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March 3, 2022

Steven D. Pearson, MD, MSc
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Re: ICER's Special Assessment of Treatments for COVID-19 Draft Report

Dear Dr. Pearson,

GlaxoSmithKline (GSK) appreciates the opportunity to provide comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report for the special assessment of the clinical effectiveness and economic value of outpatient treatments for COVID-19. As stated previously, GSK is not aligned with ICER's rationale and approach for conducting a review of COVID-19 therapeutics given the evolving epidemiological, viral, and therapeutic landscape. As an example of this dynamism, witnessed since the announcement of ICER's intended review in August 2021, SARS-CoV-2 has continued to evolve with the Omicron variant quickly emerging as the predominant variant globally[1] and across the United States[2] resulting in an impact on therapeutic options in the US[3]. In light of this landscape and the need for timely information to inform patient access to COVID treatments, we challenge the ICER team to reconsider whether the outputs of the Draft Evidence Report truly provide incremental value to healthcare decision makers as they evaluate available interventions for the treatment of COVID-19.

Given the dynamic environment and urgency of the public health emergency (PHE), GSK is aligned with ICER in that it is critical that clinicians and healthcare decision-makers have evidence-based recommendations to inform their practices and patient management. However, ICER's Draft Evidence Report fails to reflect the current status of the COVID PHE. Current treatment guidelines, such as those published by the National Institutes of Health (NIH), provide clinicians with such a framework to aid in appropriate treatment selection and are continuously updated with efficacy and safety data that are in line with the dominant variant.[4] In addition, the Department of Health and Human Services (HHS) and the Office of the Assistant Secretary for Preparedness and Response (ASPR) have issued clinical implementation guidelines to support clinical practice.[5] Furthermore, treatment recommendations for patients with mild-to-moderate COVID-19 at high risk of progression to severe disease continue to evolve. This includes modifications to Emergency Use Authorization (EUA) of monoclonal antibody (mAb) therapies restricting use based on variant profile and predominance[3]; granting of EUA for a new mAb treatment that was not

available at the initiation of ICER's review[6]; Food and Drug Administration (FDA) approval of an existing therapy for early treatment[7] and authorization of a treatment for pre-exposure prophylaxis[8]; and promising clinical development pipelines.

Notwithstanding the debate as to the appropriateness of conducting a clinical and economic review in the midst of a PHE and with less than complete data (which, admittedly, is frequently the case and the reason for which health economists utilize economic models; however, one may argue the lack of data for this particular review is exceptional), please find below GSK's comments on ICER's Draft Evidence Report.

ICER's current assessment methodology is not reflective of widely accepted best modelling practices and therefore, may limit the interpretation of outputs and relevance for decision-makers, especially those not versed in economic models:

- 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.

- 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.[9,10]

  GSK recommends ICER utilize reported or derived relative risk ratios regardless of statistical significance to more accurately assess the effectiveness of the interventions.

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.

In summary, GSK welcomes the opportunity to continue the dialogue with ICER regarding the value of healthcare interventions. As per our mission statement, GSK is a science-led global healthcare company with a special purpose: to help people do more, feel better, live longer. However, given the evolving epidemiological, viral, and therapeutic landscape of the COVID-19 PHE, we are not aligned with ICER's rationale and approach for conducting a review of COVID-19 therapeutics at this time. We are concerned that ICER's current methodologic approach is not reflective of widely accepted best modelling practices. But perhaps more concerning is the debate as to whether the outputs of the Draft Evidence Report provides incremental value to healthcare decision makers as they evaluate available interventions for the treatment of COVID-19 given the report fails to reflect the current status of the COVID PHE.

Please feel free to contact us should you wish to discuss these recommendations in further detail.

Sincerely,

Sulabha Ramachandran

Sulabha Ramachandran, PhD

VP, US and Regions, Value, Evidence and Outcomes

Sotrovimab Emergency Use Authorization

Sotrovimab has not been approved but has been authorized for emergency use by the FDA under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Sotrovimab is not authorized for treatment of mild-to-moderate COVID-19 in geographic regions where infection is likely to have been caused by a non-susceptible SARS-CoV-2 variant based on available information including variant susceptibility to these drugs and regional variant frequency. FDA's determination and any updates will be available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs.

