Ethical Framework for Allocation of Remdesivir in the COVID-19 Pandemic

This has been updated since June 1 in the following ways: Language has been modified to:

- Allow MDH to retain a small supply of RDV at the Public Health Laboratory for allocation to facilities
- Change the requirement for facilities to notify MDH of surplus RDV from 72 hours from receipt of the facility allocation to one week of receipt
- Allow for use of EUA RDV to start patients approved by Gilead for RDV under the compassionate use program on therapy

Introduction

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir (RDV) for treatment of COVID-19. As the FDA notes, “Remdesivir is a direct acting antiviral that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.... [However], it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of patients hospitalized with severe COVID-19.”

Minnesota expects to receive a limited quantity of RDV which will be allocated to health care facilities for treatment of patients hospitalized with severe disease. Allocation of this initial limited quantity raises ethical issues addressed by this document.

The hope is that future shipments will be received that will increase the amount of RDV available for future allocation. While this document addresses the June 2020 allocation, the expectation is that a fuller document will subsequently be developed, addressing the ethical issues raised by allocation of future quantities of the medication.

This document was developed by the Minnesota Department of Health (MDH) working with a subgroup of the Minnesota COVID Ethics Collaborative (MCEC) including the co-leads, with

1 U.S. Food and Drug Administration. May 1, 2020. Letter to Ashley Rhoades, MBS, RAC, Gilead Sciences, Inc.
additional clinical inputs. The document addresses relevant past guidance developed at MDH, key ethical values, and how allocation should occur at two levels: (1) allocation among health care facilities in Minnesota, and (2) allocation among patients within each health care facility.

Past Guidance & 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: the Minnesota Pandemic Ethics Project (www.health.state.mn.us/communities/ep/surge/crisis/panethics.html), and Ethical Considerations - Crisis Standards of Care (www.health.state.mn.us/communities/ep/surge/crisis/ethical.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 must 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 commitment 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; and
- 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; and
- strive for fairness and protect against systematic unfairness and inequity.

Allocation of scarce resources should be grounded in maximizing the number of lives saved, taking into account both risk and expectation of benefit. Evaluation of clinical prognosis, construed here as survival to discharge from an acute care facility, should be based upon well-accepted clinical tools and individualized assessment. This framework provides guidance about allocation to health care facilities across the state, as well as to patients within a given facility.
In existing ethical guidance for public health emergency response in Minnesota, recommended allocation of antivirals has included some prioritization of key workers, both due to considerations of reciprocity (what is owed to workers by virtue of the risk they take on) and instrumentality (what is owed to workers based on their role in response and recovery). Given extreme scarcity and the time pressures associated with initial RDV allocation, it may be logistically impractical to satisfy these obligations - and so key worker status should not be considered in the May and June 2020 RDV allocation. However, future documents should address previous guidance providing some priority for key workers as more resources become available.

**Ethical Criteria for Allocation of Remdesivir**

**Ethical strategy for distribution throughout the state**

Distribution of RDV to health care facilities across the state should be proportional to the total number of COVID-positive patients currently admitted to the facility who are not currently on RDV for any reason (e.g., under compassionate use, a clinical trial, or previous allocations of RDV). In other words, more resources should be sent to facilities with greater numbers of prioritized recipients, so that prioritized patients have maximal access to the scarce resources.

**Process for allocation among facilities in Minnesota**

For allocation of the June 2020 allocation of RDV to health care facilities, MDH should estimate how many patients at each facility (or system, if facility data are unavailable) fit the allocation criteria listed immediately above. Based on those numbers, MDH should calculate the proportion of that total associated with each facility (or system), and distribute the relevant proportion of the total supply of RDV to each facility (or system). If the state’s allocation of RDV goes to a system instead of a single facility, that system should allocate proportionately to its facilities based on the number of prioritized patients in each facility.

In allocating the RDV supply to facilities, MDH should generally assume all patients need a 5-day course of treatment, with the option to make adjustments as needed based on the number of patients in the highest and second highest priority groups at facilities.

In the event that a patient receives RDV or is ordered RDV under this framework and is later transferred to another facility inside or outside of Minnesota, the remainder of the course should follow that patient. Systems that have facilities located outside of Minnesota should only be allocated RDV for their in-state facilities.

