Supplemental Table 2: Health economic evaluation assumptions

Assumption	Rationale
Therapeutic remdesivir administration • We assumed the unit cost of remdesivir across all jurisdictions from previously estimated costing in Ontario	Pharmaceutical pricing/costing would likely reflect national/provincial formulary across all jurisdictions
Concurrent co-interventions (e.g. anti-viral, antibiotic, anti-fungal administration, immunomodulators, other medications under investigation for COVID-19, other investigations (labs/radiology)) • We assumed that utilization of various concomitant co-interventions would be low/minor, and hence were excluded from analysis (e.g. osteltamivir, acyclovir, ganiciclovir, lamivudine, valacyclovir, ritonavir, darunavir, efavirenz, convalescent plasma, hydroxychloroquine, baracitinib, sarilumab, anakinra, interferon beta)	In, general, various line-items were excluded (even if measured from CATCO CRF) if the following conditions were met: - Low incidence of resource utilization - Low overall unit cost per line-item - Not plausibly expected to be impacted biologically/clinically by remdesivir administration - Not expected to have incremental differences between remedesivir or placebo groups
Variability in investigations and treatment practice of disease/illness • Based on variability in incidence of disease/illness, we will investigate the incidence of each illness severity, and average resource utilization for a particular illness • We will utilize the mean costs for a particular illness (we will attempt to directly derive this variability from the case report forms) For patients who undergo multiple investigations, treatment (medications/procedures/surgeries) for a particular disease/illness, we will assume the lowest number of potential interventions to treat the disease/illness, as well as mean resource utilization for such events from CATCO	Various clinical diagnoses will have variability in severity, and therefore, variability in the way they are investigated and treated (i.e. *seizures* could be investigated/treated with a range if interventios: e.g. CT head, EEG, anti-epileptic drugs), therefore, we assumed the minimum amount of investigations/treatments for each specific illness

Investigation/interventions of other outcomes
• Certain assumptions will need to be made for healthcare resource utilization for certain services, investigations, procedures/surgeries, as they may not be explicitly captured in CATCO, but can be gleaned indirectly from the case report forms:
   ○ broncho-alveolar lavage (BAL) cultures were assumed to have a bronchoscopy procedure to perform them
   ○ other viral etiologies were assumed to have a viral NAT swab sent
	There are certain investigations or interventions that would be expected to be associated with various disease state suspicions (and given correct circumstances, we would assume these would be tested/treated in these ways)

- outcome of pneumothorax was assumed to require a chest tube (even if not formally recorded)
- pulmonary embolism/VTE diagnoses were assumed to have had a CT chest
- seizure diagnoses were assumed to have CT head, EEG and anti-epileptic drug prescription for standard interval (e.g. phenytoin weight based load
- stroke diagnoses were assumed to have CT head
- Congestive heart failure diagnosis would entail a TTE
- Gastrointestinal bleed would entail an EGD
- High dependency unit days were costed using ICU unit costs
- NIV days were costed using IMV unit costs
- UF/CRRT/IHD unit costs were equivalent
- ECMO utilization includes per day cost, alongside cannulation costs (e.g. surgeon, anesthesia, nursing)
- initiation (on the first day) of intermittent hemodialysis or continuous renal replacement therapy would incur a cost of central venous hemodialysis line placement
- all hospital admissions would incur pan-cultures (urine, sputum, blood cultures)
- daily blood work assumed at minimum CBC, Cr, electrolytes
- ICU admission would assume ABGs twice daily, and placement of arterial line
- CXR were assumed to be performed during admission to hospital, admission to ICU and following intubation
- Following intubation and IMV initiation, assumed central line placement also
- Immunmodulator (tocilizumab) dosing: 400mg IV x 1 per patient (given shortage and dose rationing)
- Days of antibiotics were broken down by early antibiotics (e.g. for community acquired pneumomia) and later ventilator-associated pneumonias (or assumed to be VAP)
  - Ceftriaxone 1g IV q24h x 7 days
  - Azithomycin 500mg x 1, then 250mg x 4 days
  - Additional antibiotic courses/days assumed to be:
    - Pipercillin-tazobactam 3.375g IV q6h x 7 days

