August 19, 2015

BY ELECTRONIC DELIVERY

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American Society of Clinical Oncology
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Alexandria, VA 22314

RE: American Society of Clinical Oncology's (ASCO's) Value Framework

Dear Dr. Vose:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide feedback on the American Society of Clinical Oncology's (ASCO's) Value Framework released on June 22, 2015.[1]

BIO represents 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 represents an industry that is devoted to discovering, and ensuring patient access to, innovative treatments. Accordingly, we closely monitor payment policies for their potential impact on medical innovation and patient access to drugs and biologicals, and appreciate the opportunity to review a draft of the Value Framework. BIO is very much aligned with ASCO's goal of making clinically meaningful progress against cancer through research and the delivery of high-quality care to all patients with cancer. BIO also supports ASCO's broader goal of creating tools "to assist the physician and patient in shared decision making with regard to cancer treatment."[2] We agree that patients and providers should have access to all of the relevant information when choosing a treatment regimen. However, we are concerned that the structure of the Value Framework as drafted will not achieve this goal.

Specifically, we are deeply concerned that the Value Framework does not meaningfully and systematically account for patient preferences and the need to construct individualized treatment plans. In fact, the Value Framework appears to focus on population-based, rather than personalized, decision-making. We also are concerned that the proposed cost measures do not provide sufficiently comprehensive information with regard to the costs and savings of a specific treatment regimen to patients and are not relevant in the context of individual patient/provider decision-making. Additionally, while ASCO does identify the

[1] Schnipper, L. E., N. E. Davidson, D. S. Wollins, C. Tyne, D. W. Blayney, D. Blum, A. P. Dicker, *et. al.* 2015. American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. *Journal of Clinical Oncology*, available at: http://jco.ascopubs.org/content/early/2015/06/16/JCO.2015.61.6706.
[2] Id. at p. 4.

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limitations of the Value Framework—as they pertain to the net health benefit (NHB) and cost measures—BIO remains concerned that there is a significant potential for other stakeholders to use this information out of context, and to the direct detriment of patient access to needed therapies.

BIO also has identified a number of additional methodological issues with the Value Framework that we believe could negatively impact patient access to the most appropriate treatments for them, thereby contradicting the goals of personalized medicine. These include: the lack of clarity with regard to the scope of studies that will be included in the Value Framework; the lack of context for the Value Framework's summary measures; and the potential that the Value Framework's proposed methodology may yield inaccurate and/or incomplete information to patients and providers with regard to the value of innovative oncology therapies. We strongly urge ASCO to work with a diverse group of stakeholders to address each of these concerns before finalizing the Framework. We also urge ASCO to invite additional public input on any future iterations of the Value Framework – and to publicly explain how they are considering this input – to ensure that these efforts promote informed, individualized decision-making between cancer patients and their providers at the point of care.

BIO's concerns are discussed in greater detail throughout the remainder of this letter.

I. ASCO Should Take into Account the Need for Individualized Treatment Plans That Incorporate a Patient's Preferences.

Throughout the discussion of the Value Framework, ASCO notes the importance of patient preference in clinical decision-making, which BIO continues to recognize as crucial to the practice of personalized medicine. Not only is patient preference critical to incorporate, but individualized treatment plans also are necessitated by the fact that patient responses to cancer treatment may differ (e.g., dose reductions are common in cancer care to improve tolerability to help patients get through a treatment cycle).[3] However, BIO is concerned that the Value Framework does not establish a concrete mechanism to take into account patients' treatment priorities, their preferences, and the impact of societal and/or cultural differences when calculating the NHB score. ASCO also does not detail how the heterogeneity of patient groups will be reflected in the summary NHB score and whether and how it will take into account variable clinical circumstances. For example, ASCO mentions that the relative weights of the clinical benefit and toxicity scores (and the bonus points awarded in the advanced disease framework) can be varied to account for an individual patient's preference to maximize clinical benefit/quality of life or minimize toxicity. However, there is no guidance with regard to how those weights should be changed to meaningfully reflect these priorities. In the absence of discrete mechanisms to take patient preferences into account, BIO is concerned that the Value Framework will encourage one-size-fits-all oncology care, which directly contradicts ASCO's stated of goal of improving information at the point of decision-making to drive appropriate care for each individual patient.

