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Re: Value Assessment Methods for "Single or Short-Term Transformative Therapies" — Proposed Adaptations to the ICER Value Assessment Framework; opportunity to comment

VIA ELECTRONIC DELIVERY

Dear Sir or Madam,

On behalf of The ALS Association, we are pleased to provide comments on Value Assessment Methods for "Single or Short-Term Transformative Therapies" (SSTs).

The ALS Association is the only national non-profit organization fighting ALS, also known as Lou Gehrig's Disease, on every front. The mission of The ALS Association is to discover treatments and a cure for ALS, and to serve, advocate for, and empower people affected by ALS, so they may live their lives to the fullest.

Amyotrophic Lateral Sclerosis (ALS), a progressive neurodegenerative disease, is a particularly cruel disease that destroys a person's ability to control all muscle movement. As the disease progresses, patients become trapped inside a body they no longer can control, often unable to walk, talk, eat, breathe, or even blink an eye. U.S. prevalence statistics vary in different studies, ranging from approximately 16,000 with a definite diagnosis of ALS, according to the National ALS Registry, to about 25,000 when considered more broadly as part of the spectrum of motor neuron diseases, which include progressive muscular atrophy (PMA), primary lateral sclerosis (PLS), and progressive bulbar palsy (PBP).¹ This relatively low prevalence arises in part from the rapid progression of the disease, obscuring the fact that about 1 of every 400 Americans develops ALS in their lifetime, making it the most common adult-onset motor neuron disorder (MND).²

Because of the cruelty of this disease, and the lack of treatment options, the ALS community views risks and benefits of treatments differently than many other disease areas. We want to ensure that any systematic efforts to assess value are sensitive to the needs of our community, and most importantly, that everyone with ALS has full access to every treatment that might offer them benefit as they define it. Given the range of potential ALS therapies that could be considered as SSTs, currently in the pipeline, the ALS Association would like to provide the following comments.

¹ https://www.cdc.gov/mmwr/volumes/67/wr/mm6707a3.htm?s_cid=mm6707a3_e

² N Engl J Med. 2017 Jul 13;377(2):162-172. doi: 10.1056/NEJMra1603471. Amyotrophic Lateral Sclerosis. Brown RH(1), Al-Chalabi A(1);

Proposed Method Adaptations:

1. Determining those treatments for which adapted assessment methods will be used

1.1. ICER will use an adapted approach to value assessment for “single and short-term transformative therapies” (SSTs). These are defined as *therapies that are delivered through a single intervention or a short-term course of treatment that demonstrate a significant potential for substantial and sustained health benefits extending throughout patients’ lifetimes*. SSTs include two subcategories:

- ***Potential cures*** that can eradicate a disease or condition; and
- ***Transformative therapies*** that can produce sustained major health gains or halt the progression of significant illnesses.

1.2 Scoping: ICER will include in its initial draft scoping document a statement on whether a therapy is judged to meet the above definition. Following formal public comment, ICER will make a final decision on whether the therapy meets these criteria and will be assessed using an adapted approach.

ALSA Comment: The ALS Association asks for additional clarification or expansion on the definition of SSTs as some potential ALS gene therapies may provide a significant halt in progression or even improvement, but require re-dosing at various times, and potentially throughout an individual’s life. Based on the current definition, as we understand it, such gene therapies would be excluded as SSTs and the proposed adapted assessment methods.

2. Assessing and Describing Uncertainty

2.2 Time horizon threshold analyses for durability of effect: When the SST price is known or can be estimated, assessments of SSTs will also include a scenario with a threshold analysis determining the duration of beneficial effect (e.g., cure) for those patients receiving short-term benefit that would be needed to achieve standard cost-effectiveness thresholds (e.g., \$150,000/QALY).

ALSA Comment: The ALS Association urges ICER to take into consideration the priorities of the ALS Community as well as the specific devastating effects of the disease when determining the benefit that would be needed to achieve a standard cost-effectiveness threshold. ICER should include ALS experts, clinicians, patients and caregivers when evaluating such cost-effectiveness as nuances of a potential therapy’s impact and the true value to the patient and caregiver could be overlooked. For example, the ability for a patient to use their legs for a longer amount of time, even though arm function may have already been lost, provides a profound impact on a patient’s wellbeing and independence.

2.3 Introducing a new economic review section on “Controversies and Uncertainties”: We propose including a new section in the “Long-Term Cost-Effectiveness” section of ICER reports which will discuss “Controversies and Uncertainties” related to the economic evaluation. Although the current layout of ICER reports includes information on these issues, we feel it will be helpful to consolidate and expand discussion of factors related to uncertainty, including lack of information on natural history, limitations of the data on patient outcomes, and difficulties translating existing data into measures of quality of life. This section will also be used to expand discussion of alternative model structures or inputs suggested by manufacturers or other stakeholders. This proposed change to ICER’s report structure will be considered for all ICER reports, not just those for SSTs.

ALSA Comment: The ALS Association is intrigued by the newly proposed economic review section on “Controversies and Uncertainties” and ICER’s consideration of factors related to uncertainty, including lack of information on natural history, limitations of the data on patient outcomes and difficulties translating existing data into measurements of quality of life. ALS is a very heterogenous disease and progression can vary between individuals which can complicate the data on natural history. We appreciate ICER allowing for the exploration of many different scenario variations and look forward to providing input to ICER on alternative models that may exist during the review of ALS therapies.

3. Additional Elements of Value

3.1 Additional elements of value: ICER proposes to add two additional domains of “potential other benefits or disadvantages” for voting by our independent appraisal committees:

- (1) A potential advantage for therapies that offer special advantages by virtue of having a different balance or timing of risks and benefits versus other treatments; and**
- (2) a potential disadvantage for therapies that, if not successful, could reduce or even preclude the potential effectiveness of future treatments.**

This change is proposed for all ICER reviews, including SSTs.

ALSA Comment: The ALS Association welcomes the addition of the two additional domains of “potential other benefits or disadvantages” and elements of value, particularly the “value of hope”, which is so critical to those living with ALS and their caregivers. With only one disease modifying therapy available to ALS patients, having the ability to choose between therapies with different benefit and risk profiles would be very beneficial to our community as the benefit-risk threshold varies between individuals and is best left to the patient and their physician to determine the most appropriate course of treatment.

We encourage ICER to also ensure that ALS experts, industry members, and particularly ALS patient organizations are a part of the process used to evaluate these additional elements in the review of ALS therapies. The ALS Association, through its ALS Focus initiative, is in the process of developing extensive patient experience data, including the identification of outcomes of interest to ALS patients and caregivers that includes items not typically measured in clinical trials (e.g., social role limitations), but are found to significantly impact patients' lives.

5. Affordability and Fair Sharing of Economic Surplus

5.1 Shared savings: ICER proposes to provide a “shared savings” scenario analysis for SSTs as an adjunct to the base case. For this scenario analysis cost offsets will accrue to the innovator during the first 12-year period in the model, a time frame intended to approximate the average time to loss of exclusivity for new prescription drugs in the United States. The scenario will assume that all cost offsets following year 12 in the model will accrue to the health system, i.e. cost offsets will be set to zero in the model after year 12. The overall goal is to produce a different incremental cost-effectiveness ratio and related value-based price benchmark that reflect an alternative sharing of the economic surplus of treatment between innovators and the health system.

ALSA Comment: The ALS Association finds ICER’s proposal to provide a “shared savings” scenario analysis for SSTs as an adjunct to the base case to be promising as it could apply to potential ALS therapies in the future. We also would like to bring to ICER’s attention that the 12-year horizon proposed may not be relevant for orphan or other drugs with longer exclusivity periods and recommend ICER consider an additional analysis beyond 12 years for such therapies.

Conclusion

The ALS Association greatly appreciates ICER providing the opportunity for stakeholders to provide comments on Value Assessment Methods for SSTs and the proposed method adaptations. Should ICER have any questions on these comments or wish to discuss the implications to the ALS community further, please do not hesitate to reach out to Dr. Neil Thakur at nthakur@alsa-national.org.

Sincerely,



Neil Thakur, Ph.D.
Executive Vice President, Mission Strategy
The ALS Association

AMGEN COMMENTS ON ICER'S PROPOSED METHODS ADAPTATIONS FOR ASSESSMENTS OF POTENTIAL CURES AND OTHER TRANSFORMATIVE THERAPIES

Amgen appreciates the opportunity to comment on ICER's *Proposed Methods Adaptations for Assessments of Potential Cures and Other Transformative Therapies*. Although curative therapies are still quite rare, ICER has identified the need to expand upon traditional valuation methods. It is our hope that the resulting methods will continue to incentivize the development of curative therapies through balanced, science-based assessments of these unprecedented therapies that will likely provide an increasing proportion of health benefits in the future.

More pharmaceuticals are truly transforming outcomes: ICER can lead by putting principles of full and fair valuation from multiple perspectives ahead of uninformed reactions and perceptions attached to such treatments. Health care is a continuum of treatment types, from daily incremental symptom fixes, to one-dose curative therapies for previously incurable diseases. That said, an increasing number of pharmaceutical disease treatments are characterized by durable and meaningful disease improvements that were only imagined 10-20 years ago. This may present a seemingly new analytic challenge of comparing the value of more typical 'incremental' treatments that the healthcare system is accustomed to, with the increasing number of new treatments that might produce years or even decades of benefit. Potential cures and other transformative therapies may be more challenging to value for several reasons, driven by issues related to methods, equity and perception, including:

- The greater uncertainty (and accompanying actuarial risk) associated with larger and longer-term benefits compared with short term, incremental and lower cost health care. (Methods question regarding uncertainty).
- Mismatch between when payment might occur (today), with when benefits may accrue (over decades). (Methods question regarding discounting and uncertainty).
- Increasing concentration of benefit for a few people gaining large benefits (e.g., curative therapies for rare cancers) as opposed to many people deriving small benefits (e.g., NSAIDs for a headache). (Equity question regarding distribution).
- Less intuitive familiarity by society in general with these types of treatments and what they are 'worth'. (Perception issue).
- The high cost of higher value treatments compared with what seems 'normal'. (Perception issue).

There is an increasing need to help society understand the value of reshaping entire diseases by using *metrics* that will fully capture the value of curative therapies. This helps in making the inevitable trade-offs between short- and long-term health goals, while at the same time providing incentives to prioritize the higher effort (and much greater long-term rewards) of such progress. This approach should be grounded in robust methods, and once the methods are correct, then adjust for factors such as equity, and finally overcome unfounded perceptions of what the answer should be.

Although there may be a sense of urgency to address these questions, the introduction of curative therapies is still a somewhat rare event in healthcare. It is important that these discussions do not preempt the development and evolution of multiple valuation methodologies, as well as the incentives and funding mechanisms for curative therapies. We appreciate that ICER has taken a collaborative approach to broadly engage stakeholders in this dialogue. We also agree that the evolution of the assessment of cures in ICER's framework should be an iterative process allowing for change and adaptations as various stakeholders evaluate and interpret the methods. Strategically ICER should also be looking for solutions to help overcome inherent system bias against longer-term, more uncertain, and less equally shared transformative treatments, since most other agents in health care will likely be incentivized to deliver 'here and now' health care. Done well, ICER can help promote

societally equitable long-term realization of full health for more people, compounded over time, and encompassing multiple generations that more myopic analyses may undervalue.

ICER's initial problem statement contains some indication that the proposed valuation methods development exercise may be at risk of being driven by perception. ICER's proposal articulates that the extremely high value of cures requires *"a solution to the most egregious prices that would otherwise be recommended by traditional cost-effectiveness methods."*¹ This introduces a perspective that the value of curative therapies is already a 'problem' that requires a solution, *even when that value is supported by established methods*. From a value assessment standpoint, it is imperative that the value assessor, in this case ICER, maintain objectivity and ensure impartial scientific methods. In the case of transformative treatments, the methods that HTAs, including ICER, employ to value 'typical' treatments should not be discarded based on a matter of perception and instinct for what health care 'should' cost because our health care system has not yet invented better ways to share the costs and risks of cures. Any new methodologies for the valuation of a potential cure or transformative therapies should not artificially decrease their high estimated value to fit into a preconceived notion of what the 'right' cost should be. We encourage ICER to follow the science of valuation and allow society, stakeholders, and others to debate what might appear to be uncomfortable answers and tradeoffs as a related discussion that is separate from valuation.

It is critical that ICER craft methodologies that accurately capture a curative therapy's value, separate from affordability: this will ensure optimal investment in healthcare which impacts generations to come. With this goal in mind, Amgen's guidance on this initiative focuses on three main recommendations: 1). Ensure a broad, flexible and intuitive cure definition, characterized by longevity and quality of life for present and future patients indistinguishable from that of the general population as the ultimate objective (abandoning the term "single or short-term transformative therapies (SSTs)"; 2). Account for areas where modeling and discounting go directly against empirical findings in human behavior and preferences for curative therapies; and 3). Endorse dynamic methods that capture value fairly over time and place contextual and alternative considerations of value quantified on par with the quality-adjusted life-year (QALY). Below we present our key recommendations in more detail in answer to the issues raised in ICER's proposed adaptations.

1. Defining potentially curative and transformative therapies by durability and outcome achieved

Amgen recommends abandoning the term "single or short-term transformative therapies" (SSTs) and simply referring to cures as "potentially curative or transformative therapies". We appreciate ICER has broadened their proposed definition of cures to be more inclusive. Recognizing that this is a dynamic space that will evolve in the coming years, this definition needs to be intuitive to patients and stakeholders, and durable as it is refined over time. The term "SSTs" introduces a complex and unnecessarily time-bound definition that is confusing and may impede this quest for a unifying set of methods to help stakeholders appropriately value transformative innovations in all of healthcare. Instead of utilizing the term SSTs, ICER should simply call it what it is – potentially curative or transformative therapies and anchor the definition to relevant transformative domains: 1) marked improvement in outcome achieved, and 2) marked increase in durability of effect, as informed by disease experts which will vary by therapeutic area and impacted population. Having a cures definition with valid conceptual underpinnings will support a stronger foundation for the relevant methods, which can then inform the appropriate valuation. Moreover, appropriate terminology will help frame a more balanced assessment and help avoid prematurely diminishing a curative therapy based on the perception of one-time or all-inclusive high prices, timing of payments vs. benefits, and affordability, which are separate from 'value.'

2. Cost and benefits time divergence: eliminate or apply lower discount rates to curative therapies

Discounting should begin when the patient gaining the benefit starts their treatment to avoid discounting intrinsic value for future patients. Most health economic analysis employs discounting for treated individuals starting from the present and discounting over time. A more controversial issue when calculating societal costs and benefits is whether we should speak for current and future generations of undiagnosed patients by discounting the value of benefits they will receive when they are diagnosed in the future. Put another way: if a person somehow knew they were going to be diagnosed with cancer in ten years, how much less would they value a cure being developed today, even if they would not get to use it for 10 years? The perspective of present and future patients both warrant consideration.

While ICER's proposed approach tests both different discount rate values and differential rates, this approach does not address the issue of how to balance the needs of the patients known to us today versus those who will need cures in the longer term. ICER typically models a hypothetical cohort, with limited consideration for a treatment needed in the future. This is a complex area that might not be immediately clear to a lay person or patient, but it is important that patients understand that this approach involving distribution and equity, devalues the curative therapies that patients could need in the next few years. Discounting health is a contentious ethical issue. In fact, the farther in the future this benefit occurs, the more discounting brings the 'current' benefit to zero, with a severe impact on those treatments that have the greatest long term benefits. (We recommend ICER refer to other discount rate research such as environmental economics.^{2,3,4,5})

Non-constant time discounting should be incorporated. Static discount rates developed in 1937 and used by ICER, are out of step with more recent research on discount rates that suggests that individuals apply dynamic discount rates in reality.⁶ Psychology and behavioral economist field experiments have uncovered strong evidence of human 'preference reversals', where individuals prefer x today over y tomorrow, but choose y in a year and a day over x.⁷ Individuals empirically exhibit preferences for dynamically changing discount rates that are not constant, which might for example, echo a hyperbolic pattern of a 1-3% discount rate initially followed by a far lower rate over time.⁸ For specific rates, ICER should at minimum use the latest Treasury Green Book guidance of 3.5% for costs and 1.5% for health benefits for curative therapies.⁹ An accurate discount rate that reflects individual preference is germane to curative therapies to prevent policy that results in disproportionately reduced cure development, especially for younger and pediatric patients.¹⁰ Further, recent research supports a hyperbolic discounting effect (even outside of the market failure characteristic of healthcare) as application of static rates could lead to unpredicted collapse in innovative healthcare resources, in this case with curative therapies. Amgen suggests ICER revisit this.^{11,12}

3. Uncertainty: Ensure methods are objectively applied

ICER should apply real-world evidence and clinical data to alleviate uncertainty and ensure there is not an over-reliance on sensitivity analyses. Just as discounting favors short-term over long-term treatments, using higher uncertainty to reduce value will also work against longer-term treatments and future societal benefits. In fact, discounting and uncertainty used together produce a rapidly compounding effect that highly favors short-term and incremental treatments. Consideration should therefore be given as to whether using both discounting and uncertainty to reduce present value is a form of double discounting. Sensitivity analysis must capture the extent to which discounting and uncertainty assumptions lead to big shifts in realized value to avoid reinforcing short term preferences, including analyses where discounting and uncertainty are assumed to be negligible.

ICER puts considerable thought into uncertainty and proposes several approaches, and then where feasible, does an excellent job of testing these in existing models of CAR-T, SMA, and Hemophilia A. A few additional concerns:

- **For all sensitivity analyses, Amgen recommends ICER simulate only plausible scenarios, not a set of pre-specified analyses.** ICER proposes to test varied assumptions on durability, safety and effectiveness as well as provide analysis at different time horizons. Modeling methods that include extreme and implausible scenarios can lead to incorrect conclusions. For example, ICER's suggestion of varying time periods could lead to incorrect decisions, given the body of economic research that demonstrates that time horizon has an extensive impact on health economic analyses results.^{13,14,15}
- **The assessment of value for curative therapies should be separate from policy paradigms on outcomes-based contracting.** ICER's proposal appears to suggest tying outcomes-based arrangements (OBAs) to probabilistic sensitivity analysis (PSA) results. Layering longer term transformative treatments with more assumptions around payment, on top of the potential for discounting and uncertainty, further clouds the intrinsic value of curative therapies. All of these value modifiers are, in effect, mechanisms that penalize any treatment where the benefits are not matched with the costs at every moment in time, which is in effect, an accounting problem rather than a health outcomes value problem. It is important that ICER maintain objectivity and separation in value assessments and allow payers and other stakeholders to evaluate both intrinsic health outcomes value as well as the potential financial value of outcomes-based contracting based on the resulting health economics. Finally, ICER should also acknowledge the fundamental limitations of PSA, even when uncomplicated by multiple and additive forms of discounting noted above.^{16,17} PSA results even with modest discounting will likely appear to lead to far more uncertain results than an equivalent analysis of a treatment with lower upfront costs and short term returns. So even PSA itself could potentially lead policymakers to incorrect conclusions and poor choices if applied without a high degree of transparency and clarity in communication.
- **Different discount rates should be tested in sensitivity analyses.** ICER's proposed adaptations suggest that a test of differing discount rates in the sensitivity analysis is not necessary, however, as ICER's testing of discount rates has shown,¹⁸ discount rates have a disproportionately large impact on the cost-effectiveness results that would be valuable for any decision-maker to see.

In particular for potential rare disease curative therapies, uncertainty must be appropriately balanced with the need for breakthrough therapies which has necessitated the FDA to deem it is in the public's interest to approve a treatment. Without this consideration, there is greater risk for harm to patients and society. Rather than re-adjudicate the value of trials, new methods for valuing curative therapies should tolerate more uncertainty than might normally be the case. ICER should answer these methods questions and focus on the best ways to extrapolate trial results into the future, by acknowledging signposts of potential future medical value.¹⁹

4. Actively incorporate additional dimensions of value

We urge ICER to actively test and refine approaches to incorporate additional aspects of value for the assessment of cures. ICER's proposed adaptations explore the addition of new elements of value for curative therapies highlighted in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)'s technical brief towards developing a value-framework, but ICER concludes that these cannot be applied empirically.²⁰ In ICER's 2017-2019 Value Framework, the QALY (which has significant limitations) is everything, meaning that it has such a disproportionate impact on an assessment that it eclipses other aspects of value. Although the QALY may be an appropriate starting point given a lack of valid alternatives, it needs to be

heavily supplemented to account for its limitations. Per ICER's current framework guidance, products falling above \$175,000 cost per QALY would automatically be labeled 'low value', hence silencing any role for other elements of value, which are then discussed and considered afterwards by the Panel. This approach confounds the true value of therapies, which would be particularly amplified in the assessment of a cure.

ICER should continue to engage in, and apply findings from its methods research into its assessments, including considering an earlier MCDA type approach with weightings informed by patients/experts.

There is a precedent for ICER conducting research to help inform more accurate and appropriate methods for the capture of alternative dimensions of value. ICER should invest in cure value methods related research similar to ICER's investment in modeling. This should be accompanied by other major changes in both ICER assessments and their engagement with stakeholders, independent panel composition, and voting processes. We recommend ICER re-attempt multi-criteria decision analysis (MCDA), embedding it earlier in the process, with patient / expert input data to inform the relative rankings of the criteria rather than the panel's implicit vote.²¹ Thus, ICER should incorporate novel elements of value into the base-case of every cure assessment. Additionally, ICER should encourage manufacturers and academic groups to generate appropriate evidence of novel elements of value for curative therapies prior to an ICER assessment, incorporating them into the base case.

5. Economic Surplus: Focus on curative therapy assessment, leaving surplus to policy makers

Rather than focusing on economic surplus, incorporate the natural reductions in price resulting from competitive entrance and loss of exclusivity (LOE) into models. Full valuation of potential curative therapies may result in prices that seem high to some, but will ensure that we are not potentially mortgaging future cure discovery by succumbing to inappropriate pressure to discount the most transformational aspect of curative therapies: future outcomes. ICER suggests that *"Transformative treatments offer the potential for magnitudes of health gain and /or cost offset that raise concerns that traditional cost-effectiveness methods will allocate too much of the economic surplus to innovators and will assign fair prices to transformative treatments that are manifestly unaffordable in the near term"*²² This has not been supported by research into consumer surplus nor in empirical research.^{23,24} As an empirical example, in research analyzing consumer and producer surpluses for HIV/AIDS drug therapies in the late 1980's onwards, innovators appropriated only 5% of the social surplus.²⁵

CONCLUSION

There are approximately 20,000 diseases today, but most do not have cures and lack treatments.²⁶ Current development of treatments consists of chronic and/or symptomatic therapy but rarely involves a curative aspect, wherein morbidity and mortality are eliminated. Curative therapies, first and foremost, are cures for *society*, allowing subsequent generations to live free from the threat of morbidity and mortality from disease. These need to be recognized for the life changing value they bring. When a cure goes off patent, the price radically declines with biosimilar and generic competition, as is often the case for non-curative treatments. The correct approach to valuing a cure begins with having correct methods, and then adjusting for matters such as equity and distribution and overcoming issues with perception of what the 'right' answer should be. ICER should ensure a broad, intuitive and flexible cure definition. This definition should represent the value of a cure characterized by longevity and quality of life for present and future patients equivalent to the general population as the ultimate objective. It should account for areas where modeling and discounting go directly against empirical findings in human behavior and preferences for curative therapies. It is important that ICER incorporate methodologies that reflect value fairly over time, placing contextual and alternative considerations of quantified value on par with the QALY with the goal of more inclusive and representative decision-making processes.

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To Whom it May Concern:

The American Society of Gene and Cell Therapy (ASGCT) welcomes the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) proposed value assessment framework adaptations for single or short-term transformative therapies (SSTs). ASGCT is a professional membership organization representing over 3,000 individuals, including scientists, physicians and other professionals in gene and cell therapy, working in settings such as academic institutions, hospitals, and biotechnology and pharmaceutical companies. Many of our members have spent their careers in this scientific field performing the underlying research that has led to today's robust pipeline of transformative therapies.

A core portion of the Society's mission is to advance the discovery and clinical application of genetic and cellular therapies to alleviate human disease. To this end, while ASGCT does not endorse any individual pharmaceutical company pricing decisions, the society supports adequate reimbursement to providers and the enabling of value-based and payment-over-time models in order to foster patient access.

We appreciate ICER's attention to the differences between SSTs and currently available therapy options for patients. In many cases, SSTs under investigation will be the first therapies with the potential to impact the underlying cause of a disease, rather than simply treating its symptoms and co-morbidities. In others, SSTs will provide long-term benefit without burdensome treatment regimens or side effects that can profoundly impact the lives of patients and their families. These fundamental benefits of SSTs warrant consideration during economic review. Our comments will focus on the high-level impacts of the proposal on the field of gene and cell therapy and the patients who could benefit directly from the SSTs our members have spent their careers advancing.

Determining those treatments for which adapted assessment methods will be used

ASGCT supports ICER's proposal that both "*potential cures* that can eradicate a disease or condition" and "*transformative therapies* that can produce sustained major health gains or halt progression of significant illness" that are given through a single intervention or short-term course of treatment be eligible for the adapted SST value assessment. Both types of products have great potential for patient and caregiver benefit and warrant special consideration during economic assessment.

The Society appreciates that ICER will review available information from stakeholders regarding the nature of a treatment to make a preliminary judgment whether it should be considered as an SST. We would recommend specifically adding scientific experts to the list of stakeholders with which ICER will seek consultation during this process to assure that their significant technical understanding is reflected in the assessment of new therapies.

Assessing and Describing Uncertainty

Food and Drug Administration (FDA) approval of any new drug or biologic product reflects a scientific determination that the product is safe and effective, or reasonably likely to produce clinical benefit.¹ More information about a product will always be gathered the longer it is on the market and the more patients are exposed, irrespective of whether the product is a conventional drug or an SST. Given that uncertainty is not unique to SSTs, and that SSTs are subject to the same FDA approval standards as conventional products, we are concerned about ICER's underlying presumption that uncertainty about SSTs at the time of approval warrants greater consideration in economic assessments than conventional products.

We do, however, agree that the uncertainty surrounding SSTs has differential impacts on providers, payers, and patients. In the case of a conventional product, more data collected over time will impact the practice of health providers and market forces for payers, of both current and future patients. In the case of SSTs, administered only once or a few times with accompanying upfront costs, greater data can only have an impact on future patients' providers and payers under traditional payment models. We therefore support ICER's proposal for greater discussion of alternative payment model structures in the new proposed "Controversies and Uncertainties" section for all future ICER reviews. ASGCT supports enabling value-based and payment-over-time mechanisms that allow for future risk sharing based on the durability and product performance for individual patients.

ASGCT agrees with comments submitted during the open input period which suggest that as the amount of data supporting a product grows, there should be a formal process to allow for

¹ 21 USC 355, 21 USC 356(c)(1)(A)

an economic reanalysis. We recommend that if ICER chooses to adopt the proposal to provide incremental cost-effectiveness analyses at multiple time horizons of potential benefit (e.g. longest clinical trial follow up data, 5 years, 10 years, and lifetime), it should also build in a reassessment of the cost-effectiveness analysis at set time frames after approval. ICER's proposed changes to the current evaluation model allow for uncertainty at the time of drug approval to negatively impact the analysis, but do not provide a mechanism for greater information to favorably impact the analysis over time. Additional follow-up data may also provide important information regarding impacts to patients, in addition to the durability of therapy, which may impact the analysis (discussed further below).

Additional Elements of Value

Delay of Treatment

The potential harms associated with delay of an effective therapy should be given greater consideration in the proposed new domain of "potential other benefits and disadvantages." As is discussed by Towse and Fenwick,² "[d]elaying adoption while waiting for long-term evidence has the challenge that patients who can be expected to benefit from the treatment will be denied access and the potential health losses are high." While this proposed new domain considers the potential advantage of the choice of an SST with differential risks and benefits from current standards of care and the risks of precluding treatment with future therapies, it does not specifically address the disadvantage of delay.

Many genetic diseases are progressive, and the longer patients wait for a treatment, the more potentially irreversible damage may be done. For example, new SSTs, whether curative or transformative (per ICERs proposed definitions), may only be able to preserve a patient's quality of life at the time of treatment but not fully reverse the course of a disease or correct associated co-morbidities. Therefore, delays in receiving treatment will reduce the potential positive impact of such SSTs. In addition, delaying access to an SST prolongs the negative aspects of current standards of care (e.g. time and economic burdens associated with hospitalizations, infusions, inability to attend work or school, poor outcomes, side effects). While standards of care have more data to support their use and outcomes, the potential improvements over standards of care SSTs may provide, especially on patients' lives, warrant strong consideration during economic assessment.

² Towse A, Fenwick E. Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment? *Value in Health: Journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2019;22(6):677-683

Scientific Impacts

ASGCT believes that the impact on future innovation is an important element of value for SSTs, especially in this early time. Treatments that provide a novel mechanism of action may lead to other more valuable therapies in the future—scientific spillovers—that should be considered for novel types of SSTs.

Underestimating the potential of new therapies will have a chilling effect on further scientific innovation in this field. The discovery and application of scientific breakthroughs merit the assignment of additional value. Encouraging the development of treatments for diseases with great unmet need, such as the many rare diseases that may be treated by innovative SSTs, through acknowledgment of the additional value of novel treatment mechanisms is key to continued scientific and medical progress.

Rationale for Considering Additional Elements of Value

ICER states it is not considering additional, more qualitative elements of value, such as scientific spillover, in part because they are unidirectional and will only adjust the value upward. The assumed directionality of effect should not be a factor in determining whether an element is worthy of inclusion in a value assessment. In addition, whether these elements will always add value is uncertain since the long-term impact on qualitative patient metrics for SSTs is not yet fully known.

An additional reason ICER identifies for not using additional elements of value is that methods for measuring them consistently across different types of treatments are not mature. However, value assessment methods in general measure constructs that are difficult to measure and contain subjective, somewhat arbitrary quantitative value assignments. For example, it is not straightforward to compare a year of full health to, for example, a year living with vision loss of varying degrees across individual patients. The subjective nature of some assessments limits the utility of QALY as an assessment tool for accurately determining the value of SSTs. However, since ICER does attempt to quantify value through rather subjective mechanisms in general, the Society would encourage improvement of assessment through quantification of additional elements of value to more fairly and comprehensively assess value of SSTs.

Conclusion

We appreciate ICER's consideration of how value assessments can better reflect the changing and improved nature of new treatment technologies in order to encourage patient access to these transformative treatments. We know from the limited number of products currently approved by the FDA that meet ICER's SST definition, that payers have erected barriers to patient access to delay or deny treatment, often for the patients who could most benefit from

an SST. We believe the consideration ICER is affording SSTs as science continues to produce innovative products is a positive first step. We look forward to working with you on continued adaptations to the framework to benefit the patients and families for whom we are all working to improve care. Please let us know if you have questions, by contacting the ASGCT Executive Director, David Barrett, at 414-278-1341, dbarrett@asgct.org.

Sincerely,

A handwritten signature in black ink, appearing to be 'Gao' with a stylized flourish.

Guangping Gao, PhD
President



American Society for
Transplantation and Cellular Therapy

Institute for Clinical and Economic Review
Steven D. Pearson, MD, MSc, President
Two Liberty Square Ninth Floor
Boston, MA 02109

September 6, 2019

Dr. Pearson:

The American Society for Transplantation and Cellular Therapy (ASTCT) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) proposed changes to the 2020 Value Assessment Framework. ASTCT continues to report on the value framework in relation to Chimeric Antigen Receptor T-Cell (CAR-T) Therapy. ASTCT is a professional membership association of more than 2,200 physicians, scientists, and other health care professionals promoting blood and marrow transplantation and cellular therapy through research, education, scholarly publication and clinical standards. The clinical teams in our society have been instrumental in developing and implementing clinical care standards and advancing cellular therapy science, including participating in trials that led to current the Food and Drug Administration (FDA) approvals for CAR T-cell therapy.

Hematopoietic cell transplantation (HCT), also known as stem cell transplantation (SCT), is a medical sub-specialty comprised of physicians with Board Certifications in Internal Medicine, Medical Oncology, Pediatrics, Hematology and/or Immunology. Due to their unique clinical expertise and training, ASTCT member clinicians and cellular therapy programs are currently the primary individuals and teams initially providing CAR-T to patients in need of treatment. We anticipate that CAR-T is the first of many engineered cellular therapies to be approved in the coming decade.

ICER's method for defining single and short-term transformative therapies (SSTs) is a useful approach in considering alternative methods for potential cures. At ASTCT our work focuses on the development of gene and cellular therapy and delivering new innovative technologies that are FDA approved and soon to be approved. These new therapies not only transform the lives of patients who receive them, but also have the potential to be curative treatments. ICER's adaptive assessment methods will take into consideration the ability providers have to administer life altering treatments.

ICER proposes cure proportion modeling for evaluating uncertainty from evidentiary limitations. ICER notes that this type of modeling might be beneficial in analyzing survival data where some patients may be cured or benefit from a complete halt in the progression of serious illness. While ASTCT agrees that it is important to have standards for evidentiary limitations, for therapies such as CAR-T, there is still such limited data available because of its newness and innovative nature that there may be some instances where modeling or providing a scenario analysis similar to other approaches would be limiting for such therapies.



American Society for
Transplantation and Cellular Therapy

As ASTCT has noted before in its previous letter on the ICER CAR-T specific draft evidence report, the value of this potentially curative therapy cannot be understated and we must be careful to not limit its potentially curative abilities based on cost-effectiveness scenarios. We continue to maintain the position that an evaluation of CAR-T is premature at this time given the limited clinical and financial data available. While there are now more centers offering CAR-T therapies to patients, this therapy still has the lowest adoption rate among oncology treatments. The low adoption rates have led to insufficient and inaccurate data for these therapies.

ASTCT is interested in value based pricing for therapies but wants to make sure we are still advocating for the best therapy available for patients. ICER's proposal of "Long-term Cost-Effectiveness" is a beneficial way to include stakeholder input on alternative model structures' limitations and difficulties in existing data. This is important for therapies such as CAR-T given the limited data currently available. Additionally, cost-effectiveness as a guide for value-based pricing to promote a shared savings among innovators and the health care system is an interesting approach to SSTs. While ASTCT is supportive of cost saving measures, we are also concerned with potential limitations on innovation and the ability for more therapies to be readily available for patients in need. We welcome the opportunity to learn more about this proposal and how it would apply in reference to these therapies.

ASTCT is grateful for the opportunity to provide input to the proposed changes for the 2020 Value Assessment Framework. ASTCT leaders, member clinicians, and policy staff are always available as a resource. Please do not hesitate to reach out whenever we may be of assistance.

Sincerely,

A handwritten signature in black ink, appearing to read "Navneet Majhail".

Navneet Majhail, MD, MS
Director, Blood and Marrow Transplant Program, Cleveland Clinic
President, American Society for Transplantation and Cellular Therapy



Via Electronic Submission:

September 6, 2019
Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA
RE: Valuing a Cure Proposed Adaptations

Dear Dr. Pearson,

Bayer HealthCare Pharmaceuticals (Bayer) appreciates the opportunity to comment on the recently announced set of proposed adaptations for assessments of single or short-term transformative therapies (SSTs), as part of ICER's *Valuing a Cure* project.

Bayer is a global enterprise with core competencies in the Life Science fields of health care and agriculture with nearly 25,000 employees in 30 sites across the United States. Our products and services are designed to benefit people and improve their quality of life. At the same time, we aim to create value through innovation and are committed to the principles of sustainable development and to our social and ethical responsibilities as a corporate citizen.

We appreciate the opportunity to provide feedback on this project, given that we are currently investigating pipeline products that, if successful, would be classified as SSTs. Our comments below address three crucial items outlined in the *Proposed Adaptations for SSTs* project draft methods and technical brief.

I. Section 2.4 Assessing and describing uncertainty: Probabilistic sensitivity analysis (PSA) linked to policy recommendation for outcomes-based payment

We have concerns with ICER's proposition to recommend outcomes-based contracting as the preferred method of payment for all therapies exceeding an incremental cost-effectiveness ratio of >\$200,000 per QALY in at least 25% of PSA scenarios.

It is essential for ICER to recognize that there is a multitude of alternative payment models (eg, annuity-based arrangements, risk pooling, etc) that should be considered outside of outcomes-

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September 6, 2019

Todd Williamson
Vice President
Data Generation and
Observational Studies
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based payments.¹ The NEWDIGS FoCUS consortium, which works to address the need for novel financing and reimbursement models for durable and potentially curative therapies, argues that “*one size does not fit all*” when considering financing solutions for potentially curative therapies, and “*a precision financing toolkit is required.*”¹ The selection of appropriate payment methods for SSTs should therefore be tailored to consider the size of the target population, nature of clinical benefit, durability of effect, therapeutic modality, and delivery setting.¹

In circumstances where it is determined that an outcomes-based arrangement may be the most appropriate payment method, there are a myriad of additional factors that must be considered alongside the incremental cost-effectiveness ratio. Specifically:

- Outcomes-based contracting requires payers to have support from appropriate data infrastructure, without which the feasibility of measuring outcomes can be nearly impossible.²
- Some endpoints that demonstrate efficacy of treatment may not be easily measureable within a limited, pre-defined time frame.^{2,3}
- Risks associated with outcomes-based contracts can vary greatly based on payer preferences.³
- The ability of a payer to transfer liability of an outcomes-based contract to another payer in the event that the patient changes health plans.

Moreover, the literature supporting the use of an incremental cost-effectiveness threshold to direct the uptake of an outcomes based payment is conceptual, not evidentiary. Indeed, Kaltenboeck and Bach (2017), cited by ICER in the Technical Brief, note that “*Policymakers should not dive into this pool; we propose a toe in the water at most.*”⁴ ICER itself notes in the proposed SST adaptation document (page 6) that “*there is no principled way to decide how to select the specific threshold for this kind of uncertainty criterion*” belying the proposed approach.⁵

- **Recommendations:**

- We urge ICER to consider all available payment methods outside of outcomes-based arrangements in its policy recommendations to account for the diversity of patients and conditions and the heterogeneity of the treatment landscape.
- Payment method decisions should not be based solely on the incremental cost-effectiveness ratio. There are numerous, equally relevant, factors that must be considered on a case-by-case basis by health plans.
 - Any decision to pursue an outcomes-based contract must consider the

influence of other important factors on the feasibility of implementing outcomes-based contracts, such as payer price sensitivity, payer risk tolerance, time to reach outcomes of interest, duration of treatment efficacy, money-back guarantee arrangements, and infrastructure capability to monitor outcomes appropriately.¹⁻⁷

- Finally, when evaluating the incremental cost-effectiveness thresholds and PSA scenarios, a range of options should be considered since there is no definitive precedent for the \$200,000 per QALY threshold or the 25% threshold. Both should be inclusive of a broader range to accommodate differences that may occur in a real-world setting.

II. Section 3: Additional elements of value

We previously recommended that ICER should consider additional elements of value unique to curative therapies.⁸ We appreciate that ICER has proposed the inclusion of two additional domains of “potential other benefits or disadvantages” as a step toward a more complete representation capturing additional elements of value.

- ***Recommendation(s):***

- As previously noted in earlier communications with ICER:
 - We reemphasize our recommendation that these additional elements of value be summarized in a table or graphic side-by-side with the comparative effectiveness, long-term value, and short-term affordability evidence to provide a comprehensive description of value as part of the Report-at-a-Glance.
 - This format would allow readers to readily view and interpret key determinants of value of an intervention as a whole rather than in silos.
 - Any summaries must also be inclusive of the full range of values estimated under varying assumptions to ensure full transparency of the uncertainty underlying them.

III. Section 5.1 Affordability and fair sharing of economic surplus

We have concerns with ICER’s proposal to conduct a “shared savings” scenario analysis for SSTs as an adjunct to the base case. Several of the concerns are related to the 12-year time frame that ICER proposed for its model.

A main concern is that this shared savings scenario analysis will not adequately demonstrate long-term economic benefits for SSTs. All benefits after year 12 are assumed to be zero in the shared savings scenario analysis to approximate the shift of benefit to the healthcare system. In doing so, many of the long-term economic benefits associated with SSTs (e.g., extension of life, ability of a child to reach adulthood, sustained long-term major health gains, costs of chronic therapy avoided, etc.), will be excluded from the shared savings scenario analysis. Therefore, the shared savings scenario will ignore the downstream costs avoided due to these important health benefits and likely underestimate the “true” economic benefit of SSTs when evaluated in a cost-effectiveness model. Additionally, the shared savings scenario does not consider the value of therapies that are used in disease states where the impact on the health system is not fully realized until after the 12-year mark, nor does it account for payment arrangements where manufacturers offer a money-back guarantee.

Recommendations:

- We urge ICER to reconsider the time frame included in its shared savings scenario analysis to more appropriately reflect the long-term benefit and downstream savings of SSTs.
 - The 12-year period appears to be an arbitrary cutoff based on several assumptions, so ICER should consider presenting a range options (eg, 12 years, 15 years, 20 years, 30 years) to more accurately simulate the economic benefit from the societal perspective.
- To best communicate results of a shared scenario analysis we recommend that ICER adopt a graphical format, similar to ICER’s graphic for potential budget impact scenarios, which includes analyses over ranges of several parameters. This graphic will offer stakeholders a meaningful source of information that is inclusive of varying parameters which can be readily utilized to inform decision making that are more relevant. Variations across the following parameters should be captured in the graphic:
 - Loss of exclusivity by year post-launch
 - Price of product
 - Cost-per-QALY threshold
 - Percentage of probabilistic sensitivity analysis (PSA) simulations that have incremental cost-effectiveness ratios below a given threshold

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Page 5 of 6

We greatly appreciate the opportunity to provide feedback on the *Valuing a Cure* project, and look forward to working with ICER to ensure access to needed medications and improved patient care.

Kind regards,

Todd Williamson, MSc

Vice President, Data Generation & Observational Studies,

Bayer HealthCare Pharmaceuticals Inc.

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8. Bayer Comment Letter. June 10, 2019. ICER 2020 Value Assessment Framework Open Input.

September 6, 2019
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Submitted via email to publiccomments@icer-review.org

RE: Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs) Proposed Adaptations to the ICER Value Assessment Framework

The Blue Cross Blue Shield Association (“BCBSA”) appreciates the opportunity to provide comments on ICER’s document, *Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs) Proposed Adaptations to the ICER Value Assessment Framework*, which was released for comment on August 6, 2019.

BCBSA is a national federation of 36 independent, community-based, and locally operated Blue Cross and Blue Shield Plans that collectively provide healthcare coverage for one in three Americans. For more than 80 years, Blue Cross and Blue Shield companies have offered quality healthcare coverage in all markets across America – serving those who purchase coverage on their own as well as those who obtain coverage through an employer, Medicare and Medicaid.

ICER Proposed Value Framework Adaptations for SSTs

BCBSA acknowledges and supports ICER’s interest in careful assessment of single or short-term transformative therapies (SSTs), given the recent approvals of gene therapies and cellular immunotherapies, as well as those in the near-term pipeline.

We provide the following commentary as it pertains to the draft document:

- **Selection Process for Use of the SST Framework:** The selection process for therapies that will be evaluated as SSTs will be critically important. We ask that ICER further define a ‘short-term course’ by either specific timeframes or by providing a clinical care episode framework (i.e. a single point of directed intervention within a longer series of clinical events). We acknowledge that each therapy will also have a scoping period and opportunity for stakeholder commentary, but suggest that it may be useful to have general boundaries that allow for filtering of potential topics.
- **Definition of SSTs:** More clarity is needed in regards to the subcategories of SSTs proposed. “Potential cures that can eradicate a disease or condition” needs augmentation around the type of disease or condition. One would presume the types of diseases or

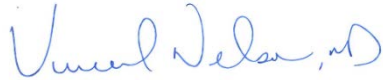
conditions in question would be near-term life-threatening or severely debilitating, or those that would cause a life-long significant disability (i.e. blindness) if left untreated, but that specification is not provided in the current description. In the materials, ICER also seems to identify only biologics as SSTs, vs. other types of clinical interventions (surgeries, vaccines) that may result in the same types of health gains stipulated in the proposal. If ICER means to specifically focus on drugs as SSTs, as presumed by the framing of the document, additional clarity should be provided.