Sotrovimab is not authorized for use in the following patient populations: adults or pediatric patients who are hospitalized due to COVID-19, adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, or adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen. Benefit of treatment with sotrovimab has not been observed in patients hospitalized due to COVID-19. SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

The emergency use of sotrovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

For information on the authorized use of sotrovimab and mandatory requirements under the Emergency Use Authorization (EUA), please review the FDA Letter of Emergency Use Authorization, Fact Sheet for Healthcare Providers, and Fact Sheet for Patients, Parents, and Caregivers.

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March 2, 2022

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RE: Public Comments ICER Draft Evidence Report for COVID Treatments

Dear Dr. Pearson:

The Innovation and Value Initiative (IVI) appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review (ICER) Draft Evidence Report for Treatments for COVID-19.

IVI is a 501(c)(3) nonprofit research organization committed to advancing the science, practice, and use of value assessment in healthcare to make it more meaningful to those who receive, provide, and pay for care. Founded in 2017, the organization includes members from the research, patient, payer, purchaser, clinician, and innovator stakeholder communities. IVI's work emphasizes collaboration and exploration of new solutions that address our common values of patient-centricity, transparency, and vigorous enhancement of economic evaluation methods.

The COVID-19 pandemic has highlighted the uncertainties associated with evaluating the clinical and economic value of novel treatments. We agree with ICER that it is important to assess the health and economic outcomes of drugs for the treatment of mild-to-moderate newly diagnosed COVID-19. After review of the Draft Report, however, we have several concerns about the process and substance of the analyses.

IVI supports value assessment approaches that produce credible and relevant information to support decision making that maximizes benefits to patients with the greatest efficiency for the health system. To that end, IVI encourages ICER to conduct analyses that reflect and align with several key principles for value assessment:

Sustains Authentic Patient Centricity

- 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.

- 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.
- 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.

Advances Transparency

- 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.

Focuses Value Discussion Across Treatment Interventions

- 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.

Improves Clinical and Real-World Data

- 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.

Facilitates Customizable Decision-Making

- 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.

Adapts To and With Evolving Evidence

- The report rightly acknowledges the ongoing evolution of evidence related to the pandemic and treatment strategies. Given the uncertainty of both treatment impacts and societal impacts, a more transparent and collaborative approach to this model's future development is warranted.
- ICER's draft report notes the many limitations of the evidence base but may not fully convey the inherent uncertainty from these limitations. Additional scenario analyses would help outline the potential magnitude of changes if uncertain assumptions are varied.

Supports Health Equity

- Subgroup analyses to consider and account for lack of representativeness in data should be clearly articulated.
- ICER noted that they reached out to manufacturers to ask for additional data by subgroup "such as race, vaccination status, variant of concern, time since randomization, serum antibody status, and individual risk factors for progression to severe disease" and stated that "data was [sic] either not available or insufficient to assess differential effectiveness in these populations". ICER also noted the "lower proportion of Black populations in the Phase III trials for molnupiravir and Paxlovid".
- 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.

Fosters Long Run Innovation

- 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.

Cultivates Modernized Methods

- Given the prevalence of COVID-19 and its profound societal impacts on a global scale, this is an opportunity for us to advance methods to incorporate some of the additional elements of value from the "value flower" developed by the ISPOR special task force (e.g., fear of contagion, equity considerations) and patient input/perspectives.

We appreciate the opportunity to provide input to ICER's Draft Evidence Report for Treatments for COVID-19. Please do not hesitate to contact us for further discussion.

Sincerely,

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March 3, 2022

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Re: Comments on ICER Draft Evidence Report

Dear Dr. Pearson:

Thank you for the opportunity to provide comments on the ICER analysis of COVID-19 Treatments. At this time, we would like to provide comments on the ICER Draft Evidence Report released on February 3, 2022.

Merck's Response Document for the Special Assessment of Outpatient Treatments for COVID-19 Draft Evidence Report

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 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."

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.[1] The IDSA guidelines only recommend the use of fluvoxamine in the context of a clinical trial.[2]

Recommendation:

a. 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.

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.[3-5] 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:

a. 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 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.[7] 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. [7]

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.

7. ICER should provide balanced evidence and improve consistency in the structure and presentation of product discussions.

