INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Special Assessment of Outpatient Treatments for COVID-19
Response to Public Comments on Draft Evidence Report

March 28, 2022

#	Comment	ICER Response
Manufacturers		
GlaxoSmithKline		
1.	ICER consistently mentions throughout the report that due to limitations stemming from differences in patient populations and clinical trial design (i.e., timing of studies, usual care arms, outcomes), comparisons could not be made across treatments. Despite this acknowledgement of differences, ICER has chosen to pool the control arms of the trial populations without adjustment for the systematic differences highlighted in the draft report, and in effect has created a "common comparator" for all interventions in the economic model. GSK suggests rather than utilizing pooled controls arms in the economic evaluation, compare each intervention with its respective clinical trial comparator. This method, aligned with previous ICER assessments, would help to minimize the limitation regarding differences in clinical trial design and patient population as well; however, comparisons across therapies remain inappropriate. GSK recommends that ICER compare each intervention to its respective clinical trial comparator and forego the use of the pooled analysis for the usual care arm.	The purpose of pooling across the comparator arms of the pivotal trials is not to compare across interventions, but instead to create a more generalizable comparator across time, variants, patient composition, etc. These factors, which influence the risk of hospitalization for the comparator arm, vary among the pivotal trials, and thus, we pool the comparator arms of each pivotal trial to generate a comparator that encompasses variation in time, variants, and patient composition. The key input that is generated by pooling across the comparator arms of each pivotal trial is the risk of hospitalization in the comparator arm of the model. Our pooled US estimate of hospitalization for the comparator arm is supported by US Centers for Disease Control and Prevention estimates and other real-world evidence studies in the US. Further, this input is varied widely within the one-way sensitivity analysis, probabilistic sensitivity analysis, and numerous scenario analyses. If we had chosen to compare each intervention to its own usual care arm in its pivotal trial, we would have provided very context-specific results. Pooling across the usual care arms of these pivotal trials allowed us to be more generalizable to the eligible population and representative of various secular trends observed. Given the wide differences in usual care outcomes across the trials, we believe the pooled comparator approach we used will be less likely to provide results that could be misinterpreted. Another reason for our selection of a pooled comparator approach was driven by input from clinical experts. Experts advised us that, with the exception of the pregnancy limitations on molnupiravir and drug-drug interaction concerns with Paxlovid, clinicians will view these drugs as possible choices for the same population of patients. Therefore, we pooled the demographic characteristics (e.g., age and sex) across the pivotal trials to unify the population characteristics in the economic model. Given that we pooled the demographic characteristics, it was imperative that we also pool the outcomes (hospitalization, death) given the documented relationship between age and these outcomes. There may be systematic differences between the trials that could influence the relative effectiveness estimates for each treatment, which is why we clearly state we are not comparing the treatments to one another. However, we think the systematic differences in the comparator arm strengthen our pooled comparator approach by generating a more generalizable and comprehensive comparator.

2.	ICER assumes a treatment effect with a relative risk of 1.0 when there is not a statistically significant difference from standard of care. This assumption suggests that lack of statistical significance is a proof of lack of treatment effect which may not be appropriate or accurate, particularly in the context of economic evaluation. Perhaps a more appropriate approach should be that the base-case analysis should use the reported or derived point estimates for the inputs, and associated uncertainty (which is typically expressed by statistical significance criteria) should be explored via sensitivity analyses. The assumption of a relative risk of 1.0 when there is not statistically significant difference likely introduced bias into the assessment and is inconsistent with good modelling practices. GSK recommends ICER utilize reported or derived relative risk ratios regardless of statistical significance to more accurately assess the effectiveness of the interventions.	This assumption is not a key driver of the results. The key driver of the results—the treatment's effect on preventing hospitalizations—was statistically significant for all treatments evaluated. We are comfortable with this assumption given the small absolute numbers within these studies. As an example, REGEN-COV had a 0.5 relative risk for patients requiring mechanical ventilation. This was not statistically significant and had a very large confidence interval. This is because there were two (out of 748 people total) people in the placebo arm that required mechanical ventilation as compared to one (out of 736 people total) person in the REGEN-COV arm that required mechanical ventilation. One additional occurrence in either arm would dramatically change the relative risk due to the small absolute numbers. Because of the very small absolute numbers, the relative risk estimate is very sensitive when statistical significance is not achieved.
3.	Additionally, ICER's inclusion/exclusion criteria for assessed treatments are not well defined with a mix of both EUA therapies and an unapproved/unauthorized treatment. In addition, ICER's draft report is lacking treatments recently approved or authorized by the FDA. An alternative exists to ICER's current treatment selection that would have provided increased value over the current assessment, i.e., focus only on those therapies for which an EUA or FDA approval exists, or which are currently being considered for EUA by the FDA. This would allow the assessment to align more closely with current and potential future guidelines committee treatment recommendations. GSK recommends that ICER standardize their approach to selecting interventions and disclose these criteria.	All treatments in this assessment meet the suggested criteria of possessing an EUA, are approved, or are being considered for an EUA. Sotrovimab, molnupiravir, and Paxlovid have EUAs for the population of interest. Fluvoxamine is already FDA-approved for obsessive compulsive disorder and is currently being considered for EUA for the population of interest. Two additional treatments that received EUAs for our population of interest near the time of the posting of our draft Evidence Report were remdesivir and bebtelovimab. Language in the report explains that while these treatments emerged too late for us to consider, we note that the Interactive Modeler will be available on ICER Analytics after the final Evidence Report is complete. Decisionmakers can input clinical and economic data on other available treatments to generate cost-effectiveness results and health-benefit price benchmarks. Please see our responses to Merck Comment 3 and Pfizer Comment 13 for additional details regarding our rationale for included treatments.
Merck		
1.	ICER should apply the effect of molnupiravir on mortality as observed in the MOVe-OUT clinical trial. ICER's model underestimates the clinical benefit of molnupiravir, particularly the mortality benefit and the reduction of severity of COVID-19 among hospitalized patients who were treated with molnupiravir during outpatient management. In ICER's cost effectiveness model, the COVID-19-asociated mortality rates in the decision tree are estimated as 0.476% for usual care, and 0.333% for molnupiravir, resulting in a relative risk reduction of 0.300. However, in the MOVe-OUT clinical trial, the relative risk reduction in COVID-19-associated mortality is reported to be 0.8905 (molnupiravir arm: 1/709, placebo arm: 9/699). The ICER model assumptions should be consistent with clinical trial results. Without incorporating	We modeled deaths averted indirectly based on hospitalizations averted and higher levels of respiratory support within a hospitalization averted. Trial estimates of the mortality in the intervention arm were not used given the small numbers and clinical rationale that the deaths averted should result from a treatment's effect on averting hospitalizations or reducing the severity of hospitalizations. The WHO-11 ordinal scale data for the full population was provided to us as academic-in-confidence from the manufacturer. The rationale for its inclusion/exclusion from the model was communicated directly to the manufacturer to preserve the confidential nature of the data.

