patient is scheduled for their appointment, or at the time of the appointment. Confirming eligibility prior to time of infusion/injection would be preferable, as it would prevent having to turn away patients who appear for appointments, if their confirmatory screening indicates that they are not clinically eligible.

To ensure that patients who lack internet access or who do not speak English are not denied equitable access, patients who may have difficulties with the centralized MNRAP web screener should be directed to their health system, which should answer questions and help individuals fill out the screening tool. Patients who do not have a regular provider may contact the MDH public hotline to get contact information for the infusion facility nearest to them, so that the patient may seek help with the MNRAP web screening at that facility. The information campaign run by MDH should also publicize these options for accessing screening. Moreover, medical proxies, providers, or other personnel approved by the individual may assist them in completing the MNRAP screening tool. MDH should work to ensure that the MNRAP website is accessible to the diverse populations of the state.

Patient ability to pay should not control access to mAbs under circumstances of scarce or sufficient supply. Infusion/injection facilities (or the health care systems/organizations with which they are affiliated) should work with patients to identify sources of payment for mAbs, including based on patient eligibility for insurance, subsidized care, or any program that will enable access. Note that the ability to pay relates not only to the cost of mAbs (which has initially been provided free of charge through the federal government), but also related infusion- or injection-associated costs such as provider reimbursement and facility fees. Fair access to mAbs will also depend on effective messaging to diverse populations in the state about the availability of mAbs for PEP, the importance of rapid testing and early treatment, the availability of and timely results from testing, and the ability and willingness of health care systems and infusion/injection facilities to accept referrals from outside their systems to provide care for patients who lack a regular primary care provider.

Figure 2: Patient interaction with the centralized mAbs allocation process through the MNRAP website.



The steps shown in the image above are: patient enters basic contact information on the MNRAP website, including address and primary health care system, if any; prospective patient takes clinical screening tool; then takes SNF/LTC and Critical Worker in High Risk Setting screening. Clinically eligible patients participate in weighted random selection process for scarce resource. Patients eligible for treatment and immunocompromised patients eligible for PEP take priority over to others eligible for PEP. Chances are improved for: health care workers treating COVID-19 patents (if priority is activated); other CWHRS (if priority is activated); SNF/LTC residents (if priority is activated); and clinically-prioritized patents. Patients are informed whether or not they were selected; contact information of those selected is sent to a scheduler.

Sufficient supply and scarcity

For treatment of COVID-19-positive patients during conditions of both sufficient supply and scarcity, the following applies:

- Patients being considered for mAbs must have COVID-19 infection confirmed either by RT-PCR or by antigen testing. Home tests may be used if the patient can provide proof of the positive result. Patients must also have at least one COVID-19 symptom.
- Patients should be treated within 10 days of onset of COVID-19 symptoms and as soon as possible after their positive test result (PCR or antigen, not serology).
- Patients should meet other clinical inclusion criteria as specified by the FDA EUAs for mAbs.
- Vaccinated patients should remain eligible for mAbs if they develop breakthrough infections and unvaccinated patients should not be penalized.
- Clinicians and health systems may consider whether a patient has heightened risk of progression to severe COVID-19 associated with race and ethnicity when determining eligibility for mAbs.
  - The FDA has acknowledged that in addition to certain underlying health conditions, race and ethnicity "may also place individual patients at high risk for progression to severe COVID-19."[20]
  - FDA's acknowledgment means that race and ethnicity alone, apart from other underlying health conditions, may be considered in determining a patient's eligibility for mAbs. It is ethically appropriate to consider whether a patient has elevated risk of poor COVID-19 outcomes and that this risk cannot be adequately addressed by determining eligibility based on underlying health conditions (perhaps due to impaired access to health care and underdiagnosis of health conditions that elevates risk of poor COVID-19 outcomes). When making decisions about whether individual patients are eligible for mAbs, it is always the case that health care providers "should consider the benefit-risk for an individual patient."[20]
- Clinicians and health systems may consider heightened risk of progression to severe COVID-19 associated with disability (including being immunocompromised or on immunosuppressive medications) when determining eligibility for mAbs.
  - FDA directs clinicians to consider CDC's acknowledgement that:

    "Long-standing systemic health and social inequities have put various groups of people at increased risk of getting sick and dying from COVID-19, including … people with disabilities. … People with disabilities are more likely than those without disabilities to have chronic health conditions, live in congregate setting,

