September 12, 2016

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BY ELECTRONIC DELIVERY

RE: National Call for Proposed Improvements to its Value Assessment Framework

Dear Dr. Pearson:

The Biotechnology Innovation Organization (BIO) appreciates the opportunity to provide feedback in response to the Institute for Clinical and Economic Review's (ICER's) National Call for Proposed Improvements to its Value Assessment Framework (the "Framework").[1] BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place. In that way, our members' novel therapeutics, vaccines, and diagnostics not only have improved health outcomes, but also have reduced healthcare expenditures due to fewer physician office visits, hospitalizations, and surgical interventions.

BIO appreciates the efforts ICER has made over the last several months toward improving the public comment process associated with each step of a Drug Review, including the current national call for feedback on the underlying Value Framework methodology. The responsibility to take into account broad stakeholder perspectives and address stakeholder concerns is increasingly important given the emerging evidence that ICER Reviews have the potential to impact patient access to needed medicines.[2] However, while ICER has taken steps to improve the ability to collect stakeholder feedback, the Institute's stated goal of "work[ing] collaboratively with patient groups, clinical experts, and life science companies" requires a much clearer understanding with regard to how stakeholder input is meaningfully incorporated.[3] In this letter, BIO addresses this and other outstanding issues and responds to the four major categories of issues ICER identifies in the call for comments.

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[1] ICER. 2016 (July14). *ICER Opens National Call for Proposed Improvements to its Value Assessment Framework*, available at: https://icer-review.org/announcements/improvements-value-framework/ (last accessed August 1, 2016).
[2] JCP Editors. 2016 (June). Conferences: Perceptions of ICER Reports and Health Technology Assessments in the United States. *Journal of Clinical Pathways*, available at: http://www.journalofclinicalpathways.com/article/perceptions-icer-reports-and-health-technology-assessments-united-states (last accessed August 31, 2016).
[3] ICER. 2016. *Addressing the Myths About ICER and Value Assessment*, p. 2, available at: http://icer-review.org/wp-content/uploads/2016/08/icer_myths_facts.pdf (last accessed August 31, 2016).

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Though the majority of the methodological concerns BIO has raised in the past persist,[4] and are reiterated throughout this letter, we continue to raise several primary issues that must be resolved in the new iteration of the Framework.

- First, ICER should not continue to conflate the impact of a therapy on patient health outcomes, including quality of life, with the potential budget impact to any individual payer or group of payers. To clarify, BIO supports the concept of assessing the value of different therapies to an individual patient to facilitate the right medicine getting to the right patient at the right time. However, we also adamantly assert that the final decision of which therapy, or combination of therapies, is most appropriate for a patient must: be left to the patient working with his or her provider; consider the *individual* clinical circumstances of the patient; and assess the impact of a therapy on a patient over the long term. The updated Framework should facilitate—not hinder—this aim.
- Second, we continue to strongly urge ICER to ensure that the Framework relies on robust and validated methodological standards and applies them consistently and transparently.
- Third, we appreciate and agree with ICER's stated goal of undertaking a value assessment that, among other aims, seeks to "fairly reward innovators for the value they bring to patients, and provide them ample incentive to pursue the investments and research that will lead to the innovative treatments of tomorrow."[5] However, the Framework does not work to achieve this aim. For example, it does not address significant concerns with regard to the potentially negative impact on the innovation ecosystem, nor does it attempt to quantitatively account for the need to sustain innovation. Moreover, the current structure of the budget impact threshold penalizes increased regulatory efficiency that results in bringing more therapies to market each year.
- Fourth, while we acknowledge ICER's progress with respect to broader stakeholder engagement (e.g., evidenced by the extended duration of certain public comment opportunities), we strongly urge the Institute to establish a robust engagement strategy with patients in particular. The Institute should work with patients to identify how their input can inform each step of the process, how to standardized engagement with this community, and identify the primary point of contact at the Institute for patients who may have questions outside of an official comment period.

These issues, as well as related methodological and process concerns, are discussed in detail throughout the remainder of this letter. We urge ICER to address each of these issues—and BIO's accompanying recommendations—in an updated version of the Framework, or, describe why ICER believes these changes were not warranted.

[4] BIO. 2016 (May). *Follow-Up on BIO's Comments in Response to the ICER Value Framework*, available at: https://www.bio.org/letters-testimony-comments/follow-bio%E2%80%99s-comments-response-icer-value-framework (last accessed August 31, 2016).
[5] ICER. 2016. *Addressing the Myths About ICER and Value Assessment*, p. 2, available at: http://icer-review.org/wp-content/uploads/2016/08/icer_myths_facts.pdf (last accessed August 31, 2016).

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I. Persistent Operational Considerations: ICER should clarify critical facets of its process for operationalizing the Framework that remain opaque to most stakeholders.

BIO reiterates our appreciation of changes ICER has made over the course of the last several months to increase the duration of public comment periods tied to certain elements of the Drug Review process. We encourage ICER to continue to dialogue openly on this issue and reassess whether the duration should be further extended to allow a broader audience to participate. As we have noted previously, public comment periods shorter than 30 days—for draft scoping documents—and 60 days—for more dense documents like the draft evidence review—are recognized standards for public comment periods.

Despite this progress, BIO continues to express concern that aspects of the ICER Drug Review process remain opaque to stakeholders. The process for Reviews is not consistently standardized, leaving many stakeholders to devote significant resources to engaging ICER, and effectively prohibiting those stakeholders without such resources from being able to offer feedback in the first place. The following areas are key examples of the need for great clarity in how each element of the Drug Review process functions:

- The process for choosing therapeutic areas/clinical indications to study and obtaining input from clinical experts;
- Whether and how completed Drug Reviews can be updated based on emerging evidence;
- Which stakeholders ICER engages in the development of a Draft Scoping Document and how the feedback received is taken into account;
- The timeline and notification process for posting detailed model analysis plans; and
- Sufficient details with regard to the data relied on and the model assumptions made to allow stakeholders to reproduce the Value Framework methodology as applied to an individual Drug Review.