[3] For example, a recent survey of thousands of oncology patients, conducted by the Cancer Support Community (CSC), asked patients to respond to the question, "When considering your cancer experience, how do you define value?" Among the survey's primary findings was that "[w]hile there are some consistent themes across the various diagnoses, people with different kinds of cancer have issues that are more specific, or even unique to their diseases." For more information on the survey results, *see* CSC. 2015. How Do Patients Define Value in Cancer Care? *The Huffington Post Blog*, available at: http://www.huffingtonpost.com/kim-thiboldeaux/how-do-patients-define-va_b_7939662.html.

II. ASCO Should Reconsider the Inclusion of the Two Proposed Cost Measures Since, as Drafted, They Are Not Meaningful to Patients and Providers.

The Value Framework proposes to present two measures of cost alongside the NHB score: patient cost and drug acquisition cost. Both measures will reflect costs for an individual treatment or treatment regimen over a defined period of time, and the former will be based on the specific benefit design of an individual patient's insurance plan. In discussing why these measures were chosen, ASCO notes that they were "a readily available, although admittedly incomplete, estimate of cost."[4] With regard to the Value Framework's use of the patient cost metric, BIO is concerned that this information may reflect only a small piece of patients' potential total expenditures for care and does not reflect the potential cost-savings related to a course of treatment at all (e.g., the need for fewer hospitalizations, fewer physician office visits, less time away from work). For example, patients may need to rely less on supportive medications, taken concomitantly with certain cancer treatments, if their primary treatment regimen results in fewer side-effects or is shorter in duration. Additionally, it represents costs for patients at a specific point in time, a fact that should be clarified in the Framework. An incomplete estimate of a patient's total potential costs and savings will yield incomplete information that can serve to misrepresent patients' total costs of care, confusing rather than clarifying this input into a patient's decision-making process.

With regard to the drug acquisition cost, we note that it is unclear how this measure is meant to be calculated based on the draft Value Framework (in the examples provided, both average sales price data at an arbitrary date and payer-specific acquisition costs are used).[5] However, no matter how it is calculated, we urge ASCO not to retain this measure in any final version of the Value Framework because it is not meaningful to patients or providers. Clinical decision-making should be based entirely on what treatment regimen is most appropriate for an individual patient to achieve the best possible outcomes in line with his/her healthcare goals. While we agree that a patient's individual out-of-pocket costs must be a factor in any healthcare decision, the abstract measure of drug acquisition cost is not relevant in this context and may inappropriately establish incentives to underutilize appropriate care. This, in turn, can lead to poorer health outcomes for individual patients and an increase in overall healthcare expenditures (e.g., due to increased hospitalizations and physician office visits).

III. ASCO Should Address Concerns that the Value Framework's Summary Metrics Will Be Taken Out of Context.

BIO remains concerned that there is a significant potential for other stakeholders to use the proposed NHB and cost metrics out of context, and to the direct detriment of appropriate patient care. This concern stems from the lack of guidance on how to interpret summary metrics from different trials comparing the same treatment regimens and from the potential for payers to misuse these metrics to limit patient access to certain therapies. Each concern is discussed, in turn, below.

A. <u>ASCO should provide additional guidance to providers to prevent inaccurate comparisons between the summary metrics of different studies referencing the same treatment regimens.</u>

[4] Schnipper, L.E., *et. al.*, at p. 12.
[5] <u>Id</u>. at p. 9. The text explaining Figure 3 notes that "[c]osts based on average sales price as of October 2014 for intravenous therapies and on information from UnitedHealthcare for oral drugs."

BIO has serious concerns that, despite ASCO's acknowledgement that comparisons between NHB scores are inappropriate, these scores can be taken out of context to the detriment of patient access to needed therapies. For example, it is unclear how providers and patients should interpret or reconcile multiple NHB scores from eligible studies that compare the same two treatment regimens. This uncertainty can confuse, rather than clarify, clinical decision-making. Thus, additional guidance is necessary prior to implementing a final Framework to ensure that these limitations are well understood and do not negatively impact patient care.

B. ASCO should reassert the inappropriateness of using the Value Framework's summary metrics for coverage and reimbursement decisions and establish mechanisms to identify potential misuses of the final Framework once it has been implemented.