[20] FDA. June 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab). (www.fda.gov/media/145611/download)
See also FDA. May 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. (www.fda.gov/media/145802/download)

and face more barriers to healthcare. Studies have shown that some people with certain disabilities are more likely to get COVID-19 and have worse outcomes."[21]

- It is ethically appropriate to consider disability status in mAbs eligibility decisions when a patient with a disability faces elevated risk of progression to severe COVID-19 and that risk cannot be adequately addressed by determining eligibility based on underlying health conditions. When making decisions about whether individual patients are eligible for mAbs, it is always the case that health care providers "should consider the benefit-risk for an individual patient."[22]

For PEP, during both conditions of sufficient supply and scarcity, the following applies:

- Patients should meet clinical inclusion criteria as specified by the FDA EUA for mAbs.
- MAbs for PEP should be administered within 10 days from exposure for eligible patients who are not expected to mount an adequate immune response – e.g., those with immunocompromising conditions or on immunosuppressive medications – and within five days from exposure for all other eligible patients.
- Clinicians and health systems may consider heightened risk of progression to severe COVID-19 associated with race and ethnicity when determining eligibility for mAbs.
  - The FDA has acknowledged that, in addition to certain underlying health conditions, race and ethnicity "may also place individual patients at high risk for progression to severe COVID-19."[22]
  - The FDA's acknowledgment means that race and ethnicity alone, apart from other underlying health conditions, may be considered in determining a patient's eligibility for mAbs. It is ethically appropriate to consider whether a patients has elevated risk of poor COVID-19 outcomes and that risk cannot be adequately addressed by determining eligibility based on underlying health conditions (perhaps due impaired access to health care and underdiagnosis of health conditions that elevate risk of poor COVID-19 outcomes). When making decisions about whether individual patients are eligible for mAbs, it is always the case that health care providers "should consider the benefit-risk for an individual patient."[22]
- Clinicians and health systems may consider heightened risk of progression to severe COVID-19 associated with disability (including being immunocompromised or on immunosuppressive medications) when determining eligibility for mAbs.
  - The FDA directs clinicians to consider CDC's acknowledgement that:

    "Long-standing systemic health and social inequities have put various groups of people at increased risk of getting sick and dying from COVID-19, including … people with disabilities. … People with disabilities are more likely than those without disabilities to have chronic health conditions, live in congregate setting, and face more barriers to healthcare. Studies have shown that some people with certain disabilities are more likely to get COVID-19 and have worse outcomes."[21]
  - It is ethically appropriate to consider disability status in mAbs eligibility decisions when a patient with a disability faces elevated risk of progression to severe COVID-19 and that risk cannot be adequately addressed by determining eligibility based on underlying health conditions. When making decisions about

[21] Centers for Disease Control and Prevention. May 13, 2021. COVID-19: People with Certain Medical Conditions. (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html)

[22] FDA. June 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab). (www.fda.gov/media/145611/download)
See also FDA. May 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. (www.fda.gov/media/145802/download)

whether individual patients are eligible for mAbs, it is always the case that health care "providers should consider the benefit-risk for an individual patient."[23]

- As systems schedule appointments for eligible patients, they should work to ensure that patients needing mAbs for treatment of infection and patients seeking PEP who are not expected to mount an adequate immune response – e.g., those with the immunocompromising conditions or on immunosuppressive medications specified above – are scheduled first, since access to mAbs is especially time-sensitive in these groups. When there is a sufficient supply, all eligible patients will be able to access mAbs; this scheduling provision is meant to ensure that allocation is as responsive to patient need as possible. Please note that those individuals who are seeking PEP who are not expected to mount an adequate immune response should not be exposed to those individuals who have tested positive for COVID-19 seeking mAb treatment.

When there is a **sufficient supply** of mAbs (including, as outlined above, sufficient inventory as well as appointments), the resource should be allocated in line with competent medical care, shared decision-making with patients, and appropriate stewardship of medications, but not a triage or weighted random selection model. The centralized MNRAP screener will assess provisional clinical eligibility for the resource and provide referrals to facilities for all provisionally eligible patients. For patients being cared for by health care systems that have opted out of MNRAP, their health care system will perform this function.