First, it remains unclear how ICER chooses which therapeutic areas will be studied: while BIO appreciates ICER's release of a list of disease and conditions likely to undergo a review at the beginning of 2016, stakeholders have little insight into the criteria used to compile the list, what stakeholders had input into the list, and how often the list will be updated. Stakeholder input is important insofar as it could inject practical considerations into this process, including preemptively identify methodological concerns with the study of certain therapies. A prime example is BIO increasing concern with ICER's aim to assess therapies that have not yet been approved by the FDA. As a result, these therapies often lack sufficient clinical effectiveness data to allow the therapy to be considered are not yet priced to be able to be included in economic models, and those for which there are limited data to study off-label use.

For example, ICER's review of obeticholic acid for treatment of nonalcoholic steatohepatitis (NASH) preceded FDA approval for this therapy, and concerns were raised by those in the patient and provider community that it preceded a clinical consensus on standard of care for these patients.[6] FDA is the national regulatory authority responsible for judging clinical safety and efficacy and bases approval decisions on a robust body of evidence that has been specifically submitted to the Agency for this purpose. While in some cases, robust clinical evidence already exists at the time of FDA review of an off-label use of an approved medicine—for example, in the form of inclusion in nationally recognized clinical guidelines documents—this is not always the case (exemplified by the obeticholic acid example). In the absence of such evidence, any effort to pre-judge the appropriateness of a therapy to treat a specific clinical indication before a planned FDA review has been completed inappropriately supplants the Agency's authority. Thus, in the future, BIO strongly urges ICER to omit any therapies currently under review by FDA from a Framework evaluation until such a time as the Agency has ruled on approval.

Following ICER's choice of a topic of study, it is also unclear whether the Institute seeks input from clinical experts to identify the comparative clinical effectiveness questions that are most relevant to patient care. This is a critical component of the development of an assessment of the comparative value of health interventions, which can help ensure the result is relevant to patients and their providers. BIO appreciates that ICER identifies the "Expert Report Consultants" who contributed to each Draft Evidence Report, but we encourage the Institute to identify specifically: when in the Drug Review development process ICER engages clinical experts to obtain input on the scope and direction of the clinical comparative effectiveness review sections of the Review; what process is utilized to engage and obtain input from clinical experts; and how that input is considered and incorporated, or not, into the various draft documents associated with a drug review (for additional discussion with regard to this issue, see section II(B)).

Second, BIO continues to be concerned that ICER has not acknowledged whether, and through what process, the Institute will update a Drug Review in the face of an evolving standard of care and/or new evidence. This is of particular concern given that these reviews are conducted in the absence of a full picture of a therapy's benefits and disadvantages and that these reviews will continue to be relied upon by other stakeholders even after additional data (e.g., real-world evidence) emerge. When BIO has voiced this issue previously, it has been based on the concern the reality of clinical practice results in an ever-burgeoning body of evidence that is added to continuously, a stark contrast to ICER's static estimate. In this letter, we also note the shorter-term example of the consequences of failing to take into account the most recent evidence in a drug review that is underway.

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[6] For example, see *Statements of Donna Cryer, President and CEO, Global Liver Institute, to the New England Comparative Effectiveness Public Advisory Council (New England CEPAC)*, available at: https://icerwatch.org/comments/cepac-public-comments-obeticholic-acid-donna-cryer-jd (last accessed August 1, 2016).

For example, the Draft Evidence Report for ICER's Rheumatoid Arthritis Review is scheduled to be released in the midst of the American College of Rheumatology's annual meeting.[7] Annual academic medical conferences are routinely the venue in which manufacturers and academic researchers publish novel data and the latest evidence in a field. In fact, these stakeholders plan their publication development and release schedules around these annual meetings, and it is very difficult, if not impossible, to accelerate or change course with regard to such releases on short notice. In the case of the Rheumatoid Arthritis Review, the timing of the release of the Draft Evidence Report deprives the initial report of this updated evidence. Though it is our assumption that ICER's updated Final Evidence Report would take into account these novel data, there is a significant benefit to including these data from the beginning to allow all stakeholders to review and respond to a more complete dossier of evidence.

Third, BIO raises concerns with the information available at the time of the public release of draft scoping documents. The draft scoping document is the first indication of how ICER intends to approach a specific topic. We appreciate that ICER has noted increased outreach to stakeholders to seek guidance in drafting this document, and that ICER has created a new "Open Input" period to inform the drafting of the scoping document. However, we urge ICER to clearly identify which groups it engages, how stakeholders can get involved in this early stage of planning if such opportunities exist outside of the "Open Input" period, and to what extent stakeholders' feedback is incorporated in the draft scoping document.

Fourth, there is not a consistent timeline for posting detailed model analysis plans, and ICER does not uniformly announce when such plans have been posted. Despite the ICER's publishing of the *Manufacturer Engagement Guide*, BIO members report that this guidance is not uniformly applied to topics currently under study.[8] For example, with regard to the Non-Small Cell Lung Cancer Review, stakeholders did not know when to expect a detailed model analysis plan to be available after a revised scoping document had been released. The availability of this plan, with sufficient time to allow stakeholders to review and reproduce it, is critical to stakeholders' ability to provide meaningful comments on the model ahead of—or in response to—a draft evidence report. Based on the resources required to analyze such models, BIO recommends that this detailed model analysis plan be available to stakeholders no less than 30 days before the draft evidence report is released.

Moreover, while ICER alerts stakeholders to documents newly posted on the various Public Advisory Council boards' websites, the Institute does not regularly alert stakeholders that new documents have been posted on the Open Science Framework website. For example, ICER does not always update its "Topics" page when new documents or notices are announced related to a previously announced topic. While this may seem like a relatively benign issue, it

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[7] According to ICER's current Drug Review schedule, the Draft Evidence Report will be released on November 14, 2016, see ICER. 2016. *Arthritis*. Key Dates, "Draft Evidence Report," available at: https://icer-review.org/meeting/arthritis/ (last accessed September 1, 2016). The American College of Rheumatology's annual meeting is scheduled to take place November 11 through 16, see American College of Rheumatology. 2016. *Annual Meeting*, available at: http://www.rheumatology.org/Annual-Meeting (last accessed September 12, 2016).