BIO has serious concerns that payers may ignore the limitations of the Value Framework's NHB score since the Framework does not identify the broader context for decision-making, provided by all available data on varying treatment regimens, and does not provide information on the aspects of a study that can impact the applicability of its findings to a given patient/patient population (discussed throughout this letter). This situation may lead payers to attempt to make coverage and reimbursement decisions based on an NHB score, or a comparison of NHB scores, that would result in delaying or denying a patient's access to the most appropriate for them individually. In turn, this can establish perverse clinical practice patterns that can lead to underutilization of appropriate care, resulting in poorer health outcomes for individual patients and higher overall expenditures for the healthcare system, due to increased need for hospitalizations, physician office visits, and surgical interventions. In fact, concerns are already being raised that payers may use the Value Framework's summary metric to inform clinical pathways, which can financially incentivize providers to prescribe one treatment regimen over all others for the majority of their patient population (without regard to the highly-individualized nature of cancer treatment).[6]

Given these potential negative outcomes of the Value Framework as drafted, BIO strongly urges ASCO to reiterate that the NHB is not appropriate in the context of coverage and reimbursement decisions given its very limited scope. ASCO should work with diverse stakeholders to identify mechanisms to mitigate the potential negative uses of the Framework and to ensure that patient quality of care is not compromised before its methodology is finalized. Finally, if and when the Framework is operationalized, BIO urges ASCO to work continuously to ensure that its metrics are not used to limit patient access to needed therapies. One way to do this would be to establish robust monitoring and feedback mechanisms within its own membership to scrutinize provider and patient experiences utilizing the Framework and make refinements to the methodology as necessary.

IV. ASCO Should Clarify the Scope of the Randomized, Prospective Trials That Will be Included in the Value Framework and the Process for Including Emerging Evidence.

As an initial matter, ASCO notes that the Value Framework is meant to summarize data derived from a prospective randomized trial that compares a new treatment regimen with a control protocol for a specific clinical cancer indication.[7] BIO appreciates ASCO's focus on

[6] For example, *see* Kelly, C. 2015 (July 14). ASCO Value Framework Could Inform Clinical Pathways. *The Pink Sheet*, available at (by subscription only): https://www.pharmamedtechbi.com/publications/the-pink-sheet/77/28/asco-value-framework-could-inform-clinical-pathways-payers-say.

[7] Schnipper, L.E., *et. al.*, at t p. 4.

high-quality evidence, and on developing a Framework "that is well grounded in the available medical evidence and provides the most objective assessment" of the potential benefit of a treatment or treatment regimen.[8] However, it is unclear how broad the eligibility criteria are for studies that ASCO intends to include in the Value Framework: for example, while the studies used to support the examples provided in the Framework have been published in prominent peer-reviewed journals, the Framework does not note this as a specific criterion for inclusion. BIO agrees that publication in such a peer-reviewed journal does not necessarily assure that a study was conducted rigorously or that the author's findings are appropriate given the data analyzed; though the quality of the journal is often used as proxy for a study having met minimum quality standards. In turn, since a study's methodological rigor will drive the reliability of its findings, we urge ASCO to clarify how that rigor will be assessed and to address concerns that the proxy of where the study was published may be a necessary, but not sufficient, aspect of such an assessment.

Another crucial aspect of high-quality evidence, in addition to methodological rigor, is the extent to which the evidence reflects the most up-to-date medical and clinical advancements. The field of oncology is rapidly evolving, and if the Value Framework is not able to keep pace, it risks misinforming patients and their providers about the appropriateness of a treatment regimen. Moreover, unless the Value Framework is able to keep pace with emerging evidence, it risks undervaluing innovation to the detriment of individual patients who may benefit and to the broader ecosystem that is responsible for fostering a climate that rewards advances in medicine and science. To address this concern, it is crucial that ASCO develop and seek stakeholder feedback on a process for updating the Value Framework as new studies are published, prior to implementing the Framework.

V. ASCO Should Provide Sufficient Context for the Value Framework's Summary Measures to Ensure Cancer Patients Receive the Most Appropriate Care.

Based on the Value Framework's proposed scope—reflecting only the findings of prospective randomized trials—it may have limited utility for certain patients and clinical scenarios (e.g., in terms of whether their disease and/or individual characteristics match those of patients included in the trials being summarized). These limitations will be important to recognize to ensure that the Framework does not result in misconstruing the appropriateness of applying study findings to a specific clinical scenario or misinforming a patient and his/her provider about which treatment option is most appropriate given their individual circumstances.

In assessing the context for the Value Framework, BIO is concerned that ASCO has not provided sufficient guidance to oncologists with regard to how to present the Value Framework's summary measures in the context of a patient's specific circumstances, nor has ASCO taken into consideration all of the outcome benefits that matter to patients. Our concerns are identified in the subsections below.