- **Incremental Cost-Effectiveness Scenarios at Multiple Time Horizons:** We appreciate ICER's identification of various time horizons being important to different stakeholder groups. We suggest that ICER consider providing the scenario results at years 1-10, in addition to the time point standards of lifetime and the longest real world follow-up data point. This would give healthcare purchasers and payers additional information that could be considered in the context of the specific patterns relevant to that stakeholder. These include annual Medicaid budget considerations, 2-3 year member shifts across commercial payers and variable rates of movement of employees across job sectors.
- **Additional Dimensions of Value:** We appreciate and support the additional dimensions of value discussion outlined in the Technical brief. We suggest that ICER may also take into consideration potential downsides associated with receiving the first transformative therapy in a field, in that individuals treated with such a therapy may not be able to receive subsequent therapies and that those subsequent therapies may utilize improved clinical platforms resulting in improved effectiveness, durability and safety.
- **Controversies and Uncertainties:** We support the addition of this section and encourage a listing of unanswered questions identified during the analysis within this portion of the report.
- **Value of Long-Term Data Tracking:** Modeling of long-term benefit, clinical services utilization and durability of effect are core to ICER's scope, yet we do not see any overt discussion in current analyses of the long-term data tracking mechanisms associated with therapies and the value those data tracking mechanisms bring back to patients, clinicians and payers. The information gleaned from these data mechanisms can inform the way individuals are treated and validate or disprove initial projections; therefore, the anticipated value of the information that may come from tracking a disease state or therapy is something that needs additional consideration. Those therapies with a robust data collection strategy or that will be integrated into an established mechanism may bring additional future value to the larger network of healthcare stakeholders than those that simply fulfill FDA post-market reporting requirements. We ask that ICER consider a way to assess and integrate the potential value of known or planned data-tracking mechanisms into the value framework.
- **Modeling Techniques:** We were unable to gather additional specific feedback from the BCBS companies on the technical modeling adaptations proposed due to the limited timeframe allowed for comment submission. We would recommend that ICER consider issuing a 'preview' document in advance of formally opening technical framework

comment periods so that stakeholders can view areas of interest to ICER and begin assemblage of relevant working group members in advance of the specific proposals being published.

Thank you for the opportunity to provide comments on the draft proposal. We would be pleased to discuss our comments with you at your convenience. Questions regarding these comments can be directed to Stephanie.Farnia@bcbsa.com.

Sincerely,



Vincent Nelson, MD
Vice President
Office of Clinical Affairs



Lisa Mostovoy, PharmD
Executive Director, Clinical Value
Office of Clinical Affairs

September 6, 2019

BY ELECTRONIC DELIVERY

Steven D. Pearson, M.D., M.Sc., FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Proposed Adaptations to the ICER Value Assessment Framework For “Single or Short-Term Transformative Therapies” (SSTs)

Dear Dr. Pearson:

We are writing on behalf of the Biotechnology Innovation Organization (BIO) to provide comments on the Institute for Clinical and Economic Review’s (ICER’s) solicitation for input on draft revisions to its Value Assessment Framework for the assessment of “single or short-term transformative therapies” (SSTs). BIO is the world’s largest trade association representing biotechnology companies, academic institutions, state biotechnology companies, 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 have also reduced health care expenditures due to fewer physician office visits, hospitalizations, and surgical interventions.

We appreciate ICER’s recognition that the burgeoning field of transformative and curative therapies requires serious discussion around how these treatments are valued by not just payors, but society at large. These therapies have the potential to fundamentally change how we view the treatment of disease. Yet as we strive to shift our health care system to one that rewards valuable care, BIO is concerned that the science of value assessment for all therapies – not just those that are curative or transformational – is woefully behind where it should be for these tools to be used in a substantive way.

BIO has commented previously on our concerns with the methodology of ICER’s value framework, and we have proposed both substantive and process-related changes that would be needed for these assessments to accurately capture a therapy’s value. Although ICER has attempted to incorporate more contextual considerations into its value framework, its fundamentally flawed structure remains the same: a direct cost effectiveness model that does not capture the societal perspective and other critical value components.

As ICER refines and modifies its value assessment framework, we encourage the organization to recognize that the science and methods around value assessment are not settled and broadly agreed upon by all stakeholders. The fact that ICER engages in regular updates to its value framework evidences the dynamic nature of how we understand value assessment. We recommend ICER work to better communicate the fact that the science of value assessment is not static and incorporate *that* as a fundamental aspect of ICER’s work. In this way, ICER can be a partner in working with all stakeholders in advancing the science and methods of value assessment, and not simply dictate what those methods should be.

Below, please find our comments on the specific revisions ICER proposes when assessing SSTs. We note that for some of these changes that are proposed for both the SST modifications, as well as ICER's standard value framework methodology update, we may provide additional comments in our subsequent comment letter on the 2020 modifications.

Section 1: Determining those treatments for which adapted assessment methods will be used

1.1 ICER will use an adapted approach to value assessment for "single and short-term transformative therapies" (SSTs). These are defined as therapies that are delivered through a single intervention or a short-term course of treatment that demonstrate a significant potential for substantial and sustained health benefits extending throughout a patients' lifetimes. SSTs include two subcategories:

- *Potential cures that can eradicate a disease or condition; and*
- *Transformative therapies that can produce sustained major health gains or halt the progression of significant illness*
- ICER should provide clear and transparent inclusion/exclusion criteria around how the SST framework will be applied. Terms such as "transformative," "substantial," and "sustained" are inherently subjective. While we understand that whether to apply the adapted approach will be debated during the open input and scoping document process, we believe it should be evidently clear ahead of time when a therapy will be assessed using the modified framework.

Section 2: Assessing and describing uncertainty

2.1: Cure proportion modeling

- We support the adaptation that allows for cure proportion modeling for SSTs. This method better captures patient heterogeneity and is better aligned with the current science of value assessment.
- We also note that while survival data may present an important opportunity to adjust model fit for therapies that cure disease, other patient-relevant outcomes could be used to better predict model fit for non-life-threatening chronic diseases. We encourage ICER to explore ways to expand on this adjustment for these types of conditions.

2.1: Incremental cost effectiveness scenarios at multiple time horizons

- We support the retention of the lifetime horizon as the base case for the value-based price benchmark.
- However, we are concerned that ICER will conduct CEAs using multiple time horizons, and specifically with how ICER will present these analyses to the public.
- This issue illustrates our concerns with ICER conducting assessments of products that have not yet or just recently come to market. The data manufacturers use to

obtain FDA approval of a product serve a very distinct purpose: to demonstrate the product's safety and efficacy. The same data cannot be used in isolation to support the product's value assessment.

- We recommend ICER explore ways to make this distinction clear to avoid confusion. Analyses at the longest follow-up data available, 5, and 10 years may indeed be of interest to stakeholders as a thought experiment. But they should not be misinterpreted as the product's actual value proposition. At a minimum, we recommend limiting these analyses to the body of the report and not include them as part of the Report-at-a-Glance or related summary material.

2.3: Introducing a new economic review section on "Controversies and Uncertainties"

- We support the consolidation and addition of a section in ICER's reports that explores the inherent uncertainty in conducting value assessments – in both assessments for SSTs and for all ICER reports.
- Material in this section should be summarized and included prominently in the Report-at-a-Glance.
- We recommend this section include a discussion around the difficulties in developing a single incremental cost-effectiveness ratio for a treatment, given the many modeling assumptions and uncertainties used to produce the cost-effectiveness and value-based price benchmarks. In this section, we encourage ICER to present multiple plausible incremental cost-effectiveness ratios.
- ICER should provide clarification related to how material will be chosen for this section (e.g. Will appraisal committees vote on what constitutes a "controversy"? Will alternative models from manufacturers whose products are under review be automatically included if submitted?).

2.4: Probabilistic sensitivity analysis linked to policy recommendation for outcomes-based payment

- Including a recommendation related to how payors should finance a product ignores the complex legal and regulatory barriers to executing outcomes-based payments.
- The selection of 25% or more PSAs at or above \$200,000/QALY is arbitrary and has no scientific basis.
- Making these recommendations is outside of ICER's purview. Without policymakers addressing the barriers to these types of payment arrangements, recommending their adoption may needlessly complicate both payors and manufacturers ability to enter into them.
- There are many different potential options for outcomes-based agreements, with implications for cost-effectiveness as well as short and long-term administration and operationalization. ICER is not in a position to make judgements or recommendations about these elements of outcomes-based contracts.

Section 3: Additional elements of value

3.1: Addition of two domains of “potential other benefits and disadvantages” for voting by appraisal committees:

(1) A potential advantage for therapies that offer special advantages by virtue of having a different balance or timing of risk and benefits versus other treatments; and

(2) a potential disadvantage for therapies that, if not successful, could reduce or even preclude the potential effectiveness of future therapies.

- We are encouraged that ICER has acknowledged the existence of additional domains of value that will be voted on by the appraisal committees. However, we are deeply concerned that these elements will not be integrated quantitatively into the assessment of SSTs or therapies being assessed under ICER's standard value framework.
- ICER's concern with more substantive incorporation of these benefits appears to rest on the opinion that these concepts are “exploratory” and “lack any consensus among academic health economists.” However, as an entity engaged in value assessment, ICER has a duty to advance a discussion around methods, not simply throw up its hands in the face of a spirited debate.
- We also note that while there may be ongoing discussion about how these elements of value should be included, concepts such as the value of hope, real option value, insurance value, equity value, etc., have been the subject of significant academic research and peer-review study. The same cannot be said, however, of some of the concepts ICER proposes to introduce in the modification of its framework for SSTs. While ICER offers rationales for its choices of 25% of PSAs above \$200,000/QALY (see comment above) or for the entire concept of its “shared savings” scenario (see comment below), we are not aware of any robust scientific discussion of these concepts' inclusion in value assessment.
- We encourage ICER to further explain why these untested and arbitrary concepts should be included in its SST framework while other, more robust, concepts should be discarded entirely.

Section 4: Time Divergence Between Costs and Benefits

4.1: Discounting: ICER proposes to continue its use of a 3% discount rate as standard for both costs and outcomes

- We believe the nature of these therapies requires a smaller discount rate than is used for traditional therapies, given that the level of analysis will be over the lifetime of the patient.
- Using the same discount rate for traditional therapies underestimates the uncertainty of the outcome for these therapies to make outcomes comparable across disease areas and indications.

- We recommend ICER be more flexible in setting discount rates for these therapies. At a minimum, assessments of SSTs should explore the impact of divergent discounts rates for these versus other therapies so that stakeholders can see the impact and understand its implications.

Section 5: Affordability and Fair Sharing of Economic Surplus

5.1: ICER will develop a “shared savings” scenario analysis for SSTs as an adjunct to the base case. Cost offsets in this scenario will accrue to the innovator for the first 12-year period in the model, and thereafter cost offsets will accrue to the health system generally.

- We are deeply concerned with the inclusion of this new scenario analysis and recommend ICER refrain from including it in the SST framework until further stakeholder input and methodological concerns can be addressed.
- As noted above, the selection of a 12-year exclusivity period is arbitrary. If interpreted strictly by payors, this scenario analysis would penalize manufacturers that develop products with durability of benefit that falls outside of ICER’s artificial range.
- Assigning 100% of cost offsets to the health system after 12 years also ignores the incremental, dynamic nature of innovation.
- We note that in its standard framework, ICER declined to make assumptions about the loss of exclusivity, even when there is a level of certainty that the product under evaluation will encounter patent expiry during the model time horizon, asserting that this component is “difficult to estimate.” We find it contradictory to make assumptions about the timing of loss of exclusivity and the supposed lack of generic competition for these technologies in the context of this “shared savings” scenario analysis.
- Concepts such as the assignment of economic surplus are political questions that should be resolved openly and transparently through the political process. We believe ICER is an inappropriate venue for such decision-making.

Dr. Pearson
September 6, 2019
Page 6 of 6

Conclusion

If you have any questions regarding our comments or if we can be of further assistance, please do not hesitate to contact us at (202) 962-9200.

Sincerely,

/s/

Crystal Kuntz
Vice President
Healthcare Policy and Research



September 6th, 2019

Dear Dr. Steve Pearson,

Thank you for the opportunity to comment on the Proposed Adaptations to the ICER Value Assessment Framework for Single or Short-Term Transformative Therapies (SSTs), which will complement and build on the overall ICER value assessment framework.

In this letter, we provide direct feedback on ICER's proposed adaptations and comment on ICER's value assessment approach more generally, including for SSTs. Biogen values credible, reliable scientific and economic evidence that is based on robust and extensive data packages, valid assessment methodologies, and meaningful input from subject matter experts and patient communities. High-quality evidence and robust analyses are most useful when they are inputs into a rigorous value assessment framework that captures and appropriately values all important benefits of treatment. Biogen feels this is where the current ICER approach continues to fall short.

Biogen believes that value assessment and CEA are important tools for understanding the benefits and risks of treatment to patients. **As ICER considers updates to its overall value assessment framework and adaptation for SSTs, it should consider making critically important updates to its current approach, which is too heavily reliant on the point-estimate conclusions of formal cost-effectiveness analyses, without appropriate acknowledgement of uncertainty, patient outcomes not captured by the QALY, or benefits of treatment that extent to broader society.**

After careful review, we believe that the ICER proposals miss an opportunity to address these important limitations within the current value framework, especially for SSTs. The proposed adaptations focus on several narrow technical issues. Biogen believes a more fundamental consideration of the SST value framework is required, including consideration of the quality of evidence and alternative value frameworks that go beyond cost-effectiveness threshold analyses.

Our key comments and recommendations for each of ICER's proposed adaptations for the assessment of SSTs are as follows:

1. The definition of "SST" is important as adaptation of methods for different types of therapies will lead to differences in what elements are considered in an assessment and in turn can affect ICER recommendations. We recommend that ICER more clearly define the term "SST", including with objective and quantifiable criteria where possible, so that all stakeholders are aware of how this definition impacts assessment and ultimately how assessments will impact payer recommendations.
2. The adapted methods do not address a key concern regarding the use of the Evidence Ratings Matrix and level of evidence uncertainty within an SST value

- assessment. We recommend that ICER revisit the evidence ratings matrix and the application of this matrix within the adapted value assessment framework for SSTs.
3. Additional elements of value in the proposed adaptations are important, however, the focus on a narrow cost effectiveness assessment framework has resulted in methodological inflexibility. We recommend that ICER consider methods and approaches that extend the assessment framework to capture quantitative and wider aspects of value such as caregiver burden and productivity.
 4. The approach to uncertainty outlined in the proposed adaptation is too narrowly focused on describing uncertainty within a cost effectiveness analytical setting. We recommend that a broader methodological focus on uncertainty, including uncertainty with regards to efficacy and safety, is considered with recommendations for longer term evidence requirements.
 5. The assessment of “shared savings” and the assumptions underpinning this analysis are flawed. We recommend that this analysis be removed.

Detailed Comments and Recommendations

1. **The definition of “SST” is important, since the adaptation of methods for some therapies will lead to differences in the elements being considered when evaluating a treatment. We recommend that the definition of SSTs be more clearly defined and quantified where possible so that all stakeholders are aware of how this definition impacts ICER’s approach and ultimately recommendations to payers.**
 - In the UK, it has been highlighted that some technologies fall between differing HTA programmes and this then can influence NICE recommendations.¹ It is important to clearly define what constitutes an SST versus a chronic therapy so that all stakeholders understand ICER’s process.
2. **The proposed adaptations do not address key concerns regarding the methods and application of the Evidence Ratings Matrix, including for the assessment of evidence uncertainty. We urge ICER to revisit the methods and use of the Ratings Matrix.**
 - A core element of the evidence matrix is the level of certainty around the evidence. We are concerned that in recent assessments, trials of significantly differing quality (i.e. an open label, single arm non-randomized trial versus an RCT) have been given the same evidence rating and that ICER’s cost effectiveness analyses do not appropriately capture the uncertainty resulting from a reliance low-quality clinical evidence. For example, recent evidence reports in 2018 assigned Phase III RCTs evidence

¹ <https://pink.pharmaintelligence.informa.com/PS140729/197m-Payments-Made-Under-New-UK-Pricing-Scheme-But-Access-Promises-Still-To-Materialize>

ratings of C+ to B+ whereas a Phase I open-label study received an evidence rating of A for an SST.²

- In our response to ICER's SMA Draft Evidence Report, we expressed our concern that ICER's evidence ratings are unclear, appear to be applied inconsistently, and do not capture significant differences in the strength of evidence.
- We urge ICER again to revisit the methods and use of the ratings matrix in value assessments. In the SMA Final Evidence Report, ICER did acknowledge that "*manufacturers can and should seek to conduct larger, randomized trials with long follow-up*".³ This recommendation and feedback should also be applied to the evidence rating methodology.

3. Capturing additional elements of value as proposed in the ICER's adaptations is important; however, the focus on a narrow cost effectiveness assessment framework results in methodological inflexibility. We recommend that ICER consider methods and approaches that extend the assessment framework to quantitatively capture these wider aspects of value.

- The emergence of SSTs will have a profound impact on individuals, families and society. ICER adopts a modified societal perspective, however there is a need to further explore and incorporate elements of value that go beyond the patient within a formal framework. It is recognized that some new SSTs could extend survival and have transformative benefits (e.g., halting or slowing disease progression) that patients experience 40, 50, or 60 years after treatment.
- There is widespread recognition that HTA processes need to evolve to address the challenges presented by SSTs, many of which fall within the orphan drugs assessment framework. A recent paper on HTA processes for orphan drugs in Europe highlights the need for wider considerations of disease and treatment experiences from a multistakeholder standpoint and that HTA agencies are extending beyond traditional cost/QALY frameworks.⁴
- The inclusion of two additional elements within the ICER value assessment framework illustrates one of the key limitations of using cost effectiveness thresholds and related uncertainty analysis to guide decision making. The

² Institute for Clinical and Economic Review (ICER). Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report. 24May2019; Institute for Clinical and Economic Review (ICER). Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. Final Evidence Report. 4October2018; Institute for Clinical and Economic Review (ICER). Voretigene Neparvovec for Biallelic RPE65-Mediated Retinal Disease: Effectiveness and Value. Final Evidence Report. 14Feb2018.

³ Institute for Clinical and Economic Review (ICER). Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report. 24May2019

⁴ Nicod et al. HTA program response to the challenges of dealing with orphan medicinal products: Process evaluation in selected European countries, Volume 123, Issue 2, February 2019, Pages 140-151

two additional elements are assessed qualitatively, however their impact are not reflected in ICER's formal assessment of cost effectiveness. We believe ICER has missed an opportunity to think differently and address key issues relating to the quantification of additional elements of value within a transparent value framework. We recommend that the broader implications of introducing SSTs be further considered and incorporated into a value framework, such as MCDA, that could eventually move beyond or complement cost effectiveness analysis.

4. The approach to addressing uncertainty outlined in the proposed adaptations is too narrowly focused on describing and assessing the uncertainty surrounding cost utility analysis (QALY) estimates. We recommend that a broader methodological focus on uncertainty be considered. This broader approach should consider long-term evidence needs. We also recommend that contracting decisions are not linked to an arbitrary PSA threshold, since additional research is needed to understand the meaningfulness of different PSA thresholds.

- There is often limited information on QALYs since utility values are often associated with higher uncertainty as a result of the limited research having been conducted in rare or orphan conditions. Long-term evidence of benefit will also be limited for SSTs, which makes estimating lifetime QALYs a challenge. Globally, payers rely on different approaches to deal with this uncertainty. For example, efficacy data are never extrapolated for long-term benefit assessment in Germany if data on clinical effectiveness are limited or absent.
- QALYs do not adequately capture the wide variety of other benefits that a successful therapy can achieve, including a person's return to economic productivity, their performance in school, ability to function as a caregiver for others, and so on.
- Uncertainty is important in contracting but is not the only factor that needs to be addressed. Importantly, outcomes-based contracts may not always be optimal from an execution perspective (e.g. administration and clinical practice burden, IT requirements).
- For other health systems and payers like the UK (NICE), managed access agreements are set-up to monitor long-term efficacy and safety of a therapy to address uncertainty for a minimum amount of time (e.g 3 years). We recommend that these types of agreements be considered for SSTs to address the uncertainty in evidence associated with SSTs.

5. The assessment of “shared savings” and the assumptions underpinning this analysis are flawed. We recommend that this analysis be removed.

- Affordability and sustainability are central to Biogen’s pricing principles. We recognize that it is the shared responsibility of all healthcare stakeholder to find solutions that ensure patients can afford new innovations. Biogen partners with healthcare systems so patients can access our medicines in a sustainable way. And we remain flexible to enable affordability for patients across economic circumstances
- The proposed cost sharing approach, which adds a scenario where cost offsets that occur after 12 years are not considered, is an inappropriate and arbitrary method to inform value-based pricing assessment and could potentially create negative incentives for innovation.
- Whilst gene therapies may not face generic competition, the current system encourages innovative drug development and multiple innovative therapies will be developed which will increase competition. The proposed focus and methods would therefore be counterproductive to innovation.
- More fundamentally, Biogen is concerned that ignoring cost offsets beyond 12 years will penalize conditions where the most important outcomes and costs avoided occur beyond the 12-year time horizon (e.g Alzheimer’s).
- Treating SSTs differently from ongoing therapies has the potential unintended consequence of creating economic inefficiencies by incentivizing ongoing therapies over curative therapies.
- Given the potential impact of this approach on innovation and its limited use in informing value-based pricing discussions and overall impact on health system effectiveness, Biogen recommends that this analysis is not included as a standard part of ICER reports.

Biogen thanks ICER for the opportunity to comment on the proposed adaptations to the ICER Value assessment Framework for SSTs. We would be happy to discuss any of the outlined concerns in more detail if needed.

Sincerely,
Chris Leibman
Sr. Vice President, Value and Access, Biogen

September 6, 2019

Steven D. Pearson, MD, MSc
President
Institute for Clinical & Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Comments on Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs): Proposed Adaptations to the ICER Value Assessment Framework

Dear Dr. Pearson:

On behalf of BioMarin, I appreciate the opportunity to comment on Institute for Clinical & Economic Review (ICER)’s proposed value framework adaptations for single or short-term transformative therapies (SST). BioMarin is a global leader in developing and commercializing innovative therapies for patients with life-threatening rare and ultra-rare genetic diseases. We appreciate ICER’s efforts to ensure SSTs are appropriately considered for the full set of benefits provided to patients, their families, the healthcare system, and society; this is especially important for SSTs indicated for rare disease patients with high unmet need. The purpose of this letter is to provide our perspective and input on select proposals for assessing SSTs as ICER seeks to refine its value framework for application to SSTs.

Definition of a treatment evaluated as SST. As defined by ICER, SSTs will require a new set of criteria for both clinical and cost evaluations under health technology assessment (HTA). We agree with ICER that both potential cures and disease-modifying SSTs can provide transformative results for patients, and that these merit appropriately tailored adjustments to the current ICER value framework. SSTs can provide benefits to patients that go well beyond other available treatments, including disease-modifying chronic therapies or those used for symptom management. Challenges in the assessment of such existing treatments lead to shortcomings for patients’ health outcomes, resulting in increased risk of comorbidities, complications, and mortality. SSTs may present substantial improvement over chronic therapy options including mitigation of adherence challenges and improved quality of life. Consequently, SSTs have potential to provide substantial benefits for not only patients, but their families, the healthcare system, and society. With a focus on uncertainty of long-term benefits of SSTs as they relate to cost, ICER should consider methods that capture the full value SSTs can provide to each of the aforementioned stakeholders and to consider benefits of disease modification within existing clinical evidence as well as in models.

Incremental cost-effectiveness at multiple time horizons. ICER is proposing to assess incremental cost-effectiveness of SSTs at multiple time horizons including five years, 10 years, and throughout a patient’s lifetime. ICER should consider scenario analyses for lifetime benefit, as failure to do so could artificially underestimate the full potential of an SST’s benefit for patients and ignore substantial costs associated with long-term use of chronic therapies. Additionally, ICER should assess SSTs for rare diseases with different methodology from SSTs for more prevalent disease states, given known challenges with rare diseases health technology assessment that ICER has cited via its ultra-orphan framework.

Dr. Steven Pearson

September 6, 2019

Re: Comments on Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs): Proposed Adaptations to the ICER Value Assessment Framework

Page 2

ICER should also consider developing methods that can be tested and refined to accurately consider durability of effect and fully consider associated benefits, rather than relying solely on model scenarios across different timeframes. Failure to do so would artificially truncate clinical benefits likely accrued from SSTs beyond these time horizons. ICER should consider that treatment can provide other benefits in addition to clinical endpoint defining response, e.g., eliminating treatment adherence issues, improving quality of life, reducing caregiver burden, providing a value of hope, and adding additional benefits to society, which aligns with the existing value framework including for rare diseases.

Additional elements of value. ICER is also proposing to consider additional advantages of an SST based on the balance of benefits and risks in comparison with other therapies. We would support this as a critical element of ICER’s review, as SSTs can achieve benefits for patients such as improved quality of life, reduced treatment adherence challenges, improved overall health status, reduction of comorbidities and complications over time, reduction in mortality, improved work productivity, and improved ability to return to work, all of which are important to consider individually as well as in aggregate to assess benefits and value.

As ICER continues to refine its value framework to include formal adaptations for SSTs, we look forward to the opportunity to provide additional input. We understand from experience with rare disease therapy value assessment in ex-US markets that incorporating clinical benefit and cost to determine value into decision-making presents undeniable challenges, some of which will also apply to evaluations of SSTs for rare disease. We encourage ICER to prioritize consideration of benefits that SSTs bring to patients, and implement a transparent methods-development and application process with all stakeholders.

Sincerely,

A handwritten signature in blue ink, appearing to read 'A. Quartel', with a stylized flourish at the end.

Adrian Quartel, MD

Group Vice President, Global Head of Medical Affairs
BioMarin Pharmaceutical Inc.



Bristol-Myers Squibb

U.S. Pharmaceuticals

P. O. Box 4500, Princeton, NJ 08543-4500

September 6, 2019

Steven D. Pearson, M.D., M.Sc. FRCP President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109

RE: Call for Public Comment on Proposed Methods Adaptations for Assessments of Potential Cures and Other Transformative Therapies

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson,

Bristol-Myers Squibb Company (BMS) is pleased to respond to the Institute for Clinical and Economic Review's (ICER) call for suggestions on how to improve its proposed methods adaptations for assessments of potential cures and other transformative therapies. BMS also supports the industry trade association comments submitted by BIO, NPC and PhRMA.

As a research and development (R&D)-focused organization, we believe in the power of science to address some of the most challenging diseases of our time. We have a high bar for innovation focused on areas where our medicines can truly make a difference for patients. Our focus on these unmet needs comes at an unprecedented time, where scientific breakthroughs are advancing the treatment of disease like never before.

Fueled by robust R&D capabilities, we are advancing science through internally discovered medicines as well as new discoveries we bring into the company through academic, biotech and biopharma partnerships. This is true in each of our four therapeutic areas: Oncology, Immunoscience, Cardiovascular and Fibrosis.

Our scientists are passionate in their pursuit of new and better medicines, knowing that there are patients who currently have few or no options. We have a legacy of transforming patient outcomes in major diseases such as cancer, cardiovascular disease, HIV and HCV. We pioneered a class of medicines that harness the power of the immune system to treat cancer. Our decades of work in cancer have resulted in major advances in life extending therapies and improved survival; progress that the majority of Americans value highly.¹ We are also pursuing medicines with transformational potential in diseases such as heart failure, liver fibrosis and rheumatoid arthritis.

With incredible advances in technology and diagnostic capabilities, we are leveraging translational medicine and data analytics to understand how we can deliver the right medicine to the right patient at the right time to achieve the best outcome. BMS is also dedicated to sharing

¹ Harvard T.H. Chan School of Public Health. (2016, March). *American Attitudes About Cancer*. Retrieved March 20, 2017, from <https://cdn1.sph.harvard.edu/wp-content/uploads/sites/94/2016/03/Stat-Harvard-Poll-Mar-2016-Cancer.pdf>



and disseminating the results of our research to ensure that our research can benefit the widest range of patients; we share our clinical trial data through scientific congress and peer-reviewed journals.

BMS supports the importance of promoting a rigorous, comprehensive and inclusive approach to value that aligns with best practices in value assessment. The comments and recommendations that appear below are shared with this approach in mind, and follow the formatting/numbering of ICER's document for consistency and convenience.

“2. Assessing and Describing Uncertainty”

2.1 “Cure proportion modeling” and “Incremental cost-effectiveness scenarios at multiple time horizons”

Cure Modeling. BMS applauds ICER for making cure proportion modelling its reference case when assessing “single or short-term transformative therapies (SSTs).” Methodologies for data extrapolation continue to develop and evolve, and BMS strongly recommends that ICER frequently review this literature, and incorporate the most rigorous and appropriate methodologies in an objective manner. For example, in the field of immuno-oncology, more advanced methods have been developed since these treatments received regulatory approval. Through longer term follow-up data from randomized clinical trials (RCTs), researchers have validated that more flexible models for these treatments can better capture the complex hazard functions observed in RCTs.²

Time Horizon. The choice of the length of time horizon(s) when conducting cost-utility analyses should not be an arbitrary decision. Time horizons should be chosen in a meaningful way that is reflective of the respective disease area, and sufficiently captures all health and economic outcomes associated with the intervention(s). Thus, a one-size-fits-all approach of applying arbitrary time horizon lengths of 5 and 10 years is not sound science nor appropriate for accurately assessing value.³ Moreover, data that is used for regulatory approval is generated for the purpose of demonstrating safety and efficacy, and does not always capture the full range of clinical and economic outcomes associated with a treatment. As such, applying a “time horizon representing the longest-available follow-up data for a significant number of treated patients” will likely wildly misrepresent the value of the intervention(s) assessed. This is particularly true for interventions that “demonstrate a significant potential for substantial and sustained health benefits extending throughout patient’s *lifetimes*”, which are the exact interventions that ICER’s proposed methods adaptations purport to address. Instead of using arbitrary time horizons to perpetuate flawed and misleading conclusions on value, BMS recommends that ICER stick to the standard lifetime time horizon, and utilize the rigorous and widely utilized data extrapolation methods, real-world data and other fit-for-purpose data that are available when conducting its value assessments. Finally, as new data become available over time, ICER should commit to

² Bullement A, Latimer NR, Gorrod HB. Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study. *Value in Health*. 2019:276-283.

³ Neumann PJ, Sanders GD, Russell LB, et al. *Cost-Effectiveness in Health and Medicine*, Second Edition. Oxford University Press. 2017.



updating all of its assessments to ensure the accuracy of their work and conclusions.

2.3 “Introducing a new economic review section on ‘Controversies & Uncertainties’”

Provide Ranges. BMS supports ICER’s plans to expand discussion around the uncertainty and limitations of the work that it does. Though BMS believes that “expanded discussion” is a step in the right direction, we are strongly recommending that ICER address the uncertainty directly by providing ranges of all output estimates rather than the single point estimates that it often portrays in its materials. BMS believes in rigorous and transparent scientific processes, including communication and dissemination, and thus recommends that ICER not only address uncertainty in a direct (ie. quantitatively) manner consistently and throughout its “Evidence Reports”, but also upfront and transparently in its “Report-at-a-Glance” and any other communications it generates.

Underscore Uncertainty. Moreover, we recommend that ICER explicitly state that its results and conclusions are preliminary in nature, due to ICER’s decision to rush to assess new treatments. As a result of this haste, ICER is often unable to include real-world, non-trial data collected from post-market studies, patient registries, and electronic health records (EHR), which are helpful in mitigating uncertainty. These data are often only available well after product launch, and thus provisions should be made by ICER to periodically revisit their assessments to include these data.

2.4 “Probabilistic sensitivity analyses linked to policy recommendation for outcomes-based payment”

Manufacturers and Payers Lead Outcomes Arrangements & Reforms. BMS does not agree ICER should have a role between manufacturers and payers in outcomes-based arrangements. Outcomes-based payments are but one type of voluntary arrangement between two parties, manufacturers and payers, and ICER risks chilling what already takes place in the market when appropriate and desired. For several years now the market has been working towards value based contracting in an incremental way until the legal and regulatory barriers are meaningfully and comprehensively addressed to allow for a broader shift.⁴ In contrast to a market-based approach, proposals such as this one by ICER that arbitrarily recommend contractual agreements risk chilling or even potentially reversing these market advancements. The proposal also fails to explore beyond downside uncertainty and ICER should consider upside uncertainty when using probabilistic scenario analyses.

As such, recommendations and criteria as to when to consider entering such arrangements should be left to the two parties involved, and not a third party such as ICER. ICER’s methodology uses population level input parameters, which are often not reflective of a given payer’s population, and thus any recommendations that ICER makes are likely not relevant and are at significant risk of inaccuracies. For these reasons, BMS recommends that ICER refrain from making policy recommendations that are based on arbitrary thresholds and input assumptions that lack

⁴ PhRMA. Delivering Results for Patients: The Value of Value-Based Contracts. Available at: <https://www.phrma.org/report/delivering-results-for-patients-the-value-of-value-based-contracts>



relevance and nuance.

“3. Additional Elements of Value”

3.1 “Additional elements of value”

Need Additional Elements of Value. BMS is disappointed to see that ICER has chosen not to incorporate additional elements of value in any meaningful way and we strongly encourage ICER to reconsider their decision to not incorporate consensus-based elements of value such as value of hope, which has undergone peer review.⁵ Neither of the proposed domains of “potential other benefits or disadvantages” that ICER proposes are included in the ISPOR Special Task Force on U.S. Value Assessment recommendations.⁶ In addition, patient advocacy organizations recommend including patient preferences and value into frameworks despite the added complexity.⁷ Moreover, BMS does not agree with ICER’s argument against incorporating additional elements of value on the basis of them being “unidirectional.” BMS believes in patient centricity and scientific objectivity, and thus that all elements of value should be incorporated, irrespective of their directionality. We strongly encourage ICER to strive for the same level of patient centricity and scientific objectivity. ICER argues that methods for measuring additional value elements are “not mature”, and that “the only consensus among health economists seems to be that further research is needed before it can be determined how to measure them.” This is a broad stroke statement that we believe is highly debatable. Finally, BMS recommends that ICER incorporate the value of the broader effects of treatment on productivity, of both patients and their caregivers, irrespective of the modelling perspective that ICER takes in its assessments as we believe these are critical components to determining the value of a therapy.

“4. Time Divergence Between Costs and Benefits”

4.1 Discounting

As ICER acknowledges, the science is not settled on what the discount rate should be in order to appropriately account for time divergence between costs and benefits. The decision to apply different discount rates across costs and benefits, as well as the beliefs as to what the appropriate discount rate(s) should be varies widely.⁸ As such, we recommend allowing for flexibility in the discounting rate to inform the ongoing debate, and ensure transparency around the uncertainty of estimates.

⁵ Lakdawalla DN, Romley JA, Sanchez Y, Maclean JR, Penrod JR, Philipson T. How cancer Patients Value Hope and the Implications for Cost-Effectiveness Assessments of High-Cost Cancer Therapies. *Health Affairs*, 31;4:676-682 (2012). Available at: <https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.2011.1300>

⁶ Lakdawalla DN, Garrison LP, Phelps CE, et al. “Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report.” *Value in Health*. February 2018.

⁷ Addario BJ, Fadich A, Fox J, Krebs L, Maskens D, Oliver K, et al. Patient value: Perspectives from the advocacy community. *Health Expect*. 2018;21(1):57–63.

⁸ NICE. European Network for Health Technology Assessment Guideline: Methods for health economic evaluations.



“5. Affordability and Fair Sharing of Economic Surplus”

5.1 Shared savings

BMS is concerned that ICER seeks to be the single subjective entity that would determine economic surplus distribution, and agrees that any plans to treat cost offsets differently for SSTs than for other treatments simply because ICER estimates high value-based prices is unfair.⁹ The competitive market in the US continues to make complex determinations about the value of medicines as the many heterogeneous, decentralized purchasers assess their own needs in light of available evidence. In the area of gene therapy alone, projections of gene therapy launches estimate over the duration of 10 years around half the 40-60 estimated launches are expected to be in B-cell (CD-19) lymphomas and leukemias, which signals there will be robust competition.¹⁰ It is extremely premature to suggest the free market dynamics that have led to 90% generic utilization in the US will fail with a different type of treatment modality. In addition, ICER’s ability to project basic aspects such as market share are still a long way off from being accurate. For example, an analysis of ICER reports of new therapies found that projections on uptake estimates exceeded real-world estimates by factors ranging from 7.4 to 54.¹¹ BMS believes not only that the proposed methodology is arbitrary and lacks rigor both theoretically and in its application, but also that ICER is entirely not an appropriate entity to be making judgements and recommendations as to the sharing of economic surplus. As such, BMS strongly recommends that ICER completely remove this proposed concept from its scope.

Summary & Conclusions

BMS supports defining value from the patient perspective, with an emphasis on patient-centric outcomes, desires, goals, and experiences. Healthcare is a complex, multifaceted process, and thus individual treatments and therapies should not be considered in isolation. BMS believes value assessment should be a rigorous, comprehensive approach that sufficiently addresses patient and disease heterogeneity, and the plethora of different treatments, interventions, and diagnostic tests that patients receive along the entire continuum of care. If the goal of ICER is to contribute high-quality information to the healthcare value dialogue, then ICER’s current value assessment approach of developing prescription drug-focused, static, one-off evidence reports that evaluate a single treatment in isolation utilizing traditional cost-effectiveness analysis is wholly insufficient. Along with principles developed by the Healthcare Leadership Council,¹² we support the development of value frameworks that meet these eight criteria:

- Measure value, focusing on long-term improvements in health care and societal benefit;

⁹ Institute for Clinical & Economic Review. Value Assessment Methods and Pricing Recommendations for Potential Cures: A Technical Brief – A Draft Version. August 6, 2019.

¹⁰ MIT NEWDIGS. Research Brief 2018: Projections from the existing pipeline of cell and gene therapies - Launches and patient numbers. October 29, 2018. Available at: <https://newdigs.mit.edu/sites/default/files/FoCUS%20Research%20Brief%202018F210v027.pdf>

¹¹ Snider JT, Sussell J, Tebeka MG, Gonzalez A, Cohen JT, Neumann P. (2019). Challenges with Forecasting Budget Impact: A Case Study of Six ICER Reports. Value in Health 22:332-339.

¹² Healthcare Leadership Council. Principles on Value Assessment Frameworks. 2017. Available at <https://www.hlc.org/app/uploads/2017/05/HLC-Final-Principles-on-Value-Frameworks.pdf>



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- Are adequately tested, transparent, reproducible, and open to formal peer review and are regularly updated to keep pace with medical advancements;
 - Are based on health economics methodologies that are consistent with acceptable standards;
 - Are dynamic: accommodate individual patient preferences and are regularly updated to keep pace with medical advancements;
 - Focus broadly on all aspects of the health care system, not just medications;
 - Avoid biopharmaceutical budget caps that unduly delay patient access to innovation;
 - Include sensitivity analyses that are addressed when material; and
 - Incorporate clinical benefits and harms in a manner that recognizes the heterogeneity of the treatment effect as well as the average response

BMS appreciates the opportunity to comment and suggest improvements to ICER's proposed methods adaptations for assessments of potential cures and other transformative therapies. We fully embrace maintaining an innovation ecosystem to discover, develop and deliver transformational treatments for patients in the US and globally. BMS has outlined a number of areas in ICER's proposed adaptations that, if improved, could strengthen ICER's methodology and approach. We hope that ICER seriously considers these recommendations. Significant modification of methodologies, additional scientific rigor and increased transparency must occur before many stakeholders will see ICER as an objective and credible voice on healthcare value assessment.

Sincerely,

Mitch K. Higashi, PhD

Head of US Medical Health Economics and Outcomes Research

Consultation on ICER's Pricing recommendations for potential cures

ICER's research in this exciting but challenging area is to be applauded. By drawing on the literature and expert consultation ICER have succeeded in summarising the key issues and helpfully illustrate the most promising methods using their case studies. While thorough, many of the methods reviewed by ICER and the conclusions ICER draw are familiar. The arguments for and against differential discounting for example are well travelled.

Of greater interest are ICER's proposals that the economic surplus of new single or short-term transformative therapies (SSTs) should be shared. An approach which, as they note, is currently not applied in economic evaluations.

While ICER justify this on the basis of concerns regarding maintained extended exclusivity (as well as affordability), applying them in this context opens the possibility of two areas of inconsistency:

- a) manufacturers being forced to share economic surplus for these radically innovative technologies which they would not have had to do if they had developed therapies with less transformative benefit (for example, because the patient had to routinely take the intervention, their prognosis was not dramatically altered or substantial costs savings were not accrued) and
- b) the sharing of one aspect of economic surplus (cost offset/savings) while another aspect (as a result of health benefit in terms of QALYs) is not.

Though from a purist's perspective "b" is inconsistent we recognise that this approach may be more ideal than a full sharing of economic surplus (both cost offsets and due to QALY gains) given prior US healthcare conventions. Given pragmatic policy making considerations it is therefore more defensible compared to "a".

As regards inconsistency "a" the proposed approach of sharing the economic surplus of some proportion of cost savings seems arbitrary and therefore contentious. The two approaches proposed for sharing of surplus are defended partially on the basis that 1. there should not be an award to pharmaceutical companies for purchase of smaller companies developing SSTs (potentially receiving government funding) and 2. that SSTs may never experience generic competition.

In terms of the former of these two approaches quantifying the criteria for economic surplus and how they interact requires clearer articulation and a consistent ethical framework on which to base the analysis, in addition the principle still applies that if something like this goes in it should be for all drugs and not just SSTs as the issue of reward for products which receive government funding for development does not only apply to SSTs.

In terms of the second of the methods proposed, it would be good to assess the plausibility of this assumption as well try to reach consensus on the assumption of 12 year cut-off (beyond which cost offsets are set to zero) with all key stakeholders (e.g. during the scheduled multi-stakeholder meeting for this consultation in September 2019). If this assumption is supported and some consensus reached by majority of stakeholders, then there may be merit in ICERs "LOE scenario shared savings approach". However, given uncertainty, we would argue that:

- a) ICER routinely make a context specific assessment about the "risk" of generic competition for all medical interventions (to improve consistency). If the risk is deemed low (or same as SST), then this approach is unlikely to be needed; and

- b) Where the risk is deemed high this approach should be applied as a scenario for pricing purposes and not as the base case; and
- c) ICER consider the way the approach is applied as the current method assumes all patients start at year 0 (appropriate for c/e modelling but not for consideration of the impact of affordability / patent exclusivity as patient numbers are unlikely to remain constant over time)

We would also like to raise a few more minor specific comments on the consultation document:

- a) Section 1.1: while it is understandable that ICER wants to retain certain level of flexibility to decide if an intervention can be regarded as an SST on a case by case basis, it would be good to provide a “normal” threshold for the eligible “short-term” therapy, e.g., a maximum treatment duration of no more than 2 months based on label or expected label and a disclaimer that meeting this criterion will not guarantee the “short-term” status, on which ICER will make a final judgement. This would increase clarity on the “short-term” criterion, especially for pharmaceutical companies
- b) Section 2.1 and 2.2 (last two sections on page 3 and relevant discussion on page 4): there are some inconsistencies regarding terminology and discussion of modelled time horizon (e.g. longest available follow up, 5 and 10 years) and duration of cure benefit effect in the discussion section. These two terms/concepts should be clearly distinguished; modelled time horizon refers to the time frame within which the decision maker believes costs and health impact are still relevant for the decision, while duration of cure benefit effect is more a clinical and modelling assumption for the specific SST of interest. As SST by definition has significant health impact (and consequently cost impact) for the patient’s remaining life we believe that a lifetime horizon should be the base case and would argue other time horizon scenarios (e.g. longest available follow up, 5/10/15 years) do not need to be routinely performed. Therefore, we think Section 2.1 can be removed as this aspect should be no different to the overall ICER value assessment framework. We agree assessing uncertainty around duration of cure benefit effect is very important, so we suggest, apart from the threshold analysis suggested in Section 2.2, scenario analyses assuming the duration of cure lasts up to year 5/10/15 and, if relevant, up to the longest-available follow-up data would be useful and incorporated into Section 2.2 as well. Using a lifetime horizon, we would deem cure benefit lasting a lifetime as the most optimistic scenario and cure benefit lasting only up to the longest-available follow-up data as the most conservative scenario.
- c) Section 4.1.1: with respect to the application of cure proportion modelling based upon research which we currently have in publication cure modelling techniques may also fail to provide sensible predictions where data are overly mature as well as where data are immature (although clearly this is a nice problem to have!) In this case the cure fraction is based on those lost from the study and not the plateau in the middle of the survival curve. Cure modelling works best when most disease-related events have occurred and the majority of other-cause mortality events are yet to occur.