When supply of mAbs is approaching scarcity, the following strategies should be used:

- MDH should work to increase supply by seeking more doses and/or encouraging health systems working within MNRAP as well as systems that have opted out of MNRAP to increase availability of appointments.
- If capacity to provide mAbs infusions/injections in systems participating in MNRAP cannot be increased sufficiently to address need, then MDH should explore whether health systems in the region that have opted out of MNRAP have available capacity. Care should be exercised to ensure that sending referrals to opted-out facilities does not result in treatment barriers for those patients and greater scarcity in those systems than in the systems participating in MNRAP. Systems or facilities that have opted out of MNRAP should notify MDH when they are operating close to infusion/injection capacity.
- If greater supply is still needed after attempts to implement the strategies outlined above, then MNRAP should refer some patients to facilities in adjacent regions if they have available supply. Efforts should be made to determine if the patient has the ability to travel to access mAbs; patients who lack the resources needed for such travel should be prioritized for referrals for mAbs within their region.

A weighted random selection process should not be used to ration mAbs unless strategies to expand capacity and prioritize based on clinical risk are insufficient to meet need. In addition, **opted-out systems should not activate a weighted random selection process within their facility unless MDH indicates the state is in scarcity**. In situations where MNRAP shows capacity, but an opted-out system is in scarcity, opted-out facilities should refer clinically eligible patients who were declined in their weighted random selection process to MNRAP.

In order to maximize benefit and appropriately steward this resource under conditions of scarcity, if **MDH projects with reasonable confidence that the inventory of mAbs or infusion/injection appointments will likely be insufficient to meet patient needs even after implementing the clinical prioritization strategy detailed above**

[23] FDA. June 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab). (www.fda.gov/media/145611/download)
See also FDA. May 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. (www.fda.gov/media/145802/download)

(in section entitled "Stage 1: Clinical prioritization") (considering both MNRAP and opted-out systems), mAbs should be allocated via a weighted random selection mechanism through the MNRAP platform, as follows:

- All clinically eligible patients will have a base chance of receiving mAbs when scarce, with that chance calculated by available supply and predicted demand for the day the patient submits the screener on the MNRAP platform.
  - Given high risks of quick progression to severe disease, COVID-19-positive patients who are eligible for mAbs **treatment** and not expected to mount an adequate immune response – i.e., those with the highly immunocompromising conditions or on immunosuppressive medications specified above – should receive priority for allocation of mAbs over other patients eligible for treatment and over patients eligible for PEP.
  - COVID-19-positive patients eligible for mAb treatment and expected to mount an adequate immune response, and patients eligible for PEP who are **not** expected to mount an adequate immune response – e.g., those with immunocompromising conditions or on immunosuppressive medications – should receive priority for allocation of mAbs over other patients eligible for PEP.
  - If patients eligible for PEP enter the weighted random selection process and later test positive for COVID-19, they will be able to enter the weighted random selection process again one time to seek a treatment dose of mAbs (with a second chance overnight as described above and below).
- Certain priority groups will have higher chances of success relative to groups with the base chance:
  - Groups that MDH determines, based on available data, have conditions or factors associated with eligibility for mAbs that elevate risks of progression to severe disease significantly more than others.
  - **Health care workers treating COVID-19 patients**, if authorized by MDH as described above.
    - If MDH authorizes an allocation priority for health care workers treating COVID-19 patients due to an acute shortage of such personnel, the first step in allocation will be to identify all clinically eligible health care workers directly interacting with COVID-19 patients, so they can be referred to treating facilities, supply permitting. The justification and operationalization of this item is outlined in the "Priority for Clinically Eligible Health Care Workers" section above. Note that this provision is context-dependent and MDH should end this priority as shortages in the health care workforce are resolved.
  - Remaining **critical workers in high-risk settings** (CWHRS) (i.e., those with high occupational risk of exposure to COVID-19) or a subset as described above, if MDH deems that such priority is warranted given the levels of risk faced by such workers on the job or workforce shortages.
    - Information about the CWHRS priority can be found in the section on "Allocation Among Patients" above.
  - **Residents of skilled nursing facilities (SNF) or other long-term care (LTC) facilities**, such as assisted living or group homes, if MDH deems that such priority is warranted given the levels of risk faced by residents of these facilities.
    - This does not imply that these facilities will directly administer mAbs to patients, but that such patients should have access to the therapy. Because mAbs are authorized for use in outpatient settings, it represents an important potential countermeasure for residential care facilities, given increased risk of progression to severe COVID-19 for patients in these settings.
- Relative chances will be specified by MDH in consultation with MCEC and MDH's Science Advisory Team (SAT).
- On the launch of a weighted random selection process, relative chances will reflect an aim of providing mAbs access first to all clinically eligible health care workers treating COVID-19 patients, if MDH determines the workforce shortage currently justifies health care worker priority for a region or statewide.