	the full clinical benefit as observed in the MOVe-OUT trial into the cost effectiveness model, ICER may underestimate the clinical value of molnupiravir. Recommendation: The post-hoc analysis of the WHO-11 ordinal scale, as requested by ICER, shows that patients treated with molnupiravir were associated with lower severity of hospital care before death. ICER should incorporate the WHO-11 ordinal scale analysis in the decision tree part of the model to fully account for the observed mortality benefits of molnupiravir.	
2.	Merck agrees with ICER's intent to discourage direct comparison due to the significant differences in trial populations. However, ICER's pooling of usual care arms across trials and presentation of the study results side-by-side implies direct comparisons can be made by the reader. The clinical trial data underpinning ICER's analysis were standalone trials that were designed to test their respective hypotheses versus usual care arms. By pooling across usual care arms, ICER is implying results can be compared across treatments, which is inappropriate given individual trials have disparate characteristics. Pooling should be limited to analyses that allow for adjustments across trial datasets. For example, ICER has not accounted for observed differences across trials in the proportion of patients with comorbidities, antibody status at baseline and differences resulting from the exclusion of patients with contraindications related to potential drug-drug-interaction for some COVID-19 therapeutics. Recommendation: a) The base-case analysis should represent individual trial setting and present results separately for each treatment. ICER should present individual product analyses in separate tables. If comparisons are attempted, the selection of the population should depend on the inclusion and exclusion criteria of each clinical trial and note limitations, differences between populations and potential impacts on results. b) If ICER continues to report results for multiple products in a single table, footnotes should be added to each such table so readers are reminded of the caution that should be applied when interpreting findings and to refrain from directly comparing across products. The footnote might read, "Readers should not compare the cost effectiveness between interventions given the systematic differences in the trial populations and design."	We have added a footnote to each result table using the language suggested.

3.	Fluvoxamine is not recommended or approved for the treatment of COVID-19 in the US. Therefore, ICER should exclude it from its review and only evaluate outpatient treatments that have emergency use authorization or are fully approved in the US.
	
	ICER should only include outpatient treatments that already have emergency use authorization or are fully approved in the US. According to the US National Institutes of Health (NIH) COVID-19 Treatment Guideline, fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is approved by the US Food and Drug Administration (FDA) for the treatment of obsessive-compulsive disorder and is used for other conditions, including depression. Fluvoxamine is not FDA-approved or authorized for the treatment of any infection. There is insufficient evidence for the NIH COVID-19 Treatment Guidelines Panel (the Panel) as well as the Infectious Diseases Society of America (IDSA) to recommend either for or against the use of fluvoxamine for the treatment of COVID-19. The IDSA guidelines only recommend the use of fluvoxamine in the context of a clinical trial.
	
	Recommendation: ICER should remove fluvoxamine from this assessment because the treatment has not been approved, authorized, or recommended for the treatment of COVID-19 in the US.
		As described in the Report Aim section of the report, our inclusion of treatments was based on several factors. We summarize these factors and how fluvoxamine meets these criteria:
		
		Expected FDA approval:
		• Per our response to GlaxoSmithKline Comment 3, fluvoxamine is currently being considered for EUA for the population of interest by the FDA
		
		The timing of expected availability of clinical evidence:
		• There were results from several clinical trials that could be evaluated
		
		Clinical expert input on which treatments would be likely to have the greatest relevance for patients and clinicians:
		• Our discussions with clinical experts indicated that patients, providers, and payers will want to know the clinical and cost effectiveness of fluvoxamine
		• Our decision to include fluvoxamine is further supported by several recent developments that have limited the number of available treatment options for the population of interest:
		  • Evolution of SARs-CoV-2 leading to resistance to several neutralizing antibody treatments
		  • Near-term supply constraints on treatment options that have EUAs

4.	ICER should exclude vaccination parameters from the base case analysis because it may not be methodologically appropriate to assume consistent treatment effects for vaccinated populations from trials which included only unvaccinated patients. Vaccinated patients were not studied in any of the pivotal trials included in this assessment; thus, it may not be appropriate to assume the observed treatment effect from the trials for non-vaccinated populations can be extrapolated to a vaccinated population. It is also important to note that real world vaccine effectiveness is not constant. The expected baseline risk of hospitalization within vaccinated populations changes over time depending on the evolving epidemiology and circulating strains.6 Using a fixed number to adjust hospitalization risk in the pooled estimates of the usual care arm is likely to generate biased results. Currently, there are ongoing real world effectiveness studies of molnupiravir (i.e., Merck and non-Merck studies) that include vaccinated populations. We are willing to share these data when the studies are completed later this year. Recommendation: ICER should exclude vaccination parameters from the base case analysis because it is not methodologically sound to assume consistent treatment effects for vaccinated population in trials which included	Clinical experts advised that these treatments, once widely available, are unlikely to be reserved solely for unvaccinated patients, and, in fact, would likely be widely prescribed for patients who are not at high risk of progression, leading to lower absolute risks of hospitalization and death than those seen in the clinical trials. Further, the current EUAs are not restricted to unvaccinated individuals. We have used the best available evidence for the treatment effects at this time, but understand this is an area that will likely have additional evidence in the future. We include a scenario analysis that restricts the population to unvaccinated patients only; however, our base-case assumptions include vaccinated patients to better reflect how these treatments are likely to be used in practice.

	only unvaccinated patients. It would be best to explore each individual treatment effects using rates from clinical trials. Merck suggests vaccination impact be explored as a sensitivity analysis by testing a range of hospitalization rates and mortality rates that estimate various scenarios of vaccination and circulating variants. This will provide an estimation of future scenario with new variants and varying hospitalization rates and mortality rates.	
5.	ICER should not apply unrelated health care costs for the patients who survived an initial hospitalization into the cost-effectiveness (CE) model, as this accrues a health care cost penalty to innovations that save lives. ICER applied unrelated health care costs for the patients who had survived an initial hospitalization into their cost-effectiveness (CE) model. This approach is biased because healthcare costs associated with each subsequent year of life essentially accrue a health care cost penalty to those who survived and a financial penalty to innovations that save lives. ICER senior leadership has acknowledged the limitations to applying unrelated health care costs during discussions on its remdesivir report. Recommendation: a) ICER should exclude unrelated health care costs from the model because it has naturally forced QALYs to accrue at a higher price. Further, if ICER is interested in analyzing the impact of unrelated health care costs, it is important to include all relevant consequences of treatment (survival) to represent the real resource use. ICER should present the analyses in a disaggregated manner for decision-makers and other stakeholders to estimate cost-effectiveness ratios based on their perspectives and guidelines. In this way, the value of outpatient treatments used for COVID-19 are demonstrated in both scenarios – when unrelated health care costs are included and excluded. b) Inclusion of unrelated health care costs should only be considered when the analysis is conducted from a full societal perspective for cost-offsets of treatment (survival) to be included in a comprehensive way. The current societal perspective is not inclusive of all spillover effects of the treatment into other sectors of the economy. This prevents the balanced presentation of results when considering unrelated health care costs.	The Second Panel recommends the inclusion of future related and unrelated medical costs in both the health care sector and societal perspective (Sanders, Gillian et al, 2016). The debate on whether to include or exclude future unrelated health care costs has been long-standing, with the arguments supporting exclusion receiving rebuttals. Importantly, there is not a health care penalty associated with including these costs because the QALYs accrue at a cost lower than our lowest cost-effectiveness thresholds. ICER's report on remdesivir also included future unrelated health care costs in the base-case analysis. We understand the philosophical argument, and thus, have added a scenario analysis that excludes future unrelated health care costs, but we have not changed our base case.