Dawn Lee, Yang Meng, Ron Akehurst and Daniel Gladwell

On behalf of BresMed



September 6, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: ICER Proposed Methods Adaptations for Assessments of Potential Cures and Other Transformative Therapies

Dear Dr. Pearson,

I am writing on behalf of Celgene in response to the Institute for Clinical and Economic Review's (ICER) proposed adaptations for assessing potential cures and treatments that qualify as "single or short-term transformative therapies," or SSTs. We appreciate that ICER recognizes the potential for cell and gene therapies to provide "truly transformative advances for patients and their families," and is considering modifications to its existing methodology to better account for the truly unique value these treatments can provide.

Celgene is committed to the development of therapies leveraging T cells with chimeric antigen receptors (CARs) across multiple cancer indications. We are proud of the work we are doing to bring these innovations to patients and currently have two therapies in late stage clinical development. Celgene believes CAR T cell therapies hold significant promise for patients who are underserved by existing treatment options—and cell therapies are exactly the type of treatments we expect ICER is looking to address with this framework adaptation. We also recognize that there is an essential link between value and price, as outlined in our [Principles for the Pricing of Innovative Medicines](#); assessing one without considering the other can lead to an environment where patient access to these potentially transformative treatments is undermined.

In the proposed changes document, ICER notes that its framework, "creates an explicit place and role for consideration of elements of value that are important to individual patients but that fall outside traditional clinical measures." Celgene agrees that these "additional elements of value" are critically important to patients and are essential to any comprehensive discussion of value. Celgene has long been transparent in how we define value and how we measure our progress as a company working to improve healthcare. Earlier this year, we released our [2019 Value and Innovation Framework Report](#), which looks at how Celgene and other biopharmaceutical companies deliver on value and innovation and adds meaningful data to the ongoing effort to improve healthcare and expand access. The report also outlines Celgene's approach to value, as understood through the stakeholders engaged in healthcare innovation and delivery, defining value as:

- 1) Value to patients



- 2) Value to the health system
- 3) Value to the economy and society
- 4) Value to future innovation

These pillars are representative of our belief that value is holistic and multi-dimensional and any attempt to measure a therapy's value in the short-term, or through the lens of only one or some of these pillars, is insufficient. Celgene's perspective on value assessment is further articulated in our [Patient-Centered Principles on Value Assessment](#) and on the company's [Value Hub](#).

Celgene believes that measurable **value for patients** comes from improvement in patient outcomes, improvement in quality of life and provision of patient education and support. At Celgene, there are currently 1,885 patients enrolled in 12 Celgene-sponsored clinical trials for CAR T cell therapies in lymphoma and multiple myeloma. Across the biopharmaceutical sector, there are clinical trials underway to study CAR T cell therapies in the front-line treatment of aggressive cancers like glioblastoma and B-cell lymphoma.¹ Patients diagnosed with these aggressive cancers have few options currently, and those options can sometimes lead to suboptimal outcomes. Optimization of front-line therapy with CAR T cell therapies has the potential to result in clinically meaningful outcomes for individual patients.

Adopting an overly narrow definition of value for CAR T cell therapies could lead to restricted access for patients, including those with relapsed or refractory disease. Restricted access, in turn, creates barriers that limit patients' ability to benefit even as the FDA approves new products, additional indications are recognized, and CAR T cell therapies are incorporated into more treatment guidelines and compendia.

As we think about the rapidly evolving science of CAR T cell therapy, it is critical that any value assessment framework has adequate flexibility to account for the current and future value these therapies contribute to the health system. Celgene defines **value to the health system** as including cost savings when better therapies reduce the need for other services like hospital stays; investment in academic research, investigator-initiated clinical trials and real-world evidence; and support for physician education and other healthcare system capacity building efforts.

The emerging safety profile of CAR T cell therapies suggests that some CAR T cell therapies, in certain patient populations, have low rates of side effects or late onset of side effects that make immediate hospitalization at time of infusion unnecessary. As experience with CAR T cell therapy increases, and cell therapy evolves, we anticipate that toxicity management will become easier, that earlier identification of toxicities will allow for earlier intervention, and the side effect profiles of each therapy more defined, potentially allowing use in more settings of care.

Celgene defines **value to the economy and society** as a combination of: increases in patient productivity, contributions to local, regional, national and global economies, and benefits to families and caregivers of patients. Due to the complexity of developing CAR T cell therapies, there are a limited number of institutions equipped to deliver FDA-approved CAR T therapies



currently. This means that many patients and their families may need to travel long distances for treatment, forego CAR T cell therapy altogether, and/or utilize a suboptimal treatment option. Expanding geographic access for patients to these innovative treatments is a primary goal for Celgene.

To this end, Celgene is currently conducting clinical trials to demonstrate that for specific patient populations, CAR T cell therapies can be administered safely and effectively in both inpatient and outpatient settings.² The emerging safety profile, mentioned above, combined with a knowledgeable integrated medical team—a team that functions seamlessly consisting of oncologists, nurse coordinators, neurologists, ICU physicians, and emergency room, infusion center and clinic staff—means that CAR T cell therapies may be available for more patients. The increased availability for patients means less travel, fewer days off work, and less time away from home not just for the patient, but for their family and caregivers, as well.

All of these elements—less travel, more time at work, better mental and physical health, and more time with family—benefit both patients and caregivers, as well as contribute to the well-being and productivity of the economy and society as a whole. ICER should also consider these broader elements of value, where quantifiable, in their additional elements of value analysis.

Finally, Celgene is proud of its core commitment to discovering and developing life-changing medicines. We define **value to future innovation** as investment in discoveries about existing medications; investment in medical innovation for new therapies addressing significant patient need; and contribution to the development of a competitive, yet collaborative, medical R&D ecosystem. Over the last five years, Celgene has reinvested 39% of its revenues back into research and development.³ In fact, Celgene has the highest rate of R&D intensity (defined as the ratio of R&D spending to net sales) of any large biopharmaceutical company in the world, and we rank third globally among companies across all industrial sectors, according to the European Commission.⁴

Celgene has seen firsthand how yesterday's innovations have paved the way for advances like CAR T cell therapies—our investment in CAR T cell therapies would not have been possible without the commercial viability of other treatments we have brought to market. We are concerned about two proposed changes to ICER's value assessment framework that serve to undermine the value of innovation. First, Celgene is concerned that ICER's proposal to cap cost-offset calculations at 12 years has the potential to dramatically underrepresent the value of these life-changing therapies, particularly for durable therapies that have the potential to deliver decades or even a lifetime of benefits to patients while concurrently reducing health system costs.

Inflexibility around how the full and long-term value of SSTs, including CAR T cell therapies, is determined means future research and investment in this area could be hindered, to the detriment of patients, the healthcare system, the economy and society at large. The adverse effect of ICER's decision to ignore cost offsets after 12 years will negatively impact the ability to sustain and enhance innovation; this should not be minimized.



Second, as a company committed to ongoing innovation, we are opposed to ICER's use of a budget impact threshold and disappointed by the decision to lower the budget impact threshold for 2020 by almost 20%, from \$991 million to \$819 million, especially because the reduction appears to be driven by an increase in new drug approvals. With this calculation, ICER is suggesting that biopharmaceutical companies should be penalized for increases in innovation.

Celgene recognizes the need for and supports the current national dialogue around healthcare spending, including biopharmaceuticals. We also recognize that much depends on ICER striking the right balance in assessing the value of transformative medicines like CAR T cell therapies. We encourage ICER to undertake a holistic examination of value, one that explores what value means to all healthcare stakeholders and allows for the flexibility to accommodate a rapidly evolving field.

Sincerely,

A handwritten signature in black ink, reading 'Richard H. Bagger'.

Richard H. Bagger

Executive Vice President, Corporate Affairs and Market Access

¹ Clinicaltrials.gov: Study evaluating efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Participants With High-Risk Large B-Cell Lymphoma, available at <https://clinicaltrials.gov/ct2/show/NCT03761056?term=NCT03761056&rank=1>; A study evaluating EGFRvIII CAR T Cells for Newly-Diagnosed WHO Grade IV Malignant Glioma (ExCeL), available at <https://clinicaltrials.gov/ct2/show/NCT02664363?term=NCT02664363&rank=1>; A study evaluating Up-front CART-BCMA With or Without huCART19 in High-risk Multiple Myeloma, available at <https://clinicaltrials.gov/ct2/show/NCT03549442?term=NCT03549442&rank=1>

² Clinicaltrials.gov: A Safety Trial of Lisocabtagene Maraleucel (JCAR017) for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL) in the Outpatient Setting, available at <https://clinicaltrials.gov/ct2/results?cond=&term=NCT03744676&cntry=&state=&city=&dist=>; Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-NHL-006), available at <https://clinicaltrials.gov/ct2/show/NCT03483103?term=NCT03483103&rank=1>

³ Numbers based on Generally Accepted Accounting Principles (GAAP) from Celgene Data on File.

⁴ Hernández H, Grassano N, Tübke A, Potters L, Gkotsis P, Vezzani A. The 2018 EU industrial R&D investment scoreboard. European Commission – Joint Research Centre. 2018. doi:10.2760/131813.

September 6, 2019

Steven D. Pearson, M.D., M.Sc.
President
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Two Liberty Square
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Dear Dr. Pearson:

We read with interest ICER's proposed adaptations to its framework and processes in the setting of "single or short-term transformative therapies" (SSTs). While we agree that some accommodation for therapies that meet this definition may be necessary, we feel that greater clarity is required for some considerations. Our concerns and associated recommendations are organized by section of the adaptation document below.

Section 1: Definition

While the criteria for defining an SST are clearly described, what remains unclear is the type of therapy that would potentially meet the definition. Most of the language seems to be directed at drug therapies, but one-time device implantation and/or invasive procedures could easily be considered SSTs, and one might argue that some of the SSTs currently on the market are actually drug/device hybrids.

In addition, the document does not describe whether an SST designation would ever be revisited. It is entirely possible that a therapy deemed to be an SST does not live up to that promise upon further data collection. Indeed, the currently marketed forms of chimeric antigen receptor T-cell (CAR-T) therapy, which would likely be considered SSTs, have always had challenges of "antigen escape", in which the cancer re-emerges in a form negative for the antigen targeted by the CAR-T.¹ Should this problem increase with further follow-up, these CAR-Ts would no longer qualify as SSTs. We propose that, with the regularly scheduled updates that ICER is now proposing, a revisiting of the SST designation be an integral part of the scoping process for the update. We also recommend that, should new data emerge that calls into question the status of a high-profile SST, a revisiting of the designation be considered even prior to the next scheduled update.

Section 2: Addressing and Describing Uncertainty

Section 2.1 describes the use of cure proportion modeling as a reference case standard as well as assessment of cost-effectiveness at multiple timepoints. We understand the use of cure proportion modeling when there is an identifiable flattening in the survival and/or progression curve, but other

transformative therapies might result in similar improvements in disease progression and/or quality of life but without a similarly identifiable point of inflection. Indeed, one might argue that many disease-modifying drugs for autoimmune disease fit the description of transformative therapy but through the pathway of sustained response rather than a “curative” or “progression halting” event, and it is conceivable that even a single or short-term treatment might act in a similar way. We would recommend that ICER explicitly describe the reference case approach in situations like this. We believe that standard methods for estimating cost-effectiveness for SSTs with clinical improvements outside of the curative realm should be sufficient.

While we agree that examination of cost-effectiveness findings at multiple timepoints would be beneficial when there is significant uncertainty around the duration of benefit, we recommend that the timepoints chosen be reflective of both the nature of treatment and the clinical trajectory of disease.² For example, if a disease is indolent for a period of time before becoming rapidly progressive, 5 years may be too soon to assess differences between treatments.

Section 2.4 pertains to the use of probabilistic sensitivity analysis (PSA) to inform whether a recommendation regarding outcomes-based payment should be made. Specifically, it proposes that if a therapy’s price yields PSA results in which >25% of iterations produce cost-effectiveness ratios above \$200,000 per QALY gained, a policy recommendation will be triggered for consideration of outcomes-based agreements with payers. While some will undoubtedly quibble with the arbitrary nature of 25% or \$200,000 thresholds, our concern is more about how to operationalize this approach. The proposal significantly elevates the use of PSA from an adjunct element buried in an ICER report appendix, yet the current ICER reference case says little about how a PSA should be done. As the 2nd Panel on Cost-Effectiveness in Health and Medicine notes, a PSA both addresses and introduces uncertainty, given that choices about parameter distribution often must be made in the absence of any actual data on their distributional form.³ We recommend that ICER significantly expand its reference case text regarding the conduct of PSA, including recommended minimums for the number of iterations as well as the conduct of scenario analyses around PSA design. The below excerpt from the methods guide of the National Institute for Health and Care Excellence (NICE) may be useful:

“Probabilistic sensitivity analysis...enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes. The mean value, distribution around the mean, and the source and rationale for the supporting evidence should be clearly described for each parameter included in the model. The distributions chosen for probabilistic sensitivity analysis should not be arbitrarily chosen, but chosen to represent the available evidence on the parameter of interest, and their use should be justified. Formal elicitation methods are available if there is a lack of data to inform the mean value and associated distribution of a parameter. If there are alternative plausible distributions that could be used to represent uncertainty in parameter values, this should be explored by separate probabilistic analyses of these scenarios.”⁴

We also note that, in non-linear modeling situations, NICE recommends using PSA results rather than deterministic findings to inform the base case.⁴ We strongly recommend that ICER consider this

approach for relevant SST situations, given the likelihood of significant parameter and structural uncertainty that will accompany the accelerated nature of many SST approvals.

Finally, while the use of PSA for this purpose implies the injection of some level of precision into policy recommendations, the recommended instrument (i.e., the outcomes-based agreement) is rather bluntly and variably applied in the U.S., and is not always used with the intent of arriving at a specific, cost-effective price. We feel that a general recommendation regarding methods to achieve additional price reduction should be sufficient, with outcome-based agreements being one of several possible approaches.

Section 3: Additional Elements of Value

Section 3.1 describes two additional contextual elements to be considered by ICER voting committees, one of which focuses on a potential advantage for therapies based on the balance or timing of risks and benefits. An example is offered in assessing a new treatment with a higher likelihood of serious side effects and/or death but a greater chance of long-term survival than standard treatment. Given that standard methods for cost-effectiveness analysis already include an approach to value tradeoffs such as these, we are unsure why a quantitative method was not proposed. It is quite feasible to imagine a set of scenario analyses that move away from the average costs and effects that populate a base case and focus on varied probabilities, effect sizes, and even willingness to pay; some empirical work has already been performed in this area, which is often referred to as the “value of hope.”⁵ We would recommend that such a set of scenario analyses be considered in situations with the potential for extremes in the risk-benefit tradeoff.

Section 4: Time Divergence between Costs and Benefits

We agree with the conclusion that, while appropriate levels of discounting remains a topic of debate and ongoing research, a standard and identical discount rate should be applied to both costs and effects in base case analyses. In many situations (e.g., life-saving therapies for young children, therapies that significantly halt or slow functional decline) it may be worth exploring how sensitive model results are to changes in the discount rate.

Section 5: Affordability and Fair Sharing of Economic Surplus

ICER proposes to develop a “shared savings” scenario analysis in which any cost offsets from SST treatment will accrue to the innovator for the first 12-year period in the model, based on the average time to loss of patent exclusivity for new drugs, with cost offsets set to zero thereafter to reflect a shared savings between drug manufacturers and the health system. We are unsure why actual estimates of time to loss of exclusivity could not be used for every topic, as public information on the timing of patent filing is readily available and adjustments can be made for drugs receiving orphan or other special status.

If a savings-based analysis is of interest, we would recommend that ICER instead explore “dynamic pricing” approaches in a scenario analysis, as health-system savings are perhaps more realistically achieved through price relief from generic or biosimilar market entry than the proposed approach, which assumes that modeled cost offsets would approximate those achieved in any given real-world health system. Analyses could be conducted that vary the timing and price changes associated with generic entry that would achieve certain cost-effectiveness thresholds, for example.

In conclusion, we applaud ICER for exploring methods to recognize the potential for the significant health benefits that may be achieved with single- or short-term transformative therapies. We urge ICER to consider where and when a departure from standard methods is truly warranted, and hope our recommendations will be of use in these considerations.

Sincerely,

Daniel A. Ollendorf, PhD
Joshua T. Cohen, PhD
James D. Chambers, PhD, MPharm
David D. Kim, PhD
Tara Lavelle, PhD
Pei-Jung Lin, PhD
Peter J. Neumann, ScD

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September 6, 2019

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Institute for Clinical and Economic Review – Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs); Proposed Adaptations to the ICER Value Assessment Framework

Dear Dr. Pearson,

On behalf of the Cancer Support Community (CSC), an international nonprofit organization that provides support, education, and hope to people impacted by cancer, we appreciate the opportunity to respond to the request for public input for the Institute for Clinical and Economic Review’s (ICER) Value Assessment Methods for “Single or Short-Term Transformative Therapies (SSTs). As the largest direct provider of social and emotional support services for people impacted by cancer, and the largest nonprofit employer of psychosocial oncology professionals in the United States, CSC has a unique understanding of the cancer patient experience. Each year, CSC serves more than one million people affected by cancer through its network of over 45 licensed affiliates, more than 170 satellite locations, and a dynamic online community of individuals receiving social support services. Overall, we deliver more than \$50 million in free, personalized services each year to individuals and families affected by cancer nationwide and internationally.

Additionally, CSC is home to the Research and Training Institute (RTI)—the only entity of its kind focused solely on the experiences of cancer patients and their loved ones. The RTI has contributed to the evidence base regarding the cancer patient experience through its Cancer Experience Registry, various publications and peer-reviewed studies on distress screening, and the psychosocial impact of cancer, and cancer survivorship. This combination of direct services and research uniquely positions CSC to provide valuable patient and evidence-informed feedback on ICER’s value assessment frameworks.

Inclusion of Patients and Patient Advocates

First, we would like to note that ICER interviewed three patient groups, none of which were cancer-specific. We do not believe that this is an appropriate quantity of patient group interviews, and based on the fact that several SSTs are in oncology, we also do not believe that due diligence was done to ensure that it reflected the voices of cancer patients, survivors, and caregivers. Moving forward, we ask that ICER proactively and regularly engage patients and/or

caregivers living with the disease under assessment, allowing ample time for them to provide input and feedback on all aspects of the assessment process.

Timing of Assessments

ICER states in this proposed adaptation document that “at the time of regulatory approval, SSTs will very rarely have data on patient outcomes beyond a relatively short period of time...). As stated in our previous comments regarding CAR-T cell therapies, we believe that value assessments conducted on therapies with limited data and real world evidence are premature. We believe that sufficient time should be allowed for new therapies to be studied in both clinical and real world populations before rendering a value assessment. However, if ICER engages in such assessments, we believe that they should be revised on a regular basis when new evidence becomes available or previous information becomes outdated.

Regardless of our stated hesitations regarding value assessments on SSTs, we would like to point out several issues of concern if this adaptation moves forward.

Additional Elements of Value

ICER notes that challenges of “additional elements of value” with a specific focus on “the value of hope.” ICER notes that they “believe there are significant risks or double counting within the QALY or within existing “other benefits” or “contextual considerations” that ICER already includes as part of its value framework.” ICER also notes that such additional elements of value are all “unidirectional” and would all “add” to treatments, and none have negative scores that would help balance out added value within an opportunity cost framework for determining the cost-effectiveness threshold.” Finally, it is noted that methods for measuring additional elements of value are “not mature” and “further research is needed before it can be determined how to measure them.” As a result, ICER proposes that “no quantitative integration of additional elements of value” will be included in the value assessments framework for the assessment of SSTs. However, patient input will be sought regarding the “value of choice among treatments with a different balance and timing of risks and benefits.” We do not believe that the stated “value of choice” appropriately captures the concept of the “value of hope.” In the accompanying technical brief, ICER states:

We believe that naming this dimension of the value of “hope” is unfortunate and misleading. It conflates two things: the potential for a treatment to offer an added benefit by providing a distinctive spectrum or timing of risks and benefits; and the “hope” held by essentially all patients with a life threatening condition that some treatment might be found that can offer a glimmer of a chance of benefit for them, even if that chance is vanishingly small. We therefore believe that the dimension of value labeled “value of hope” would be usefully renamed the “value of having the *choice* among treatments with a different balance and timing of risks and benefits.” Not as succinct as value of hope, but far less likely to be misconstrued and misapplied in discussions regarding the potential benefits of SSTs.

We disagree that the concept of the value of having the choice among treatments with different balance and timing of risks and benefits captures the same concepts as the value of hope. We are currently validating a new tool called the “Valued Outcomes in the Cancer Experience” or the

VOICE measure. This project began as a study of what patients hope for and has evolved into a measure of their values and how much control they believe they have over what they consider most valuable. We believe that this measure could be useful to ICER and propose a meeting to discuss potential collaboration on this topic.

Additionally, ICER will consider the potential disadvantage “that some SSTs might have if, by their mechanism of action or triggering of immune responses, could lead to decreased chance at effective treatment by a future generation of therapies in the pipeline.” We find that the inclusion of this concept is in contrast with the exclusion of “additional elements of value” that are potentially positive for some patients while including this potential disadvantage.

Affordability and Fair Sharing of Economic Surplus

The mission of ICER is to “help provide an independent source of analysis on effectiveness and value to improve the quality of care that patients receive while supporting a broader dialogue on value in which all stakeholders can participate fully.” It is unclear how “fair sharing of economic surplus” is aligned with this mission statement. ICER states that a proposed shared savings scenario “could provide policymakers with information to stimulate a broader dialogue on what the “appropriate” sharing of the economic surplus should be between innovators and the health system...” It is unclear what this means and if ICER is using this adaptation as an opportunity to expand upon its mission as it seemingly appears, it is vital that such an expanded mission is transparently discussed and open for comment.

In closing, thank you for the opportunity to submit these comments. We welcome the opportunity to engage in further discussions with you to ensure the patient experience is valued and all patients have access to high-quality health care. If you have questions regarding our comments, or if we can serve as a resource, please reach out to me at Efranklin@cancersupportcommunity.org.

Sincerely,



Elizabeth F. Franklin, MSW
Executive Director, Cancer Policy Institute
Cancer Support Community Headquarters

September 3, 2019

The Drug Pricing Lab appreciates the opportunity to provide input to ICER's draft Value Assessment Methods for "Single or Short-Term Transformative Therapies" (SSTs)

General: We appreciate the serious contemplation by ICER regarding additional methodologies it might apply to assess treatments given for a short duration but with highly uncertain expected benefits both in terms of type and duration (labeled Single or Short-Term Transformative Therapies, or SST's). As ICER pursues its work we encourage the Institute to focus on the descriptive framework for the methodologic problem it feels these therapies pose, use exclusively dispassionate descriptors, and avoid advocacy for payment or cost saving schemes that are clearly inflationary.

Statement of the problem: One clear and neutral way to characterize the methodologic problem ICER feels it faces is that certain therapies coming to market have very high expected asking prices that are justified almost entirely on extrapolated estimates of their benefits. This is because the underlying data are unusually thin. We encourage ICER to consider the full range of data limitations for these therapies. They are not only the disconnect between the empiric observed time horizon and the extrapolated time horizon in the ICER models. Small sample sizes undermine the precision of estimation. Studied cohorts are often non-representative, for instance deriving exclusively from patients at academic centers, hampering generalizability. Indicated population often extends well beyond the intended use population in the approval studies. But we emphasize that neither these data deficiencies nor the astronomical prices of these therapies are intrinsic features. Quite the contrary, the innovator company has under its control both how much data are developed before seeking marketing approval and what asking price the product then carries. So the challenges ICER now articulates in determining a sensible price for these therapies are challenges of the sponsor's own making.

Terminology: We strongly discourage ICER from using terminology that deviate from the well accepted catalog of dispassionate descriptors used in health economics and epidemiology. For instance, "cure" is not a term for health economic assessment, it is a colloquialism. Same goes for 'transformational therapies'. Worse, these vague terms connote uniquely favorable attributes. Who would not find a 'cure' incrementally desirable? Who does not long for 'transformational therapies'? But ICER's role is to coolly and carefully assess interventions and measure objectively how those interventions affect health (and other relevant outcomes). It is a troubling and irreversible step for ICER to adopt hype-laden terms, routinely advanced by the pharmaceutical industry as their preferred descriptors, as a way of segmenting their methods. Rest assured, there will never be a wave of therapies that the industry does not argue needs special treatment due to its uniqueness. Remember 'targeted therapy'?

While a great deal has been written about the pointlessness and false promise of terms such as 'cure', it is worth noting that the term 'transformational therapy' is widely sprinkled across a variety of unrelated treatments, evidence the term has no coherent meaning. In a scan of the medical literature we found the term used to describe oral drugs that treat [cystic fibrosis](#), targeted [anti-cancer](#) drugs that change a surrogate marker, and [music therapy](#).

Also please note that you refer to potentially creating a category of SST's that can 'eradicate' a disease or condition. At least in epidemiology that term has a specific meaning that is unlikely to apply, as it means to eliminating a condition from the face of the earth permanently.

Uncertainty: We encourage ICER to acknowledge that much of the uncertainty surrounding these therapies is a product of pharmaceutical corporations' decisions to conduct the minimally viable clinical research necessary to achieve marketing approval. The paucity of data is, in other words, not a feature of the treatment – it is a decision of the sponsor. While we salute the effort to examine alternative parametric survival models, we would encourage ICER to hew to the tradition of conservative analysis until such time that there is meaningful contravening data documenting that the underlying heterogeneity of treatment effect, which is a feature of all therapies, is so extreme as to require an alternative modeling framework. In other words, ICER should use the most simply parameterized model until those models no longer explain the observations, rather than imposing a hoped-for heterogeneity of treatment effect that could overweight rare chance events.

Outcomes based contracts: ICER's advocacy for outcomes contracts is inappropriate as the framework fails to acknowledge that these contracts shift risk once borne by the sponsor onto society. Quite simply outcomes based contracts provide an option to the sponsor to earn the full price of a therapy if it proves as effective as hoped, instead of proving it is that effective before selling it. This is a windfall for the sponsor, until ICER performs the work to determine what a sensible upper bound price should be when the performance of a product has not yet been established. ICER should not enable charging high prices for unproven therapies, it should propose prices that are based on available data and lay the ground work for price changes based on accrued actual evidence instead.

Fair share of economic surplus: We appreciate ICER's exploration of sharing economic surplus but have some concerns. From our view, there is a dual purpose of health technology assessment for determining a fair price for a medical product. First as a method of societal allocation, as HTA can define the highest price the payer should be willing to pay for the gains the product produces, whereas any higher would mean there were better uses of money. But critically in the management of monopoly markets, it is used as a surrogate for the unknowable level of reward the pharmaceutical innovator should receive so that the firm and other firms like it will chase the challenge of creating new and important drugs. Under this theory the ceiling price for a product should actually be the lesser of these two values if each were knowable. No more money should be spent than can be justified with regards to other uses of the money, and no more money should go to the innovator than that amount required to incentivize the innovation. The tension between these two alternative price points becomes most apparent at the extremes of the 'intended use population' sizes. Markets that are very small may require unit prices that exceed conventional cost-effectiveness thresholds to satisfy incentive needs, while markets that are enormous produce likely outsized rewards if prices are based on cost-effectiveness. What defines either of these outliers is poorly understood, but we encourage ICER to consider this matter directly and impose guardrails in each direction (as it has to some extent with using alternative multipliers for rare diseases at one extreme and setting budget impact thresholds at the other).

Creating a shared savings framework for SST's is not in keeping with this theory for HTA and has several concerning consequences. To the extent you aim to share back savings for a new product, the social value of improvement in efficiency would be captured by the innovator for an extended period of time (ICER proposes a dozen years). Given that we can easily anticipate new innovations in this treatment area with a more rapid cycle length than a dozen years, we could be in a perpetual cycle of successive innovations in which the innovator keeps all the system savings. Then there is the problem that fair price finding for new therapies should be consistent in its methodology. Under a model where savings (or cost offsets) are shared back with innovators a consistent framework would have innovators being charged when their treatments lead to additional external health care expenses. Such coherence however would seriously disadvantage treatments that reverse rapidly fatal conditions in some cases, which would be an undesirable consequence. Lastly, we note that many health economists have sought to measure the portion of the surplus captured by the innovator that new therapies generate, and those estimates are in general quite low in percentage terms. Philipson and Jena [estimated](#) that the innovators captured around 5% of the surplus created by new treatments for HIV. Camejo and colleagues [estimated](#) that for branded lipid lowering therapies the portion of the social surplus captured by the innovator was on the order of 25%. We propose ICER use this range of benchmarks when determining what would be a fair share for the innovator corporation if it pursues this approach.

We are also unsure how ICER arrived at twelve years as the period during which the surplus should go to the innovator. We appreciate that ICER notes that this is the typical duration of monopoly protection, but we do not see that statistic as either accurate or probative. The twelve-year exclusivity for biologic drugs is somewhat arbitrary and oft criticized. It is around twice the period policymakers intended for small molecule drugs. If ICER's goal is to use its HTA approach to circumscribe the period of high reward levels for new treatments, and align that with policy makers' intents, that seems an appropriate objective. But the means of doing that should focus on price, not on the sharing of surplus.

Thank you for the opportunity to provide our comments on this matter.



September 6, 2019

Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

Dear ICER Review Panel:

Genentech, a member of the Roche Group, appreciates the opportunity to provide input on ICER's *Proposed Adaptations to the Value Assessment Framework for Single or Short-term Transformative Therapies (SSTs)*.¹ As a leading biotechnology company, Genentech discovers, develops, and manufactures novel medicines to treat patients with serious and life-threatening conditions. We support the goal of policymakers to lower health system and patient out-of-pocket costs. To achieve this optimally, stakeholders must work together to find sustainable, system-wide solutions that lower costs while also protecting scientific innovation and access to breakthrough treatments. We believe innovative payment models combined with robust and comprehensive market competition mechanisms will be important components of an effective long-term strategy.

We share in ICER's belief that SSTs have far-reaching implications. SSTs provide both the promise of life-altering benefits and present urgent challenges to the current medical reimbursement system. We respond to ICER's public call for comment based on the belief that the scientific methods used in these value assessments must be rigorous. We comment on the following priorities:

1. We recommend that ICER focus efforts on quantifying additional elements of value, advancing the application of real-world evidence (RWE), and expanding multi-stakeholder collaborations to evolve value frameworks around new payment arrangements for SSTs.
2. We believe that cost-effectiveness analyses (CEAs) do not fully reflect the societal value of SSTs. Should cost-effectiveness models be used, we recommend that ICER assess uncertainty around treatment effects and allow for flexibility of model assumptions.
3. ICER should remove "shared savings" scenarios from the assessment of value.

These recommendations are further described below:

1. Focus efforts on quantifying additional value elements, increasing application of RWE, and expanding multi-stakeholder collaborations to evolve value frameworks around new payment arrangements for SSTs.

1a. Methods to incorporate additional elements of value should be developed.

We agree there is a lack of consensus on how additional value elements should be quantified and measured. However, this should not preclude these elements from consideration, as they represent what often lacks from health technology assessments (HTA) - the perspectives and

benefits to patients and society. Several of these elements are important in evaluating the long-term value of SSTs, particularly as related to the value of hope, scientific spillover, severity of disease, unmet need, and caregiver burden.²

As discussed during the recent ICER webinar series: *Perspectives on US Cost-Effectiveness Thresholds*, there is more work to be done in this area with regard to quantifying the benefits of the additional value elements.³ When quantifiable, ICER should include a mechanism to better incorporate the value of additional elements into the review, beyond the qualitative notations. This is an opportunity for ICER to work directly and increase engagement with patient groups in developing a methodology to measure these elements. By doing so, ICER would place patients at the center of the assessment by accounting for heterogeneity in characteristics, preferences, as well as the perspective of patients' caregivers and communities.⁴

The limited clinical experience with SSTs, and the natural history of the diseases they target, result in unreliable incremental cost-effectiveness ratios with wide confidence intervals, as highlighted by ICER's SST technical brief.¹ For this reason, CEAs should not be the sole determinant of value or value-based price of SSTs. A multi-criteria decision analysis (MCDA) may ultimately lead to results which better capture the weight of the additional elements. We encourage ICER to focus their efforts on exploring alternative frameworks, like MCDA, keeping patients at the center of these assessments. Moreover, partnering with stakeholders on developing value frameworks around novel payment arrangements would more likely ensure that the full value of SSTs is realized.

1b. The application of RWE should be increased.

To address uncertainty in assessment models, ICER can play an important role in advancing data standardization and use of RWE to inform optimal value-based agreements. In our experience with commercial payers, we identified scalability challenges due to the effort required to harmonize across heterogeneous data systems.⁵ For meaningful value-based arrangements to thrive across the health care ecosystem, particularly when addressing the challenges for SSTs, we collectively need to find a solution that encourages simplicity and the streamlined collection, synthesis, and exchange of data. Further, it requires an agreement on the definitions of value and outcomes.

Registries could provide detailed clinical and longitudinal data, including a more heterogeneous patient population than is included in typical clinical trials.⁶ Pierce et al. recently highlighted the importance of establishing a global registry for hemophilia gene therapies and the consequences of not.⁷ Additionally, if ICER were to utilize registry data to inform its reports, there is a potential to elevate patient reported outcomes and potentially incorporate their value into assessments, when quantifiable.⁸ The newly launching Rare Disease Cures Accelerator-Data and Analytics Platform, funded by a cooperative agreement through the FDA, may be a perfect opportunity to leverage the effort of the Critical Path Institute and the National Organization for Rare Disorders.⁹

1c. Multi-stakeholder collaborations should be extended to evolve value frameworks around new payment arrangements.

It is a tremendous undertaking to develop frameworks for assessing SSTs that have far-reaching effects for patients and society. ICER cannot do this alone and we encourage a multi-stakeholder

approach that results in a fair assessment of value for patients, health care providers, health systems, payers, manufacturers, and others involved.

The Massachusetts Institute of Technology led collaborative, NEWDIGS consortium FoCUS Project, proposes several customizable payment models for durable and curative therapies.¹⁰ The models include payment over time, pay-for-performance, and mobility. The precision financing strategies offer viable alternatives to large single payments without hindering innovation. Other organizations are committed to developing solutions to the challenges inherent to SSTs (Table 1).

There are a number of opportunities for ICER to engage the broader stakeholder community in developing new solutions to accessing and paying for SSTs. ICER can build assessment frameworks that allow for expansion of value-based arrangements. Such a framework would incorporate shared risk to account for uncertainty around long-term effects, adding an element of fairness among the involved stakeholders. The framework should be designed to encourage transparency about outcomes and shared risks, and to remove barriers that often preclude interested innovators and payers from willfully engaging in these types of arrangements. Measuring clinical outcomes over time can be resource intensive and will likely require a multi-stakeholder effort, such as a clinical data registry.¹¹

Table 1: Ongoing multi-stakeholder collaborations around value of SSTs

Organizations Active in SSTs	Areas of Innovation
Agency for Healthcare Research and Quality, Evidence-based Practice Centers ¹²	Outcomes-based payment models
Innovation and Value Initiative ¹³	<u>OpenSource Value Project</u> - Development of disease-specific economic models <u>Insurance Value</u> - New therapies not only benefit patients, but also healthy people at risk of future illness
Massachusetts Institute of Technology NEW Drug Development ParadIGMs, (NEW DIGS) (FoCUS) Project ¹⁰	Precision financing models for SSTs (Financing and reimbursement of cures in the US)
National Health Council ¹⁴	Patient-centric value elements

2. ICER should more rigorously assess uncertainty and allow for flexibility of model assumptions.

ICER addresses many concerns related to the evaluation of SSTs such as survival analytic techniques, sensitivity analyses, time horizons, and expanded discussions of uncertainty. To account for some of this uncertainty, we offer considerations for ICER during the analytic conduct of SSTs:

- A comprehensive assessment of outcomes related to the current standard of care and the curative potential of the SST should be detailed.
- It is important to ensure that the data informing the cure proportions are appropriate and representative of the patient populations of interest. For example, a disease-specific mortality endpoint must be available to estimate a survival curve for those uncured.

- With SSTs, data immaturity will be a common occurrence that limit identifying a sustained plateau. Scenario analyses using various survival analytic techniques should be conducted to characterize the range of potential results that may plausibly fit the available data to date.
- A clear process to inform model assumption should be outlined when there are no available data. For example, the use of clinical expert opinion or alternative data sources may be utilized.
- Model assumptions should be agreed upon by expert consensus in the therapeutic areas of interest. This requires ICER to expand their engagement process to solicit input from therapeutic area experts.
- The probabilistic sensitivity analysis should highlight the estimated price range for both the downside as well as upside risk accounting for the range of uncertainty in the value-based price.
- To interpret any PSA results, the variance around the uncertainty of parameter estimates should be appropriately characterized. ICER should detail this in their report.
- ICER should increase their acceptance of assessments and model inputs from multiple stakeholders, including manufacturers, and adopt more flexibility with model assumptions when uncertainty is high.

3. ICER should remove “shared savings” scenarios from the assessment of value.

3a. The “shared savings” scenario does not result in savings to all health care stakeholders.

“Shared savings” does not result in uniform savings across the multiple stakeholders within the health care ecosystem. Importantly, the “shared savings” scenario does little to incorporate patient-centric outcomes (i.e., caregiver burden and productivity). The reality of “shared savings”, which most benefits payers, are highlighted below:

- Payers experience a cost offset due to a lower price.
- Patients and caregivers experience no change in premium or co-pay.
- Health care providers experience no change in reimbursement.
- Hospital or care systems may experience offsets due to reduced resource utilization, but it is uncertain whether this translates into savings.
- Manufacturers may reduce R&D spend as a result of devaluing innovative treatments.

The reality of the constrained US health care budget is that there is no economic surplus. Rather there are cost-offsets overlaid on a budget constrained health care system.¹⁵

3b. Several underlying assumptions in the approach proposed by ICER have limited validity.

- The “shared savings” scenario assumes that curative treatments will not have generic competition and does little to consider branded competition. It is far too early to assume whether generics or alternative treatments that compete similarly to generics will exist in the future. While competition is limited with SSTs today, the current body of ongoing clinical trials suggest otherwise. For example, there are more than 10 registered clinical trials involving gene therapy in hemophilia alone.¹⁶
- The test cases to inform “shared savings” in the loss-of-exclusivity (LOE) scenario are arbitrary and unlikely to reflect the lifetime value of a SST. Only one LOE case (Hemophilia A) demonstrated reductions in the value-based price. For SMA and CAR-T,

the LOE scenario decreased the value-based price by approximately 4.5% and 6.3%, respectively.

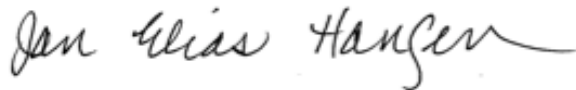
- The proposal implies that drug manufacturers are separate from the system. This premise ignores the substantial financial inputs from the pharmaceutical industry into the health system in the form of research and development.¹⁷ The benefits accrued by manufacturers are returned to society and the health care system through the funding and development of future innovation.

ICER can alternatively explore scenarios around shared-risk amongst various stakeholders, in addition to the other value-based arrangements and payment models recommended in section 1c.

In closing, we thank ICER for pursuing this much needed endeavor. ICER's collaborations with NICE, CADTH, and academic thought leaders is an important first step. Given the far-reaching impact of SSTs, the development of a value assessment framework cannot be done alone or in silos. Genentech is committed to being part of the solution and partnering with organizations, such as ICER, in addressing the challenges of implementing innovative payment models and advancing the science of value measurement for this new era of treatments. As part of our ongoing commitments, we are active in a variety of private sector outcomes-based contract pilots, developing frameworks to standardize data and outcomes measurement that will ultimately inform optimal value-based payment agreements, and developing methods to assess the impact of scientific spillover and MCDA to move beyond traditional HTA evaluations.

We invite ICER and others to collaborate with us in these efforts and appreciate this opportunity to provide our recommendations.

Sincerely,

A handwritten signature in dark ink, reading "Jan Elias Hansen". The signature is fluid and cursive, with a long, sweeping underline that extends to the right.

Jan Elias Hansen, PhD.
Vice President, Evidence for Access Medical Unit
US Medical Affairs, Genentech, Inc.

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November 8, 2019

Steven D. Pearson, M.D., M.Sc. FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

DELIVERED ELECTRONICALLY

RE: Proposed SST/Cures Adaptations to the ICER Value Framework

Dear Dr. Pearson:

On behalf of Gilead Sciences, we appreciate ICER's invitation to provide comments on Value Assessment Methods for Cures: *"Single or Short-Term Transformative Therapies" (SSTs): Proposed Adaptations to the ICER Value Framework*.

Gilead Sciences is a research-based biopharmaceutical company that discovers, develops, and commercializes innovative medicines in areas of unmet medical need. Gilead's therapeutic areas of focus include HIV/AIDS, liver diseases, cancer, and inflammatory and respiratory diseases. Our portfolio of more than 25 products contains a number of category firsts, including complete treatment regimens for HIV and chronic hepatitis C infection available in once-daily single pills and the first CAR T therapy approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.

ICER in the accompanying technical brief to their adapted methods has performed a thorough exploration of issues associated with the assessment of a cure and further, tested a number of assumptions to better understand the potential empirical implications of the adoption of several of these modifications to their 2020 Value Framework. This work has given some context to this initiative, but also raises a number of issues that require detailed examination. We would like to propose the following recommendations:

- Accurately capture 'quantum leaps' that SSTs potentially afford to patients and society
- Define clear criteria on what defines an SST
- Exclude shared saving analysis from SST assessment
- Use lower differential discounting rates on both costs and outcomes
- Calculate cost-effectiveness at the time point most *clinically relevant* to disease resolution

- Do not link innovative/alternative payment models such as outcomes-based contracting recommendations to model simulations
- Address lack of contextual consideration impact on SST voting

We look forward to continuing the robust dialogue on the topic.

General Considerations

Accurately capture ‘quantum leaps’ that SSTs potentially afford to patients and society

- The onset of an age of innovation in cures requires equal innovation in new ways to measure their value. New developments in virology, gene therapy and stem cell technologies are catalyzing discovery of cures including chimeric antigen receptor T-cell (CAR T) therapies for cancers, prevention and eradication of HIV and cures for hepatitis C. Yet, most methodologies in the assessment of the value of new drugs have not changed materially for 30 years.
- ICER’s currently proposed SST adaptation appears to be incremental with hardly any noticeable differences from the existing value framework. We recommend ICER structure their assessment methodologies to more closely align towards the potential value a cure brings. Yet with the adapted methods and technical brief, ICER appears poised to move in an opposite direction.