- The initial relative chances will be set based on the best available data and adjusted over time by MDH in consultation with MCEC. Higher relative chances are the primary means of reflecting an elevated priority for groups. Relative chances will be adjusted by MDH over time in consultation with MCEC and the SAT.
- In the event of scarcity requiring a weighted random selection process, the vaccination status of eligible patients should not be considered in determining their level of priority. Vaccinated patients should remain eligible for mAbs if they develop breakthrough infections and unvaccinated patients should not be penalized.
- MDH should monitor allocation patterns and periodically revisit these priorities. An initial review should take place within two months after a weighted random selection process is first implemented.

By default, supply (inventory and appointments) will be divided into one-seventh the weekly allocation for use on a daily basis. This daily allocation will be set at the beginning of the week, and the platform will calculate necessary adjustments from default based on assessments of expected growth or decline in case incidence over the course of the coming week. Any supply that remains unobligated at the end of a day will be rolled over for the next day's use. Facilities should report how many days a week they are open for infusions/injections to MDH to reflect their daily allocation more accurately.

Infusion/injection facilities will be asked to report to MDH daily the number of doses delivered to patients. The MNRAP screening website will allocate doses of mAbs, both in circumstances of scarcity and when inventory and capacity are not scarce. That is, approximately one-seventh of the week's pool should be made available each day, with any leftover added to the following day. This will avoid running out of doses in the first several days after a shipment during scarcity, which would disadvantage patients who seek care later in the week. If facilities do not operate each day of the week, their weekly supply will be divided evenly over the number of days in operation, as above, and when in operation, facilities are expected to have daily capacity to meet the assigned number of infusions/injections.

Operationalizing the MNRAP weighted random selection process

If mAbs are in scarcity even after employing the clinical prioritization strategy explained above (refer to "Stage 1: Clinical prioritization"), then a weighted random selection process for allocating among those patients will be employed by MDH. If the MNRAP screening process provisionally determines that a patient meets clinical eligibility criteria, the weighted random selection process will be used to determine if the patient will be allocated a dose of mAbs. Patient allocation decisions will be made by this system immediately, and infusion/injection facilities (which may include opted-out systems) will receive a referral email for patients provisionally selected to receive mAbs. Once the randomization process is completed, the referral for mAb infusion/injection should be sent to an infusion/injection center (with immediate notification to the patient) or the patient should be notified immediately that they will not receive a dose due to scarcity.

Employing an end-of-day holdback or reserve

Under conditions of scarcity when the clinical prioritization strategy is active or the MNRAP weighted random selection process is operational, the MNRAP system will initially employ an **end-of-day holdback** to mitigate inequities associated with system startup. The fairness of the weighted random selection process depends upon the accuracy of the modeling built into the system to predict demand for mAbs throughout the course of the week. If the prediction is inaccurate – as it very likely will be, given the number and types of variables that affect when patients might use the screener – patients who are similarly situated (and so should receive roughly equivalent chances at allocation) would in reality have varying chances. To mitigate this equity risk, everyone who does not get selected over the course of the day will get a second chance overnight, using supply that will be held back for this purpose (holdback size to be determined by MDH).

Over time, as predictive models improve, the holdback will shrink, thus decreasing the numbers of patients who will experience delay in access related to the screening process. A second chance approach protects against specific challenges to equitable access. First, if the system under-allocates because demand is lower than predicted, some individuals that should have received access (had predictions been more accurate) be denied allocation on the first chance. Overnight, if there is more supply than demand, all would receive access.

The second way an overnight holdback mitigates equity risk is when the system over allocates because demand is higher than predicted, and more individuals are selected than should have been. Functionally, in these circumstances the system would run out before the end of the day. A second chance feature will help participants who show up after the system has run out have some chance overnight.

On the second chance allocation, the system can account for the characteristics of all patients competing for the mAbs. As such, the weighted random selection approach will become more precise, since patient characteristics and total demand will be known rather than predicted (as must occur with the instant read approach during the day).

The relative priority between the groups established by MDH will also be utilized during the holdback allocation. Patients receiving provisional selection for mAbs on their second chance will automatically be matched with providers that have infusion/injection capacity (which may include opt-out systems). As with the instant weighted random selection function, electronic referrals from the holdback allocation are automatically be sent to the facility, which then calls the patient to schedule. Patient notification also occurs immediately by email or by automated phone message.