An integral part of ICER's Evidence Reports is the rigor it applies to its review and evaluation of the available evidence to inform its comparative clinical effectiveness analysis. However, despite ICER's transparent approach in the appraisal and synthesis of the available information, the structure and balance of that information across products should be consistent.

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.[8] 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.

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.

Recommendations:

a. 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.
b. 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.[8]
c. 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 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.[9]

Thank you again for this opportunity to provide comments. We look forward to continuing this engagement throughout the evaluation period. If you have questions, please feel free to contact me.

Sincerely,

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References:

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2 March 2022

Dear Dr Pearson

SPECIAL ASSESMENTS OF OUTPATIENT TREATMENTS FOR COVI-19

I refer to your recently released Draft Evidence Report for Special Assessments of Outpatient Treatments for COVID-19 [1]

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science [2] . That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of modern measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. This has been detailed in a recent publication in F1000Research (awaiting peer review) which has addressed the manifest deficiencies in the CHEERS 22 guidance for constructing imaginary worlds, described as the ISPOR/ICER meme or belief system for inventing (non-evaluable by design) value claims for cost-effectiveness [3] [4]. An analytical dead-end.

The lack of understanding by CHEERS 22 and the ISPOR/ICER meme of the standards for modern measurement theory and failure to appreciate that the standard is for value claims expressed as unidimensional attributes is undeniable. Indeed the overwhelming majority of both generic and disease specific PROs produce nothing but ordinal scores. They are incapable of a robust estimate of response to therapy. CHEERS 22 and its companion textbook primer for creating imaginary value claims seem unaware of this limitation [5].

This lack of appreciation of modern measurement theory is seen in your attempt to apply ordinal preference to create imaginary QALY claims (you can't multiply time spent by an ordinal score). The preference or utility scores that support the cost-per-QALY claims in the ICER model are from two recent papers reporting values for the EQ-5D-3L/5L [6] [7] . Unfortunately, neither paper considered the issue of modern measurement theory [8]. To create a QALY you need a bounded

ratio measure; that is, a measure with interval properties (or invariance of comparison) and with a true zero, capped at unity. As a worthy complement to ICERAnalytics, is the well-established Tufts University Medical Center's Cost Effectiveness Analysis (CEA) registry of over 36,000 ordinal preference scores (health state weights) and cost-per-QALY claims from over 8,000 cost-per-QALY studies and assembled over the past 46 years [9] . The Tufts CEA, as an example, includes negative values as part of the registry of preference scores (e.g., opioid abuse -0.064; tuberculosis -0.55) without realizing the implications of this for any claim given that the scores are only ordinal with the absence of a true zero Again, in common with ICER, the Tufts CEA assumes that the ordinal preference have ratio measurement properties; in retrospect this belief, like the ICER model claims, appears a waste of time. The error, made over 30 years ago, was to fail to recognize that if you are to create a PRO that yields interval or ratio properties then it has to be designed to create those measures [10] . In the absence of this the default position is that the PRO instrument can only report, usually composite, ordinal preference scores.

This complete lack of understanding of the limitations imposed by ordinal scores is demonstrated in the application of Covis-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.

Of course, these criticisms are beside the point as they merely challenge impossible mathematical constructs. The fact that in COVID-19, on one set of claims, health states are worse than death means a negative impossible QALY or (I-QALY); as opposed to a positive I-QALY for another set of preferences [11]. The modeling is clearly a waste of time; but it is your business model.

Yours sincerely

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March 3, 2022

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Submitted via email: publiccomments@icer-review.org

RE: Pfizer Comments on ICER's "Special Assessment of Outpatient Treatments for COVID-19" Draft Evidence Report

Dear Dr. Pearson and ICER COVID-19 Review Team,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the *Special Assessment of Outpatient Treatments for COVID-19* Draft Evidence Report (DER).[1]

We appreciate ICER's efforts to seek input from a broad range of stakeholders. Pfizer is committed to discovering medicines that enhance the health of patients, their families, and society, with the goal of offering breakthroughs that will change patients' lives. In addition, we are dedicated to working with all stakeholders to identify solutions for creating a more effective, efficient, and equitable health care system for patients.