Define clear criteria on what defines an SST

- ICER defines SSTs as therapies that are delivered through a single intervention or a short term course of treatment that demonstrate a significant potential for substantial and sustained health benefit extending through patients’ lifetimes. ICER should ensure that there is clear understanding on how treatments are judged as substantial and how ICER determines sustained health benefits. Moreover, ICER should provide objective and transparent criteria on the time period for a course of treatment that qualifies as an SST, and conversely, what constitutes chronic therapy that would rule out an SST categorization.

Shared Savings

Exclude shared saving analysis from SST assessment

- ICER suggests that SSTs will deliver such extreme health gain and/or cost offset such that cost-effectiveness methods will allocate too much of the economic surplus to innovators amplified by the fact that many transformative treatments will not follow a traditional pathway toward generic competition following the end of exclusivity.¹ This has been disproven by research which suggests that the length of exclusivity and patent protection can deliver insufficient savings to innovators.² For example, HIV/AIDS drugs introduced in the 1980s onwards delivered only 5% of the shared savings to pharmaceutical manufacturers.³
- There are competitive market mechanisms that naturally adjust for price and value. ICER’s assumption on shared savings neglects the impact of the introduction of competitive products on the price of each drug in a given indication or market. Products on patent are still subject

to competitive pressure from other market entrants which functions to reduce net prices. ICER also fails to account for the impact of generic entrants as branded drugs reach the end of their period of exclusivity.⁴ In addition, the presence of competition in the market provides natural net price erosion to the brand name drug.

- Another issue with connecting a drug's value to economic surplus is the concept of leapfrogging: namely, that one innovative drug renders breakthrough existing drugs obsolete. For example, both Vertex's hepatitis C drug Incivek and Merck's Victrelis were considered highly innovative when launched in 2011, but saw rapid sales contraction only three years later when Gilead launched Sovaldi.⁵ Notably, Incivek and Victrelis were discontinued prior to going off patent due to dwindling patients and the overwhelming superiority of newer direct-acting antiviral agents. This is but one example that argues for preserving a balance in economic surplus between innovator and society.^{6,7}
- There is economic surplus already lost from ICER's proposed Value Framework cost inclusion (limited to the payer) and value measurement (limited to the QALY) that will also apply to SSTs. The concept of shared savings does not fit with ICER's current and proposed 2020 Value Framework, which takes the healthcare payer perspective where all costs and cost-offsets (reduced future treatment/management costs) relate to the payer: nothing is assigned to the innovator. By narrowing related cost inclusion and cost exclusion to the payer, (and excluding lost productivity costs and other areas of value), ICER's proposal for shared savings appears to eliminate a proportion of the future savings in treatment/management costs (due to a cure), in order to lower the price needed to reach the cost/QALY threshold and ultimately ICER's budget impact threshold.
- ICER should consider the impact on innovation incentives from such an approach. Reducing or controlling the economic surplus of cures may deliver short term gains to payers but in the long-term could lead to a negative impact on society by reducing the number of cures and slowing down their development.^{8,9}

Discounting

Use lower differential discounting rates on both costs and outcomes

- ICER should consider lower differential discount rates of <3% on costs and <1.5% on outcomes. While ICER has tested both different discount rate values and differential rates, they have decided to standardize a 3% cost and outcome discount rate "as there is no persuasive evidence for the use of another rate at this time".¹⁰ It should be noted that the 3% discount standard was implemented by the 2nd Panel of Cost Effectiveness in an era when SSTs did not exist, necessitating revisiting discounting for these transformational therapies.
- Discounting has a significant, disproportionate and detrimental effect on SST value calculations. Typical of cures is a survival and benefit time horizon that is extremely long. Hence, the application of a constant discount rate can make the effect of benefits in the future close to zero.¹¹ This is inequitable to future generations in the valuation of cures resulting in the artificial prioritization of more traditional chronic disease treatments which lose their

impact over long time horizons. Moreover, discounting future outcomes skews incentives for innovation away from long-term curative and transformational therapies.

- ICER further states that it does not propose presenting sensitivity analyses that vary the discount rate, as they do not believe this provides additional information useful to the decision-makers. There is persuasive evidence that incorporating different discount rates for SSTs would categorically help decision-makers make decisions, not only for member per month impact assessments but for societal policy makers as well.¹² Omitting the impact of multiple discount rates catastrophically diminishes the transformational nature of SSTs, obscuring the quantum change that cures deliver and that society and policy makers will need to understand.

Uncertainty

Calculate cost-effectiveness at the time point most *clinically relevant* to disease resolution

- Rather than performing incremental cost-effectiveness scenarios at arbitrary time horizons, we recommend ICER calculate incremental cost-effectiveness according to what is most relevant to clinical decision making and patient outcomes. Evidence in literature has repeatedly stated that the assumed time horizon in a health economic analysis can substantially impact the value of a medical intervention.¹³ To best capture the associated costs and effects to be assessed, ICER should select an analytic horizon most clinically relevant to the intervention. Longer or shorter time points may add irrelevant costs and impact the results in ICERs SST modelling.¹⁴

Do not link innovative/alternative payment models such as outcomes-based contracting recommendations to model simulations

- Central to the objective evaluation of SSTs is preserving the ability to purely measure the value of an innovation before calculating its impact on budget or affordability. ICER proposes to link probabilistic sensitivity analysis (PSA) results to outcomes-based arrangements (OBA) at a price where 25% of simulations of cost-effectiveness results are great than \$200,000 per QALY.¹⁵ A fundamental aspect of this approach is that it conflates value (cost-effectiveness) with affordability (budget impact), which are completely different concepts, requiring separation so as not to confound decision-making. Calculating holistic and inclusive value of an SST should be the goal of an ICER assessment. Independently, affordability should be the purview of payers and other stakeholders, empowering them to make decisions empirically relevant to their budget and individual priorities. Moreover, if the value based price of a treatment is unaffordable as a single payment then alternative payment schedules could be explored (as with Zolgensma) to manage the budget impact.
- Directly linking model simulations (PSA) to OBA would bypass many critical steps and considerations in the development of an OBA. For example, these include how data would be collected and by whom; feasibility of agreements for patients covered by payers where there are statutory provisions that impede OBAs;¹⁶ empirical challenges in determining the appropriate outcome; and how and when to measure and audit this outcome. All these are details requiring consideration for an OBA on a case-by-case basis, invalidating inflexible policies. A further challenge is how to incorporate payments where cures/SSTs outperform initially set OBA performance criteria. Much in the way that advanced alternative payment

models (APM) have two-sided risk arrangements, OBA will need to evolve to ensure that all parties that are taking risk are appropriately rewarded.

- A further technical consideration is that PSA has a number of limitations. PSA methods have known risks in that these do not account for interactions between parameters: this confounds results. PSA is also dependent on the choice of which variables to test and susceptible to subjective bias in results interpretation.¹⁷ It is further important that ICER explicitly define the number of PSA simulations needed to make a determination on uncertainty. Moreover, the best PSAs cannot overcome unknowns or flaws in the fundamental structural integrity of any model. All of this opens up the likelihood that payers and policy-makers could make the wrong decisions if over-reliant on this method.¹⁸ ICER recognized the methodological weaknesses of PSA when it stated: *“PSA is just one way to evaluate uncertainty, and it is unclear if it is the best way to capture the uncertainty related to duration of effect that is so central to the assessment of SST’s. Any criterion for the percent of PSA runs that would need to be below a certain threshold in order to satisfy decision-makers would be arbitrary...”*¹⁹ To navigate uncertainty, we recommend ICER use future points in time to re-assess a value-based price through developments in durability, safety, clinical practice as well as use in other patient sub-populations.

New Voting Elements

Address lack of contextual consideration impact on SST voting

- Cures are particularly differentiated in their ability to offset long-term caregiver and patient costs and increase ability to work: these should be reflected in SST assessment. The inclusion of costs not only incurred by the healthcare payer but also those incurred by the patient, employer and caregiver, (including offsets in earnings) are fundamental to good health technology assessment practice (reflected in the global First (1996) and Second (2017) Panels on Cost-effectiveness).^{20,21} Moreover, this is exceedingly important in cures where the bulk of benefit and cost-offsets occur not with the payer but with society. Excluding these costs obscures cost savings and may result in the prioritization of chronic treatments over cures. For example, in HIV/AIDS before treatment and prevention such as PrEP, non-medical costs incurred by society were as much as 6.5 times direct medical costs.²² Similarly, 80% of total costs for cirrhosis and chronic liver disease are indirect costs.²³
- ICER proposes to adopt two more voting elements in the contextual considerations for SSTs however, there is no evidence that ICER contextual considerations have any impact on the voting on value or the value-based price. Moreover, SST CEPAC and CTAF voting affords a small group of less than 20 people to theoretically determine the price and value for thousands of patients and future generations afflicted with diseases that SSTs could cure. This is a process that ICER needs to evolve to address issues of equity and inclusiveness for SST valuation.

Gilead appreciates the opportunity to provide comment on the value of a cure. We would welcome the opportunity to become a thought partner to ICER in this area.

Sincerely,



Bill Guyer
Senior Vice President and Head of Medical Affairs

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September 6, 2019

Institute for Clinical and Economic Review (ICER)
Two Liberty Square, 9th Floor
Boston, MA 02109

<Via email: publiccomments@icer-review.org>

Re: Public Comment on Proposed Methods Adaptions for Assessments of Potential Cures and Other Transformative Therapies

To Whom It May Concern:

The Goldwater Institute submits the following public comment on the proposed methods adaptions for assessments of potential cures and other transformative therapies. The Goldwater Institute is a public policy research organization based in Phoenix, Arizona, which works in courts, legislatures, and communities nationwide to defend and strengthen the freedom guaranteed in the constitutions of the United States and the states. Among its other projects, the Institute focuses on market-based reforms for medical care.

The stated purpose of the proposed adaptions to ICER's value framework is to evaluate the value of "single or short-term transformative therapies" or SSTs. Unfortunately, this approach relies on the same, fundamentally flawed and often outdated approach of its original value assessment framework.

In a Goldwater Institute report released last year, Goldwater Visiting Fellow in Healthcare Policy [Dr. Rafael Fonseca](#), who is also a renowned hematologist and oncologist, and his co-authors included [a critique of the ICER approach](#) as it related to multiple myeloma and wrote:

"Regarding myeloma, the conclusions reached by ICER's evaluation are problematic and do not reflect a bona fide approach to understand best practices for the treatment of myeloma better. The ICER process was largely limited by the lack of myeloma experts in its panels, the lack of meaningful input by key stakeholders, the lack of consideration of biologic variability among myeloma cases, and the fact that by the time of this writing, its conclusions are already outdated given the rapid pace of clinical research in myeloma."

The authors went on to point out that:

“ICER’s process is not peer-reviewed to a scientific standard, does not include disease experts as evaluators or authors, does not use patient-centered endpoints or definitions of value, does not reflect current standards of evaluation for evidence-based medicine, and lacks a mechanism for continuous review and revision.”

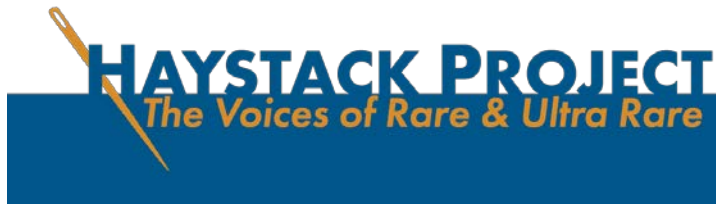
The current proposal for SSTs not only face the exact same shortcomings, but they also ignore the insurance innovations already taking place to address these treatments’ high costs.¹ There is no doubt that the cost of treatment is complex and deserves more attention, but is this the approach that we should follow, especially when lives hang in the balance? ICER’s approach of setting a dollar amount on the value of a patient’s life is not only immoral, but dangerous for all of us.

Sincerely,



Naomi Lopez Bauman
Director of Healthcare Policy

¹ For example, see Joseph Walker and Anna Wilde Mathews, “Insurers Pitch New Ways to Pay for Million-Dollar Therapies,” *Wall Street Journal*, September 5, 2019 at <https://www.wsj.com/articles/insurers-pitch-new-ways-to-pay-for-million-dollar-therapies-11567677600?shareToken=staf0f673c0baf47368a434f2a034c1f4a>.



September 6, 2019

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: Proposed Adaptations to the ICER Value Assessment Framework: Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs)

Submitted electronically: publiccomments@icer-review.org

Dear Dr. Pearson,

Haystack Project and the Rare Cancer Policy Coalition (RCPC) appreciates the opportunity to respond to the Institute for Clinical and Economic Review’s (ICER’s) proposed value framework adaptations for single or short-term transformative therapies (SSTs).

Haystack Project is a non-profit organization enabling rare and ultra-rare disease patient advocacy organizations to coordinate and focus efforts that highlight and address systemic reimbursement obstacles to patient access. Our core mission is to evolve health care payment and delivery systems with an eye toward spurring innovation and quality in care toward effective, accessible treatment options for all Americans.

The Rare Cancer Policy Coalition (RCPC) is a Haystack Project initiative that brings together rare cancer patient organizations. RCPC gives participants a platform for focusing specifically on systemic reimbursement barriers and emerging landscape changes that impact new product development and treatment access for rare cancer patients. It is the only coalition developed specifically to focus attention on reimbursement, access and value issues across the rare cancer community. Working within the Haystack Project enables RCPC participants and rare and ultra-rare patient advocates to leverage synergies and common goals to optimize advocacy in disease states where unmet need is high and treatment inadequacies can be catastrophic.

We recently provided feedback on ICER’s updated value framework, emphasizing many of the challenges patients with rare and ultra-rare diseases face within the context of the ICER value framework and its reliance on population-level indices of quality and value. We appreciate ICER’s recognition that traditional cost-effectiveness methodologies do not capture the potential value of emerging therapies that provide enhanced patient outcomes (and/or potential cures) extending well beyond the treatment period.

BACKGROUND ON RARE AND ULTRA-RARE CONDITIONS

Over 35 years ago, Congress recognized that commercial realities associated with research and development discouraged innovation in treating serious medical conditions affecting small populations. Countless lives have been improved, or saved, by new therapies stimulated by the set of statutory incentives for orphan drugs. Although millions of Americans affected by a rare disease are still waiting and hoping for treatment or a cure, there are many for whom treatments that are already available or in the pipeline are out of reach due to the realities of current reimbursement structures.

- Of the approximately 7,000 rare diseases identified to date, 95% have no FDA-approved treatment option;
- 80% of rare diseases are genetic in origin, and present throughout a person's life, even if symptoms are not immediately apparent;
- Approximately 50% of the people affected by rare diseases are children;
- 30% of children affected by a rare disease will not live to see their 5th birthday; and
- Approximately half of identified rare diseases do not have a disease-specific advocacy network or organization supporting research and development.

Foundational assumptions and policy goals driving ICER's framework and proposed adaptations disproportionately disadvantage transformative therapies for rare and ultra-rare disorders

Innovation in how we understand and address disease mechanisms is currently advancing at a previously unthinkable pace. ICER'S proposed framework adaptation seeks to respond to the emergence of targeted cancer treatments, gene therapy and regenerative medicine, and immunologic approaches to rare, serious, and life-threatening conditions that give renewed hope to patients and their caregivers.

We remain concerned that, even with the proposed adaptations, ICER's framework of "willingness-to-pay" thresholds and panel votes to categorize treatments as low, medium or high value in monetary terms is in diametric opposition to the US health care ecosystem's efforts toward a patient-centered perspective on "value." The US health care system is not driven by vertical equity; it is based on the concept that an insured individual is covered for medically-necessary treatments whether their disease is common and its treatment cost low, or their disease is rare with one, costly, available treatment.

Similarly, ICER's reliance on a payer perspective and its operational paradigm of "risk" as a mathematically-derived sum that can be allocated between payers and manufacturers relegates patients to bystander status. It also discounts the ability of commercial and public entities to mitigate and respond to risk over time with price changes (for manufacturers) and marginal premium increases, formulary strategies, and other tools (payers).

Patients unable to access potentially life-saving treatments, or parents and caregivers struggling to ensure that their child receives the only therapy with potential to halt disease progression, bear the true consequences of risk allocation. We urge ICER to ensure that its concerns about

emerging treatments unduly burdening the health care system be resolved in a manner consistent with US healthcare policy, i.e., that patients insured by public or private payers are entitled to the treatment they need regardless of whether their condition is common and treatment costs low, or their disease is extremely rare and treatment costs are very high.

The proposed framework adaptations will not sufficiently address the unique challenges of valuing transformative treatments for extremely rare diseases.

Haystack Project supports efforts to expand equitable access to quality health care.

Unfortunately, ICER's efforts to date suggest that, even with its proposed framework adaptations for transformative therapies and ultra-rare disorders, ICER evaluations of emerging ultra-rare disease treatments will likely function only to impede access and inject sufficient uncertainty to chill future innovation.

We reiterate our recommendation that ICER approach review of new treatments for rare and ultra-rare diseases, including those that are transformative or potentially curative, with cautious consideration of both the inherent uncertainties in quantifying "value" of these treatments within a more general population health paradigm and the potential that the risk associated with these uncertainties will fall on rare patients denied access.

A recent example is ICER's review of Spinraza and Zolgensma for Spinal Muscular Atrophy (SMA), which yielded the dire statement that "[t]he US health care system cannot sustain paying prices far above traditional cost-effectiveness levels for the growing tide of treatments for ultra-rare disorders." It appears, from ICER's SMA example in its technical brief, that the framework adaptations proposed would have little, if any impact on review of high-cost transformative treatments for ultra-rare disorders. We see this SMA example as providing a clear barometer on the threshold issue of whether or not ICER's adaptations may be a sufficient accommodation for curative or transformative ultra-rare disease treatments because:

- SMA is a catastrophic disorder with some subtypes sufficiently severe to make it unlikely that a baby will survive to age two.
- ICER's New England CEPAC acknowledged "the remarkable effectiveness and many additional potential benefits and contextual considerations of Spinraza and Zolgensma."
- ICER lauded Biogen for its randomized, controlled clinical trial design and its robust enrollment, noting that "their efforts to generate such high-quality evidence sets a standard of excellence which other manufacturers should follow."
- Despite the catastrophic nature of the disease, and the high quality of evidence demonstrating efficacy, ICER's framework drove a unanimous panel vote that Spinraza - until very recently, the only SMA treatment available - represented *low long-term value for the money* due to its *high price*. Spinraza was introduced to the market in 2016, but Zolgensma was not even commercially available at the time of ICER's review.

We believe that it is highly likely that novel approaches to ultra-rare conditions and many rare cancers will similarly fail to clear ICER's hurdles, even with the proposed framework adaptations, until they have been used in clinical practice for a sufficient number of years to establish that the value demonstrated in FDA pivotal trials translates to ICER's view of value

over the long-term. Even then, the treatments we need – existing and yet-to-be-developed – will not demonstrate “value” unless that concept is relevant to the disease and its small patient population, and the model reflects the values of the US health care system.

We urge ICER to refocus its proposed framework adaptations toward refinements that can be integrated quantitatively into ICER assessments.

Haystack Project and the RCPC support efforts to identify disease-specific indicia of value from the patient perspective and appreciate ICER’s acknowledgement that additional domains of value exist. Unfortunately, ICER’s concerns that quantifying these additional benefits is “exploratory” and without consensus among academic health economists ignores the fundamental reality that by **not** substantively incorporating a quantified value, ICER is erroneously setting the value at zero. For patients with rare and ultra-rare disorders, each ICER decision to approach unknown or novel considerations by reverting to a “gold standard” applied to common conditions with multiple treatment options places an additional layer of distortion on the disease-specific value of a specific therapy.

Haystack Project and RCPC had hoped that ICER would rise to the challenge of placing patients, including those with disabilities and rare conditions, at the center of the value equation. We firmly believe that QALY limitations and deficiencies are most pronounced when applied to rare and ultra-rare conditions. A comprehensive study on the use of incremental cost per QALY gained in ultra-rare disorders by Schlander et al., discussed that a growing body of literature considers cost per QALY economic evaluations in ultra-rare diseases as flawed, and likely to set inequitable benchmarks that treatments for ultra-rare diseases cannot meet.

Despite the shortcomings in utilizing QALY for the diverse set of rare and ultra-rare conditions with emerging treatment options, ICER continues to rely on its use and relegate the disease-specific considerations that are more closely aligned with value to sidebar discussions that are likely to be ignored as extraneous or irrelevant. Patients in countries with technology assessment approaches that use QALY and rigid willingness-to-pay criteria experience treatment delays, coverage denials, and decreased associated survival rates.

We strongly believe that patients and their caregivers deserve innovation in health care economics and value assessments that rise to meet the innovations we are seeing in treating diseases that have long been untreatable and incurable. When ICER articulated these framework adaptations for ultra-rare conditions, it stated :

When there are challenges translating the outcome measures used in clinical trials and available patient-reported data into QALYs, ICER will conduct a search for “mapping” studies that may allow translation of surrogate outcomes into quality of life measures. The validity of these mapping studies will be discussed with manufacturers, clinical experts, the patient community, and other stakeholders in order to get their input on the most feasible way to translate these other measures of patient outcome into QALYs.

Although ICER has embraced a role in assessing value for each new treatment for an ultra-rare disorder, we are unaware of any instances for which it accommodated the unique circumstances of a specific disease by attempting to translate surrogate outcomes into QALY. We firmly believe that patients with an emerging transformative or potentially curative treatment for their rare or ultra-rare disease present a compelling case for ICER to either quantify patient perspectives on high-value outcomes within its framework or decline review.

Haystack Project and RCPC actively encourage patient advocates to explore and gather data on what outcomes are most important to patients. Patient advocates, armed with sufficient time to devise proactive and meaningful input, can not only improve the validity of ICER's assessments, but increase patient acceptance of and agreement on the results of its reviews. While we appreciate ICER's concern that incorporating patient priorities, preferences and views on outcomes into its QALY framework on a disease-specific basis is new territory, the weight of evidence indicates that general population perceptions of high-value outcomes within QALY have little validity across rare and ultra-rare diseases. We therefore strongly believe that any concerns on validity of cost-effectiveness and value assessments in rare diseases are as, if not more, compelling when ICER adheres to a QALY-based framework that is recognized as a poor fit for these conditions.

To the extent that disease-specific considerations cannot be incorporated in a quantitative manner, we urge ICER to recommit to its position that when it "judges that it is not feasible to translate measures of patient outcome into QALYs, ICER will provide analyses of the potential costs and consequences of treatment, and will not produce a value-based price benchmark." Although ICER did not adhere to these limitations in more recent reviews, for transformative treatments addressing rare and ultra-rare conditions, the analyses would fulfill ICER's goal of supporting informed decisions between patients and their providers.

Conclusion

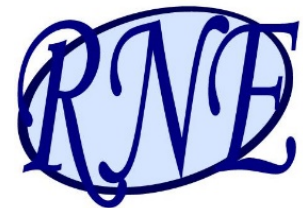
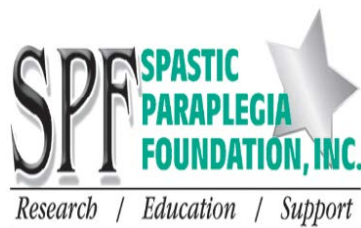
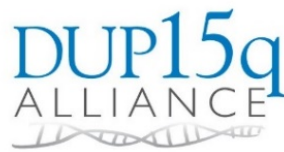
Where providers, patients, and payers have a set of treatment options approved for a specific condition, ICER can play an important role in informing decisions. We are, however, concerned that ICER's proposed changes and adaptations to its framework over time have yielded assessments that judge the novel treatments we hope for and need to live full and productive lives as "low value." Specifically, we believe that ICER's framework(s):

- Inappropriately conflates 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;
- Fails to consistently and transparently apply standards that are validated for use within the disease state;
- Will have the unintended consequence of discouraging innovation;
- Fails to incorporate real-world data, and pricing decisions; and
- Fails to incorporate patient and caregiver perspectives of value.

While we do not believe the framework adaptations sufficiently address these methodological deficiencies, we appreciate ICER's efforts toward improving the relevance and validity of its assessments. Once again, we appreciate the opportunity to comment on the proposed framework adaptation. As the voice of rare and ultra-rare disease advocates, we look forward to working with you in the future to facilitate patient and caregiver engagement, and to further inform your rare and ultra-rare disease policies, proposals, and frameworks. If you have any questions or would like to discuss our comments and recommendations, please contact Saira Sultan at 202-360-9985.

Sincerely,





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September 6, 2019

Steven D. Pearson, MD, MSc
President, Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

ISPOR is pleased to respond on behalf of its membership to the call for comments on proposed adaptations to your value assessment framework for Single or Short-Term Transformative Therapies. We strongly agree that these are important issues to address with input from a wide variety of stakeholders, and thank ICER and its collaborators for this opportunity to provide our comments.

ISPOR is a scientific and educational society with many of its members engaged in some aspect of health economics and outcomes research (HEOR) related to evaluation of pharmaceuticals. Our membership includes over 20,000 individuals across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government, and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

This response was formulated with the assistance of ISPOR's most senior and representative Council, the Health Sciences Policy Council, as well as our Institutional Council and members of our recent Special Task Force on US Value Assessment Frameworks. It was reviewed by and approved by our current President and myself. Given the 4-week response period, however, we were unable to conduct the poll of membership that we typically do for such consultations. This area is of great interest to ISPOR and its members and we would be happy to engage in further consultation in this area. We would also welcome conference submissions or other suggestions for broadening the discussion about these issues.

ISPOR would be happy to answer any questions about our response. Please consider Richard Willke, PhD, our Chief Science Officer, as the contact person in this area.

Sincerely,



Nancy S. Berg
CEO & Executive Director
ISPOR

ISPOR's comments below are provided by section of the "Proposed Adaptations" document:

1. Determining those treatments for which adapted assessment methods will be used

ISPOR supports the definition of these therapies and their need for additional consideration in economic evaluation. However, it is important to delineate the potential reasons for doing so. From a pure welfare maximization approach, there is no clear need for a "new" model for economic evaluation of these therapies: standard CEA/threshold-based decision approaches are still relevant, given their understood limitations. Nevertheless, single and short-term transformative therapies (SSTs) do involve a few unique considerations, both practical and conceptual. On the practical side, the potential for major health gains as well as large cost offsets, and their inherent uncertainty, call for additional care in those calculations. Similarly, the financial and affordability risk due to large upfront payments for lifetime benefits, or the alternative of staged payments, distinguish this class of drugs, leading to concerns about what may constitute a viable pricing and payment system for them consistent with their economic value. Finally, on the conceptual side, is the controversial concern about whether pricing of drugs for very small populations should explicitly consider R&D costs in some systematic way (Drummond & Towse, 2019).

We also encourage ICER to provide clear inclusion and exclusion criteria for potential SSTs, at least to the extent that these adaptations will only be applied to those included in this definition. For example, some oncologics clearly qualify, some clearly don't, but there are certainly some that may or may not.

2. Assessing and Describing Uncertainty

Cure proportion model: The cure proportion modeling technique fits better than other models to survival data with a cured portion. To accurately estimate the cure rate and the survival probability of the uncured patients, long-term follow up is normally needed. ICER acknowledges this as the condition to apply the cure proportion models and we agree with its adoption as a reference case when appropriate.

In cases where long-term follow-up data are not available, ICER's position is that "the presentation of results from several types of survival models can be used to develop a range around estimated long-term survival until more data become available". We would like ICER to elaborate on what types of survival models are acceptable in such situations. We would recommend the finite mixture model or other latent class mixture models as options to capture heterogeneity of response in a more general way than simply cure/non-cure proportions. Even when there are no long-term data showing the survival curve plateaus after certain time, there may be good reason to believe that the patients are heterogeneous (they respond to the treatment differently), so mixture models may fit the data better than other single population parametric models. We recognize that such models may be difficult to fit in some cases, but when they do fit they can help inform the modeling of longer-term survival.

Time horizon threshold analyses for durability of effect: We understand that estimating cost-effectiveness ratios at specific time horizons is a recognized type of sensitivity analysis on this dimension of cost-effectiveness calculations. However, it is an indirect approach to capturing uncertainty in the durability of a treatment effect—isn't it better to model that uncertainty directly? Using specific time horizons, especially to calculate an array of value-based prices, has little clinical rationale, risks creating greater confusion about results, and could disproportionately impact curative and transformative therapies for children and adolescents; this approach should be used with great caution.

Probabilistic sensitivity analysis linked to policy recommendation for outcomes-based payment: We also understand that PSA is a standard tool for measuring uncertainty in CEA results, and that uncertainty in outcomes is a reason for considering outcomes-based agreements (eg, Cohen et al, 2019). However, this is another indirect connection that should, at best, be used cautiously, given the probably-pragmatic-but-still arbitrary “25% over 200K” threshold proposed. Should recommendations for payers be based on this particular criterion before more consensus is developed about it? And what about the flip side of this story—if a new medicine/ intervention is most likely cost-effective (based on PSA), should it be recommended that payers grant open access to all patients with low co-pays and no prior authorization criteria, using value-based insurance design principles?

3. Additional Elements of Value

In its technical brief on “Methods for Potential Cures,” ICER considers including additional elements of value, including “insurance value.” We appreciate ICER’s interest in this concept and wish to clarify several aspects of their discussion. The brief summarizes its views as follows: “a major overriding factor that would argue against the inclusion of additional value domains cannot be overstated: their inclusion would raise fundamental equity concerns. Higher spending on certain SSTs (or other treatments) that get extra credit for these additional value domains would lead to opportunity cost effects either inside or outside the health system.”

ICER views all these new value elements as additive, when in fact “insurance value” is *corrective*. ICER’s underlying assumption is that “classical” cost-effectiveness methods produce estimates of value that are substantively correct and that align with the rank-ordering of medical technologies. This view is not supported by recent research. In their work identifying insurance value, Lakdawalla, Malani, and Reif (2017) demonstrate that traditional cost-effectiveness methods, including those used by ICER, wrongly assume that healthcare consumers are risk-neutral. This is incorrect for numerous reasons. For example, if consumers were risk-neutral, they would not be interested in health insurance! By properly accounting for risk-aversion, Lakdawalla, Malani, and Reif show that the traditional approach overvalues treatments for mild disease and undervalues treatments for severe illness. Thus, the sickest, most vulnerable patients are penalized by this analytical error in traditional cost-effectiveness methods.

Similarly, ICER argues that “it is also not clear that willingness to pay for ‘peace of mind’ would not apply equally to societal spending in areas other than health care.” In fact, deploying insurance value aligns cost-effectiveness analysis with well-accepted welfare economics approaches that are used in the rest of the economy. For at least 80 years, economists have recognized that consumer preferences must be

accurately incorporated when valuing governmental programs and social spending (Samuelson 1977). This includes incorporating realistic risk-aversion preferences. CEA has stood apart from the rest of welfare economics in assuming that consumers are risk-neutral. Failure to incorporate insurance value into CEA perpetuates this misalignment and may systematically undervalue health spending compared to spending on other programs. Moreover, “insurance value” has implications for how medical technologies are rank-ordered, not just for the total level of healthcare spending. Put differently, even if we held healthcare spending fixed, insurance value would alter the way those fixed dollars are allocated; it would shift dollars toward more severe illnesses and away from milder ones.

There are two specific domains that are recommended for consideration by the independent appraisal committee:

- (1) A potential advantage for therapies that offer special advantages by virtue of having a different balance or timing of risks and benefits versus other treatments; and
- (2) A potential disadvantage for therapies that, if not successful, could reduce or even preclude the potential effectiveness of future treatments.

The first one, also known as “value of hope” (a preference for positively skewed outcomes), now has enough empirical support to be given serious consideration, and we agree with its inclusion. We are not sure the new label is an accurate or better description; it does not seem specific enough to the situation. If value of hope is too non-specific as well (though we still like it), maybe call it something like “preferential weighting of highly positive outcomes.”

The second one appears to be a “negative” aspect of “real option value,” in that a therapy may reduce or eliminate the potential benefits of a future therapy. If this is to be included, however, it seems inconsistent not to include the “positive” side of real option value, i.e., that some additional survival due to a therapy increases the potential to be further treated by a new therapy that may become available during that survival time. We agree, however, that there is some risk of double-counting, and that further research is needed to sort that out.

Finally, curative and transformative treatments can have a very significant impact on the family of the patients in terms of productivity and quality of life. Since ICER is very interested in the societal and health system impact of SST, and in keeping with the recommendations of the 2nd Panel, we encourage further consideration of these broader societal elements of value and their impact to the health system and society.

4. Time Divergence Between Costs and Benefits

Discounting: We understand and endorse the 3% standard for discount rates. However, given ICER’s propensity to consider sensitivity analyses for many other factors, we are not sure it’s consistent to rule out sensitivity analysis on the discount rate used for these therapies, especially when over a lifetime it can make quite a difference (e.g., a fully healthy 75 years of life expectancy becomes 30.6 years at a 3% discount rate, but is 39.5 years at 2% and 24.6 years at 4%).

5. Affordability and Fair Sharing of Economic Surplus

ICER's presentation of the concept and application of the concept of "shared savings" is a great starting point for beginning a discussion about appropriate rewards for innovative so-called SSTs. On a minor terminological point, the section heading refers to "Fair Sharing of Economic Surplus", but "fair" is never defined or explained. In health economics, "fair" is most commonly used in discussion of equity issues (which are not being discussed here) or about a "fair market", where participants compete on a proverbial "level playing field." In this case, the use is probably closer to the latter meaning, but the term "appropriate" (as used on p. 9) would be better. And by "appropriate", we would mean a system that aims to promote "dynamic efficiency", viz., the optimal amount and mix of medicines innovation across different types of medicines—small molecules, biologics, and SSTs.

As noted, under the current regulatory and legal system, innovative small molecules and biologics in the U.S. have a net exclusivity period of approximately 12 years. The expectation is that the generics or biosimilars will enter the market after 12 years, and the price of these substitutes will eventually be considerably lower than that of the branded originator product. One might think that creating a level playing field for SSTs would apply a similar rule, as ICER proposes. However, as ICER notes, not all SSTs are the same and some could be "cures" in very small (ultra-orphan) population. There is a case for running the proposed shared savings as a scenario analysis—but not as the base case for the VBP.

As we have noted elsewhere, ignoring several potential "novel" elements of value related to uncertainty could seriously bias the assessment of some technologies (Lakdawalla and Phelps, 2019)—and particularly in the case of health-catastrophic ultra-orphan conditions. There is likely to be an interaction among severity of disease, financial risk protection, health risk protection, and the value of hope (for a cure) (Jena and Lakdawalla, 2017; Garrison et al., 2019). Under conventional CEA, this would imply a higher cost-effectiveness threshold for QALY gains. Or using a net monetary benefit estimate from augmented CEA, this would imply adding value beyond cost-offsets and the QALY gain times the standard threshold.

A calculation of "shared savings" based only 12 years of exclusivity and the QALY gains would ignore these factors. We would urge ICER to give this more thought before launching without further study of the impact on different types of SSTs—and particularly those for health-catastrophic ultra-orphan conditions.

Conclusion

We congratulate ICER on its thorough and very well-written recommendations and are pleased to be able to provide the comments above. One final comment may be about the general relevance of many of these considerations—would they change final recommendations about the products, at least for the purposes of payers, who are a primary audience for ICER's scenarios? Based on the examples shown in section 5 of the Technical Brief, very few of the scenarios shown would have caused the incremental CER to cross a \$150K/QALY threshold. On the other hand, the differences in the value-based price were

sometimes large, which could matter if they were implemented. On the whole, however, these proposed adaptations do address – perhaps with some potential modifications – many of the issues that arise in the economic evaluation of SSTs.

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September 6, 2019

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Comments to ICER's proposed value assessment framework to address "single or short-term transformative therapies (SSTs)"

Dear Dr. Pearson:

The Innovation and Value Initiative (IVI) appreciates the opportunity to offer comments on the draft set of methodological adaptations to the Institute for Clinical and Economic Review's (ICER) value assessment framework to assess treatments deemed "single or short-term transformative therapies (SSTs)."

IVI is a non-profit research organization whose mission is to advance the science and improve the practice of value assessment in healthcare by adapting a more collaborative, open and tailored approach to examining value, exploring new methods and building models that can support flexible decision making.

Before offering IVI's specific comments to ICER's recommendations, at the outset, we believe it is important to reiterate a point made in our recent response to ICER's proposed changes to the 2020 Value Assessment Framework: namely, ICER's stated goal of estimating long-term value while providing short-term budget estimates in a market where decision makers are incentivized to act primarily based on short-term costs.¹ While this is a concern in the use of all ICER value assessments, it is particularly acute in the case of SSTs, which are more likely to involve high upfront costs with benefits arising over a long timeframe. We do not suggest that ICER is responsible for altering these incentives. We do, however, highly encourage ICER to address these issues head-on in all reports, especially related to recommendations for outcomes-based contracts and other non-traditional financing strategies.

¹ Specifically, our previous response included the following: "A further challenge exists regarding the need for a long-term view when quantifying the value of a medical technology and the frequent short-term budget-driven perspective of decision making. We agree that the long-term value of a therapy is the most important consideration, and this is certainly true for patients, their families, and society at large. In a system where health plans make coverage decisions based on short-term budget impacts, however, there is little incentive for insurers and others to prioritize investments in therapies with higher short-term costs but 2 greater long-term value. This issue is acknowledged and discussed in the existing ICER value framework. We are concerned, however, that merely listing long-term value alongside short-term budget impact leaves the decision-maker with the easy option to ignore long-term value. The potential disincentives to invest in treatments with long-term societal benefits are a pressing issue that confronts our society as whole, but through the reports and policy analyses produced by ICER, there is an opportunity to educate audiences on the issue and generate discussion about potential solutions."

Please find our response to specific proposed changes below. IVI's response is organized to correspond to ICER's "Proposed Adaptations to the ICER Value Assessment Framework" dated August 6, 2019.

2. Assessing and Describing Uncertainty

2.1 Cure proportion modeling: ICER proposes to make cure proportion modeling its reference case standard when relevant, but to address uncertainty we will also provide survival analysis based on other modeling approaches when feasible.

IVI applauds ICER for considering survival analysis with multiple approaches, including using cure fraction models. If the models used to quantify value are primarily based on parametric survival functions, model averaging can be implemented in a relatively straightforward way, and we strongly recommend that ICER do so to capture structural uncertainty (beyond the parameter uncertainty). To overcome many of the practical challenges with implementing multiple structures for more complex models, we recommend syntax-based programming languages (such as R) rather using Excel spreadsheets. This also allows for efficient programming of model averaging techniques.²

When multiple studies are considered in the estimation of time-to-event outcomes, it is important to consider multivariate (network) meta-analysis and indirect comparison methods that allow for estimating time-varying treatment effects based on the complete survival distributions of the studies of interest. These methods have been developed for parametric survival functions, fractional polynomials, and splines.³ However, evidence synthesis in the context of cure fraction models is not yet established. As such, defining cure-fraction modeling as the reference standard may be challenging when the findings of multiple studies need to be combined.

In the absence of mature data regarding longer term survival outcomes, formal expert elicitation methods may be considered to help inform extrapolation of outcomes over time in a more transparent and reproducible manner.⁴

² Incerti D, Thom H, Baio G, Jansen JP. R you still using Excel? The advantages of modern software tools for health technology assessment. *Value Health*. 2019;22:575-579.

³ Dias S, Ades AE, Welton N, Jansen JP, Sutton A. *Network meta-analysis for decision-making*. Wiley. 2018, Chapter 10.

⁴ Cope S, Ayers D, Zhang J, Batt K, Jansen JP. Integrating expert opinion with clinical trial data to extrapolate long-term survival: A case study of CAR-T therapy for children and young adults with relapsed or refractory acute lymphoblastic leukemia. *BMC Med Res Methodol*. In press.

2.1 Incremental cost-effectiveness scenarios at multiple time horizons: ICER’s assessments of SSTs will include cost-effectiveness analyses and associated value-based prices at multiple time horizons: at the time horizon representing the longest-available follow-up data for a significant number of treated patients; and also, at 5 years, 10 years, and the standard lifetime horizon. The official ICER value-based price benchmark will remain that generated by a lifetime horizon analysis, but other results will be provided as important context with which to assess the impact of uncertainty on cost-effectiveness results.

Incremental cost-effectiveness analysis is performed to quantify the value, and IVI strongly agrees that value should be estimated over a lifetime time horizon. When benefits are expected to accrue over that lifetime time horizon, providing estimates over shortened timeframes may potentially bias results when outcomes are not proportional over time – for example, when costs are higher in the short term and clinical and non-clinical benefits accrue over the lifetime. In the case of SSTs with the potential to cure or transform the course of disease, this approach may be particularly likely to underestimate benefits of therapies.

We do agree that uncertainty in long-term outcomes is a significant concern in the case of many SSTs, but we also acknowledge that evidence on long-term outcomes is limited on new therapies in general. The resulting uncertainty in value estimates should certainly be explored and thoroughly reported, but this is better accomplished using methods for examining structural uncertainty (e.g., comparing results from multiple model structures⁵) and parameter uncertainty (e.g., using probabilistic sensitivity analysis (PSA)).

2.3 Introducing a new economic review section on “Controversies and Uncertainties”: We propose including a new section in the “Long-Term Cost-Effectiveness” section of ICER reports which will discuss “Controversies and Uncertainties” related to the economic evaluation. Although the current layout of ICER reports includes information on these issues, we feel it will be helpful to consolidate and expand discussion of factors related to uncertainty, including lack of information on natural history, limitations of the data on patient outcomes, and difficulties translating existing data into measures of quality of life. This section will also be used to expand discussion of alternative model structures or inputs suggested by manufacturers or other stakeholders. This proposed change to ICER’s report structure will be considered for all ICER reports, not just those for SSTs.

IVI welcomes this recommended change to ICER’s reports and supports its implementation in all ICER reports.

2.4 Probabilistic sensitivity analysis linked to policy recommendation for outcomes-based payment: At a price at which greater than 25% of PSA simulations of the base case produce incremental cost-effectiveness ratios above \$200,000 per QALY, we propose to

⁵ Linthicum M. The Impact of Structural Uncertainty on Cost-Effectiveness Estimates. Value Blueprints research brief. September 3, 2019. Available at https://www.thevalueinitiative.org/wp-content/uploads/2019/09/2019-09-03.Value-Blueprint_Structural-Uncertainty_FINAL.pdf

include a policy recommendation that payers and manufacturers view outcomes-based contracting as the preferred method of payment. This methods change is proposed for all ICER reports, including SSTs.

IVI interprets ICER's proposed modification to mean that the cost-effectiveness of SSTs will be evaluated such that the most-likely (or average) incremental cost-effectiveness ratio across PSA simulations will still need to be less than the threshold of \$150,000/QALY for a SST to be deemed cost-effective, but that if there is a high degree of uncertainty, outcome-based contracting is recommended.

We agree with the underlying reasoning for this proposed modification, but we are concerned by specific elements of the approach. In particular, the arbitrary selection of thresholds – both the percentage of PSA iterations that must fall above the \$200,000 threshold, and the \$200,000-per-QALY threshold itself – suggests a level of consensus on thresholds that does not exist. Instead of this approach, we suggest that ICER continue to present (pairwise) cost-effectiveness acceptability curves which effectively provide the same information but for a range of different thresholds.