Patients that do not receive mAbs in either their first or second chance will remain in the pool for additional chances against future end-of-day holdbacks until their eligibility window expires. They may also be considered by opted-out sites during this time. Patients do not need to 're-enter' MNRAP for additional attempts at randomization in later days. This approach should be communicated clearly to the general public.

Handling differential demand through the weighted random selection process

When the weighted random selection process is operational, the MNRAP system will set the probability of provisional selection for accessing mAbs based on supply of medication and infusion/injection slots relative to **predicted** demand, weighting relative chances between groups per the section above. If the demand is much lower than expected, it is plausible that patients will be told they were not selected for scarcity reasons when, in fact, by the end of the day there is still supply left. Fortunately, a feature of the end-of-day holdback above is that these patients will be selected during their second chance if they are clinically eligible (since supply exceeds demand). A more problematic scenario is if demand is much higher than expected; in that case, supply will be depleted before the end of the day. Patients who access the MNRAP screener after supply has been depleted will be considered in the end-of-day holdback only.

Confirming clinical eligibility is necessary

Whether supply is scarce or sufficient, the allocation of mAbs to a patient through the MNRAP system is provisional because patients must undergo confirmatory screening when scheduled for their appointment, or at time of infusion/injection. Confirming eligibility prior to time of infusion/injection would be preferable, as it would prevent having to turn away patients who appear for infusion/injection appointments, if their confirmatory screening indicates that they are not clinically eligible. Those who are not clinically eligible would not receive mAbs. In times of scarcity, those who should not be clinically prioritized will also not receive mAbs.

Determining clinical eligibility

At this time, the EUAs identify which types of patients are eligible and ineligible for mAbs, but do not offer sufficient clinical information to construct clinical priority tiers – this is why MDH will use the M-MASS clinical prioritization score.

For treatment, per the EUAs, mAbs are not authorized for use in patients:

- Who are COVID-19-positive, but asymptomatic, or
- Who are symptomatic, but do not have a positive COVID-19 test, or
- Who have severe COVID-19 illness requiring hospitalization, or
- Who require oxygen therapy due to COVID-19, or
- Who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

In May and June of 2021, the FDA updated eligibility criteria for mAb treatment. Per the EUAs, mAbs **are authorized** for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 – 17 years of age weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization[24] and who do not meet exclusion criteria above. High risk is defined as patients who meet **at least one** of the following criteria medical conditions or other factors:

- Older age (for example 65 years of age and older).
- Obesity or being overweight (for example, adults with BMI greater than 25 kg/m^2, or if ages 12-17, a BMI at or greater than the 85th percentile for their age and gender based on CDC: Clinical Growth Charts (www.cdc.gov/growthcharts/clinical_charts.htm).
- Pregnancy.
- Chronic kidney disease.
- Diabetes.
- Immunosuppressive disease or immunosuppressive treatment.
- Cardiovascular disease (including congenital heart disease) or hypertension.
- Chronic lung diseases (for example, chronic obstructive pulmonary disease; asthma, moderate to severe; interstitial lung disease; cystic fibrosis; and pulmonary hypertension).
- Sickle cell disease.
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies).
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19).[24]

[24] FDA. June 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab). (www.fda.gov/media/145611/download)
See also FDA. May 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. (www.fda.gov/media/145802/download)

The FDA advises that:

"Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of [monoclonal antibody therapies] under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: People with Certain Medical Conditions (www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Healthcare providers should consider the benefit-risk for an individual patient."[25]

Also, allocation decisions should **consider whether the patient is imminently and irreversibly dying or terminally ill with life expectancy under 6 months** (e.g., eligible for admission to hospice). If supply of mAbs is scarce, patients in this group should not receive priority for access. If supply is sufficient, then patients who are terminally ill with life expectancy under 6 months should be considered as candidates for mAbs.

For PEP, per the EUAs, mAbs are authorized for use in:

"adult and pediatric individuals (12 years of age and older weighing at least 40 kg) … who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- *not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (for example, individuals with immunocompromising conditions including those taking immunosuppressive medications12) and*
  - *have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per Centers for Disease Control and Prevention (CDC)13 or*
  - *… at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (for example, nursing homes, prisons)."*[26]

Under scarcity, providers treating PEP patients should confirm they meet additional criteria related to immunocompromised status (refer to "Stage 1: Clinical prioritization" above). Otherwise, criteria for determining which patients are at high risk of progression to severe COVID-19 are the same as those listed for treatment uses of mAbs above.