6.	ICER should present the modified societal perspective as the co-base case. The rapidly evolving but still incomplete COVID-19 evidence base does not currently allow for the inclusion of the complete economic and psychological benefits of outpatient treatments, which may generate significant societal benefits. Furthermore, as ICER recognizes in its Value Framework, models focused on the health care perspective often fail to account for or even acknowledge important societal priorities, which results in an underestimation of a product's true value. Presenting the societal model as a co-base may help consumers of ICER's analysis better appreciate the somewhat narrow focus of the current base case and the broader societal value of the therapies being evaluated. Recommendations: a) Given the evolving epidemiology and limited published data on the broad societal impact of COVID-19, ICER was not able to include important societal parameters in their model. Therefore, ICER should provide a detailed narrative on the limitations of not fully capturing the societal impact of COVID-19 in its analysis (i.e. a modified health care perspective, less than a complete societal perspective). Without accounting for broader societal benefits, ICER's cost effectiveness ratios (ICERs) will underestimate the value of the products reviewed. b) ICER did not include the cost per QALY columns in Tables 4.10. ICER should provide information in these table(s) in the same format as table 4.4 for the societal perspective, including cost per QALY information.	The ICER Reference Case provides examples of when the health sector perspective is presented in tandem with the modified societal perspective as a co-base case. The Reference Case states, "Examples include when the incremental cost-effectiveness ratio changes by greater than 20% or by greater than $200,000 per QALY, and/or when results cross thresholds of $100,000-$150,000 per QALY." Although some of the incremental cost-effectiveness ratios change by greater than 20% (partially explained by low incremental cost-effectiveness ratios in the health sector perspective), the incremental cost-effectiveness ratios do not change by greater than $200,000 per QALY and the results do not cross the threshold of $100,000-$150,000 per QALY. The table that provides the cost per QALY, cost per evLY, and cost per life year gained is available in Report Supplement Section E.
7.	First, the virological data specific to molnupiravir need further clarification based on available evidence. An example can be found on page 19. ICER presents a theoretical concern for the potential that molnupiravir will lead to the emergence of novel variants. In fact, there is no clear evidence that emergence of spike protein amino acid changes in MOVe-OUT was associated with a rebound in viral RNA shedding, or prolonged detection of infectious virus beyond treatment Day 3. ICER should also note that the SARS-CoV-2 spike protein acquires genetic changes frequently, regardless of any molnupiravir induced errors activity. Currently, there is no evidence that direct-acting oral antiviral agents contribute to the emergence of circulating variants. Natural immune responses and other beneficial treatments and vaccines can also influence SARS-CoV-2 evolution.	We feel our language is fairly clear, but we agree with the statement that there is "no clear evidence that emergence of spike protein amino acid changes in MOVe-OUT was associated with a rebound in viral RNA shedding, or prolonged detection of infectious virus beyond treatment day 3." We have added this statement to the Uncertainties section of the Report.

8.	In addition, in the report's Uncertainties and Controversies section, the presentation of topics within products is not consistent. For some products ICER revisits concerns related to generalizability, or safety or the depth of the evidence base but not for others; potentially implying to readers certain dimensions are more important for one product and less important for another. Another example of this can be seen in the Comparative Clinical Effectiveness section of the Executive Summary in which ICER chooses to raise safety concerns for molnupiravir and fluvoxamine but fails to raise important safety concerns for Paxlovid, including labeled contraindications for drug-drugs interactions and precautions. In the Clinical Benefits and Harms section, ICER notes that molnupiravir is also suspected to cause embryo-fetal toxicity and bone and cartilage toxicity. This information warrants additional context as it may be interpreted that there are human data demonstrating these toxicities. Additionally, the bone and cartilage toxicity, observed in five times the human NHC (N-hydroxycytidine) exposures in rapidly growing rats, is not pertinent to adults, and molnupiravir is not authorized for use in pediatric patients.	We have edited the Executive Summary to include precautions due to known drug-drug-interactions with Paxlovid. We have also edited the Clinical Benefits and Harms section to more clearly state that molnupiravir's suspected bone and cartilage toxicity and embryo-fetal toxicity is based on data from animal models. The draft Evidence Report already stated that molnupiravir is not recommended for use during pregnancy and is not authorized for use for patients under 18 years of age.
9.	To improve the readability, clarity and balance of the report, it is recommended ICER revisit the presentation of the information in each section to ensure it is structured consistently across products.	We have reviewed and adjusted our report accordingly.
10.	ICER should more explicitly contextualize the theoretical risk and the lack of clear empirical evidence supporting the hypothesis that the viral mutations observed will have negative consequences for patients treated with molnupiravir or the development of future variants. ICER should include the following text to provide additional context surrounding the theoretical concerns raised regarding molnupiravir: In MOVe-OUT, no molnupiravir participants with treatment-emergent spike substitutions had infectious virus recovered beyond Day 3 and had no or only low viral RNA shedding by Day 29. All, but one spike substitutions have been previously reported in circulating SARS-CoV-2 isolates.	In response to Merck Comment 7, we stated the below: We feel our language is fairly clear, but we agree with the statement that there is "no clear evidence that emergence of spike protein amino acid changes in MOVe-OUT was associated with a rebound in viral RNA shedding, or prolonged detection of infectious virus beyond treatment day 3." We have added this statement to the Uncertainties section.
11.	ICER should more explicitly contextualize the embryo-fetal toxicity and bone and cartilage toxicity. ICER should include the following to provide additional context: Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, molnupiravir is not recommended for use during pregnancy. Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity	In response to Merck Comment 8, we stated the below: We have also edited the Clinical Benefits and Harms section to more clearly state that molnupiravir's suspected bone and cartilage toxicity and embryo-fetal toxicity is based on data from animal models. We have already previously stated that molnupiravir is not recommended for use during pregnancy and is not authorized for use for patients under 18 years of age.