[8] ICER. 2016 (July). *Manufacturer Engagement Guide [Updated]*, available at: http://icer-review.org/wp-content/uploads/2016/02/ICER_Mfr_Engagement_Guide_070816.pdf (last accessed August 31, 2016).

contributes to diminishing the efficiency of the comment process for both stakeholders and ICER. ICER should also consider making explicit their decision process in incorporating feedback at various stages in the review process (i.e., identifying comments received in response to the draft scoping document and later documents, and providing a rationale for including or not including comments), a persistent issues.

Fifth, ICER should provide sufficient detail to allow stakeholders to reproduce the Framework methodology as applied to an individual Drug Review. For example, an analysis of ICER's Multiple Myeloma Drug Review found that "a major technological drawback of the ICER report is the inability for fellow stakeholders to re-create their exact analysis given that the report is a static pdf document. In addition, some methods are not described in detail in the evidence report."[9] Similarly, with regard to the application of the Value Framework to the Non-Small Cell Lung Cancer Draft Evidence Report, it remains unclear: the exact methodology used in the network meta-analysis (NMA) and comparative effectiveness analysis (CEA), given the lack of a sufficiently detailed research protocol (e.g., the Draft Report did not consistently identify whether constant or time-varying hazard ratios were used, or present alternatives considered to the NMA models mentioned); the clinical rationale for all of the modeling assumptions (e.g., rationale for the model choices in NMA and CEA); and the full details regarding the results (e.g., model fit statistics for all models assessed).[10] ICER should ensure that all future applications of the Framework are reproducible, as this is important as a principle of the scientific method as well as key to ensuring that stakeholders can provide ICER with the most relevant, useful feedback in response to comment opportunities.

[9] This analysis goes on note that: "[m]ost meta-analyses require data points to be accompanied by variance measures or 95% confidence intervals (CIs). This is the case with the network meta-analysis (NMA) found in the ICER evidence report. Two direct comparisons failed to report the variance or 95% CI for the hazard ratio in the reference studies. However, the ICER NMA reported these measures and did not include a replicable source and/or methodology. The calculation of these missing values is within the realm of reasonable data configuration, however it is important that these manipulations are made transparent within the ICER report methods. It is important to note the authors did mention, 'When 95% confidence intervals were not available, uncertainty ranges were based on plausible values from the published literature' (pg. 74). However, without further clarification, the validity of these data should be approached with caution." (emphasis added) See. Husain, F., Y. Kuang, A. Grijalva, B. Kerr, R. Saad, C. Whittington, and T. Feinman. 2016 (May). Growth Replicator: ICER Multiple Myeloma. *Doctor Evidence*, available at: http://growthevidence.com/wp-content/uploads/2016/05/Final-GROWTH-Replicator-ICER-Multiple-Myeloma-Replication-Report.pdf (last accessed September 9, 2016).

[10] See ICER. 2016 (August 19). *Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value*, available at: https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_Draft_Evidence_Report_081916.pdf (last accessed September 12, 2016).

II. Integrating Patient and Clinician Perspectives and the Role of Cumulative Innovation into the Framework: ICER should ensure that the Framework does not shortchange the impact of innovative medicines on individual patients.

A. ICER must capture information that is meaningful to patients more holistically in the Framework's summary metrics.

The first category of issues on which ICER requests specific input is "[m]ethods to integrate patient and clinician perspectives on the value of interventions that might not be adequately reflected in the scientific literature, elements of value intended to fall in the current value framework within 'additional benefits or disadvantages' and 'contextual considerations'[.]"[11] BIO appreciates ICER's recognition that there should be a more rigorous inclusion of this type of information than the Framework currently allows. We agree that this is necessary to better reflect and incorporate the information that is important to patients and caregivers. While the full text of an ICER Drug Review may include a narrative discussion of patient and clinician perspectives, there is a continued reliance on summary metrics that obscure any nuance and detail that may have been captured in the Review text. In particular, the summary metrics may obscure important differences in the preferences and clinical characteristics of patient subpopulations, both of which may be better taken into account with improved and meaningful patient engagement in applying the Framework. Moreover, these summary metrics, like Care Value, oversimplify and reduce to an "average" the impact of innovative therapies on the full range of a patient's quality of life and on the healthcare system as a whole.

An example is the often qualitative review of "additional benefits or disadvantages" in comparison to the quantitative dollar per quality-adjusted life year metric, which drives the Care Value metric. Additionally, this metric does not uniformly incorporate the impact of a therapy on a patient's ability to return to their daily routines, and does not take into account the full impact on society, including through improvements to worker productivity and the broader impact of a healthier population. One mechanism to address this issue that ICER should employ is to incorporate indirect costs or cost-savings into economic models as sensitivity analyses to assess the impact of these "contextual considerations" on any cost-effectiveness ratio.

Not only should ICER more comprehensively take into account patient perspectives in the Framework, but also, BIO notes the importance of ensuring that patient perspectives are represented on the Public Advisory Councils, which are responsible for reviewing and voting on the content in the final Drug Reviews. While we appreciate ICER's recent announcement of the appointment of a patient advocate to the ICER Governance Board, this does not replace the need for true subject matter expertise—including with respect to patients' perspectives—on the Councils themselves.[12]

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[11] ICER. 2016 (July14). *ICER Opens National Call for Proposed Improvements to its Value Assessment Framework*, available at: https://icer-review.org/announcements/improvements-value-framework/ (last accessed September 6, 2016).

[12] ICER. 2016 (July 21). *ICER Elects Patient and Consumer Advocacy Experts to Governance Board*, available at: https://icer-review.org/announcements/icer-gov-board/ (last accessed July 22, 2016).

B. ICER must recruit subject matter experts to participate on the health technology assessment (HTA) panels that review, and vote on, the Drug Reviews.

To improve clinical accuracy of their assessments, ICER should include clinicians who have expertise in the disease area and are currently treating patients and/or conducting research in the disease area. Especially in the case of chronic, complex conditions, only clinical experts can be expected to keep pace with the rapid evolution of the standard of care and the nuance of individual clinical decision making. Not only should subject matter experts be involved in vetting the comparative clinical effectiveness questions that a drug review identifies (discussed above, see Section I), but it is important that they have a role in reviewing and validating the model inputs in any clinical and cost-effectiveness analyses. The inclusion of clinical experts on the HTA organizations that ultimately review the Framework's application and vote on the Care Value metric will also improve ICER's ability to update drug reviews based on emerging evidence.