Patient decision-making and consent to mAbs

Under all circumstances – scarce or sufficient supply – **patients who are capable of decision-making are entitled to partner with their care team in deciding whether to consent to administration of mAbs**. For patients who are not capable of making decisions, their authorized decision-maker should be consulted. When patients are provisionally screened for eligibility to receive mAbs and selected to receive the resource through MNRAP, they should be informed whether they have been deemed eligible for and have been allocated a course of mAbs under this framework.

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[25] FDA. June 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of REGEN-COV (casirivimab and imdevimab). (www.fda.gov/media/145611/download)
See also FDA. May 2021. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. (www.fda.gov/media/145802/download)

[26] FDA. July 30, 2021. Letter to Yunji Kim, PharmD, Regeneron Pharmaceuticals, Inc. (www.fda.gov/media/145610/download)
See also FDA. September 16, 2021. Letter to Christine Phillips, PhD, RAC, Eli Lilly and Company/ (https://pi.lilly.com/eua/bam-and-ete-eua-fda-authorization-letter.pdf)

The MNRAP centralized screening website should provide patients with information about mAbs, including that they are not FDA-approved, but are available under an EUA. The website should also offer patients sufficient information to allow them to decide whether to seek mAbs, including information regarding alternatives and whether receiving mAbs may limit their access to other interventions or research studies.

At the infusion/injection facility, informed consent conversations will occur immediately prior to infusion/injection. To promote equity, consent forms/patient information sheets should be available in the diverse languages of a facility's patient populations, and appropriate translation services should be available during screening and upon presentation at the facility in order to foster appropriate consent discussions.

The authorized decision-maker should be the person appointed by the patient (or otherwise authorized by law) to make decisions on their behalf. If the patient has not indicated who that person should be, the clinical team should work with the patient's spouse, partner, family, or close friend. All personnel involved in patient decision-making processes should work to follow Minnesota guidance and law on surrogate decision-making. If patients or their authorized decision-makers express interest in accessing mAb treatment, but have concerns about ability to pay, infusion/injection facilities (or the health care systems/organizations with which they are affiliated) should work with patients to identify sources of payment for mAbs.

What allocation decisions should not consider or be based upon

- Race; ethnicity; gender; gender identity; sexual orientation or preference; religion; citizenship or immigration status; or socioeconomic status (this does not limit consideration of factors that data indicate are associated with heightened risks of progression to severe COVID-19 when assessing individual patient prognosis).
- Ability to pay.
- Age as a criterion in and of itself (this does not limit consideration of a patient's age in clinical prognostication, if data indicates that age is associated with heightened risks of progression to severe COVID-19).
- Disability status or comorbid condition(s) as a criterion in and of itself (this does not limit consideration of a patient's physical condition in clinical prognostication, if data indicates that disability is associated with heightened risks of progression to severe COVID-19).
- Predictions about baseline life expectancy beyond the current episode of care (i.e., life expectancy if the patient were not facing the current crisis), unless the patient is imminently and irreversibly dying or terminally ill with life expectancy under 6 months (e.g., eligible for admission to hospice).
- First-come, first-served, because this approach tends to provide advantage to privileged populations.
- Judgments that some people have greater quality of life than others.
- Judgments that some people have greater social value than others.

Importance of documentation and confidentiality

All information provided by patients in the screening process should be treated as **private patient data** and available only to MDH, the relevant health care system and hospital, and the infusion/injection facility. Under all circumstances – scarce or sufficient supply – patients who receive mAbs should have an order and treatment notes documented in the patient's health record. In addition, allocation decisions should be recorded by the care setting in a **facility-wide log** to allow for transparency and retrospective review. Under conditions of scarcity, when mAbs are allocated via triage, this log should include which patients were eligible for mAbs, which patients received the mAb allocation, and how randomization occurred.

MDH will conduct routine audits for quality improvement purposes to determine if this framework or its operationalization, including the MNRAP centralized online screener, require refinement to meet the fundamental moral commitments and objectives guiding mAb allocation.

Appendix

Therapeutic Options for COVID-19 Patients (www.health.state.mn.us/diseases/coronavirus/hcp/therapeutic.html)
Information and resources on mAb treatment.

Exposure Assessment for Critical Workers with Job-related risk of COVID-19 (www.health.state.mn.us/diseases/coronavirus/hcp/mabassess.pdf)
Critical worker in high-risk setting screening tool.