A. The Value Framework's use of the term "Net Health Benefit" is inaccurate.

As drafted, the Value Framework's quantitative assessment of the benefit and toxicity of a new treatment regimen as compared to an existing standard of care, will be presented as a single numerical term, the "net health benefit (NHB)."[9] While we understand that the broad

[8] Id. at p. 8.
[9] In the case of the advanced disease version of the Value Framework, "bonus points," which represent a quantitative comparison of the new treatment's impact on palliation and/or treatment-free interval versus that of the control treatment also is included in the NHB score, *see* Schnipper, L.E., *et. al.*, at p. 4.

purpose of the Value Framework is to compare the potential net benefit of a treatment regimen to that of an existing control protocol, the comprehensiveness implied by the term "net health benefit" is inaccurate. The NHB only reflects a limited number of benefit metrics (i.e., median overall survival (OS), progression-free survival (PFS), and/or response rate (RR) as reported by the trial), toxicity metrics (frequency of grade 3 through 5 toxicity as defined by the Common Terminology Criteria for Adverse Events (CTCAE)). With regard to the advanced disease model, the Framework only represents limited metrics of palliation. Moreover, the NHB as drafted does not reflect measures related to therapy adherence or patient-reported outcomes at all. BIO's concerns with the absence of reporting on these metrics in the Value Framework are discussed in further detail in the methodology section below. Nonetheless, given the reality that any summary metric employed by the Value Framework will not be comprehensive or universally applicable to all patients, we urge ASCO to consider utilizing a narrower term for this metric, such as "relative summary of measured benefits." A narrower term would help to avoid confusion among providers and patients who may utilize the Framework as a piece of information in their healthcare decision-making process.

B. <u>The Value Framework does not adequately describe how the structure of a study can impact the NHB score.</u>

In describing the Value Framework, ASCO recognizes that it does not account for how the structure of the trial may impact the NHB score (e.g., the impact of patient population/subpopulation enrolled, primary endpoint used, timeframe over which benefit/toxicity was measured, trial design, treatment regimen used as the comparator). While we appreciate that ASCO clearly identifies this limitation of the Framework, BIO is concerned that, in the absence of this crucial context, the NHB score cannot be meaningfully applied to an individual clinical scenario. For example, a study's inclusion/exclusion criteria may have been established to target a small subset of cancer patients based on a similar physical, physiological, or pathophysiological profile when comparing a new treatment regimen to a control regimen. Yet, when a provider aims to use the Value Framework to glean information about the outcome of that study, the NHB score will not reflect the specific subset of patients targeted, despite the critical impact that information may have on the relevance of the study findings to an individual patient (i.e., in the event that the patient does not resemble the study population).[10] Given this issue, BIO is seriously concerned that the Framework's NHB score, in particular, may dramatically oversimplify the clinical complexity of applying trial findings to an individual patient circumstance. Thus, we urge ASCO to address the need for greater context about the elements of a study that can impact its findings. We believe this context is critical to avoid providing inaccurate and/or incomplete information to providers and patients about the appropriateness of one treatment regimen over another for a specific clinical scenario.

C. <u>The Value Framework does not describe the broader context in which a study's findings should be assessed.</u>

[10] The Value Framework's original NHB score of zero for the therapy Alimta is an illustrative example of BIO's concerns that the Framework does not adequately reflect the importance of how a study is structured to how its findings can be interpreted. This therapy was approved for patients with non-squamous, non-small cell lung cancer (nsNSCLC). However, the study used to derive this NHB score assessed Alimta in treating diseases beyond its label indication. While off-label prescription of therapies is an important and legitimate aspect of high-quality individualized patient care, the exclusion of this crucial information—noting the difference between the study's patient population and that of the label indication—led to an NHB score that was not reflective of the therapy's value to nsNSCLC patients. It is noteworthy that ASCO published an addendum to the Value Framework draft that corrected this initial zero-score on July 6, 2015 (the Publisher's Note identifying this correction is available at: http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.61.6706/suppl/DC1).

BIO appreciates ASCO's commitment to relying only on high-quality evidence for the purposes of clinical decision-making. However, we are concerned that reliance on prospective randomized trials alone ignores the sophisticated efforts that are ongoing within the industry, in coordination with the Food and Drug Administration, to use alternative study designs, like observational studies. These alternative study designs are similarly statistically powerful to randomized trials but can demonstrate safety and efficacy in shorter timeframes and in smaller patient populations to accommodate the trends in increasingly personalized medicine. Such alternative study designs can better take into account the highly individualized nature of cancer disease and disease progression to treat the disease as it evolves in response to an individual patient's immunological response (e.g., continued development and commercialization of immuno-oncology therapies).

