

## Ethical Framework for drug shortages that occur during the COVID-19 pandemic in Ontario

**Background:** While drug shortages across Canada occur frequently, the COVID-19 pandemic may exacerbate existing shortages or create new shortages due to a number of factors, including the novel use of existing agents as COVID-19-specific therapies or as ancillary drugs for supportive care (e.g., drugs for cardiorespiratory issues), and collateral drug shortages related to increased demand (i.e., stockpiling) and/or supply chain disruption. This document focuses on drug shortages during the COVID-19 pandemic. See **Appendix I** for examples of potential categories of drug therapies affected during the COVID-19 pandemic.

**Issue:** What novel issues exist within the COVID-19 pandemic that warrant specific modifications to the [existing provincial ethical framework on resource allocation during drug shortages](#)? See **Appendix II** for an overview of the existing provincial ethical framework (from 2012).

**New Issues:** COVID-19 is a novel virus for which there are no formally approved drug therapies other than supportive care. However, there is emerging evidence of efficacy of a range of existing drugs for both the treatment of patients with, and post-exposure prophylaxis of healthcare workers exposed to, COVID-19. A number of these agents are in ongoing COVID-specific trials or under consideration for inclusion in [COVID-19 clinical practice guidelines](#). The recent focus has been on hydroxychloroquine and remdesivir. Therefore, additional focus is needed to consider issues like equity of access to unapproved drugs available only in clinical trials or approved drugs available via off-label prescribing. Additionally, consideration must be given to how to prioritize allocation amongst individuals receiving the drug for an approved indication versus those accessing it in an experimental context in which no other proven or approved treatment options exist. Finally, specific consideration of the value of systematic collection of emergent evidence related to the safety and efficacy of relevant candidate drugs employed to treat COVID-19 is necessary, particularly when studies have not undergone the usual peer review processes.

### COVID-19 Drug Shortage Ethical Framework:

#### *Ethical Principles (in alphabetical order, not rank-ordered)*

Principle & Meaning	Modifications for COVID-19
Beneficence  Maintaining highest quality of safe and effective care with resource constraints	<ul style="list-style-type: none"><li>• Promote standards of care based on best available evidence across treatment indications</li><li>• Protect drug supply for established indications with proven clinical effectiveness</li><li>• Where clinical indications overlap, aim to use the most appropriate drug to clinical context, based on best available evidence (e.g., distinct pathways of common agents for palliation vs. ICU sedation)</li><li>• Maximize drug/therapy substitutions where appropriate</li></ul>

	<ul style="list-style-type: none"> <li>• <i>Non-abandonment</i>: when patients are unable to access a preferred medication or switched to an alternative, they will not be abandoned. Efforts will be made to minimize suffering and provide best available care.</li> </ul>
<p>Equity</p> <p>Promote just/fair access to resources</p>	<ul style="list-style-type: none"> <li>• Facilitate fair drug allocation between COVID-19 and non-COVID patients through ongoing assessments of need and evidence</li> <li>• Explore mechanism to ensure fair inter and intra-provincial distribution of scarce drugs</li> <li>• Promote fair access to drugs regardless of geographic location</li> <li>• Seek to minimize ‘double disadvantage’: privilege access to therapeutic alternative or second-line therapy for those denied first-line therapy</li> </ul>
<p>Reciprocity*</p> <p>Respond to each other in similar ways that recognize mutual dependence</p>	<p><i>Application</i>: Mitigate disproportionate burdens by prioritizing those who have incurred significant personal risk or harm (e.g. essential healthcare workers or individuals ineligible for other healthcare services such as critical care)</p> <ul style="list-style-type: none"> <li>• Give healthcare workers priority access to primary and secondary prophylaxis to mitigate the increased risk of exposure to COVID-19</li> </ul>
<p>Solidarity</p> <p>Build, preserve and strengthen inter-professional / institutional / sectoral / provincial collaborations and partnerships</p>	<ul style="list-style-type: none"> <li>• Collaborate cross-institutionally and cross-jurisdictionally to maximize benefit for all Ontarians</li> <li>• Endorse and apply a consistent ethical framework</li> <li>• Share planning for inventory management with manufacturers, wholesalers and distributors and between inpatient and outpatient pharmacies, including public and privately-run pharmacies</li> <li>• Collate and maintain a provincial inventory of critical COVID-19 related therapies, agree on optimal institutional stocks and redistribution</li> <li>• Given the potential impact of individual behavior in a pandemic, foster an understanding and appreciation of the duties required to support solidarity</li> </ul>
<p>Stewardship</p> <p>Use available resources carefully and responsibly</p>	<ul style="list-style-type: none"> <li>• Tailor prioritization guidelines to integrate emerging evidence for interventions</li> <li>• Facilitate fair drug allocation through ongoing assessments of need and evidence</li> <li>• Support rational prescribing and preserve supply for established indications with good evidence of safety and efficacy</li> <li>• Implement pharmacy/prescriber/dispensation limitations across relevant jurisdictions to prevent stockpiling</li> </ul>