- If still on antibiotics past 2 weeks: ○ Imipenem-cilastin 500mg IV q6h x 7 days (for any other additional courses) - If on antibiotics past 3 weeks: ○ At least one week course of Vancomycin (1.5g IV x 1 then, 1g IV q12h x 7 days) ○ Proning was assumed to occur 2x per day (with at least 5 people involved with proning, with their associated personal protective equipment: 1 gown, 1 N95 mask, 1 face-shield, 1 pair of gloves, 1 surgical mask)	
Imputation of missing data (missing resource use or unit costs) - For those patients with missing data from a clinical outcomes perspective, multiple imputation methods will be utilized – including generalized estimating equations (GEEs) - For missing unit costs (which are not attainable from public jurisdiction databases or trial site-specific inquiries), we will utilized a mean-unit cost approach - A mean unit cost approach was used, where the mean unit cost within a particular provinces (e.g. remainder of 6 provinces, if missing) was used to impute the missing jurisdictions unit costs ("mean cost approach")	We will utilize standard multiple imputation methods to handle missing clinical outcome data, or costing-ratio or mean cost approach methodology for missing unit costs
Data collection: hospital time horizon and resource use natural units - Although collected, we only included resource use and outcomes to hospital discharge (as there was no mechanism to ensure accurate resource use collection as an outpatient - Many resource uses were not measured necessarily by dosage on CATCO CRFs (e.g., opiates, vasopressor/inotropes) ○ Therefore, if there was an appropriate "standard dose" for non-titratable medications, it was applied to the resource use in question (usually measured in days on medication, or days intubated, or days in ICU) ▪ Micafungin 200mg IV x 1, then 100mg IV daily x 6 days • No assumption made for possible COVID associated pulmonary aspergillosis (micafungin poses as surrogate	These various assumptions derived either from main study CATCO methodology, our systematic review of health economic literature from probiotics, or from consultation with the E-CATCO steering committee Higher weight-based dosing (85kg) was assumed given the higher propensity of these patients in hospital compared to historical epochs (normally would assume 70kg)

for voriconazole)
- ▪ Phenytoin for seizures was assumed to be 15mg/kg IV load, then 100mg IV q8h x 7 days
- ▪ Amiodarone for VT/VF/arrhythmia was 1mg/hr x 18 hours, then 0.5mg/hr x 30 hours, then stopped
- ▪ Dalteparin VTE dosing was assumed to be 125 units/kg for patients with known VTE
- ▪ Inhaled nitric oxide was assumed to be the cost of the non-disposable circuit x 50ppm (based on per day usage/unit costing)
  - ○ If there was a clinically appropriate "medium dose" for titratable medications (e.g. vasopressors/inotropes, opiate infusions, sedation infusions) were estimated for various medications
    - ▪ Neuromuscular blockade use days were assumed to be rocuronium, and at a standard dose of 10mcg/kg/min (based on ventilator days)
    - ▪ Propofol use days assumed a medium dose of 50mcg/kg/min (built into ventilator days)
    - ▪ Midazolam use days assumed a 5mg/hour (built into ventilator days)
    - ▪ Hydromorphone use assumed to be 2mg/hour (built into ventilator days)
    - ▪ Illness severity scores (e.g. APACHE) were used to estimate medium doses
      - • Norepinephrine dosing included 0.05mcg/kg/min & 0.15 mcg/kg/min based on illness severity
      - • Dobutamine dosing: 2.5mcg/kg/min
- • All weight-based dosing was assumed to be for 85kg adult (instead of 70kg)
- • Base-case analysis patient to nurse ratios assumed to be: 1:1 in ICU, 1.5:1 in high dependency units, and 4:1 on the ward

ABG = arterial blood gas; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; BAL = broncho-alveolar lavage; CATCO = Canadian Treatments for COVID-19; CBC = complete blood count; COVID-19 = coronavirus disease-19; Cr = creatinine; CRF = case-report forms; CRRT = continuous renal replacement therapy; CT = computerized tomography; CXR = chest x-ray; E-CATCO = Economic evaluation alongside CATCO; ECMO = extracorporeal membrane oxygenation; EEG = electroencephalogram; g = grams; ICU = intensive care unit; IHD = intermittent hemodialysis; IV = intravenous; kg = kilograms; mcg =

micrograms; mg = milligrams; min = minute; TTE = transthoracic echocardiogram; UF = ultrafiltration; VAP = ventilator-associated pneumonia; VF = ventricular fibrillation; VTE = venous-thromboembolism; VT = ventricular tachycardia;