	was observed in rats after repeated dosing. Growth cartilage is not present in mature skeletons, therefore the bone and cartilage findings are not relevant for adult humans but may be relevant for pediatric patients.	
Pfizer		
1.	Within its Value Assessment Framework, ICER indicates that the health system perspective will serve as the base case perspective in its evaluations, and only under special circumstances would the societal perspective be elevated to a co-base case. Given that the COVID-19 pandemic has had a profound impact on the global economy, in addition to regional health systems, ICER should consider the societal perspective as a co-base case for the following reasons: • COVID-19 is projected to cost the United States $16 trillion over the next decade in financial costs; nearly half of this burden is due to lost income from the pandemic-induced recession, while the other half is due to economic effects of premature mortality and long-term health impairments. Decreases in productivity have been caused by a range of factors attributable to COVID-19, such as premature death and impairments to long-term health and quality of life. A study encompassing 9 European countries estimated that the total paid premature costs due to excess mortality were €1.07 billion, from initial country outbreaks to May 2020. With most patients surviving COVID-19, long-term impairments to the health and quality of life of survivors could carry even greater impacts on productivity that have yet to be observed • The Second Panel on Cost-Effectiveness in Health and Medicine, which serves a gold standard for economic evaluations, recommends the inclusion of a reference case from the societal perspective due to "the importance of capturing broad consequences of health interventions, including consequences outside the healthcare sector." The Second Panel suggests that the societal perspective include patient and informal caregiver time costs, transportation costs, effects on future productivity in added years of life, and other relevant costs outside of the healthcare sector. Doing so, the Panel indicates, will provide a wider and more valuable benefit to a range of stakeholders and decision makers.	The ICER Reference Case provides examples of when the health sector perspective is presented in tandem with the modified societal perspective as a co-base case. The Reference Case states, "Examples include when the incremental cost-effectiveness ratio changes by greater than 20% or by greater than $200,000 per QALY, and/or when results cross thresholds of $100,000-$150,000 per QALY." Although some of the incremental cost-effectiveness ratios change by greater than 20% (partially explained by low incremental cost-effectiveness ratios in the health sector perspective), the incremental cost-effectiveness ratios do not change by greater than $200,000 per QALY and the results do not cross the threshold of $100,000-$150,000 per QALY. The impact of COVID-19 on the economy is undeniable. We recognize the potential effects on non-health sector impacts and have included these in the modified societal perspective, which includes impacts on productivity and ICU capacity, but we do not elevate it to a co-base case due to the reasons described above.
2.	There are wide-ranging effects of COVID-19 borne by patients beyond the direct medical costs and benefits of treatment. These include lost future income, rising unemployment, and increased mental health concerns. The ICER model does not comprehensively capture societal costs, thus representing an underestimation of the burden of disease to society and an underestimation of the potential benefits of treatment. ICER includes some text in its report acknowledging that not all benefits to	Thank you for this comment. This is an area where we have had extensive conversation, and an area we continue to think about. The Second Panel recommends the inclusion of productivity losses in the societal perspective analysis, recognizing that "… many challenges remain, such as valuation of effects outside the health care sector … Addressing these challenges will continue to provide opportunities to advance the field of cost-effectiveness analysis" (Carias, Christina et al, 2018).

	society are captured; however, given the magnitude of potential societal costs associated with a global pandemic, we recommend that ICER more clearly acknowledge that the modified societal perspective provides a significant underestimation of societal costs. • In the DER, ICER accounted for lost productivity only during the period in which the patient was infected with COVID-19, assuming that patients were not working during the duration of their symptom days. In other words, ICER evaluated the short-term consequences of COVID-19 from the employer's perspective but did not include lost future income due to premature mortality or disability due to COVID-19 (among others), thereby missing potentially important components of societal costs. ICER's selected approach is contrary to the recommendations made by the Second Panel, which advocates for the inclusion of costs incurred during added years of life (i.e., "future costs") due to an intervention, which include healthcare costs and productivity consequences While ICER acknowledges that long-term sequelae are an important modeling consideration over a five-year period, ICER does not assume the same theoretical approach for modeling lost productivity costs, instead assuming a short-term (acute) duration for evaluation. We recommend that ICER adopt a more comprehensive approach for modeling productivity costs. Doing so would align with shifts in health economic guidelines, which broadly recommend the use of the long-term approach.	The Second Panel's updated recommendations do suggest the inclusion of future related and unrelated "… health care costs that occur during the additional life-years produced by an intervention" (which we have included in our analysis), however, the inclusion of non-health-sector costs that occur during life extension is less clear and subject to considerations for other potential cost-offsets that extend beyond productivity costs and may impact costs in either direction (i.e., cost-saving or added costs). Further, the average age at death for COVID-19 is greater than 70 years, and although there are ways to create productivity benefits at any age, we feel this average age of death for COVID-19 will make this less of a driver of the results.
3.	The COVID-19 pandemic has led to increased mental health concerns among the general public and not just among patients diagnosed with COVID-19. An ISPOR Special Task Force Report suggests that other negative externalities, specifically the fear of contagion, should be considered as potential costs.	We are aware of the ISPOR Special Task Force Report suggesting these potential negative externalities, but we are also aware that this report calls for ongoing research on how to do this. We will continue to track and contribute to this evolving area of methodological research.
4.	ICER compares the primary interventions to usual care, which is informed via the pooling of each primary intervention's placebo arm from the respective clinical trials. Pooled estimates inform model baseline characteristics, proportions of patients in health states (i.e., highest settings of care and respiratory support level received in hospitalization), and probability of death among hospitalized patients. We believe that the use of a pooled placebo arm raises significant challenges with the generalizability of ICER's findings. ICER should instead compare each intervention to its own placebo arm, thereby removing the need for the estimation of a pooled placebo arm. There are several issues that exist with the pooled placebo approach further described in the following section:	The purpose of pooling across the comparator arms of the pivotal trials is to create a more generalizable comparator across time, variants, patient composition, etc. These factors, which influence the risk of hospitalization for the comparator arm, vary among the pivotal trials, and thus, we pool the comparator arms of each pivotal trial to generate a comparator that encompasses variation in time, variants, and patient composition. The key input that is generated by pooling across the comparator arms of each pivotal trial is the risk of hospitalization in the comparator arm of the model. Our pooled US estimate of hospitalization for the comparator arm is supported by US Centers for Disease Control and Prevention estimates and other real-world evidence studies in the US. Further, this input is varied widely within the one-way sensitivity analysis, probabilistic sensitivity analysis, and numerous scenario analyses.