There are several models ICER can emulate to address this recommendation. For example, the National Comprehensive Cancer Network (NCCN) establishes individual panels of clinicians and researchers that share a specific expertise to develop and update the NCCN Guidelines for oncology care.[13] These experts utilize their clinical expertise and existing evidence to make recommendations, and routinely update these recommendations based on emerging evidence. A similar example can be found in the statutory requirement that the Patient-Centered Outcomes Research Institute (PCORI) establish expert advisory panels to consult on the funding of research that is related to rare diseases and clinical trials.[14] In fact, the inclusion of a requirement for subject matter expertise as a statutory provision demonstrates that this is a standard with regard to comparative clinical effectiveness.

Yet another example is the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), which maintains a pool of up to 100 experts in various fields and, from that advisory group, chooses "no more than 15 members with knowledge specific to the topic in question to serve on the panel for each MEDCAC meeting."[15] MEDCAC also has an established mechanism to "recruit non-MEDCAC members who have relevant expertise to provide additional input to panel members and invite experts to make formal presentations to the MEDCAC for a particular meeting."[16] While BIO has raised issues with MEDCAC's application of the model in practice in the past, the general structure of their process can serve as

[13] National Comprehensive Cancer Network. *About the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*, available at: https://www.nccn.org/professionals/default.aspx (last accessed on August 22, 2016).
[14] See ACA § 6301(d)(4). It is worthwhile to note that, while statute only identifies the topics of "clinical trials" and "rare disease" as the subject of required PCORI expert advisory panels, it permits the formation of others, and PCORI has established 7 such panels on the following subjects: assessment of prevention, diagnosis, and treatment options; improving healthcare systems; addressing disparities; patient engagement; clinical trials; rare disease; and communication and dissemination research. See PCORI. 2016 (June). *Join an Advisory Panel*, available at: http://www.pcori.org/get-involved/join-advisory-panel (last accessed September 1, 2016).
[15] Centers for Medicare and Medicaid Services. 2016. *Medicare Evidence Development & Coverage Advisory Committee*, available at: https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/MEDCAC.html.
[16] Id.

an example nonetheless.[17] No matter how ICER decides to implement this recommendation, we strongly urge the Institute to do so immediately such that ongoing reviews benefit from the participation of subject matter experts.

C. The Framework should reflect the role of cumulative innovation in improving the treatments available to patients over time.

BIO continues to raise the concern that the Framework does not consider the impact of cumulative innovation, which could be accomplished through an expansion of the "contextual considerations" category in each Review. Cumulative innovation describes the concept that relatively modest improvements in patient outcomes that result from individual innovative therapies build on each other to advance the scientific field forward, and result in major advancements on the standard of care over time. Each individual advance is important to the overall improvement in treatment for these patients. For example, the cancer death rate has fallen by 20 percent since 1991, in large part due to medicines.[18] The survival rate among children with cancer is approximately 83 percent compared to 58 percent in the mid-1970s. Yet, despite this reality, the ICER Framework does not take into account cumulative innovation, and thus, shortchanges the value of innovative therapies to the detriment of patient access.

III. Replacing Metrics That Obscure the Impact of Personalized Medicine: ICER should not rely on metrics that do not take into the impact of innovative medicines on individual patients.

A. ICER must ensure that the Framework relies on robust methodological standards and applies them consistently.

ICER's second category of particular interest for stakeholder input is the structure of the Framework's incremental cost-effectiveness ratios, specifically the appropriate threshold to set, and best practices in capturing health outcomes through quality-adjusted life years (QALYs). However, as a threshold matter with regard to ICER's evidence review, this subsection reviews BIO's increasing concerns with the assumptions that are used to identify comparators in a given clinical comparative effectiveness review and to assess clinical effectiveness and comparative clinical effectiveness.

Regarding the former, BIO identifies a lack of objectivity when determining the comparators in the draft scoping document, which is not necessarily based on systematic literature review of treatments in the disease area or actual utilization data on most commonly used treatments. For example, the draft scoping document for primary progressive multiple sclerosis (PPMS) included only ocrelizumab (not yet approved by the FDA at the time of the

[17] BIO. 2014 (August 29). *Comments in Response to the Proposed Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) Charter*, available at: https://www.bio.org/advocacy/letters/bio-submits-comments-hhs-regarding-proposed-medicare-evidence-development-and-cover.

[18] PhRMA. 2014 (May 14). *Five Facts About the Value of Innovative Cancer Medicines*, available at: http://catalyst.phrma.org/five-facts-about-the-value-of-innovative-cancer-medicines (last accessed September 12, 2016).

release of the draft scoping document) and rituximab, while other more commonly used disease modifying therapies (DMTs)) for PPMS were not included.[19] For NSCLC, ICER mentioned the evaluation of cancer immunotherapy use in the first-line setting, but included atezolizumab, which did not have clinical data in first line.[20] Wherever possible, draft scoping documents should be supported by systematic literature review and the viewpoints of subject matter experts.

Regarding clinical effectiveness assessments, BIO identifies the following example as illustrative of our concerns: in defining a threshold for response in rheumatoid arthritis in the revised scoping document, there is a simplistic assumption made that meeting the ACR20 threshold directly translates to a 20 percent improvement in physical function;[21] instead, this multidimensional outcome measure requires at least a 20 percent improvement in a core measures set, and benefits from the use of a regression model across a data set to infer comparative clinical effectiveness.

To address this issue, at least in part, BIO recommends that ICER incorporate the International Society For Pharmacoeconomics and Outcomes Research's (ISPOR's) Multi-Criteria Decision Analysis (MCDA) methods to improve the quality of the Framework's assumptions and its application to drug reviews by providing structure, consistency, and transparency to this effort. Moreover, we urge ICER to consistently assess the uncertainty of any cost-effectiveness analyses that may be incorporated in the updated version of the Value Framework through deterministic or probabilistic sensitivity analyses.[22] In addition to taking into account variances in clinical effectiveness and cost, such analyses also should consider the impact of existing policies that can impact patient access, which, when considered across a population, could subsequently impact any global assessment of cost effectiveness. The results of these sensitivity analyses and key assumptions and drivers of the model should always be emphasized—including in any reported summary metrics—rather than just the base case ratio.