The range of model output estimates obtained with a PSA is directly influenced by a number of modeling decisions: e.g. the number of model input parameters considered; the upper and lower bound for each of the model input parameters; the assumed parametric distribution; the incorporating correlation between different parameters; etc. Given the potential policy implications, it is important that there be full transparency regarding the implementation of a PSA for a given model, and as much detail as possible needs to be pre-defined in the protocol/analysis plan.

3. Additional Elements of Value

3.1 Additional elements of value: ICER proposes to add two additional domains of “potential other benefits or disadvantages” for voting by our independent appraisal committees:

- (1) A potential advantage for therapies that offer special advantages by virtue of having a different balance or timing of risks and benefits versus other treatments; and**
- (2) a potential disadvantage for therapies that, if not successful, could reduce or even preclude the potential effectiveness of future treatments.**

General Response:

We applaud ICER for examining the possibility of incorporating novel dimensions of value but wish to clarify several aspects of the discussion. According to the technical brief, ICER's view on additional dimensions of value is as follows: “A major overriding factor that would argue against the inclusion of additional value domains cannot be overstated: their inclusion would raise fundamental equity concerns. Higher spending on certain SSTs (or other treatments) that get

extra credit for these additional value domains would lead to opportunity cost effects either inside or outside the health system.”

It appears that ICER views new value elements as *additive*, when in fact concepts like “insurance value” and (the misleadingly named) “value of hope” are *corrective*. ICER’s underlying assumption is that its cost-effectiveness methods produce estimates of value that are substantively correct and that align with the rank-ordering of medical technologies. This outmoded view is refuted by recent research. In their work identifying insurance value,⁶ Lakdawalla, Malani and Reif (2017) demonstrate that traditional cost-effectiveness methods, including those used by ICER, wrongly assume that healthcare consumers are risk-neutral. For example, if consumers were risk-neutral, they would not be interested in health insurance. Thus, traditional cost-effectiveness methods themselves pose fundamental equity concerns. By properly accounting for risk-aversion, Lakdawalla, Malani, and Reif show that the traditional approach actually *overvalues* treatments for mild disease and *undervalues* treatments for severe illness. Thus, the sickest, most vulnerable patients are penalized by this analytical inaccuracy in traditional cost-effectiveness methods.

Similarly, ICER argues that “it is also not clear that willingness to pay for ‘peace of mind’ would not apply equally to societal spending in areas other than health care.” In fact, deploying insurance value aligns cost-effectiveness analysis with well-accepted welfare economics approaches that are used in the rest of the economy. For at least 80 years, economists have recognized that consumer preferences must be accurately incorporated when valuing governmental programs and social spending.⁷ This includes incorporating realistic risk-aversion preferences. Cost-effectiveness analysis has stood apart from the rest of welfare economics in forcibly assuming that consumers are risk-neutral. Failure to incorporate insurance value into cost-effectiveness analysis perpetuates this misalignment and may systematically undervalue health spending compared to spending on other programs. Moreover, “insurance value” has implications for how medical technologies are rank-ordered, not just for the total level of healthcare spending. Put differently, even if we held healthcare spending fixed, insurance value would alter the way those fixed dollars are allocated; it would shift dollars toward more severe illness and away from milder ones.

Response to proposed domain additions:

We are encouraged that, though ICER does not find sufficient evidence or support for novel value dimensions to include them in quantitative analyses, ICER does acknowledge their potential importance. The addition of new domains related to these issues is an encouraging step. IVI strongly believes, however, that ignoring these developing concepts until they are fully established in the field both does a disservice to stakeholders in the U.S. healthcare system and fails to take responsibility for actively working to improve methods used in value assessment. IVI calls on ICER to take an active role in efforts to test and improve evolving methods for value

⁶ Lakdawalla DL, Malani A, Reif J. The insurance value of medical innovation. *Journal of Public Economics*. 2017; 145:94-102

⁷ Samuelson PA. Reaffirming the existence of “reasonable” Bergson-Samuelson social welfare functions. *Economica*. 1977;44(173):81-88.



assessment, including but not limited to application of novel value components such as those discussed. IVI would gladly collaborate with and support ICER in any such efforts.

IVI supports the addition of a domain that addresses the **“potential advantage for therapies that offer special advantages by virtue of having a different balance or timing of risks and benefits versus other treatments.”** It is important to note, however, that this domain may apply to non-SST therapies as well as SSTs, and it should therefore be included in all ICER value assessments.

Regarding the addition of a domain addressing the **“potential disadvantage for therapies that, if not successful, could reduce or even preclude the potential effectiveness of future treatments,”** IVI is concerned that meaningful inclusion of this domain may be challenging given the degree of uncertainty around both long-term clinical effects and future therapeutic developments.

We would like to thank ICER for its willingness to make its recommended value framework alterations public and accepting feedback. IVI believes that collaboration is essential to raise the level of discussion regarding value in healthcare and finding common ground in the approach to measuring value. To that end, we appreciate ICER’s process as it seeks to update its framework and hope we have offered substantive recommendations that can be incorporated, tested and refined as the community jointly works to improve the science and implementation of value assessment analyses.

Sincerely,

A handwritten signature in dark ink, reading 'Jennifer L. Bright', is positioned above a thin horizontal line.

Jennifer Bright, MPA
Executive Director
Innovation and Value Initiative

JANSSEN SCIENTIFIC AFFAIRS, LLC

Response to Public Comments on: ICER's Value Assessment Methods for "Single or Short-Term Transformative Therapies" (SSTs)

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COMMENTS

At Janssen, our research and development efforts reflect our commitment to developing medicines that transform patients' lives. We're committed to ensuring patients have access to life-changing innovations today and can look forward to the innovations of tomorrow.

The evolution of medicines from small molecules to proteins has driven remarkable therapeutic benefits. In a similar way, the next generation of cell and gene therapies holds tremendous promise for patients, but only if these therapies are available and accessible.

We appreciate the opportunity to provide comment on the Institute for Clinical and Economic Review's (ICER's) *Value Assessment Methods for "Single or Short-Term Transformative Therapies" (SSTs)*.

However, we believe that ICER's proposed methods will likely encourage inappropriate access restrictions with potentially serious and lasting effects on the quality and length of patients' lives. And because its analysis would be conducted from the insurer's perspective, ICER would systematically underestimate the value of transformational medicines and thus impede the progress of medicine and stand in the way of a healthier future for patients.

We also disagree with ICER's reliance on the QALY as a key measure of treatment impact. The QALY has many documented shortcomings. It underestimates the value of medicines for the sickest patients and those who are elderly and disabled, discriminating against the patients most in need of care. Moreover, QALYs may not capture important aspects of patients' perspectives on value. Any value assessment that does not sufficiently capture their preferences is fundamentally flawed.

Furthermore, we believe that ICER's use of cost-effectiveness thresholds for value assessment and price recommendations is problematic. The World Health Organization (WHO) has stated that:

"Our view is that a fixed cost-effectiveness threshold should never be used as a stand-alone criterion for decision-making. Above all, the indiscriminate sole use of the most common threshold – of three times the per-capita GDP per DALY averted – in national funding decisions or for setting the price or reimbursement value of a new drug or other intervention must be avoided. WHO-CHOICE has never recommended this practice, which would be a distortion of the intention and meaning of the GDP-based thresholds proposed by the Commission on Macroeconomics and Health."¹ ([link](#))

In its draft proposal ICER has not provided methods that capture the overall value of transformative therapies. Nor has it proposed approaches to ensure access for patients who could benefit. Rather, ICER has chosen to view value from the narrow perspective of the insurer, failing to capture the full spectrum of patient views on treatments and include the broader societal point of view.

Our key points are below.

Unclear definition of curative therapies and “SSTs”

We are concerned that ICER’s definition of SSTs is unclear. We are also concerned that its recommendations would potentially conflict with FDA’s rigorous scientific assessments of benefit and risk and unmet medical need and that ICER would create barriers to therapies the FDA has deemed valuable.

In addition to these concerns, we would note that it is the role of FDA – one of the most rigorous and respected agencies in the world – to settle questions regarding which therapies meet the criteria to be considered “breakthrough” and/or merit “priority review” (or in lay terms, be considered transformational). The United States Food and Drug Administration (FDA) has Congressionally established authority to evaluate biopharmaceuticals in the US, assess benefits and risk, and determine whether a therapy is marketed. “Over the past three decades, Congress has established five programs aimed at expediting patient access to important drugs that treat serious or life-threatening conditions. These programs allow FDA to facilitate and expedite development of medicines that fill unmet medical needs, while maintaining FDA’s gold standard of safety and efficacy.”² ([link](#))

FDA has hundreds of clinical experts with decades of collective experience in and perspective on drug development. In the US, they alone have unique access to comprehensive patient-level data from all trials prior to launch and have the expertise to understand the strengths and limitations of the research and appropriately weigh the risks and benefits of innovation.

Innovative payment models can be used to manage the risks associated with clinical uncertainty

ICER argues that transformative therapies require new approaches because of “increased uncertainty with unrecoverable costs.” New technologies may have significant upfront costs, but they can also provide immediate benefits that continue to accrue over a lifetime. In fact, innovation such as personalized medicine is precisely designed to decrease clinical uncertainty either by creating therapies that are tailored to individuals, or by creating therapies and diagnostics that give us more information about the sub-populations that are most likely to benefit. Managing this type of uncertainty requires exploring other payment models rather than resorting to underestimation of the value of innovation.

Today, manufacturers and payers routinely assess any financial risk that may be associated with clinical uncertainty and manage it through contracting and payment models. ICER is not involved in these discussions, as it is not accountable for either the financial *or* medical outcomes of these decisions. When it comes to enabling greater access for patients, contracts are the most flexible tools, as they allow independent parties, each with a different set of needs, to appropriately determine the best way to account for clinical uncertainty.

ICER ignores key elements of value

ICER's proposed approach fails to recognize the full value of potentially curative therapies to patients, caregivers, and society overall. Against the scientific consensus, it ignores key elements of value, such as value of hope, caregiver burden, insurance value, option value, and productivity.

These omissions result in a framework that produces incorrect and biased results. While there is added complexity in incorporating all elements of value into a cost per QALY framework, such complexity does not diminish their importance in value assessment. ICER wants its recommendations to be acted upon, but when it fails to include all elements of value (because of the complexity of doing so), it shows an unwillingness to acknowledge and be accountable for the importance of the decisions it attempts to influence.

ICER also assumes that some patients who receive the transformational treatments of today could become ineligible for future therapies. On the contrary, it is most likely that effective treatments would increase patients' chances of being alive long enough to have access to therapies approved in the future. In oncology, for example, each new therapy is typically approved in patient populations that have had prior exposure to the currently approved classes of therapy. In addition, for patients with life threatening diseases, like cancer, the chance of survival improves with earlier and more effective intervention in the disease process.

Consider the example of multiple myeloma. Over the course of 20 years, treatment options and associated prognosis have improved dramatically. Initially, overall median survival rate was less than three years.³ With the development and introduction of newer and more effective therapies, the survival rates have at least doubled.⁴ This trend continues with the approval of additional therapies and expanded indications.³ In just two decades, rapid innovation has enabled patients once considered immediately terminal to survive and benefit longer from newer therapies in cases of recurrence. Breakthrough therapies of today are unlikely to be curative in all patients but will at least give patients the hope and chance to benefit from future innovation.

Affordability and sharing of economic surplus

ICER's proposal to "share the surplus" is built on a false argument: that no further innovation will displace these new therapies and thus competition would be limited or absent; therefore, curative therapies would result in "unfair" allocation of economic surplus. The recent history of the biopharmaceutical industry contradicts ICER's reasoning. We have seen unprecedented innovation and breakthroughs in medicine and numerous competitors entering brand-new disease areas. Indeed, FDA has reported that there are over 800 cell and gene therapies in development.² ([link](#))

Hepatitis C treatment provides a vivid recent example of innovation and competition. When launched, the first new Hepatitis C therapies offered substantial and significantly higher cure rates, with shorter treatment duration than interferon-based therapy. Then within two years, new competitors brought additional options with higher cure rates, and with increased competition, prices fell. Had ICER intervened and acted on the false premise that innovation would not come, new competitors may not have been developed or launched, and society would not have benefited from the increasing cure rates and lower prices.

If implemented, ICER's proposed shared saving scheme will significantly undervalue new transformative medicines, lowering the incentive for innovation, limiting new options for society, and effectively *decreasing* the likelihood of innovation and subsequent competition.

We recognize cost can be a barrier to access and we strive to help achieve broad and timely access to our medicines in a way that is affordable. Comprehensive solutions can stem from a broad-based dialogue among all stakeholders. As proposed, ICER's methods for redistributing economic surplus for pharmaceuticals targets one segment and its design benefits insurers; it does not consider the patient or society and thus may have a significant limiting impact on future health gains.

The dialogue about access to transformational medicines must be patient-focused and responsible

It is imperative that all stakeholders engage in a responsible dialogue around the best way to ensure access to transformative therapies. We need to assess their value from society's perspective, not just the insurers'. Failing to do so will underestimate their value and restrict patient access. We also need to ensure we do no harm to the innovation ecosystem which made these cures possible in the first place. ICER's proposed methods may create a disincentive for future innovations, stunting research for a healthier tomorrow.

Breakthrough medicines have provided enormous health gains for society. Our healthcare system has reacted with payment mechanisms for managing cost that do not discourage future innovation. Given ICER's lack of accountability, and apparent bias toward insurers' near-term economic interests above those of patients and society, we are concerned about the impact this framework will have on patients' access to life saving treatments today and in the future.

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September 6, 2019

Institute for Clinical and Economic Review
Two Liberty Square
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Boston, MA 02109

Re: Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs): Proposed Adaptations to the ICER Value Assessment Framework

Dear Dr. Pearson,

The Muscular Dystrophy Association (MDA) thanks the Institute for Clinical and Economic Review (ICER or the Institute) for the opportunity to comment on ICER’s “Value Assessment Methods for ‘Single or Short-Term Transformative Therapies’ (SSTs): Proposed Adaptations to the ICER Value Assessment Framework.”

MDA is the nation’s leading nonprofit organization dedicated to transforming the lives of individuals living with muscular dystrophy, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA) and other neuromuscular diseases (NMDs) through innovations in science and innovations in care. MDA fulfills its mission by funding biomedical research, providing access to expert clinical care and support through its national MDA Care Center Network which is comprised of expert medical clinics at more than 150 of the top health care institutions across the US, and by championing public policies and programs that benefit those it serves. Since inception, MDA has invested more than \$1 billion in research grants to accelerate treatments and cures for neuromuscular disorders, making MDA the largest source of neuromuscular disease funding in the U.S. outside of the federal government.

One gene therapy for an NMD, spinal muscular atrophy (SMA), has already been approved by the Food and Drug Administration (FDA)—the second gene therapy for a genetic disease ever approved in the US. With a dedicated research community, and with the SMA therapy as a catalyst, many exciting gene therapy approaches, including gene editing technologies, are currently under development to treat a variety of NMDs, including Duchenne muscular dystrophy (DMD), Friedreich’s Ataxia (FA), Limb-girdle muscular dystrophy (LGMD) and Facioscapulohumeral muscular dystrophy (FSHD). In fact, the future of therapeutic development for NMDs is heavily focused on “single or short-term transformative therapies.”

Consequently, conversations around the economic valuation and impact of SSTs, and subsequent access strategies and considerations, are of particular importance to the NMD community and MDA. Perspectives, recommendations, and suggestions that impact when, where, how, and to whom such therapies will be made available can be significantly impacted by such discussions, and it will be important to keep the perspective of the patient and their families at the forefront of

such activities. Therefore, MDA is pleased to share our comments on ICER's proposed alterations to their value assessment methods for SSTs.

We appreciate that ICER acknowledges the unique challenges SSTs pose to access, coverage, and reimbursement systems, as well as the valuation techniques that help guide these systems. However, we find that ICER's decision to deliberately exclude certain elements of value that are important to the patient population because of their apparent complexity to quantify to be, at best, troubling. The current form of the SST framework, as acknowledged by ICER, disregards some of the most important values patients may derive from SSTs, resulting in an analysis that is not necessarily reflective of the needs of the patient community.

Single or Short-Term Transformative Therapies in Neuromuscular Diseases

In many ways, neuromuscular diseases are at the forefront of the ongoing revolution of transformative technologies. Indeed, Novartis's Zolgensma for SMA has only accelerated conversations on the promise of these groundbreaking therapies, and the challenges they pose to our coverage and payment systems.

There are many SSTs on the horizon for NMDs, only further heightening the urgency. As of October 2018, over 275 clinical trials for 195 therapies were ongoing for NMDs.¹ Of these 195 potential therapies, 14 percent are gene therapies, all of which could qualify as SSTs if approved. As explained in a recent study of the neuromuscular disease space,

“The accessibility of muscle and the potential for its cells to amplify the impact of nuclear-targeted therapies due to their being multinucleate, make it an attractive target for gene therapy and novel genome editing technologies. Additionally, breakthroughs in targeting the motor neurons of the central nervous system have also accelerated gene therapy efforts for these diseases.”²

With one approval already in place and with many SSTs in the pipeline for NMDs, the urgency to establish access to such therapies is pressing.

Framework Revisions for SSTs:

As ICER sets out in its report, SSTs create unique challenges to value assessments that may not be presented by conventionally administered therapies. Thus, we agree that a modified framework to satisfy the unique aspects of SSTs is in order.

ICER sets out four unique challenges with the valuation of SSTs, including: increased uncertainty and unrecoverable costs, additional dimensions of value, time divergence between costs and benefits, and affordability and economic surplus concerns. Each of these situations presented by SSTs requires an amended evaluation, and we encourage other decisionmakers and

¹ Understanding Neuromuscular Disease Care: Current State and Future Prospects (2018, October 30). Retrieved September 6, 2019, from <https://www.iqvia.com/institute/reports/understanding-neuromuscular-disease-care>

² Id., at 32

policy makers in the coverage and reimbursement space to follow ICER's lead in acknowledging the immediate necessity of considering the uniqueness of gene therapy and SST approaches.

Exclusion of Critical Additional Elements of Value:

While MDA is supportive of much of ICER's proposal, we are troubled by ICER's decision to exclude seemingly all potential unique values that patients may derive from SSTs that do not fit within classic cost effectiveness analysis. We believe this decision could strongly skew ICER's findings and exclude many values that patients derive from these innovative therapies.

Added Dimensions of Value: MDA rejects ICER's concern about "adding dimensions of value that only increase the assessed value of some forms of treatment – and thus would support higher prices for them – without creating some mechanism for balancing this when the resultant opportunity cost and attendant health losses due to other treatments foregone."

We fail to understand how unique values derived from transformative therapies should somehow be disqualified due to the opportunity cost of not taking another therapy. If this is the case, why is ICER not ignoring all unique aspects of SSTs and simply treating SSTs exactly like all other therapies? We fail to understand the distinction ICER is trying to make between excluding unique elements of value in SSTs, but including other unique considerations of SSTs, such as their potential permanence, ambiguous long-term value, and more. Without further explanation, ICER's decision appears arbitrary.

Value of Hope: ICER appears to misunderstand the "value of hope" in a way that allows the Institute to exclude this important value from its evaluations. ICER defines the "value of hope" to be the "value of having the *choice* among treatments with a different balance and timing of risks and benefits." MDA disagrees with this alternative definition. The "value of hope" is about the potential for a more healthy and happy life in the future than was previously expected. SSTs offer patients the possibility of substantially healthier lives many years into the future, and with this brings the hope of attending college, getting married, and other important life experiences. ICER's alternative definition ignores the hope for experiencing these seminal moments entirely.

Insurance Value: The exclusion of insurance value is concerning to MDA. ICER acknowledges that insurance value has been empirically measured by Lakdawalla et al. and through "explicit mathematical models of consumer utility maximization."³ However, ICER dismisses these empirical values of SSTs by stating that insurance value, "overlaps significantly with considerations given to severity or burden of illness." We disagree; there is not enough overlap between insurance value and burden of illness to justify excluding insurance value. Burden of illness studies pertain mostly to those directly affected by the disease while insurance value pertains to those not yet affected. Insurance value, as ICER acknowledges, is about peace of mind for individuals who do not have the disease, and therefore such values are not captured within burden of illness values.

³ Lakdawalla DN, Doshi JA, Garrison LP, Jr., Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(2):131-139.

Additionally, ICER's assertion that including insurance value within its assessments in an empirical manner would result in too substantial of an impact is discouraging. If one takes this argument to its conclusion, it can safely be assumed that all substantial values of new therapies would need to be discarded due to their financial impact, and only values that fit within ICER's vision for appropriate spending levels should be included. We view this as an incredibly subjective method for approaching value assessments.

Scientific Spillover Effects: ICER's exclusion of empirical values pertaining to scientific spillover effects is subjective and serves to skew its value assessments. ICER again acknowledges that scientific spillover effects have been empirically measured but disregards such values as duplicitous with the value the future therapies will derive, and problematic due to the opportunity costs they will create for other patients.

MDA is concerned by ICER's stance on behalf of unnamed patients that including alternative values of therapies will present opportunity costs for other patients in the healthcare system. This argument can be used for any value anywhere within our healthcare system, (or our society in general), but ICER is only applying this concern to these additional elements of value.

In general, MDA is disappointed that ICER appears to be subjectively picking and choosing which empirical values it includes within its assessments based upon opinion and insufficient reasoning. We request that ICER reconsider excluding these empirical values.

Potential Exclusion from Future Therapies:

MDA is supportive of ICER's intention to include considerations of the implication of SSTs potentially excluding patients from being able to take future SSTs due to the mechanism of action or immune response. We are aware that certain disease modifying therapies, particularly gene therapies and gene editing technologies, provide irreversible effects. These therapies may also disqualify patients from future ability to take other SSTs or disease modifying therapy.

This is a very real issue that patients today must grapple with. Including this possibility in an empirical manner within ICER's assessments is appropriate. However, including this potential harm of an SST while excluding many potential unique benefits is troubling. If ICER is to include the potential unique harms of SSTs, it must also include the potential unique benefits.

Time Horizons:

MDA encourages ICER to flexibly approach time horizons within upcoming evaluations of SSTs as each SST may require a unique variety of time horizons to be considered. Within ICER's proposal, the Institute proposes to assess cost-effectiveness scenarios, "at 5 years, 10 years, and the standard lifetime horizon." We encourage ICER to consider a flexible approach in which more than these three horizons are considered based upon the expected, or potential, duration of the effectiveness of the therapy.

Additionally, we caution ICER against deferring to “decision-makers” as they, “may wish to apply their own judgement on the time horizon for which judgements of value should be based.” While decision-makers will use whichever criteria they would like, we do not encourage ICER to simply defer this choice to decision-makers (which we interpret to be private or public payers who may use ICER reports in their coverage decisions). Instead, we recommend that ICER publish a variety of time horizons, or at the very least publish the time horizons that make the most sense for the specific therapy, for public consumption and consideration. This will allow the public to consider all time horizons decision-makers may choose to use in their analysis.

Flexible Cost-Effectiveness Thresholds:

MDA believes that all orphan therapies (a category which encompasses every approved therapy for neuromuscular diseases) deserve a flexible approach to their cost-effectiveness evaluations. ICER has shown this flexibility within its ultra-orphan therapy adjusted framework by increasing the societal willingness-to-pay threshold to \$450,000 per QALY compared to the lower values within its standard framework. However, ICER refuses to flexibly approach its cost-effectiveness threshold for ultra-orphan therapies by keeping the highest threshold at \$150,000 per QALY.

We believe this will once again prove problematic in evaluating SSTs as they will likely all be orphan therapies and will once again have to meet the same cost-effectiveness thresholds that common disease therapies meet. This runs counter to several international agencies who have raised the cost-effectiveness threshold for orphan therapies in their evaluations as well as the increased societal willingness-to-pay.

MDA encourages ICER to revisit whether the \$150,000 cost-effectiveness threshold is appropriate for SSTs, and other orphan therapies. A flexible approach to SST cost-effectiveness thresholds, as employed in other systems, could be warranted.

Controversies and Uncertainties:

MDA supports the addition of a section to identify uncertainties as ignoring them would result in an incomplete evaluation. However, we caution against the use of the word “controversies” within the title of the section. There will be uncertainties in economic reviews, and within those uncertainties there may be diverging views and perspectives, but divergent thinking and analysis does not necessarily result in controversy.

Within this section, we support ICER’s intention to discuss alternative model structures submitted by outside stakeholders and would urge that any considerations and/or modeling that is proposed by outside stakeholders be published and responded to in finalized recommendations by ICER. Knowing the source of outside counsel is essential in the community evaluation of the recommendation, and transparency will be essential in such valuation exercises. We encourage ICER to remain open to alternative ways of measuring the value of SSTs. By allowing for outside submissions, ICER will create a more inclusive process.

Probabilistic Sensitivity Analysis and Outcomes-Based Payments:

MDA appreciates ICER's discussion on aligning prices and payments to the value the health intervention brings. As the Institute discusses, SSTs naturally bring added ambiguity to the value of the therapy as expected values could be stronger or weaker than initially anticipated due to the lack of long-term data upon administration of the therapy. Consequently, MDA is eager to participate in deliberations on how best to reorient our payment and pricing incentives to better align with value, particularly where uncertainty of the therapy's long-term value is present.

Patient-Focused Expected Outcomes:

As ICER evaluates the long-term potential value of a new SST, the Institute will assess what "expected outcomes" can be derived from the therapy. MDA asks that ICER clarifies the definition of "expected outcomes." Will ICER only evaluate the therapy's expected outcomes using the primary or secondary endpoints from the clinical trials?

We encourage ICER to also include additional outcome measures that may be more important to patients, or outcomes derived from patients using innovative clinical outcomes assessments driven by real world evidence (RWE). MDA also encourages ICER to consider patient preference information (PPI) and patient experience data (PED) when choosing which outcomes the Institute will use to evaluate a therapy's long-term value.

These patient-focused outcomes are critical to assessing the salience of a therapy to a patient population. ICER's recent review of therapies for DMD offers a perfect example. DMD patient representatives (mostly parents of children with DMD) emphasized that the six-minute walk test, the primary endpoint for most clinical trials for FDA-approved therapies for DMD, is a poor way to measure the progression of the disease, or the efficacy of a drug. Instead, other measures are much more salient to the patient's experience. Consequently, we encourage ICER to consider patient-focused outcomes when assessing the long-term value of SSTs rather than simply clinical trial endpoints that may or may not actually matter to patients and their families.

Cure Proportion Modeling:

MDA is supportive of exploring cure proportion modeling and flag that it will be essential to engage the patient community to help define what is considered curative for this purpose.

We again thank ICER for the opportunity to comment and look forward to continuing to work with the Institute to ensure clinical and economic evaluations of transformative therapies are thorough, accurate, and beneficial and inclusive to the neuromuscular disease community. For questions regarding MDA or the above comments, please contact advocacy@mdausa.org.

Sincerely,



Paul Melmeyer, MPP
Director of Regulatory Affairs



September 6, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston MA 02109 USA

RE: ICER Methods Adaptations for Single or Short-Term Transformative Therapies

Dear Dr. Pearson:

Merck thanks ICER for the opportunity to review the value assessment methods adaptations for single or short-term transformative therapies (SSTs). We share your interest in promoting fair, transparent, scientifically robust methods for value assessment. Therefore, we would like to offer the following comments and suggestions regarding the methods adaptations for SST assessment.

Merck believes that ICER's proposal to include a "shared savings" scenario analysis for SSTs is unnecessary, inappropriate, and lack of sound scientific reasoning.

In this proposed scenario, ICER assumes that all cost offsets accrue to the innovator during the first 12-year period and all cost offsets will accrue to the health system after 12 years. This assumption is very arbitrary and lack of scientific reasoning. How the long-term economic benefits of SSTs should be allocated needs to be determined based on extensive discussions and consensus building among all involved stakeholders in the society including patients, families, innovators, payers, and policy makers. It is inappropriate for ICER to make this decision on behalf of these stakeholders. This task is beyond the role or expertise of ICER as an HTA entity.

For SSTs that may have sustained long-term clinical benefits, we suggest ICER use the societal perspective, instead of a health system perspective, to develop the base case of CEA for price benchmarking. Under the current U.S. health system, many patients who receive SSTs, especially those who receive the treatments at a very young age, may shift insurance programs after the treatment. Multiple payers or health systems may accrue the long-term cost offsets of SSTs. In this case, taking the broader societal perspective in CEA would be a more appropriate approach. This will also make it unnecessary for ICER to make any arbitrary assumptions regarding how long-term economic surplus shall be shared between health systems and innovators.

It is inappropriate for ICER to recommend outcomes-based contracting based on probabilistic sensitivity analysis (PSA) alone or include such policy recommendation in its evidence reports.

While we appreciate ICER's intention to conduct additional analyses to address uncertainty, we do not think it is within ICER's purview to make policy recommendation regarding outcomes-based payment arrangement as proposed. Making this policy recommendation purely based on PSA ignores the legal, regulatory, and business complexity in outcomes-based contracting. ICER's criteria—greater than 25% PSAs at or above \$200,000 per QALY—is also arbitrary and lack of scientific ground. We think



ICER should refrain from making recommendations regarding value-based contracting or other innovative payment arrangements. Those decisions should be left to payers and innovators. ICER needs to continue focusing on generating scientifically robust reviews to support the decision makers.

Again, we appreciate the opportunity to comment on the proposed methods adaptations for SSTs assessment. We look forward to continued collaboration with ICER to further improve the rigor of value assessment methodology.

Sincerely,

A handwritten signature in black ink that reads "Fang Sun". The signature is written in a cursive, flowing style.

Fang Sun, M.D., Ph.D.
Director, Medical Policy, HTA & Value Assessment
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September 6, 2019

BY ELECTRONIC DELIVERY

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Boston, MA 02109

RE: Comments on Value Assessment Methods for Single or Short-Term Transformative Therapies (SSTs)

Dear Dr. Pearson:

The National Health Council (NHC) is pleased to provide comments on the Institute for Clinical and Economic Review's (ICER) solicitation for feedback on the, "Value Assessment Methods for Single or Short-Term Transformative Therapies (SSTs)." Founded in 1920, the NHC brings diverse organizations together to forge consensus and drive patient-centered health policy. The NHC provides a united voice for the more than 160 million people with chronic diseases and disabilities and their family caregivers. Made up of more than 125 diverse, national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient advocacy organizations, which control its governance and policy-making process. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities and businesses representing biopharmaceutical, device, diagnostic, generic, and payer organizations.

We envision a society in which all people have access to quality health care that respects personal goals and aspirations and is designed around the patient experience to promote their best possible health outcomes. We agree with ICER that methods adaptations are necessary for value assessment of SSTs.

Many of these new therapies have the potential to cure or substantially modify diseases, giving patients hope of a better life. They also come with significant upfront costs with the potential for significant downstream savings.

Unfortunately, the organization that pays for the treatment today will rarely be the organization that realizes the future savings without innovative contracting and financing mechanisms. Thus, traditional value assessment may not truly capture the value of products with longer-term, downstream advantages, creating the need for adapted approaches. Therefore, we appreciate ICER's effort to capture these issues and provide suggested solutions.

Below, we provide our comments on the set of proposed adaptations and recommendations to ICER the proposals. Our comments follow the organization of ICER's August 6, 2019 document.

Introduction

ICER's additional proposed models, sensitivity analyses, and opportunities to engage will add complexity for researchers developing models, but also for stakeholders to provide information for building and providing feedback on the assessments. We strongly suggest ICER partner with members of the patient and research communities to understand realistic timeframes for engaging, providing input, and preparing comments. Since ICER's recommendations may impact patients' access to care in the real world, it is critical that ICER emphasize high-quality methods and not impose unnecessarily aggressive timelines on either the researchers who must conduct the work, nor stakeholders interested contributing valuable insights. Whenever possible, we recommend that a comment period of at least 90 days be offered to allow for the patient community to have adequate time to prepare a thoughtful response. Patient groups may need to convene scientific or medical advisory boards of volunteers or engage large numbers of patients to gather sufficient data to be responsive.

1. Determining those treatments for which adapted assessment methods will be used

We appreciate ICER's effort to offer a definition for SSTs. This is a critically important starting point for this dialogue. We also appreciate that the patient community is an acknowledged partner and that formal public comment will be sought. **It would also be beneficial to have a very clear process articulated that delineates how the patient community will be engaged and at what point(s) in time in the process this will happen, specifying what the patient community role will be.** Since SSTs include those therapies that produce a "transformative health gain," it should be those people and families experienced with living with the condition every day that define what "transformative" means in each context. Patient, caregiver, and family-member input will be a necessary requirement in this definition for each condition considered. We recommend that a clearer pathway for how that will happen be codified and are happy to help collaborate on what that process could look like.

2. Assessing and describing uncertainty

This section describes the use of incremental cost-effectiveness analysis scenarios at multiple time horizons. While we understand the desire to develop a consistent and predictable time horizon, **we believe that it will important to establish time periods that are meaningful to the specific condition and population to be treated.** The examples provided at five or 10 years may or may not be meaningful to a given condition. It also indicates that, "decision makers may wish to apply their own judgment on the time horizon." These judgments should not be made independently by payer decision-makers. The time periods should be established with patient and clinical community input to be relevant to the condition and sensitive to meaningful change. This should be part of the process ICER uses when defining what is curative or transformative. Curative or transformative at what time point(s) from the patient and clinician perspective should be part of the earliest dialogue. We recommend these time points be established as part of defining what is curative or transformative for the specific condition.

In section 2.3, introducing a new economic review section on “Controversies and Uncertainties,” we suggest that the phrase, “data on patient outcomes,” be changed to, “data on patient-centered outcomes.” We believe it is also important to indicate which outcomes are important to patients, which typically includes but often extends beyond quality of life. For example, this section would make it transparent that a particular assessment is focused on specific endpoints (e.g., clinical trial endpoints) as data on them are available from clinical trials. But, this section would point out that they are not patient-centered endpoints as patients did not prioritize their importance. We recommend that this clarification be included for transparency to the reader and potential user of the information.

As noted in our 2017 report, “Policy Recommendations for Reducing Health Care Costs,”¹ outcomes-based contracting can be helpful in creating patient access to new therapies. We believe this is especially true of SSTs. However, it is unclear whether ICER’s proposed cut off [of 25% of probabilistic sensitivity analysis (PSA) simulations over \$200,000/QALY threshold] is appropriate or if outcomes-based contracts should be more broadly recommended.

It seems, as well, that PSA is being used narrowly here, and it could inform users by elucidating uncertainty throughout the various inputs to the model across the board. As also mentioned elsewhere in the document, there can be a “most conservative scenario” and “a most optimistic scenario.” Rather than narrow the PSA to one use, to only encourage outcomes-based contracts, which we believe can be very positive for patients, ICER should take advantage of PSA to capture what could be a range of realistic scenarios given the outcomes and time points captured in early patient and clinician engagement. We recommend ICER consider the use of PSA and other appropriate methods to transparently capture and articulate implications of uncertainty about any model input.

3. Additional elements of value

The NHC supports consideration of “additional elements of value.” However, we are concerned these additional elements will be disregarded by decision makers unless they are either considered quantitatively or specifically and transparently highlighted as important/critical caveats to interpreting the entire assessment. For example, NHC members have seen instances where information or recommendations included in various parts of an ICER value assessment document (such as the section on “Contextual Considerations”) have been ignored by payers since the information was not included in the value-based price calculation. Thus, we recommend ICER consider an approach that either quantitatively considers these elements or sufficiently conveys to potential value-assessment users what the contribution or impact is as a caveat to interpretation of the base case.

We suggest that ICER provide additional information and rationale for the proposal to add “a potential disadvantage for therapies that, if not successful, could reduce or even preclude the potential effectiveness of future treatments.” While the technical document provides additional detail on many of the other suggested methodological adaptations, we did not find additional data related to this recommendation. We are concerned with it potentially reducing the availability of approved medicines based on attributes of treatments that are not and

¹ National Health Council. Policy Recommendations for Reducing Health Care Costs. Available from: <http://www.nationalhealthcouncil.org/sites/default/files/NHC%20Policy%20Proposals%20for%20Reducing%20Health%20Care%20Costs%20UpdatedFINAL052217.pdf>

may, if fact, never be approved. We recommend that ICER reconsider this proposal at this time until its implications can be better understood.

4. Affordability and fair sharing of economic surplus

We appreciate ICER's effort to "stimulate a broader societal discussion on the use of cost-effectiveness analyses to guide value-based pricing." We believe this is a discussion that needs to happen in general, not just for SSTs. Here, the conversation is directed at what "appropriate sharing" of the economic surplus from an SST between the innovator and the health system. We believe the conversation should be broader.

We recommend that the term, "shared savings," not be used in this context. This is a term used by the Centers for Medicare and Medicaid Services (CMS) to refer to some of its value-based payment programs. In the CMS vernacular, this is the savings to CMS generated when providers agree to value-based payment rather than fee for service payment. CMS then shares the savings CMS incurs with those providers who generated the savings. We believe using this term in the circumstance described by ICER will lead to confusion and different term should be used.

We are concerned that potential impact on innovation is not sufficiently considered, which could have significant implications for patients and the potential for having future "choice among treatments with a different balance and timing of risks and benefits." It would be important to understand how that would also be incorporated into the analysis and its implication for surplus.

Since the discussion on fair sharing of economic surplus must be in a broader societal context, it is not in alignment with ICER's general approach or approach to SSTs, which focuses on a base case scenario conducted from the payer perspective. It seems that these offsets would actually be retained by the payer in the current payment system and not shared with providers or patients. This discussion would be more in alignment with a base case from the societal perspective. It is incongruent to produce a value-assessment report that primarily provides findings on value to the payer (cost effectiveness from only the payer perspective) and to then insert a tangential discussion for policymakers where cost offsets are retained by the system. A base case that focuses on the societal perspective better captures outcomes important to the patient community and would be in alignment with a discussion on providing policymakers with information about economic surplus, with the surplus made relevant to society and not only payers.²

For these reasons, **we believe inclusion of a discussion on fair sharing of economic surplus in ICER value assessment reports is premature and recommend ICER not include the analyses or this section at this time.** That is not to say that we do not think it is important. However, we suggest additional exploration of this topic, to include public dialogue; development of case examples that include SSTs, as well as treatments for rare and chronic conditions; and discussion of how economic surplus has implications for patients in terms of access to current treatments, out-of-pocket costs, and access to future SSTs and "choice among treatments with a different balance and timing of risks and benefits." The NHC would be happy to collaborate in exploration of these topics.

² Asthma and Allergy Foundation of America. Asthma and Allergy Foundation of America Responds to Premature ICER Review of New Peanut Allergy Treatments. Available from: <https://www.aafa.org/media/2439/aafa-statement-on-icer-final-report-for-peanut-allergy-therapies.pdf>

The NHC welcomes additional opportunities for members of the patient community to engage with ICER. As previously recommended, the impact of patient input and patient-group-submitted data should be clearly articulated in value assessment reports. The current document describes that patient input will be sought, but not how it will be sought or how its impact on the assessment will be described. We believe this is an important aspect of patient-centered value assessment and recommend more detail be provided and added to all future reports.

Our recommendations are intended to increase patient centricity in value assessment. Patient-centered value assessment exists when patients have been engaged, heard, understood, and respected throughout the entire process, and their input is incorporated and guides decision-making. We hope to see even greater impact of patient engagement on value assessment moving forward.

We at the NHC are happy to discuss these comments and recommendations with you, to clarify any suggestions we have made and to hear from you about how we can be supportive of their implementation. As always, please do not hesitate to reach out to Dr. Elisabeth Oehrlein, NHC's Senior Director of Research and Programs at eoehrlein@nhcouncil.org or 202-973-0540, with any questions.

Sincerely,

Marc Boutin, JD
Chief Executive Officer
National Health Council

September 6, 2019

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs)

To Whom It May Concern:

The National Hemophilia Foundation (NHF) and Hemophilia Federation of America (HFA) are national non-profit organizations that represent individuals with bleeding disorders across the United States. Our missions are to ensure that individuals affected by hemophilia and other inherited bleeding disorders have timely access to quality medical care, therapies, and services, regardless of financial circumstances or place of residence. Both organizations accomplish this through advocacy, education, and research. We appreciate the opportunity to provide these comments to the Institute for Clinical and Economic Review (ICER) on Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs).

As you know, the bleeding disorders community is on the cusp of approval for gene therapy and other SSTs that have the potential to transform the lives of eligible individuals with hemophilia and their families. Accordingly, we remain very interested in how ICER would conduct reviews on SSTs for our patient community and are pleased to share these comments:

SST Model and Interaction with ICER’s Ultra-Rare Framework

First, we agree with ICER that the existing value assessment method is insufficient for evaluating SSTs, given the likelihood of uncertainty regarding patient outcomes due to smaller population sizes and limited time to assess the durability of treatment effects. We support ICER’s proposal to modify the existing value assessment framework to accommodate this uncertainty, as well as other aspects of SSTs that add complexity to the review process. Our organizations worked with you to contribute the patient perspective during ICER’s 2018 review of a novel therapy in hemophilia; and it was clear that the use of ICER’s ultra-rare framework was critical to evaluating the clinical and cost effectiveness of that treatment. Please clarify whether and how the SST Model and the ultra-rare framework would intersect if the treatment under review met both criteria.

Patient-Centeredness and Affordability

As we have shared in prior letters to ICER, we believe the patient voice must be incorporated at every stage, from identification of research topics through research design, clinical trials, long-term follow-up, and ultimately health technology assessment and payer decision-making. Accordingly, the global bleeding disorders community has advocated for inclusion of patient-relevant outcomes across this spectrum, and expert consensus processes have led to the development of several value-based frameworks and patient-reported outcome tools for hemophilia treatments generally, and hemophilia gene therapy in particular. We reiterate our recommendation that ICER include these resources

when reviewing SSTs for hemophilia, and urge ICER to work with patient and provider communities to include any relevant patient-centered tools when conducting other reviews.

Finally, we recognize that while potentially curative therapies may be cost-effective relative to existing, expensive, life-long therapies, this does not mean that payers will cover those treatments, or that patients will be able to afford them. We appreciate that ICER intends to include shared savings models in the review to illuminate some of these issues. This modeling, however, may not fully describe or be responsive to broader affordability concerns. Structural limitations of the existing US health care financing system mean that public and private payers do not yet have the tools to accommodate creative approaches. We encourage ICER to work with the relevant patient communities on assessing affordability for patients and budgetary impact for health care system.

Innovation in Economic Models and Discounting

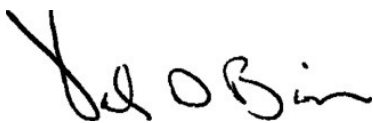
ICER describes its current thinking about discount rates and its ultimate decision to model the same 3% discount rate for costs and outcomes for SSTs along with non-SSTs. In the technical brief, ICER describes how other HTA agencies view this issue differently and shares the reasoning whereby it decided not to model varied discount rates in its SST reviews. We encourage ICER to reconsider this stance and to indeed model different discount rates in SST reviews, both to partially respond to the uncertainty inherent in SST reviews and also to help advance the literature on appropriate discount rates to be used in HTA reviews. More generally, in looking at the long-term value of elements such as career, educational, and employment choices, appropriate discount rates should be considered that account for the long-term value of the health effects in relation to the costs. These are elements which will yield benefit over a lifetime, well beyond the timespan of a limited observational study.

Conclusion

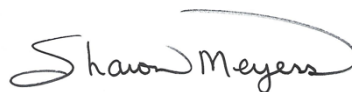
Our organizations look forward to participating in several webinars and meetings with ICER staff and other stakeholders to discuss these issues and ones related to ICER's more general value assessment framework in the coming weeks. We will use those opportunities to refine our perspectives on these issues and will share additional comments with ICER in response to its proposed changes to the overall value assessment framework later this fall.

We appreciate the opportunity to provide these comments and thank you for your consideration.