	• A fundamental challenge with the use of a pooled placebo comparator relates to the numerous differences across the clinical trials included in ICER's analysis. In the DER, ICER acknowledges several differences across baseline clinical trial characteristics, such as differences in the proportion of patients who are obese, have diabetes, and the geographic distribution of patients across studies, among others. In addition to baseline characteristics, there are observable differences in the outcomes of the trials, including the placebo rates across treatments and the proportion of patients who were hospitalized across each of the trials. Moreover, there are also important differences in the probability of death across interventions. Yet despite these potentially important differences, ICER holds that treatment effects across interventions were "generally indistinguishable from the average treatment effect." We believe that the differences in design and baseline characteristics across trials limit the generalizability of a pooled placebo arm. • We note that, despite ICER's removal of REGEN-COV from the evaluation, ICER still used the placebo arm from the REGEN-COV trial in its pooled estimates. If ICER elects to maintain the pooled placebo arm for its economic analysis, we recommend that ICER remove the placebo arm from the REGEN-COV trial in its pooled estimates, given that REGEN-COV is no longer considered in base case analyses.	If we had chosen to compare each intervention to its own usual care arm in its pivotal trial, we would have provided very context-specific results. Pooling across the usual care arms of these pivotal trials allowed us to be more generalizable to the eligible population and representative of various secular trends observed. Given the wide differences in usual care outcomes across the trials, we believe the pooled comparator approach we used will be less likely to provide results that could be misinterpreted. Another reason for our selection of a pooled comparator approach was driven by input from clinical experts. Experts advised us that, with the exception of the pregnancy limitations on molnupiravir and drug-drug interaction concerns with Paxlovid, clinicians will view these drugs as possible choices for the same population of patients. We therefore pooled the demographic characteristics (e.g., age and sex) across the pivotal trials to unify the population characteristics in the economic model. Given that we pooled the demographic characteristics, it was imperative that we also pool the outcomes (hospitalization, death) given the documented relationship between age and these outcomes. There may be systematic differences between the trials that could influence the relative effectiveness estimates for each treatment, which is why we clearly state we are not comparing the treatments to one another. However, we think the systematic differences in the comparator arm strengthen our pooled comparator approach by generating a more generalizable and comprehensive comparator.
5.	ICER's approach discriminates against interventions that provide benefit to older patients at an increased risk of death in three distinct ways. First, the primary interventions under review are associated with higher recovery ages relative to usual care, due to higher proportions of older patients surviving. Interventions which prevent deaths of older patients, incur higher healthcare costs and lower benefits per recovered patient compared to usual care due to their higher recovery age.	The COVID-19 evidence base suggests an increased risk of mortality among the older age population. The higher recovery ages relative to usual care stem from this evidence base suggesting an increased risk of death at a higher age. Because the average age at death is greater than the average age treated with these treatments, there is a differential age of recovery.
6.	Secondly, although recovery age is not varied in ICER's sensitivity analyses, it is a key model driver due to its role in determining age-adjusted follow-up costs, life expectancy, and quality of life.	Although recovery age is not directly varied in our sensitivity analyses, it is a dependent input on mortality, which is varied in our sensitivity analyses. Therefore, it is varied indirectly in our sensitivity analyses.
7.	Finally, the use of the life-year (LY) and equal-value LY, which ignores or minimizes quality of life benefits, will not fully account for this source of bias, as it additionally affects per-recovered patient costs	We provide numerous outcomes for decisionmakers to review in our report. The per-recovered patient costs are less than the lower bound of the threshold range we use.

8.	In the section of ICER's report titled "Potential Other Benefits or Disadvantages," ICER indicates that oral treatments should reduce access inequities if distributed fairly, compared to intramuscular (IM) and intravenous (IV) therapies. ICER further notes that certain infusion treatments may exacerbate inequities in local health system capacity given requirements regarding administration and post-infusion monitoring by a healthcare professional. We recommend that ICER further highlight the benefits of oral therapies compared to IM/IV treatments, given the following considerations. • Low uptake: A recent analysis found that only 7.2% of non-hospitalized Medicare beneficiaries with a COVID-19 diagnosis received mAb therapy between November 2020 and August 2021; additionally, it was found that those at highest risk of critical disease were the least likely to receive mAbs. Furthermore, geographic distribution has been suggested to play a key role in access to mAb therapies. Rural communities face a number of access challenges, including lack of high-speed networks to be used for telehealth, a generally sicker population due to poorer social determinants of health, increased distance to healthcare professionals, and understaffing of local hospitals; all of these barriers may make the distribution, administration, and monitoring of mAb therapy more difficult. • Patient preference: In a general emergency room setting, 66% of patients indicated a preference for oral therapies, compared to 19% for IV, and 15% for IM therapies. Patients have noted a number of reasons for preferring oral medications, such as a dislike of needles and pain from injections. This trend in preference of oral vs. IM and IV has been observed in several disease areas, including venous thromboembolism, rheumatoid arthritis, and oncology.	Thank you for this comment. We have added additional language highlighting these potential benefits and included additional references.
9.	In the section of ICER's report titled "Potential Other Benefits or Disadvantages," ICER indicates that COVID-19 has had a "low impact" on patients' ability to achieve life goals and a similar "low impact" on caregivers' quality of life and ability to achieve life goals. We recommend that ICER alter the text in column 2 of Table 5.2 (PDF page 39) to indicate that the impact of COVID-19 on patients' and caregivers' quality of life and ability to achieve life goals is "inconclusive."	While we do not think the impact is inconclusive, we note that the public meeting will provide an opportunity for the voting panel to discuss and determine whether the impact is indeed inconclusive.

10.	Additionally, in Section 2 "Patient and Caregiver Perspectives," ICER indicated that three patients were interviewed to better understand the impact of COVID-19 on patients; ICER described only one patient's experiences in detail. As the pandemic has progressed, there are several patient advocacy organizations related to COVID-19 that have been established. We recommend that ICER expand its engagements with these entities, and that ICER interview a broader group of patients to better understand the implications of COVID-19.	Thank you for your comment. We attempted to engage with several patient advocacy groups, but they declined to participate in our review. As an alternative, we conducted several long-format interviews with individual patients as described in the report.
11.	In the absence of a budget impact model, we recommend that ICER report the decision tree results of its analysis separately from the full decision tree plus lifetime Markov model analysis. This would allow stakeholders to better understand the short-term economic implications of COVID-19 treatment.	Thank you for this comment. As stated in our report, a potential budget impact analysis was not conducted for this Special Assessment. Given that these treatments could accrue costs and benefits over a lifetime because of the potential for life extension, and in alignment with recommendations in the field of modeling, our time horizon is that of a lifetime.
12.	ICER included fluvoxamine as a primary intervention in the cost-effectiveness model. The primary outcome of the included placebo-controlled Phase 3 trial of fluvoxamine was a composite endpoint of COVID-19-related admission to an emergency setting (defined as observation for more than six hours) or referral to a tertiary hospital due to COVID-19 progression within 28 days. Given the lack of comparability with more conventional endpoints from the other trials under evaluation, ICER should exclude fluvoxamine from the base case analysis and instead reserve fluvoxamine's results to a supplemental finding, akin to how ICER elected to handle presentation of results for REGEN-COV.	We state numerous times throughout the report that we do not compare across treatments, with this difference in the composite endpoint being one reason.
13.	On PDF pages 9 and 15 of the DER, ICER indicates that it may include remdesivir in this evaluation at a later date based on the Emergency Use Authorization granted for this therapy in this population. We note that inclusion of remdesivir in the next iteration of the report would preclude stakeholders from evaluating and commenting on remdesivir. Given ICER's approach to public review and feedback, we recommend ICER limit its analysis to the treatments identified as being under scope in the current review, and only add additional treatments during future updates.	We have now revised the report to describe remdesivir as another potential treatment and to indicate that it emerged too late for us to consider in the report. We note that the Interactive Modeler will be available on ICER Analytics after the final Evidence Report is complete.