ICER also could address these issues by submitting the methodology for each drug review through a peer-reviewed process to act as an external arbiter of the validity and reliability of the assumptions made to evaluate clinical comparative effectiveness. While we recognize and appreciate that the methodology used to assess PCSK-9 inhibitors was peer reviewed recently, the Value Framework methodology has evolved since this 2015 review was conducted.[23]

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[19] ICER. 2016 (September 6). *Disease Modifying Therapies for Relapsing-Remitting and Primary Progressive Multiple Sclerosis: Effectiveness and Value Final Addendum to Background and Scope*, available at: https://icer-review.org/wp-content/uploads/2016/09/CTAF_PPMS_Final_Scope-_Addendum_090216.pdf (last accessed September 12, 2016).

[20] ICER. 2016 (August 19). *Treatment Options for Advanced Non-Small Cell Lung Cancer: Effectiveness and Value: Draft Evidence Report*, available at: https://icer-review.org/wp-content/uploads/2016/08/MWCEPAC_NSCLC_Draft_Evidence_Report_081916.pdf (last accessed September 12, 2016).

[21] See ICER. 2016. *Rheumatoid Arthritis: Revised Scoping Document* [and accompanying analysis model], available at: https://icer-review.org/topic/arthritis/.

[22] Caro JJ, Briggs AH, Siebert U, et al. 2012. Modeling good research practices - overview: A report of the ISPOR-SMDM modeling good research practices task force-1. *Value Health* 15:796-803.

[23] Kazi, D. S., *et. al.* 2016. Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease. *The Journal of the American Medical Association* 316(7):743-753.

Submitting each Drug Review analysis—or at a minimum, each iteration of the Value Framework—for peer review can improve and help to ensure its methodological rigor, and will provide sufficient detail such that stakeholders can understand how a review was conducted and, as a result, any implications for patient care.

B. ICER should not use a QALY-dependent clinical comparative effectiveness threshold, as it shortchanges the impact of innovative medicines on individual patients and undermines efforts to support personalized medicine.

As a threshold matter, BIO urges ICER not to include a cost-per-benefit threshold as a feature of the Care Value metric in the updated Value Framework. We raise serious concerns with the premise of imposing an average cost-per-benefit metric in a value assessment framework as it inherently obscures the benefits of increasingly personalized medicines to individual patients. This type of metric will not be able to distinguish between the costs and cost offsets of a therapy to different stakeholders (e.g., a patient, a provider, a payor, and/or the federal government). In fact, a cost-per-benefit threshold does not reflect the importance of assessing a therapy's comparative impact on patient health outcomes separately from the budget impact to any given stakeholder, discussed in the introduction of this letter in more detail.

BIO specifically urges ICER not to use QALYs—and by extension, QALY-based thresholds—in the updated version of the Value Framework. We recognize that a clinical comparative effectiveness review is a key feature of the Value Framework, but posit that such an assessment can be undertaken without the use of the QALY summary metric. If ICER chooses to explore other mechanisms, we urge the Institute to convene experts from diverse perspectives to assist in identifying an alternative (or potentially several alternatives to be applied depending on the disease or condition to be studied).

Our opposition to the continued use of the QALY is based on our concern that the reliance on QALYs is not meaningful in the context of a multi-payer insurance system, as we have in the U.S. Here, in contrast to countries with a single payer system, there is no single budget against which to determine "willingness to pay" over the lifetime of the patient. More importantly, QALYs cannot adequately capture the comprehensive value an innovative therapy offers individual patients, the healthcare system, and society. QALYs are arbitrary and do not holistically assess the value of a therapy to an individual patient.[24] Additionally, it is unclear to what extent changes in quality of life as measured by changes in QALYs are meaningful to patients. Assessing the individual impact of a therapy on a patient is increasingly becoming the premise of clinical care as medical science advances toward personalized medicines that take into account patients' individual characteristics, including their genetics, and the disease

[24] For example, QALYs are not able to distinguish between net gains (or losses) that are driven by a small gain (or loos) to a large number of patients or a large gain (or loss) to a small number of patients. For a broader discussion of this issue, see BIO. 2007 (October 25). *The Complexities of Comparative Effectiveness*. Appendix Two: Conversion to a Common Metric, p. 24, available at: https://www.bio.org/articles/complexities-comparative-effectiveness (last accessed August 5, 2016).

pathophysiology. ICER has yet to address the well-documented disadvantages of using QALYs to assess the value of a therapy.[25]

Among those disadvantages is the fact that QALYs may be particularly ill-suited for determining the utility of the change in quality of life to patients with certain types of chronic conditions—including autoimmune conditions. The variability of outputs resulting from different assumptions under the QALY methodology for these types of patients makes direct comparisons under the Framework infeasible. Moreover, the cost-per-QALYs paradigm is biased against certain types of therapies, such as those that treat complex, chronic conditions, and those that treat diseases that affect only small populations. In both instances, medicines can often have higher associated costs per individual. Therapies that treat rare diseases may never meet this threshold, which would ostensibly indicate that biopharmaceutical developers should not invest in bringing these therapies to market. Yet that conclusion does not match the societal view of the importance of these medicines (e.g., as evidenced by the passage of the Orphan Drug Act into law).

The National Institute for Health and Care Excellence's (NICE's) "highly specialised technologies programme" was developed on the basis of this bias, and NICE has recognized exactly this failing of the cost-per-QALY threshold, noting that:

> Given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these vary rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their research and development investment because of the very small populations treated.[26]

Additionally, assessments that rely on QALY comparisons may inherently attribute a higher value to therapies for which overall survival data are available (though we recognize that QALYs can take into account quality of life associated with other outcomes, such as

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[25] For example, concerns have been raised with regard to: the assumption that health status/utilities can be measured on a cardinal scale; the assignment of utility weights to disease states can be done in a way that captures the various perspectives of patients with a certain disease; the narrow range of health benefits captured by QALY measurements; testing the theoretical assumptions attributed to the use of QALYs; whether QALYs are the same regardless of to what stakeholder they accrue; equity-weighted utility maximization; and the use of condition-specific measurements in QALY analyses. For additional information, see Whitehead, S. J., and S. Ali. 2010. Health outcomes in economic evaluation: the QALY and utilities. *British Medical Bulletin* 96(5-21); see also Griebsch, I., J. Coast, and J. Brown. 2005. Quality-adjusted life-years lack quality in pediatric care: a critical review of published cost-utility studies in child health. *Pediatrics* 115(5):e600-614.