Sincerely,



Val Bias
Chief Executive Officer
National Hemophilia Foundation



Sharon Meyers, M.S., CFRE
Interim President and CEO
Hemophilia Federation of America

Novartis' Feedback on ICER's Proposed Adaptations for Assessments of Single or Short-term Transformative Therapies

Novartis appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER's) Single or Short-Term Transformative Therapies Framework. We agree that it is important to be clear about how single or short-term transformative therapies (SSTs) are being valued compared to chronic care.

At Novartis, we are united by a single purpose: reimagining medicine to improve and extend people's lives. Novartis medicines deliver value in four interdependent value dimensions: patient, clinical, healthcare systems, and societal value. For one-time treatments with the potential to cure, a beneficial clinical outcome will lead to improved quality and quantity of life free of disease, reduced or no hospital care in the end and societal gains as the patient can return to work, take care of their family or have hope for a cure. Critically, with a one-time treatment, there are no drug costs after the initial treatment period versus continued costs for life. Similarly, while transformative therapies do not eradicate disease, it can produce substantial long-term health benefits or halt disease progression. Keeping this in mind, Novartis has outlined below follow-up from previous feedback and some new feedback in response to ICER's SSTs Framework:

Previous Novartis Feedback

We made several recommendations during the open input period for ICER's SSTs Framework. Some of the main recommendations that we made were: to consider novel value elements, to address uncertainty by sharing risk between health companies and payers, ensuring no patient access delay and to use alternative modeling methods such as cure fraction model for curative treatments. We are in agreement with ICER on the two items of incorporation. First, the addition of dimensions of value with a focus on insurance value, option value, the value of hope and scientific spillover. Second, the use of both cure proportion modeling (e.g. mixture cure models), and model averaging to address structural and patient-based uncertainties. While Novartis agrees with ICER on these elements, we fundamentally disagree on ICER's recommendations on addressing uncertainty.

In creating a separate framework for evaluating SSTs, ICER is trying to account for the uncertainty in outcomes for SSTs, as the initial evaluations will occur at a time when only short-term data from clinical trials are available. However, ICER's approach for doing so is primarily to account for model uncertainty, which is a technical point that may not be well understood by ICER's broader audience.

New Feedback on Revised Framework

1. Base case reporting format

Although ICER is making a good effort to account for the uncertainty scientifically, only base case results are reported in the "Report at a Glance," press releases, and in any subsequent media mentions. We are concerned that this will lead to a distortion in the messaging resulting from an ICER evaluation. We would welcome greater transparency in reporting around the summary of results[1] and would like to better understand how certain results are selected for high-level

documentation and the “Report at a Glance.” In order to address this issue, we recommend a work stream composed of different stakeholders, with the aim of making the process fair and balanced, and to ensure that all critical parts of the evaluation are highlighted appropriately, including outcomes and variance of cost-effectiveness and for multiple cost-effectiveness thr

esholds, as well as uncertainties and other methodological challenges[2, 3]. Along those lines, we argue for a more involved and early stakeholder engagement process relative to the existing standard engagement process, including regular stakeholder consultation meetings.

2. Incremental cost-effectiveness scenarios at multiple time horizons, including at longest available follow-up data across trials, 5, 10, and lifetime

ICER should reconsider reporting over multiple time horizons. According to ICER’s definition of treatments that qualify for this framework, a short time horizon seems inadequate to capture the benefit of treatment. Specifically, when relying on a short time frame, an evaluation would unnecessarily anchor healthcare decision-makers to overly conservative cost-effectiveness calculations [4, 5]. For many SSTs in particular, health benefits manifest in the long-term, and thus, limiting the evaluation period to five years would inevitably curb the therapy value[4]. We, therefore, recommend using a lifetime cost-effectiveness scenario as the base case, and both five and ten-year time horizons as alternative scenarios in the case of reasonable medical concerns. In addition, we suggest considering follow-up data on Phase 1 patients (including efficacy data if available) to take advantage of longer follow-up data.

3. Approach to dealing with long-term uncertainty and alternative sources of evidence

We urge ICER to consider real-world evidence to supplement clinical trial data. Particularly in the case of cures and transformative treatments for rare diseases, the FDA recommends that alternative sources of evidence, including electronic health records, billing databases, as well as product and disease databases should be considered [6]. Similarly, the European Medicines Agency (EMA) emphasizes the importance of considering non-traditional, yet regularly collected data on a patient’s health status or the delivery of health services.[7] Despite increased regulatory attention however, a clear, universal guideline for the collection and analysis of real world evidence is still missing, thus leading to a lack of standardization and harmonization. We recommend that ICER work with these global HTAs and the FDA to identify a path to incorporating real world data into economic evaluations of pharmaceutical treatments. In light of the FDA’s recommendations for real-world evidence and real-world data [8], we thus suggest that ICER carry-out condition updates at predetermined intervals, for example, 3 years after market entry.

In addition, we believe that incorporating real-world evidence and considering alternative data sources as part of the evaluation process, ICER will be able to address the long-term uncertainty of SSTs more effectively. As such, examining available data for Phase 1 patients at the time of reimbursement is an important, yet an often under-utilized source of information when evaluating these kinds of transformative treatments. To mitigate the uncertainty inherent in this alternative source of evidence and to gain a more nuanced understanding of best practices in monitoring long-term outcomes, as well as the potential risks involved in gene silencing, we urge ICER to actively involve worldwide experts. ICER further raises the concern that SSTs “could

lead to a decreased chance at effective treatment by a future generation of therapies in the pipeline.” We believe that while experts pointing to potential negative externalities should be heard in the evaluation process, equal weight should be given to experts on the questions of long-term effectiveness.

4. Threshold analysis to determine the duration that a benefit would need to be sustained to meet standard cost-effectiveness thresholds.

The objective of a threshold analysis as described by ICER suffers from several risks that could result in reduced access for patients. First, any approach that favors a longer duration of benefits will necessarily discount older patient populations. In addition, given the likely uncertainty around the data at the time of the ICER evaluation, this suggestion could lead payers to weigh the result of this calculation against the average duration of beneficiaries covered by a particular health plan and to deny coverage if plan duration is shorter than the required benefit duration[9]. Given these limitations, we strongly urge ICER to consider alternative cost-effectiveness threshold in their evaluation of SSTs, including \$200K, \$250K, \$300K and upwards to \$500K, similar to ICER’s previous threshold for ultra orphan diseases.

5. Threshold alert to indicate when payers and manufacturers should consider an outcomes-based contract.

ICER initially proposed that payers and manufacturers ought to consider an outcomes-based contract when more than 25% of the probabilistic sensitivity analyses simulations produce incremental cost-effectiveness ratios above \$200,000 per QALY. PSA is more suited when there is uncertainty around a sample estimate (e.g. how different could the estimate be if a different sample was drawn). Long-term outcomes uncertainty, on the other hand, is not a statistical/model uncertainty. Therefore, long-term effectiveness will be an assumption. Thus, calculating long-term uncertainty through a more quantitative approach may be inappropriate. We are supportive of deploying outcome-based agreement to address uncertainty as a principle, but do not consider PSA or a threshold (\$200K per QALY) meaningful.

Rather than using unweighted QALYs, ICER should consider imposing QALY weights to reflect key population-based factors critical to the evaluation of SST benefits. Furthermore, we believe that in addition to using QALYs, targeting a disease-specific, most desirable health outcome would be valuable[10]. In the areas of oncology, for example, disease free survival would be a suitable objective. If progression is slowing, a QALY-based approach would likely underestimate the cost-effectiveness of a treatment under review[5].

Lastly, developing an outcome-based contract is a highly complex undertaking that goes beyond threshold-based economic modeling as it involves detailed discussions between manufacturers and payers, establishing an appropriate counterfactual, identifying the appropriate target population, and a number of other highly sensitive and complex items outside the scope of an ICER evaluation[11]. While ICER is right to highlight financing issues as a primary concern for SSTs, we believe that rather than advocating for outcomes-based contracts between payers and manufacturers, ICER ought to explore alternative financing scenarios as part of its sensitivity analyses. ICER’s approach to evaluating treatments is well suited to informing policy, but should not be used to lend advice on how to structure outcomes-based contracts.

6. Shared savings calculation to split the value of cost offsets for expensive chronic conditions between innovators and society

Providing a proper value assessment framework as described above is in place, we are willing to discuss shared savings.

We believe it is still very premature to determine which mechanism should be used for SSTs. In particular, we believe setting a certain percentage of sharing or creating a 12 year mock patent cliff could create an unfortunate precedent, without proper consideration of key factors

Some key factors which should be taken into account are: 1) timing & level of Gx competition; 2) extent of prevalent patients addressed by first movers; 3) effect of brand-to-brand competition. The effect may differ largely depending on disease area or product. In addition, cost offsets and choice of comparators need to be clearly defined. However, the mechanisms which ICER has raised so far (capped QALY, % sharing, mock patent cliff) do not seem to adequately reflect this. We recommend to consider a mechanism based on key factors.

We look forward to further discussions. SSTs are a new space for patient advocacy groups, HTA agencies, payers and manufacturers. In-depth work and multi-stakeholder discussions are required. As a result, we recommend ICER to continue to collaborate with manufacturers to test these assumptions on some SSTs products and to have ongoing multi-stakeholder roundtables to discuss a proper adjustment mechanism.

7. Uniform vs. differential discounting

We believe that refusing to use differential discounting is a deviation from many HTAs when benefits are accrued over a long time period, and costs occur upfront, in the short-term. Notably, the UK-based Joint Committee on Vaccination and Immunisation (JCVI) recently spoke out in favor of differentially discounting costs and benefits:

“In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used.. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered.”[13]

As the standard practice in the US is to discount benefits at the same rate as costs, the benefit of potentially curative medicines may be severely misrepresented. In the meantime, given the considerable public attention to ICER reports beyond the field of health economics, it would be beneficial to patients and members of the public for an undiscounted survival benefit to be published, as well as a value-based price, representing undiscounted benefits. To illustrate the considerable difference that alternative discounting strategies can have on the cost-effectiveness estimates of an ICER evaluation, we point to ICER’s draft evidence report of the evaluation for spinal muscular atrophy, involving ZOLGENSMA [14]: Table E10 (page 167) reports a gain of 32.4 undiscounted life years for the ZOLGENSMA cohort. To test the ICER per QALY, we

multiplied the corresponding utility value for each health state (using 0.88 as an average for walking) by the undiscounted LYs (by health state) for ZOLGENSMA to yield the undiscounted QALYs. Our calculations show ZOLGENSMA yields 22.4 undiscounted QALYs; in the base case (3% discounting) ZOLGENSMA yields 11.33 QALYs. Removing discounting nearly doubles the QALYs. Using costs from Table 4.13 (page 70) shows the benefit of differential discounting (3% costs, 0% utilities), as the ICER for ZOLGENSMA compared to BSC drops to \$123,000 per QALY, from the base case of \$247,000 per QALY. While somewhat of an extreme case, these calculations clearly show that cost-effectiveness estimates are highly sensitive to the choice of discount rates and the overall approach to discounting. Attema and colleagues (2018) further point out that QALYs are typically derived through patient elicitation and are thus subject to individual time preferences. Further discounting QALY estimates would, therefore, lead to a double-discounting, thus severely undercounting true benefits derived from a treatment [15]. We thus believe that in the very least, differential discounting needs to be included as a sensitivity analysis, both in ICER's overall evaluation framework for SSTs, and the "Report at a Glance" publication.

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September 6, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Value Assessment Methods for Single or Short-Term Transformative Therapies

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

The National Pharmaceutical Council (NPC) shares your interest in promoting a dynamic, innovative health care system and in placing scientific methods of evidence analysis and transparency at the heart of value assessment processes. With this view in mind, NPC appreciates ICER's call for public comments on the *Value Assessment Methods for "Single or Short-Term Transformative Therapies (SSTs)." [1]*

NPC is a health policy research organization dedicated to the advancement of good evidence and science, and to fostering an environment in the United States that supports medical innovation. NPC is supported by the major U.S. research-based biopharmaceutical companies. We focus on research development, information dissemination, education and communication of the critical issues of evidence, innovation and the value of medicines for patients. Our research helps inform critical health care policy debates and supports the achievement of the best patient outcomes in the most efficient way possible.

Although ICER's proposed updates provide several incremental improvements to its framework to better support analysis of SSTs, further revision and refinement of the framework is necessary. The areas requiring further revision include: 1) definition of SSTs, 2) characterization of uncertainty, 3) representation of societal benefits, and 4) handling of affordability concerns.

Our comments below are organized around the sections included in the Proposed Adaptations to the ICER Value Assessment Framework dated August 6, 2019.

1. Determining those treatments for which adapted assessment methods will be used

ICER's definition of SSTs is somewhat ambiguous. For instance, the current SST definition may be interpreted to include vaccines and all anti-infective therapies. We do not believe this to be ICER's intention. It is NPC's recommendation that further SST inclusion and exclusion criteria be developed.

In addition, the current definition may be interpreted to include curative therapies that are not biopharmaceuticals (e.g., implantable cardioverter defibrillator), which NPC views as positive. As stated in NPC's *Guiding Practices for Patient-Centered Value Assessment*, "Value assessments should focus broadly on all aspects of the healthcare system, not just on medications." [2] It is NPC's recommendation that non-biopharmaceuticals be included in ICER's portfolio of SST evaluations.

2. Assessing and Describing Uncertainty

NPC appreciates that ICER has taken steps to improve its value assessment framework to better account for the greater uncertainty associated with SSTs. Positive steps include the use of a lifetime horizon for the primary value-based price estimate, the incorporation of additional modeling techniques such as cure proportion modeling, the inclusion of multiple time horizon thresholds, and probabilistic sensitivity analysis.

However, we are concerned that the proposed measures will not adequately communicate the significant uncertainty associated with SST population-based value price estimates. The recommendations below are actions that ICER could take to improve both the credibility and transparency of proposed methods to address uncertainty.

Including Upside Risk

The proposed adaptations include the use of probabilistic sensitivity analysis (PSA), which is a powerful tool for conveying uncertainty. However, ICER's planned application is limited to the inclusion of an outcomes-based contracting recommendation when 25% of PSA simulations exceed the \$200,000 per quality adjusted life-year (QALY) threshold. As currently planned, PSA will only be used to highlight downside risk for payers. However, there is also upside potential as uncertainty swings both ways.

Identifying the full range of prices is important for two reasons: 1) credibility requires full transparency of SSTs' value-based price estimate uncertainty, and 2) the inclusion of potential upside will identify ways for payers to extract greater value which is equally important to managing downside risk for SSTs. PSA provides a way in which ICER can fully characterize and communicate both the upside and downside uncertainty associated with its estimates. Therefore, it is NPC's recommendation that ICER provide a PSA estimated price range both on the upside and the downside in both its Final Report and its Report-at-a-Glance.

Including Tornado Charts in Report-at-a-Glance

ICER's stated goal of PSA is to identify where outcomes-based agreements are needed to manage risk. Tornado charts are a good way to achieve this goal as they identify sources

of risk and uncertainty, which will enable payers to more effectively manage these therapies. It is NPC’s recommendation that tornado charts, which are currently included in the Final Report, be included as part of the Report-at-a-Glance.

Including Value to Individual Responder by Duration of Response

The proposed inclusion of multiple time horizons is a positive step toward facilitating the use of outcomes-based agreements. However, it does not go far enough. Population-based estimates of a “fair price” may be fine for those payers who do not wish to participate in outcomes-based agreements, but will not be adequate for those payers trying to maximize the value of each dollar spent.

Many of the traditional gene therapies have small patient populations. This is also true for many of the SSTs in the oncology space. Given the small size of these treatment populations, population estimates are highly unlikely to truly reflect the value experience within any given plan. Plans desiring to more actively manage this risk will need information beyond population estimates.

Fortunately, these information requirements are clear from payment techniques being developed by MIT NEW Drug Development ParadIGmS (NEWDIGS) Financing and Reimbursement of Cures in the US, Alliance for Regenerative Medicine, Duke-Margolis Value-Based Payment Consortium, Network for Excellence in Health Innovation and others. [3,4] Specifically, these plans would need to know the value of an individual responder by duration of response. A general example is provided below, but the outcomes of interest and duration of response in years would need to be customized for each disease.

Duration of Response in Years	Value Based Price Estimate for Individual Responder
1	Value Based Price Range 1
2	Value Based Price Range 2
3	Value Based Price Range 3
⋮	⋮
10	Value Based Price Range 10

This information presented in the above chart is readily accessible as it is included within the models used to estimate the population-based value price. Therefore, it is NPC’s recommendation that the value of a responder by duration be included in the Final Report and Report-at-a-Glance as a supplement to the population-based estimates.

Replace Outcomes-Based Contracting (OBC) Recommendation with OBC Considerations Chart

The proposed adaptations include an outcomes-based contracting recommendation when 25% of PSA simulations exceed the \$200,000 per QALY threshold. However, the decision on whether or not to engage in OBC is based on a multitude of factors that extend beyond a single threshold including economies of scale, feasibility of measuring outcomes, regulatory barriers, administrative burden, and payer contracting abilities. [5] Therefore, it is NPC's recommendation that ICER provide a chart that captures the various outcome considerations for a given therapy rather than a binary recommendation of whether or not to participate in OBC. Beyond the percent of PSA simulations in excess of \$200,000, this chart could identify:

- Dollars at stake per person and plan (for a fixed number of plan sizes)
- Which outcomes, if any, lend themselves to OBC

Incorporate New Evidence When Possible

ICER's proposed changes to its broader value assessment framework include a proposal to conduct a review of new evidence developments one year after the final report is issued. [6] This review would indicate whether a new review is required, the evidence does not justify a new review, or if the prior estimates are still valid. [6] Shortening the timeframe between reviews provides an opportunity to remove uncertainties with the incorporation of new evidence, including real-world evidence (RWE).

SSTs, by their nature, have greater uncertainty that will be reflected in the value-based price estimates. Shortening the time between SST review cycles provides an opportunity for the incorporation of new evidence, such as registries. Clinical registries are a potential source of longitudinal clinical data for a population that is more heterogeneous than what is represented in a clinical trial. This is just one example of how new evidence could be a valuable source of information to reduce uncertainty in SST value-based price estimates. [7] NPC recommends that ICER both check for new evidence development on annual basis after the final report and incorporate new evidence (when available and suitable) in revised estimates for SSTs.

3. Additional Elements of Value

We are pleased that ICER will add an additional element of value to better reflect the unique nature of these therapies. However, we believe that this step does not go far enough as the incorporation of the full benefits into value assessment is important. [8,9] This is critical for “potential cures” as the magnitude and type of benefits produced are much greater than the benefits traditionally captured in the QALY. Examples include caregiver burden, employer

productivity gains, and insurer value. It is critical that these benefits be quantified where data allows.

Furthermore, it is our belief that these benefits need to be quantified in a manner similar to ultra-rare diseases where the societal benefit is presented as a co-base case. Per the addendum for rare diseases, “When the impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial and these costs are large in relation to health care costs, ICER will present its base case health system perspective model results in tandem with the results of a scenario analysis inclusive of broader societal costs. Similarly, a value-based price benchmark (VBPB) linked to the societal perspective analysis will be presented alongside the standard VBPB.” [10] For these reasons, it is NPC’s recommendation that the societal scenario be presented as a co-base case for all therapy evaluations including SSTs.

Under the current approach, a subjective approach is used to evaluate additional elements of value to determine whether or not the cost per QALY threshold should be toggled. The addition of an element that may negatively impact this threshold highlights the need to have a structured transparent decision process for the cost per QALY threshold. Therefore, it is NPC’s recommendation that ICER use a scientifically robust method such as Multi-Criteria Decision Analysis (MCDA) or a similar process to evaluate whether the cost per QALY threshold should be toggled as a result of non-quantifiable elements of value.

4. Affordability and Fair Sharing of Economic Surplus

As noted in the technical brief, ICER believes that many cures will not only substantially extend life, but will also create substantial cost savings. [11] In today’s world, developers typically “price in” these cost savings. However, ICER is concerned that this approach will lead to unreasonably high prices. NPC believes that the benefits of the proposed approach, which adds a scenario where cost offsets that occur after 12 years are not considered, are outweighed by the risks, including the potential to create negative incentives for innovation.

The technical appendix includes examples using this approach on spinal muscular atrophy (SMA) type 1, hemophilia A, and B-cell lymphoma therapies. Only hemophilia A had a substantial reduction to the value-based price. The changes to the value-based prices for SMA type 1 and B-cell lymphoma therapies were marginal. This analysis highlights that diseases with large ongoing cost offsets, such as hemophilia A, are likely to occur on a less frequent basis.

In addition, the conditions with the highest potential budget impact are likely to have competition that drives down costs over time, thus mitigating the risk of “value-based prices of extreme levels.” Hepatitis C provides a recent example of the impact of competition driving down treatment costs when the market attracts multiple entrants. There are five therapies for hemophilia A currently in clinical trials, which is a strong indicator of future competition. [12] All of these factors point to the benefits of the proposed approach being limited.

More importantly, NPC fears that treating SSTs differently than ongoing therapies has the potential unintended consequence of creating economic inefficiencies by incentivizing ongoing

therapies over curative therapies. Specifically, NPC is concerned that ignoring cost offsets beyond 12 years will penalize conditions where the most important outcomes and costs avoided occur beyond the 12-year time horizon. ICER's technical analysis is limited to conditions where there are either recurring cost offsets (hemophilia A) or where the expected patient survival is several years or less under current treatment options (SMA type I, B-cell lymphoma).

This is not an adequate disease mix representation. It is our opinion, that if the analysis included metabolic, cardiovascular, neurological (e.g. Alzheimer's disease) and ophthalmic conditions that the proposed approach would significantly favor ongoing therapy over SSTs due the long-time horizon associated with key outcomes. For instance, a cure for Alzheimer's disease given at age 50 might not avoid major costs until age 65. Similarly, a cure for cardiovascular disease given at age 50 might not generate significant savings until a decade later. In these scenarios, the proposed approach will favor ongoing therapies over SSTs.

This incentivizes an inefficient health system, which is not desirable. This point is especially salient because analyses by MIT have found that gene therapies are expected in these very conditions over the next 10 years. [13,14,15] Given the marginal impact on value-based price estimates and potential for unintended consequences, NPC recommends that ICER not include the sharing of economic surplus approach as a standard part of its reports.

We appreciate the opportunity to provide input on the key methodological questions associated with *Value Assessment Methods for "Single or Short-Term Transformative Therapies (SSTs)."* [16]

We look forward to continued dialogue as this project moves forward.

Respectfully submitted,

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Robert W. Dubois, MD, PhD

Chief Science Officer & Executive Vice President

National Pharmaceutical Council

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September 6, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Value Assessment Methods for Single or Short-Term Transformative Therapies

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

The National Pharmaceutical Council (NPC) shares your interest in promoting a dynamic, innovative health care system and in placing scientific methods of evidence analysis and transparency at the heart of value assessment processes. With this view in mind, NPC appreciates ICER's call for public comments on the *Value Assessment Methods for "Single or Short-Term Transformative Therapies (SSTs)." [1]*

NPC is a health policy research organization dedicated to the advancement of good evidence and science, and to fostering an environment in the United States that supports medical innovation. NPC is supported by the major U.S. research-based biopharmaceutical companies. We focus on research development, information dissemination, education and communication of the critical issues of evidence, innovation and the value of medicines for patients. Our research helps inform critical health care policy debates and supports the achievement of the best patient outcomes in the most efficient way possible.

Although ICER's proposed updates provide several incremental improvements to its framework to better support analysis of SSTs, further revision and refinement of the framework is necessary. The areas requiring further revision include: 1) definition of SSTs, 2) characterization of uncertainty, 3) representation of societal benefits, and 4) handling of affordability concerns.

Our comments below are organized around the sections included in the Proposed Adaptations to the ICER Value Assessment Framework dated August 6, 2019.

1. Determining those treatments for which adapted assessment methods will be used

ICER's definition of SSTs is somewhat ambiguous. For instance, the current SST definition may be interpreted to include vaccines and all anti-infective therapies. We do not believe this to be ICER's intention. It is NPC's recommendation that further SST inclusion and exclusion criteria be developed.

In addition, the current definition may be interpreted to include curative therapies that are not biopharmaceuticals (e.g., implantable cardioverter defibrillator), which NPC views as positive. As stated in NPC's *Guiding Practices for Patient-Centered Value Assessment*, "Value assessments should focus broadly on all aspects of the healthcare system, not just on medications." [2] It is NPC's recommendation that non-biopharmaceuticals be included in ICER's portfolio of SST evaluations.

2. Assessing and Describing Uncertainty

NPC appreciates that ICER has taken steps to improve its value assessment framework to better account for the greater uncertainty associated with SSTs. Positive steps include the use of a lifetime horizon for the primary value-based price estimate, the incorporation of additional modeling techniques such as cure proportion modeling, the inclusion of multiple time horizon thresholds, and probabilistic sensitivity analysis.

However, we are concerned that the proposed measures will not adequately communicate the significant uncertainty associated with SST population-based value price estimates. The recommendations below are actions that ICER could take to improve both the credibility and transparency of proposed methods to address uncertainty.

Including Upside Risk

The proposed adaptations include the use of probabilistic sensitivity analysis (PSA), which is a powerful tool for conveying uncertainty. However, ICER's planned application is limited to the inclusion of an outcomes-based contracting recommendation when 25% of PSA simulations exceed the \$200,000 per quality adjusted life-year (QALY) threshold. As currently planned, PSA will only be used to highlight downside risk for payers. However, there is also upside potential as uncertainty swings both ways.

Identifying the full range of prices is important for two reasons: 1) credibility requires full transparency of SSTs' value-based price estimate uncertainty, and 2) the inclusion of potential upside will identify ways for payers to extract greater value which is equally important to managing downside risk for SSTs. PSA provides a way in which ICER can fully characterize and communicate both the upside and downside uncertainty associated with its estimates. Therefore, it is NPC's recommendation that ICER provide a PSA estimated price range both on the upside and the downside in both its Final Report and its Report-at-a-Glance.

Including Tornado Charts in Report-at-a-Glance

ICER's stated goal of PSA is to identify where outcomes-based agreements are needed to manage risk. Tornado charts are a good way to achieve this goal as they identify sources

of risk and uncertainty, which will enable payers to more effectively manage these therapies. It is NPC's recommendation that tornado charts, which are currently included in the Final Report, be included as part of the Report-at-a-Glance.

Including Value to Individual Responder by Duration of Response

The proposed inclusion of multiple time horizons is a positive step toward facilitating the use of outcomes-based agreements. However, it does not go far enough. Population-based estimates of a “fair price” may be fine for those payers who do not wish to participate in outcomes-based agreements, but will not be adequate for those payers trying to maximize the value of each dollar spent.

Many of the traditional gene therapies have small patient populations. This is also true for many of the SSTs in the oncology space. Given the small size of these treatment populations, population estimates are highly unlikely to truly reflect the value experience within any given plan. Plans desiring to more actively manage this risk will need information beyond population estimates.

Fortunately, these information requirements are clear from payment techniques being developed by MIT NEW Drug Development ParadIGmS (NEWDIGS) Financing and Reimbursement of Cures in the US, Alliance for Regenerative Medicine, Duke-Margolis Value-Based Payment Consortium, Network for Excellence in Health Innovation and others. [3,4] Specifically, these plans would need to know the value of an individual responder by duration of response. A general example is provided below, but the outcomes of interest and duration of response in years would need to be customized for each disease.

Duration of Response in Years	Value Based Price Estimate for Individual Responder
1	Value Based Price Range 1
2	Value Based Price Range 2
3	Value Based Price Range 3
⋮	⋮
10	Value Based Price Range 10

This information presented in the above chart is readily accessible as it is included within the models used to estimate the population-based value price. Therefore, it is NPC's recommendation that the value of a responder by duration be included in the Final Report and Report-at-a-Glance as a supplement to the population-based estimates.

Replace Outcomes-Based Contracting (OBC) Recommendation with OBC Considerations Chart

The proposed adaptations include an outcomes-based contracting recommendation when 25% of PSA simulations exceed the \$200,000 per QALY threshold. However, the decision on whether or not to engage in OBC is based on a multitude of factors that extend beyond a single threshold including economies of scale, feasibility of measuring outcomes, regulatory barriers, administrative burden, and payer contracting abilities. [5] Therefore, it is NPC's recommendation that ICER provide a chart that captures the various outcome considerations for a given therapy rather than a binary recommendation of whether or not to participate in OBC. Beyond the percent of PSA simulations in excess of \$200,000, this chart could identify:

- Dollars at stake per person and plan (for a fixed number of plan sizes)
- Which outcomes, if any, lend themselves to OBC

Incorporate New Evidence When Possible

ICER's proposed changes to its broader value assessment framework include a proposal to conduct a review of new evidence developments one year after the final report is issued. [6] This review would indicate whether a new review is required, the evidence does not justify a new review, or if the prior estimates are still valid. [6] Shortening the timeframe between reviews provides an opportunity to remove uncertainties with the incorporation of new evidence, including real-world evidence (RWE).

SSTs, by their nature, have greater uncertainty that will be reflected in the value-based price estimates. Shortening the time between SST review cycles provides an opportunity for the incorporation of new evidence, such as registries. Clinical registries are a potential source of longitudinal clinical data for a population that is more heterogeneous than what is represented in a clinical trial. This is just one example of how new evidence could be a valuable source of information to reduce uncertainty in SST value-based price estimates. [7] NPC recommends that ICER both check for new evidence development on annual basis after the final report and incorporate new evidence (when available and suitable) in revised estimates for SSTs.

3. Additional Elements of Value

We are pleased that ICER will add an additional element of value to better reflect the unique nature of these therapies. However, we believe that this step does not go far enough as the incorporation of the full benefits into value assessment is important. [8,9] This is critical for “potential cures” as the magnitude and type of benefits produced are much greater than the benefits traditionally captured in the QALY. Examples include caregiver burden, employer

productivity gains, and insurer value. It is critical that these benefits be quantified where data allows.

Furthermore, it is our belief that these benefits need to be quantified in a manner similar to ultra-rare diseases where the societal benefit is presented as a co-base case. Per the addendum for rare diseases, “When the impact of treatment on patient and caregiver productivity, education, disability, and nursing home costs is substantial and these costs are large in relation to health care costs, ICER will present its base case health system perspective model results in tandem with the results of a scenario analysis inclusive of broader societal costs. Similarly, a value-based price benchmark (VBPB) linked to the societal perspective analysis will be presented alongside the standard VBPB.” [10] For these reasons, it is NPC’s recommendation that the societal scenario be presented as a co-base case for all therapy evaluations including SSTs.

Under the current approach, a subjective approach is used to evaluate additional elements of value to determine whether or not the cost per QALY threshold should be toggled. The addition of an element that may negatively impact this threshold highlights the need to have a structured transparent decision process for the cost per QALY threshold. Therefore, it is NPC’s recommendation that ICER use a scientifically robust method such as Multi-Criteria Decision Analysis (MCDA) or a similar process to evaluate whether the cost per QALY threshold should be toggled as a result of non-quantifiable elements of value.

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Robert W. Dubois, MD, PhD

Chief Science Officer & Executive Vice President

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Public Comments on Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs) - Proposed Adaptations to ICER Value Assessment Framework

Patients For Affordable Drugs

September 3, 2019

Introduction

Single or Short-Term Transformative Therapies (SSTs) offer great hope for millions of American patients and their families. They may mean the difference between life and death, or a lifetime of treatment vs. a life lived without the need for ongoing medical care.

The hope for SSTs is tempered, however, by deep concerns about prices being set for these drugs. The first drugs that potentially qualify as SSTs as ICER proposes to define them have come to market at prices ranging from \$373,000 to \$2,125,000.^{1,2} These therapies have been for indications affecting relatively small numbers of patients — but SSTs for larger populations are right around the corner and pose a threat to a system already buckling under unjustified high prices.

CMS Administrator Seema Verma articulated this fact after the Administration announced a national coverage determination for CAR-T drugs which effectively set a reimbursement level at 65 percent of list price. Verma said “such expensive treatments are ‘begging the question of how the system is going to pay for this over the long term. *This is something we are extremely concerned about.*”³

There are more than 400 Phase II and III trials underway for new cell and gene therapies.⁴ The FDA predicts that by 2025 “the FDA will be approving 10 to 20 cell and gene therapy products a year.”⁵

ICER’s proposed adaptations are a well-intended and timely attempt to address the challenges we face in valuing SSTs. However, we believe some of the proposed changes fail to adequately address the issue, others take us in the wrong direction, and some may lead to unjustified high prices that threaten patient access and will lead to rationing. Finally, we believe strongly that in order to appropriately evaluate and offer guidance to policymakers on SSTs, ICER must finally

¹ <https://khn.org/news/staggering-prices-slow-insurers-coverage-of-car-t-cancer-therapy/>

² <https://www.biopharmadive.com/news/zolgensma-set-a-new-drug-pricing-bar-insurers-show-some-signs-of-pushback/558101/>

³ <https://www.washingtonpost.com/health/2019/08/07/medicare-will-cover-pioneering-cancer-treatment-nationwide/>

⁴ http://alliancerm.org/wp-content/uploads/2019/05/ARM_Q1_2019_Web.pdf

⁵ <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics>

address taxpayer contribution to new therapies, the costs of research and development, and reasonable return on investment.

Section 1: Determining those treatments for which adapted assessment methods will be used

We question the proposed definition for drugs that would be assessed under this framework. ICER's use of the terms "cures" and "transformative therapies" gives us great concern. This nomenclature is unwarranted and introduces emotion that serves the drug industry — not patients or the aims of rigorous HTA.

In addition to the word "cure" being heavily-freighted and the problem that many of these therapies will arrive without data to support that designation, there is a definitional challenge. A number of previous treatments could fit your definition of transformative therapies. Some definitions say a cure is to relieve a patient of the symptoms of a disease. But many treatments do that today. Immunomodulatory drugs (IMiDs) have been transformative for people with multiple myeloma — extending life with durable responses for extended periods. Penicillin, insulin and the polio vaccine were all transformative by any definition. Organ transplantation is transformative. Laparoscopic surgery has been transformative delivering huge advantages for patients. Yet, no one suggests ICER should place these medicines and treatments in the kind of separate category that you propose for future drugs.

We suggest that ICER maintain the nomenclature "single or short-term therapy" or another designation that does not put future drugs with high impact in a different category from those in the past.

Section 2: Assessing and Describing Uncertainty

We have significant concerns about this section. We agree that uncertainty about the durability of effect must be addressed, especially since many SSTs are coming to market without extensive and rigorous data. For example, ICER should not assess long-term value based on effectiveness shown in short-term, single-arm clinical trials with non-representative patient samples. Instead, ICER should peg price to the existing evidence at the time of approval and allow the price to rise only if the promise of the drug is realized through post-market studies. Otherwise, the drugmaker essentially receives the best-case scenario price up front, while shifting the burden of conducting post-market trials onto payers, patients, and taxpayers for a drug that may not live up to its promise.

We strongly urge ICER against advocating for certain payment models. In doing so, the Institute departs from its mission to be "an independent source of analysis of evidence on effectiveness

and value”.⁶ Outcomes-based contracting simply enables drugmakers to command high prices on unproven therapies by spreading the pain of payment over time. Extending payment over time does not lessen the global budget impact; in fact it may increase the global budget impact by increasing the total payment to cover interest charges built into the price. These contracts can also increase prices, since drugmakers have the data necessary to bake failure rates into their launch price to offset losses.

Section 3: Additional Elements of Value

We agree with the approach proposed in this section.

Section 4: Time Divergence Between Costs and Benefits

We agree with the discount rate proposed.

Section 5: Affordability and Fair Sharing of Economic Surplus

We strongly object to the “shared savings” proposal.

We recognize that ICER’s current model places a high value on SSTs when cost offsets are taken into consideration and agree that this methodology must be considered. But drug manufacturers should not receive all potential cost offsets through high value prices and profit that matches those for current treatments, especially since many existing treatments are already priced too high.

No one else in our health care system is paid this way. A surgeon who repairs a congenital defect at birth does not get paid based on savings for future care that will not be required or on quality life years gained. A transplant team is not paid this way. We did not price the polio vaccine based on all the kids who did not have to live in iron lungs. Rather, in addition to value as ICER evaluates it, our nation should establish prices based on research, development and production costs plus some reasonable profit — which is how prices are set in the rest of our health care market. Value is but one key component for sellers and payers to understand and consider. This is, for example, our understanding of how the Veterans Administration employs value analysis.

But under your shared savings proposal drug companies almost certainly will realize enormous unearned windfalls under a new system that works well for manufacturers but not for society.

Here’s a very rough example:

6

<https://icer-review.org/wp-content/uploads/2016/01/ICER-FAQ-052316.pdf#targetText=ICER's%20mission%20is%20to%20help,interests%20of%20the%20insurance%20industry.>

Take a simple calculation for the 100,000 people with Sickle Cell disease today. A report in 2016 estimated the lifetime cost of treating a patient with SCD was around \$1 million by age 45.⁷ For this simple calculation, let's spread the cost equally over each year — about \$22,000 per year. Twelve years of care averaging the cost each year and that is \$267,000. For 100,000 people currently with Sickle Cell disease, that totals almost \$27 billion that you propose to give the drug company if 12 years is used for shared savings. That is patently absurd and unaffordable for patients and our health care system given the investment to research, develop and produce these drugs

Here is why. Let's assume the sickle cell treatment cost \$1.2 billion to bring to market — the cost claimed by Novartis for the first CAR-T drug, Kymriah.⁸ Let's also assume cost of production is similar to therapies like CAR-T at a high end of \$80,000 per treatment.⁹ For 100,000 patients, that totals \$9.2 billion to develop and produce. Under the shared savings proposal, the drug company receiving \$27 billion in shared savings would earn a 300 percent profit per year for 12 years — far exceeding any benchmark for the industry, and far exceeding any reasonable return necessary to incentivize investment.

The proposed shared-savings approach has the additional flaw of pricing new therapies based on already overpriced drugs and reference treatments. Americans pay twice as much for prescription drugs as other nations.¹⁰ Americans pay far more than other nations for health care in general.¹¹

Should ICER decide to use shared savings, it must absolutely not use the “average time to loss of exclusivity for new prescription drugs in the United States.” That would reward patent abuse and anticompetitive behavior by the pharmaceutical industry. Drug companies employ an array of tactics to extend exclusivity beyond what is intended under law.¹² Instead, ICER could set a time frame of no more than seven years — the current exclusivity for orphan drugs.

Finally, if ICER's goal is to ensure a proportion of savings are shared with society, it must also consider societal investment in new drugs. U.S. taxpayers foot a huge and critical portion of the bill for the high-risk, early science that leads to new drugs. In fact, NIH is the largest single source of biomedical research in the world — investing over \$39 billion in 2019. Based on a survey of PhRMA's own member companies, one out of every three dollars spent on drug

⁷ <http://www.scdcoalition.org/pdfs/ASH%20State%20of%20Sickle%20Cell%20Disease%202016%20Report.pdf>

⁸ <https://www.forbes.com/sites/matthewherper/2017/08/30/novartis-ceos-dilemma-is-475000-too-much-for-a-leukemia-breakthrough-or-is-it-not-enough/#68c06631556e>

⁹ https://elpais.com/sociedad/2019/03/06/actualidad/1551884979_711151.html

¹⁰ <https://www.theatlantic.com/health/archive/2019/03/drug-prices-high-cost-research-and-development/585253/>

¹¹ <https://www.healthsystemtracker.org/chart-collection/how-do-healthcare-prices-and-use-in-the-u-s-compare-to-other-countries/>

¹² <https://www.judiciary.senate.gov/meetings/intellectual-property-and-the-price-of-prescription-drugs-balancing-innovation-and-competition>

research comes from American taxpayers.^{13,14} Furthermore, every single drug approved by the FDA from 2010-2016 was based on science funded by taxpayers through the NIH.¹⁵

This raises another question as ICER considers a value-based price for SSTs: should a drug company that takes a drug from zero to all the way to market earn the same price/profit as a company that acquires a drug that taxpayer resources took 40, 50 or 60 percent of the way? This is an essential issue to consider when arriving at a price.

For example, take Novartis's CAR-T cancer drug, Kymriah. American taxpayers invested more than \$200 million in CAR-T's discovery and development.¹⁶ Dr. Carl June, a pioneering scientist behind the development of CAR-T said, "When Novartis licensed the CAR-T from us in 2012, it was ready to go. They were in catchup mode compared to where the clinical trials were. All the trials had happened in academia."¹⁷ But Novartis priced its CAR-T drug at \$475,000 per treatment, and to date, it has refused to acknowledge the significance of taxpayers' investment.¹⁸

NIH acknowledges the taxpayer role not just in basic science, but in drug development. Mark L. Rohrbaugh, a federal official who coordinates the patenting and commercial licensing of inventions made by NIH scientists [says](#): "The public sector now has a much more direct role in the applied-research phase of drug discovery."¹⁹

Taxpayers should not have to pay exorbitant amounts for drugs that they've already invested millions of dollars in — especially given that taxpayers will pay again for many of these drugs through out-of-pocket costs and taxes that fund Medicaid and Medicare. If ICER moves forward with a multi-year shared savings model, the time frame should be lowered if the drug benefited from taxpayer investment.

Instead of the shared savings approach, ICER should a) consider the investment of American taxpayers in the science that fuels drug research and development and b) finally reach the issue of fair return on investment at a level necessary to sustain invention. At a minimum, ICER should address these issues in the Key Policy Recommendations section of its reports.

¹³ <https://www.sciencemag.org/news/2018/09/nih-gets-2-billion-boost-final-2019-spending-bill>

¹⁴ <https://www.phrma.org/advocacy/research-development>

¹⁵ <https://www.pnas.org/content/115/10/2329>

¹⁶ Analysis of NIH funding by Diane Singhroy, PhD. Knowledge Ecology International. NIH data accessed July 25, 2017.

¹⁷ <https://www.statnews.com/2018/09/06/car-t-carl-june-nih-sean-parker/>

¹⁸ <https://www.forbes.com/sites/matthewherper/2018/02/08/patient-advocate-says-novartis-475000-breakthrough-should-cost-just-160000/#51fb1a195152>

¹⁹ <https://www.nytimes.com/2018/05/28/us/politics/drug-prices.html>

Bottom line: We believe the proposed shared savings model will virtually assure drug developers will realize economic rents. Patients and our health care system need to pay the lowest possible price necessary to sustain innovation — not the highest possible amount.

Conclusion

Objective evaluation of the clinical and economic value of prescription drugs, medical tests, and other health care and health care delivery innovations is one essential input to arrive at an appropriate price for a treatment. As the leading provider of independent health technology assessment in the U.S., ICER's work is critical to arrive at drug prices that not only reward invention but ensure access for patients. Instead of enabling the pharmaceutical industry's high prices, ICER should consider a fair return on investment at a level necessary to sustain invention.

Most importantly, ICER's work must be based on data — not hopes or dreams. Treat new therapies as you have others in the past; use your existing methodology to arrive at a value-based price. Offer periodic price updates based on observed outcomes. Adjust price based on contribution of taxpayers to research and development, and on payer and patient contribution to post-market evaluation. Provide policymakers with information they need to combine ICER HTA with other relevant data on investment in research and development by the drug maker.



September 6, 2019

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
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Boston, MA 02109 USA

RE: Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs)
Proposed Adaptations to the ICER Value Assessment Framework

Dear Dr. Pearson:

Patients Rising Now is happy to provide comments on ICER’s August 6th proposal for adaptations to its value assessment framework for “Single or Short-Term Transformative Therapies” (SSTs), (Paper), and the accompanying Technical Brief, (Draft Brief).

We appreciate ICER’s understanding that its basic value assessment framework is not robust enough to adequately account for the challenges presented by some curative or transformative therapies (and potentially diagnostics). We also note that the August 6th proposal documents are directly connected to ICER’s activity for updating its base framework for 2020¹, and that ICER also has put forth and utilizes (in certain cases) modifications to its base value framework for “ultra-rare” diseases (URDs).