Research/Patient Organizations		
Innovation and Value Initiative		
1.	The Draft Report includes qualitative input from only three patients, which may not be seen as a representative sample for the purposes of this assessment. Given the differential impacts of COVID on different subgroups in our society, it is crucial to engage with patients from diverse communities in the conceptualization of an economic model.	Thank you for your comment. We attempted to engage with several patient advocacy groups, but they declined to participate in our review. As an alternative, we conducted several long-format interviews with individual patients as described in the report.
2.	Some of the key model inputs might not fully account for the impacts of COVID-19 and its treatments on patients. Long-term sequelae after a COVID-19 infection and its disutility are sourced from an earlier paper (Sheinson et al.) that may not adequately reflect the long-term impacts of COVID hospitalization/recovery on patients. This report should acknowledge how little we know here, and that this is an area where patient engagement is crucial.	We agree completely. This is included in our report.
3.	Several highlighted factors of importance to patients may not be adequately accounted for – specifically impacts on work and productivity. More robust estimates of costs for lost work for individuals and caregivers should be estimated as part of such analyses given evidence of impact. This is particularly important from an equity standpoint, as impacts on career salaried employees are likely markedly different than impacts on hourly wage or service industry employees where loss of employment may be a factor.	Thank you for this comment. The estimates used are what we found to be the best available. If the Innovation and Value Initiative is aware of a specific source with more appropriate estimates, we will happily review that source for potential inclusion in the report.
4.	IVI believes that full access to the methodologies, calculations, and functioning of the model should be standard. By undertaking this analysis, ICER is endeavoring to contribute real-time learning in an evolving pandemic. More complete transparency of the model concepts and functioning would align with this commitment to common shared learning in the health economics and outcomes research (HEOR) space. This transparency and model access are especially important here, given the evolving evidence base and need to continually update inputs and uncertain assumptions… …As stated above, allowing more open access to the cost-effectiveness model would allow interested stakeholders to customize analyses to match relevant populations more closely, to test different assumptions, or to include alternative or updated inputs as they become available. An “open-source”, flexible, and transparent approach to model development, would allow stakeholders to work together as new evidence comes in, making the model more relevant and credible to various stakeholders.	Thank you. We continue to work with the academic health economic community to advance transparency. Intellectual property and academic interests can make this challenging. However, we feel that ICER’s Interactive Modeler is an effective way for stakeholders, including patient groups, to be able to access the model in a manner that allows the goals you refer to.

5.	While the scope of this assessment is clearly focused on treatment interventions for mild to moderate COVID-19, IVI sees a missed opportunity by not addressing an obvious comparator: prevention measures, including masks and vaccination. As this assessment concludes that cost-effectiveness is similar for all available treatments and efficacy among sub-populations is established by ever-evolving evidence, there is limited utility for the findings to change practice or policy. Comparison with preventive measures – which could substantially change the trajectory of both the pandemic and its economic impact – could contribute important context and science-based insight to ongoing policy debates about resource allocation to prevention policies compared to treatment and mitigation.	Thank you for your comment. The scope of report does not include preventive measures.
6.	As acknowledged by ICER, the model relies heavily on sparse clinical trial data, which could limit its applicability in the real world, especially in an environment where the virus is mutating rapidly and the treatment strategies to treat and/or prevent COVID are also rapidly evolving. To ensure this analysis delivers meaningful and accurate insights, IVI recommends that ICER postpone finalization of the report until more detailed clinical and real-world data are available, or that explicit plans for ongoing updating of analyses be developed and followed.	In the second paragraph of the Executive Summary, we indicate that our report is a Special Assessment due to the rapidly evolving epidemiological landscape and evidence base for potential treatments for COVID-19. However, we recognize that given the unprecedented immediacy and scale of COVID-19, an independent review of existing evidence on comparative clinical effectiveness and value of these treatment options will be helpful for informing near-term policies by decisionmakers. Further, Report Supplement Section D describes our search strategy for capturing real-world studies included in our report, which we have continued to update. Finally, we note that the Interactive Modeler will be available on ICER Analytics after the final Evidence Report is posted. This will enable decisionmakers to update results using inputs as new evidence becomes available.
7.	Where clinical trial data might not reflect disparities in effectiveness or treatment outcomes in the real world, some indication of the likely impacts on under-represented subgroups (even if qualitative) could be useful to readers. Data inputs derived from a sample not representative of the target population might also result in model insights that could further exacerbate disparities.	While there is uncertainty about the differential impact of treatments in subgroups, there is insufficient evidence that would allow for a meaningful sensitivity analysis around this issue.
8.	A limited societal perspective was included as a scenario analysis, but it does not account for the full range of benefits potential treatments could have in the broader economy. This could lead to an under-estimate of the value of these therapies, which may be not only cost-effective, but also cost saving. Reimbursement and coverage decisions based on incomplete estimates could also deter long-run incentives for innovation.	We heard from stakeholders that the societal benefit most plausibly attributed to these outpatient treatments may stem from their ability to reduce hospital capacity, which we include in our modified societal perspective scenario analysis.

Solve ME		
1.	Our primary feedback is the need to include the impact a therapeutic may have on Long Covid (post-Covid conditions, or post-acute sequalae of Covid-19) in addition to the effect on the acute phase. Given the significant health deterioration in this condition and related cost, any future cost-effectiveness analysis of interventions in non-hospitalized outpatients with mild-to-moderate disease should look at the potential to reduce this burden. The long-term outcomes are potentially an added dimension of benefit, on top of reducing hospitalization and prevention of death. We therefore suggest to expand the classification of the severity of symptomatic infections to mild, moderate, severe, critical disease and long-term (sub-chronic). This model will allow for including analysis of Long Covid. We propose to use the WHO case definition: “Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.” Although Long Covid is listed under "Patient-Important Outcomes", PASC (Long Covid) is a secondary outcome in only one study reviewed in the Special Assessment. It is the study of Fluvoxamine (COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19)), using a specific questionnaire. We urge ICER to encourage drug developers to include Long Covid assessments in their studies, so that it could be included in cost-effective analysis to demonstrate an additional benefit. Recently, the GAO estimated that up to 23 million Americans have been impacted by Long COVID, highlighting the urgency and scope of this immense public health crisis. The evidence suggests that Long Covid can have a significant impact on people even in lower-risk populations, including patients with full vaccination that had mild acute infection (recent research does suggest that vaccines reduce the risk for Long Covid by approximately 50%).	Thank you for your comments. In alignment with recent recommendations, we were able to incorporate the costs and consequences of the long-term sequelae of COVID-19 in our economic modeling work. As you note, this is an evolving area of research and an area with some current uncertainty. Decisionmakers will be able to update the model inputs on the incidence, severity, and consequences of this long-term sequelae in our Interactive Modeler. We are also looking forward to discussing future research needs during our policy roundtable at the public meeting and including these discussions in our policy recommendations.

