

Treatments for COVID-19

Draft Background and Scope

August 26, 2021

Background

COVID-19 is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. As of August 2021, there have been over 35 million confirmed COVID-19 cases and 600,000 COVID-19 deaths in the United States (US).¹ The direct medical costs of health care utilization from COVID-19, while substantial (>\$100 billion² over the expected course of the pandemic) are overshadowed by the costs of reduced economic output (>\$7 trillion).³ Further, COVID-19 has uneven clinical and economic impacts as older individuals, those living with comorbidities, and Black and Hispanic populations are at higher risk of infection, hospitalization, and mortality⁴ while younger individuals, women, and Hispanics are at higher risk of unemployment.⁵

Roughly 30% of individuals with COVID-19 are asymptomatic.⁶ Among those who are symptomatic, 80% develop mild-to-moderate disease while the other 20% go on to require oxygen and/or mechanical ventilation.^{7,8} Symptoms typically appear two to 14 days after infection with symptoms including fever, dry cough, fatigue, joint/muscle pains, nasal congestion, loss of smell/taste, sore throat, headache, diarrhea, nausea/vomiting, shortness of breath, cyanosis, persistent chest pain, loss of appetite, or confusion. The severity of symptomatic infections can be classified into four levels,^{9,10} as illustrated below.

1. **Mild disease:** Individuals have symptoms but do not have shortness of breath or abnormal chest imaging.
2. **Moderate disease:** Individuals show evidence of lower respiratory tract disease but have oxygen saturation (SpO₂) ≥94%.
3. **Severe disease:** Individuals have pneumonia and one of the following: SpO₂ <94%, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen <300, require more than 30 breaths per minute, or have >50% lung infiltrates.
4. **Critical disease:** Individuals have respiratory failure, septic shock, and/or multiple organ dysfunction.

Treatment guidelines for COVID-19 are rapidly changing, in part reflecting the multiple drugs that are under development. For non-hospitalized outpatients with mild-to-moderate disease who are

at high risk of progression to severe disease, current guidelines from the Infectious Diseases Society of America (IDSA) and the National Institutes of Health (NIH) recommend treatment with either sotrovimab or casirivimab plus imdevimab (REGEN-COV).^{11,12} High risk is defined in Table 1.¹³⁻¹⁵ These intravenous treatments are monoclonal antibodies that bind to the receptor-binding domain of the SARS-CoV-2 virus' spike protein, inhibiting either attachment or fusion to human cells. Both treatments are available under Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA). REGEN-COV also has an EUA for subcutaneous injection, primarily for post-exposure prophylaxis, and sotrovimab is being tested for intramuscular injection.¹⁶

Table 1. Factors or Conditions that Place Individuals at High Risk for Progression to Severe COVID-19 Disease¹³⁻¹⁵

Age ≥65 years
Obesity or being overweight
Pregnancy
Chronic kidney disease
Diabetes
Immunosuppressive disease or immunosuppressive treatment
Cardiovascular disease or hypertension
Chronic lung diseases
Sickle cell disease
Neurodevelopmental disorders
Having a medical-related technological dependence (e.g., tracheostomy)
Other conditions that confer medical complexity (e.g., genetic syndromes)
Other conditions or factors (e.g., race) that may place individual patients at high risk

New infections with COVID-19 have risen substantially in recent months due to the higher contagiousness of the delta variant and failure to reach population vaccination goals. Additional options for outpatient treatment of mild-moderate disease are therefore needed, and oral options that are safe and effective are particularly needed to help improve access to treatment across diverse communities in the US. Multiple oral agents against COVID-19 are in varying stages of development, and evaluation of the evolving evidence of the comparative clinical effectiveness and potential cost effectiveness at different pricing levels for highly anticipated emerging outpatient treatments will be important to guide clinical practice and policy decision-making.

Early Stakeholder Input

This draft scoping document was developed following discussions with diverse stakeholders, including clinicians, researchers, and manufacturers of the agents of focus in this review. We would like to encourage input on this draft scoping document from members of the patient community, including caregivers. A revised scoping document will be posted following a three-week public comment period.

Clinical experts advised that the definition of individuals at “high risk” in the EUAs is quite broad and that clinicians tend to prioritize treatment for patients viewed as having the highest risk for progression (e.g., older adults, individuals who are immunocompromised, or have heart or lung disease or are obese), in alignment with NIH guidance.¹³ Since demand has been rising for outpatient treatment, and the two currently available treatments are primarily administered intravenously, clinicians and delivery system leaders said that there is currently a constraint on treatment due to the lack of availability of infusion sites and staff with the necessary expertise to administer intravenous drugs. Clinical experts also advised that the clinical and policy context of treatment should be guided by the need for treatment to begin as rapidly as possible after diagnosis in order to maximize potential treatment effectiveness.