Based on our review of the DER, we have identified several issues with ICER's methodology that likely impact the generalizability of its results. Specifically, our comments below focus on:

1. A more comprehensive characterization of a societal approach
2. Challenges associated with the pooled placebo comparator
3. Equity concerns related to patients and caregivers, and
4. Other considerations

1. Comprehensive Characterization of the Societal Approach

In the DER, ICER included the societal perspective as a scenario analysis. We recommend that ICER (1) promote the societal perspective to a co-base case and (2) indicate that the analysis provides an underestimation of total societal costs.

a. Promotion of the societal perspective to a co-base case

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:

i. Large societal burden of the COVID-19 pandemic: 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.[2] 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. **Error! Bookmark not defined.** 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.[3] 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.**Error! Bookmark not defined.**

ii. Second Panel's recommendations: 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."[4] 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.[4] Doing so, the Panel indicates, will provide a wider and more valuable benefit to a range of stakeholders and decision makers.[4]

b. Indicate the current analysis underestimates costs borne by society

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.[2,3,5,6,7] 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 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. The rationale for this recommendation is presented below.

i. Estimation of short-term lost productivity only: 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.[2] 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.[4]

We note that two recent publications have estimated lost productivity associated with COVID-19 due to premature mortality. Hanly et al. discuss the importance of this approach by arguing that population health, as measured by increased life expectancy and reduced mortality, is positively and substantially associated with societal economic welfare and growth.[3] Similarly, Sheinson et al. estimated societal costs associated with market productivity (e.g., wages, salaries, self-employment income, and employer-paid benefits) and non-market productivity (e.g., childcare, eldercare, household services) losses due to COVID-19.[8] Several components of the Sheinson et al. framework have been applied by ICER to its analysis, including Shienson's overall model structure and their approach to estimating the consequences of long-term sequelae over a five-year period. 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.[9]

ii. Exclusion of additional negative externalities: The COVID-19 pandemic has led to increased mental health concerns among the general public and not just among patients diagnosed with COVID-19.[5,6,7] An

ISPOR Special Task Force Report suggests that other negative externalities, specifically the fear of contagion, should be considered as potential costs.[10]

2. Use of a Pooled Placebo Comparator

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.

a. Issues with comparability across clinical trials

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."[1] We believe that the differences in design and baseline characteristics across trials limit the generalizability of a pooled placebo arm.

ICER notes that "substantial differences in patient populations across the Phase III trials preclude …direct comparisons across these trials."[1] Yet despite this acknowledgement, ICER has still elected to adopt a cost-effectiveness model using a pooled comparator. In the absence of an indirect treatment comparison, a common comparator should be avoided, and baseline disease burden should be determined based on the clinical trial.

b. Inclusion of data from an excluded product

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.

3. Equity Concerns related to Patients and Caregivers

We believe that some of the methodologic decisions that ICER has made have important implications related to equity. We outline these decisions below and make recommendations on how ICER's approach may be adapted to reflect on these issues.

a. Age of recovery calculation and implications

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. However, ICER's methodologic approach of using a pooled placebo arm exacerbates the differences in the average age of recovery across interventions, based on the heterogeneity of the baseline age of study populations.

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.

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.

The challenges associated with the age of recovery calculation stem in large part from ICER's decision to use a pooled comparator group. As previously noted, we recommend that ICER instead compare each intervention to its own placebo arm, thereby removing the need for the estimation of a pooled placebo arm.

b. Patient access to treatment

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.[1] 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.

i. 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.[11] 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.[12]

ii. 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.[13] Patients have noted a number of reasons for preferring oral medications, such as a dislike of needles and pain from injections.[14] This trend in preference of oral vs. IM and IV has been observed in several disease areas, including venous thromboembolism, rheumatoid arthritis, and oncology.[14,15,16,17]

c. Impact on patients and caregivers

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.[1] 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".

The evidence base related to both the short and long-term humanistic impacts of COVID-19 is still in early stages of development, but early evidence indicates that COVID-19 infection may impact the heart, lungs, and brain, increasing the risk of developing secondary complications and diseases.[18] A recent study by Blomberg and colleagues assessed the long-term side effects of COVID-19 in home-isolated patients and

found that patients had persistent COVID-19 symptoms including loss of taste/smell, fatigue, dyspnea, impaired concentration, and memory problems at 6-months post-infection.[19] Current research indicates that the disease may significantly decrease health-related quality of life for patients as well as impact the mental health of patients' partners and families, inducing worry, frustration, and sadness.[20,21,22]

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.