Given the multiple connections among ICER’s base value framework, its existing modifications for URDs, the proposed modifications for SSTs, and the proposed updates to the base framework for 2020, our comments here will include the amalgam of all of those along with particular comments about the proposals and analyses related to SSTs. We expect to have additional – and more specific – comments about updating the base framework for 2020.

General Concerns About ICER’s Processes, Frameworks, and Modifications:

As we have noted many times, we are concerned that patients’ perspectives, concerns, and viewpoints are not adequately included in ICER’s methodology and overall activities. We find that this persists in the current proposal Paper and Draft Brief. For examples, ICER states, “We hope that this technical brief can serve as a foundation to spur discussion among researchers, insurers, life sciences companies, and policymakers to find ways to support innovation without financially crippling the health care system.”² This statement does not include patients as part of this important dialogue, reflecting ICER’s dismissal of patients’ perspectives for health care decision making. Our position is that health assessment methodologies should be robust, flexible and transparent so as to be able to consider all innovative interventions, including therapeutics, diagnostics, screening tests, direct services (such as procedures), as well as broader health system operational or organizational changes. Therefore, we are concerned that the need for “modifications” to ICER’s base model reflects its underlying inadequacies. That is, rather than have add-ons, we would recommend that ICER revise its underlying model so that it better fits the real world. For example,

¹ We are somewhat perplexed as to why the proposed modifications for SSTs was not done as part of the proposed 2020 update.

² Draft Paper, p. 57.

perhaps ICER could examine Medicare's New Technology Add-on Payment (NTAP) process³ as a model for how an actual transparent payer handles novel innovations.

1. Determining SST Treatments

We agree with ICER's general description of the characteristics of SSTs and concur that different treatments meeting ICER's definition of SSTs will likely be used for different patient populations.

Some of the assertions about SSTs in the Draft Brief are highly questionable. For example, ICER's documents have some very curious – and wrong – statements about market competition, e.g., “the likelihood that many SSTs will never face true generic/biosimilar competition.”⁴ The assertion that SSTs will have limited or no competition forever, and thus “the innovator capturing all the economic surplus from the treatment in perpetuity”⁵ is preposterous both from the perspective of ongoing innovations (which will almost certainly create competition), and the concept of projecting the future “in perpetuity.” As a recent review noted, “the economics profession has an abysmal track record when it comes to seeing into the future.”⁶

History has many examples of how medical innovations entirely or partially replacing treatments with options that are more effective, have fewer or lessor side effects, or are easier for clinicians or patients, e.g., antifungals, antivirals and other antimicrobials; catheter delivered replacement heart valves; and anterior hip replacement. ICER's ongoing frozen-in-time perspective and resistance to appreciating the historical nature of biomedical and care innovations – and what that means for future care – is extremely problematic and disturbing.

Similarly, the assertions that “there is only one real distinctive challenge presented by transformative treatments: the requirement to pay an extremely high price in the short-term despite substantial uncertainty about the long-term benefits,”⁷ infers that there are some “requirements” for high prices when it is well known that prices in the U.S. for almost all health care goods and services are very variable and subject to both appropriate and counter-productive market forces, e.g., transparency can paradoxically drive up health care prices.⁸

In addition, ICER's mischaracterizes patents. While patents are for 20 years from the date of issue by the PTO, biopharmaceuticals may be eligible for extensions under U.S. law for some of the patent time spent prior to FDA approval, with a maximum of 5 years of extension, for a total post FDA approval patent time of no more than 14 years. There also may be an opportunity for an additional 6

³ To get additional payments under NTAP, care technologies must be not only new and expensive (beyond a certain threshold), but also demonstrate a clinical improvement in the Medicare population. As with most government activities, the process has transparent criteria. And in fact, the NTAP process is how Medicare has addressed the new CAR-T therapies for cancer. (<https://www.oncologynurseadvisor.com/home/cancer-types/hematologic-cancers/cms-increases-reimbursement-rate-for-product-cost-of-car-t-therapy/>) It is also important to recognize the Temporary nature of NTAP of 2-3 years which allows Medicare's underlying payment methodology to be adjusted for the new technology. That is, the system has an internal design to accommodate outliers and then adjust.

⁴ Draft Paper, p.54.

⁵ Draft Paper, p.14.

⁶ www.newyorker.com/magazine/2019/09/02/the-rich-cant-get-rich-forever-can-they

⁷ Draft Paper, p.3.

⁸ <https://www.theatlantic.com/health/archive/2013/04/how-price-transparency-could-end-up-increasing-health-care-costs/274534/>

month extension based upon the company conducting pediatric trials. Thus, the final effective length of the patents, (i.e., from the time of FDA approval until expiration) cannot exceed 14.5 years.⁹

2. Assessing and Describing Uncertainty

One of ICER's ongoing challenges is how to conduct evaluations in a landscape containing so much uncertainty – particularly before FDA approval when prices, labelling, or even the assurance of approval are all unknown and have to be speculated by ICER. The SSTs may incur additional uncertainties because some may lack comparator groups in clinical trials, and potentially have a small number of people in the trials.

It is evident to all clear thinkers, that models operating with estimated numerical inputs, produce quantitative results that reflect the imprecision of those inputs, and the farther out such projections forecast, the more imprecise they become until they are quickly overtaken by the noise in the model. Such projections are even more problematic when they do not consider information about potential new treatments, diagnostics, demographic or other changes.

3. Additional Elements of Value

We completely agree that “real option value could be considered as an added benefit of any life extending treatment, not just SSTs,”¹⁰ which is why we have repeatedly urged ICER to consider this aspect of “value” in other assessments it has attempted. However, we reject ICER's conclusion that just because it is difficult to do this, that it shouldn't be done.

We are also concerned that ICER dismisses Scientific Spillover effects because “estimating the likelihood that any specific new therapy will or will not lead to unforeseen future benefits is impossible.”¹¹ We completely disagree that such estimations are “impossible.” Estimating and modeling may be very hard, and laden with uncertainties – as ICER has repeatedly demonstrated – but are definitely not “impossible.” This is another example of ICER's imprecise use of language,¹² which we have noted before.

And lastly, we are confused by statements in the Draft Brief about “opportunity costs” and “attendant health losses.” For example, “There are also intrinsic equity concerns about adding dimensions of value that only increase the assessed value of some forms of treatment -- and thus would support higher prices for them -- without creating some mechanism for balancing this with **the resultant opportunity cost and attendant health losses due to other treatments foregone.**”¹³ [Emphasis added.] This may be economic techno-talk that we are unable to decipher, therefore please explain in simple language and give examples of what is meant by that final phrase and terminology.

⁹ <https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-patent-term-restoration-program> and <https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity>

¹⁰ Draft Paper, p. 12.

¹¹ Draft Paper, p. 11.

¹² Another example of imprecise language in the Draft Brief is “A major overriding factor that would argue against the inclusion of additional value domains cannot be overstated: their inclusion would raise fundamental equity concerns.”(p. 12) Certainly it can be overstated. It could be overstated in many ways. It could be described as leading to the end of life on earth. It could be described as directly leading to the return of human bondage. It could be described as the cause of global warming – all ridiculous, but all overstatements. You DB.

¹³ Draft Paper, p. 9.

4. Time Divergence Between Costs and Benefits

The potentially long delay between payment for a treatment and clinical or economic benefits is the most significant real-world challenge for SSTs because people change payers, so if there is a single up-front payment that cost may be disconnected from long-term benefits or cost-savings. Discussion of various options for discounting rates in this section of ICER's documents diverts attention from that core issue.

5. Affordability and Fair Sharing of Economic Surplus

We are very disturbed that ICER does not explore the issue of either Affordability or Sharing of Economic Surplus from the perspectives of patients. Specifically, in the realm of "affordability" ICER once again only conceptualizes a uniform U.S. health system while the debate about health care in the U.S. focuses on specific stakeholder groups or payer organizations, e.g., affordability for patients who purchase their own insurance or costs to specific parts of Medicare (i.e., Parts A, B or D). Similarly, for sharing of savings, ICER does not consider the possibilities or ramifications for patients. For example, it could easily be stated that sharing savings with payers might reduce premiums or cost-sharing (or limit increases). However, that would benefit all patients in a plan rather than the individuals receiving SSTs. Therefore, we are deeply disappointed that ICER did not discuss how savings could be shared directly with patients, such as already occurs from health plans if MLR percentages are exceeded.

We also note with some amusement how comfortable ICER is with uncertainty in its own assessments, yet it cites uncertainty about financial risk as a reason why risk sharing contracts would be problematic: "it is unclear how to determine the magnitude of the risk that should be borne by the innovator as opposed to the payer."¹⁴

We are also deeply disturbed by ICER's ongoing failure to understand how pricing decisions are made in the U.S. First, ICER's refractory focus on "prices" and "pricing" is non-sensical and disconnected from reality. The elusive nature of "prices" has recently been seen by the Trump Administration's attempts at mandating transparency for hospital prices.¹⁵ Focusing on the "price" – when "price" is a term that may have limited meaning – reflects ICER's simplistic portrayal of financing for health care services and products. And second, ICER's ongoing fixation about the false concept that development and input costs are relevant information for what would be fair payment by payors,¹⁶ or that "federal investment in research"¹⁷ should be part of this dialogue of "value" assessments related to reimbursements is contrary to standard economic theory and is potentially dangerous to patient's access to innovative treatments, including SSTs.

Additional Comments:

- Despite what the Draft Paper claims, ICER did not invent the concept of "shared saving."¹⁸
- ICER self-describes itself as a Health Technology Assessment (HTA) organization¹⁹ – but it has no official role connecting it to any public or private entity with decision making authority about

¹⁴ Draft Paper, p. 21.

¹⁵ <https://www.healthaffairs.org/doi/10.1377/hblog20190822.353918/full/>

¹⁶ Draft Paper, pp. 26-27.

¹⁷ Draft Paper, p. 54.

¹⁸ Draft Paper, p. 26.

¹⁹ Draft Paper, p. 41.

coverage, utilization or payment, and is not a member of the INAHTA.²⁰ And we note that ICER describes its work as “...generalized to national uptake figures and therefore has limited applicability to any particular payer in the diverse US health system.”²¹ Therefore, we disagree with characterizing ICER as an HTA group.

- We could not find supporting evidence for the statement in the Draft Brief that “we know already that some of the gene therapies in development will modulate the effectiveness of other treatments and are not expected to produce transformative outcomes,”²² in the reference for that statement. Please explain your thinking and evidence for that statement.

Conclusions:

While SSTs represent a cutting edge of biomedical research, and are potentially new treatment options and cures, innovations of this magnitude compared to standard of care have occurred in the past. Therefore, we strongly question the need for radically different thinking about how to assess the value or utility of such new therapies. The major challenge for SSTs is how to integrate appropriate reimbursement and financing mechanisms into the reality of the U.S. health care system that includes many different health plans and delivery systems that vary in many ways, including their patient characteristics, ownership (public and private), and financial arrangements. We are disappointed that ICER does not recognize this fundamental reality, and the real-world challenges and needs related to SST. Nor does ICER adequately take into account patient perspectives, views, wants, or concerns.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

²⁰ http://www.inahta.org/members/members_list/

²¹ Draft Paper, p. 25.

²² Draft Paper, p. 5.



PARTNERSHIP TO FIGHT CHRONIC DISEASE

September 6, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: Value Assessment Methods for “Single or Short-Term Transformative Therapies”

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

The Partnership to Fight Chronic Disease (PFCD) offers input on ICER’s proposed adaptations for Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SST Methods), with a focus on issues of concern to people living with chronic conditions. PFCD is an internationally recognized organization of patients, providers, community organizations, business and labor groups, and health policy experts committed to raising awareness of the number one cause of death, disability, and rising health care costs: chronic disease. We appreciate the opportunity to contribute to the evolution and improvement of ICER’s practices and models.

Though many are preventable and/or highly manageable, chronic diseases remain the primary driver of health care costs—accounting for 90 cents of every dollar we spend on health care in this country. Moving the health care system to one that emphasizes value in the health outcomes and societal benefits requires a focus on patient-centered and informed strategies for understanding health care value and effectiveness holistically, and in support of health care investments and outcomes that have meaning to all Americans.

The advent of potential cures for deadly, disabling, and otherwise devastating diseases offers not only to profoundly transform the lives of those suffering from these diseases, but also the health care system and our overall economy as a whole. We recognize the need for new financing models informed by the benefits and associated risks – human, financial, and

economic – of new treatments and access to them. Such novel treatments will require equally novel approaches to coverage and assessing value. To that end, we offer several comments on the SST Methods grouped below first by general comments and then those referring to specific sections.

General Thoughts and Recommendations:

Novel treatments require novel approaches to assessing value that must include open consideration of a variety of perspectives and expertise, including those with divergent viewpoints. We agree with ICER’s characterization of the challenges presented in assessing the value of SSTs, including uncertainties at launch, accrual of benefits over long periods of time, high upfront costs, and added dimensions of value. Given the stakes involved, challenges presented, and need for novel approaches, we were disappointed to see that in developing this proposal, ICER limited its consultation with U.S. health economists to those with which it already has existing relationships on ICER’s existing models.¹ Development of the proposed methods, key assumptions, and policies of what to include and exclude should involve a variety of perspectives, not merely seeking verification of proposed methods from experts already vested in the existing model. We were unable to identify disclosure of these existing ties anywhere in the SST Methods documentation, which raises troubling questions about transparency as well.

Open comment periods are appreciated and helpful, but are much less effective in shaping assumptions, models and methods than in the genesis of such proposals when consulting with and being open to expertise and diverging opinions has greater impact. To that end, we recommend that ICER revisit its proposal and, after consulting with a wide variety of experts, present a new approach to evaluating SSTs that captures the significance SSTs represent and the need for novel approaches for assessing value. To the extent that ICER decides to proceed with the proposed methods adaptations with improvements, we offer the following comments.

We were pleased to see that the proposed definition of SSTs is broad enough to include treatments in addition to biopharmaceuticals, such include medical devices, potential surgical methods, and other treatments. Potential cures and transformational treatments may take many forms. We encourage ICER to keep a broad perspective in the selection of treatments to assess to include a broad array of treatment options and modalities.

¹ ICER Technical Brief, Table A3. University of Washington: <https://blogs.uw.edu/uwicer/project-team/>; University of Colorado-Denver: https://pharmacy.ucsd.edu/sites/pharmacy.ucsd.edu/files/Campbell_presentation.pdf.

Recommendations on Specific Sections

Assessing and Describing Uncertainty

ICER's proposed use of shortened time horizons for assessing value of SSTs will grossly underestimate the long-term benefits of curative therapies and exclude their consideration in ICER's analyses and conclusions. Traditionally, U.S. economists calculate value as discounted lifetime benefits relative to costs, as shorter timelines are arbitrary and not accurately measuring value. We strongly recommend that ICER not use short-term time horizons in presenting cost effectiveness findings. Using short-term time horizons will necessarily exclude the long-term benefits of therapies that cure, for example, diseases that manifest in advanced age – such as Alzheimer's disease, other dementias, and many cardiovascular conditions. For example, the bulk of benefits a cure for Alzheimer's disease would offer may not fully manifest for 20 year or more after its administration. None of those benefits would be reflected in ICER's proposed consideration of clinical trial follow up data, 5-year, 10-year, or 12-year time horizons. The examples ICER gives – that of CAR-T therapy, SMA gene therapy, and a hypothetical cure for Hemophilia A – accrue benefits in a much shorter time span, though without consideration over a lifetime, even those benefits would be short changed.

This section also includes a number of assumptions and proposed substitution of models based on still more assumptions instead of actual evidence – clinical or otherwise. We have significant concerns as to the degree of assumptions and speculations that will be incorporated into the proposed analyses and the potential presentation of the end results as being clinically driven, evidence-based or factually representative of real-world observations or expectations.

For example, ICER notes the uncertainty present “at the time of regulatory approval,” but despite regular comments during value assessments, continues to rebuff recommendations to wait for additional evidence, and, increasingly, has started value assessments before regulatory approval processes have completed. For SSTs, ICER proposes including an assessment based on the “longest follow up data available,” which likely would not extend much beyond clinical trials, given ICER's starting reviews before all data are available. By incorporating questions relating to the strength of clinical evidence on benefit and comparative benefits as key components in assessing value, ICER significantly tilts the scales in favor of a negative assessment of value before any evaluation has begun. Similarly, for SSTs, ICER proposes to present value in terms of available follow up data, this would tilt the scales even more in the case of SSTs and their anticipated high upfront costs. We strongly recommend that ICER revisit policies that proceed in evaluations with limited evidence and present the results as being evidence-based and dispositive on value.

Considering Additional Elements of Value

PFCD recognizes that people living with chronic disease often have multiple and/or complex conditions and confront challenges in health care nearly every day. For many, barriers seem to arise from a systemic lack of understanding, sensitivity, inclusion, and respect for their unique circumstances in health, health care and life. Value calculations that focus on only part of the health care continuum are inconsistent with how people access and manage their health and lead their lives.

PFCD strongly recommends that ICER include and place a value on the benefits of new treatments from both an individual and societal perspective as a substantial core component, and that this perspective is visible in the model, deliberations, determinations, summaries, reports, and related communications. This is particularly important for SSTs given the extent of and types of benefits are likely to be much greater than those captured in the QALY.

Including a societal perspective of value would provide a more holistic understanding of the persons most closely associated with the treatment under review, with important factors such as functional ability, productivity, caregiver support, and quality of life taken fully into account. We recommend including a societal perspective on value as an additional base case for SSTs.

The failure to account for non-traditional elements of value ignores broad stakeholder consensus regarding their importance, and novel methods to incorporate them quantitatively into value assessment. Moreover, the ultimate healthcare decision-makers are the purchasers, not benefit administrators. They include public and private employers, public insurance programs, and individuals, all of whom are directly concerned with elements of value beyond those limited to the medical care system. This reality affects all value assessments, but arguably affects SSTs more acutely.

PFCD appreciates the opportunity to provide input on potential changes to ICER's proposed SST Methods. PFCD is committed to the health and well-being of people with chronic conditions, their families and all Americans. Ongoing efforts to improve value assessment tools that help patients, physicians, payors, and other stakeholders to make informed decisions about all aspects of health treatments and care are critical.

Respectfully submitted,



Kenneth E. Thorpe, PhD
Chair, [Partnership to Fight Chronic Disease](#)



Pfizer Inc
235 East 42nd Street
New York, NY 10017

September 6, 2019

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor, Boston, MA 02109
Submitted via email: publiccomments@icer-review.org

RE: Public Input for Value Assessment Methods for “Single or Short-Term Transformative Therapies”

Dear Dr. Pearson,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the proposed ICER Value Assessment Framework regarding single or short-term transformative therapies (SSTs).¹ Pfizer is committed to discovering medicines and vaccines that enhance the health of patients, their families, and society. At the same time Pfizer is committed to identifying solutions for creating a more effective, efficient, and equitable health care system in the US.

We appreciate ICER’s efforts to evolve its value assessments and its call for comments on SSTs from a variety of stakeholders. Accurately assessing and establishing the value of medicines is a complex undertaking, and thus deserves careful attention and continuous, collaborative effort. We also appreciate ICER decision to design a different framework for SST to capture the complexity of assessment due to the transformative nature of these therapies. This is a significant opportunity to develop a value assessment that capture the complexity of SST by including: 1. a consistent and heterogeneous definition of value, 2. patient insights, 3. diverse stakeholder perspectives 4. explicit inclusion and exclusion criteria for the assessment of SSTs in alignment with FDA definitions or curative and breakthrough therapies, 5. moving beyond the QALYs framework.

We acknowledge ICER is recognizing in its proposed value framework the different nature of SST vs chronic care. However, we believe that the current proposal does not address the complexity of SST and the real value SST bring to patients and their caregivers, the health care system, and the society. We are recommending ICER to actively listening to the different stakeholders and make improvements to the

¹ Value Assessment Methods for “Single or Short-Term Transformative Therapies” (SSTs). Institute for Clinical and Economic Review. Published August 6, 2019. https://icer-review.org/wp-content/uploads/2019/08/ICER_SST_ProposedAdaptations_080619-2.pdf

proposed framework to better assess the value of transformative therapies in the US health care system and distinguishing them from traditional treatments.

In our comments we will address the following focus areas:

1. *SST Definition*
2. *Assessing and Describing Uncertainty*
3. *Additional Elements of Value*
4. *Time Divergence Between Costs and Benefits*
5. *Affordability and Fair Sharing of Economic Surplus*

1. Definition: Determining those treatments for which adapted assessment methods will be used

As curative and transformative therapies such as gene and cell therapies continue to advance and play a larger role in the paradigm shift from traditional treatments, it is important to carefully consider what is defined as “single or short-term transformative therapies”. The current ICER’s definition of SSTs is “...*therapies that are delivered through a single intervention or a short-term course of treatment that demonstrate a significant potential for substantial and sustained health benefits extending throughout patients’ lifetimes*” and“*can produce sustained major health gains or halt the progression of significant illnesses*” would require additional inclusion and exclusion criteria regarding how “*substantial and health benefits*” and “*major health gains*” will be measured. Without defining a valid metric to health gains, this definition can be subject to bias.

We recognize that ICER is basing its definition on the Duke Margolis definition of transformative therapies

(https://healthpolicy.duke.edu/sites/default/files/u31/advancing_vbp_for_transformative_therapies.pdf):

- 1) delivered through a single or short-term administration or intervention;
- 2) intended as an irreversible treatment;
- 3) aim to address an underlying disease condition or modification; and
- 4) aspire to produce a long-term, durable response.

We would recommend ICER to use the same language as Duke Margolis for transformative therapies as it is less subject to bias.

Moreover, the current definition provided by ICER does not recognize breakthrough therapy designations from the FDA: “*intended alone or in combination with one or more other drugs to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug*

may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.”²

It would be relevant to understand how future generation of therapies in the pipeline will be defined—whether they will be assessed in the same manner as a first in the category.

Lastly, Pfizer proposes changing the naming convention of “single and short-term” to *curative and/or transformative therapies*, as single or short term just refer to one of the elements (administration) that define a transformative therapy.

Recommendations:

- Pfizer recommends that ICER provide clear inclusion and exclusion criteria for potential SSTs including how “*substantial and health benefits*” and “*major health gains*” will be measured against a therapy. In addition, the definition should recognize FDA Breakthrough Designations.
- ICER should consider changing the current naming of SSTs as single or short-term does not define the transformative nature of a therapy but just refer to its mode of administration.

2. Assessing and Describing Uncertainty

Pfizer appreciates ICER’s efforts to develop a separate value assessment framework for SST to better account for the greater uncertainty associated with these therapies.

Cure Proportion Modeling

ICER’s proposal, to make cure proportion modeling its reference case standard when relevant, fully captures the uncertainty and complexity of curative/transformative therapies. We agree with ICER that mixture cure models in general fit better than other traditional parametric curves due to the heterogeneity of the population. To accurately estimate the cure rate and the survival probability of the uncured patients, long-term follow up is normally needed. ICER is proposing to assess whether data are not mature enough to determine if the survival curve actually shows a sustained plateau; if not, ICER’s position is that “*the presentation of results from several types of survival models can be used to develop a range around estimated long-term survival until more data become available*”. Pfizer recommends ICER to use finite mixture model as one of the options to assess uncertainty. This is because although there are no long-term data showing the survival curve plateaus after a certain time, there is a good reason to believe that the patients are heterogeneous (they respond to the treatment differently) and the mixture models should fit the data better than other single parametric models.

² Fact Sheet: Breakthrough Therapies. U.S Food and Drug Administration. Published March 28, 2018 <https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fact-sheet-breakthrough-therapies>

Recommendation: use finite mixture model as an alternative to cure proportion modeling when there is not sufficient long-term follow up to reach sustained plateau.

Incremental cost-effectiveness scenarios at multiple time horizons

ICER's assessments of SSTs to include cost-effectiveness analyses and associated value-based prices at multiple time horizons is not based on clinical rationale and could disproportionately impact curative and transformative therapies for children and adolescents. As per ICER definition curative and transformative therapies have the potential "*for substantial and sustained health benefits extending throughout patients' lifetimes*", therefore it is not clinically clear why ICER would want to run scenario analysis at 5 and 10 years follow up.

Recommendation: Follow up period should be assessed based on clinical rationale. If the benefits will extend throughout patients' lifetime no other time follow up than lifetime should be used. A lifetime approach (where relevant) could demonstrate even greater cost-effectiveness, where loss-of-exclusivity / loss of patent becomes a factor.

Probabilistic sensitivity analysis linked to policy recommendation for outcomes-based payment:

Probabilistic sensitivity analysis (PSA) is a very important component of a cost-effectiveness analysis and always needs to be performed for assessing the level of uncertainty around the model type and underlying assumptions. The aim of a PSA is not to inform outcome-based payments (OBA). The decision of initiating an OBA and its best design is a discussion between the payer and the manufacturer. The decision is based on a variety of elements not just uncertainty around cost-effectiveness. Please note that Pfizer is very supportive of the market move from volume to value and to the use of innovative agreements to demonstrate the value of innovation.

We recommend ICER to report PSA for the various inputs used in the model to assess the main drivers of uncertainty in results. This would be useful when there are "*controversies and uncertainties*" on the assumptions around certain inputs.

If ICER still decides to run a PSA to assess whether outcome-based payments should be the best way to contract with manufacturers, then it would be fair that PSA is also used to assess whether a curative/transformative therapies are very likely to be cost-effective and therefore, payers should grant open access to all patients without prior authorization criteria in place. In its current application from ICER, the PSA does not consider both the upside and downside of outcomes uncertainty.

Recommendations:

- ICER should run PSA to assess the main drivers of uncertainty around the reference value-based price and identify “*controversies and uncertainties*” on the assumptions around certain inputs.
- The decision to initiate innovative agreements should be made by the interaction between a payer and a manufacturer as there are various reasons behind this decision.

3. Additional Elements of Value

Pfizer appreciates ICER’s consideration of additional elements of value to the standard QALYs approach given the shortcomings of QALYs and the nature of SSTs. We acknowledge the positive step of adding two additional domains of “*potential other benefits or disadvantages*” for voting by the independent appraisal committees. For potential curative/transformative therapies alternative elements of value other than QALYs are essential to fully assess their value. These therapies will change the treatment paradigm for the underlying disease condition and QALYs are not suitable to assess their added value vs traditional treatments. A qualitative approach is a step forward but not enough to fully capture additional elements of value to the value-based price. This is why Pfizer recommends ICER to also include a quantitative approach to additional elements of value.

ICER has decided not to include the recommendations from the Second Panel on Cost Effectiveness (Neumann et al. 2017)³ in their framework. The Panel not only emphasized the need to add more elements of value to QALYs to address its shortcomings and better assess value but also to use the societal perspective, which brings a broader point of view, as the reference case. The societal perspective should include elements such as informal health care sector costs and relevant non-health care sector costs (Pfizer recognizes that the inclusion of social services, consumption, legal/criminal, justice, education, housing, and environment may be considered only for specific diseases and conditions).

If ICER decides not to use the totality of the elements of value recommended by the second panel, the analysis should at least include productivity, insurance value, and value of hope in particular to capture of the complexity of SST. Lakdawalla and team have developed the “Quality- and Risk-Adjusted Life-Year” (QRALY) to adjust QALYs and include value of hope and insurance value.⁴ The QRALY can be used just like a standard QALY in incremental cost effectiveness ratios.

Curative/transformative treatments can have a huge impact on the family of patients regarding productivity and quality of life. The impact of these potentially curative therapies is much greater than benefits generally assessed by QALYs and applied to traditional treatments.

³ Neumann et al. (2017) “Cost-effectiveness in Health and Medicine. Second Edition”. Oxford University Press.

⁴ Lakdawalla et al. (2016) “The Insurance Value of Medical Innovation.” NBER Working Paper Series, March 2015

Recommendations:

- Pfizer supports the recommendations by the Second Panel on Cost Effectiveness (Neumann et al. 2017) to include a societal perspective and to augment the use of QALYs by including additional elements of values (given the limitations of QALYs).

4. Time Divergence Between Costs and Benefits

Single or short-term transformative therapies (SSTs) can have “*significant potential for substantial and sustained health benefits extending throughout patients’ lifetimes*”. Thus, although the therapy costs will be absorbed by the health system in the short term, the benefits will be gained in the long term. This is why for SST it is very important to run sensitivity analyses using different discount rates (1-2%).

Recommendation: We recommend ICER to run sensitivity analyses using different discount rates.

5. Affordability and Fair Sharing of Economic Surplus

ICER’s proposal to evaluate a shared savings approach in which cost offsets are included in a drug’s price only until a patent-exclusivity cliff at 12 years can potentially lead to adverse incentives. Pfizer recommends that this analysis should not be included in ICER reports.

Although some transformative treatments may never go generic, they produce sustained major health and societal gains by curing a patient from the underlying condition or halting the progression of very severe conditions; thus the indirect cost-savings can be substantial. For some of these underlying conditions, current survival (without SST) may be less than 12 years. There may be other underlying conditions in which SST cost offsets will be recurring over a period longer than 12 years. Therefore, this proposed approach could create disadvantages for diseases in where significant outcomes (for rare diseases this is very common) and costs offsets occur after 12 years.

Moreover, the entrance of competition will significantly reduce the price—bringing benefits to the society and the health care system well before 12 years.

If ICER decides to implement the fair sharing approach anyway, then by logic they should also modify the current pricing approach for the assessment of chronic conditions (price should be assumed to become generic after 12 years).

Finally, we believe additional clarity is needed on whether affordability and fair share are analyzed from a payer’s, health care system perspective or that of patients, society.

Recommendation: Pfizer’s recommendation is not to include the fair sharing of economic surplus analysis in the SST framework.

We appreciate this opportunity to provide input to ICER's Value Assessment Methods for SSTs. Given the ongoing work of ICER to refine its value framework, it is significant to reiterate that many aspects of value will continue to be contended by diverse perspectives and they require robust clinical and scientific evidence. As transformative therapies will play a more significant role in providing patients with optimism of potential cures, we hope that ICER will incorporate comments from a variety of stakeholders to enhance the validity of the value assessment and fully capture the value these curative/transformative therapies bring to patients and their caregivers, the health care system, and the society as a whole.

Sincerely,



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September 6, 2019

Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, Massachusetts 02109

Re: Call for Public Input on Proposed Adaptations for Assessments of Single or Short-term Transformative Therapies

To Whom It May Concern:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to respond to the Institute for Clinical and Economic Review's (ICER) request for feedback on its proposed methods adaptations for the assessments of potential cures and other transformative therapies. PhRMA is a voluntary, non-profit organization representing the nation's leading research-based pharmaceutical and biotechnology companies which are devoted to inventing medicines that allow patients to lead longer, healthier, and more productive lives.

PhRMA is also a long-standing supporter of evidence to support health care decision-making, including value assessment frameworks. Advancing better evidence and tools to support sound health care decision-making, including support for advancing the science and use of value assessment frameworks, is a core principle adopted by our members and is central to our policy agenda.^{1,2}

PhRMA understands that many of these therapies present unique challenges to the health care system – a limited evidence base, exceptional effectiveness, and potential one-time use or administration. To address these challenges, we continue to support innovative contracting arrangements between manufacturers and private payers predicated on the ongoing development of evidence, to ensure access for patients to these treatments. However, we also continue to have concerns about the role of traditional, one-size-fits-all value assessments being used to determine the “right” price for incredibly complex, innovative treatments.

We are disappointed that ICER's proposed approach to assessing the value of single, short-term transformative therapies (SSTs) is not actually novel. As PhRMA has repeatedly noted in the past, traditional methods of QALY-based value assessment fail these treatments in many ways.³ These treatments require innovative methods of value assessment that can match the novelty of the science underpinning them. Instead, the proposed approach makes minor modifications to the existing framework and does little to change the underlying method or to promote alternative, non-traditional approaches to value assessment (such as multi-criteria decision analysis). As noted in literature, the unique characteristics of this category and of associated treatments call for modified approaches to the economic evaluation process.⁴

¹ PhRMA. “Policy Solutions: Delivering Innovative Treatments to Patients.” Available at: <http://phrma-docs.phrma.org/sites/default/files/policy-solutions.pdf>

² PhRMA Value Collaborative. Available at: <http://www.phrma.org/advocacy/the-value-collaborative>

³ PhRMA Response to Public Input on ICER Value Framework. June 2019.

⁴ Drummond, MF, Neumann, PJ, Sullivan, SD, et al. “Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy”. Value in Health. June 2019. Available at: [https://www.valueinhealthjournal.com/article/S1098-3015\(19\)30186-X/pdf](https://www.valueinhealthjournal.com/article/S1098-3015(19)30186-X/pdf)

Consequently, application of those methods by payers and other stakeholders creates access barriers patients, and does not provide an objective, sound basis for supporting health care decision making, nor facilitate movement towards a value-based health care system.

Furthermore, it appears that ICER's proposed modifications cherry pick what information (including scenario analyses) is deemed helpful to payers in making decisions. We support the provision of a range of results based on different scenarios, but many of these choices, including those related to time horizons, discount rates and "fair" sharing of economic surplus, appear designed specifically to arrive at artificially low prices for SSTs. ICER's framework should be aimed at providing rigorous, high-quality evidence that supports decision-making at all levels.

We urge ICER to continue to improve its framework, including exploring entirely novel methods of value assessment. If ICER persists in applying a modified version of its value framework to curative therapies, we have numerous concerns with how it does so, including the following:

- I. Incorporation of a shared savings scenario with a 12-year time horizon is an arbitrary decision that contradicts the realities of the health care marketplace.
- II. Solutions to address uncertainty will result in artificially negative results regarding the potential value of curative therapies.
- III. Failure to account for non-traditional elements of value ignores broad stakeholder consensus regarding their importance, and novel methods to incorporate them quantitatively into value assessment.
- IV. Failure to provide scenario analyses based on different discount rates runs contrary to ICER's stated goal of providing payers with important context around the value of treatments to support decision making.

We appreciate ICER's consideration of our recommendations. PhRMA believes that, if these recommendations are adopted and ICER's revised framework is fully validated, it could play a positive role in the movement towards better value in health care. We provide more detail below as to specific concerns, as well as steps that ICER can and should take to address them.

I. The incorporation of a shared savings scenario with a 12-year time horizon is an arbitrary decision that contradicts the realities of the health care marketplace.

PhRMA has significant concerns with ICER's proposal to account for "shared savings" in the cost-effectiveness model with the goal of producing an alternate incremental cost-effectiveness ratio and the related value-based price benchmark. ICER proposes a scenario in which the model assumes that all cost offsets accrue to the innovator during the first 12-year period, and following the 12-year period, all cost offsets will accrue to the health system.⁵ Assuming and applying an arbitrary 12 year loss of exclusivity to the model has potential to severely undervalue novel therapies, and appears to intentionally hamper the value of these treatments in the name of "fairness". The shared savings scenario has not been validated, nor is it supported by scientific research. As

⁵ ICER Proposed Methods Adaptations for the Assessment of SSTs. Available at: https://icer-review.org/wp-content/uploads/2019/08/ICER_SST_ProposedAdaptations_080619-2.pdf

previously stated, PhRMA is supportive of ICER providing a range of results based on different scenarios, but those scenarios should have a logical and scientific basis.

ICER justifies its choice by stating that many SSTs, particularly cell and gene therapies may never face equivalent of generic competition of the kind that has led to sharing the economic surplus resulting from curative therapies with the health care system. This speculation would contradict the incredible weight of historical context around competition in the health care marketplace. Over the next twelve years, there will inevitably be changes to the standard of care that will drive down the price of these treatments. This competition does not necessarily have to come from generic versions of curative therapies – it may come in the form of brand-to-brand competition, treatments that come with more convenient methods of administration, or treatments with fewer side effects. For example, when first curative therapy for Hepatitis C was released, stakeholders expressed significant concern that these treatments would bankrupt our health care system. However, since other brand name treatments have entered the market, net prices have fallen by approximately 83%.⁶ ICER eventually amended its own assessment of Hepatitis C treatments to acknowledge the price decrease.⁷ Similar price decreases connected to brand-to-brand competition have been seen in treatments for high cholesterol and diabetes. ICER's decision to conduct a scenario analyses that caps the incorporation of cost offsets at 12 years is methodologically unjustified and will result in an artificially low price for therapies that will provide a lifetime of benefits not just to patients, but the health care system.

The scenario proposed by ICER also assumes that the health care system does not benefit from the profits earned by pharmaceutical companies. Since 2000, PhRMA members have invested more than \$900 billion into the global health system to advance the science in search of novel and curative treatments, including approximately \$71 billion in 2017 alone.⁸ A significant share of the benefits accrued by manufacturers are returned to society and the healthcare system through the funding and development of future innovation.

To address the aforementioned issues PhRMA proposes the following:

- *Refrain from incorporating the shared savings scenario in its Final Report for SSTs*

II. ICER's proposed solutions to address uncertainty will result in artificially negative results regarding the potential value of curative therapies.

PhRMA has several notable concerns following our review of ICER's proposed methods adaptations for assessing and describing uncertainty. First, ICER proposes to assess both the 5 and 10-year time horizons (in addition to employing a lifetime horizon for the base case) in the cost-effectiveness models. As previously stated, SSTs hold potential to offer substantial long-term benefits to patients with conditions in which there are no known cures. Scenarios based on shortened time horizons will fail to account for the long-term benefits of curative therapies from being incorporated and recognized in ICER's analyses. As the proposal stands, any transformative or life-altering medications for patients will not accrue the full extent of their benefits in cost-effectiveness analyses despite the full cost burden remaining incorporated, resulting in an artificially-inflated cost per QALY ratio. Consequently, the proposed adaptation highlights ICER's inherent bias against innovative therapies, contradicts ICER's commitment of ensuring rigorous and evidence-based methodological processes.

⁶ PhRMA Analysis of SSR Health Data.

⁷ Available at: <https://icer-review.org/announcements/new-lower-prices-for-gilead-hepatitis-c-drugs-reach-ctaf-threshold-for-high-health-system-value/>

⁸ 2019 PhRMA Annual Membership Survey. Available at: <https://www.phrma.org/Report/2019-PhRMA-Annual-Membership-Survey>

In a separate proposal to address uncertainty, ICER proposes to include a recommendation for outcomes-based contracting as the preferred method of payment when “at a price at which greater than 25% of [probabilistic sensitivity analyses] simulations of the base case produce incremental cost-effectiveness ratios above \$200,000 per QALY.” While the inclusion of PSA allows ICER to characterize and convey uncertainty, it is only effective if both downside *and* upside risks are highlighted. It is highly concerning that ICER would restrict the use of PSA to highlight a therapy’s downside risk and prevent payers from having *full* transparency of an SSTs value-based price estimate uncertainty. ICER should be transparent in how they plan to execute and report PSAs, with an emphasis that all results will be reported and not just those exceeding the 25% threshold.

Furthermore, PhRMA has significant concerns over ICER’s intent to flag any therapies for which an outcomes-based contract should be preferred.⁹ PhRMA remains a staunch supporter of value-based contracting and other innovative payment models. It is unclear how ICER would be able to reasonably provide a single contracting recommendation that impacts such a diverse pool of health plans, payment policies, and patients. ICER should refrain from making singular recommendations and instead, focus on generating methodologically-robust research for decision makers.

To address the aforementioned issues PhRMA proposes the following:

- *Focus results on lifetime time horizons and provide scenario analyses beyond 5-10 years (such as 30 years) so that the full extent of a curative therapy’s long-term benefits is recognized.*
- *Should a payment recommendation be made, expand the use of PSA to include upside uncertainty associated with its estimates, and to clearly present the full range of results based on PSA findings over wide range of cost-effectiveness thresholds. ICER should also be fully transparent about how PSAs are conducted*

III. ICER’s failure to account for non-traditional elements of value ignores broad stakeholder consensus regarding their importance, and novel methods to incorporate them quantitatively into value assessment.

In its proposed framework adaptation, ICER proposes adding only two additional domains of “potential other benefits or disadvantages” for voting by independent appraisal committees, but not for quantitative incorporation into the actual analyses. Neither of these value elements are those that the ISPOR Special Task Force on U.S. Value Assessment recommended for inclusion in its 2018 report.¹⁰ ICER’s proposal falls short of stakeholder consensus and prevents the full potential benefit of curative therapies from being incorporated into the value assessment process. Beyond what is recommended for therapies outside the scope of ICER’s proposed adaptations, leading researchers have argued that curative therapies, when effective, may result in substantial reduction in related health care costs. As such, they suggest that inclusion of non-related health care costs and

⁹ ICER Proposed Methods Adaptations for the Assessment of SSTs. Available at: https://icer-review.org/wp-content/uploads/2019/08/ICER_SST_ProposedAdaptations_080619-2.pdf

¹⁰ Lakdawalla, DN, Garrison, LP, Phelps, CE, et al. “Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report”. Value in Health. February 2018.

consequences, such as impact on caregivers and other novel value elements, can have a profound effect on whether a transformative therapy is deemed cost-effective at any given price.¹¹

ICER's argument that these elements shouldn't be included because there aren't enough costs to outweigh them seems to reveal an inherent bias towards an artificially low value-based price. We also disagree with ICER's argument that the methods do not exist to quantify these value elements. First, some elements of value, such as caregiver burden (which is particularly relevant to pediatric indications, such as Spinal Muscular Atrophy) should be relatively simple to quantify. Data on wages and productivity are readily available and can be easily incorporated into cost effectiveness analyses. To say that methods do not exist to quantify these elements indicates a lack of awareness of recent research in this space. Based on ICER's own summary of comments received in response to the open input period, it appears other stakeholders felt quite strongly about this as well. Incorporation of such elements should be standard practice.

Second, over the last several years, there has been significant work to develop methods for quantification of even more novel value elements. For example, the Innovation and Value Initiative has developed methods to incorporate both insurance value and the value of hope into their open-source models for value assessment. Additionally, the PhRMA Foundation has recently provided funding to researchers to obtain quantitative measures of the value of hope in cancer care.¹² ICER should work with these stakeholders to leverage their knowledge and experience in measuring non-traditional elements of value.

To address the aforementioned issues PhRMA proposes the following:

- *Fully incorporate relevant value elements (e.g. value of hope, caregiver burden, insurance value, option value, employer productivity gains, etc.), when data is made available, to ensure a complete value profile.*

IV. ICER's decision to not provide scenario analyses based on different discount rates runs contrary to its stated goal of providing payers with rigorous evidence to support decision making.

ICER proposes to continue use of the 3% discount rate for both costs and outcomes. While PhRMA recognizes the Second Panel on Cost- Effectiveness's recommendation of a 3% discount rate for health economic evaluations, we remain adamant that the unique characteristic of this category and the novel benefits associated with treatments suggest that additional scenario analyses are needed to account for varying discount rates.¹³ This is consistent with PhRMA's position that ICER should focus on providing a range of rigorous comparative and cost effectiveness information to payers based on multiple scenarios, and there is no single "correct" value-based price.

The use of varying discount rates is not uncommon. ICER itself has acknowledged that varying discount rates, often between 1.5-5%, are utilized by other assessment bodies.¹⁴ Furthermore, the National Institute for Health and Care Excellence (NICE), with whom ICER collaborated on this process, considers differential discounting of

¹¹ Drummond, M, Neumann, PJ, Sullivan, S., et al. "Analytic Considerations in Applying a General Economic Evaluation Reference Case to Gene Therapy." *Value in Health*. June 2019. Available at: [https://www.valueinhealthjournal.com/article/S1098-3015\(19\)30186-X/fulltext](https://www.valueinhealthjournal.com/article/S1098-3015(19)30186-X/fulltext)

¹² Available at: <https://healthpolicy.duke.edu/news/phma-foundation-awards-two-grants-value-based-and-cost-effectiveness-research>

¹³ Neumann PJ, Sanders GD, Russell LB, et al. "Cost-Effectiveness in Health and Medicine, Second Edition". Oxford University Press. 2017.