Center for the Evaluation of Value and Risk in Health, Tufts Medical Center		
1.	Increase estimated excess deaths per ICU admission from 0.195 to 0.75. ICER estimated excess deaths caused by each COVID ICU admission from CDC information describing the empirical relationship between excess deaths and national ICU utilization. ICER reasoned that we can attribute each excess death equally to each ICU bed occupied. Increasing the estimated number of excess deaths caused per ICU admission from ICER's value of 0.195 to our estimated value of 0.75 substantially increases the QALY gain attributable reducing excess deaths (compare Columns 4 and 5 in Table 1 – i.e., the QALY contribution of the modified societal perspective).	In our draft Evidence Report, we wanted and needed to give benefit to the treatments on reducing ICU capacity, but we were left trying to develop a method on our own. As presented in our draft Evidence Report, we pitched a novel and preliminary approach, but noted this was a particular area where we were hopeful to receive feedback. As CEVR points out, the slope we were calculating in our draft Evidence Report was from 0% to 74%. The slope you are suggesting is between 70% and 80%. After reading your public comment, we agree that using 0% as our lower bound was likely inappropriate. We have used your feedback to update the estimates in our revised Evidence Report. We now calculate a slope from 64% (which equates to the non-COVID-19 ICU capacity) to 74% (which equates to the total ICU capacity including COVID-19 infections). The slope of this line equates to 0.52 excess deaths per ICU admission averted. The lower bound equivalent to the non-COVID-19 ICU capacity is likely more evidence-based than the 0% we used in our draft Evidence Report and the 70% used in the calculations you provided.
2.	We could not identify information in the ICER report needed to estimate definitively the impact of our revised assumption on costs. It does seem that the incremental costs for each therapy are larger in ICER's modified societal perspective analysis (ICER Draft Report, Table 4.9) than they are in the health care sector perspective analysis (ICER Draft Report, Table 4.3). For example, sotrovimab's incremental cost is $303,800-300,200=$3,600 for the modified societal perspective and $300,700-297,800=$2,900 for the health care sector perspective. It is unclear why the modified societal perspective's incremental cost is higher. If this difference reflects the added cost of caring for more patients when there are fewer excess deaths, we would argue that ICER should present cost-effectiveness estimates calculated both with and without this contribution. Otherwise, the analysis could perversely penalize COVID therapies because they promote the goal of keeping non-COVID patients from dying due to degraded health care quality in highly utilized hospitals.	We included future unrelated health care costs, which is the reason for this. The Second Panel recommends the inclusion of future related and unrelated medical costs in both the health care sector and societal perspective. The debate on whether to include or exclude future unrelated health care costs has been long-standing, with the arguments supporting exclusion receiving rebuttals. Importantly, there is not a health care penalty associated with including these costs because the QALYs accrue at a cost lower than our lowest cost-effectiveness thresholds. We present a scenario analysis excluding these costs.
3.	Why ICER should report the modified societal perspective findings as a co-base case… • ICER states that ICU capacity concerns will likely diminish as the Omicron surge fades. We offer two responses. First, ICER provides no evidence indicating that ICU utilization is likely to be substantially less in the future than the 74 percent rate ICER used in its analysis. That rate, according to ICER, corresponds to November 2021, before the arrival of the omicron variant in the United States and hence before the Omicron-related surge in ICU-utilization, although the Delta variant was prevalent in November 2021. Moreover, data from the mid-2000s	The ICER Reference Case provides examples of when the health sector perspective is presented in tandem with the modified societal perspective as a co-base case. The Reference Case states, "Examples include when the incremental cost-effectiveness ratio changes by greater than 20% or by greater than $200,000 per QALY, and/or when results cross thresholds of $100,000-$150,000 per QALY." Although some of the incremental cost-effectiveness ratios change by greater than 20% (partially explained by low incremental cost-effectiveness ratios in the health sector perspective), the incremental cost-effectiveness ratios do not change by greater than $200,000 per QALY and the results do not cross the threshold of $100,000-$150,000 per QALY.

	suggest ICU utilization rates averaged 68 percent even before the pandemic, not much below ICER's 74 percent assumption. Second, the assessment's estimate of value should reflect therapy benefit when therapies are likely to be used. While a lower COVID prevalence in the future implies a lower baseline ICU utilization rate and hence fewer prevented excess deaths for each averted COVID patient ICU admission (see Figure 1), use of these therapies is also likely to be lower during periods of low COVID prevalence. Instead, future use of these therapies is likely to be concentrated during periods when COVID prevalence is elevated, and during these periods, ICU utilization is likely to be greatest, which means that the number of excess deaths prevented per averted ICU admission will likewise be higher. In short, COVID therapy use is likely to peak at those times when the societal value conferred by these therapies is also elevated. As an analogy – just as a snow shovel's value should reflect its utility on the days when it will be used, rather than during mid-summer, assessments should estimate COVID therapy values weighted to reflect the conditions when patients will most likely use them.	In regard to your comment about ICU capacity, we did not think the benefits of these treatments on ICU capacity should be modeled at the peak, but rather at the best current estimate of their relative impact on the ability to care for other patients. However, the dynamic nature of this Special Assessment and the potential difference in value over time will be extensively discussed during the policy roundtable at the public meeting.
4.	ICER states that the apparently continuous relationship between ICU utilization and excess deaths is an illusion. ICER implies that most ICU admissions cause no material impact to care delivered to other patients: "in the real-world, numerous ICU admissions may need to be prevented … for excess deaths to be prevented." Even if that claim is valid, ICER's point would be salient only if we anticipate that the number of patients who will receive COVID therapies will be small. In that case, we might appropriately say that COVID therapies have a substantial probability of preventing no excess deaths, but a small probability of preventing a notable number of such deaths. In reality, however, it is likely that many patients with COVID will use these therapies, so these dichotomous outcomes collapse to what is for all practical purposes a continuous relationship. The large number of patients receiving these therapies means that the reduction in hospital admissions achieved by COVID therapies will (almost certainly) translate to an actual reduction in excess deaths. The slope of the relationship characterized by CDC corresponds to the number of excess deaths that lower ICU utilization will avert. Reporting the modified societal benefit findings as a co-base case, rather than as a scenario analysis, has important implications. First, it would guarantee that ICER's value-based prices more accurately reflect the societal health benefit contributions conferred by these therapies. Second, the modified societal perspective	We have updated the language around the societal perspective, but it remains a scenario analysis. The ICER Reference Case provides examples of when the health sector perspective is presented in tandem with the modified societal perspective as a co-base case. The Reference Case states, "Examples include when the incremental cost-effectiveness ratio changes by greater than 20% or by greater than $200,000 per QALY, and/or when results cross thresholds of $100,000-$150,000 per QALY." Although some of the incremental cost-effectiveness ratios change by greater than 20% (partially explained by low incremental cost-effectiveness ratios in the health sector perspective), the incremental cost-effectiveness ratios do not change by greater than $200,000 per QALY and the results do not cross the threshold of $100,000-$150,000 per QALY.

	results would appear in ICER summary products that ICER often publishes alongside its technical document. Media reports are more likely to report findings that appear in these summary products. ICER points out that its analysis that restricts attention to health care sector benefits finds that at their current prices, the four therapies analyzed satisfy conventional cost-effectiveness criteria. But ICER also points out that conditions are changing that might make the cost-effectiveness of these therapies less favorable. These factors include, for example, lower hospitalization rates for people infected with the Omicron variant than with the Delta variant, and use of the therapies in vaccinated populations. These factors might imply a lower number of COVID patients receiving these therapies who might otherwise require ICU care and hence a reduced benefit for therapies that avert hospitalization. It is possible, however, that even if such factors render the estimated cost-effectiveness of these therapies unfavorable when calculated using the health care sector perspective, they might remain favorable when calculated using the modified societal perspective. That difference could have material implications for decisions regarding reimbursement at existing prices. For that reason, reporting value-based prices using both perspectives remains important.	