Drug manufacturers highlighted the importance of noting the differences in patient populations within clinical trials, notably in the penetrance of different COVID-19 variants in the population at the time trials are conducted. Given the rapidly evolving evidence base as these treatments move through EUA and on to final approval, manufacturers also noted that ICER will need to be mindful of the incomplete data that may be available publicly for review, even if academic-in-confidence material is provided. Health system leaders encouraged ICER to pursue the review given the immediacy of the issues related to plans for coverage and pricing of multiple new and potentially competing agents.

ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of casirivimab/imdevimab (REGEN-COV), sotrovimab, molnupiravir, PF-07321332/ritonavir, and fluvoxamine for the treatment of mild-to-moderate newly diagnosed COVID-19. The [ICER Value Framework](#) includes both quantitative and qualitative elements to ensure that the full range of benefits, harms, and costs are explored and put into a broader context of comparative clinical effectiveness and value.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be sought from many different sources. Available evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will also include input from patients and patient advocacy organizations, data from

regulatory documents, information submitted by manufacturers, and from other sources when the evidence meets ICER standards (for more information, see ICER’s [grey literature policy](#)).

All relevant evidence will be synthesized qualitatively or quantitatively. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

Populations

The population of focus for the review is adults and adolescents ages 12 and older with mild-to-moderate newly diagnosed COVID-19 (confirmed with a positive SARS-CoV-2 polymerase chain reaction [PCR] or antigen test) and a high risk of progression to severe disease or hospitalization (Table 1).

Interventions

The proposed list of interventions to be evaluated includes:

- Casirivimab/imdevimab (REGEN-COV, Regeneron)
- Sotrovimab (GlaxoSmithKline and Vir Biotechnology)
- Molnupiravir (Merck)
- PF-07321332/ritonavir (Pfizer)
- Fluvoxamine (investigator initiated)

Comparators

We intend to compare each treatment to outpatient “usual care” involving only symptomatic treatments, as found in the clinical trials of each product. Data permitting, we will explore indirect comparisons of interventions but acknowledge that patient populations and the natural history of care and outcomes for patients with COVID-19 have been evolving rapidly, making formal quantitative indirect comparisons challenging.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
 - Time to symptom resolution
 - Return to work or usual activities
 - Symptom severity

- Severe illness
- Oxygen therapy
 - Conventional oxygen therapy
 - High-flow nasal cannula
 - Noninvasive positive pressure ventilation
- Mechanical ventilation
- Medically attended visit
- Hospitalization
 - Length of stay
- Intensive care unit (ICU) admission
- Long COVID
- Death
- Adverse events including:
 - Side effects
 - Anaphylaxis
- Other Outcomes
 - Viral load
 - SARS-CoV-2 clearance
 - Oxygen saturation (SpO₂)
 - Antiviral resistance
 - Inflammatory markers
 - Adverse events including:
 - Treatment-emergent adverse events and serious adverse events

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

The primary focus will be on care settings in the US, but relevant clinical outcomes data from international settings will not be excluded from consideration. We will pay particular attention to the geography and timing of the studies in considering differences between patient populations and outcomes.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Considerations*
Acuity of need for treatment of individual patients based on the severity of the condition being treated
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)
Potential Other Benefits or Disadvantages†
Patients’ ability to achieve major life goals related to education, work, or family life
Caregivers’ quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients’ ability to manage and sustain treatment given the complexity of regimen
Society’s goal of reducing health inequities
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

†Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the clinical evidence review, we will develop an economic model to assess the cost effectiveness of the treatments of interest relative to general supportive care. If outcomes data are available from reasonably comparable patient populations, cost effectiveness may be investigated relative to other active agents. The model structure will be based in part on a literature review of prior published models of COVID-19.¹⁷⁻¹⁹ The model will be built to evaluate results from a health care system perspective (i.e., focus on direct medical care costs only), and from a modified societal perspective that includes productivity impacts and other indirect benefits and costs. This modified societal perspective analysis will be considered as a co-base case if the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than \$200,000 per quality-adjusted life year (QALY), and/or when the result crosses the threshold of \$100,000 to \$150,000 per QALY gained.

The target population will consist of adults and adolescents ages 12 and older with mild-to-moderate COVID-19 and a high risk of progression to severe disease or hospitalization. A cohort of patients will transition between health states during predetermined cycles of one month over a lifetime time horizon, modeling patients from treatment initiation until death. The model will consist of health states for alive and dead, with the initial cycle(s) tracking the infected period and the level of health care utilization (e.g., outpatient, hospitalization) required. Long-term consequences of COVID-19, as measured by disutilities and costs, will be included in cycles after the infected period as data allow.