[26] National Institute for Health and Care Excellence (NICE). 2013. *Interim Process and Methods of the Highly Specialised Technologies Programme*. Paragraph 36, p. 8, available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf (last accessed August 31, 2016).

progression-free survival, response rate, albeit with varied weight). This too may bias a QALY-based comparative assessment between older therapies—for which these data are more likely to be available—and therapies recently on the market, especially those that received approval through an accelerated approval pathway (e.g., breakthrough therapy designation). A more detailed discussion of this issue is included in the next section (III(C)).

In light of concerns we identify throughout this section, BIO continues to strongly urge ICER not to rely on the QALY metric. However, if the Institute continues to use QALYs as the key feature of its cost-effectiveness analysis despite this opposition, we urge ICER to address all of the issues described in this section of the letter. Additionally, we urge ICER to routinely incorporate sensitivity analyses around QALY measurements and to reflect these analyses in any summary metric. ICER should recognize the limitations of a QALY-based analysis in each drug review, both in the narrative discussion sections and as part of the summary metrics.

If, in spite of opposition, ICER continues to use a cost-per-QALY threshold to drive the Care Value metric, we strongly urge ICER to develop a range of thresholds specific to the disease or condition under study. The current iteration of the Value Framework applies a one-size-fits-all threshold of $100,000/QALY or $150,000/QALY without regard to the condition. As described above, certain conditions—based on the complexity and time course of the disease and/or the size of the patient population—have higher associated per-patient costs, and a static cost-per-QALY threshold inherently penalizes therapies that treat these conditions. In establishing thresholds for a certain disease or condition, or even a patient subpopulation within a disease or condition, ICER should clearly identify the evidence on which it relies and obtain feedback from various stakeholders—in particular patients—to inform its thinking.

C. <u>The static nature of ICER's evidence review inherently disadvantages newer-to-market therapies, for which there may not be as much published evidence as may exist for therapies that have been on the market longer.</u>

BIO is committed to the use of high-quality evidence in the assessment of the value of any health intervention, as the outcome of the assessment is only as valid as the data inputs. That said, we recognize that the timing of the application of the Framework to drug reviews—namely, as close to FDA approval of a new therapy—creates a distortion in the relative amount of available data for review and analysis. Specifically, therapies that have been on the market longer—and thus have more data available for analysis—may be at an advantage compared to newer-to-market therapies. This distortion is exacerbated by the absence of a process to update drug review findings based on emerging evidence. ICER must account for this difference is available published data when calculating Care Value to avoid summarily penalizing newer therapies under the Framework. One way to accomplish this is to establish explicit data quality standards, as many medical specialty societies do in advance of their clinical landscape reviews.[27] This mechanism would allow ICER to rely on a variety of high-quality evidence, not

[27] For example, the American College of Rheumatology (ACR) has published Policy and Procedure Manual for Clinical Practice Guidelines, in which ACR clearly identifies how evidence will be rated. <u>See</u> ACR. 2015 (January). *Policy and Procedure Manual for Clinical Practice Guidelines*. Guideline Development, Phase 2: Development, Use of GRADE to Evaluate the Evidence and Develop Recommendations, pp. 14-15, available at:

just published literature, when applying the Framework to individual drug reviews. BIO acknowledges that this is not the only mechanism to address the distortion created by ICER's current static value assessment, and we encourage ICER to engage stakeholders to explore other approaches to address this pressing issue.

IV. Overhauling the Price and Product-Update Assumptions and Restructuring the Short-Term Budget Impact Measure: ICER should ensure that all assumptions rely of robust evidence reflective of marketplace realities, and completely restructure the short-term budget impact measure to ensure that it reflects the impact of innovative medicines on individual patient care.

A. ICER's assumptions around the price and uptake of new-to-market therapies should reflect the realities of the marketplace.

The third category of issues on which ICER is seeking specific comment is methods to estimate the market uptake and potential short-term budget impact of new interventions that "may raise affordability concerns without heightened medical management, lower prices, or other measures."[28] In response, BIO reiterates our concerns with the Framework's two primary uptake assumptions. First, as BIO has noted in previous comments to ICER, the use of the wholesale acquisition cost (WAC) is problematic.[29] WAC does not reflect the discounts and rebates that are widely negotiated in the marketplace, nor does it reflect the rebates required by federal healthcare programs (e.g., Medicaid, 340B drug discount program, and the Coverage Gap Discount Program that applies to Medicare Part D). Thus, WAC is misleading with regard to the "cost" of the therapy to any individual payer, and does not reflect the costs to a patient. While we understand that the exact rebate amounts are not available to be used, this does not absolve ICER of the responsibility to use evidence-based estimates of actual spending in the base case (e.g., since the government is the largest payer, ICER could start by applying the average rebate percentage applicable to government healthcare programs to WAC as the base case).

Second, we continue to question ICER's assumption of unrestricted access to a new therapy in the first five years it is available on the market. This assumption is not reflective of

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http://www.rheumatology.org/Portals/0/Files/ACR%20Guideline%20Manual_Appendices_updated%202015.pdf (last accessed August 31, 2016).

[28] ICER. 2016 (July14). *ICER Opens National Call for Proposed Improvements to its Value Assessment Framework*, available at: https://icer-review.org/announcements/improvements-value-framework/ (last accessed August 1, 2016).