Similarly, the Value Framework does not account for the growth in our understanding of a therapy's benefits and risks, the impact on downstream treatment decisions and broader utilization of healthcare services, and the effectiveness for certain patient subpopulations over time. As described in a recently-released White Paper on the emerging benefits of oncology therapies over time, "FDA approval marks the 'starting point' for additional study of [a] therapy, followed by the development of a larger body of evidence to help us understand the full value of the treatment and, more importantly, to help clinicians understand how best to use available therapies when treating their patients."[11] The inability to reflect this evolution shortchanges the calculation of the value of a therapy to an individual patient. At a minimum, this diminishes the utility of the Value Framework to patients and their providers, and in some cases this can actually result in providing inaccurate and/or incomplete information with regard to the most appropriate course of treatment.

To address these concerns, BIO strongly urges ASCO to provide simultaneous guidance for providers that contextualizes the final Value Framework within the broader universe of data needed to make an appropriate, individualized treatment decision.

VI. ASCO Should Address Significant Gaps in the Value Framework's Methodology That May Result in the Provision of Inaccurate and/or Incomplete Information to Patients and Providers.

BIO has identified two significant gaps in the Value Framework's methodology that we recommend ASCO address before finalizing the Framework. These include that the Framework:

- Places too much importance on the measure of median OS to the detriment of including other, increasingly important, measures of clinical benefit and other relevant patient outcomes that may have clinical and economic benefits (i.e., cost offsets); and
- Does not distinguish the significant differences between CTCAE-defined toxicity grades.

Both of these issues are discussed in more detail in the subsections below. Taken together, these methodological gaps can result in misinforming patients and providers about the benefits of innovative oncology therapies, which can effectively limit patient access to the most appropriate therapies for them. This, in turn, can result in negatively impacting the delivery of the highest quality care. Such a result stands in direct opposition to the goal of

[11] Sweeney, N. and T. F. Goss. 2015 (May). The Value of Innovation in Oncology: Recognizing Emerging Benefits Over Time. *Boston Healthcare*, available at: http://www.phrma.org/sites/default/files/pdf/bha_value_of_cancer_innovation-whitepaper.pdf.

improving individualized care for oncology patients through enhanced information at the point of decision-making.

A. The Value Framework does not take into account all relevant measures of clinical benefit.

As structured, the Value Framework only takes into account three measures of clinical benefit in the NHB score: median OS, PFS, and RR. Moreover, the Framework gives preference to the median OS measure above all other study outcomes by proposing to accord median OS a higher weight, of 16, in the NHB calculation than other measures of clinical benefit (i.e., PFS is weighted by 11, and RR by 8). Not only are these weightings arbitrary, but we find the Framework's reliance on median OS unsound for several reasons. First, median OS in the advanced disease model may not be as appropriate a measure of the benefit of newer therapies (e.g., immuno-oncology therapies) as it is for older chemotherapeutic agents. This is, in part, because newer therapies may have a more significant impact on long-term survival and result in delayed clinical effects when compared to older cytotoxic and pathway-specific agents. Thus, relying on median OS can result in "undervaluing" a new therapy regimen or "overvaluing" a control regimen and, in turn, provide inaccurate and/or incomplete information to patients and providers.[12] For example, in the case of a study comparing two drugs—in which two percent of patients taking the control drug lived beyond two years and ten percent of patients taking the newer drug lived beyond two years—the median OS rates may not look much different. However, if compared through the lens of a metric that more appropriately captures the benefits of the newer therapy (e.g., survival at two years), the NHB score may provide more meaningful information to patients and providers.

Second, median OS also may be more difficult to measure than other metrics in certain types of cancers or for certain patient subpopulations because it requires larger trial populations and longer study times.[13] As treatment for cancer becomes increasingly personalized, studies are likely to recruit smaller, but more homogeneous, patient populations in terms of the characteristics of the individual patient and his/her disease. Measuring median OS in these studies may prove challenging, or practically impossible, perhaps limiting the inclusion of this valuable information in the Value Framework, or leading the Framework's NHB score, as it is currently structured, to provide an inaccurate and/or incomplete analysis of the benefits of a new therapy for such a patient subpopulation.