<p>Trust</p> <p>Foster and maintain public, patient and healthcare provider confidence in health systems</p>	<ul style="list-style-type: none"> <li>• Foster and maintain public, patient and healthcare workers confidence in the fair allocation of drugs.</li> <li>• Empower patients with information to provide informed consent</li> <li>• Ensure fair drug allocation through ongoing assessments of need and evidence</li> <li>• Publicly post ethical framework and maintain relevant information for the public on shortage details</li> <li>• Encourage formal opportunities to revise COVID clinical practice standards or guidelines in light of new evidence, including feedback from patients and the public</li> </ul>
<p>Utility</p> <p>Maximize the greatest possible good for the greatest possible number of individuals</p>	<ul style="list-style-type: none"> <li>• Prioritize scarce therapies to those most likely to benefit</li> <li>• Maximize survival</li> <li>• Maximize drug sharing amongst facilities, to support those with greatest additional burden of need and populations most likely to benefit</li> <li>• Prioritize access to drugs in situations in which evidence collection is most likely to occur and inform an emerging evidence base</li> </ul>

\*New ethical principle that has been added to the ethical framework

<b>Fair Process Principles</b>	
<b>Principle</b>	<b>Meaning</b>
Relevance	Decisions are made on the basis of reasons (evidence, principles, values) relevant under the circumstances and by credible, accountable stakeholders
Publicity	Decisions are made using an open and transparent process, enabling understanding of the rationale
Revision	Decisions are revisited and revised as new information emerges, and stakeholders have opportunities to voice concerns
Empowerment	Stakeholders have meaningful opportunities to participate in/inform the decision-making process
Enforcement	Mechanisms exist to ensure that these fair process principles are sustained throughout the response

### **Amendments to Allocation Criteria:**

The following allocation principles apply generally to all types of drug shortages across the healthcare continuum. They provide a foundation to inform discussion and decision-making at the relevant governance level. Stage 1 focuses on conservation strategies, sharing/borrowing and alternative sourcing of the drug. Stage 2 prioritizes access to drugs in short supply based on risk of harm. Stage 3 prioritizes access *between persons within a level of priority as described in Stage 2* using a fair allocation procedure (e.g., randomization). See **Appendix III** for an illustration of the 3 progressive stages.

**Stage 1. Implement strategies to preserve or approximate standard of care to the extent possible within available drug supply. Ideally efforts in 1a, 1b and 1c could be occurring simultaneously to maximize timely success with these efforts, which avoids Stage 2.**

*When there is risk of drug shortage,*

1a. Conserve existing supply of drugs using strategies such as:

- Appropriate governance levels should develop a list of drug shortages and review regularly in collaboration with industry
- Review current usage practices in light of emerging safety and effectiveness evidence. When relevant, communicate to prescribers in a manner to inform prescribing behaviour.
- Reduce wastage of drugs through rational use and compounding stewardship (e.g., reduce waste from single use vials by ordering aliquots of smaller sizes, practice aseptic procedures to use single-dose containers for preparing multiple doses, batch prepare doses)
- Use alternative drugs where evidence suggests similar safety and effectiveness to the drug in short supply
- Cancel non-urgent or elective procedures that require use of drugs in short supply with appropriate transparency and communication to those affected
- Review the drug protocol for essential services that use large amounts of drugs in short supply to see if drug doses may be reduced without affecting efficacy or if alternative treatment options are possible
- Revise frequency of dosing or drug administration where evidence suggests harm would be negligible or minor
- Consider dose sharing where harm would be negligible or minor when patients consent to such a change
- Use expired drugs if evidence suggests they are safe and effective to use when patient consents to such a change; in absence of evidence, balance potential risk of use and harm of not using an expired product. Additionally, apply knowledge and consensus guideline regarding potency and sterility.
- Delay new enrollment in clinical trials unrelated to COVID-19 using drugs in short supply
- Stop existing clinical trials unrelated to COVID-19 using drugs in short supply where it can be done safely and without undermining the scientific integrity of the trial (e.g. trials that are almost complete).