[29] In BIO's May 2016 comments, we raised concerns that not only is the use of WAC in an inaccurate reflection of the cost of therapies given the market realities of the U.S. healthcare system, but also, ICER does not appear to use the same metric for all drug reviews. For example, the Review of therapies treating high cholesterol and severe asthma with eosinophilia utilized WAC, while the Review of therapies treating congestive heart failure utilized WAC minus a calculated discount, and it is unclear what measure was utilized by the Review of therapies treating diabetes (ICER lists "annual drug costs" simply as "calculated"). In the absence of a consistent and transparent measure of cost to different stakeholders, including to patients individually, the Framework is missing a critical element of the calculation of value. See CTAF. 2016 (March 14). *Insulin Degludec (Tresiba®, Novo Nordisk A/S) for the Treatment of Diabetes: Effectiveness, Value, and Value-Based Price Benchmarks*. Table 7, p. 30, available at: https://icer-review.org/wp-content/uploads/2016/03/CTAF_Degludec_Final_Report_031416.pdf (last accessed September 12, 2016).

reality and negatively skews the assessment of therapies that treat large patient populations.[30] In assuming unrestricted patient access, ICER's application of the Framework does not comply with internationally-accepted guidelines on calculating budget impact established by ISPOR.[31] Moreover, such an assumption does not reflect reality: one study estimates that payers impose utilization management restrictions on over 70 percent of covered therapies that treat certain diseases/conditions in certain segments of the health insurance market.[32] A recent study suggests that ICER may be grossly overestimating the budget impact of new therapies and therefore present misleading information to its stakeholders. For example, researchers found that based on the initial quarters of reported sales, the actual one-year cost of the two novel PCSK-9 Inhibitors studied reached $83 million, or 1.2 percent of ICER's predicted $7.1 billion.[33] Thus, the Framework must reflect the realities of market uptake of a new therapy, either by delaying the study of a therapy until real-world evidence is available or used market uptake assumptions that are justified based on examining real-world utilization data of previous drug launches in the disease area (e.g., from claims databases or other sources).

It is also unclear why ICER takes a "heath system perspective" in establishing cost-effectiveness models in some Reviews (e.g., the Review assessing high cholesterol therapies) but takes a payer perspective in others (e.g., the Review assessing severe asthma with eosinophilia therapies).[34] The perspective ICER assumes is important because it dictates the inclusiveness of the cost offsets that ICER considers, which, in turn, impacts the value-based price benchmark. To address this, and considering BIO's broader recommendations throughout this letter, we

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[30] For a more detailed discussion on issue, see BIO. 2016 (May). *Follow-Up on BIO's Comments in Response to the ICER Value Framework*. Section III(A): Utilization, in the context of the Provisional Health System Value metric, is assessed inconsistently and biases Reviews against therapies that treat large patient populations, pp. 6-7, available at: https://www.bio.org/letters-testimony-comments/follow-bio%E2%80%99s-comments-response-icer-value-framework (last accessed August 1, 2016).

[31] ISPOR. *Principles of Good Practice for Budget Impact Analysis*, available at: http://www.ispor.org/workpaper/BudgetImpactAnalysis/BIA_TF0906.asp (last accessed August 31, 2016).

[32] Avalere Health. 2014 (March 24). *Consumers Face More Hurdles to Accessing Drugs in Exchange Plans Compared to Employer Coverage*, available at: http://avalere.com/expertise/life-sciences/insights/more-controls-on-drug-access-in-exchanges (last accessed August 31, 2016).

[33] An upcoming study, described by researchers in a news piece on August 11, 2016, found "that predictions of health care costs made prior to the introduction of new drugs are often dramatically overestimated." One example provided was ICER's assumptions on unmanaged utilization of PSCK-9 Inhibitors in the 2016 Drug Review of these therapies. According to the report, the researchers found that, based on the initial quarters of reported sales, the actual one-year cost of the two novel PCSK-9 Inhibitors reached $83 million, or 1.2 percent of ICER's predicted $7.1 billion. See PR Newswire. 2016 (August 11). *Billion Dollar Blunder: On the 1-Year Anniversary of a New Class of Cholesterol Medicines, Study Finds Actual Cost of New Drugs Is Billions Less than Predicted Independent analysis of pre-launch predictions of 14 new drugs finds predicted cost many times the true cost*, available at: http://www.prnewswire.com/news-releases/billion-dollar-blunder-on-the-1-year-anniversary-of-a-new-class-of-cholesterol-medicines-study-finds-actual-cost-of-new-drugs-is-billions-less-than-predicted-300311969.html (last accessed August 31, 2016).

[34] See ICER. 2015 (November 24). *PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks: Final Report*. Section 6.2 "Incremental Costs per Outcomes Achieved," p. 30, available at: https://icer-review.org/wp-content/uploads/2016/01/Final-Report-for-Posting-11-24-15-1.pdf (last accessed September 12, 2016); see also ICER. 2016 (March 14). *Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks: Final Report*. Section 6.3 "Incremental Costs pre Outcome Achieved," p. 20, available at: https://icer-review.org/wp-content/uploads/2016/03/CTAF_Mepolizumab_Final_Report_031416.pdf (last accessed September 12, 2016).

recommend that ICER take a holistic, societal perspective when considering benefits, costs, and cost offsets. At a minimum, ICER should standardize the perspective used across drug reviews, and/or describe why one perspective is considered to be more appropriate for a specific review.

B. ICER's Provisional Health System Value metric is not meaningful in the context of clinical care and relies on an inappropriately short time frame for the review of new therapies.

As a threshold matter, BIO continues to urge ICER to disaggregate the assessment of clinical comparative effectiveness and budget impact to specific payors. At a minimum, ICER should rename the "provision health system value" metric to identify its focus on short-term budgetary impact (i.e., revise the name to "short-term budgetary impact" metric).

BIO continues to express concern with regard to ICER's continued use of only a five-year measurement window to assess budget impact (i.e., Provisional Health System Value). This is especially true since ICER has, and continues to, target chronic conditions for its Reviews, including rare diseases. These conditions manifest over multiple years or even decades, and can have a differential impact on patients depending on their personal (including genetic) characteristics. Especially in the case of rare diseases, this impact can be challenging to study given the size of the patient population. Thus, the five-year assessment window and the metrics of "average" value, which are not unique to individual patient experiences, are inadequate to capture the full range of benefits, costs, and cost offsets of an innovative therapy to individual patients, the healthcare system, and society.

If ICER does not expand the time horizon over which budget impact is considered, the Institute may contribute to stifling the innovation ecosystem by systematically undervaluing therapies that have relatively high upfront costs but represent significant improvements in the standard of care and can improve longer-term patient health outcomes and decrease longer-term healthcare system expenditures. If ICER insists on continuing to utilize the 5 year budget impact window, we urge the Institute to model—and report as summary metrics—budget impact at several time intervals, including 7 and 10 years to more adequately demonstrate the potential impact of cost offsets across the course of a patient's disease. An expansion of the modeling in this manner will be particularly relevant to certain types of payors, including those in integrated healthcare systems, large employers (e.g., those likely to see lower rates of turnover in their beneficiary populations), and federal healthcare programs (e.g., Medicare).