Third, median OS may not be the primary endpoint of a trial, but under the structure of the current Value Framework, even if overall survival is only reported as a secondary endpoint, it is incorporated in the NHB metric and potentially accorded a higher weighting than the study's primary outcome. BIO finds this concerning because secondary endpoints may not have been measured in the entire study population, or may be impacted differently by confounding factors than the primary endpoints. Both of these realities may have a significant impact on the appropriateness of applying the study's findings to an individual patient, though neither would be reflected in the NHB.

[12] For a general discussion on the appropriateness of metrics to describe the value of chemotherapeutics involved in chronic cancer care compared to newer therapies with curative potential, *see* Johnson, P., W. Greiner, I. Al-Dakkak, and S. Wagner. 2014. *Review Article*: Which Metrics Are Appropriate to Describe the Value of New Cancer Therapies? *BioMed Research International*, available at: http://www.hindawi.com/journals/bmri/2015/865101/.

[13] Pazdur, R. 2008. Endpoints for Assessing Drug Activity in Clinical Trials. *Journal of the Society for Translational Oncology* 13(S. 2): 19-21.

Fourth, the Value Framework does not address the incorporation of other metrics of clinical benefit that studies may measure, and may be meaningful to patients and providers. This includes: complete response; long-term survival; time to tumor progression; overall response rate (i.e., the portion of patients with a tumor size reduction of a predefined amount for a minimum time period); time to treatment failure; event-free survival; benefits of maintenance therapy; or any patient-reported outcomes (e.g., ease of use, impact on health-related quality of life)). The exclusion of these measures may result in the Value Framework's mischaracterization of the value of innovative oncology therapies and thus, result in obscuring relevant information on the potential benefits of these therapies for an individual patient.

Fifth, the proposed preference for median OS and the relatively low weighting for RR may not accurately reflect the potential benefits of a breakthrough therapy approved on the basis of a single arm trial. Especially in areas of high unmet need, these therapies may represent significant benefits over the control protocol that may not be captured adequately based on the proposed weighting methodology and the limited measures of clinical benefit included. Undervaluing these breakthrough therapies could limit access to them by patients who could otherwise stand to benefit.

Without addressing all of these gaps in the methodology for assessing clinical benefit, BIO is seriously concerned that the Value Framework will not accurately reflect the value of innovative oncology therapies. These new therapies represent a shift in the paradigm of cancer treatment, and can radically improve long-term survival for cancer patients. Capturing that shift in value will be critical to ensuring that patients can access these innovations and that the marketplace fosters continued scientific and medical progress.

B. <u>The Value Framework is insensitive to the significant differences in CTCAE-defined toxicity grades.</u>

ASCO proposes to calculate the toxicity component of the NHB score by comparing the frequency of CTCAE-defined grade 3 to 5 toxicities in study participants taking the new therapy to that of participants randomized to the control regimen. A score between -20 and 20 will be assigned depending on the percent difference in frequency of these toxicities between the new therapy and control populations. Based on this description of the toxicity score, BIO is concerned that, as drafted, it is insensitive to important aspects of toxicity to cancer patients in two ways. First, this mechanism accounts for toxicity across all grade 3 to 5 toxicities, despite the significant differences between them: grade 3 toxicity is defined as "severe or medically significant but not immediately life-threatening"; grade 4 as "life-threatening consequences [for which] urgent intervention [is] indicated"; and grade 5 as "death related to [adverse event]."[14] This can lead to an incomplete understanding of the difference in toxicity between two treatment regimens in any trial for purposes of clinical decision making. Second, as drafted, there has to be a greater than 50 percent change in the frequency of grade 3 to 5 toxicities to impact the Value Framework's toxicity score. Thus, clinically meaningful changes in toxicity to patients will be undervalued in the Framework if they do not meet that 50 percent threshold. Before moving forward to finalize the Framework, ASCO must improve the sensitivity of the toxicity score to differences in toxicity that are meaningful to patients. These differences can be central to patient/provider decision-making, and as structured, the Framework does not provide sufficiently granular information to meet the goal of better informing treatment decisions.

[14] Department of Health and Human Services, National Institutes of Health National Cancer Institute. 2009 (May 28). Common Terminology Criteria for Adverse Events (CTCAE): Version 4.0, available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

VII. Conclusion

BIO reiterates our appreciation for the opportunity to provide feedback on the Value Framework and for ASCO's consideration of the concerns we have identified in this letter. While we share the goal of improving information at the point of clinical decision-making between patients and providers, we do not believe that the Value Framework, as current structured, will further this goal. Nevertheless, we would like to work with ASCO to identify opportunities to make progress toward this shared goal. 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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