Each facility (or system) should identify points of communication for MDH to contact with information about 1) pending shipments and 2) number of patients currently being treated with RDV for any reason. This guidance recommends that RDV status be recorded in the Electronic Health Record for ease of access to information.
Facilities may have more patients who are prioritized for access to RDV than available doses. As noted below, allocation among equally prioritized patients within facilities should be by a fair, random process. If a surplus is expected following a shipment of RDV to the state, MDH may retain a small supply of remdesivir to store at the Public Health Lab (PHL) for allocation to facilities as needed. Providers should contact Sarah Lim at MDH (sarah.lim@state.mn.us) if they require additional courses or additional doses to make up a treatment course.

In order to maximize benefit of this resource, **facilities should not hold courses from the June 2020 allocation for future use.** All courses should be immediately allocated. If facilities have RDV doses left over after an allocation window of one week from receipt of the shipment at the facility, they should contact MDH to discuss whether a portion of the supply should be reallocated (Sarah Lim, sarah.lim@state.mn.us).

### Allocation within Institution

**Ethical strategy for distribution within a facility**

**Clinical prognosis should ground allocation decisions.** Prognosis should be understood to include both need for the resource (i.e., risk of serious morbidity or mortality if the patient were not to receive the resource), and the likelihood that the patient will benefit from access to the resource by recovery to hospital discharge. **Substantial differences** in prognosis are what is ethically relevant in differentiating between patients; small differences should be viewed as morally equivalent and should not be used to allocate resources to or withhold resources from patients.

After discussion with infectious disease experts and members of the MCEC, and updated with preliminary data from the published Beigel et al. RDV trial published on May 222 and data from the Gilead open-label RDV trial comparing a 5-day and 10-day course in a subset of patients,3 clinical criteria for the June 2020 allocation was determined based on risk and likelihood of greatest benefit.

**Highest Priority Patients**

The patients receiving the highest priority for allocation of RDV are: Patients with laboratory-confirmed COVID-19 (by RT-PCR testing on a respiratory specimen) who are not already on RDV (e.g., for clinical trials or compassionate use) and 1) are on advanced respiratory support (high-flow nasal cannula; CPAP; BiPAP) OR 2) who **have three of the four** characteristics:

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< 94% oxygen saturation on room air
• Respiratory rate > 30
• Lung infiltrates on imaging
• Using supplemental oxygen

Patients should meet other clinical inclusion criteria as specified by the FDA EUA for RDV (GFR ≥30ml/min, ALT < 5 times upper limit of normal).

Based on the EUA and the Gilead open-label trial, the recommended dose for adults and pediatric patients weighing >40 kg not on mechanical ventilation or ECMO is a single loading dose of 200mg on Day 1 followed by 100mg once daily for Days 2 through 5 (for a total 5-day course). At five days, patients who are not mechanically ventilated or on ECMO can be evaluated for possible continuation of RDV if needed, for a possible total 10-day course.

When patients are otherwise of equal priority in the highest priority group of patients (i.e., there is no substantial difference in risk and likelihood of benefit) and there is not sufficient RDV for all patients in this group, the Triage Officer or Team should use a random process to allocate the resource (as explained below).

Second Highest Priority Patients

If facilities have met the needs of the highest priority group of patients, facilities should then allocate RDV based on the following criteria:

• Patients with laboratory-confirmed COVID-19 (by RT-PCR testing on a respiratory specimen) who are not already on RDV (e.g., for clinical trials or compassionate use) and who have been mechanically ventilated for 5 days or less or are on ECMO for 5 days or less. Patients should meet other clinical inclusion criteria as specified by the FDA EUA for RDV (GFR ≥30ml/min, ALT < 5 times upper limit of normal).

Under the Emergency Use Authorization (EUA) for remdesivir, the recommended dose for adults and pediatric patients weighing >40 kg on mechanical ventilation or ECMO is a single loading of 200mg on Day 1 followed by 100mg once daily for Days 2 through 10 (for a total 10-day course).

When patients are otherwise of equal priority within a priority group of patients (i.e., there is no substantial difference in risk and likelihood of benefit) and there is not sufficient RDV for all patients in that group, the Triage Officer or Team should use a random process to allocate the resource (as explained below).

In both priority groups, patients who have started a course of RDV who later no longer meet clinical criteria for eligibility because of worsening kidney or liver function should be considered for discontinuation of RDV. It should not be discontinued for purposes of reallocating to other patients.
Also, in both priority groups, in addition to prognosis of surviving current illness to hospital discharge, 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). Given the scarcity of supply of RDV, patients in this group should not currently receive priority for access.