V. Discontinuing the Use of the Budget Impact Threshold: ICER should not continue to employ the budget impact threshold as it is not meaningful in the context of clinical decision-making and obscures the nuance and detail of the impact of an innovative therapy on an individual patient.

The fourth issue category on which ICER specifically requests feedback is the structure of the threshold for a potential short-term budget impact that "can serve as a useful 'alarm bell'

for policymakers."[35] BIO continues to question the premise of the budget impact threshold and its relevance to clinical decision making. This threshold applies a one-size-fits-all standard to therapies regardless of their impact on patients' lives and the overall healthcare system, and is not meaningful in the context of clinical decision-making between patients and providers. In this way, it is anchored to the status quo of current innovation, which does not reflect society's call for better treatments and cures (e.g., evidenced by the Cancer Moonshot and Precision Medicine Initiatives).

Moreover, the budget impact threshold is based on the narrow assumption that annual spending on novel prescription drugs should not exceed gross domestic product (GDP) growth plus one percent, without a thorough analysis of the impact of this spending on U.S. GDP. In particular, ICER does not account for the potentially positive aspects of a growth in prescription drug spending that result in healthier patients and improved efficiency and effectiveness in the system. For example, healthier patients may be more productive, which positively contributes to GDP growth.[36] Similarly, there also is no consideration of the observation that rising income leads to higher expenditures on health (which could mean that patients are finally able to obtain the care they need).[37] Thus, artificially tying annual spending on new prescription drugs to GDP growth may result in unintended consequences that introduce inefficiencies into the healthcare system, not least of which through decreasing patient access to needed therapies. BIO agrees with the commentary in a 2016 research article, which discusses the policy implications of budgetary caps on prescription drug spending, that "[i]t seems neither fair nor efficient that patient access to new therapies should now swing with the vagaries of the business cycle or the choice of forecasting agency."[38]

Additionally, BIO questions why ICER has focused on estimating the sum total cost of a therapy to all healthcare payers when this is not a meaningful metric in our multi-payer health insurance system. The threshold was established, in part, to mirror the "acceptable" growth formula established for the Independent Payment Advisory Board (IPAB) under the Affordable Care Act. Yet employing this benchmark is inappropriate given that the IPAB has jurisdiction only over the Medicare program, whereas ICER applies its threshold collectively across all payors. Additionally, a "global" approach to assessing costs and cost offsets ignores the specific costs to the patient, which research has shown directly impacts adherence to therapy and downstream healthcare system spending.[39]

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[35] ICER. 2016 (July14). *ICER Opens National Call for Proposed Improvements to its Value Assessment Framework*, available at: https://icer-review.org/announcements/improvements-value-framework/ (last accessed August 1, 2016).
[36] Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation (ASPE). *The Effect of Health Care Cost Growth on the U.S. Economy*, available at: https://aspe.hhs.gov/sites/default/files/pdf/75441/report.pdf (last accessed August 29, 2016).
[37] Id. at 9-11.
[38] Goldman, D. P., D. N. Lakdawalla, J. R. Baumgardner, and M. T. Linthicum. 2016 (January). Are Biopharmaceutical Budget Caps Good Public Policy? *The Economists' Voice* [ed. By Cragg, M., J. Stiglitz, and J. Zwiebel.] ISSN (Print) 2194-6167, Section 8, p.10.
[39] Eaddy, M. T., C. L. Cook, *et. al.* 2012. How Patient Cost-Sharing Trends Affect Adherence and Outcomes: A Literature Review. *Pharmacy and Therapeutics* 37(1):45-55.

The so-called "alarm bell" also directly influences ICER's value-based pricing benchmark summary metric, which detracts from the nuance of treatment decisions and the impact of innovation on patients, the healthcare system, and society as a whole. The threshold is driven by the inaccurate assumptions of uptake and cost used to construct the Provisional Health System Value metric (discussed in an earlier section of this letter), and therefore, inherently disadvantages the assessment of therapies that treat large patient populations. This bias against therapies that treat large patient populations appears to exist regardless of the value such medicines may have to individual patients and the healthcare system. Ultimately, such a bias can support inefficient, inappropriate healthcare choices, by discouraging the utilization of medicines that may offer significant health benefits, and diminish investment in treatments and cures for large patient populations, resulting in missed opportunities to help reduce overall health expenditures. Thus, ICER should not continue to employ a budget impact threshold in the Framework, but instead, significantly restructure the narrative discussion of the potential short- and long-term financial impact of a therapy on specific stakeholders in each drug review.

VI. Conclusion

BIO appreciates the opportunity to provide comments on the underlying Framework methodology, but remain concerned that this is the first such opportunity to do so in the year since the methodology was revised and used to conduct almost a dozen drug reviews. Moving forward, ICER must establish a formal process for soliciting and incorporating stakeholder feedback on the underlying methodology in a more timely fashion as the standard for value assessment evolves.

We reiterate the need for ICER to identify how stakeholder feedback is incorporated in each stage of the drug review process, and, in particular, provide greater clarify around the Institute's efforts to incorporate the patient perspective into each review.
We reiterate our recommendation that ICER reform the summary metrics of the Value Framework through the recommendations discussed in this letter to avoid obscuring the nuance of treating patients with complex, chronic conditions.

Finally, we urge ICER to more clearly state that its work is only a single input into the broader discussion on improving the efficiency and effectiveness of healthcare decision making. The Institute also should emphasize the limitations of the drug reviews and support the importance of individual patient/provider decision making in any discussions that address payers' coverage and reimbursement determination processes. As a substantive contributor to the discussion of value, ICER has a responsibility to ensure that its process is inclusive, its methodology is reflect of the realities of patient care, and its findings are interpreted in the appropriate context.

BIO looks forward to opportunities to contribute to ICER's ongoing work, and continues to encourage the Institute to refine the Framework to ensure that it promotes, rather than acts at odds to, patient-focused health care. Please feel free to contact me at (202) 962-9200 if you have any questions or if we can be of further assistance. Thank you for your attention to this very important matter.

Respectfully submitted,

/s/

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