Special Assessment of Outpatient Treatments for COVID-19

Revised Background and Scope
September 24, 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 billion[2] 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 mortality[4] 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 and include 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 below.[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 Disease[13-15]

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 necessary 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 rapidly 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 revised scoping document was developed following discussions with diverse stakeholders, including clinicians, researchers, and manufacturers of the agents of focus in this review.

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, 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 new oral treatment options were the most important area of development in the outpatient setting, and that analyzing the relative benefits and safety of different emerging options and comparing them to the leading intravenous and intramuscular treatment options, would be of greatest value. 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 onto 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 outpatient treatments.

Report Aim

Due to the unprecedented immediacy and scale of COVID-19, ICER recognizes the need for a timely review to inform policy and practice but also that full information on all treatments and outcomes of interest may not be available at the time of review. The treatments for this review were chosen based on the timing of expected availability of clinical evidence, expected EUA or approval as well as clinical expert input on those treatments viewed as likely to have the greatest relevance for patients and clinicians. Using these criteria, we have selected to 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 COVID-19 among patients at high risk of progression to severe disease. 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 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 (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 include real-world evidence as appropriate, explore indirect comparisons of interventions but we 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
    - Progression to severe or critical illness
    - Degree of respiratory support
        - Conventional oxygen therapy
        - High-flow nasal cannula
        - Noninvasive positive pressure ventilation
        - Mechanical ventilation
    - Medically attended visit
    - Hospitalization
        - Length of stay
        - Readmission
    - Intensive care unit admission
    - Long COVID
    - Death
    - Adverse events including:
        - Side effects
        - Anaphylaxis
- Other outcomes
    - Viral load
    - SARS-CoV-2 clearance
    - Oxygen saturation
    - 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 among patient populations, viral variants, 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. Elements of interest 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 short-term risk of death or progression to permanent disability
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 and the potential for drug-drug interactions
Society's goal of reducing health inequities
Society's goal of limiting the course of the pandemic with multiple potential benefits including restoring social and economic transactions, managing health system capacity, and reducing SARS-CoV-2 transmission
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.

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 interventions of interest relative to usual 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,[17-20] with additional components added to the model structure to account for the outpatient nature of the interventions of interest for this review. 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 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 an upfront decision tree followed by a lifetime Markov model. The upfront decision tree will represent the infected period and will track the highest level of care received (e.g., outpatient visit, emergency department visit, hospitalization [with stratifications for respiratory support received as data allow]). The lifetime Markov model will consist of health states for alive and dead. Long-term consequences of COVID-19, as measured by disutilities and costs, will be included in the Markov model 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 as well as other model inputs will be estimated using the best available evidence.

Health outcomes and costs will be dependent on the highest level of care required, time spent in each health state, clinical events, adverse events, and direct medical costs. The health outcomes 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 usual care, 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.

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