In order to maximize benefit of this resource, facilities should not hold courses from the June 2020 allocation for future use. If facilities have RDV doses left over after an allocation period of one week from receipt of the shipment at the facility, they should contact MDH to discuss whether a portion of the supply should be reallocated (Sarah Lim, sarah.lim@state.mn.us). If facilities have insufficient courses or doses to meet patient need, they should contact MDH to ascertain whether additional courses are available.

**Patient decision-making & consent to RDV**

On intake, clinical teams should discuss the patient’s interest in receiving therapies not yet approved by the FDA but available under an EUA, should they become available, and document the discussion in the EHR. In addition, patients may be asked whether they would be interested in receiving investigational therapies, if they qualify for access through compassionate use or a clinical trial. (Access and consent to those investigational uses are not addressed by this framework.) Patients should be informed if they have been deemed eligible for and selected to receive an RDV course under this RDV framework, even if they had previously indicated they were not interested in receiving unapproved therapies. A patient who is capable of decision-making is entitled to partner with their care team in deciding whether to consent to administration of RDV. Patients should be informed that RDV is not FDA-approved but is available under an Emergency Use Authorization. For patients who are not capable of making decisions, their authorized decision-maker should be consulted. If the patient lacks decision-making capacity but no authorized decision-maker is available, clinicians should allocate the RDV if the patient is eligible in keeping with the best interests of the patient, unless the patient previously refused to consent to unapproved therapies. The authorized decision-maker should be the person appointed by the patient 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. Clinicians and health care organizations should work to follow Minnesota guidance and law on surrogate decision-making.

Facilities should make sure to note in the patient’s records how to reach the authorized decision-maker rapidly.

**Children and pregnant women** are currently eligible to receive RDV through compassionate use from Gilead and so will not be prioritized for the June 2020 allocation. If a patient is approved for RDV under the compassionate use program but a delay in initiating therapy is expected (e.g., due to the time needed to ship RDV) that may adversely affect the patient’s clinical course, a facility may use their EUA supply to start the patient on treatment, as long as 1) there is sufficient supply available to allocate to other patients until the compassionate use RDV arrives, 2) the excess supply
received under the compassionate use program is used to replenish the EUA supply, and 3) initiation of therapy complies with applicable institutional and FDA rules including IRB involvement.

**Patients who are already receiving RDV** (e.g., through clinical trials or compassionate use) will not be eligible to receive doses from this round of drug allocation.

**Key workers** will not receive prioritization during this round of allocation, for the reasons noted earlier in the document.

**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;
- Ability to pay;
- Age as a criterion in and of itself (this does not limit consideration of a patient’s age in clinical prognostication of likelihood to survive to hospital discharge);
- 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 of likelihood to survive to hospital discharge);
- 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 (should not distinguish between patients when treatment has not yet been started on equivalent patients);
- Judgments that some people have greater “quality of life” than others;
- Judgments that some people have greater “social value” than others.

**Process for allocation within a facility**

**Separation of roles -- triage decision-making and bedside care**

Randomization decisions should be made by a Triage Officer or Team that is separate from the clinicians providing care at the bedside. This approach to decision-making promotes the ability of bedside clinicians to advocate for their patients, thus protecting the integrity of the patient/provider relationship. It also helps to ensure that allocation decisions are made fairly, consistently, and based on objective data to allow comparisons across cases. The separation of roles does not imply that the Triage Officer or Team may not communicate with treating clinicians. For example, the Triage Officer or Team may need to consult the treating clinician to clarify factors relevant to the triage decision. In any communication between the treating clinician and Triage Officer or Team, all should be mindful that, to the extent possible, the Triage Officer or Team should not be provided with
patient characteristics identified above as impermissible to consider in allocation decisions. While bedside clinicians will not make allocation decisions, they will be expected to follow the directives of the Triage Officer or Team, so that resources may be ethically stewarded.

Facilities that do not yet have Triage Officers or Teams established should set up an ad hoc triage process for the June 2020 shipment of RDV to maintain separation of roles, for example using the administrative head of pharmacy to randomize among eligible patients.

Importance of documentation

Patients who receive RDV should have the order (including length of course) documented in the patient’s Electronic Health Record (EHR). Allocation decisions should be logged and recorded by facility to allow for transparency and retrospective review. This log should include which patients were eligible for RDV, which patients received the RDV allocation, and how randomization occurred. Documentation is important to ensure appropriate care of the patient across clinicians and shifts, to ensure transparency and accountability to the patient and family, to allow Triage processes to work properly, and to enable retrospective review to spot and resolve problems.