Other		
Partnership to Improve Patient Care		
1.	ICER's model does not capture the full societal benefits of COVID-19 treatments. The virus has had a shattering impact on society writ large, and for that reason it is even more important than usual that the societal impact is captured in the base case. Though ICER attempted to capture some minimal societal impacts in one of its scenarios, we strongly recommend including the societal perspective in its base case and urge ICER to explore all avenues to capture the holistic societal burden of COVID-19. The virus does not only impact the productivity of the ill patient, but the productivity of his or her healthy neighbors when they are unable to continue working as usual due to business and school closures. For example, there is a growing body of evidence indicating rising anxiety and depression in the nation's youth following several years of educational and social disruption.	Although the impact of COVID-19 on the economy is undeniable, we heard from stakeholders that these outpatient treatments that may reduce the severity of disease will have minimal effects on the broader economy. The societal benefit most plausibly attributed to these outpatient treatments may stem from their ability to reduce capacity, which we include in our modified societal perspective scenario analysis. Further, we heard from clinical experts and some manufacturers that due to the state of vaccination in the US, the influence of these outpatient treatments on transmission is expected to be quite limited.
2.	COVID-19 has also had a disproportionate impact on our health care system, beyond just capacity of intensive care units. One of the biggest burdens of COVID-19 has been the impact on the health care system's ability to treat routine health problems. Treatments for cancer, chronic diseases, and scheduled or emergency surgeries have been delayed or cancelled. This has had a significant and documented effect on health outcomes and non-COVID mortality. With this in mind, an accurate representation of the value of successful treatments for COVID-19 should include this wider impact on the zero sum of scarce healthcare resources as a marginal public health value as previous studies have shown.	We heard from stakeholders that the largest expected impact on the health care system will be on ICU capacity by way of preventing this type of utilization. As documented in Report Supplement E and our response to the Center for the Evaluation of Value and Risk in Health Comment 1, we describe the data available and our approach to modeling the impact of the outpatient treatments of interest on ICU use and outcomes for other patients. Further, it is possible that outpatient health system capacity may decrease in the presence of these outpatient treatments due to patients needing to engage with the health system in order to be prescribed these treatments. Having said that, please share any literature you have documenting this effect on health outcomes. We will review it for potential inclusion.
3.	ICER must be transparent about the fact that the burden of COVID-19 falls more heavily on communities of color, people who are immunocompromised, seniors, and uninsured populations. , Given that the burden of disease in general falls more heavily on these groups, and access to healthcare is also lower in these groups, effective therapeutic interventions can have an impact on reducing underlying health inequities. ICER should examine the fact that not only are effective treatment options impactful for individual patients, but they also have the potential to address systemic health inequalities. We urge ICER to include a specific section on the report addressing health equity and effective treatments' potential impact on health disparities.	We discussed the disproportionate burden of COVID-19 in the Background, Patient and Caregiver Perspectives, and Potential Other Benefits or Disadvantages sections of the draft Evidence Report. We have also now lengthened our discussion of the potential for COVID-19 treatments, if distributed fairly, to reduce inequities.
4.	ICER continues to use the quality-adjusted life year, which is widely known to discriminate against people with disabilities, patients with chronic conditions, and older adults – populations hit hardest by the pandemic. Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions and people with disabilities. There is widespread recognition that the use of the QALY is discriminatory. The QALY has	ICER follows common academic and health technology assessment standards by using the cost per QALY gained, but also presents cost per life year gained and cost per evLY gained. The QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives and has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years.

	historically been opposed by the American public and policy makers. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments. Throughout the pandemic, people with disabilities and chronic conditions have been hit hardest by COVID-19. They have experienced worse health outcomes, been subjected to discriminatory crisis standards of care, and too often have been viewed as disposable. Effective treatments for COVID-19 have the potential to be most meaningful to these individuals. Therefore, the QALY, which is known to undervalue treatments for people with disabilities, should not be used in this assessment.	ICER has a Value Assessment Framework that includes flexibilities for deliberation that can include key other benefits and contextual considerations (e.g., equity, severity, unmet need, etc.) specific to COVID-19 that may not be possible to incorporate in the cost-effectiveness model.
5.	ICER should use a transmission model when assessing treatments for infectious diseases. Markov models and decision trees are commonly used for non-communicable diseases, as they are loosely based around disease progression over the course of the disease. Models used to represent communicable diseases have a very different structure. The population of interest is not just those with the disease at the onset of the model timeline, but also others within the population who may become infected. Even if the agents being evaluated are for treatment, not prevention, more effective treatment tends to mean lower periods of incubation and infection, which impacts transmission. Transmission models are regarded as best practice for estimating cost-effectiveness in infectious diseases with recent examples in HCV, HIV, HPV, influenza, pneumonia, and COVID-19. Using a transmission model would also allow the report to more ably assess the wider economic burden of failing to control an epidemic and its impact on economic and social wellbeing more broadly. Numerous commentators have made the point that where there are no therapeutic interventions available, the only options are to enforce considerable behavioral restrictions on society, which comes at great economic and mental health cost.	We heard from clinical experts and some manufacturers that due to the state of vaccination in the US, the influence of these outpatient treatments on transmission is expected to be quite limited.

Paul Langley, PhD, College of Pharmacy, University of Minnesota		
1.	This complete lack of understanding of the limitations imposed by ordinal scores is demonstrated in the application of Covid-19 related disabilities (Table E9). The first step, mathematically disallowed, is to create an age adjusted utility (0.87) by discounting the unit utility of perfect health (an ICER adjustment). As the preference scores are ordinal you cannot multiply. The second step, also disallowed, is to consider four disutilities ranging from emergency department visits (-0.30) to hospitalization with mechanical ventilation (-0.60). In this last case the presumed, yet mathematically impossible utility is 0.87 – 0.60 to give a utility score of 0.27. This entire exercise is absurd because the ordinal scale lacks invariance of comparisons; the EQ-5D-3L/5L algorithms, which give quite different scores for the same health state, were not designed to create scores with interval, let alone ratio properties. It is worth noting that these disutilities do not match the utility weights presented in the website of the Tufts CEA registry where all COVID-19 health state weights are negative (i.e., health state worse than death) which is not the case for the ICER report where the COVID-19 health states are all positive. Presumably you select the preference scores which best suit your model and its assumptions. According to the Tufts registry health state weights presented on the website (which capture direct and indirect multiattribute preference scores), a preference score of 0.27 (the worst outcome in the ICER model) is equivalent to a preoperative total hip or knee arthroplasty with COVID19 weights ranging from -0.19 to -0.6. Needless to say, the Tufts registry which is now 46 years old, has not apparently considered the implications of negative preference weights in terms of the axioms of fundamental evidence and the impossibility of applying any preference score to create QALYs.	We are not able to identify the estimates you are referring to on the Tufts CEA registry. We assume that the negative values they present are disutilities, and are not suggesting a health state worse than death, but instead a disutility that could be added onto an age-adjusted utility score.