4. Other considerations

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.

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.

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 respectfully ask that ICER acknowledge our feedback and make the necessary efforts to address these issues, so that patients, physicians, and other stakeholders can have an unbiased perspective from which to consider the value of outpatient treatments for COVID-19 during this unprecedented time. Pfizer welcomes the opportunity to discuss the recommendations outlined in this letter with ICER.

Sincerely,

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PIPC Partnership to Improve Patient Care

March 3, 2022

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Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to provide feedback on ICER's assessment of treatments for COVID-19. The COVID-19 pandemic has upended the country causing upheaval to many of our most basic institutions, from hospitals to schools. The pandemic is also widely known to have exerted more harm on certain populations, including communities of color, people with disabilities, and individuals living with chronic illness. PIPC urges ICER to capture the far reaching and disparate impact of COVID-19 in its model in order to accurately capture the value of effective treatments. From this vantage point, PIPC asks ICER to consider the following comments:

ICER's Model Omits Multiple Components of the Full Societal Benefit of an Effective COVID-19 Treatment.

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.[1]

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,[2] chronic

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diseases,[3] and scheduled or emergency surgeries[4] have been delayed or cancelled. This has had a significant and documented effect on health outcomes and non-COVID mortality.[5] 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.[6]

Treatments developed for coronaviruses now may also have considerable additional value in the future. Novel antibiotics not only have great value now because they can treat current infections, but also because they may be the only antibiotic option in the future where resistance to current therapies has been exhausted.[7] In a similar vein, antivirals cannot be evaluated in a vacuum.[8] If we have learned anything from the COVID-19 epidemic it is that coronaviruses are not static, they are constantly evolving, and an antiviral that has the potential to keep new variants from being less severe also provides value that should be captured.

ICER's Model Does Not Capture the Impact of Treatment on Health Equity

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,[9] and uninsured populations.[10,11] Given that the burden of disease in general falls more heavily on these groups, and access to healthcare is also lower in these groups,[12] 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.

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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[13] and people with disabilities.[14] There is widespread recognition that the use of the QALY is discriminatory. The QALY has 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.[15] 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.[16] 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.

Recent work shows that due to diminishing returns, traditional cost utility methods, like those ICER uses, overvalue treatments for mild illnesses and undervalue treatments for highly severe illnesses, and as a result such studies recommend underpaying for treatment of severe illnesses. ICER should be evolving away from use of the QALY, and, instead, measuring value based on the most up to date science and improved health utilities reflecting the value to the patient.

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

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cost-effectiveness in infectious diseases with recent examples in HCV,[17] HIV,[18] HPV,[19] influenza,[20] pneumonia,[21] and COVID-19.[22]

The impact of effective treatments on behavioral aspects of the population that impact how public health systems are able to manage the pandemic is also documented. The availability of effective treatments is known to have a positive effect on the probability of cases being diagnosed,[23] and how early they are diagnosed due to an increased propensity to seek testing by the general population.[24] This can result in a population level health benefit that can only be measured with the use of a transmission model.

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.[25] 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.[26]

Conclusion

PIPC urges ICER to revisit its modeling choices to ensure it is capturing the full benefit of effective COVID-19 treatments on society, including health equity considerations.

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Sincerely.

Tony Coelho, Chairman
Partnership to Improve Patient Care

Solve M.E.

To: Institute for Clinical and Economic Review

From: Solve ME/CFS Initiative

Re: **Comments to draft Special Assessment of Outpatient Treatments for COVID-19**

Thank you for the opportunity to contribute to your Special Assessment and for acknowledging that in your report (as noted on p.5). We appreciate your inviting additional public comments.