1b. Sharing and borrowing:

- Share drugs that are in short supply
- Collect drugs from programs or clinics that have been closed due to pandemic (e.g. dental offices, elective services.)

1c. Access new supply of drugs by:

- Collaborate with partners, sectors, and governments to identify and procure from alternative sources

**Stage 2. Apply Primary Allocation Principles based on risks of harm if unable to access drug in short supply:**

*When Stage 1 strategies are insufficient to meet the need for drugs in short supply, give priority access in rank order to:*

2a. Persons who are on the drug for an approved indication, demonstrating an ongoing benefit from the drug, no comparable alternatives are available, and would be at severe risk of harm (e.g., suffering, irreversible harm, or significant clinical deterioration) if unable to access drug.

2b. Persons who are on the drug for an approved indication, demonstrating an ongoing benefit from the drug, no comparable alternatives are available, and would be at moderate risk of harm if unable to access drug.

2c. Patients who are acutely or critically ill, have a high likelihood of survival, and are on the drug as part of an approved COVID-19 related clinical trial.

2d. Healthcare workers exposed to a confirmed or suspected COVID-positive person receiving experimental prophylaxis within a clinical trial.

2e. Patients who are on the drug for an approved indication, demonstrating an ongoing benefit from the drug, and may be able to access a comparable alternative, or if unable to access an alternative would be at low risk of harm if unable to access drug in short supply.

2f. Persons who are prescribed the drug for an off-label indication, demonstrating an ongoing benefit from the drug, no comparable alternatives are available, and would be at severe or moderate risk of harm if unable to access drug.

2g. Patient with minor symptoms prescribed the drug for an off-label indication.

*Meanwhile...*

- Continue with Stage 1 strategies, *and*
- Reassess new evidence on an ongoing basis to identify any changes in level of priority.

**Stage 3. Apply Secondary Allocation Principles to Ensure Fair Access to Drugs in Short Supply**

*When decisions must be made between persons within a level of priority as described in Stage 2, prioritize persons using a fair and unbiased procedure that does not discriminate between persons based on factors not relevant to their risk of harm (e.g., race, social value, sex, age) such as:*

- 3a. A procedure that is developed and sanctioned by affected stakeholders (e.g., first come first served or random selection). A randomization system would mean that only some patients would receive the drug in short supply.

*Meanwhile...*

- Continue with Stage 1 strategies, *and*
- Reassess on an ongoing basis to identify any changes in level of priority.

## Appendices:

### Appendix I

#### Examples of categories of drug therapies potentially affected during the COVID-19 pandemic:

1. COVID-19-directed therapies: There is emerging evidence of activity and/or efficacy of a range of drugs both existing and experimental for the treatment of patients with, and post-exposure prophylaxis of healthcare workers exposed to, COVID-19. A number of these agents are in ongoing COVID-specific trials or [guidelines](#). Drugs under investigation for efficacy in treating COVID-19 include:

- Chloroquine
- Hydroxychloroquine
- Azithromycin
- Tocilizumab
- Anakinra
- Emapalumab (Not Approved)
- Ribavirin
- Remdesivir (Not Approved)
- Lopinavir/Ritonavir
- Interferon- $\beta$
- Favipiravir (Not Approved)
- Baloxavir (Not Approved)
- Umifenovir (Not Approved)
- Aerosolized  $\alpha$ -interferon
- Eculizumab
- Artesunate
- Convalescent serum
- *This list may expand*

Given the extent of the pandemic, the acuity of patients, and the political dimensions of the crisis, demand-side shortages (i.e. stockpiling) of a number of these drugs are evident or anticipated. Principal concerns at present focus on hydroxychloroquine.