¹⁴ ICER Proposed Methods Adaptations for the Assessment of SSTs. Available at: https://icer-review.org/wp-content/uploads/2019/08/ICER_SST_ProposedAdaptations_080619-2.pdf

healthcare costs and benefits in cases where a therapy's effect is substantial in restoring health and sustained over a long time horizon (~30 years).¹⁵ Additionally, the Joint Committee on Vaccination and Immunization uses the standard 3% discount rate for costs and benefits, but will often present the findings of sensitivity analyses using 1.5% and 0% discount rates.¹⁶

Given that many of these therapies are curative, and therefore have an exceptionally long time horizon of benefits, PhRMA believes the discount rate would play a substantial role in computing the value of transformative and novel products. If a 3% discount rate is assumed, a year of perfect health (1 QALY) 50 years into the future is equivalent to approximately 3 months of perfect health (0.23 QALYs) at present day.

In justifying the continued use of a 3% discount rate, ICER states that presenting sensitivity analyses with varying discount rates "would not prove valuable for decision makers". PhRMA challenges this assertion and reiterates concerns regarding ICER's inherent bias against the manufacturers developing these innovative and life-changing treatments. Similar to how ICER's proposal to reduce time horizons serves to artificially inflate the cost per QALY ratio, ICER's failure to vary the discount rate of future benefits results in a cost per QALY ratio that remains constant. In essence, ICER claims that scenario analyses with varying time horizons provides valuable context for decision makers, while scenario analyses to vary the discount rate for benefits would not be beneficial. Both proposals are intended to benefit payers during contracting negotiations and continue to demonstrate ICER's bias against manufacturers.

To address the aforementioned issues PhRMA proposes the following:

- *Incorporate varying discount rates of 1-2% in its' scenario analyses.*

PhRMA and ICER have a mutual interest in the development of sound, patient-centered evidence to support decision-making. We appreciate ICER's engagement with our industry in the development of methods to evaluate curative therapies, and hope that you consider incorporating our feedback as your methodology evolves.

Sincerely,



Randy Burkholder
Vice President, Policy & Research



Lauren A. Neves
Senior Director, Policy & Research

¹⁵ National Institute for Health and Care Excellence. "Discounting of health benefits in special circumstances."

¹⁶ National Institute for Health and Clinical Excellence. Briefing paper on updates to the methods guide. 2011. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/DSU_TAMethodsGuideReviewSupportingDocuments.pdf



September 6, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: “ICER Seeks Public Comment on Proposed Methods Adaptations for Assessments of Potential Cures and Other Transformative Therapies”

Submitted electronically via publiccomments@icer-review.org

Dear Dr. Pearson,

Sanofi is pleased to provide comments to the Institute for Clinical and Economic Review’s (ICER) request for open input on its proposed adaptation of methods for the value assessment of potential cures and other transformative therapies (SSTs) in the US. We appreciate ICER’s continuing efforts to evolve its value assessment methodology and to engage with stakeholders, and it is in this spirit that we provide our comments on the draft proposal.

Sanofi shares ICER’s interest in promoting rigorous, evidence-based, and transparent methods to assess the value of potential curative or otherwise transformative therapies. A full understanding of the value of these treatments is important to providing access for all patients in need. These innovative therapies may provide significant clinical and economic benefits to patients, society, providers, and the health care system. At Sanofi, we are committed to generating relevant evidence on multiple dimensions of value to meet the evidence requirements of all stakeholders. This holistic approach to value evidence generation guides the plans for therapies in development, the product life course, and the foundation of our US Pricing Principles.¹

We agree that conventional methods of value assessment may not fully capture the potential value of SSTs. If the assessment of healthcare interventions is not comprehensive and situationally and contextually grounded, there is a potential risk of denying patients’ appropriate access to treatments. A comprehensive value assessment based on a multiple-criteria decision analysis (MCDA) framework to evaluate the value of technology can and should also be applied to SSTs.

Although we commend ICER for considering novel value assessment methods in this initiative and the accompanying technical brief, we have significant concerns with the resulting current draft proposal. ICER’s proposed modifications are limited and do not fully capture all potential aspects of the value of SSTs or fully represent the needed evidence that is important to stakeholders. We encourage ICER to adopt a broader approach that better reflects the likely impacts of such novel therapies on multiple aspects of value. We also reiterate our concerns with ICER’s continuing foundational reliance on conventional quality-adjusted life-year (QALY)-based approaches with minimal modifications. As we have previously noted, it is well-recognized that the QALY represents a limited subset of potential benefits resulting from therapies with many other limitations in practice.² We hoped that ICER would, at least, embrace the idea of measuring and integrating novel elements of value such as



those identified in the recent ISPOR Special Task Force report by Lakdawalla et al³, however, the current proposal only minimally addresses this opportunity.

Our specific recommendations are as follows:

- Clarify the criteria for SSTs' designation for which adapted assessment methods will be used
- Ensure transparency and clarity when characterizing uncertainty
 - Retain lifetime horizon as multiple/shortened time horizons may underestimate the long-term benefits of curative therapies
 - Refrain from the use of the cost-effectiveness threshold (CET) of \$150,000 per QALY gained as this is not representative of typical practice and is an inappropriate threshold for SSTs
 - Rename the proposed “Controversies and Uncertainties” section to correctly reflect the intent of this component and provide clarity on its content
 - Remove the proposal to link probabilistic sensitivity analysis (PSA) to policy recommendations for outcomes-based payment
- Incorporate multi-dimensional elements of value to ensure the full benefits of SSTs are measured
- Use differential discounting approach for costs and outcomes
- Eliminate the proposal for a shared savings scenario in the final report and replace this with methods to fairly reward innovation

Clarify the criteria for SSTs' designation for which adapted assessment methods will be used

ICER's definition of SSTs needs clarification and transparency. The current definition — transformative therapy that can produce sustained major health gains — is insufficient for a full understanding of the determinative process by which SSTs will be identified. It is important that ICER develops specific inclusion and exclusion criteria to further clarify the current definition. Moreover, ICER should consider how to differentiate and/or adopt assessments for ultra-rare conditions from that of SSTs.

We support ICER's scoping process which will include input from stakeholders to make a preliminary judgment as to whether a new drug should be considered as an SST and suggest that the process would benefit from the formal inclusion of a preliminary discussion with innovators before the designation is finalized, to ensure full understanding. In general, ICER should work with multiple stakeholders throughout as they define and refine the definition of SSTs.

Ensure transparency and clarity when characterizing uncertainty

Cure proportion modeling

We see potential value in the cure proportion modeling, given the specialized distributional assumptions required for curative therapies and patient heterogeneity. However, for non-life-threatening diseases, the focus should not be on survival extrapolation.

We support the need to use other survival analysis techniques to address uncertainty. However, additional clinical validation that is specific to the disease state may be required.

Incremental cost-effectiveness scenarios at multiple time horizons

We support the retention of the lifetime horizon as the base case for the value-based price benchmark instead of adding multiple time horizons as 1) use of multiple time horizons would create an inconsistency with overall value frameworks, and 2) may dismiss long-term benefits of curative therapies from shortened time horizons. For uncertainty with lifetime horizons, we recommend using modified Delphi approach as it elicits a variety of perspectives and reaches consensus across participants on what is important to evaluate (ie, strength and meaning of evidence).⁴ Moreover, rather than including cost-effectiveness analysis (CEAs) and associated value-based prices at multiple time horizons, we suggest consideration of MCDA as an alternative process and methodology for value appraisal. MCDA enables the comprehensive measurement of value in a structured and transparent way. A growing number of decision-making bodies and HTA agencies are either using or starting to explore these approaches to improve their transparency and accountability.^{5,6}

Time horizon threshold analyses for durability of effect

A CET of \$150,000 per QALY gained is not representative of typical practice. Willingness to pay for any given individual payer is driven by multiple factors that are specific to the plan and population. Thus, for individual payers, whether a therapeutic option falls within a single CET is largely unrelated to decision making and adds little to the conversation at the population level and may limit access.

We recognize that ICER has shown willingness to adapt CETs for specific categories of treatments and patient population, notably in the case of therapies for ultra-rare conditions.⁷ Although ICER has discussed a CET range of a maximum of \$500,000 per QALY, as we have mentioned in a previous response, we continue to be concerned that this threshold is not reflective of orphan drugs in practice. A 2015 review of published cost-effectiveness analyses for approved ultra-rare treatments in the US and EU concluded that the median base-case incremental cost-effectiveness ratio was \$591,200/QALY, with the median estimate in the sensitivity analyses of \$1,958,674/QALY.⁸

We also want to reiterate that the limitations of using formal cost-effectiveness analyses for orphan drugs are widely recognized and urge ICER to revisit its current procedures for these and other categories of specialized treatments such as gene therapies in its planned update of the overall VAF as well as specialized assessment adaptation procedures.^{9,10} The generalized quality of life measures typically used in cost-effectiveness analysis do

not do justice to the patient perspective in rare disease, and it is often the case that researchers must create disease-specific measures. These measures require time and careful consideration to develop and validate, particularly because both the patient population is so small and many of these conditions affect children, requiring caregivers to act as patient proxies. Traditional cost-effectiveness analysis does not include caregiver, family, and societal impacts of new treatments, which are more prominent for rare conditions. In addition, many have suggested that the use of traditional QALYs is not appropriate for rare diseases, because it assumes individual health gains are valued equivalently regardless of context.¹¹

Introducing a new economic review section on “Controversies and Uncertainties”

We are generally supportive of ICER’s proposal to include a new economic review section aimed to discuss the uncertainties related to economic evaluation in order to explore inherent uncertainty in conducting value assessments - in both assessments for SSTs and for all ICER reports. In addition, we are pleased with the opportunity for various views to be represented and discussed in the evidence reports.

Although supportive of this new addition, we recommend changing the title from “controversies and uncertainties” to “alternative perspectives from the scientific exchange” to correctly reflect the context of this section. We also suggest that greater clarity be developed for the proposed content of this section.

PSA linked to policy recommendation for outcomes-based payment

We do not support ICER’s recommendation to link PSA to a policy recommendation for outcomes-based payment. ICER, an evidence assessor, should not be in the position to use PSA to determine outcomes-based contracts (OBC) as this is outside of ICER’s scope as an HTA body. The selection of 25% or more PSAs at or above \$200,000/QALY is arbitrary, and a clear delineation of ranges is needed. Moreover, this is inconsistent with the principle that OBCs were designed to address — a high degree of uncertainty in translating a treatment effect derived from clinical research findings to clinical practice.

However, we support ICER’s decision on the following:

- Rejection of the proposal that would require 90% of PSA simulation results be less than \$150,000/QALY
- Consideration of modified proposal that requires 75% of PSA simulations be below a higher threshold, but still not proposing an “uncertainty-adjusted” value-based price if this criterion is met

Incorporate multi-dimensional elements of value to ensure the full benefits of SSTs are measured

A growing demand for patient and societal perspectives in the value assessment process calls for the incorporation of more comprehensive dimensions of value. To address this need, ISPOR’s recent task force report on defining elements of value identified twelve critical dimensions for measurement and evaluation.³

- Four —quality-adjusted life-years, net costs, productivity, and adherence-improving factors—are conventionally included or considered in value assessments.
- Eight others, which would be more novel in economic assessments, are defined: reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers.

Although supportive of ICER's inclusion of an additional element of value, we believe this is not sufficient. The magnitude of the full benefits that produced from SSTs are much greater than the benefits traditionally captured in QALY. ICER should acknowledge holistic value by transparent and multifaceted methodologies that involve these additional novel elements as new information arises. The explosion of evidence generation accompanying the introduction of digital technologies into healthcare poses opportunities for current VAFs.¹² Thus, ICER should consider comprehensively incorporating 'novel' measurements (ie, insurance value) for upcoming 'novel' treatments and take this as an opportunity to be a leader in the assessment process; this suggestion should not be limited to SSTs, but all value assessments.

Use differential discounting approach for costs and outcomes

ICER's proposal to continue its use of a 3% discount rate as standard for both costs and outcomes would not be an appropriate method for accurately reflecting the value of SSTs. Curative or transformative medicines will have dramatically different costs and benefits than traditional medicines evaluated in ICER's previous value assessments. Therefore, the traditional discount rate of 3% for both costs and benefits will not be appropriate. The Second Panel on Cost-Effectiveness raises questions about whether costs and health outcomes should have the same discount rate.¹³ Implementing a definitive 3% discount rate without further assessment of the implications would be irresponsible. Also, setting such a definitive cap may send signals about the extent to which health systems value (or do not value) SSTs. Although equal and uniform discounting of costs and outcomes is the dominant practice across national economic evaluation guidelines, this approach is under review in some very mature HTA bodies.¹⁴

We recommend a differential discounting approach, in which costs and outcomes are discounted at 3% and 1.5%, consecutively. The rationale for differential discounting is supported by empirical studies demonstrating greater positive time preference for health than for money.¹⁵ For instance, in the case of SSTs, costs are incurred through a single or short-term intervention, while long-term health benefits may be substantial.

NICE has also recently introduced the option of considering differential discounting in cases where therapies offer long-term health benefits.¹⁶ In a case of hemophilia, the value-based price that used differential discounting (3% for costs and 1.5% outcomes) differed only slightly from the base case value-based price. Moreover, there are several agencies requiring a differential discounting approach in which outcomes are discounted at a lower rate than costs (Netherlands [1.5%], Belgium [1.5%], Poland [3.5%], UK is under review, Russia [0%]).¹⁷ ICER already noted that having the same rate for costs and outcomes is correct only if the CET remains constant.^{17,18} This statement is contradictory to ICER's own proposals where differing CETs are used throughout the SST value framework (i.e. \$150,000/QALY and \$200,000/QALY).

It may also be worthwhile to investigate the interest of declining the discount rate overtime versus keeping it constant. Another topic that has not received a lot of attention is double discounting in the QALY estimates (through utility elicitation using Time Trade-Off technique) leading to an under-estimation of clinical/economic value.



Eliminate the proposal for a shared savings scenario in the final report and replace this with methods to fairly reward innovation

We also have concerns with ICER's proposal to account for "shared savings" in the cost-effectiveness model with the goal of producing an alternative incremental cost-effectiveness ratio and related value-based price benchmark. We recognize and share ICER's interest in maximizing the benefits of SSTs across the healthcare system, but we are concerned that this proposal is not conceptually mature, may result in unexpected negative effects on incentivizing innovation, and is broadly impractical in the US healthcare system. First, this proposal exceeds ICER's role as an evidence evaluator and diverges conceptually from ICER's stated position that advocates driving patient outcomes while rewarding innovation.¹⁹ The proposal imposes an inappropriate process to reallocate resources after a predefined time period. We are concerned that this process would negatively impact innovator's incentives to devote extensive time, human capital, and other investments in the discovery and development of such novel therapies.

Moreover, ICER's proposal to conduct a scenario analysis that caps the incorporation of cost offsets at 12-years may be arbitrary. We recommend that ICER refrains from incorporating this proposed scenario analysis in its final proposal. Overall, issues such as the concept of assignment of the economic surplus should be considered and resolved at the societal level rather than in the evidence evaluation context. Finally, we believe that the practical ramifications of implementing such an unproven proposal could have unknown consequences increasing uncertainty for patients' access. We recommend ICER to eliminate this component of the proposal.

Decision making in health care is inherently complex as numerous objectives need to be balanced. The diverse U.S. healthcare system deserves sophisticated methods and processes to provide the best guidance to decision-makers based on the assessment of the best possible scientific evidence and the holistic understanding of the value of therapies during the appraisal and decisions processes.

We thank ICER for soliciting input on this draft proposal and hope that our recommendations will be considered and integrated into the final approach. We are pleased to engage in additional discussion on these issues or otherwise assist at any time.

Sincerely,

A handwritten signature in blue ink, appearing to read 'Alicia Granados'.

Alicia Granados
Head of Global HTA Strategy

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September 6, 2019

VIA ELECTRONIC DELIVERY

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review (ICER)
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Spark Therapeutics' Comments on ICER's Value Assessment Methods for "Single or Short-Term Transformative Therapies": Proposed Adaptations to the ICER Value Assessment Framework

Dear Dr. Pearson:

Spark Therapeutics ("Spark") is submitting comments in response to the Institute for Clinical and Economic Review's (ICER's) August 6, 2019 proposed methods adaptations for assessments of Single or Short-Term Transformative Therapies (SSTs).

As Spark has previously noted, a value-assessment framework specific to SSTs should recognize that the nature of benefits and costs of such therapies may fundamentally differ from those for traditional chronic therapies that alleviate symptoms/complications of a condition but do not affect the underlying disease mechanism. We appreciate that ICER has moved towards considering models that measure patient-level effects but are discouraged that many of the other proposed changes do not differentiate the process of SSTs relative to ICER's general review process for more traditional therapies.

Even with similar clinical efficacy to a chronic therapy, a one-time treatment can have additional benefits for patients due to a decreased administration burden and a reduction in potential adverse events from administration of chronic therapies, not to mention a reduction to the negative psychological effects that are associated with long-term, chronic treatments.¹ Thus, although ICER should acknowledge and appropriately account for these distinguishing features of one-time, transformative therapies, half of the suggested changes (e.g., adaptations 2.3, 2.4, 3.1 and 4.1) are non-specific to SSTs. Moreover, one of ICER's proposed changes that should be applied to chronic therapies as well as SSTs (adaptation 5.1), is only applied to SSTs, disadvantaging SSTs more than chronic therapies. As a result, we feel the overall proposed adaptations are not sufficient to appropriately assess SSTs relative to traditional therapies as part of the ICER process.

We recommend that ICER go further to distinguish the value framework for SSTs compared to traditional, chronically administered therapies. Many of the concerns we have with the proposed SST methodology are addressed in the comments made by the National Pharmaceutical Council (NPC), Biotechnology

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Innovation Organization (BIO) and Alliance for Regenerative Medicine (ARM). In addition to supporting those comments, we expand upon two of ICER's specific proposed adaptations below and provide suggestions for improvement.

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Spark's Comments on ICER's Proposed Adaptations for SSTs

Below are our comments on two of ICER's proposed adaptations that we think are most important to change in order to recognize the differential value SSTs provide to patients.

- *4.1 Discounting: ICER proposes to continue its use of a 3% discount rate as standard for both costs and outcomes.*

Although we acknowledge ICER's point that literature does not currently exist in the US to support the use of a discount rate other than 3% for SSTs, we disagree that using only the 3% rate is the right conclusion. As we discussed in our 2020 Value Assessment Framework comments, we think it is important to show both discounted and undiscounted rates in ICER reports.² Not only does reporting undiscounted values provide more transparency in the calculation of the cost-effectiveness measures, it allows readers to understand how the different discounting assumptions impact the final assessment of "value for money". Calculation of discounted and undiscounted quality-adjusted life years (QALYs), costs and incremental cost-effectiveness ratios (ICERs) is recommended by other well-known health technology assessment review processes including the one by England's National Institute for Health and Care Excellence (NICE) when results are sensitive to different rates.³ Furthermore, in cases where the treatment effect is long-lasting and substantial, as expected to be the case with SSTs, NICE suggests an even lower discount rate of 1.5%.⁴ In fact, ICER's own reference case for economic evaluations indicates

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⁴ *Ibid.*

both discounted and undiscounted outcomes should be reported; however, this does not appear to be included consistently in practice in ICER's final evidence reports.⁵

Since the costs associated with one-time gene therapies are predominantly up-front, discounting practices used in economic analyses bias against one-time therapies, in similar fashion to the bias against preventative therapies recognized in the literature.⁶ Given this theoretical issue with discounting one-time therapies like SSTs, we suggest ICER consider an independent analysis to understand if people in the US would discount the benefit of a potentially immediate and curative therapy differently than standard therapies. This is the type of informed decision making we think is necessary when developing new frameworks for innovative therapies.

- *5.1 Shared savings: ICER proposes to provide a “shared savings” scenario analysis for SSTs as an adjunct to the base case. For this scenario analysis cost offsets will accrue to the innovator during the first 12-year period in the model, a time frame intended to approximate the average time to loss of exclusivity for new prescription drugs in the United States. The scenario will assume that all cost offsets following year 12 in the model will accrue to the health system, i.e. cost offsets will be set to zero in the model after year 12. The overall goal is to produce a different incremental cost-effectiveness ratio and related value-based price benchmark that reflect an alternative sharing of the economic surplus of treatment between innovators and the health system.*

As we initially recommended, it is important that ICER acknowledge that science is still in the early stages of development for one-time, transformative therapies. Future research will ideally continue to support efficiencies and improvements in technologies as this field of research and drug development grows. We feel strongly that ICER's new approach should not skew incentives away from potentially curative therapies by making it virtually impossible to illustrate cost-effectiveness using standard cost-effectiveness thresholds. ICER's proposed use of the shared savings scenario analysis for SSTs makes it increasingly difficult to meet these thresholds.

ICER does not provide sufficient justification for why this analysis is relevant to SSTs and not other, more traditional chronic therapies. Specifically, it is not clear why the benefits of an SST to the system in terms of cost offsets should be treated differently than the cost offsets that the system experiences with traditional therapies. By focusing on cost offsets in particular, this analysis targets therapies that are likely to save the system the most money over the long-run, which are precisely the type of therapies the system should be encouraging.

More importantly, this approach is inconsistent with ICER's general value assessment. Most therapies have a patent expiration and the threat of either generic or biosimilar entry at some point in time. Yet, the potential reduction in cost of treatment due to patent expiration, that is well documented in the

⁵ ICER, “ICER's Reference Case for Economic Evaluations: Principles and Rationale,” July 16, 2018. Available at: https://icer-review.org/wp-content/uploads/2018/07/ICER_Reference_Case_July-2018.pdf.

⁶ Per Severens and Milne (2004): “On pragmatic grounds, since discounting discriminates against well-accepted, once-off preventive and other programs that are characterized by early investment and late health outcome, including screening and pediatric vaccination, some authors argue that future benefits of such programs should not be discounted. If this principle were accepted, it might be necessary to develop detailed guidelines for discounting the benefits of other types of well-accepted health-care programs such as lipid screening coupled with (ongoing) lipid lowering therapy, which are also designed largely for risk management.”

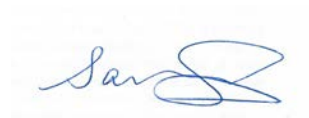
Severens JL, Milne RJ. Discounting Health Outcomes in Economic Evaluation: The Ongoing Debate. *Value in Health*. 2004;7(4):397-401.

literature,⁷ has never been accounted for in ICER's value assessment of traditional therapies. It is unscientific and biased for ICER to try to incorporate patent expiration into a sensitivity for SSTs and therefore, ICER should remove this cost sharing sensitivity from their assessment of SSTs.

We appreciate ICER's further consideration of our comments on the proposed changes to their valued assessment as it relates to SSTs.

Please do not hesitate to contact me at sarah.pitluck@sparktx.com or 202-431-6706 with any questions.

Sincerely,

A handwritten signature in blue ink, appearing to read "Sarah Pitluck", with a stylized flourish at the end.

Sarah Pitluck
Head, Global Pricing & Reimbursement

⁷ IMS Institute, "Price Declines after Branded Medicines Lose Exclusivity in the U.S.," Report, January 2016, Available at: <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf> ; Mulcahy A, Predmore Z, Mattke S. The Cost Savings Potential of Biosimilar Drugs in the United States. Rand Corp [Internet]. 2014;16. Available from: <http://www.rand.org/pubs/perspectives/PE127.html>.



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More importantly, this approach is inconsistent with ICER's general value assessment. Most therapies have a patent expiration and the threat of either generic or biosimilar entry at some point in time. Yet, the potential reduction in cost of treatment due to patent expiration, that is well documented in the

⁵ ICER, “ICER's Reference Case for Economic Evaluations: Principles and Rationale,” July 16, 2018. Available at: https://icer-review.org/wp-content/uploads/2018/07/ICER_Reference_Case_July-2018.pdf.

⁶ Per Severens and Milne (2004): “On pragmatic grounds, since discounting discriminates against well-accepted, once-off preventive and other programs that are characterized by early investment and late health outcome, including screening and pediatric vaccination, some authors argue that future benefits of such programs should not be discounted. If this principle were accepted, it might be necessary to develop detailed guidelines for discounting the benefits of other types of well-accepted health-care programs such as lipid screening coupled with (ongoing) lipid lowering therapy, which are also designed largely for risk management.”

Severens JL, Milne RJ. Discounting Health Outcomes in Economic Evaluation: The Ongoing Debate. *Value in Health*. 2004;7(4):397-401.

literature,⁷ has never been accounted for in ICER's value assessment of traditional therapies. It is unscientific and biased for ICER to try to incorporate patent expiration into a sensitivity for SSTs and therefore, ICER should remove this cost sharing sensitivity from their assessment of SSTs.

We appreciate ICER's further consideration of our comments on the proposed changes to their valued assessment as it relates to SSTs.

Please do not hesitate to contact me at sarah.pitluck@sparktx.com or 202-431-6706 with any questions.

Sincerely,

A handwritten signature in blue ink, appearing to read "Sarah Pitluck", with a stylized flourish at the end.

Sarah Pitluck
Head, Global Pricing & Reimbursement

⁷ IMS Institute, "Price Declines after Branded Medicines Lose Exclusivity in the U.S.," Report, January 2016, Available at: <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf> ; Mulcahy A, Predmore Z, Mattke S. The Cost Savings Potential of Biosimilar Drugs in the United States. Rand Corp [Internet]. 2014;16. Available from: <http://www.rand.org/pubs/perspectives/PE127.html>.



www.teushealth.com

September 6, 2019

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, Massachusetts 02109

Re: SST Adaptations and Risk

Dear ICER Team:

Thank you for your value assessment work and the opportunity to offer comments on your proposed value assessment framework adaptations.

I have reviewed your document "Single or Short-Term Transformative Therapies" (SSTs): Proposed Adaptations to the ICER Value Assessment Framework' and the accompanying Technical Brief. I am concerned that your proposed method for valuing SSTs does not project best estimates of future costs or properly assess risk and therefore greatly overvalues the one-time (or short-term) price that healthcare payers should be willing to pay for SSTs.

1. **The framework allows SSTs to capture a projected lifetime of overpricing for the current non-SST therapies.** The value-based price for an SST, per the ICER framework, is the \$150,000 for each incremental QALY plus the value of current treatment cost offsets, where both the QALYs and current treatment cost offsets are projected over a lifetime and then discounted at 3% per annum. Yet, there is no reason to believe that the costs of today's expensive therapies will continue unabated for decades.

For example, the technical brief suggests that \$85 million is a value-based price for a SST for hemophilia A patients with inhibitors (pg. 37). The price is due to the exceedingly high cost of the of today's BPA prophylaxis therapy being projected over decades, an unreasonable projection given that there will inevitably be prophylaxis competitors and lower prices.

2. **The framework overlooks potential sources of detrimental consequences.** Many of the new and forthcoming SSTs work via new therapeutic pathways. While we have high hopes for the success of SSTs, innovation is never guaranteed, the trials that led to their approval were for a few years at most, and we do not know the long-term consequences of the therapies. Emergent consequences will impact incremental QALYs and net cost offsets. While the adapted framework considers the possibility of loss of effect over time, the realm of possible consequences is more diverse and potentially dire than loss of effect. For

example, even those treatments that successfully “cure” the original disease might ultimately have disabling, teratogenic, or carcinogenic effects which both reduce QALYs and generate extraordinary new costs.

3. **The framework excludes important patient-centered values and risks, such as lost opportunity, from the central cost-effectiveness analysis and includes them on the margin as “additional elements of value”.** I feel that patient-opportunity risk should be central, not marginal, to the value assessment. While SSTs offer the hope of escaping the ongoing burden of disease, they may not be effective and may preclude the use of future hopeful therapies – either because the future therapy will not work on a previously treated patient or because the payer may be unwilling to make an additional investment. An SST may be a one-way path for patients. In contrast, patients on non-SST therapies can from month to month based on ongoing efficacy.
4. **The present values produced under the framework are not adjusted for the risk inherent in the projected future values, an omission that dramatically inflates the value-assessment.** The riskier a future outcome, the less value it has today. Risk is particularly abundant for SSTs that have never been tested in the real world. Yet, the framework assigns the same value to estimated future outcomes (the present value of the estimate, discounted at 3% per annum) regardless of whether the outcome is estimated from real-world historical data or a multi-decade exercise in wishful thinking. Financial theorists have various methods to reduce present values based on risk, including risk-adjusted discount rates and certainty equivalent cashflows.¹
5. **Much of today’s healthcare is funded by employers and they do not have a lifetime horizon.** Employer value for an SST is contingent upon employee attrition estimates and the risk thereof, both of which are omitted from your framework. Absent government regulation, employers will not be willing to pay a lifetime value for an SST if there is a non-SST drug that can be paid on a pay-as-you-go method. If an SST is priced at lifetime value, employers will, at most, make the SST available for only the few people whose lives are immediately endangered and for whom non-SSTs are not effective.
6. **Lifetime investments are funded or mandated by governments, who generally demand a societal return on investment and, even then, choose to invest after considerable debate.** An SST is a human capital investment. Our society has to select from among many human value investments, including education. SSTs require a return comparable to other investments.
7. **Society has an interest in a price point that makes SSTs available to most people and not a privileged few.** The science being leveraged to create today’s and future SSTs is new, but curative therapies are not new. We already have many curative therapies, including

¹ This link provides a brief overview of risk adjusted value:
<http://people.stern.nyu.edu/adamodar/pdfiles/valrisk/ch5.pdf>.

antibiotics, and certain surgeries. Conceptually, vaccines are the ultimate curative therapy as they prevent disease from happening. Curative therapies have greatly benefited our society. No one wants to live in a world without antibiotics, vaccines, and appendectomies. That would be the world for everyone except the most privileged, however, if these curative therapies were priced using the proposed framework. Curative therapies have been a societal success by virtue of being affordable and available to nearly all members of society.

8. **SSTs should be subject to routine re-evaluation.** Because so much is unknown about new SSTs, initial value assessments are a “shot in the dark” that will soon become obsolete. As noted in your technical brief, present value calculations are very sensitive to changes in assumptions. I recommend that any assessment explicitly include a plan for updating the assessment as additional data emerges.

Thank you for considering my comments.

Sincerely,



Tia Goss Sawhney

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September 6, 2019

Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, Massachusetts 02109

Re: Call for Public Input on Proposed Adaptations for Assessments of Single or Short-term Transformative Therapies

To Whom It May Concern:

UCB is a global biopharmaceutical company, with U.S. headquarters located in Atlanta, Georgia. Our focus is on innovating new medicines to treat chronic, severe diseases in neurology, immunology, and bone that treat nearly three million patients worldwide. We are nearly 7,500 people globally, inspired by patients and driven by science. We have consistently demonstrated our commitment to creating more value for patients, investing about a quarter of total revenues into research and development for new therapies for the past several years.

UCB thanks the Institute for Clinical and Economic Review (“ICER”) for the opportunity to provide feedback on its proposed adaptations to its Value Assessment Methods for “Single or Short-Term Transformative Therapies” (“SSTs”). UCB is committed to delivering solutions that improve the lives of patients living with severe diseases and we firmly believe that patient-centered outcomes and patient experience should be at the core of our mission. As such, we fully support equipping decision-makers with a reliable and transparent evaluation of SSTs. We hope that ICER will consider and incorporate our recommendations for strengthening the framework to pursue value-based pricing of SSTs and foster innovation of transformative new therapies that will be affordable to individual patients and to the health system at large.

UCB understands that SSTs present many unique challenges to the healthcare system, including uncertainty about risks and long-term effects, and limited real-world evidence. Despite the challenges and benefits unique to SSTs, we support the use of varying value assessment methods that consider the innovative nature of these treatments, rather than reliance on a traditional, one-size-fits all approach to value assessment. A novel treatment necessitates a novel approach to value assessment.

Summary of recommendations:

- Assessment of value for transformative therapies should begin by measuring value to the patient, exclusive of any consideration of price. An assessment for different subgroups of patients may be needed if evidence reveals there are patients that experience unique benefits.
- Recognize the limitations of existing metrics such as Quality Adjusted Life Years (“QALYs”) and Patient Reported Outcomes (“PROs”) for measuring the value of transformative therapies and consider use of novel metrics that better capture patient-centered definitions of value to avoid underestimating what is important to the patient before translating the value assessment into a price estimate.
- Recognize that the true value of a product may not be quantified prior to market launch and permit time for additional evidence, including real world evidence, to accumulate.
- When assessing willingness-to-pay (“WTP”) thresholds and defining price levels, which reflect treatment’s value to the patients, consider the holistic budgetary tradeoffs that should occur in order to accurately reflect the amounts available for making transformative treatment options accessible to patients that would otherwise utilize other medical services.
- Build into the value assessment of transformative therapies the ability to update assessments as new evidence becomes available.

A. Assessment of value must move beyond QALYs to capture patient experience and long-term improvement of well-being.

UCB is discouraged that ICER's framework does not account for the holistic and long-term value of a treatment to the patient. The existing framework, methods and context, is limited to capturing efficacy, safety, and Health-Related Quality of Life ("HRQoL"), driven by generic PROs. Yet, value elements important to the patient are missing. For purposes of this letter, we group these elements and collectively refer to them as "patient experience". Any assessment of value of SSTs should begin by measuring the value of the treatment to the patient, exclusive of any consideration of price.

At UCB, we strive to deliver unique patient experiences, providing solutions with the highest possible impact. Rather than a pure scientific approach, we start with the patient to understand their perspective, considering the full impact of the disease and its effects on every part of the patient's life. We believe that patients should be at the center of value assessment and urge ICER to modify its framework to reflect the importance of the patient experience. It is becoming increasingly common, in other value assessment frameworks, to formally include components of shared decision-making, which allow patients' voice and preferences to carry weight.

To consider survival as the only patient-relevant outcome, underestimates the power of the quality of life of the patient, which is highly impacted by their experience. A patient's experience is eventually connected to their quality of life, adherence rates, satisfaction, disease activity, and motivation for sustained performance and behavioral change. Generic PROs that are being used to inform health utility values that inform the QALY and the end ICER estimates only partially capture the holistic essence of what matters to the patients. There are elements that generic PROs are not sensitive enough to capture. QALYs capture patient benefit relating to clinical outcomes of an intervention, as measured through efficacy, safety, and HRQoL endpoints. However, these endpoints are traditionally guided by the requirements of regulatory authorities and payers and may not necessarily best measure what matters to patients in terms of efficacy, safety, and HRQoL.

In short, under the prevailing status quo we see that the value of a treatment captured by the QALY reflects value as perceived to be important by regulators or payers, which may be misaligned to the value as perceived by patients. Even when genuinely patient-centric HRQoL outcomes are collected, the QALY framework only allows those HRQoL outcomes that can be translated into utility values to be captured in the value assessment. This typically means generic PROs. Key decision-makers have stated an explicit preference for utilities to be derived from such generic outcomes (e.g. EQ-5D).¹ Payer desire to use these generic measures that facilitate trade-off decisions across diseases is understandable. However, generic PROs are restrictive in terms of the components of patient value that they capture.² For example, the EQ-5D and SF-6D have been shown to be insensitive to changes in vision and perceived visual function for patients with primary open-angle glaucoma.³ Similar findings have been reported in other chronic conditions, including macular degeneration, rheumatoid arthritis, asthma, and resistant epilepsy.⁴

¹ National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. <https://www.nice.org.uk/process/pmg9/chapter/the-reference-case>.

² Efthymiadou O, Mossman J, Kanavos P. Health related quality of life aspects not captured by EQ-5D-5L: Results from an international survey of patients. *Health Policy* 2019; 123:159-165.

³ Bozzani FM, Alavi Y, Jofre-Bonet M, et al. A comparison of the sensitivity of EQ-5D, SF-6D and TTO utility values to changes in vision and perceived visual function in patients with primary open-angle glaucoma. *BMC ophthalmology* 2012; 12:43

⁴ Espallargues M, Czoski-Murray CJ, Bansback NJ, et al. The impact of age-related macular degeneration on health status utility values. *Investigative ophthalmology & visual science* 2005; 46:4016-4023; Szende A, Leidy N, Ståhl E, et al. Estimating health utilities in patients with asthma and COPD: evidence on the performance of EQ-5D and SF-6D. *Quality of Life Research* 2009;18:267-272.

The focus of generic PROs on daily function means that the QALY also fails to capture wider dimensions of value that matter to patients, caregivers, and society at large. The QALYs also fail to account for differences in patient preference. For example, treatments can be associated with multiple characteristics that influence patient experience, such as patient perception of the treatment and patient-friendliness of the intervention, or the extent to which treatment addresses patients' priorities regarding the effects of interventions on caregivers, family, or friends.⁵ These elements are important and influential to a patient's treatment adherence for this patient. This is reflected in published draft guidance from the U.S. Food and Drug Administration ("FDA") on how to submit meaningful patient experience data to capture "patients' experiences, perspectives, needs, and priorities".⁶ Similarly, the European Medicines Agency has concluded a pilot project on direct patient involvement in assessment of benefits and risks, and Health Technology Assessment agencies in general are trending in this direction. Instruments such as the Treatment Satisfaction Questionnaire for Medication ("TSQM") are available that can partially capture patient experience; however, these are not routinely used to inform the QALY due to the convention to use generic PROs.

Ultimately, the use of QALYs as the value measure may lead to a discrepancy between payer and patient perceptions of product value. Differences in opinion on value between these two stakeholders are to be expected. Payers may decide that they are not willing to pay for a treatment, in spite of the value the innovation brings to patients and the decrease in associated opportunity costs. However, we argue the starting point for value assessment should be that payers have the best possible understanding of the patient value of a product, so that they can make informed decisions regarding their willingness to pay for the treatment. Theoretically, the QALY framework does not preclude measurement of true patient value, but a generic PRO that could capture and enable quantification (in the form of utility values) of all relevant value elements across all disease areas, accounting for any heterogeneity in patient preference or priority, would be required. Since the feasibility of developing such an instrument is low, we propose an additive approach of value elements that are not captured in the QALY to ensure that they are accounted for in payer decision-making.

To summarize, the QALY suffers from issues with regards to measurement of directly tangible elements of HRQoL in some diseases. We expect that this will be increasingly challenging for short-term interventions, where a patient's overall long-term experience should be significantly improved but will not be captured in clinical trial data for proper incorporation in the ICER's framework.

To effectively value a treatment, ICER must recognize the limitations of existing metrics and consider novel metrics that better capture patient-centered definitions of value and appropriately recognize what the patient values. These factors must be considered when quantifying a treatment's value into a price estimate. Outputs, other than QALYs and PROs, should be included in decision-making. For example, cost-per-event avoided, cost-of-time saved, and cost-per-day free of symptoms. When assessing WTP thresholds and defining price levels that reflect a treatment's value to the patient, we urge ICER to consider holistic budgetary tradeoffs that should occur, in order to accurately reflect the cost and benefit of making a cure accessible to patients who would otherwise utilize other medical services.

Harrison MJ, Davies LM, Bansback NJ, et al. The validity and responsiveness of generic utility measures in rheumatoid arthritis: a review. *The Journal of Rheumatology* 2008; 35:592-602; Mukuria C, Young T, Keetharuth A, et al. Sensitivity and responsiveness of the EQ-5D-3L in patients with uncontrolled focal seizures: an analysis of Phase III trials of adjunctive brivaracetam. *Quality of Life Research* 2017; 26:749-759.

⁵ Neumann PJ, Cohen JT. QALYs in 2018—advantages and concerns. *Jama* 2018; 319:2473-2474.

⁶ Food and Drug Administration. Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data Guidance for Industry and Other Stakeholders - Draft Guidance. December 2018.; Food and Drug Administration (FDA). Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm610442.pdf>.

We ask that ICER expand its method of cure proportion modeling with more patient-relevant outcomes, especially in the case of non-life-threatening chronic diseases.

B. Comparative evidence required for the ICER Integrated Evidence Rating matrix should be updated.

The ICER Integrated Evidence Rating matrix should be revisited, given that we need to acknowledge and accept that: a) there will be no appropriate comparative evidence for most of the interventions; and b) the Integrated Evidence Rating matrix may not be able to reflect and accommodate the innovation of the science of new treatment options.

C. Value assessment must account for the inherent uncertainty of SSTs.

There is high uncertainty expected for trials to demonstrate long-term benefits given their short duration. The assessment framework should account for: a) subpopulation analyses that may benefit more than others and their access to the innovation should not be restricted; and b) the uncertainty seen at launch and the expectation that it will decrease as in-market effectiveness evidence accumulates and prices can be readjusted accordingly.

At UCB, we strive to create value for discrete groups of patients, meeting their specific needs, rather focus on a one-size-fits all treatment approach for the general patient population. Moving forward, as more evidence is gathered and assessed, it may be necessary to create different assessments for different subgroups of patients if the evidence reveals that certain patient populations achieve a unique benefit from an innovative treatment.

SSTs are ground-breaking and, initially, there is limited real-world evidence about any one treatment. As such, there is an amount of uncertainty about the specific balance of risk and benefit that accompanies a treatment, specifically long-term risks and benefits. The true value of a treatment may not be assessed until after launch and evidence of its risks and effectiveness have been gathered and analyzed. UCB feels strongly that the ICER framework should take these unique circumstances into account and reflect the evolving nature of the value of a treatment. In the same vein, the framework should be flexible and allow for updates to assessments as more evidence becomes available.

Any discount rate utilized must be less than that being used for other treatment options, given the analysis will be the patient's lifetime. The effects of short-term interventions are expected to be long-term and the discount rate, as applied, underestimates the uncertainty of the outcome in an effort to make outcomes comparable across disease areas and indications.

D. Willingness-to-pay levels should be refined.

We propose that ICER assess how much stakeholders are willing to pay for the outcomes outlined in its policy recommendations for outcomes-based payment, including the opportunity cost of not treating a particular patient with a curative treatment. The WTP thresholds used for economic assessment have been arbitrarily set and they must be adjusted to reflect the intrinsic value of these treatment options to patients and healthcare professionals.

At UCB, we foresee the introduction of innovative technologies initiating discussions related to how the healthcare system should re-allocate available funds, considering not only pharmaceutical and medical goods, but others as well—*i.e.* ambulatory healthcare, hospital, nursing homes, etc.—in order to balance affordability and innovation. ICER can facilitate this process, rather than concluding its assessment with a proposed price point. A discussion on prioritizing expenditures will help the healthcare system and healthcare professionals prioritize their investment in treatment options with the highest value to patients,

increasing the cost-efficiency of the system by reallocating the available budget without putting additional pressure on the price of an individual product.

E. What is transformative treatment today may not be transformative tomorrow.

Lastly, the term “transformative” has gained significant traction in recent years. When stakeholders refer to transformative effect, they often mean leaps in improvement over existing alternatives. Antibiotics, vaccines, initial monoclonal antibody treatments, the first precision medicines, and early enzyme-replacement therapies could all be viewed as transformative at the time of launch. In this way, whether a technology is viewed as transformative is often relative, benchmarked against standard of care at a given time. Hence, we request that ICER clarify what is meant by the term “transformative” and specify what criterion will be used to assess the value of a treatment to determine whether an intervention qualifies as “transformative.”

We urge ICER to continue to collaborate with stakeholders to improve its framework. UCB appreciates the opportunity to provide our perspective and are open to a continued dialogue as you move forward. We hope you will consider our suggestions for strengthening and improving your framework. Should you have questions or wish to discuss further please contact Amanda Ledford, Associate Director, U.S. Public Policy and Reimbursement, at Amanda.Ledford@UCB.com or (202) 893-6194.

Sincerely,



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