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 agree with your view supported by the evidence that there is a large number of symptoms associated with COVID-19 that may persist for many months after the initial infection. The prevalence of 205 symptoms in 10 organ systems was estimated in a global cohort of mostly (92%) non-hospitalized people, with 66 symptoms traced over seven months (Davis et.al., Lancet, 2001). Patients with Long Covid report prolonged multisystem involvement and significant disability, and two-thirds had not returned to previous levels of work by 7 months. Many patients are not recovered by 7 months, and continue to experience significant symptom burden with **fatigue** (78%), **post-exertional malaise** (72%), and **cognitive dysfunction** (55%) as the most frequent symptoms.

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 analyis 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.” (https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1).

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

(https://clinicaltrials.gov/ct2/show/NCT04510194?term=fluvoxamine&cond=COVID-19&draw=2&rank=8).

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% https://www.nature.com/articles/d41586-022-00177-5#:~:text=Vaccination%20reduces%20long%20COVID's%20incidence,the%20body%20during%20breakthrough%20infections).

We are therefore concerned about your interim conclusion that "should these treatments be used in lower-risk populations, including patients with full vaccination, their cost effectiveness would be significantly reduced." We submit that the potential of these treatments to reduce the burden of Long should must be studied. The absence of this data could produce a significant underestimation of the cost-effectiveness of these treatments, and may prevent people from having access to them.

In summary, we ask ICER to accommodate the inclusion of Long Covid impact in your models; encouraging targeting this less recognized aspect of the COVID-19 pandemic, that is of such high importance to patients and caregivers.

Sincerely,

Oved Amitay

President and CEO

Solve ME/CFS Initiative

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March 2, 2022

Dear Dr. Pearson,

This comment addresses the Draft Evidence Report entitled, "Special Assessment of Outpatient Treatments for COVID-19," published by the Institute for Clinical and Economic Review (ICER) on February 3, 2022.

We propose two revisions:

- *ICER should revise its estimate for the number of excess deaths caused by each COVID patient admitted to the intensive care unit from 0.195 to 0.75*. This revision will substantially increase the projected health benefit calculated by ICER from the modified societal perspective.
- *ICER should report its modified societal perspective assessment as a co-base case, rather than as a scenario analysis*. With our proposed revision to the assumed number of excess deaths caused by each ICU admission, the modified societal perspective assessment likely satisfies ICER's value framework criteria for reporting it as a co-base case. Doing so will also ensure that value-based price estimates reflect the substantial societal benefit that these therapies may confer.

Background

ICER's *health care system perspective analysis* projects the impact of outpatient treatments on hospitalization rates for COVID patients, the type of care they will require if hospitalized, and health outcomes – including morbidity and mortality.

ICER's *modified societal perspective analysis* posits that by reducing hospitalizations, and by possibly reducing the need for greater care when hospitalized, outpatient therapies reduce the number of COVID patients requiring care in the intensive care unit (ICU). Reduced ICU admissions, in turn, frees up hospital capacity, improving care quality for all patients and ultimately reducing excess deaths.

Algebraically, the modified societal perspective health benefit, in quality adjusted life years (QALYs), is the product of: (1) reduced ICU admissions resulting from the treatment of one COVID patient; (2) excess deaths per patient admitted to the ICU; and (3) QALYs lost per excess death. We make the following recommendations:

1. ICER should increase its estimated magnitude for this computation's second factor – the number of excess deaths per ICU admission – from 0.195 to 0.75.
2. ICER should report its modified societal perspective analysis as a co base-case, affording it the same emphasis and role as ICER's health care system perspective analysis.

Recommendation 1: Increase estimated excess deaths per ICU admission from 0.195 to 0.75.

Why ICER should revise its assumption

ICER estimated excess deaths caused by each COVID ICU admission from CDC information[1] 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.[2] Hence, to estimate the number of deaths attributable to each occupied ICU bed, ICER divided the 61,513 occupied beds (74% occupancy – the ICU occupancy level in November 2021 when ICER conducted its analysis) into CDC's estimate of the 12,000 resulting excess deaths. That calculation yielded ICER's estimate that each occupied ICU bed causes 0.195 excess deaths.[3]

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To estimate the benefit of reduced ICU utilization, however, it is more appropriate to calculate the rate at which excess deaths change in response to a change in the number of ICU beds occupied. That is, we are interested in the slope of the relationship between excess deaths and ICU beds. The CDC analysis of the excess death data provides limited information precisely specifying this relationship. The analysis does, however, plot the relationship, and the slope clearly grows steeper as utilization climbs; that is, the second derivative appears to be positive (see Figure 1).