#### 2. COVID-19 supportive care agents:

Emerging shortages of ancillary drugs relevant to the supportive care management of critically ill patients with cardiorespiratory issues include:

- Systemic and inhaled corticosteroids
- Salbutamol and other B-agonists (in IV, nebulizer, and metered dose inhaler forms)
- Opioid analgesics
- Anesthetic agents, including paralytics (e.g., propofol, rocuronium, cisatracurium)
- *This list may expand*

#### 3. Collateral drug shortages:

Finally, there are concerns about shortages related to increased demand by institutions and patients for a range of critical medicines out of concern for both real and potential supply chain disruptions and consequent unavailability (e.g., insulin for persons with Type I diabetes).

## Appendix II

### Overview of 2012 Provincial Ethical Framework:

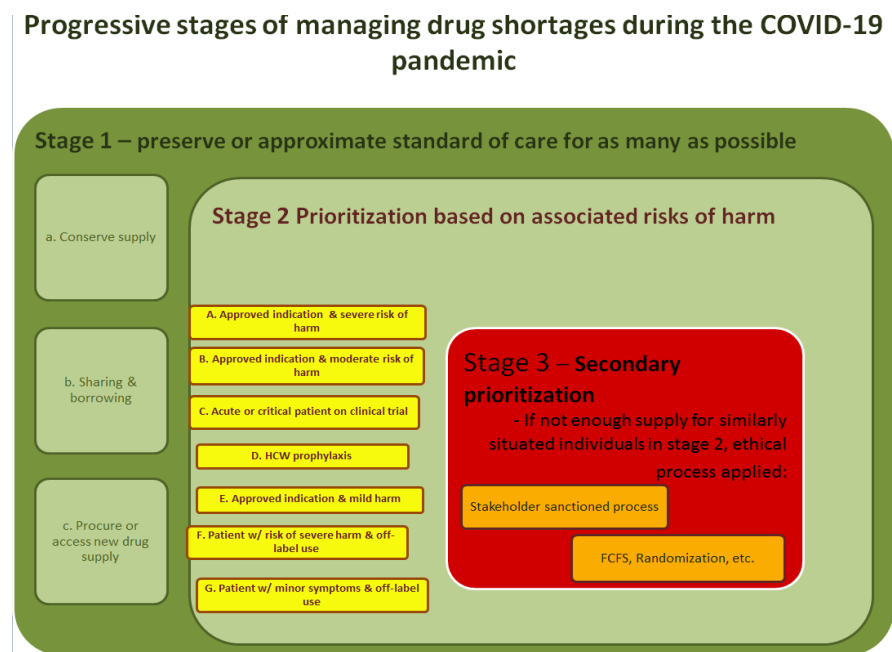
U of T Joint Centre for Bioethics: Gibson JL, Bean S, Chidwick P, et al. Ethical framework for Resource Allocation during a drug supply shortage. *Healthcare Quarterly* 2012; 15(3): 26-35.

### Ethical Principles

Substantive	
Principle	Meaning
Beneficence	Maintaining highest quality of safe and effective care with resource constraints
Solidarity	Build, preserve and strengthen inter-professional / institutional / sectoral / provincial collaborations and partnerships
Utility	Maximize the greatest possible good for the greatest possible number of individuals
Equity	Promote just/fair access to resources
Stewardship	Use available resources carefully and responsibly
Trust	Foster and maintain public, patient and healthcare provider confidence in health systems
Procedural (A4R)	
Principle	Meaning
Relevance	Decisions are made on the basis of reasons (evidence, principles, values) relevant under the circumstances and by credible, accountable stakeholders
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Revision	Decisions are revisited and revised as new information emerges, and stakeholders have opportunities to voice concerns
Empowerment	Stakeholders have meaningful opportunities to participate in/inform the decision-making process
Enforcement	Mechanisms exist to ensure that these fair process principles are sustained throughout the response



## Appendix III



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### References:

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Gibson JL, Bean S, Chidwick P, et al. Ethical framework for Resource Allocation during a drug supply pandemic. *Healthcare Quarterly* 2012; 15(3): 26-35.

Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, Zhang C, Boyle C, Smith M, and Phillips JP. Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *New England Journal of Medicine* 2020. DOI: 10.1056/NEJMs2005114