Key model inputs will include clinical probabilities, quality-of-life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using the best available evidence.

Health outcomes and costs will be dependent on the health care utilization required, time spent in each health state, clinical events, adverse events, and direct medical costs. The health outcome of each intervention will be evaluated in terms of hospitalizations averted, life years gained, QALYs gained, and equal value of life years gained ([evLYG](#)). Quality-of-life weights will be applied to each health state, including potential quality of life decrements for those who experience long-term consequences of COVID-19. The model will include direct medical costs, including but not limited to costs related to treatment acquisition and administration and condition-related care. In addition, productivity changes and other indirect costs will be included in a separate analysis if data allow. Pairwise comparisons will be made between each treatment and no active treatment, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life year gained, and cost per hospitalization averted. Pairwise comparisons may be made between interventions if data permit.

In separate analyses, we will explore the potential health care system budgetary impact of treatment with different interventions over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This potential budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow policymakers to make their own judgment of likely uptake and the corresponding need for concern regarding affordability and access. More information on ICER's methods for estimating potential budget impact can be found [here](#).

References

1. Center for Systems Science and Engineering at Johns Hopkins University. COVID-19 Dashboard. <https://coronavirus.jhu.edu/map.html>. Published 2021. Accessed Aug 10, 2021.
2. Bartsch SM, Ferguson MC, McKinnell JA, et al. The Potential Health Care Costs And Resource Use Associated With COVID-19 In The United States. *Health Aff (Millwood)*. 2020;39(6):927-935.
3. Cutler DM, Summers LH. The COVID-19 Pandemic and the \$16 Trillion Virus. *Jama*. 2020;324(15):1495-1496.
4. Mackey K, Ayers CK, Kondo KK, et al. Racial and Ethnic Disparities in COVID-19-Related Infections, Hospitalizations, and Deaths : A Systematic Review. *Ann Intern Med*. 2021;174(3):362-373.
5. Montenovo L, Jiang X, Rojas FL, et al. Determinants of disparities in Covid-19 job losses. *National Bureau of Economic Research Working Paper Series*. 2020;No. 27132.
6. Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic : A Systematic Review. *Ann Intern Med*. 2021;174(5):655-662.
7. World Health Organization. *Coronavirus disease 2019 (COVID-19): situation report, 46*. Geneva: World Health Organization;2020.
8. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *Jama*. 2020;323(13):1239-1242.
9. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. *N Engl J Med*. 2020;383(18):1757-1766.
10. COVID-19 Treatment Guidelines Panel. Clinical Spectrum of SARS-CoV-2 Infection. National Institutes of Health. COVID-19 Treatment Guidelines Web site. <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>. Published 2021. Updated April 21, 2021. Accessed Aug 19, 2021.
11. COVID-19 Treatment Guidelines Panel. Clinical Management Summary. National Institutes of Health. COVID-19 Treatment Guidelines Web site. <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/>. Published 2021. Updated July 8, 2021. Accessed Aug 10, 2021.
12. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. <https://www.covid19treatmentguidelines.nih.gov/>. Published 2021. Updated Aug 4, 2021. Accessed Aug 10, 2021.
13. (NIH) NIOH. Anti-SARS-CoV-2 Monoclonal Antibodies. <https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/>. Published 2021. Accessed Aug 25, 2021.
14. (FDA) FaDA. FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF REGEN-COVTM (casirivimab and imdevimab). <https://www.fda.gov/media/145611/download>. Published 2021. Accessed Aug 25, 2021.
15. (FDA) FaDA. FACT SHEET FOR HEALTHCARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF SOTROVIMAB. <https://www.fda.gov/media/149534/download>. Published 2021. Accessed Aug 25, 2021.
16. ClinicalTrials.gov. Intramuscular VIR-7831 (Sotrovimab) for Mild/Moderate COVID-19. U.S. National Library of Medicine. <https://www.clinicaltrials.gov/ct2/show/NCT04913675>. Published 2021. Accessed Aug 10, 2021.

17. Jiang Y, Cai D, Chen D, Jiang S, Si L, Wu J. Economic evaluation of remdesivir for the treatment of severe COVID-19 patients in China under different scenarios. *Br J Clin Pharmacol*. 2021.
18. Jo Y, Jamieson L, Edoaka I, et al. Cost-effectiveness of Remdesivir and Dexamethasone for COVID-19 Treatment in South Africa. *Open Forum Infectious Diseases*. 2021;8(3).
19. Institute for Clinical and Economic Review. Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19. https://icer.org/wp-content/uploads/2020/10/ICER-COVID_Revised_Report_20200624.pdf. Published 2020. Updated June 24, 2020. Accessed Aug 12, 2021.