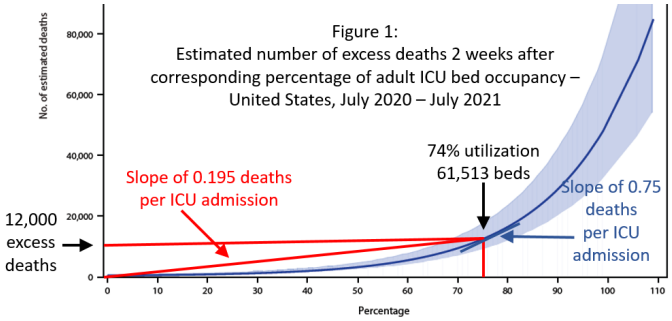

Figure from French et al. 2021. Annotations by public comment author

Importantly, the slope of the relationship between excess deaths and ICU beds occupied at the point corresponding to the November 2021 occupancy rate of 74% (the slope of the blue curve in Figure 1 at a horizontal axis value of 74%) substantially exceeds the slope of the red, diagonal line emanating from the origin in Figure 1 (which corresponds to ICER's calculation of 0.195 excess deaths per added ICU bed occupied). Because CDC did not provide further detail, we have estimated the slope of the blue curve in Figure 1 by enlarging the image in the original paper and measuring the vertical offset between the blue curve and the horizontal axis at an ICU utilization of 70 percent and again at 80 percent. Based on these measurements, we estimated the average slope of the curve in this range to be approximately 0.75 excess deaths per ICU admission. That value is nearly four times larger than ICER's estimate of 0.195.

Revision impact

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).

Table 1: Incremental QALY gains

	Column 1	Column 2	Column 3	Column 4	Column 5
Perspective	**Health care sector**		**Modified Societal Perspective**		
Treatment	**QALYs[a]**	**QALY gain vs. usual care[b]**	**ICER's calculation: QALYs[c]**	**ICER's calculation: QALY gain[d]**	**Revised calculation: QALY gain[e]**
Sotrovimab	15.9645	0.0432	15.9843	0.0198	0.0758
Molnupiravir	15.9356	0.0143	15.9419	0.0063	0.0241
Paxlovid	15.9633	0.042	15.9818	0.0185	0.0708
Fluvoxamine	15.9366	0.0153	15.9433	0.0067	0.0256
Usual care	15.9213	reference	15.9213	reference	reference

Notes: **(a)** ICER Draft Evidence Report Table 4.3, column labeled "QALYs". **(b)** Difference between this table's column 1 therapy QALYs and usual care QALYs. **(c)** ICER Draft evidence report Table 4.9, Column labeled QALYs. **(d)** Difference between this table's column 3 therapy QALYs and column 3 usual care QALYs, minus this table's column 2 health care sector QALYs. **(e)** Column 4 scaled up by the ratio of our estimate of excess deaths per ICU admission (0.75) to ICER's corresponding estimate (0.195).

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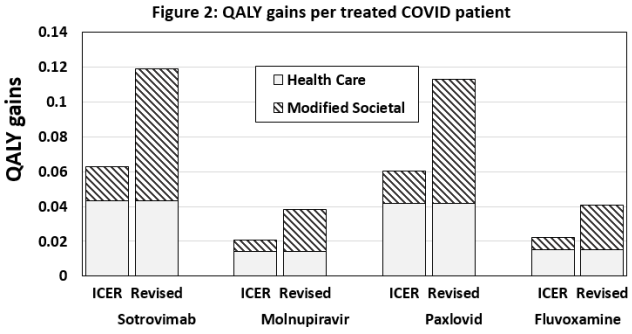
Figure 2 (based on columns 2, 4, and 5 in Table 1) illustrates how this revision affects the relative contribution of the modified societal perspective QALY gains to total health gains conferred by these therapies. In short, the QALY gains attributable to the modified societal perspective increase from nearly one-third to nearly two-thirds of the total QALY gains conferred by these therapies. In so doing, the revision nearly doubles the total health gain conferred by each therapy. Hence, the cost-effectiveness ratio's denominator increases by a factor of nearly two, all else being equal.



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.

Recommendation 2: Report modified societal perspective assessment findings as a co-base case.

Why ICER should report the modified societal perspective findings as a co-base case

ICER outlines three reasons for relegating societal benefits to a scenario analysis.[4]

(1) 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,[5] 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 suggest ICU utilization rates averaged 68 percent[6] 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

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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.

(2) 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."[7] 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.

(3) ICER states that including societal benefits in their value calculation does not qualitatively alter its conclusions.

Based on the criteria in ICER's most recent value framework, it is likely that the correctly calculated modified societal perspective results satisfy ICER's criteria for reporting them as a co-base case. ICER's value framework states that, "ICER presents a modified societal perspective as a co-base case" when "the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses thresholds of $100,000-$150,000 per QALY."[8]

As Table 2 details, the unrevised results, i.e., the results reported by ICER, satisfy the "20 percent change" criterion for Fluvoxamine. Moreover, the results for the Sotrovimab and Molnupiravir come close to doing so. That suggests that if ICER increased the modified societal perspective QALY gains by a factor of nearly 4, as described in Columns 4 and 5 of Table 1 (or even by an amount substantially less than that), the modified societal perspective cost-effectiveness ratio would differ by more than 20% from the corresponding ratio for the health care sector perspective analysis. It is plausible that even for Paxlovid, increasing the modified societal perspective QALY gain by four-fold would increase the difference between the two cost-effectiveness ratios so that it exceeds 20 percent.

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Table 2: ICER Cost-Effectiveness Estimates – By Perspective

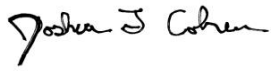
	Column 1	Column 2	Column 3
Treatment	**Health care perspective cost per QALY vs. usual care[a]**	**Modified societal perspective cost per QALY vs. usual care[b]**	**Percent difference[c]**
Sotrovimab	$69,000	$56,500	-18%
Molnupiravir	$55,000	$47,000	-15%
Paxlovid	$18,000	$21,400	+19%
Fluvoxamine	$6,000	$13,300	+122%

Notes: **(a)** ICER Draft Evidence Report, Table 4.4, column labeled "Cost per QALY gained". **(b)** ICER, Draft Evidence Report, Table E21, Column labeled "Cost per QALY gained". **(c)** ICER, Draft Evidence Report, Table 4.9, Column labeled "QALYs".

Revision impact

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 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.[9]

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.[10] 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.



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[2] ICER, Draft Evidence Report – Special Assessment of Outpatient Treatments for COVID-19, page E11 (hereafter, "Draft Evidence Report"). "… we assumed that the excess deaths over a two week period at the national-level occupancy level could be divided evenly among each ICU admission to estimate a per-treated patient effect."

[3] ICER, Draft Evidence Report. Pages E11-E12 "As of November 2021, ICU bed occupancy was at 74% nationally (61,513 of 82,692 ICU beds filled)… At an occupancy level of 74% nationally, recent research estimates an additional 12,000 excess deaths would occur within two weeks… Therefore, the 12,000 excess deaths averted nationally translated to 0.195 (12,000/61,513) excess deaths averted per ICU admission averted."

[4] See ICER Draft Evidence Report. Pages 36-37, "First, we assumed societal outcomes…" through "… as additional evidence is identified.".

[5] ICER Draft Evidence Report, page E11.

[6] Wunsch H, Wagner J, Herlim M, Chong DH, Kramer AA, Halpern SD. ICU occupancy and mechanical ventilator use in the United States. Crit Care Med. 2013 Dec;41(12):2712-9. doi: 10.1097/CCM.0b013e318298a139. PMID: 23963122; PMCID: PMC3840149. Abstract states, "Mean hourly occupancy across ICUs was 68.2%...".

[7] ICER, Draft Evidence Report. Page 37.

[8] ICER. 2020. *2020-2023 Value Assessment Framework*. January 31, 2020. Page 25.

[9] Cohen JT, Olchanski N, Ollendorf DA, Neumann PJ. 2022. "The Certainty of Uncertainty in Health Technology Assessments." Health Affairs Forefront Blog. January 26. https://www.healthaffairs.org/do/10.1377/forefront.20220125.37540/

[10] ICER Draft Evidence Report, p. 37.